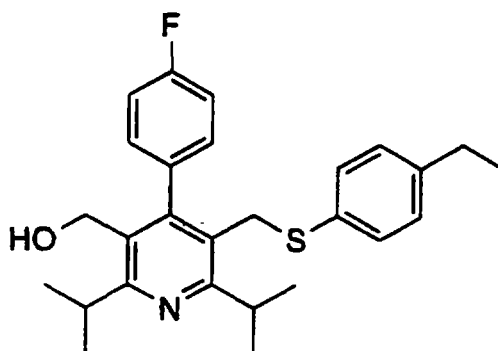


0

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3,5-dimethyl-phenyl)thio]methylpyridine

The title compound was prepared from 3,5-dimethylthiophenol according to the procedures described in Example 47. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 (m, 2 H), 7.11 (m, 2 H), 6.80 (s, 1 H), 6.69 (s, 2 H), 4.35 (d, *J* = 5.5 Hz, 2 H), 3.79 (s, 2 H), 3.44 (sept, *J* = 6.6 Hz, 1 H), 3.42 (sept, *J* = 6.6 Hz, 1 H), 2.23 (s, 6 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.33 (d, *J* = 6.6 Hz, 6 H), 1.21 (t, *J* = 5.5 Hz, 1 H). FAB-MS calcd for (C<sub>27</sub>H<sub>32</sub>FNOS) 437, found 438 (M+H). Anal. Calcd for C<sub>27</sub>H<sub>32</sub>FNOS: C, 74.11; H, 7.37; N, 3.20; S, 7.33. Found: C, 74.18; H, 7.22; N, 3.13; S, 6.86. mp 109-110°C. R<sub>f</sub> = 0.5 (20% ethyl acetate/hexane).

EXAMPLE 62



15

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-ethylphenyl)thio]methylpyridine

The title compound was prepared from 4-ethylthiophenol according to the procedures described in Example 47. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.24 (m, 2 H), 7.05 (m, 6 H), 4.35 (d, *J* = 5.5 Hz, 2 H), 3.77 (s, 2 H), 3.43 (m, 2 H), 2.60 (q, *J* = 7.7 Hz, 2 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.32 (d, *J* = 6.6 Hz, 6 H), 1.21 (m, 4 H). FAB-MS calcd for (C<sub>27</sub>H<sub>32</sub>FNOS) 437, found 438 (M+H). Anal. Calcd for C<sub>27</sub>H<sub>32</sub>FNOS: C, 74.11; H, 7.37; N, 3.20; S, 7.33. Found: C, 74.07; H, 7.23; N, 3.09; S, 7.23. mp 102-103°C. R<sub>f</sub> = 0.5 (20% ethyl acetate/hexane).

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30

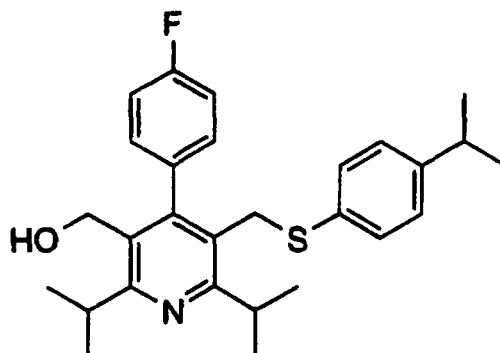


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\*G00001\*

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EXAMPLE 63

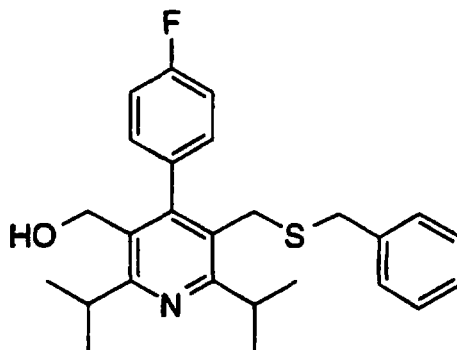
5

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-isopropylphenyl)thio]methylpyridine

10

The title compound was prepared from 4-isopropylthiophenol according to the procedures described in Example 47.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25 (m, 2 H), 7.06 (m, 6 H), 4.35 (d,  $J = 5.5$  Hz, 2 H), 3.79 (s, 2 H), 3.43 (m, 2 H), 2.86 (sept,  $J = 7$  Hz, 1 H), 1.34 (d,  $J = 6.6$  Hz, 6 H), 1.32 (d,  $J = 6.6$  Hz, 6 H), 1.22 (d,  $J = 7$  Hz, 6 H), 1.20 (t,  $J = 5.5$  Hz, 1 H). FAB-MS calcd for ( $\text{C}_{28}\text{H}_{34}\text{FNOS}$ ) 451, found 452 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{28}\text{H}_{34}\text{FNOS}$ : C, 74.46; H, 7.59; N, 3.10; S, 7.10. Found: C, 74.51; H, 7.48; N, 3.04; S, 6.85. mp 108-109°C.  $R_f = 0.5$  (20% ethyl acetate/hexane).

15

EXAMPLE 64

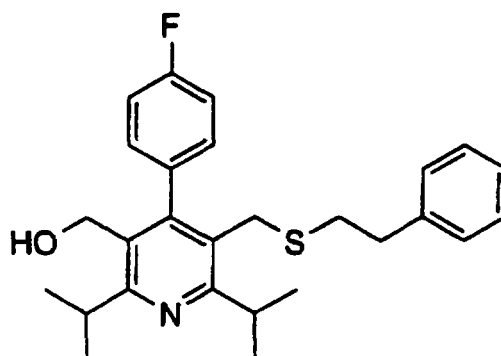
20

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-benzylthio-methylpyridine

The title compound was prepared from benzyl mercaptan according to the procedures described in Example 47.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.23 (m, 5 H), 7.08 (m, 4 H), 4.31 (d,  $J = 5.5$  Hz, 2 H), 3.55 (s, 2 H), 3.40 (sept,  $J = 6.6$  Hz, 1 H), 3.24 (s, 2 H), 3.19 (sept,  $J = 6.6$  Hz, 1 H), 1.31 (d,  $J = 6.6$  Hz, 6 H), 1.24 (d,  $J = 6.6$  Hz, 6 H), 1.17 (t,  $J = 5.5$  Hz, 1 H). FAB-MS calcd for ( $\text{C}_{26}\text{H}_{30}\text{FNOS}$ ) 423, found 424 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{26}\text{H}_{30}\text{FNOS}$ : C, 73.72; H, 7.14; N, 3.31; S, 7.57. Found: C, 73.58;

0 H, 7.25; N, 3.05; S, 7.45. mp 150-151°C.  $R_f$  = 0.5 (20% ethyl acetate/hexane).

### EXAMPLE 65



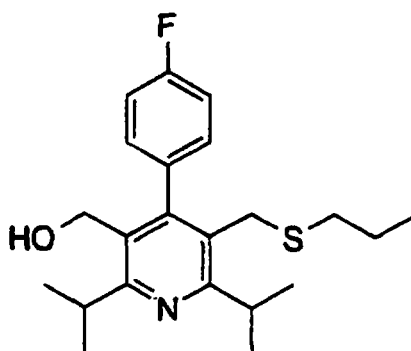
5

#### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(phenethyl)thiomethyl]pyridine

The title compound was prepared from phenethyl mercaptan according to the procedures described in Example 47.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.28 (m, 5 H), 7.11 (m, 4 H), 4.34 (d,  $J$  = 5.5 Hz, 2 H), 3.39 (m, 4 H), 2.70 (m, 2 H), 2.61 (m, 2 H), 1.33 (d,  $J$  = 6.6 Hz, 6 H), 1.32 (d,  $J$  = 6.6 Hz, 6 H), 1.20 (t,  $J$  = 5.5 Hz, 1 H). FAB-MS calcd for  $(\text{C}_{27}\text{H}_{32}\text{FNOS})$  437, found 438 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{27}\text{H}_{32}\text{FNOS}$ : C, 74.11; H, 7.37; N, 3.20; S, 7.33. Found: C, 73.99; H, 7.46; N, 2.96; S, 7.23. Gummy oil.  $R_f$  = 0.5 (20% ethyl acetate/hexane).

15

### EXAMPLE 66

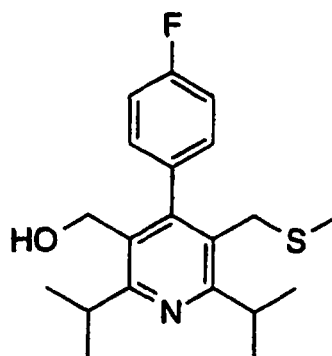


#### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(propylthio)methylpyridine

The title compound was prepared from propyl mercaptan according to the procedures described in Example 47.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.30 (m, 2 H),

- 0 7.14 (m, 2 H), 4.34 (d,  $J = 5.5$  Hz, 2 H), 3.41 (m, 2 H), 3.37 (m, 2 H), 2.31 (t,  $J = 7.0$  Hz, 2 H), 1.31 (m, 15 H), 0.89 (t,  $J = 7.4$  Hz, 3 H). FAB-MS calcd for (C<sub>22</sub>H<sub>30</sub>NFOS) 375, found 376 (M+H); Anal. Calcd for C<sub>22</sub>H<sub>30</sub>NOFS: C, 70.36; H, 8.05; N, 3.73; F, 5.06; S, 8.54. Found: C, 70.32; H, 7.97; N, 3.58; F, 4.76; S, 8.49. mp 98°C (dec.).  $R_f = 0.3$  (10% ethyl acetate/hexane).

5

EXAMPLE 67

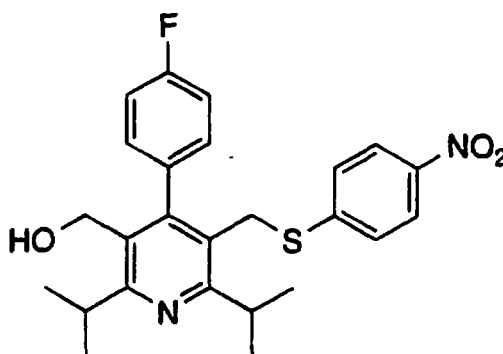
10 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(methylthio)-methylpyridine

The title compound was prepared from methyl mercaptan according to the procedures described in Example 47. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.30 (m, 2 H), 7.16 (m, 2 H), 4.35 (d,  $J = 5.5$  Hz, 2 H), 3.43 (m, 2 H), 3.38 (m, 2 H), 1.95 (s, 3 H), 1.30 (m, 12 H). FAB-MS calcd for (C<sub>20</sub>H<sub>26</sub>NFOS) 347, found 348 (M+H). Anal. Calcd for C<sub>20</sub>H<sub>26</sub>NOFS: C, 69.13; H, 7.54; N, 4.03; F, 5.47. Found: C, 69.29; H, 7.54; N, 3.91; F, 5.45. mp 49°C (dec.).  $R_f = 0.2$  (10% ethyl acetate/hexane).

15

EXAMPLE 68

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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-nitrophenyl)-thio]methylpyridine

0    Step A:        2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-  
                      [(t-butyldimethylsiloxy)methyl]pyridine

                      A solution of 3 g (8.3 mmol) of methyl 2,6-diisopropyl-4-(4-fluorophenyl)-5-hydroxymethyl-3-pyridinecarboxylate (Example 47, Step A) in anhydrous DMF (75 mL), was treated at room temperature with imidazole (1.3 g, 19 mmol), 4-  
5    dimethylaminopyridine (50 mg, 0.4 mmol) and *t*-butyldimethylsilyl chloride (1.4 g, 9.3 mmol). The reaction mixture was allowed to stir at room temperature for 48 hr. The solution was diluted with diethyl ether (200 mL) and washed with water (2 x 100 mL), 1N HCl (100 mL), sat. NaHCO<sub>3</sub> (50 mL) and brine (100 mL), dried (MgSO<sub>4</sub>) and concentrated to 4 g as an oil: R<sub>f</sub> = 0.4 (10% ethyl acetate/hexane).

10                   This intermediate (4 g) was dissolved in anhydrous THF (100 mL), stirred under argon and treated with lithium aluminum hydride (17 mL, 17 mmol, 1.0M in THF). The reaction mixture was stirred at reflux for 1 hr, then allowed to cool to room temperature. The reaction was quenched by the successive dropwise  
15    addition of water (0.6 mL), 20% NaOH (0.6 mL) and water (1.9 mL). The resulting suspension was filtered through a cake of celite and concentrated. Purification by flash silica gel chromatography (5% ethyl acetate/hexane) afforded a colorless resin (1.8 g, 4.2 mmol, 51%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.25 (m, 2 H), 7.12 (m, 2 H), 4.38 (d, *J* = 5 Hz, 2 H), 4.28 (s, 2 H), 3.44 (sept, *J* = 6.6 Hz, 1 H), 3.39 (sept, *J* = 6.6 Hz, 1 H), 1.33 (t, *J* = 6.6 Hz, 12 H), 1.24 (t, *J* = 5.5 Hz, 1 H), 0.84 (s, 9 H), -0.08 (s, 6 H).  
20    FAB-MS calcd for (C<sub>25</sub>H<sub>38</sub>FNSiO<sub>2</sub>) 431, found 432 (M+H). Anal. Calcd for C<sub>25</sub>H<sub>38</sub>FNSiO<sub>2</sub>: C, 69.56; H, 8.87; N, 3.24. Found: C, 69.70; H, 8.82; N, 3.12. R<sub>f</sub> = 0.2 (10% ethyl acetate/hexane).

25    Step B:        2,6-Diisopropyl-3-bromomethyl-4-(4-fluorophenyl)-5-  
                      [(t-butyldimethylsiloxy)methyl]pyridine

                      The intermediate obtained in Step A (1.7 g, 3.9 mmol) was dissolved in acetonitrile (50 mL) at 0°C and treated with dibromotriphenylphosphorane (2.6 g, 6.2 mmol) in portions. The suspension was then allowed to warm to room temperature and stirred for 2 hr. The solvent was removed *in vacuo* and the  
30    residue partitioned between diethyl ether (150 mL) and water (100 mL). The ether layer was washed with brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (5% diethyl ether/hexane) afforded a viscous oil (1.4 g, 2.8 mmol, 72%) which slowly solidified on standing: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.28 (m, 2 H), 7.13 (m, 2 H), 4.23 (m, 4 H), 3.37 (m, 2 H), 1.34  
35    (d, *J* = 6.6 Hz, 6 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 0.83 (s, 9 H), -0.09 (s, 6 H). FAB-MS calcd for (C<sub>27</sub>H<sub>37</sub>BrFSiNO) 493, found 494 (M+H). mp 72-73°C. R<sub>f</sub> = 0.5 (10% ethyl acetate/hexane).

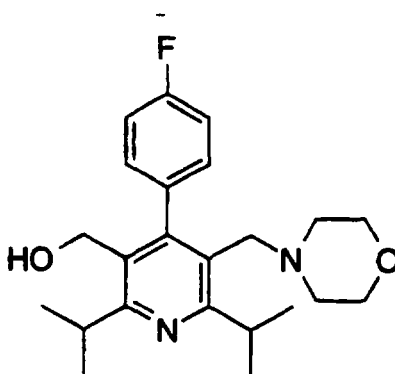
0

**Step C:**     2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-nitrophenyl)thio]methylpyridine

The intermediate obtained in Step B (200 mg, 0.40 mmol) was dissolved in anhydrous THF (5 mL), stirred under argon at room temperature and treated with  
 5 4-nitrothiophenol (118 mg, 0.6 mmol, 80% tech. grade) and N-methylmorpholine (0.2 mL, 1.8 mmol). The reaction mixture was allowed to stir at reflux for 18 hr, then cooled to room temperature. The mixture was treated with tetrabutylammonium fluoride (0.8 mL, 0.8 mmol, 1.0M in THF) and allowed to stir  
 10 at room temperature for 24 hr. The solvent was removed *in vacuo*, the residue dissolved in ethyl acetate (100 mL), washed with 1N HCl (50 mL), sat. NaHCO<sub>3</sub> (50 mL) and brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (step gradient 5-10% ethyl acetate/hexane) afforded the title compound as a lightly colored solid (130 mg, 0.28 mmol, 70%).  
 15 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.08 (d, *J* = 8.5 Hz, 2 H), 7.27 (m, 2 H), 7.13 (m, 4 H), 4.37 (d, *J* = 5.5 Hz, 2 H), 3.91 (s, 2 H), 3.46 (sept, *J* = 6.6 Hz, 1 H), 3.33 (sept, *J* = 6.6 Hz, 1 H), 1.35 (d, *J* = 6.6 Hz, 6 H), 1.34 (d, *J* = 6.6 Hz, 6 H), 1.27 (t, *J* = 5 Hz, 1 H). FAB-MS calcd for (C<sub>25</sub>H<sub>27</sub>FSN<sub>2</sub>O<sub>3</sub>) 454, found 455 (M+H). mp 178-180°C. R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

20

**EXAMPLE 69**



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**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(morpholinomethyl)pyridine**

**Step A:**     Methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(morpholino)methyl-3-pyridinecarboxylate

A solution of methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-bromomethyl-3-pyridinecarboxylate (Example 47, Step B) (500 mg, 1.22 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL)  
 30

0 was treated with morpholine (0.14 mL, 1.61 mmol) under argon. The reaction was stirred at room temperature for 48 hours. It was then diluted with CH<sub>2</sub>Cl<sub>2</sub> (70 mL), washed with saturated NaHCO<sub>3</sub> (2 x 40 mL), water (1 x 40 mL), and brine (1 x 40 mL). The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to afford a white solid (495 mg, 1.2 mmol, 98%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 2 H), 7.07 (m, 2 H), 3.54 (t, J = 4.4 Hz, 4 H), 3.49 (m, 4 H), 3.27 (s, 2 H), 2.98 (septet, J = 6.6 Hz, 1 H), 2.19 (t, J = 4.8 Hz, 4 H), 1.30 (m, 12 H). FAB-MS calcd for (C<sub>24</sub>H<sub>31</sub>N<sub>2</sub>FO<sub>3</sub>) 414, found 415 (M+H); Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub>F: C, 69.54; H, 7.54; N, 6.76; F, 4.58. Found: C, 69.55; H, 7.43; N, 6.50; F, 4.45. mp 132-134°C. R<sub>f</sub> = 0.2 (20% diethyl ether/hexane).

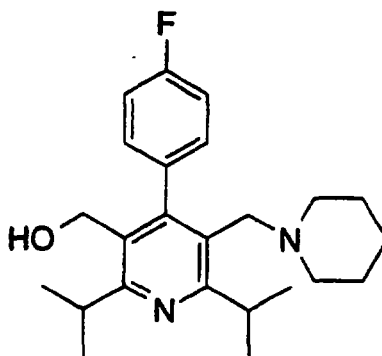
10

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(morpholinomethyl)pyridine

The intermediate obtained in Step A (375 mg, 0.905 mmol) was dissolved in dry THF (50 mL), treated dropwise with lithium aluminum hydride (1M/THF, 1.81 mL) and the reaction stirred at reflux for 24 hours. The reaction was quenched by the successive dropwise addition of water (0.1ml), NaOH 20% (0.1ml), and water again (0.3ml). Concentration *in vacuo* afforded a white residue which was partitioned between CH<sub>2</sub>Cl<sub>2</sub> and water. The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to afford an oil. The product was passed through a pad of silica (40% diethyl ether/hexanes) yielding an oil which slowly solidified to give the title compound as a white solid (295 mg, 0.76 mmol, 84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.14 (m, 4 H), 4.35 (d, 2 H), 3.53 (t, J = 4.8 Hz, 4 H), 3.45 (m, 2 H), 3.18 (s, 2 H), 2.18 (t, J = 4.5 Hz, 4 H), 1.26 (m, 13 H); FAB-MS calcd for (C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>FO<sub>2</sub>) 386, found 387 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>F: C, 71.47; H, 8.08; N, 7.25; F, 4.92. Found: C, 71.55; H, 8.16; N, 7.05; F, 4.70. mp 93.5-95.5°C. R<sub>f</sub> = 0.4 (40% diethyl ether/hexane).

30

EXAMPLE 70



0

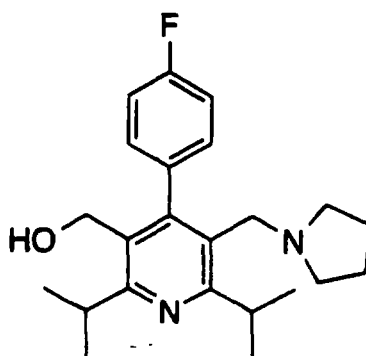
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(piperidinomethyl)pyridine

The title compound was prepared from piperidine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.05 (m, 4 H), 4.27 (d,  $J = 5.5$  Hz, 2 H), 3.38 (m, 2 H), 3.01 (s, 2 H), 2.02 (m, 4 H), 1.22 (m, 24 H). FAB-MS calcd for ( $\text{C}_{24}\text{H}_{33}\text{N}_2\text{FO}$ ) 384, found 385 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{33}\text{N}_2\text{OF}$ : C, 74.96; H, 8.65; N, 7.28; F, 4.94. Found: C, 75.13; H, 8.48; N, 6.92; F, 4.77. Gummy oil.  $R_f = 0.5$  (40% diethyl ether/hexane).

5

EXAMPLE 71

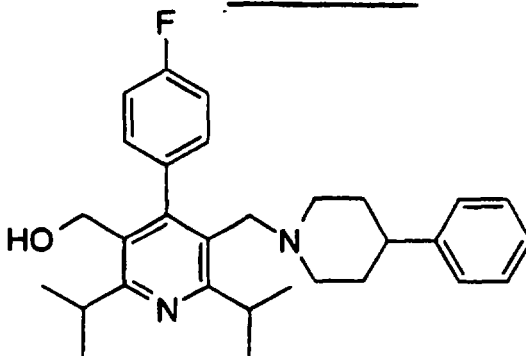
10

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(pyrrolidinomethyl)pyridine

15

The title compound was prepared from pyrrolidine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (m, 4 H), 4.34 (d,  $J = 4.8$  Hz, 2 H), 3.52 (septet,  $J = 6.6$  Hz, 1 H), 3.42 (septet,  $J = 6.6$  Hz, 1 H), 3.28 (s, 2 H), 2.22 (t,  $J = 6.3$  Hz, 4 H), 1.60 (t,  $J = 3.3$  Hz, 5 H), 1.27 (m, 12 H). FAB-MS calcd for ( $\text{C}_{23}\text{H}_{31}\text{N}_2\text{FO}$ ) 370, found 371 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{23}\text{H}_{31}\text{N}_2\text{OF}$ : C, 74.56; H, 8.43; N, 7.56; F, 5.13. Found: C, 74.67; H, 8.72; N, 7.35; F, 5.01. mp 122-124°C.  $R_f = 0.3$  (40% diethyl ether/hexane).

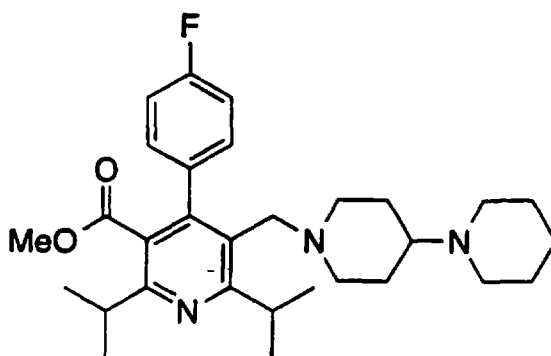
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EXAMPLE 72

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[4-phenylpiperidin-1-yl)methyl]pyridine

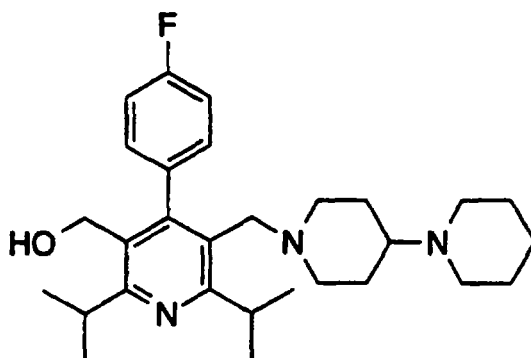
The title compound was prepared from 4-phenylpiperidine according to the procedures described in Example 69. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.29 (m, 2 H), 7.15 (m, 7 H), 4.36 (d, *J* = 5.2 Hz, 2 H), 3.48 (m, 2 H), 3.19 (s, 2 H), 2.71 (d, *J* = 11.0 Hz, 2 H), 2.38 (m, 1 H), 1.86 (m, 2 H), 1.71 (m, 2 H), 1.58 (m, 2 H), 1.58 (m, 13 H). FAB-MS calcd for (C<sub>30</sub>H<sub>31</sub>N<sub>2</sub>FO) 460, found 461 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>OF: C, 78.22; H, 8.10; N, 6.08; F, 4.12. Found: C, 78.01; H, 8.21; N, 5.96; F, 4.41. mp 66-68°C. *R*<sub>f</sub> = 0.5 (40% diethyl ether/hexane).

EXAMPLE 73

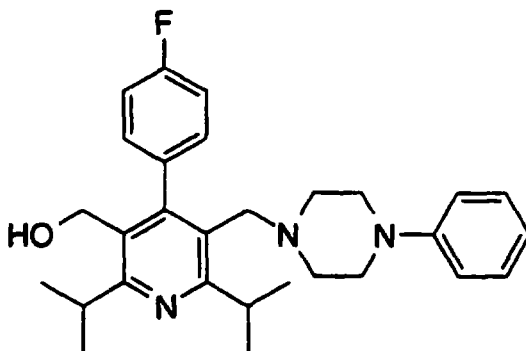


Methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(4-piperidinopiperidin-1-yl)methyl-3-pyridinecarboxylate

The title compound was prepared from 4-piperidinopiperidine according to the procedure described in Example 69 (Step A). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 2 H), 7.04 (m, 2 H), 3.51 (septet, *J* = 5.5 Hz, 1 H), 3.47 (s, 3 H), 3.20 (s, 2 H), 2.98 (septet, *J* = 6.6 Hz, 1 H), 2.65 (d, *J* = 11.0 Hz, 2 H), 2.44 (m, 4 H), 2.05 (m, 1 H), 1.62 (m, 10 H), 1.31 (m, 16 H). FAB-MS calcd for (C<sub>30</sub>H<sub>42</sub>N<sub>3</sub>FO<sub>2</sub>) 495, found 496 (M+H). Anal. Calcd for C<sub>30</sub>H<sub>42</sub>N<sub>3</sub>O<sub>2</sub>F: C, 72.69; H, 8.54; N, 8.48; F, 3.83. Found: C, 72.43; H, 8.56; N, 8.37; F, 3.74. mp 59-61°C. *R*<sub>f</sub> = 0.1 (70% diethyl ether/hexane + 1 drop MeOH).

EXAMPLE 742,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-piperidinopiperidin-1-yl)methyl]pyridine

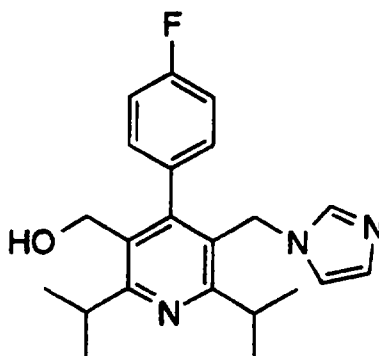
The title compound was prepared from 4-piperidinopiperidine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.12 (m, 4 H), 4.34 (d,  $J = 3.7$  Hz, 2 H), 3.45 (m, 2 H), 3.10 (m, 2 H), 2.63 (d,  $J = 11.0$  Hz, 2 H), 2.44 (m, 4 H), 2.03 (m, 1 H), 1.44 (m, 29 H). FAB-MS calcd for  $(\text{C}_{29}\text{H}_{42}\text{N}_3\text{FO})$  467, found 468 (M+H). Anal. Calcd for  $\text{C}_{29}\text{H}_{42}\text{N}_3\text{OF}$ : C, 74.48; H, 9.05; N, 8.98; F, 4.06. Found: C, 74.93; H, 9.35; N, 8.39; F, 3.83. mp 143-145°C.  $R_f = 0.1$  (50% diethyl ether/hexane + 2 drops of MeOH).

EXAMPLE 752,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(4-phenylpiperazin-1-yl)methyl]pyridine

The title compound was prepared from 4-phenylpiperazine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.16 (m, 6 H), 6.85 (m, 3 H), 4.36 (d,  $J = 5.2$  Hz, 2 H), 3.47 (m, 2 H), 3.24 (s, 2 H), 3.04 (t,  $J = 4.8$  Hz, 4 H), 2.35 (t,  $J = 4.8$  Hz, 4 H), 1.29 (m, 13 H). FAB-MS calcd for  $(\text{C}_{29}\text{H}_{36}\text{N}_3\text{FO})$  461, found 462 (M+H). Anal. Calcd for  $\text{C}_{29}\text{H}_{36}\text{N}_3\text{OF}$ : C, 75.46; H, 7.86; N, 9.10; F, 4.12.

- 0 Found: C, 75.35; H, 7.82; N, 8.80; F, 3.99. mp 111-113°C.  $R_f$  = 0.5 (40% diethyl ether/hexane).

### EXAMPLE 76

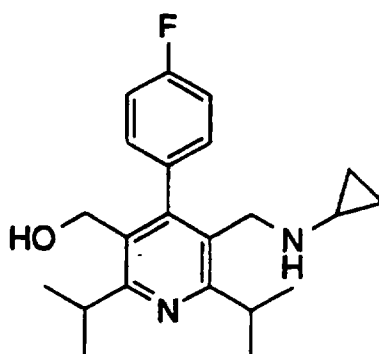


5

### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(imidazol-1-yl)-methylpyridine

- 10 The title compound was prepared from imidazole according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.01 (m, 6 H), 6.57 (s, 1 H), 4.84 (s, 2 H), 4.39 (s, 2 H), 3.49 (septet,  $J$  = 6.6 Hz, 1 H), 3.23 (septet,  $J$  = 6.6 Hz, 1 H), 1.70 (s, 1 H), 1.36 (d,  $J$  = 6.6 Hz, 6 H), 1.27 (d,  $J$  = 6.6 Hz, 6 H). FAB-MS calcd for  $(\text{C}_{22}\text{H}_{26}\text{N}_3\text{FO})$  367, found 368 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{22}\text{H}_{26}\text{N}_3\text{OF}$ : C, 71.91; H, 7.13; N, 11.43; F, 5.17. Found: C, 71.26; H, 7.24; N, 11.03; F, 5.35. mp 184-186°C.  $R_f$  = 0.1 (50% diethyl ether/hexane w/ 2 drops MeOH).
- 15

### EXAMPLE 77



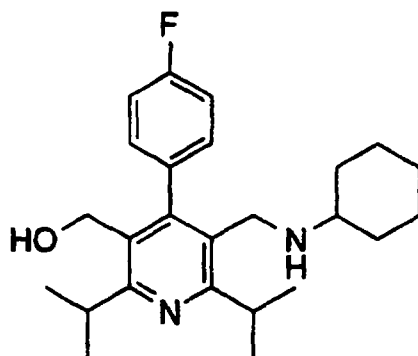
20

### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(cyclopropylamino)methylpyridine

The title compound was prepared from cyclopropylamine according to the

- 0 procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.04 (m, 4 H), 4.21 (s, 2 H), 3.35 (s, 2 H), 3.26 (septet,  $J = 6.6$  Hz, 2 H), 1.78 (m, 1 H), 1.17 (m, 13 H), 0.153 (m, 2 H), -0.006 (m, 2 H). FAB-MS calcd for  $(\text{C}_{22}\text{H}_{29}\text{N}_2\text{FO})$  356, found 357 (M+H). Anal. Calcd for  $\text{C}_{22}\text{H}_{29}\text{N}_2\text{OF}$ : C, 74.12; H, 8.20; N, 7.86; F, 5.33. Found: C, 74.29; H, 8.62; N, 7.93; F, 4.90. mp 81-83°C.  $R_f = 0.3$  (40% diethyl ether/hexane).

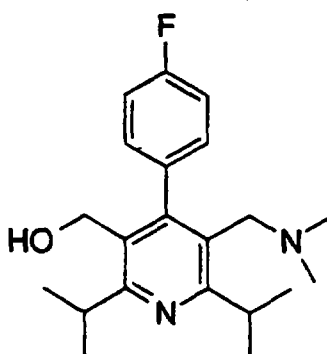
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EXAMPLE 78

- 10 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(cyclohexylamino)methylpyridine

The title compound was prepared from cyclohexylamine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25 (m, 2 H), 7.13 (m, 2 H), 4.34 (s, 2 H), 3.38 (m, 4 H), 2.16 (m, 1 H), 1.58 (m, 5 H), 1.23 (m, 16 H), 0.936 (m, 2 H). FAB-MS calcd for  $(\text{C}_{25}\text{H}_{35}\text{N}_2\text{FO})$  398, found 399 (M+H). Anal. Calcd for  $\text{C}_{25}\text{H}_{35}\text{N}_2\text{OF}$ : C, 74.12; H, 8.20; N, 7.86; F, 5.33. Found: C, 74.29; H, 8.62; N, 7.93; F, 4.90. mp 131-133°C.  $R_f = 0.1$  (40% diethyl ether/hexane).

20

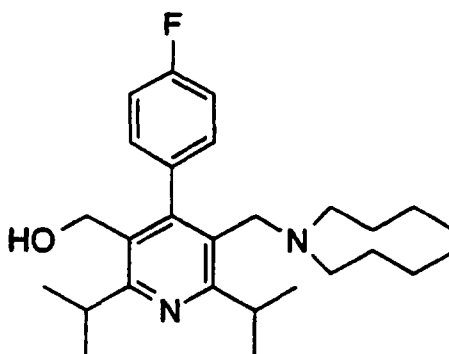
EXAMPLE 79

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(dimethylamino)methylpyridine

- 0 The title compound was prepared from dimethylamine hydrochloride according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.12 (m, 4 H), 4.25 (m, 2 H), 4.09 (m, 1 H), 3.68 (septet,  $J = 6.6$  Hz, 1 H), 3.41 (septet,  $J = 6.6$  Hz, 1 H), 2.18 (m, 1 H), 1.69 (d,  $J = 4.1$  Hz, 1 H), 1.26 (m, 12 H), 0.947 (d,  $J = 6.3$  Hz, 3 H), 0.555 (d,  $J = 7.0$  Hz, 1 H). FAB-MS calcd for  $(\text{C}_{22}\text{H}_{30}\text{NFO}_2)$  359, found 360 (M+H). Anal. Calcd for  $\text{C}_{22}\text{H}_{30}\text{NO}_2\text{F}$ : C, 73.51; H, 8.41; N, 3.90; F, 5.28. Found: C, 73.69; H, 8.40; N, 3.82; F, 5.04. mp 77-79°C.  $R_f = 0.2$  (40% diethyl ether/hexane).
- 5

### EXAMPLE 80

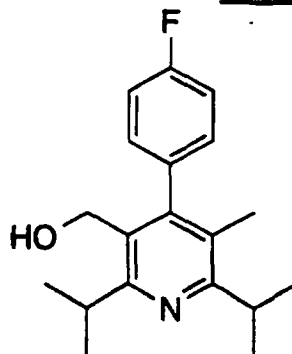
10



### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(dibutylamino)-methylpyridine

- 15 The title compound was prepared from dibutylamine according to the procedures described in Example 69.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.11 (m, 4 H), 4.33 (d,  $J = 5.5$  Hz, 2 H), 3.62 (septet,  $J = 6.6$  Hz, 1 H), 3.62 (septet,  $J = 6.6$  Hz, 1 H), 3.24 (s, 2 H), 2.12 (t,  $J = 7.0$  Hz, 4 H), 1.55 (s, 1 H), 1.33 (t,  $J = 6.6$  Hz, 6 H), 1.26 (t,  $J = 6.6$  Hz, 6 H), 1.16 (m, 8 H), 0.796 (t,  $J = 6.6$  Hz, 6 H). FAB-MS calcd for  $(\text{C}_{27}\text{H}_{41}\text{N}_2\text{FO})$  428, found 429 (M+H). Anal. Calcd for  $\text{C}_{27}\text{H}_{41}\text{N}_2\text{OF}$ : C, 75.66; H, 9.64; N, 6.54; F, 4.43. Found: C, 75.91; H, 9.83; N, 6.26; F, 4.33. Gummy oil.  $R_f = 0.6$  (40% diethyl ether/hexane).
- 20

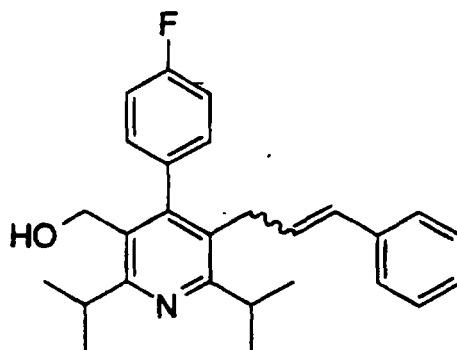
### EXAMPLE 81



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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-methylpyridine

A solution of methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-bromomethyl-3-pyridinecarboxylate (Example 47, Step B) (300 mg, 0.7 mmol), in anhydrous THF (10 mL) was stirred under argon at room temperature and treated dropwise with lithium aluminum hydride (2.1 mL, 1.0 M in THF, 2.1 mmol). The reaction mixture was heated at reflux for 1 hr, then allowed to cool to room temperature. The reaction was quenched by the dropwise sequential addition at room temperature of water (80  $\mu$ L), 20% NaOH (80  $\mu$ L) and water (240  $\mu$ L). The resulting suspension was filtered through a pad of celite and concentrated. Purification by chromatography through silica (5% ethyl acetate/hexane) afforded the title compound as a white solid (182 mg, 0.6 mmol, 85%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (d,  $J$  = 7 Hz, 4 H), 4.36 (d,  $J$  = 5.5 Hz, 2 H), 3.42 (sept,  $J$  = 6.6 Hz, 1 H), 3.26 (sept,  $J$  = 6.6 Hz, 1 H), 1.94 (s, 3 H), 1.33 (d,  $J$  = 6.6 Hz, 6 H), 1.29 (d,  $J$  = 6.6 Hz, 6 H), 1.19 (t,  $J$  = 5.5 Hz, 1 H); FAB-MS calcd for ( $\text{C}_{19}\text{H}_{24}\text{FNO}$ ) 301, found 302 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{19}\text{H}_{24}\text{FNO}$ : C, 75.72; H, 8.03; N, 4.65. Found: C, 75.62; H, 8.02; N, 4.57. mp 127-128°C.  $R_f$  = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 82

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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-phenyl-2-propenyl)pyridine

25 Step A: Methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-oxoethyl)-3-pyridinecarboxylate

Methoxymethyl triphenylphosphonium chloride (1.15 g, 3.35 mmol) was suspended in 25 mL of dry, distilled THF under argon and stirred at -78°C. Butyllithium (1.6 M/hexane, 1.2 eq., 2.1 mL) was added dropwise and then the reaction mixture was allowed to stir at 0°C for 1.0 hour. The solution was cooled

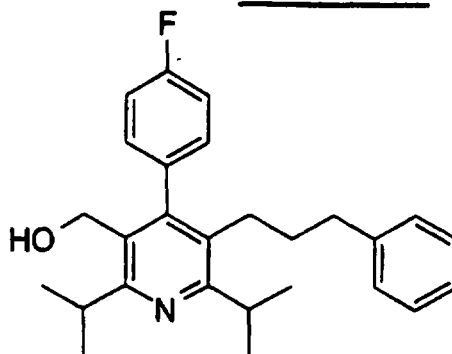
30

0 again to  $-78^{\circ}\text{C}$ , treated dropwise with a solution of 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) (1 g, 2.8 mmol) in 20 mL of dry THF, and then warmed to room temperature and stirred overnight. The reaction was quenched with 2 mL water and the THF was evaporated *in vacuo*. Diethyl ether was added and washed with water (2 x 40 mL), brine (1 x 40 mL), and dried with  $\text{MgSO}_4$ . The residue was dissolved in THF (20 mL), treated with a solution of concentrated HCl and stirred at room temperature for 1 h. The reaction mixture was diluted with diethyl ether (150 mL) washed with water (50 mL), brine (50 mL), dried with  $\text{MgSO}_4$  and evaporated *in vacuo*. Flash chromatography (10% ethyl acetate/hexane) afforded 335 mg (0.9 mmol, 32%) of product.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.62 (s, 1 H), 7.09 (m, 4 H), 3.97 (q,  $J = 7$  Hz, 2 H), 3.60 (s, 2 H), 3.06 (sept,  $J = 6.6$  Hz, 1 H), 3.00 (sept,  $J = 6.6$  Hz, 1 H), 1.32 (d,  $J = 6.6$  Hz, 6 H), 1.27 (d,  $J = 6.6$  Hz, 6 H), 0.97 (t,  $J = 7$  Hz, 3 H). FAB-MS: calcd for  $(\text{C}_{22}\text{H}_{26}\text{FNO}_3)$  371, found 372 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{22}\text{H}_{26}\text{FNO}_3$ : C, 71.14; H, 7.06; N, 3.77. Found: C, 70.91; H, 6.91; N, 3.63. mp  $69-71^{\circ}\text{C}$ .  $R_f = 0.3$  (10% ethyl acetate/hexane).

15 **Step B:** 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-phenyl-2-propenyl)pyridine

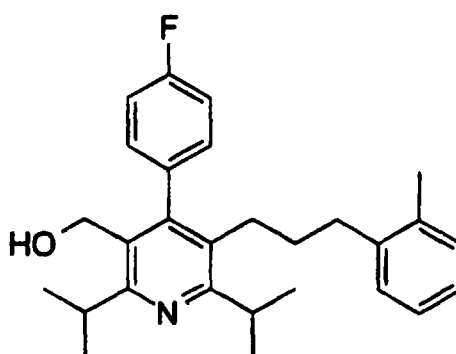
The title compound was prepared from the intermediate obtained in Step A and benzyl triphenylphosphonium bromide/sodium amide according to the procedures described in Example 1, Steps F-G. The product was obtained as a 6:4 mixture of trans:cis isomers.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.19 (m, 8 H), 6.96 (m, 1 H), 6.32 (d,  $J = 11$  Hz, 0.4 H), 6.09 (dt,  $J = 5.5, 16$  Hz, 0.6 H), 5.96 (d,  $J = 16$  Hz, 0.6 H), 5.45 (dt,  $J = 7, 11$  Hz, 0.4 H), 4.37 (d,  $J = 5$  Hz, 1.25 H), 4.33 (d,  $J = 5.5$  Hz, 0.75 H), 3.41 (m, 1.6 H), 3.25 (m, 2 H), 3.08 (m, 0.4 H), 1.35 (m, 5 H), 1.30 (d,  $J = 6.6$  Hz, 5 H), 1.21 (m, 3 H). FAB-MS: calcd for  $(\text{C}_{27}\text{H}_{30}\text{FNO})$  403, found 404 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{27}\text{H}_{30}\text{FNO}$ : C, 80.36; H, 7.49; N, 3.47. Found: C, 80.15; H, 7.44; N, 3.26. mp  $72-73^{\circ}\text{C}$ .  $R_f = 0.3$  (20% ethyl acetate/hexane).

**EXAMPLE 83**



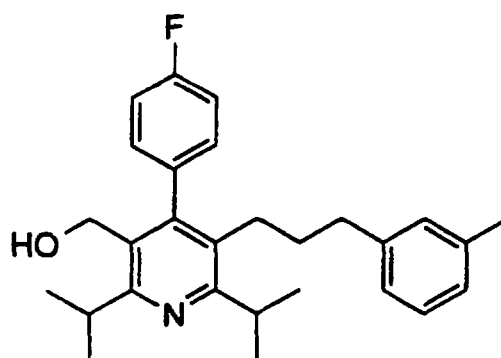
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-phenyl-propyl)pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-phenyl-2-propenyl)pyridine (Example 82) according to the procedure described in Example 1, Step H. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (m, 9 H), 4.31 (s, 2 H), 3.40 (sept, *J* = 6.6 Hz, 1 H), 3.12 (sept, *J* = 6.6 Hz, 1 H), 2.46 (t, *J* = 7.35 Hz, 2 H), 2.29 (m, 2 H), 1.62 (m, 2 H), 1.32 (d, *J* = 6.6 Hz, 6 H), 1.26 (d, *J* = 6.6 Hz, 6 H), 1.16 (bm, 1 H). FAB-MS: calcd for (C<sub>27</sub>H<sub>32</sub>FNO) 405, found 406 (M+H). mp 137-140°C. R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

EXAMPLE 842,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(2-methylphenyl)propyl]pyridine

The title compound was prepared from methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-oxoethyl)-3-pyridinecarboxylate (Example 82, Step A) and 2-methylbenzyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps F-H. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.07 (m, 7 H), 6.90 (m, 1 H), 4.31 (s, 2 H), 3.39 (sept, *J* = 6.6 Hz, 1 H), 3.15 (sept, *J* = 6.6 Hz, 1 H), 2.43 (t, *J* = 7.5 Hz, 2 H), 2.34 (m, 2 H), 2.17 (s, 3 H), 1.56 (m, 2 H), 1.31 (d, *J* = 6.6 Hz, 6 H), 1.27 (d, *J* = 6.6 Hz, 6 H), 1.15 (m, 1 H). FAB-MS: calcd for (C<sub>28</sub>H<sub>34</sub>FNO) 419, found 420 (M+H). Anal. Calcd for C<sub>28</sub>H<sub>34</sub>FNO: C, 80.15; H, 8.17; N, 3.34. Found: C, 80.12; H, 8.01; N, 3.25. mp 65-70°C. R<sub>f</sub> = 0.4 (20% ethyl acetate/hexane).

0

EXAMPLE 85

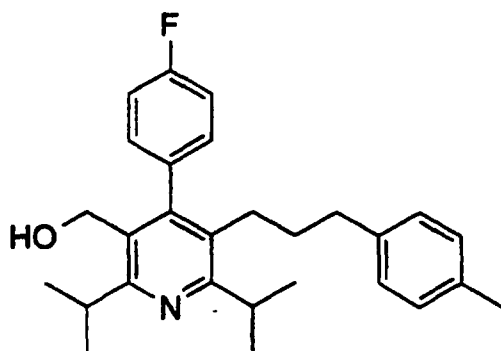
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(3-methylphenyl)propyl]pyridine

5

The title compound was prepared from methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-oxoethyl)-3-pyridinecarboxylate (Example 82, Step A) and 3-methylbenzyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps F-H. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.09 (m, 5 H), 6.98 (m, 1 H), 6.78 (m, 2 H), 4.31 (s, 2 H), 3.39 (sept, *J* = 6.6 Hz, 1 H), 3.12 (sept, *J* = 6.6 Hz, 1 H), 2.42 (t, *J* = 7 Hz, 2 H), 2.30 (s, 3 H), 2.28 (m, 2 H), 1.58 (m, 2 H), 1.31 (d, *J* = 6.6 Hz, 6 H), 1.26 (d, *J* = 6.6 Hz, 6 H), 1.15 (m, 1 H). FAB-MS: calcd for (C<sub>28</sub>H<sub>34</sub>FNO) 419, found 420 (M+H). Anal. Calcd for C<sub>28</sub>H<sub>34</sub>FNO: C, 80.15; H, 8.17; N, 3.34. Found: C, 80.23; H, 8.17; N, 3.23. mp 68-70°C. R<sub>f</sub> = 0.4 (20% ethyl acetate/hexane).

10

15

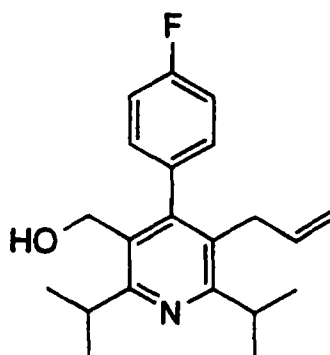
EXAMPLE 86

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(4-methylphenyl)propyl]pyridine

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The title compound was prepared from methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-oxoethyl)-3-pyridinecarboxylate (Example 82, Step A) and 4-methylbenzyl triphenylphosphonium bromide according to the procedures

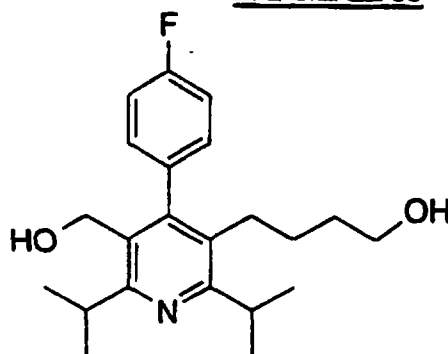
- 0 described in Example 1, Steps F-H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.08 (m, 4 H), 7.01 (d,  $J = 8$  Hz, 2 H), 6.85 (d,  $J = 8$  Hz, 2 H), 4.30 (s, 2 H), 3.39 (sept,  $J = 6.6$  Hz, 1 H), 3.13 (sept,  $J = 6.6$  Hz, 1 H), 2.41 (t,  $J = 7$  Hz, 2 H), 2.31 (s, 3 H), 2.27 (m, 2 H), 1.58 (m, 2 H), 1.31 (d,  $J = 6.6$  Hz, 6 H), 1.26 (d,  $J = 6.6$  Hz, 6 H), 1.15 (m, 1 H). FAB-MS: calcd for ( $\text{C}_{28}\text{H}_{34}\text{FNO}$ ) 419, found 420 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{28}\text{H}_{34}\text{FNO}$ : C, 80.15; H, 8.17; N, 3.34. Found: C, 80.33; H, 8.28; N, 3.22. mp 79-80°C.  $R_f = 0.4$  (20% ethyl acetate/hexane).
- 5

**EXAMPLE 87**

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**2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(2-propenyl)pyridine**

- The title compound was prepared from methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-oxoethyl)-3-pyridinecarboxylate (Example 82, Step A) and methyl triphenylphosphonium bromide according to the procedures described in
- 15 Example 1, Steps F-H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (m, 4 H), 5.73 (m, 1 H), 4.81 (dd,  $J = 4.8, 1.8$  Hz, 2 H), 4.35 (s, 2 H), 3.43 (septet,  $J = 6.6$  Hz, 1 H), 3.21 (septet,  $J = 6.6$  Hz, 1 H), 3.07 (d,  $J = 1.8$  Hz, 2 H), 1.24 (m, 13 H). FAB-MS: calcd for ( $\text{C}_{21}\text{H}_{26}\text{FNO}$ ) 327, found 328 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{FNO}$ : C, 74.17; H, 7.71; N, 4.12; F, 5.59 + 0.7  $\text{H}_2\text{O}$ . Found: C, 74.17; H, 7.57; N, 3.94; F, 5.26. mp 69-
- 20 71°C.  $R_f = 0.35$  (15% ethyl acetate/hexane).

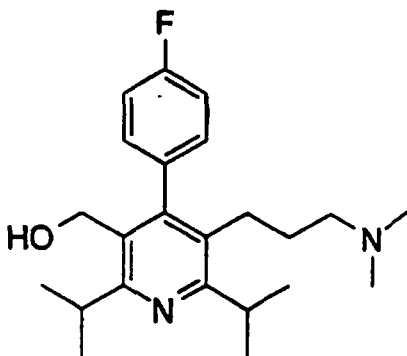
**EXAMPLE 88**

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2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-hydroxy-butyl)pyridine

To a solution of 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(1,3-dioxolan-2-yl)propyl]pyridine (Example 46) (2 g, 5 mmol) in THF (50 mL) was added 2N aq. HCl (10 mL). The solution was allowed to stir for 17 hr at room temperature. The THF was removed *in vacuo* and the residual suspension carefully neutralized to pH 7 with sat. aq. NaHCO<sub>3</sub>. The aqueous phase was extracted with diethyl ether (3 x 100 mL), the combined ether extract washed with brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (step gradient, 10%-20% ethyl acetate/hexane) afforded a white solid (1.5 g, 4.2 mmol, 83%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.57 (s, 1 H), 7.16 (m, 4 H), 4.33 (d, J = 5 Hz, 2 H), 3.42 (m, 1 H), 3.24 (m, 1 H), 2.33 (m, 2 H), 2.27 (dt, J = 1.8, 7.4 Hz, 2 H), 1.61 (m, 2 H), 1.32 (m, 12 H), 1.20 (m, 1 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>FNO<sub>2</sub>) 359, found 340 (M+H). R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

This intermediate (200 mg, 0.56 mmol) was dissolved in absolute ethanol (5 mL) and treated at room temperature, with stirring, with sodium borohydride (32 mg, 0.85 mmol). After stirring for 1 hr, the reaction was quenched by the dropwise addition of 2N HCl (3 mL). The solution was stirred 5 min, then neutralized by the careful addition of sat. NaHCO<sub>3</sub>. The aqueous phase was extracted with diethyl ether (3 x 50 mL), the combined extracts dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (20% ethyl acetate/hexane) afforded the title compound as a white solid (88 mg, 0.25 mmol, 44%): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 4 H), 4.33 (d, J = 5 Hz, 2 H), 3.46 (m, 2 H), 3.41 (m, 1 H), 2.23 (m, 1 H), 2.32 (m, 2 H), 1.40 (m, 4 H), 1.32 (m, 12 H), 1.19 (m, 1 H), 1.09 (m, 1 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>FNO<sub>2</sub>) 359, found 360 (M+H). Anal. Calcd for C<sub>22</sub>H<sub>30</sub>FNO<sub>2</sub>: C, 73.51; H, 8.41; N, 3.90. Found: C, 73.37; H, 8.41; N, 3.72. mp 135-137°C. R<sub>f</sub> = 0.4 (50% ethyl acetate/hexane);

EXAMPLE 89

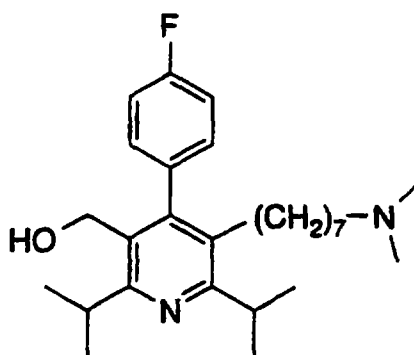
30

0 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-dimethyl-  
amino)propyl]pyridine

The title compound was prepared from 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) and (2-dimethylaminoethyl)triphenylphosphonium bromide according to the procedures described in Example 1, Steps F-H. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.17 (m, 4 H), 4.33 (s, 2 H), 3.41 (sept, J = 6.6 Hz, 1 H), 3.21 (sept, J = 6.6 Hz, 1 H), 2.32 (m, 2 H), 2.16 (m, 2 H), 2.14 (s, 6 H), 1.49 (m, 2 H), 1.32 (m, 13 H). FAB-MS: calcd for (C<sub>23</sub>H<sub>33</sub>FN<sub>2</sub>O) 372, found 373 (M+H). mp 50-51°C. R<sub>f</sub> = 0.35 (20% ethanol/CH<sub>2</sub>Cl<sub>2</sub>).

10

EXAMPLE 90



15 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-dimethyl-  
amino)heptyl]pyridine

Step A: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-  
oxobutyl)pyridine

To a solution of 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(1,3-dioxolan-2-yl)propyl]pyridine (Example 46) (2 g, 5 mmol) in THF (50 mL) was added 2N aq. HCl (10 mL). The solution was allowed to stir for 17 hr at room temperature. The THF was removed *in vacuo* and the residual suspension carefully neutralized to pH 7 with sat. NaHCO<sub>3</sub>. The aqueous phase was extracted with diethyl ether (3 x 100 mL), the combined ether extract washed with brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (step gradient, 10%-20% ethyl acetate/hexane) afforded a white solid (1.5 g, 4.2 mmol, 83%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.57 (s, 1 H), 7.16 (m, 4 H), 4.33 (d, J = 5 Hz, 2 H), 3.42 (m, 1 H), 3.24 (m, 1 H), 2.33 (m, 2 H), 2.27 (dt, J = 1.8, 7.4 Hz, 2 H), 1.61 (m, 2 H), 1.32 (m, 12 H), 1.20 (m, 1 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>28</sub>FN<sub>2</sub>O<sub>2</sub>) 357, found 358 (M+H). R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

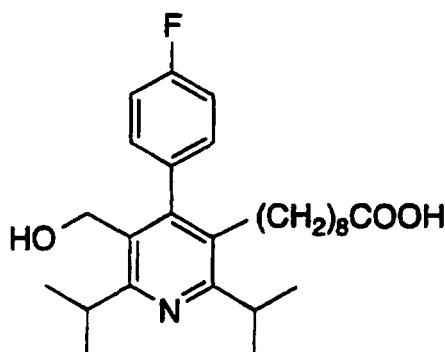
0

**Step B:** 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(3-dimethylamino)heptyl]pyridine

The intermediate prepared in Step A was treated with (3-dimethylamino)propyl triphenylphosphonium bromide according to the procedures described in Example 1, Steps F-H, to afford the title compound as a solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 4 H), 4.32 (s, 2 H), 3.41 (sept, J = 6.6 Hz, 1 H), 3.22 (sept, J = 6.6 Hz, 1 H), 2.28 (s, 6 H), 2.26 (m, 4 H), 1.43 (m, 2 H), 1.33 (d, J = 6.6 Hz, 6 H), 1.30 (d, J = 6.6 Hz, 6 H), 1.27 (m, 3 H), 1.31 (m, 6 H). FAB-MS: calcd for (C<sub>27</sub>H<sub>41</sub>FN<sub>2</sub>O) 428, found 429 (M+H). mp 85-87°C. R<sub>f</sub> = 0.1 (20% EtOH/CH<sub>2</sub>Cl<sub>2</sub>).

10

**EXAMPLE 91**



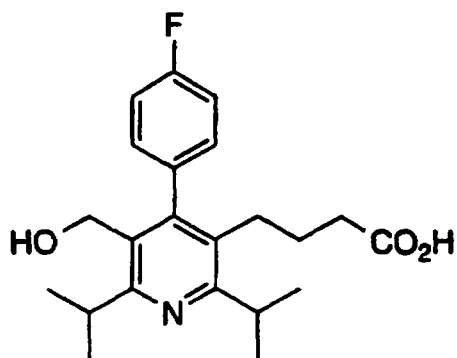
15

2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(8-carboxyheptyl)pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(4-oxobutyl)pyridine (Example 90, Step A) and (4-carboxybutyl)triphenylphosphonium bromide according to the procedure described in Example 90, Step B. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.17 (m, 4 H), 4.23 (s, 2 H), 3.44 (sept, J = 6.6 Hz, 1 H), 3.23 (sept, J = 6.6 Hz, 1 H), 2.28 (m, 2 H), 2.14 (t, J = 7.5 Hz, 2 H), 1.54 (m, 2 H), 1.28 (d, J = 6.6 Hz, 6 H), 1.24 (d, J = 6.6 Hz, 6 H), 1.22 (m, 4 H), 1.17 (m, 2 H), 1.10 (m, 4 H). EI-MS: calcd for (C<sub>27</sub>H<sub>38</sub>FNO<sub>3</sub>) 443, found 443 (M<sup>+</sup>). mp 240°C (dec). R<sub>f</sub> = 0.3 (50% ethyl acetate/hexane).

25

30

EXAMPLE 922,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(3-carboxypropyl)pyridine

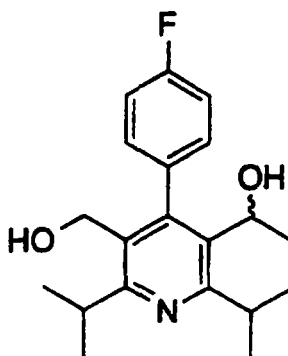
To a solution of 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[3-(1,3-dioxolan-2-yl)propyl]pyridine (Example 46) (2 g, 5 mmol) in THF (50 mL) was added 2N aq. HCl (10 mL). The solution was allowed to stir for 17 hr at room temperature. The THF was removed *in vacuo* and the residual suspension carefully neutralized to pH 7 with sat. NaHCO<sub>3</sub>. The aqueous phase was extracted with diethyl ether (3 x 100 mL), and the combined ether extract washed with brine (50 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (step gradient, 10%-20% ethyl acetate/hexane) afforded 1.5 g of the intermediate as a white solid: R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

280 mg of the intermediate was dissolved in dry pyridine (5 mL), stirred at room temperature under argon and treated with acetic anhydride (0.37 mL, 3.9 mmol). The reaction mixture was allowed to stir at room temperature for 17 hr. The pyridine was removed *in vacuo*, and the residue dissolved in diethyl ether (50 mL), washed with sat. CuSO<sub>4</sub> (10 mL), water (20 mL), sat. NaHCO<sub>3</sub> (20 mL) and brine (10 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (20% ethyl acetate/hexane) afforded 220 mg as a viscous yellow oil: R<sub>f</sub> = 0.6 (50% ethyl acetate/hexane).

200 mg of the oil was dissolved in acetone (5 mL), stirred at room temperature and treated with Jones reagent (2 mL, prepared from 67 g CrO<sub>3</sub>, 125 mL H<sub>2</sub>O and 58 mL con. H<sub>2</sub>SO<sub>4</sub>). The reaction mixture was stirred 0.5 hr, quenched by the addition of 2-propanol, filtered through a short pad of silica and concentrated. The residue was dissolved in MeOH (5 mL), treated with 20% NaOH (2 mL) and stirred 14 hr at room temperature. After neutralizing to pH 7 with aq. HCl, the solution was saturated with NaCl and extracted with CHCl<sub>3</sub> (3 x 20 mL). The combined extract was dried (MgSO<sub>4</sub>) and concentrated. Purification by chromatography through silica (1:1 ethyl acetate/hexane) afforded the title

0 compound as a white foam (22 mg).  $^1\text{H}$  NMR (300 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  7.18 (m, 4 H), 4.24 (s, 2 H), 3.46 (sept,  $J = 6.6$  Hz, 1 H), 3.33 (sept,  $J = 6.6$  Hz, 1 H), 2.34 (m, 2 H), 1.99 (t,  $J = 7$  Hz, 2 H), 1.60 (m, 2 H), 1.29 (d,  $J = 6.6$  Hz, 6 H), 1.26 (d,  $J = 6.6$  Hz, 6 H). FAB-MS: calcd for ( $\text{C}_{22}\text{H}_{28}\text{FNO}_3$ ) 373, found 374 ( $\text{M}+\text{H}$ ). mp  $160^\circ\text{C}$ .  $R_f = 0.3$  (50% ethyl acetate/hexane).

5

EXAMPLE 93

10 (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxy-ethyl)pyridine

Step A: (±)-Ethyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(1-hydroxy-ethyl)-3-pyridinecarboxylate

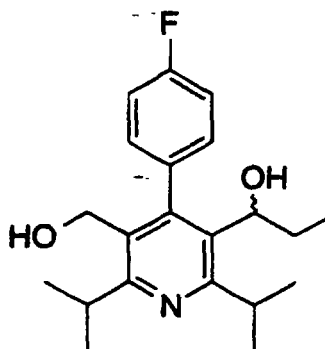
15 To 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridine-carboxaldehyde (Example 1, Step E) (1 g, 2.91 mmol) in THF (30 mL) was added methyllithium (1.4 M, 1.0 eq., 2.08 mL) dropwise at  $-78^\circ\text{C}$  under argon. The reaction was stirred for 2 hours, then quenched with water and the THF evaporated to afford a white solid. The product was partitioned between diethyl  
20 ether and water. The organic layer was then dried with  $\text{MgSO}_4$ , filtered, and concentrated to afford a white solid. The product was passed through a plug of silica (10% ethyl acetate/hexane) to afford a white solid (857 mg, 2.4 mmol, 82%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.14 (m, 4 H), 4.86 (dq,  $J = 3.7$ ,  $J = 6.6$  Hz, 1 H), 3.80 (septet,  $J = 6.6$  Hz, 1 H), 3.47 (s, 3 H), 2.96 (septet,  $J = 6.6$  Hz, 1 H), 1.65 (d,  $J = 3.7$  Hz, 1 H), 1.46 (d,  $J = 6.6$  Hz, 3 H), 1.27 (m, 12 H). FAB-MS: calcd for ( $\text{C}_{21}\text{H}_{26}\text{NFO}_3$ ) 359, found 360 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{21}\text{H}_{26}\text{NO}_3\text{F}$ : C, 69.54; H, 7.54; N, 6.76; F, 4.58. Found: C, 69.55; H, 7.43; N, 6.50; F, 4.45. mp  $169-171^\circ\text{C}$ .  $R_f = 0.2$  (10% ethyl acetate/hexane).

30

0 Step B: (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxyethyl)pyridine

The intermediate obtained in Step A (300 mg, 0.835 mmol) was dissolved in 40 mL of dry THF, for a dropwise addition of a solution of LAH (1 M/THF, 1.67 mL, 2 eq.). The reaction mixture was stirred at reflux for 24 hours then cooled to room temperature and quenched with water (70  $\mu$ L), 20% NaOH (70  $\mu$ L), and water (140  $\mu$ L). After filtration, the solvent was evaporated to afford a white residue. The product was subjected to flash chromatography (20% ethyl acetate/hexane) which afforded the title compound as a white solid (84 mg, 0.25 mmol, 30%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (m, 4 H), 4.71 (dq,  $J = 3.7$ ,  $J = 6.6$  Hz, 1 H), 4.30 (m, 2 H), 3.79 (septet,  $J = 6.6$  Hz, 1 H), 3.42 (septet,  $J = 6.6$  Hz, 1 H), 1.62 (d,  $J = 3.68$  Hz, 1 H), 1.58 (s, 1H), 1.43 (d,  $J = 6.6$  Hz, 3 H), 1.28 (m, 16 H). FAB-MS: calcd for ( $\text{C}_{20}\text{H}_{26}\text{NFO}_2$ ) 331, found 332 (M+H). Anal. Calcd for  $\text{C}_{20}\text{H}_{26}\text{NO}_2\text{F}$ : C, 76.84; H, 8.69; N, 3.90. Found: C, 76.67; H, 8.76; N, 3.77. mp 184-186°C.  $R_f = 0.2$  (20% ethyl acetate/hexane).

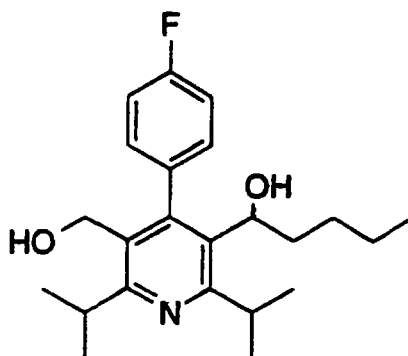
15 EXAMPLE 94



20 (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxypropyl)pyridine

The title compound was prepared from 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) and ethyl magnesium bromide, according to the procedures described in Example 93.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (m, 4 H), 4.40 (dq,  $J = 3.7$ ,  $J = 5.2$  Hz, 1 H), 4.30 (d,  $J = 5.5$  Hz, 2 H), 3.72 (septet,  $J = 6.6$  Hz, 1 H), 3.42 (septet,  $J = 6.6$  Hz, 1 H), 1.88 (m, 1 H), 1.63 (t,  $J = 5.5$  Hz, 1H), 1.27 (m, 14 H), 0.804 (t,  $J = 7.36$  Hz, 3 H). FAB-MS: calcd for ( $\text{C}_{21}\text{H}_{28}\text{NFO}_2$ ) 345, found 346 (M+H). Anal. Calcd for  $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{F}$ : C, 76.84; H, 8.69; N, 3.90. Found: C, 76.67; H, 8.76; N, 3.77. mp 173-175°C.  $R_f = 0.2$  (20% ethyl acetate/hexane);

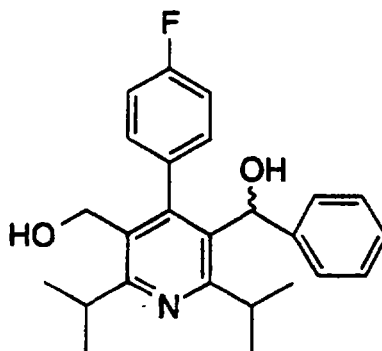
0

EXAMPLE 955 (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxypentyl)pyridine

The title compound was prepared from 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) and n-butyllithium, according to the procedures described in Example 93. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):

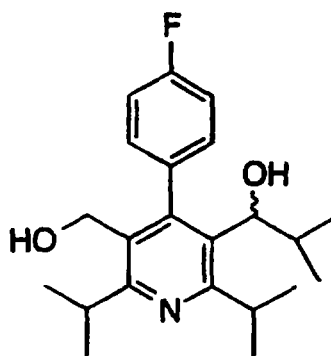
10 δ 7.16 (m, 4 H), 4.49 (m, 1 H), 4.31 (d, J = 5.5 Hz, 2 H), 3.74 (septet, J = 6.6 Hz, 1 H), 3.42 (septet, J = 6.6 Hz, 1 H), 1.88 (m, 1 H), 1.58 (d, J = 3.3 Hz, 1 H), 1.18 (m, 18 H), 0.821 (t, J = 4.1 Hz, 3 H). FAB-MS: calcd for (C<sub>23</sub>H<sub>32</sub>NFO<sub>2</sub>) 373, found 374 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>32</sub>NO<sub>2</sub>F: C, 73.96; H, 8.64; N, 3.75; F, 5.09. Found: C, 73.81; H, 8.60; N, 3.58; F, 5.02. mp 166-168°C. R<sub>f</sub> = 0.3 (20% ethyl acetate/hexane).

15

EXAMPLE 9620 (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(hydroxyphenylmethyl)pyridine

The title compound was prepared from 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) and phenyllithium, according to the procedures described in Example 93. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):

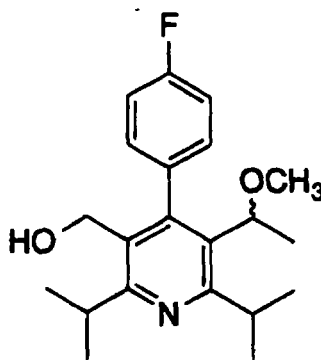
- 0  $\delta$  7.23 (m, 7 H), 7.06 (m, 2 H), 5.71 (d,  $J$  = 5.14 Hz, 1 H), 4.38 (d,  $J$  = 5.5 Hz, 2 H), 3.47 (septet,  $J$  = 6.6 Hz, 1 H), 3.12 (septet,  $J$  = 6.6 Hz, 1 H), 2.12 (d,  $J$  = 5.1 Hz, 1 H), 1.57 (s, 1H), 1.29 (m, 10 H), 0.797 (d,  $J$  = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>28</sub>NFO<sub>2</sub>) 393, found 394 (M+H). Anal. Calcd for C<sub>25</sub>H<sub>28</sub>NO<sub>2</sub>F: C, 76.84; H, 8.69; N, 3.90. Found: C, 76.67; H, 8.76; N, 3.77. mp 202-204°C.  $R_f$  = 0.2 (20% ethyl acetate/hexane).
- 5

EXAMPLE 97

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(±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-[(1-hydroxy-2-methyl)propyl]pyridine

- The title compound was prepared from 5-carboethoxy-2,6-diisopropyl-4-(4-fluorophenyl)-3-pyridinecarboxaldehyde (Example 1, Step E) and isopropyl magnesium bromide, according to the procedures described in Example 93. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.14 (m, 4 H), 4.35 (d, 2 H), 3.53 (t,  $J$  = 4.8 Hz, 4 H), 3.45 (m, 2 H), 3.18 (s, 2 H), 2.18 (t,  $J$  = 4.5 Hz, 4 H), 1.26 (m, 13 H). FAB-MS: calcd for (C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>FO<sub>2</sub>) 386, found 387 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>31</sub>N<sub>2</sub>O<sub>2</sub>F: C, 76.84; H, 8.69; N, 3.90. Found: C, 76.67; H, 8.76; N, 3.77. mp 139-140°C.  $R_f$  = 0.3 (20% ethyl acetate/hexane).
- 15
- 20

EXAMPLE 98

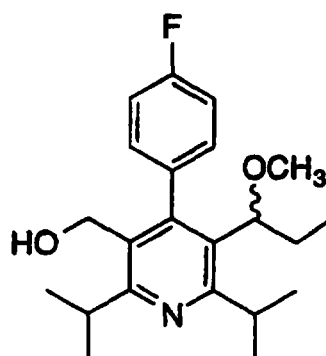
(±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-methoxyethyl)pyridine

Step A: Methyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(2-methoxyethyl)-3-pyridinecarboxylate

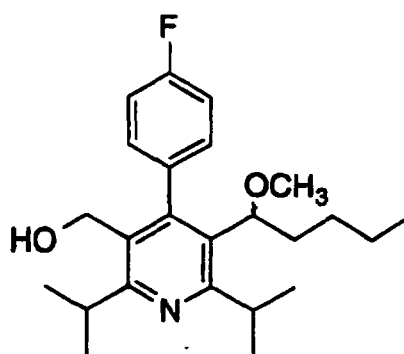
(±)-Ethyl-2,6-diisopropyl-4-(4-fluorophenyl)-5-(1-hydroxyethyl)-3-pyridinecarboxylate (Example 93, Step A) (487 mg, 1.36 mmol) was dissolved in 50 mL of dry THF, treated with NaH (0.20 g, 8.13 mmol) under argon, stirred for 15 min. and treated with methyl iodide (0.34 mL, 5.24 mmol). The reaction mixture was stirred at reflux for 2 hours, then cooled to room temperature, quenched with water, and concentrated to afford a watery residue. The product was partitioned between diethyl ether and water, the organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to afford a white solid. The product was passed through a pad of silica (5% ethyl acetate/hexane) to yield a white solid (495 mg, 1.33 mmol, 98%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13 (m, 4 H), 4.25 (q, *J* = 6.6 Hz, 1 H), 3.80 (septet, *J* = 6.6 Hz, 1 H), 3.48 (s, 3 H), 3.10 (s, 3 H), 2.97 (septet, *J* = 6.6 Hz, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.29 (m, 12 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>31</sub>FNO<sub>3</sub>) 373, found 374 (M+H). Anal. Calcd for C<sub>24</sub>H<sub>31</sub>N<sub>2</sub>O<sub>3</sub>F: C, 70.75; H, 7.56; N, 3.75; F, 5.09. Found: C, 70.70; H, 7.63; N, 3.59; F, 4.77. mp 132-134°C. R<sub>f</sub> = 0.5 (10% ethyl acetate/hexane).

Step B: (±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-methoxyethyl)pyridine

The intermediate obtained in Step A (359 mg, 0.961 mmol) was dissolved in 40 mL of dry THF, for a dropwise addition of a solution of LAH (1 M/THF, 1.92 mL, 2 eq.). The reaction mixture was stirred at reflux for 24 hours then cooled to room temperature and quenched with water (80 μL), 20% NaOH (80 μL), and water (160 μL). After filtration, the solvent was evaporated to afford a residue which was filtered through to a pad of silica (10% ethyl acetate/hexane) to afford the title compound as a white solid (281 mg, 0.72 mmol, 85%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13 (m, 4 H), 4.32 (dq, *J* = 5.2 *J* = 11.4 Hz, 1 H), 4.11 (q, *J* = 6.3 Hz, 1 H), 3.77 (septet, *J* = 6.6 Hz, 1 H), 3.42 (septet, *J* = 6.6 Hz, 1 H), 3.10 (s, 3 H), 1.29 (m, 16 H). FAB-MS: calcd for (C<sub>21</sub>H<sub>28</sub>FNO<sub>2</sub>) 345, found 346 (M+H). Anal. Calcd for C<sub>21</sub>H<sub>28</sub>NO<sub>2</sub>F: C, 76.84; H, 8.69; N, 3.90. Found: C, 76.67; H, 8.76; N, 3.77. mp 151-153°C. R<sub>f</sub> = 0.4 (20% ethyl acetate/hexane).

**EXAMPLE 99****(±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-methoxypropyl)pyridine**

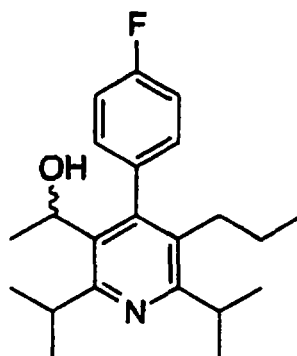
The title compound was prepared from (±)-2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxypropyl)pyridine (Example 94) according to the procedures described in Example 98. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (m, 4 H), 4.32 (m, 2 H), 3.83 (m, 1 H), 3.74 (septet, *J* = 6.6 Hz, 1 H), 3.41 (septet, *J* = 6.6 Hz, 1 H), 3.12 (s, 2 H), 1.88 (m, 1 H), 1.56 (m, 2 H), 1.27 (m, 12 H), 0.776 (t, *J* = 3.7 Hz, 3 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>NFO<sub>2</sub>) 359, found 360 (M+H). Anal. Calcd for C<sub>22</sub>H<sub>30</sub>NO<sub>2</sub>F: C, 73.51; H, 8.41; N, 3.90; F, 5.28. Found: C, 73.55; H, 8.54; N, 3.75; F, 5.06. mp 147-149°C. R<sub>f</sub> = 0.5 (20% ethyl acetate/hexane).

**EXAMPLE 100****(±)-2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-methoxypentyl)pyridine**

The title compound was prepared from (±)-2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-hydroxypentyl)pyridine (Example 95) according to the procedures described in Example 98. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.10 (m, 4 H), 4.32 (m, 2 H), 3.92 (m, 1 H), 3.76 (septet, *J* = 7.0 Hz, 1 H), 3.42

- 0 (septet,  $J = 6.6$  Hz, 1 H), 3.12 (s, 3 H), 1.87 (m, 1 H), 1.52 (m, 2 H), 1.19 (m, 16 H), 0.821 (t,  $J = 7.4$  Hz, 3 H). FAB-MS: calcd for  $(C_{24}H_{34}NFO_2)$  387, found 388 (M+H). Anal. Calcd for  $C_{24}H_{34}NO_2F$ : C, 74.38; H, 8.84; N, 3.61; F, 4.90. Found: C, 74.38; H, 8.82; N, 3.45; F, 4.90. mp 121-123°C.  $R_f = 0.5$  (20% ethyl acetate/hexane).

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EXAMPLE 101(±)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

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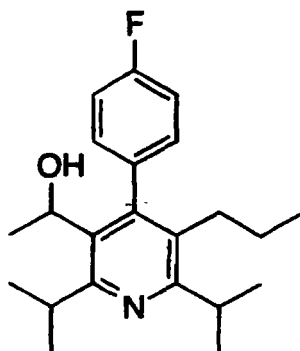
Step A: — (±)-2,6-Diisopropyl-4-(4-fluorophenyl)-5-propyl-3-pyridine-carboxaldehyde

- To a solution of 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-propylpyridine (Example 25) (5.7 g, 17 mmol) in dichloromethane (250 mL) was added Brockman I, neutral alumina (3.5 g, 34 mmol). The suspension was stirred at room temperature and treated with pyridinium chlorochromate (PCC) (7.5 g, 34 mmol). Stirring was continued at room temperature for 1 hr. The suspension was poured into 10% ethyl acetate/hexane (500 mL), filtered through a pad of silica and concentrated *in vacuo* to afford (4.2 g/12.8 mmol, 74%) as a waxy solid.  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta$  9.72 (s, 1 H), 7.15 (m, 4 H), 3.83 (sept,  $J = 6.6$  Hz, 1 H), 3.28 (sept,  $J = 6.6$  Hz, 1 H), 2.31 (m, 2 H), 1.30 (m, 14 H), 0.78 (t,  $J = 7.4$  Hz, 3 H). FAB-MS: calcd for  $(C_{21}H_{26}FNO)$  327, found 328 (M+H). mp 81-83°C.  $R_f = 0.6$  (10% ethyl acetate/hexane).

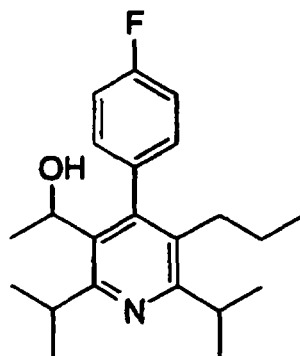
- 25 Step B: (±)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

- The intermediate obtained in Step A (400 mg, 1.22 mmol) in THF (10 mL) at -78°C under argon atmosphere was added dropwise MeLi (1.4 M, 1.2 eq, 1.05 mL). The reaction was stirred for 20 min, then another 0.5 eq. of MeLi was added, as starting material was still present. After 20 min., the reaction was quenched with

- 0 water (2 mL) and the THF is evaporated in vacuo to afford an oil. The product was partitioned between water and CH<sub>2</sub>Cl<sub>2</sub> (50 mL) and the organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to yield a gummy solid. Flash Chromatography using silica gel (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane) to afford an oil which slowly solidified to give the title compound as a solid (0.387 g/1.13 mmol, 92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.10 (m, 4 H), 4.66 (dq, *J* = 3.3, 6.6 Hz, 1 H), 3.75 (septet, *J* = 6.6 Hz, 1 H), 3.20 (septet, *J* = 6.6 Hz, 1 H), 2.17 (t, *J* = 1.5 Hz, 2 H), 1.58 (d, *J* = 5.2 Hz, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.29 (m, 14 H), 0.74 (t, *J* = 7.4 Hz, 3 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>FNO) 343, found 344 (M+H). Anal. Calcd for C<sub>22</sub>H<sub>30</sub>FNO: C, 76.93; H, 8.80; N, 4.08; F, 5.53. Found: C, 76.98; H, 8.73; N, 3.93; F, 5.80. mp 124.5-126.5°C. R<sub>f</sub> = 0.2 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

EXAMPLE 102(+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

- 15 The enantiomeric mixture of (±)-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine (Example 101) was separated by chiral HPLC with a Chiralpak AD column, isocratic elution (99% hexane/methyl *t*-butyl ether). The first enantiomer to elute was obtained in 99% ee, mp 103-104°C, [α]<sub>D</sub> +40.4°.

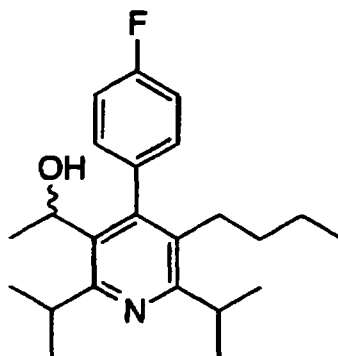
EXAMPLE 103

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2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propyl-pyridine

The enantiomeric mixture of ( $\pm$ )-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propyl-pyridine (Example 101) was separated by chiral HPLC with a Chiralpak AD column, isocratic elution (99% hexane/methyl *t*-butyl ether). The

5 second enantiomer to elute was obtained in 90% ee. mp 95-97°C.

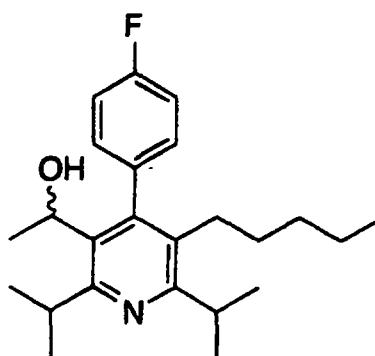
EXAMPLE 104

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( $\pm$ )-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-butyl-pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-butylpyridine (Example 24) according to the procedures described in Example 101.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.1 (m, 4 H), 4.7 (dq,  $J = 3$  Hz, 1 H), 3.7 (septet,  $J = 7$  Hz, 1 H), 3.2 (septet,  $J = 7$  Hz, 1 H), 2.2 (t,  $J = 1.5$  Hz, 2 H), 1.6 (d,  $J = 5$  Hz, 1 H), 1.4 (d,  $J = 7$  Hz, 3 H), 1.3 (m, 16 H), 0.8 (t,  $J = 7$  Hz, 3 H). FAB-MS: calcd for ( $\text{C}_{23}\text{H}_{32}\text{FNO}$ ) 357, found 358 ( $\text{M}+\text{H}$ ). mp 103-104°C.  $R_f = 0.2$  (60%  $\text{CH}_2\text{Cl}_2/\text{hexane}$ ).

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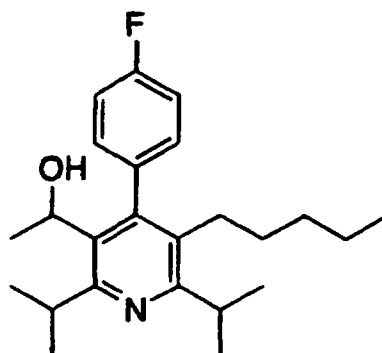
EXAMPLE 105

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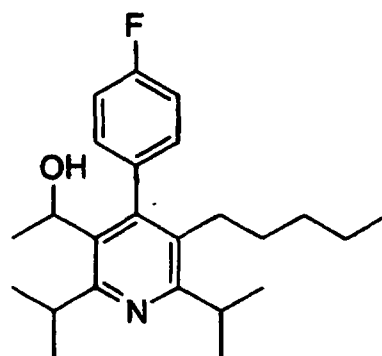
( $\pm$ )-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentyl-pyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-

- 0 (4-fluorophenyl)-5-pentylpyridine (Example 1) according to the procedures described in Example 101.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.10 (m, 4 H), 4.65 (dq,  $J$  = 2.8, 6.6 Hz, 1 H), 3.75 (septet,  $J$  = 6.6 Hz, 1 H), 3.20 (septet,  $J$  = 6.6 Hz, 1 H), 2.19 (t,  $J$  = 8.1 Hz, 2 H), 1.63 (d,  $J$  = 2.6 Hz, 1 H), 1.40 (d,  $J$  = 7.0 Hz, 3 H), 1.31 (m, 14 H), 1.11 (m, 4 H), 0.79 (t,  $J$  = 6.6 Hz, 3 H). FAB-MS: calcd for  $(\text{C}_{24}\text{H}_{34}\text{FNO})$  371, found 372
- 5 (M+H). Anal. Calcd for  $\text{C}_{24}\text{H}_{34}\text{FNO}$ : C, 77.59; H, 9.22; N, 3.77; F, 5.11. Found: C, 77.59; H, 9.34; N, 3.75; F, 5.26. mp 99-101°C.  $R_f$  = 0.2 (70%  $\text{CH}_2\text{Cl}_2$ /hexane).

EXAMPLE 1062,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine

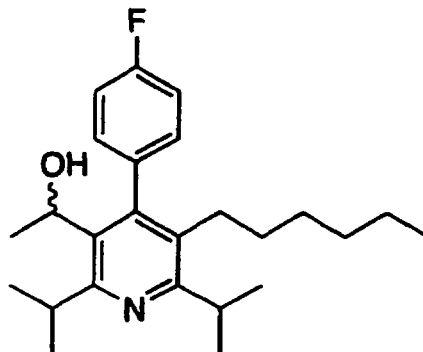
- The enantiomeric mixture of ( $\pm$ )-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine (Example 105) was separated by chiral HPLC with a
- 15 Chiralpak AD column, isocratic elution (99% hexane/methyl *t*-butyl ether). The first enantiomer to elute was obtained in 99% ee. mp 83°C.

EXAMPLE 1072,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine

- The enantiomeric mixture of ( $\pm$ )-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine (Example 105) was separated by chiral HPLC with a

- 0 Chiralpak AD column, isocratic elution (99% hexanemethyl *t*-butyl ether). The second enantiomer to elute was obtained in 93% ee. mp 84-86°C.

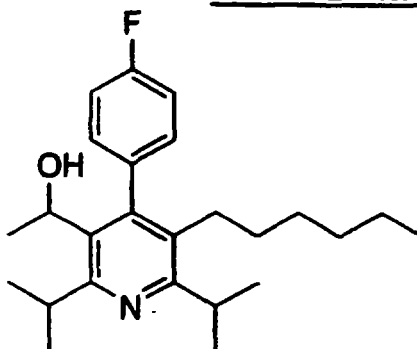
### EXAMPLE 108



#### (±)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine

- The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-hexylpyridine (Example 23) according to the procedures described in Example 101. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13 (m, 3 H), 7.04 (m, 1 H), 4.65 (m, 1 H), 3.73 (sept, *J* = 6.6 Hz, 1 H), 3.19 (sept, *J* = 6.6 Hz, 1 H), 2.18 (m, 2 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 1.30 (m, 13 H), 1.18 (m, 4 H), 1.09 (m, 4 H), 0.81 (t, *J* = 7 Hz, 3 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>36</sub>FNO) 385, found 386 (M+H). Anal. Calcd for C<sub>25</sub>H<sub>36</sub>FNO: C, 77.88; H, 9.41; N, 3.63. Found: C, 77.84; H, 9.49; N, 3.65. mp 96-99°C. R<sub>f</sub> = 0.3 (10% ethyl acetate/hexane).

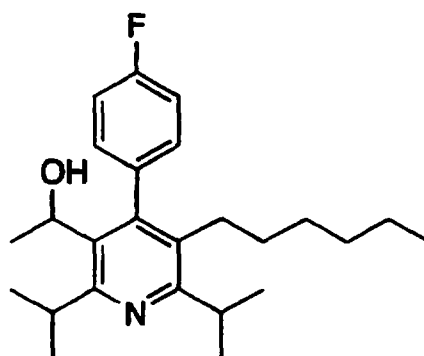
### EXAMPLE 109



#### 20 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine

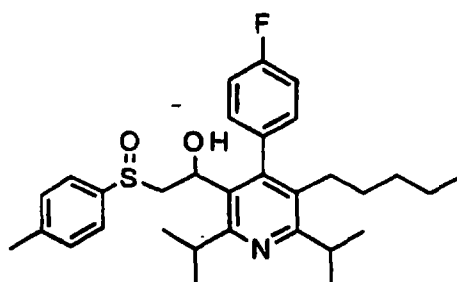
The enantiomeric mixture of (±)-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine (Example 108) was separated by chiral HPLC with a Chiralpak AD column, isocratic elution (99% hexane/methyl *t*-butyl ether). The first enantiomer to elute was obtained in 98% ee. mp 75-77°C.

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EXAMPLE 1105 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine

The enantiomeric mixture of ( $\pm$ )-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine (Example 108) was separated by chiral HPLC with a Chiralpak AD column, isocratic elution (99% hexane/methyl *t*-butyl ether). The second enantiomer to elute was obtained in 88% ee. mp 66-68°C.

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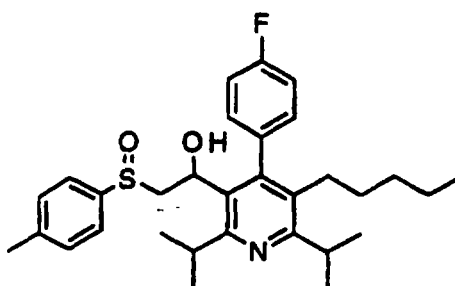
EXAMPLE 11115 2,6-Diisopropyl-3-[1-hydroxy-2-((S)-toluylsulfoxy)ethyl]-4-(4-fluorophenyl)-5-pentylpyridine

A solution of lithium diisopropylamide was prepared by the addition of *n*-butyllithium (3.5 mL, 2 eq., 1.6 M/hexane) to a solution of diisopropylamine (0.73 mL, 5.57 mmol) in anhydrous tetrahydrofuran (50 mL) at 0°C. To this was added a solution of (*S*)-(-)-methyl *p*-tolylsulfoxide (0.863 g, 5.60 mmol) in anhydrous tetrahydrofuran (10 mL) dropwise, with stirring. The mixture was stirred at 0°C for 2 hr, then treated with a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) (1.0 g, 2.80 mmol) in anhydrous tetrahydrofuran (20 mL) dropwise and with stirring. After stirring 15 min at 0°C, the reaction mixture was quenched by the addition of sat. NH<sub>4</sub>Cl (1 mL). The

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0 solvent was removed *in vacuo* and the residue partitioned between  $\text{CHCl}_3$  (150 mL) and water (50 mL). The organic phase was washed with sat.  $\text{NaHCO}_3$  (100 mL), water (100 mL) and brine (50 mL), dried over  $\text{MgSO}_4$  and concentrated. The crude product consisted of a 1.2:1 ratio of diastereomers. Flash chromatography (step gradient 5%-10%-20% ethyl acetate/hexane) afforded 740 mg (52%) of the first diastereomer to elute.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.4 (m, 4 H), 7.0 (m, 2 H), 6.7 (m, 2 H), 5.1 (m, 1 H), 4.6 (s, 1 H), 3.8 (m, 2 H), 2.6 (sept,  $J = 6.6$  Hz, 1 H), 2.5 (s, 3 H), 2.3 (m, 1 H), 2.1 (m, 2 H), 1.4 (m, 18 H), 0.8 (m, 3 H). FAB-MS: calcd for ( $\text{C}_{31}\text{H}_{40}\text{FNO}_2\text{S}$ ) 509, found 510 ( $\text{M}+\text{H}$ ). Anal. calcd for  $\text{C}_{31}\text{H}_{40}\text{FNO}_2\text{S}$ : C, 73.05; H, 7.91; N, 2.75; S, 6.29. Found: C, 72.88; H, 7.95; N, 2.50; S, 6.38. mp 170-171°C.  $R_f$  = 0.3 (20% ethyl acetate/hexane).

### EXAMPLE 112



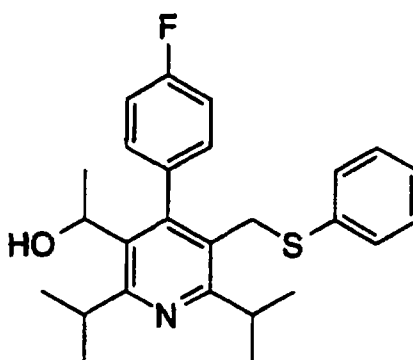
15

### 2,6-Diisopropyl-3-[1-hydroxy-2-(S)-toluylsulfoxyethyl]-4-(4-fluorophenyl)-5-pentylpyridine

From the flash chromatography described in Example 111, the second diastereomer to elute afforded 600 mg (42%) of the title compound.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.4 (m, 2 H), 7.2 (m, 2 H), 7.0 (m, 3 H), 6.8 (m, 1 H), 4.8 (m, 1 H), 3.8 (m, 1 H), 3.7 (m, 1 H), 3.2 (sept,  $J = 6.6$  Hz, 1 H), 3.1 (s, 1 H), 2.7 (m, 1 H), 2.4 (s, 3 H), 2.1 (m, 2 H), 1.3 (m, 18 H), 0.6 (m, 3 H). FAB-MS: calcd for ( $\text{C}_{31}\text{H}_{40}\text{FNO}_2\text{S}$ ) 509, found 510 ( $\text{M}+\text{H}$ ). Anal. calcd for  $\text{C}_{31}\text{H}_{40}\text{FNO}_2\text{S}$ : C, 73.05; H, 7.91; N, 2.75; S, 6.29. Found: C, 72.90; H, 7.95; N, 2.50; S, 6.54. mp 190°C.  $R_f$  = 0.1 (20% ethyl acetate/hexane).

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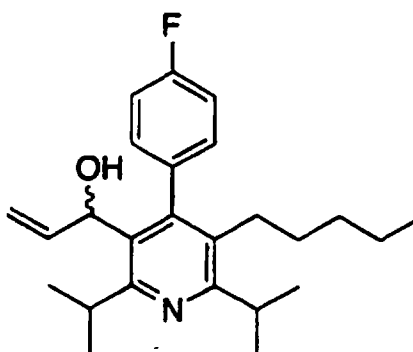
EXAMPLE 113

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(±)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-phenylthio-methylpyridine

The title compound was prepared from 2,6-diisopropyl-3-(1-hydroxymethyl)-4-(4-fluorophenyl)-5-[(phenylthio)methyl]pyridine (Example 47) according to the procedures described in Example 101. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.19 (m, 4 H), 7.09 (m, 5 H), 4.67 (m, 1 H), 3.74 (m, 3 H), 3.38 (sept, *J* = 6.6 Hz, 1 H), 1.58 (d, *J* = 4 Hz, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H), 1.31 (m, 12 H). FAB-MS: calcd for (C<sub>26</sub>H<sub>30</sub>FNOS) 423, found 424 (M+H). Anal. Calcd for C<sub>26</sub>H<sub>30</sub>FNOS: C, 73.72; H, 7.14; N, 3.31; S, 7.57. Found: C, 73.52; H, 7.12; N, 3.20; S, 7.51. mp 125-128°C. R<sub>f</sub> = 0.5 (20% ethyl acetate/hexane).

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EXAMPLE 114

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(±)-2,6-Diisopropyl-3-(1-hydroxy-2-propenyl)-4-(4-fluorophenyl)-5-pentylpyridineStep A: 2,6-Diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridine-carboxaldehyde

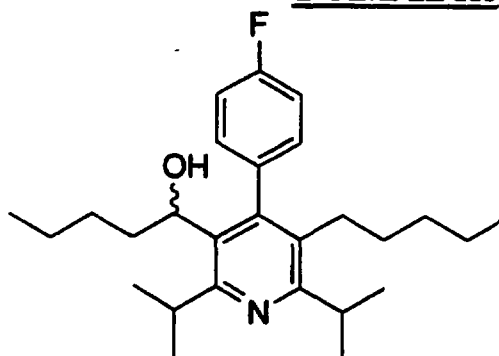
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine (Example 1) (2.30 g, 6.43 mmol) was dissolved in 175 mL of CH<sub>2</sub>Cl<sub>2</sub> under argon

- 0 atmosphere and treated with 2 eq. of alumina (neutral, 1.31 g, 12.87 mmol) followed by 2 eq of pyridinium chlorochromate (PCC) (2.77 g, 12.87 mmol). The reaction was stirred at room temperature for 1.5 h. The suspension was added to 500 mL of 1:1 hexane/diethyl ether, then filtered through a pad of silica (300 g). The pad was washed with 100 mL diethyl ether and the filtrate was combined and
- 5 concentrated *in vacuo* to afford a solid. Flash chromatography (60:40, CH<sub>2</sub>Cl<sub>2</sub>/hexane) using silica afforded 1.84 g of an off-white solid (5.2 mmol, 80%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.74 (s, 1 H), 7.17 (m, 4 H), 3.85 (septet, *J* = 6.6 Hz, 1 H), 3.30 (septet, *J* = 6.6 Hz, 1 H), 2.34 (t, *J* = 5.2 Hz, 2 H), 1.30 (m, 14 H), 1.15 (m, 4 H), 0.80 (t, *J* = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>23</sub>H<sub>30</sub>FNO) 355, found 356. Anal.
- 10 Calcd for C<sub>23</sub>H<sub>30</sub>FNO: C, 77.71; H, 8.51; N, 3.94; F, 5.34 Found: C, 77.91; H, 8.47; N, 3.83; F, 5.42. mp 75.5-77.5°C. R<sub>f</sub> = 0.4 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

Step B:      (±)-2,6-Diisopropyl-3-(1-hydroxy-2-propenyl)-4-(4-fluorophenyl)-5-pentylpyridine

- 15 To a solution of the intermediate obtained in Step A (100 mg, 0.281 mmol) in THF (10 mL) at -78°C under argon was added vinyl magnesium bromide (1 M, 1.5 eq., 0.42 mL) dropwise. After 1 h., a saturated solution of NH<sub>4</sub>Cl (2 mL) was added and the aqueous phase was extracted with diethyl ether. A precipitate formed when the NH<sub>4</sub>Cl was added and was filtered off. The ether layer was dried with
- 20 MgSO<sub>4</sub>, filtered and concentrated to yield a gummy oil. Flash chromatography (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane) afforded the title compound as a solid (38 mg, 0.1 mmol, 35%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (m, 4 H), 6.06 (d, *J* = 17.4 Hz, *J* = 10.3 Hz, *J* = 4.0 Hz, 1 H), 5.08 (q, *J* = 1.5 Hz, 1 H), 5.00 (m, 2 H), 3.51 (septet, *J* = 6.6 Hz, 1 H), 3.21 (septet, *J* = 6.6 Hz, 1 H), 2.21 (t, *J* = 4.4 Hz, 2 H), 1.74 (d, *J* = 4.1 Hz, 1 H), 1.27 (m, 14 H), 1.11 (m, 4 H), 0.783 (t, *J* = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>34</sub>FNO) 383, found 384 (M+H). Anal. Calcd for C<sub>25</sub>H<sub>34</sub>NOF: C, 78.29; H, 8.93; N, 3.65; F, 4.95. Found: C, 78.28; H, 8.97; N, 3.53; F, 5.04. mp 83-85°C. R<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).
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EXAMPLE 115

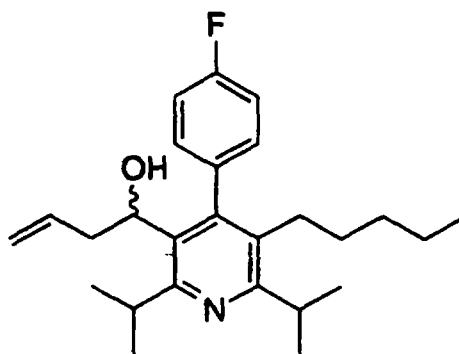


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**(±)-2,6-Diisopropyl-3-(1-hydroxypentyl)-4-(4-fluorophenyl)-5-pentyl-pyridine**

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine (Example 1) and butyllithium according to the procedures described in Example 114. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 6.95 (m, 4 H), 4.33 (m, 1 H), 3.59 (septet, *J* = 6.6 Hz, 1 H), 3.09 (septet, *J* = 6.6 Hz, 1 H), 2.08 (t, *J* = 5.2 Hz, 2 H), 1.75 (m, 2 H), 1.47 (m, 2 H), 1.04 (m, 22 H), 0.719 (t, *J* = 7.0 Hz, 3 H), 0.674 (t, *J* = 7.0 Hz, 3 H). FAB-MS: calcd for (C<sub>27</sub>H<sub>40</sub>FNO) 413, found 414 (M+H). Anal. Calcd for C<sub>27</sub>H<sub>40</sub>FNO: C, 78.41; H, 9.75; N, 3.39; F, 4.59. Found: C, 77.84; H, 9.51; N, 3.27; F, 5.08. mp 66-68°C. *R*<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

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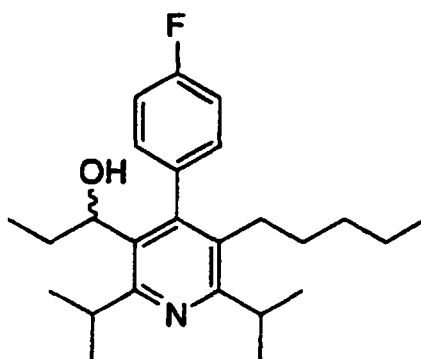
**EXAMPLE 116****(±)-2,6-Diisopropyl-3-(1-hydroxy-2-butenyl)-4-(4-fluorophenyl)-5-pentylpyridine**

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine (Example 1) and allylmagnesium bromide according to the procedures described in Example 114. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.09 (m, 4 H), 6.58 (m, 1 H), 5.06 (s, 1 H), 5.01 (m, 1 H), 4.47 (m, 1 H), 3.71 (septet, *J* = 6.6 Hz, 1 H), 3.20 (septet, *J* = 6.6 Hz, 1 H), 2.59 (m, 1 H), 2.35 (m, 1 H), 2.18 (t, *J* = 4.8 Hz, 2 H), 1.72 (d, *J* = 2.9 Hz, 1 H), 1.28 (m, 14 H), 1.11 (m, 4 H), 0.783 (t, *J* = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>26</sub>H<sub>36</sub>FNO) 397, found 398 (M+H). Anal. Calcd for C<sub>26</sub>H<sub>36</sub>FNO: C, 77.88; H, 9.41; N, 3.63; F, 4.93. Found: C, 78.10; H, 9.21; N, 3.43; F, 4.89. mp 70-72°C. *R*<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

25

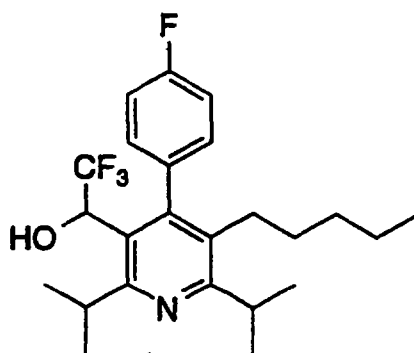
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EXAMPLE 117(±)-2,6-Diisopropyl-3-(1-hydroxy-2-propyl)-4-(4-fluorophenyl)-5-pentylpyridine

5        The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine (Example 1) and ethylmagnesium chloride according to the procedures described in Example 114. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.10 (m, 4 H), 4.35 (dq, *J* = 3.7, 8.8 Hz, 1 H), 3.68 (septet, *J* = 6.3 Hz, 1 H), 3.20 (septet, *J* = 6.6 Hz, 1 H), 2.18 (t, *J* = 5.2 Hz, 2 H), 1.86 (septet, *J* = 5.5 Hz, 1 H), 1.63 (m, 2 H), 1.28 (m, 14 H), 1.09 (m, 4 H), 0.789 (m, 6 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>36</sub>FN<sub>2</sub>O) 385, found 386 (M+H). Anal. Calcd for C<sub>25</sub>H<sub>36</sub>FN<sub>2</sub>O: C, 77.88; H, 9.41; N, 3.63; F, 4.93. Found: C, 77.44; H, 9.37; N, 3.35; F, 4.87. mp 77-79°C. R<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexanes).

15

EXAMPLE 118

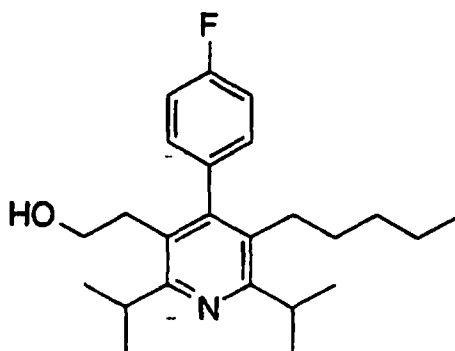
20

(±)-2,6-Diisopropyl-3-(2,2,2-trifluoro-1-hydroxy)ethyl-4-(4-fluorophenyl)-5-pentylpyridine

A stirred solution of 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) (190 mg, 0.53 mmol) in anhydrous THF (5 mL), under argon at 22°C, was treated with trimethyl(trifluoromethyl)silane (5.3 mL, 2.65 mmol, 0.5M in THF) followed by tetrabutylammonium fluoride (100

0 uL, 1.0M in THF). After stirring at 22°C for 5 min, tetrabutylammonium fluoride (3 mL, 3 mmol, 1.0 M in THF) was added and the reaction mixture stirred for 17 hr. The solvent was removed *in vacuo*, the residue dissolved in diethyl ether (50 mL), washed with 1N HCl (50 mL), saturated NaHCO<sub>3</sub> (50 mL), water (50 mL), brine (20 mL), dried (MgSO<sub>4</sub>) and concentrated. Purification by flash silica gel  
 5 chromatography (2% ethyl acetate/hexane) afforded 153 mg (68%) of the title compound as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (m, 4 H), 4.90 (bs, 1 H), 3.64 (bs, 1 H), 3.21 (sept, *J* = 6.6 Hz, 1 H), 2.35 (m, 1 H), 2.15 (m, 2 H), 1.30 (d, *J* = 6.6 Hz, 6 H), 1.29 (d, *J* = 6.6 Hz, 6 H), 1.26 (m, 2 H), 1.10 (m, 4 H), 0.77 (t, *J* = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>24</sub>H<sub>31</sub>F<sub>4</sub>NO) 425, found 426 (M+H). Anal. Calcd for  
 10 C<sub>24</sub>H<sub>31</sub>F<sub>4</sub>NO: C, 67.75; H, 7.34; N, 3.29; F, 17.86. Found: C, 67.82; H, 7.13; N, 3.02; F, 18.05. mp 88-89°C. R<sub>f</sub> = 0.35 (10% ethyl acetate/hexane).

### EXAMPLE 119



### 2,6-Diisopropyl-3-(2-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine

#### Step A: 2,6-Diisopropyl-3-(2-oxoethyl)-4-(4-fluorophenyl)-5-pentylpyridine

20 A solution of (methoxymethyl)triphenylphosphonium chloride (350 mg, 0.985 mmol) in THF (30 mL) was treated with butyllithium (1.6 M, 1.2 eq., 0.74 mL) at -78°C. The reaction was stirred at 0°C for 1 h. and then is cooled to -78°C again. 2,6-Diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example  
 114, Step A) (350 mg, 0.985 mol) in THF (5 mL) was added dropwise and the  
 25 reaction mixture allowed to come to room temperature. After 24 h., the reaction was quenched with water and the THF evaporated *in vacuo*. The residue was partitioned between ether and water. The organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to yield an oil. Flash chromatography (10% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) afforded an oil (172 mg).

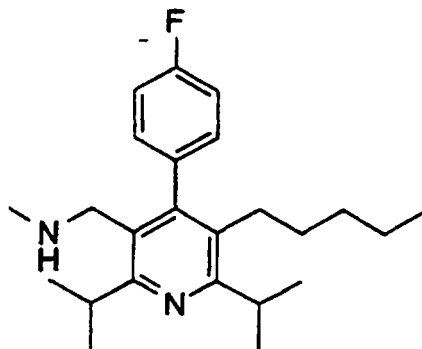
30 The oil (172 mg) was taken up in THF (15 mL) and treated with 4 mL conc.

- 0 HCl. The solution was stirred for 1.5 hours and then diluted with ether (150 mL). The reaction was washed with  $\text{NaHCO}_3$  (2 x 50 mL) and dried with  $\text{MgSO}_4$ . Filtration and concentration yielded a solid (20 mg, 0.054 mmol, 6%). The product was taken directly to the next step without further purification.

5 Step B: 2,6-Diisopropyl-3-(2-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine

- To the intermediate obtained in Step A (20 mg, 0.054 mmol) in dry THF (10 mL) was added dropwise LAH (2 eq., 1 M, 0.11 mL) under argon and the mixture was stirred at reflux for 1 h. The reaction was quenched with water (3.9  $\mu\text{L}$ ), 20% NaOH (3.9  $\mu\text{L}$ ), and water (7.8  $\mu\text{L}$ ) again. Concentration afforded a white solid. The product was subjected to a pad of silica gel ( $\text{CH}_2\text{Cl}_2$ ) to afford the title compound as a white solid (14 mg, 0.038 mmol, 70%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.39 (m, 2 H), 7.12 (m, 2 H), 3.52 (t,  $J = 5.5$  Hz, 2 H), 3.23 (m, 2 H), 2.60 (t,  $J = 2.9$  Hz, 2 H), 2.20 (t,  $J = 3.7$  Hz, 2 H), 1.30 (m, 14 H), 1.11 (m, 4 H), 0.771 (t,  $J = 6.3$  Hz, 3 H). FAB-MS: calcd for ( $\text{C}_{24}\text{H}_{34}\text{FNO}$ ) 371, found 372 ( $\text{M}+\text{H}$ ). Anal. Calcd for  $\text{C}_{24}\text{H}_{34}\text{FNO}$ : C, 77.59; H, 9.22; N, 3.77. Found: C, 77.57; H, 9.44; N, 3.05. mp 81-83°C.  $R_f = 0.6$  (10% ether/hexane).

20 EXAMPLE 120

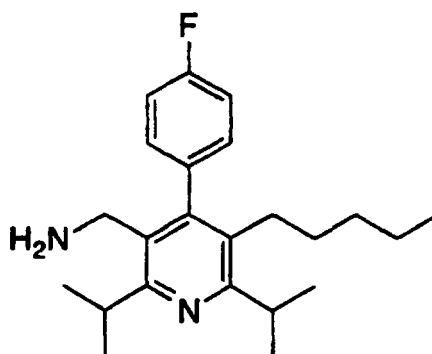


2,6-Diisopropyl-3-methylaminomethyl-4-(4-fluorophenyl)-5-pentyl-pyridine

- 25 Methylammonium chloride (37.99 mg, 0.563 mmol) was added to a stirred solution of methylamine in methanol (2 M, 0.28 mL) under argon in an oven-dried round bottom flask equipped with a stir bar. Then sodium cyanoborohydride (4 eq., 10.60 mg, 0.169 mmol) was added and 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) (100 mg, 0.281 mmol) was added as a solution in methanol (2 mL). The reaction was refluxed for 18 hours and then quenched with water. Concentration and addition of  $\text{CH}_2\text{Cl}_2$  (25 mL) allowed
- 30

- 0 washings with water (2 x 15 mL), brine (1 x 25 mL), following which the solution was dried with  $\text{MgSO}_4$ , filtered, and concentrated to afford a clear oil. Flash chromatography using silica gel (40% ether/ $\text{CH}_2\text{Cl}_2$ ) yielded the title compound as a white solid (21 mg, 0.057 mmol, 20%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (m, 4 H), 3.26 (m, 4 H), 2.24 (m, 5 H), 1.20 (m, 19 H), 0.783 (t,  $J$  = 6.6 Hz, 3 H). FAB-MS: calcd for  $(\text{C}_{24}\text{H}_{35}\text{FN}_2)$  370, found 371 (M+H). mp 77-79°C.  $R_f$  = 0.2 (20% ether/ $\text{CH}_2\text{Cl}_2$ ).
- 5

### EXAMPLE 121

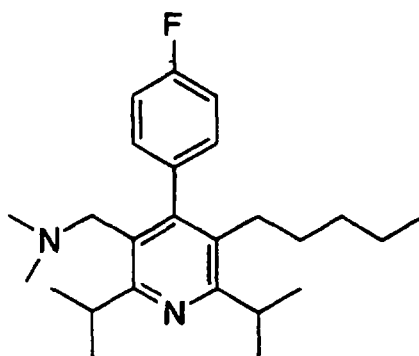


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### 2,6-Diisopropyl-3-aminomethyl-4-(4-fluorophenyl)-5-pentylpyridine

- The title compound was prepared from 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) and  $\text{NH}_4\text{OAc}$ , according to the procedures described in Example 120.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.10 (m, 4 H), 2.61 (m, 4 H), 2.20 (t,  $J$  = 5.5 Hz, 2 H), 1.17 (m, 20 H), 0.776 (t,  $J$  = 6.6 Hz, 3 H). FAB-MS: calcd for  $(\text{C}_{23}\text{H}_{33}\text{FN}_2)$  356, found 357 (M+H). Anal. Calcd for  $\text{C}_{23}\text{H}_{33}\text{N}_2\text{F}$ : C, 77.48; H, 9.33; N, 7.86; F, 5.33. Found: C, 77.42; H, 9.12; N, 7.64; F, 5.51. mp 47-49°C.  $R_f$  = 0.6 (50%  $\text{CH}_2\text{Cl}_2$ /hexanes).
- 15
- 20

### EXAMPLE 122

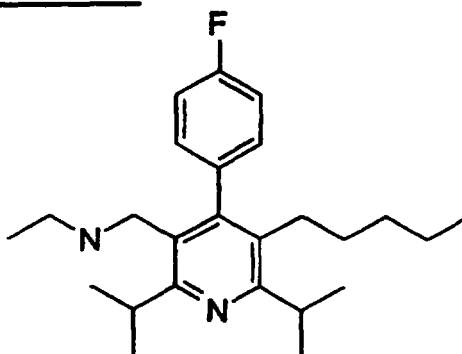


0 2,6-Diisopropyl-3-(dimethylamino)methyl-4-(4-fluorophenyl)-5-pentyl-pyridine

The title compound was prepared from 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) and dimethylamine hydrochloride, according to the procedures described in Example 120. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.09 (m, 4 H), 3.49 (septet, *J* = 6.6 Hz, 1 H), 3.21 (septet, *J* = 6.6 Hz, 1 H), 3.05 (s, 2 H), 2.22 (t, *J* = 5.2 Hz, 2 H), 1.99 (s, 6 H), 1.18 (m, 18 H), 0.790 (t, *J* = 6.3 Hz, 3 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>37</sub>FN<sub>2</sub>) 384, found 385 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>37</sub>FN<sub>2</sub>: C, 78.08; H, 9.70; N, 7.28; F, 4.94. Found: C, 77.95; H, 9.66; N, 7.12; F, 5.25. mp 69-71°C. R<sub>f</sub> = 0.4 (20% ether/CH<sub>2</sub>Cl<sub>2</sub>).

10

EXAMPLE 123

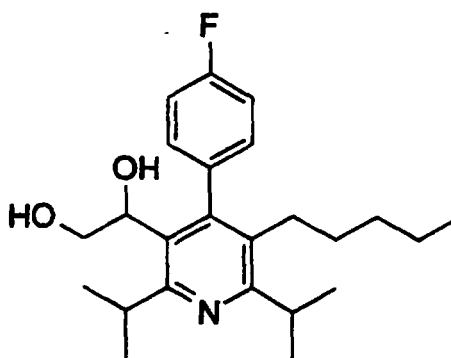


2,6-Diisopropyl-3-(ethylamino)methyl-4-(4-fluorophenyl)-5-pentylpyridine

15 The title compound was prepared from 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarboxaldehyde (Example 114, Step A) and ethylamine, according to the procedures described in Example 120. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.06 (m, 4 H), 3.18 (m, 4 H), 2.32 (q, *J* = 7.4 Hz, 2 H), 2.15 (t, *J* = 5.2 Hz, 2 H), 1.13 (m, 18 H), 0.839 (t, *J* = 7.4 Hz, 3 H), 0.698 (t, *J* = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>25</sub>H<sub>37</sub>FN<sub>2</sub>) 384, found 385 (M+H). Anal. Calcd for C<sub>23</sub>H<sub>37</sub>FN<sub>2</sub>: C, 78.08; H, 9.70; N, 7.28; F, 4.94. Found: C, 77.85; H, 9.50; N, 6.99; F, 4.79. mp 48-50°C. R<sub>f</sub> = 0.1 (20% ether/CH<sub>2</sub>Cl<sub>2</sub>).

20

EXAMPLE 124



0 (±)-2,6-Diisopropyl-3-(1,2-dihydroxyethyl)-4-(4-fluorophenyl)-5-pentyl-pyridine

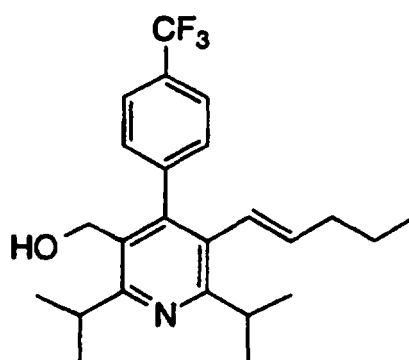
Step A: 2,6-Diisopropyl-3-ethenyl-4-(4-fluorophenyl)-5-pentylpyridine

Methyl triphenylphosphonium bromide was suspended in 15 mL of dry THF under argon and stirred at -78°C. Butyllithium (1.6 M, 0.42 mL) was added dropwise over 2 min. and then the reaction mixture was allowed to stir at 0°C for 1.5 hours. The solution was cooled again to -78°C, treated dropwise with a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-5-pentyl-3-pyridinecarbox-aldehyde (Example 114, Step A) in 5 mL of dry THF, and then stirred at 0°C for 2.5 hours. The reaction was quenched with water (10 mL) and the THF evaporated *in vacuo*. Diethyl ether was added and the mixture was washed with water (2 x 20 mL), brine (1 x 20 mL), and dried with MgSO<sub>4</sub>. Filtration, concentration and flash chromatography (30% CH<sub>2</sub>Cl<sub>2</sub>/hexanes) yielded a solid (0.132 g, 0.37 mmol, 66%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.08 (m, J = 1.1 Hz, 4 H), 6.34, 6.28 (d, J = 11.4 Hz, J = 11.4 Hz, 1 H), 5.19 (d, J = 1.8 Hz, 1 H), 4.96 (d, J = 1.8 Hz, 1 H), 3.39 (septet, J = 6.6 Hz, 1 H), 3.24 (septet, J = 6.6 Hz, 1 H), 2.30 (t, J = 5.2 Hz, 2 H), 1.20 (m, J = 2.2 Hz, 18 H), 0.979 (t, J = 6.0 Hz, 3 H). FAB-MS: calcd for (C<sub>24</sub>H<sub>32</sub>FN) 353, found 354 (M+H). Anal. Calcd for C<sub>24</sub>H<sub>32</sub>FN: C, 81.54; H, 9.12; N, 3.96; F, 5.37. Found: C, 81.46; H, 9.06; N, 3.78; F, 5.59. mp ~~44~~ 46°C. R<sub>f</sub> = 0.7 (30% CH<sub>2</sub>Cl<sub>2</sub>/hexanes).

20 Step B: (±)-2,6-Diisopropyl-3-(1,2-dihydroxyethyl)-4-(4-fluoro-phenyl)-5-pentylpyridine

To an oven-dried round bottom flask equipped with a stir bar was added the intermediate obtained in Step A (150 mg, 0.424 mmol), in pyridine (10 mL) under argon. The solution was stirred and OsO<sub>4</sub> (0.129 g, 0.509 mmol) was added in one portion. The reaction turned black as stirring continued at room temperature. After 3 hours, the pyridine was evaporated *in vacuo* and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and sat. NaHSO<sub>3</sub> (10 mL). The resulting heterogenous solution was stirred very rapidly for 18 hours. The layers were separated and the aqueous layer was extracted several times with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were dried (MgSO<sub>4</sub>), filtered, and concentrated to give a white solid. The product was subjected to a pad of silica (65/35; CH<sub>2</sub>Cl<sub>2</sub>/ether) to yield a white solid (70 mg, 0.18 mmol, 43%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.08 (m, 4 H), 4.57 (d, J = 1.5 Hz, 1 H), 3.85 (m, 1H), 3.65 (septet, J = 6.6 Hz, 1 H), 3.50 (m, 1 H), 3.20 (septet, J = 6.6 Hz, 1 H), 2.19 (m, 2 H), 1.96 (m, 1 H), 1.24 (m, 14 H), 1.07 (m, 4 H), 0.780 (t, J = 6.6 Hz, 3 H). FAB-MS: calcd for (C<sub>24</sub>H<sub>34</sub>FNO) 387, found 388 (M+H). Anal. Calcd for C<sub>24</sub>H<sub>34</sub>FNO: C, 74.38; H, 8.84; N, 3.61; F, 4.90. Found: C, 74.60; H, 9.03; N, 3.83; F, 5.04. mp 175-177°C. R<sub>f</sub> = 0.5 (65/35; CH<sub>2</sub>Cl<sub>2</sub>/ether).

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EXAMPLE 125

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2,6-Diisopropyl-3-hydroxymethyl-4-[(4-trifluoromethyl)phenyl]-5-(pent-1-enyl)pyridineStep A: Diethyl 1,4-dihydro-2,6-diisopropyl-4-[(4-trifluoromethyl)phenyl]pyridine-3,5-dicarboxylate

Following the procedure of Chucholowski (U.S. Patent 4,950,675), to a solution of 18.0 g (0.11 mol) of ethyl isobutyrylacetate and 9.9 g (56.8 mmol) of 4-(trifluoromethyl)benzaldehyde in ethanol (25 mL) was added concentrated ammonium hydroxide (3.0 mL). This reaction mixture was heated at reflux for 12 hrs. After cooling to room temperature, the reaction mixture was concentrated under vacuum to yield a yellow oil. The crude product was taken directly to the next step without purification.

Step B: Diethyl 2,6-diisopropyl-4-[(4-trifluoromethyl)phenyl]-pyridine-3,5-dicarboxylate

Prepared from the intermediate obtained in Step A by the procedure described in Example 160, Step B.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.92 (t,  $J=7.0$  Hz, 6H), 1.33 (d,  $J=6.6$  Hz, 12H), 3.14 (m, 4H), 4.0 (q,  $J=7.0$  Hz, 4H), 7.42 (d,  $J=8.0$  Hz, 2H). mp 100-101°C.

Step C: Ethyl 2,6-diisopropyl-4-[(4-trifluoromethyl)phenyl]-5-hydroxymethylpyridine-3-carboxylate

Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.91 (t,  $J=7.0$  Hz, 3H), 1.32 (d,  $J=6.6$  Hz, 6H), 1.35 (d,  $J=6.6$  Hz, 6H), 3.08 (m, 1H), 3.50 (m, 1H), 3.96 (q,  $J=7.0$  Hz, 2H), 4.43 (d,  $J=4.0$  Hz, 2H), 7.44 (d,  $J=8.0$  Hz, 2H), 7.68 (d,  $J=8.0$  Hz, 2H). mp 102-103°C.

0

**Step D:**      5-Ethoxycarbonyl-2,6-diisopropyl-4-[(4-trifluoromethyl)-phenyl]pyridine-3-carboxaldehyde

To a solution of the intermediate obtained in Step C (1.9 g, 4.6 mmol) in dichloromethane (50 mL) was added Celite (2.0 g). The suspension was stirred at room temperature and treated with pyridinium chlorochromate (PCC) (2.0 g, 9.3 mmol) in three portions. The suspension was stirred at room temperature for 1 hr, then poured into 1:1 diethyl ether/hexane (250 mL), filtered through a pad of silica, the pad washed with diethyl ether (250 mL) and the combined eluent concentrated to afford 1.7 g (93%) of the product as a viscous oil which slowly solidified. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.94 (t, J=7.0 Hz, 3H), 1.33 (d, J=6.6 Hz, 6H), 1.34 (d, J=6.6 Hz, 6H), 3.14 (m, 1H), 3.88 (m, 1H), 4.0 (q, J=7.0 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 7.71 (d, J=8.0 Hz, 2H), 9.86 (s, 1H). mp 105-106°C.

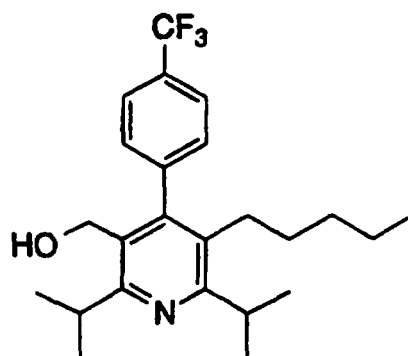
**Step E:**      Ethyl 2,6-diisopropyl-4-[(4-trifluoromethyl)phenyl]-5-(pent-1-enyl)pyridine-3-carboxylate

Prepared from the intermediate obtained in Step D by the procedure described in Example 1, Step D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.69 (t, J=7.0 Hz, 3H), 0.90 (t, J=7.0 Hz, 3H), 1.09-1.34 (m, 14H), 1.92 (δ, J=14.0, 7.0, 1.5 Hz, 2H), 3.07 (m, 1H), 3.38 (m, 1H), 3.96 (q, J=7.0 Hz, 2H), 5.29 (m, 1H), 6.05 (m, 1H), 7.31 (d, J=8.0 Hz, 2H), 7.59 (d, J=8.0 Hz, 2H). mp 70-72°C.

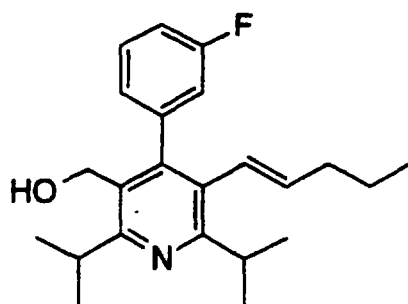
**Step F:**      2,6-Diisopropyl-3-hydroxymethyl-4-[(4-trifluoromethyl)phenyl]-5-(pent-1-enyl)pyridine

The intermediate obtained in Step E (0.91 g, 2.04 mmol) was dissolved in anhydrous THF (100 mL) under argon and treated dropwise at room temperature with lithium aluminum hydride (1.0 M in THF, 10 mL, 10 mmol). The reaction mixture was stirred at reflux for 1 hr, cooled to room temperature and quenched by the sequential addition of H<sub>2</sub>O, 20% aqueous NaOH and H<sub>2</sub>O. The resulting suspension was filtered through a cake of Celite and the filtrate concentrated and purified by flash chromatography through silica (5% ethyl acetate/n-hexane) to afford 0.77 g (1.90 mmol, 93%) of the title compound as a white foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.68 (t, J=7.0 Hz, 3H), 1.05-1.40 (m, 14H), 1.90 (δ, J=14.7, 1.5 Hz, 2H), 3.34 (m, 1H), 3.45 (m, 1H), 4.37 (d, J=5.5 Hz, 2H), 5.26 (m, 1H), 5.95 (m, 1H), 7.30 (d, J=8.0 Hz, 2H), 7.65 (d, J=8.0 Hz, 2H). R<sub>f</sub>=0.36 (10% ethyl acetate/n-hexane). mp 77-78°C.

0

EXAMPLE 1262,6-Diisopropyl-3-hydroxymethyl-4-[(4-trifluoromethyl)phenyl]-5-pentylpyridine

- 5 To 0.59 g (1.46 mmol) of the compound 2,6-diisopropyl-3-hydroxymethyl-4-[(4-trifluoromethyl)phenyl]-5-(pent-1-enyl)pyridine (Example 125) was dissolved in absolute ethanol (50 mL) and treated with 10% palladium on carbon (0.1 eq). The reaction flask was purged under aspirator vacuum and filled with hydrogen gas (3x). The reaction mixture was stirred under a hydrogen atmosphere for 6 hr.
- 10 After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed by concentration under vacuum and the crude product was purified by flash chromatography (10% ethyl acetate/n-hexane) to yield 0.58 g (1.41 mmol, 97%) of the title compound as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J=7.0 Hz, 3H), 1.12 (m, 4H), 1.31 (m, 14H), 2.26
- 15 (m, 2H), 3.25 (m, 1H), 3.42 (m, 1H), 4.29 (s, 2H), 7.34 (d, J=8.0 Hz, 2H), 7.72 (d, J=8.0 Hz, 2H). R<sub>f</sub>=0.36 (10% ethyl acetate/n-hexane). mp 99-100°C.

EXAMPLE 127

20

2,6-Diisopropyl-3-hydroxymethyl-4-(3-fluorophenyl)-5-(pent-1-en-1-yl)-pyridine

- 25 Step A: Ethyl 2,6-diisopropyl-4-(3-fluorophenyl)-5-(pent-1-en-1-yl)-pyridine-3-carboxylate

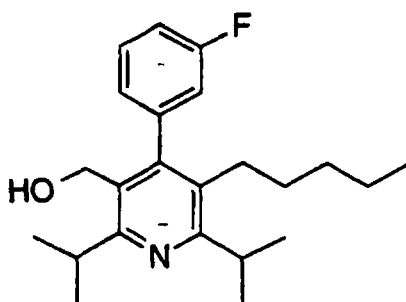
0 Prepared from 3-fluorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (reported as a mixture of olefin isomers): δ 0.76 (m, 3H), 0.97 (t, J=7.0 Hz, 3H), 1.13-1.37 (m, 14H), 1.95 (m, 2H), 3.07 (m, 1H), 3.21-3.45 (m, 1H), 4.0 (m, 2H), 5.30-5.60 (m, 1H), 6.06 (m, 1H), 6.90-7.03 (m, 3H), 7.27 (m, 1H).

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3-fluorophenyl)-5-(pent-1-enyl)pyridine

10 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.78 (m, 3H), 1.13-1.37 (m, 14H), 1.93 (m, 2H), 3.41 (m, 2H), 4.40 (s, 2H), 5.28-5.45 (m, 1H), 6.0 (m, 1H), 6.87-7.07 (m, 3H), 7.34 (m, 1H). R<sub>f</sub>=0.36 (10% ethyl acetate/n-hexane). mp 117-118°C.

15

EXAMPLE 128



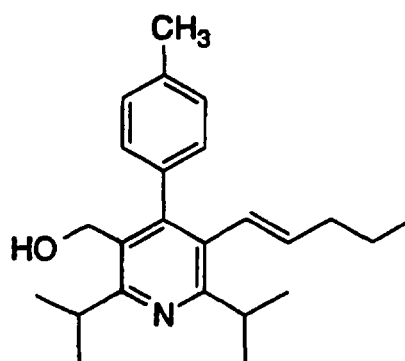
2,6-Diisopropyl-3-hydroxymethyl-4-(3-fluorophenyl)-5-pentylpyridine

20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-fluorophenyl)-5-(pent-1-enyl)pyridine (Example 127) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.79 (t, J=7.0 Hz, 3H), 1.10-1.35 (m, 18H), 2.28 (m, 2H), 3.24 (m, 1H), 3.42 (m, 1H), 4.33 (s, 2H), 6.96 (m, 2H), 7.12 (m, 1H), 7.40 (m, 1H). mp 117-118°C. R<sub>f</sub>=0.36 (10% ethyl acetate/n-hexane).

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30

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EXAMPLE 129

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2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-(pent-1-enyl)-pyridineStep A: Ethyl 2,6-diisopropyl-4-(4-methylphenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

Prepared from 4-methylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.75 (t,  $J=7.4$  Hz, 3H), 0.95 (t,  $J=7.4$ , 3 H), 1.20-1.40 (m, 14H), 1.95 (tdd,  $J=7.4$ , 7.4, 1.5 Hz, 2H), 2.35 (s, 3H), 3.10 (m, 1H), 3.40 (m, 1H), 3.99 (q,  $J=7.4$ , 2H), 5.30-5.40 (m, 1H), 6.05 (dt,  $J=16.2$ , 1.5 Hz, 1H), 7.0-7.2 (m, 4H). mp 74-77°C.

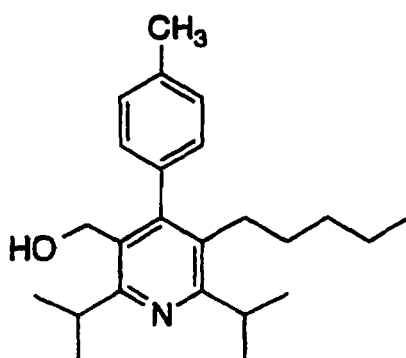
15 Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-(pent-1-enyl)-pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a mixture of olefin isomers):  $\delta$  0.77 (t,  $J=7.0$  Hz, 3 H), 1.1-1.3 (m, 15 H), 2.27 (m, 2 H), 2.42 (s, 3H), 3.4 (m, 2 H), 4.34 (d,  $J=6.0$  Hz, 2 H), 5.30-5.40 (m, 1 H), 5.90 (d,  $J=16.0$  Hz, 1 H), 7.0 (d,  $J=8.0$  Hz, 2 H), 7.18 (d,  $J=8.0$  Hz, 2 H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{33}\text{NO}$  352; found 352 ( $\text{M}+\text{H}$ , 100%).  $R_f=0.38$  (10% ethyl acetate/*n*-hexane). mp 72-75°C.

25

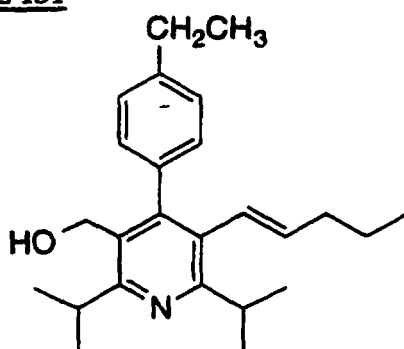
30

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EXAMPLE 130

5 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-pentylpyridine The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-(pent-1-enyl)pyridine (Example 129) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J=7.0 Hz, 3 H), 1.10-1.40 (m, 19 H), 2.27 (m, 2 H), 2.42 (s, 3 H), 3.22 (m, 1 H), 3.41 (m, 1 H), 4.34 (d, J=6.0 Hz, 2 H), 7.10 (d, J=8.0 Hz, 2 H), 7.20 (d, J=8.0 Hz, 2 H). FAB-MS: calculated for C<sub>24</sub>H<sub>35</sub>NO 354; found 354 (M+H, 100%). R<sub>f</sub>=0.38 (10% ethyl acetate/n-hexane). mp 92-94°C

10

EXAMPLE 131

15 2,6-Diisopropyl-3-hydroxymethyl-4-(4-ethylphenyl)-5-(pent-1-enyl)-pyridine

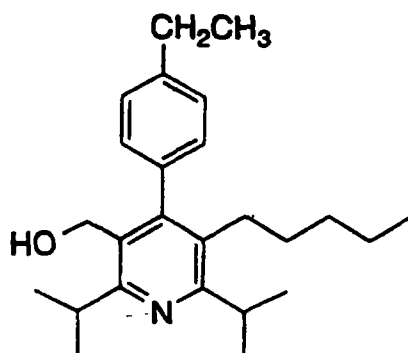
Step A: - Ethyl 2,6-diisopropyl-4-(4-ethylphenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

20 Prepared from 4-ethylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J=7.4 Hz, 3H), 0.90 (t, J=7.4 Hz, 3H), 1.10-1.40 (m, 17H), 1.94 (tdd, J=7.0, 7.0, 1.5 Hz, 2H), 2.64 (q, J=7.7 Hz, 2H), 3.0 (m, 1H), 3.40 (m, 1H), 3.96 (q, J=7.4 Hz, 2H), 5.35 (m, 1H), 6.08 (dt, J=16.2, 1.5 Hz, 1H), 7.10 (m, 4H). mp 67-68°C.

0 **Step B:** **2,6-Diisopropyl-3-hydroxymethyl-4-(4-ethylphenyl)-5-(pent-1-enyl)pyridine**

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.73 (t, J= 7.0 Hz, 3H), 1.10-1.40 (m, 18H), 1.91 (tdd, J=7.0, 7.0, 1.0, 2H), 2.68 (q, J=7.4 Hz, 2H), 3.3-3.5 (m, 2H), 4.41 (d, J= 5.5 Hz, 2H), 5.20-5.40 (m, 1H), 6.0 (dt, J=16.0, 1.0 Hz, 1H), 7.0 (d, J=8.5 Hz, 2H), 7.23 (d, J= 8.5 Hz, 2H). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>NO 366; found 366 (M+H, 100%). R<sub>f</sub>=0.31 (10% ethyl acetate/n-hexane).

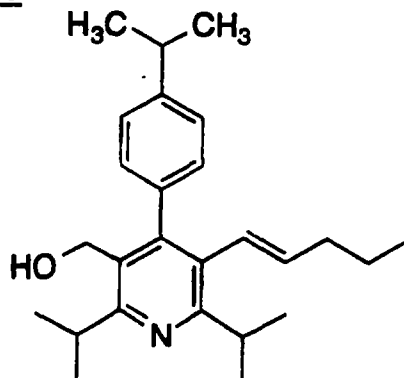
### EXAMPLE 132



**2,6-Diisopropyl-3-hydroxymethyl-4-(4-ethylphenyl)-5-pentylpyridine**

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-ethylphenyl)-5-(pent-1-enyl)pyridine (Example 131) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J=7.0 Hz, 3H), 1.0-1.40 (m, 22H), 2.28 (m, 2H), 2.73 (q, J= 7.5 Hz, 2H), 3.35 (m, 1H), 3.45 (m, 1H), 4.35 (s, 2H), 7.10 (d, J=8.0 Hz, 2H), 7.18-7.34 (d, J=8.0 Hz, 2H). FAB-MS: calculated for C<sub>25</sub>H<sub>37</sub>NO 368; found 368 (M+H, 100%). R<sub>f</sub>=0.31 (10% ethyl acetate/n-hexane). mp 87-88°C.

### EXAMPLE 133



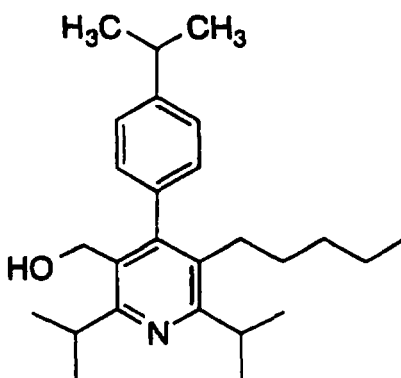
0

2,6-Diisopropyl-3-hydroxymethyl-4-(4-isopropylphenyl)-5-(pent-1-enyl)pyridineStep A: Ethyl 2,6-diisopropyl-4-(4-isopropylphenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

5 Prepared from 4-isopropylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.70 (t, J=7.7 Hz, 3H), 0.84 (t, J=7.4, 3H), 1.10-1.40 (m, 20H), 1.95 (tdd, J=7.0, 7.0, 1.5 Hz, 2H), 2.80-3.10 (m, 2H), 3.40 (m, 1H), 3.94 (q, J=7.4 Hz, 2H), 5.30 (m, 1H), 6.10 (dt, J=15.8, 1.5 Hz, 1H), 7.0-7.20 (m, 4H).  
 10 mp 41-45°C.

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-isopropylphenyl)-5-(pent-1-enyl)pyridine

15 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefins): δ 0.68 (t, J=7.4 Hz, 3 H), 1.0-1.4 (m, 21 H), 1.90 (tdd, J=7.0, 7.0, 1.5 Hz, 2 H), 2.9 (m, 1H), 3.3-3.5 (m, 2 H), 4.43 (d, J=6.0 Hz, 2 H), 5.20-5.35 (m, 1 H), 6.0 (dt, J= 16.0, 1.5 Hz, 1 H), 7.0 (d, J=8.0 Hz, 2 H), 7.25 (d, J=8.0 Hz, 2 H). FAB-MS: calculated for C<sub>26</sub>H<sub>37</sub>NO 380; found 380 (M+H, 100%). R<sub>f</sub>=0.40  
 20 (10% ethyl acetate/n-hexane).

EXAMPLE 134

25

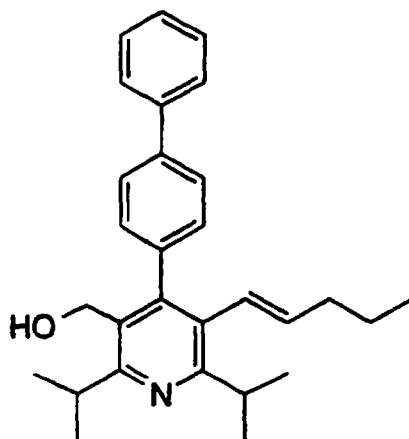
2,6-Diisopropyl-3-hydroxymethyl-4-(4-isopropylphenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-isopropylphenyl)-5-(pent-1-enyl)pyridine (Example 133) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.74 (t, J= 7.0 Hz, 3 H),  
 30 1.0-1.40 (m, 25 H), 2.25 (m, 2 H), 2.95 (m, 1 H), 3.25 (m, 1 H), 3.40 (m, 1 H), 4.35 (d,

- 0 J=6.0 Hz, 2 H), 7.1, (d, J=8.5 Hz, 2 H), 7.25 (d, J= 8.5 Hz, 2 H). FAB-MS: calculated for C<sub>26</sub>H<sub>39</sub>NO 382; found 382 (M+H, 100%). R<sub>f</sub>=0.40 (10% ethyl acetate/n-hexane). mp 42-44°C.

### EXAMPLE 135

5



### 2,6-Diisopropyl-3-hydroxymethyl-4-[4-(phenyl)phenyl]-5-(pent-1-enyl)pyridine

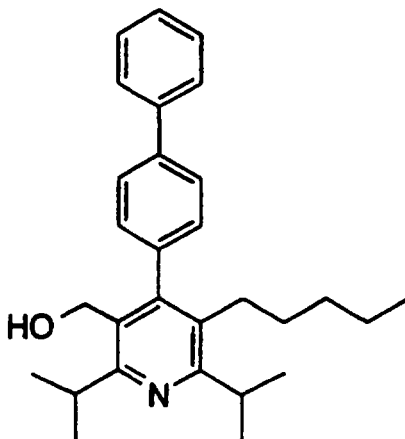
- 10 Step A: Ethyl 2,6-diisopropyl-4-[4-(phenyl)phenyl]-5-(pent-1-enyl)pyridine-3-carboxylate

Prepared from 4-phenylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.73 (t, J=7.4 Hz, 3H), 0.93 (t, J=7.0 Hz, 3H), 1.10-1.40 (m, 14H), 1.97 (tdd, J=7.0, 7.0, 1.1 Hz, 2H), 3.10 (m, 1H), 3.45 (m, 1H), 4.0 (q, J=7.4 Hz, 2 H), 5.40 (m, 1H), 6.10 (dt, J=16.2, 1.1 Hz, 1H), 7.20-7.70 (m, 9H). mp 104-106°C.

- 20 Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-[4-(phenyl)phenyl]-5-(pent-1-enyl)pyridine

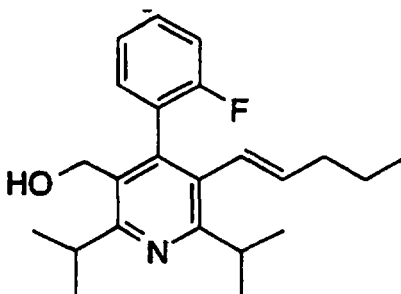
The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.70 (t, J= 7.0 Hz, 3H), 1.10-1.40 (m, 15H), 1.90 (tdd, J=7.0, 7.0, 1.5, 2H), 3.30-3.50 (m, 2H), 4.40 (d, J=6.0 Hz, 2H), 5.35 (m, 1H), 6.05 (dt, J=16.0, 1.5 Hz, 1H), 7.20-7.24 (m, 2H), 7.35-7.70 (m, 7H). FAB-MS: calculated for C<sub>29</sub>H<sub>35</sub>NO 414; found 414 (M+H, 100 %). R<sub>f</sub>=0.15 (6% ethyl acetate/n-hexane). mp 50-52°C.

0

EXAMPLE 136

2,6-Diisopropyl-3-hydroxymethyl-4-[4-(phenyl)phenyl]-5-pentylpyridine The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-[4-(phenyl)phenyl]-5-(pent-1-enyl)pyridine (Example 135) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.76 (t, J=7.0 Hz, 3H), 1.0-1.40 (m, 19H), 2.31 (m, 2H), 3.25 (m, 1H), 3.44 (m, 1H), 4.40 (d, J=5.9 Hz, 2H), 7.22-7.70 (m, 9H). FAB-MS: calculated for C<sub>29</sub>H<sub>37</sub>NO 416; found 416 (M+H, 100 %). R<sub>f</sub>=0.34 (10% ethyl acetate/n-hexane). mp 56-58°C.

10

EXAMPLE 13715 2,6-Diisopropyl-3-hydroxymethyl-4-(2-fluorophenyl)-5-(pent-1-enyl)-pyridine

Step A: Ethyl 2,6-diisopropyl-4-(2-fluorophenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

Prepared from 2-fluorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): (reported as a mixture of olefin isomers): δ 0.70 (m, 3H), 0.92 (t, J= 7.0 Hz, 3H), 1.05-1.40 (m, 14H), 1.90 (m, 2H), 3.10 (m, 1H), 3.35 (m, 1H), 3.97 (m, 2H), 5.29-5.50 (m, 1H), 6.16 (m, 1H), 7.08-7.32 (m, 4H).

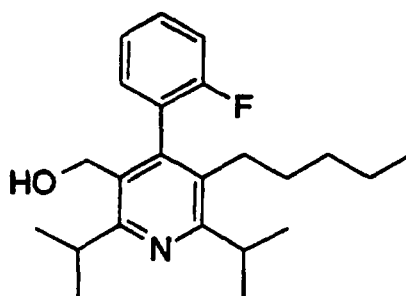
0

**Step B:**     2,6-Diisopropyl-3-hydroxymethyl-4-(2-fluorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.69-0.82 (m, 3H), 1.09-1.40 (m, 14H), 1.90 (m, 2H), 3.20-3.45 (m, 2H), 4.40 (m, 2H), 5.25-5.45 (m, 1H), 6.08 (m, 1H), 7.08-7.41 (m, 5H). R<sub>f</sub>=0.24 (10% ethyl acetate/n-hexane).

10

**EXAMPLE 138**

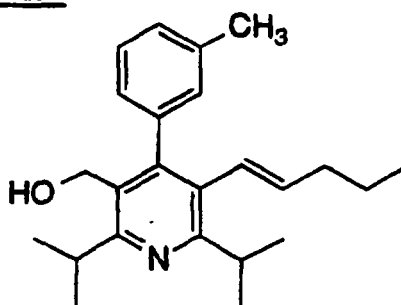


2,6-Diisopropyl-3-hydroxymethyl-4-(2-fluorophenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(2-fluorophenyl)-5-(pent-1-enyl)pyridine (Example 137) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J=7.0 Hz, 3H), 1.07-1.40 (m, 18H), 2.29 (m, 2H), 3.26 (m, 1H), 3.46 (m, 1H), 4.34 (m, 2H), 7.20 (m, 3H), 7.42 (m, 1H). R<sub>f</sub>=0.24 (10% ethyl acetate/n-hexane).

20

**EXAMPLE 139**



2,6-Diisopropyl-3-hydroxymethyl-4-(3-methylphenyl)-5-(pent-1-enyl)-pyridine

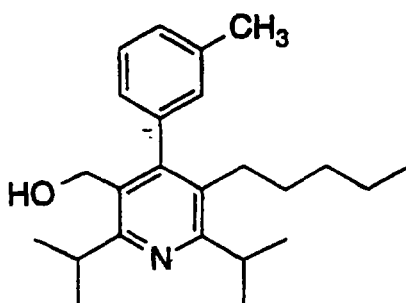
**Step A:**     Ethyl 2,6-diisopropyl-4-(3-methylphenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

0 Prepared from 3-methylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.74 (t,  $J=7.4$  Hz, 3H), 0.92 (t,  $J=7.0$  Hz, 3H), 1.10-1.40 (m, 14H), 1.95 (tdd,  $J=7.0, 7.0, 1.5$  Hz, 2H), 2.32 (s, 3H), 3.10 (m, 1H), 3.40 (m, 1H), 3.96 (q,  $J=7.4$  Hz, 2H), 5.40 (m, 1H), 6.05 (dt,  $J=16.2, 1.5$  Hz, 1H), 6.90-7.20 (m, 4H).

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3-methylphenyl)-5-(pent-1-enyl)pyridine

10 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a mixture of olefins):  $\delta$  0.73 (t,  $J=7.0$  Hz, 3 H), 1.10-1.40 (m, 15H), 1.90 (tdd,  $J=7.0, 7.0, 1.0$ , 2H), 2.36 (s, 3H), 3.30-3.50 (m, 2H), 4.40 (d,  $J=4.0$  Hz, 2H), 5.20-5.40 (m, 1H), 5.95 (dt,  $J=16.0, 1.0$  Hz, 1H), 6.90 (m, 2H), 7.10-7.30 (m, 2H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{33}\text{NO}$  352; found 352 ( $\text{M}+\text{H}$ , 100%).  $R_f=0.34$  (10% ethyl acetate/n-hexane). mp 94-97°C.

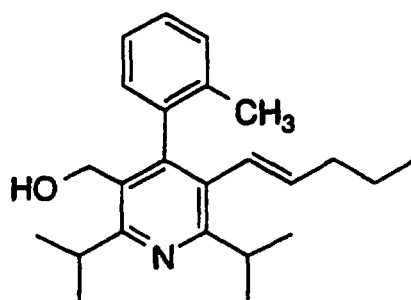
EXAMPLE 140



2,6-Diisopropyl-3-hydroxymethyl-4-(3-methylphenyl)-5-pentylpyridine

20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-methylphenyl)-5-(pent-1-enyl)pyridine (Example 139) by the procedure described in Example 126.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.77 (t,  $J=7.0$  Hz, 3 H), 1.0-1.40 (m, 19H), 2.25 (m, 2H), 2.39 (s, 3H), 3.23 (m, 1H), 3.44 (m, 1H), 4.34 (s, 2H), 6.97 (m, 2H), 7.18-7.34 (m, 2H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{35}\text{NO}$  354; found 354 ( $\text{M}+\text{H}$ , 100 %).  $R_f=0.34$  (10% ethyl acetate/n-hexane). mp 88-90°C.

0

EXAMPLE 1412,6-Diisopropyl-3-hydroxymethyl-4-(2-methylphenyl)-5-(pent-1-enyl)-pyridine

5

Step A: Ethyl 2,6-diisopropyl-4-(2-methylphenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

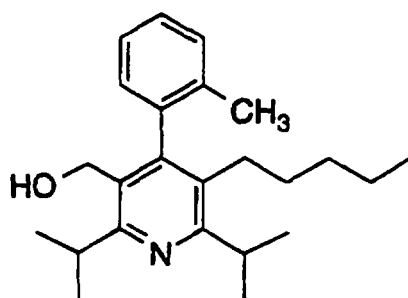
Prepared from 2-methylbenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.70 (t, J=7.4 Hz, 3H), 0.88 (t, J=7.0 Hz, 3H), 1.0-1.40 (m, 14H), 1.90 (td, J=7.0, 7.0 Hz, 2H), 2.0 (s, 3H), 3.10 (m, 1H), 3.40 (m, 1H), 3.90 (m, 2H), 5.30-5.40 (m, 1H), 6.0 (m, 1H), 7.0-7.20 (m, 4H).

15

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(2-methylphenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.70 (t, J= 7.5 Hz, 3H), 1.10-1.40 (m, 15H), 1.87 (tdd, J=7.5, 7.5, 1.5, 2H), 1.95 (s, 3H), 3.30-3.50 (m, 2H), 4.20 (m, 1H), 4.45 (m, 1H), 5.30 (m, 1H), 5.93 (m, 2H), 6.90-7.30 (m, 4H). FAB-MS: calculated for C<sub>24</sub>H<sub>33</sub>NO 352; found 352 (M+H, 100%). R<sub>f</sub>=0.32 (10% ethyl acetate/n-hexane). mp 76-79°C.

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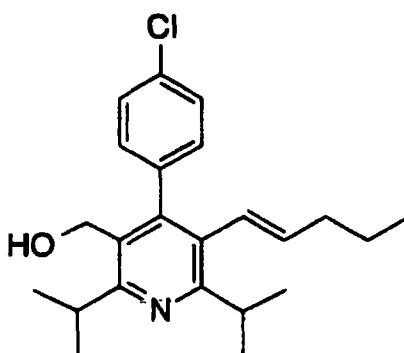
EXAMPLE 142

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2,6-Diisopropyl-3-hydroxymethyl-4-(2-methylphenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(2-methylphenyl)-5-(pent-1-enyl)pyridine (Example 141) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.76 (t, J=6.6 Hz, 3H), 1.0-1.40 (m, 19H), 1.97 (s, 3H), 2.0 (m, 1H), 2.35 (m, 1H), 3.22 (m, 1H), 3.42 (m, 1H), 4.16 (dd, J=12.0, 5.0 Hz, 1H), 4.40 (dd, J=12.0, 5.0 Hz, 1H), 7.0-7.10 (m, 1H), 7.20-7.40 (m, 3H). FAB-MS: calculated for C<sub>24</sub>H<sub>35</sub>NO 354; found 354 (M+H, 100%). R<sub>f</sub>=0.32 (10% ethyl acetate/n-hexane). mp 81-83°C.

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EXAMPLE 1432,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-(pent-1-enyl)-pyridine

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Step A: Ethyl 2,6-diisopropyl-4-(4-chlorophenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

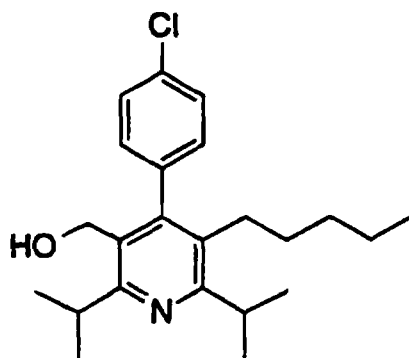
Prepared from 4-chlorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.76 (m, 3H), 0.98 (m, 3H), 1.15-1.35 (m, 14H), 1.95 (m, 2H), 3.05 (m, 1H), 3.39 (m, 1H), 4.0 (m, 2H), 5.29-5.48 (m, 1H), 6.03 (m, 1H), 7.11 (m, 2H), 7.30 (m, 2H).

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-(pent-1-enyl)pyridine

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The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 6:1 mixture of olefin isomers): δ 0.73-0.83 (m, 3H), 1.10-1.40 (14H), 1.91 (m, 2H), 3.93 (m, 2H), 4.39 (d, J=5.0 Hz, 2H), 5.25-5.45 (m, 1H), 5.98 (m, 1H), 7.11 (m, 2H), 7.35 (m, 2H). R<sub>f</sub>=0.36 (10% ethyl acetate/n-hexane).

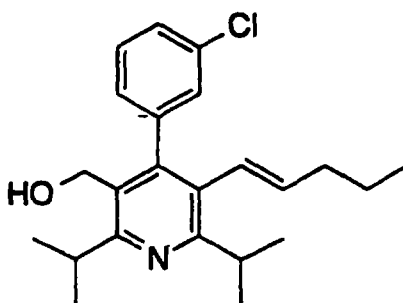
0

EXAMPLE 1442,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-pentylpyridine

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The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-(pent-1-enyl)pyridine (Example 143) by the procedure described in Example 126.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.79 (t,  $J=7.0$  Hz, 3H), 1.08-1.38 (m, 18H), 2.26 (m, 2H), 3.22 (m, 1H), 3.40 (m, 1H), 4.31 (d,  $J=5.0$  Hz, 1H), 7.13 (d,  $J=8.0$  Hz, 2H), 7.42 (d,  $J=8.0$  Hz, 2H). mp 83-85°C.  $R_f=0.36$  (10% ethyl acetate/n-hexane).

10

EXAMPLE 14515 2,6-Diisopropyl-3-hydroxymethyl-4-(3-chlorophenyl)-5-(pent-1-enyl)-pyridine

Step A: Ethyl 2,6-diisopropyl-4-(3-chlorophenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

Prepared from 3-chlorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.75 (t,  $J=7.4$  Hz, 3H), 0.98 (t,  $J=7.0$  Hz, 3H), 1.20-1.40 (m, 14H), 1.96 (tdd,  $J=7.0, 7.0, 1.5$  Hz, 2H), 3.05 (m, 1H), 3.40 (m, 1H), 4.0 (q,  $J=7.0$  Hz, 2H), 5.45 (m, 1H), 6.05 (dt,  $J=16.2, 1.5$  Hz, 1H), 7.0-7.30 (m, 4H).

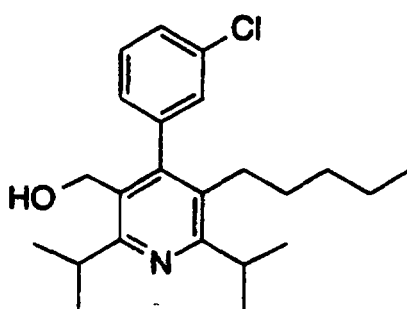
25

0    **Step B:**        2,6-Diisopropyl-3-hydroxymethyl-4-(3-chlorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.75 (t, J=7.5 Hz, 3H), 1.10-1.40 (m, 15H),  
 5    1.93 (tdd, J=7.0, 7.0, 1.0 Hz, 2H), 3.30-3.50 (m, 2H), 4.37 (d, J=12.0 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 5.20-5.40 (m, 1H), 5.9 (dt, J=16.0, 1.1 Hz, 1H), 7.0-7.40 (m, 4H). FAB-MS: calculated for C<sub>23</sub>H<sub>30</sub>NOCl 372; found 372 (M+H, 100%). R<sub>f</sub>=0.26 (10% ethyl acetate/n-hexane). mp 101-104°C.

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EXAMPLE 146

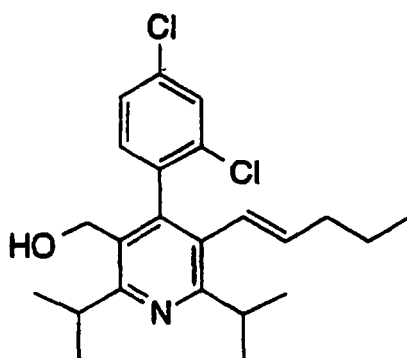


15    2,6-Diisopropyl-3-hydroxymethyl-4-(3-chlorophenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-chlorophenyl)-5-(pent-1-enyl)pyridine (Example 145) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.80 (t, J=7.0 Hz, 3H), 1.0-1.40 (m, 19H), 2.26 (m, 2H), 3.23 (m, 1H), 3.41 (m, 1H), 4.34 (m, 2H), 7.05-7.45 (m, 4H). FAB-MS: calculated for C<sub>23</sub>H<sub>32</sub>NOCl 374; found 374 (M+H, 100%). R<sub>f</sub> 0.26 (10% ethyl acetate/n-hexane). mp 94-95°C.

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EXAMPLE 147



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0 2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-dichlorophenyl)-5-(pent-1-enyl)pyridine

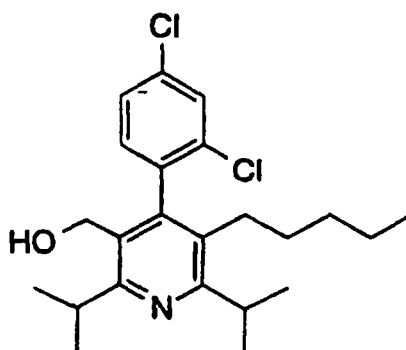
Step A: Ethyl 2,6-diisopropyl-4-(2,4-dichlorophenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

Prepared from 2,4-dichlorobenzaldehyde, ethyl isobutyrylacetate and  
 5 concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 1:1 mixture of olefin isomers): δ 0.79 (m, 3H), 0.99 (m, 3H), 1.12-1.38 (m, 14H), 1.91 (m, 2H), 3.12 (m, 1H), 3.32 (m, 1H), 4.0 (m, 2H), 5.20-5.60 (m, 1H), 6.09 (m, 1H), 7.05-7.41 (m, 3H).

10 Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-dichlorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 1:1 mixture of olefins): δ 0.75-0.87 (m, 3H), 1.13-1.37 (m, 14H), 1.65-2.0 (m, 2H), 3.20-3.51 (m, 2H), 4.30 (m, 1H), 4.42 (m, 1H), 5.31-5.50 (m, 1H), 6.0 (m, 1H), 7.05 (m, 1H), 7.28 (m, 1H), 7.47 (m, 1H). R<sub>f</sub> 0.38 (10% ethyl acetate/n-hexane).

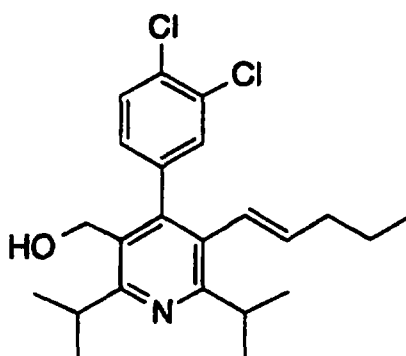
EXAMPLE 148



2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-dichlorophenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(2,4-dichlorophenyl)-5-(pent-1-enyl)pyridine (Example 147) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.80 (t, J=7.0 Hz, 3H), 1.12-1.48 (m, 18H), 2.12 (m, 1H), 2.35 (m, 1H), 3.26 (m, 1H), 3.45 (m, 1H), 4.31 (AB, J=12.0 Hz, 2H), 7.16 (d, J=8.0 Hz, 1H), 7.36 (dd, J=8.0, 2.0 Hz, 1H), 7.54 (d, J=2.0, 1H). R<sub>f</sub> 0.38 (10% ethyl acetate/n-hexane).

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EXAMPLE 149

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2,6-Diisopropyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-5-(pent-1-enyl)pyridineStep A: Ethyl 2,6-diisopropyl-4-(3,4-dichlorophenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

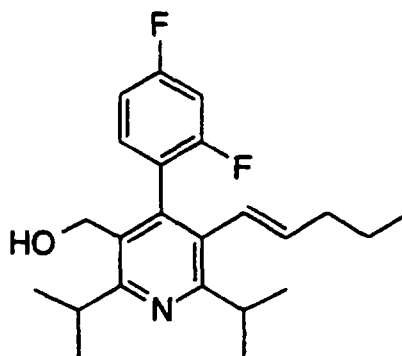
Prepared from 3,4-dichlorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 160, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 6:1 mixture of olefin isomers): δ 0.78 (m, 3H), 1.04 (m, 3H), 1.16-1.35 (m, 14H), 1.98 (m, 2H), 3.04 (m, 1H), 3.57 (m, 1H), 5.31-5.58 (m, 1H), 6.02 (m, 1H), 7.04 (m, 1H), 7.28-7.42 (m, 2H).

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Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3,4-dichlorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 6:1 mixture of olefin isomers): δ 0.80 (m, 3H), 1.16-1.57 (m, 14H), 1.95 (m, 2H), 3.40 (m, 2H), 4.41 (m, 2H), 5.28-5.42 (m, 1H), 6.0 (m, 1H), 7.05 (s, 1H), 7.30 (s, 1H), 7.45 (m, 1H). mp 46-48°C. R<sub>f</sub>=0.38 (10% ethyl acetate/n-hexane).

20

EXAMPLE 150

0 2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-difluorophenyl)-5-(pent-1-enyl)pyridine

Step A: Ethyl 2,6-diisopropyl-4-(2,4-difluorophenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

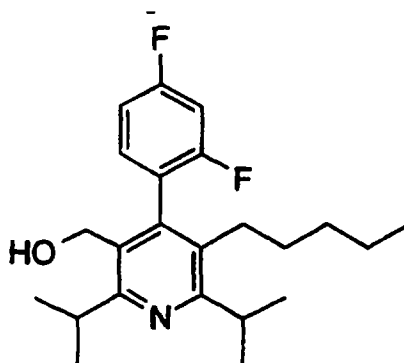
5 Prepared from 2,4-difluorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J=7.4 Hz, 3H), 1.0 (t, J=7.0 Hz, 3H), 1.10-1.40 (m, 14H), 1.93 (tdd, J=7.4, 7.4, 1.5 Hz, 2H), 3.10 (m, 1H), 3.35 (m, 1H), 4.0 (q, J=7.0 Hz, 2H), 5.30 (dt, J=15.0, 7.0 Hz, 1H), 6.10 (m, 1H), 6.80-7.20 (m, 3H).

10 Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-difluorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.75 (t, J=7.5 Hz, 3H), 1.10-1.40 (m, 15H), 1.92 (tdd, J=7.0, 7.0, 1.5, 2H), 3.30-3.60 (m, 2 H), 4.34 (dd, J=12.0, 6.0 Hz, 1H), 4.43 (dd, J=12.0, 5.0 Hz, 1H), 5.3 (m, 1H), 6.05 (d, J=16.0, Hz, 1H), 6.80-7.20 (m, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>29</sub>NOF<sub>2</sub> 374; found 374 (M+H, 100%). R<sub>f</sub> 0.24 (10% ethyl acetate/n-hexane). mp 59-62°C.

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EXAMPLE 151

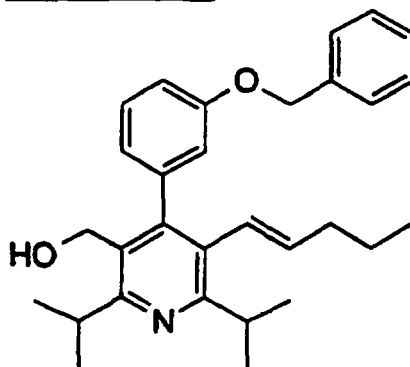


2,6-Diisopropyl-3-hydroxymethyl-4-(2,4-difluorophenyl)-5-pentylpyridine

25 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(2,4-difluorophenyl)-5-(pent-1-enyl)pyridine (Example 150) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.79 (t, J=7.0 Hz, 3H), 1.10-1.40 (m, 18H), 2.30 (m, 2 H), 3.20 (m, 1H), 3.40 (m, 1H), 4.30 (d, J=12.0 Hz, 1H), 4.36 (d, J=12.0 Hz, 1H), 6.90-7.20 (m, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>31</sub>F<sub>2</sub>NO 376; found 376 (M+H, 100%). R<sub>f</sub> 0.24 (10% ethyl acetate/n-hexane). mp 93-95°C.

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0

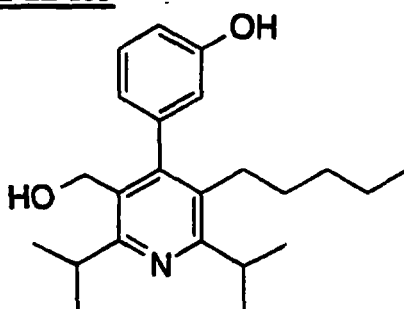
EXAMPLE 1522,6-Diisopropyl-3-hydroxymethyl-4-(3-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

Step A: Ethyl 2,6-diisopropyl-4-(3-benzyloxyphenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

Prepared from 3-benzyloxybenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 160, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J=7.4 Hz, 3H), 0.93 (t, J= 7.2 Hz, 3H), 1.25 (m, 14H), 1.93 (tdd, J=7.4, 7.4, 1.1 Hz, 2H), 3.07 (m, 1H), 3.40 (m, 1H), 3.97 (m, 2H), 5.04 (bs, 2H), 5.35 (m, 1H), 6.06 (dt, J=16.2, 1.5 Hz, 1H), 6.79 (m, 2H), 6.89 (m, 1H), 7.31 (m, 6H).

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a mixture of olefin isomers): δ 0.74 (t, J=7.4 Hz, 3H), 1.25 (m, 14H), 1.90 (m, 2H), 3.39 (m, 2H), 4.39 (d, J=6.0 Hz, 2H), 5.07 (s, 2H), 5.32 (m, 1H), 5.97 (m, 1H), 6.74 (m, 2H), 6.95 (m, 1H), 7.35 (m, 7H). FAB-MS: calculated for C<sub>30</sub>H<sub>37</sub>NO<sub>2</sub>, 444; found 444 (M+H, 100%). Elemental analysis: calculated for C<sub>30</sub>H<sub>37</sub>NO<sub>2</sub>: C 81.22; H 8.41; N 3.16, found: C 80.51; H 8.41; N 3.36. R<sub>f</sub> 0.5 (25% ethyl acetate/n-hexane).

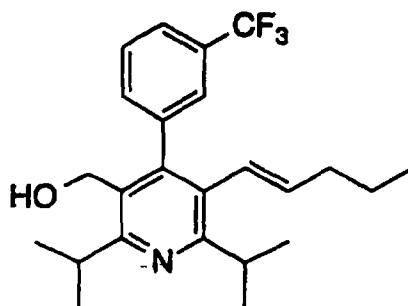
EXAMPLE 153

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2,6-Diisopropyl-3-hydroxymethyl-4-(3-hydroxyphenyl)-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-benzyloxyphenyl)-5-(pent-1-enyl)pyridine (Example 152) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J=7.0 Hz, 3H), 1.28 (m, 18H), 2.28 (m, 2H), 3.22 (m, 1H), 3.39 (m, 1H), 4.34 (m, 2H), 5.52 (s, 1H), 6.63 (m, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.81 (m, 1H), 7.26 (m, 1H). FAB-MS: calculated for C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub> 356; found 357 (M+H, 100%). Elemental analysis: calculated for C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub>: C 77.70; H 9.36; N 3.94, found: C 76.51; H 9.49; N 3.85. R<sub>f</sub> 0.21 (10% ethyl acetate/n-hexane). mp 121-122°C.

10

EXAMPLE 154

15 2,6-Diisopropyl-3-hydroxymethyl-4-(3-trifluoromethyl)phenyl-5-(pent-1-enyl)pyridine

Step A: Ethyl 2,6-diisopropyl-4-(3-trifluoromethyl)phenyl-5-(pent-1-enyl)pyridine-3-carboxylate

20 Prepared from 3-(trifluoromethyl)benzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 6:1 mixture of olefin isomers): δ 0.72 (m, 3H), 0.94 (m, 3H), 1.10-1.40 (m, 14H), 1.94 (m, 2H), 3.07 (m, 1H), 3.41 (m, 1H), 3.97 (m, 2H), 5.33 (m, 1H), 6.05 (m, 1H), 7.29-7.60 (m, 4H).

25

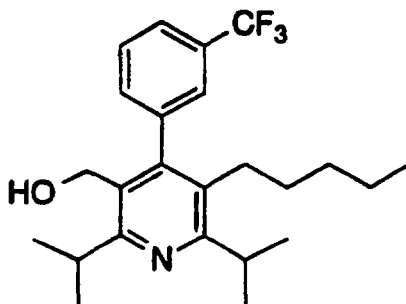
Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3-trifluoromethyl)phenyl-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) (reported as a 6:1 mixture of olefin isomers): δ 0.67-0.87 (m, 3H), 1.08-1.38 (m, 14H), 1.90 (m, 2H), 3.20-3.50 (m, 2H), 4.39 (qd, J=12.0, 5.0 Hz, 2H), 5.24-5.50 (m, 1H), 5.93-

30

0 6.02 (m, 1H), 7.37-7.62 (m, 3H). mp 100-103°C. R<sub>f</sub> 0.36 (10% ethyl acetate/n-hexane).

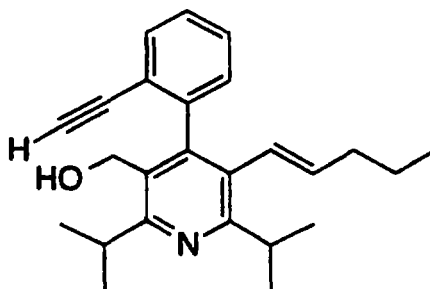
### EXAMPLE 155



### 2,6-Diisopropyl-3-hydroxymethyl-4-(3-trifluoromethyl)phenyl-5-pentylpyridine

10 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-trifluoromethyl)phenyl-5-(pent-1-enyl)pyridine (Example 154) by the procedure described in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J=6.5 Hz, 3H), 1.07-1.39 (m, 18H), 2.24 (m, 2H), 3.24 (m, 1H), 3.42 (m, 1H), 4.31 (qd, J=12.0, 5.0 Hz, 2H), 7.42 (d, J=8.0 Hz, 1H), 7.50 (s, 1H), 7.57 (t, J=8.0 Hz, 1H), 7.67 (d, J=8.0 Hz, 1H). mp 96-97°C. R<sub>f</sub> 0.36 (10% ethyl acetate/n-hexane).

### EXAMPLE 156



### 2,6-Diisopropyl-3-hydroxymethyl-4-(2-ethynylphenyl)-5-(pent-1-enyl)-pyridine

#### Step A: Diethyl 2,6-diisopropyl-4-(2-iodophenyl)pyridine-3,5-dicarboxylate

20 Prepared from 2-iodobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 125, Steps A-B. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.94 (t, J= 7.0 Hz, 6H), 1.30 (d, J= 6.6 Hz, 6H), 1.34 (d, J= 6.6 Hz, 6H), 3.19 (septet, J= 6.6 Hz, 2H), 4.0 (q, J= 7.0 Hz, 4H), 7.0-7.40 (m, 3H), 7.85 (m, 1H).

0

**Step B:**     Diethyl 2,6-diisopropyl-4-[(2-trimethylsilylethynyl)phenyl]pyridine-3,5-dicarboxylate

A solution of 1.50 g (3 mmole) of the intermediate obtained in Step A in toluene was treated with 1.48 g (15 mmole) of trimethylsilyl acetylene, 87.1 g (0.86 mol) of triethylamine, 0.1 g (0.15 mmol) of *bis*(triphenylphosphine) palladium(II) chloride, 0.2 g (0.8 mmole) of triphenyl phosphine and 0.2 g (1.17 mmole) of copper iodide. This reaction mixture was stirred at rt for 1hr and heated at 90°C, in a sealed reaction vessel, for 16 hrs. The reaction mixture was cooled to temperature, filtered through Celite, and stripped to give a dark oil which upon purification by flash silica gel chromatography to yield 1.22 g (2.5 mmole) of the product. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.0 (s, 9H), 0.93 (t, J= 7.0, 6H), 1.32 (d, J= 6.6 Hz, 6H), 1.33 (d, J=6.6 Hz, 6H), 3.18 (septet, J= 6.6, 2H), 3.90 (q, J= 7.0 Hz, 4H), 7.20-7.50 (m, 4H).

**Step C:**     Diethyl 2,6-diisopropyl-4-(2-ethynylphenyl)pyridine-3,5-dicarboxylate

A solution of 5.68 g (11.9 mmole) of the intermediate obtained in Step B in 800 mL ethanol was treated with 2.8 g (20.3 mmole) of potassium carbonate and the reaction mixture was allowed to stir at room temperature for 16 hours. The mixture was diluted with ethyl acetate and washed with saturated aqueous solution of ammonium chloride, brine and separated. The organic layer was dried over magnesium sulfate, filtered and concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography, eluting with 10 ethyl acetate/n-hexane, to give 3.95 g (9.6 mmole) of the product. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.90 (t, J= 7.0 Hz, 6H), 1.32 (m, 12H), 2.97 (s, 1H), 3.21 (septet, J=6.6, 2H), 3.90 (q, J= 7.0, 4H), 7.2-7.6 (m, 4H).

**Step D:**     Ethyl 2,6-diisopropyl-4-(2-ethynylphenyl)-5-(pent-1-enyl)-pyridine-3-carboxylate

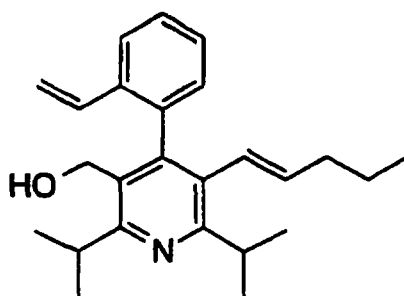
Prepared from the intermediate obtained in Step C by the procedures described in Example 125, Steps A-E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.68 (t, J=7.4 Hz, 3H), 0.88 (td, J=7.0, 2.4 Hz, 3H), 1.20-1.40 (m, 14H), 1.88 (tdd, J=7.0, 7.0, 1.1 Hz, 2H), 2.92 (d, J= 2.4 Hz, 1H), 3.0-3.40 (m, 2H), 3.90 (m, 2H), 5.28 (dt, J=16.2, 7.0 Hz, 1H), 6.15 (dt, J=16.2, 1.5 Hz, 1H), 7.10-7.60 (m, 4H).

**Step E:**     2,6-Diisopropyl-3-hydroxymethyl-4-(2-ethynylphenyl)-5-(pent-1-enyl)pyridine

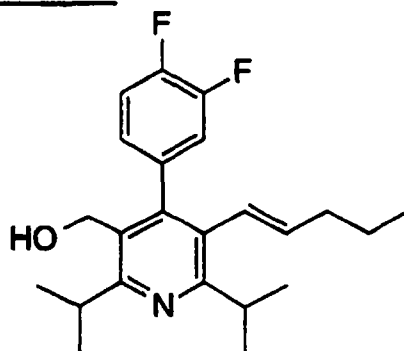
The title compound was prepared from the intermediate obtained in Step D

- 0 by the procedure described in Example 125, Step F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a mixture of olefin isomers):  $\delta$  0.81 (t,  $J = 7.4$  Hz, 3H), 1.0-1.40 (m, 15H), 1.75 (m, 2H), 2.98 (d,  $J = 3.3$  Hz, 1H), 3.20-3.60 (m, 2H), 4.20-4.50 (m, 2H), 5.40 (m, 1H), 6.0 (m, 1H), 7.0-7.60 (m, 4H).  $R_f = 0.23$  (10% ethyl acetate/n-hexane).

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EXAMPLE 1572,6-Diisopropyl-3-hydroxymethyl-4-(2-ethenylphenyl)-5-pentylpyridine

- 10 The title compound was prepared from ethyl 2,6-diisopropyl-3-hydroxymethyl-4-(2-ethynylphenyl)-5-(pent-1-enyl)pyridine-3-carboxylate by the procedure described in Example 125, Step F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a mixture of olefin isomers):  $\delta$  0.60-0.90 (m, 3H), 1.0-1.40 (m, 15H), 1.60-1.90 (m, 2H), 3.20-3.50 (m, 2H), 4.20-4.40 (m, 2H), 5.14 (dt,  $J = 11.0, 1.0$  Hz, 1H), 5.40 (m, 1H),  
15 5.90 (m, 1H), 6.30 (m, 1H), 7.0-7.70 (m, 4H). FAB-MS: calculated for  $\text{C}_{25}\text{H}_{33}\text{NO}$  363.5; found 364 ( $M+H$ , 100%).  $R_f$  0.28 (10% ethyl acetate/n-hexane).

EXAMPLE 158

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2,6-Diisopropyl-3-hydroxymethyl-4-(3,4-difluorophenyl)-5-(pent-1-enyl)pyridine

Step A: Ethyl 2,6-diisopropyl-4-(3,4-difluorophenyl)-5-(pent-1-enyl)pyridine-3-carboxylate

0 Prepared from 3,4-difluorobenzaldehyde, ethyl isobutyrylacetate and concentrated ammonium hydroxide by the procedures described in Example 1, Steps A-E.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a 8:1 mixture of olefin isomers):  $\delta$  0.78 (m, 3H), 1.03 (m, 3H), 1.18-1.33 (m, 14H), 1.97 (m, 2H), 3.04 (m, 1H), 3.38 (m, 1H), 4.04 (m, 2H), 5.30-5.45 (m, 1H), 6.02 (m, 1H), 6.89-7.17 (m, 3H).

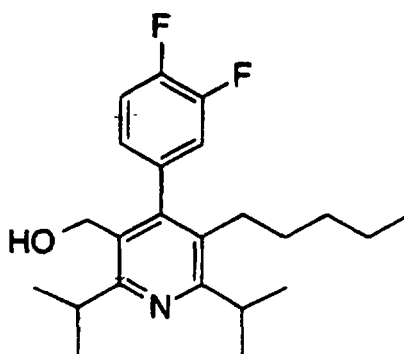
5

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-(3,4-difluorophenyl)-5-(pent-1-enyl)pyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 125, Step F.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) (reported as a mixture of olefin isomers):  $\delta$  0.75 (m, 3H), 1.05-1.38 (m, 14H), 1.90 (m, 2H), 3.35 (m, 2H), 4.35 (m, 2H), 5.25 (m, 1H), 5.91 (m, 1H), 6.80-7.20 (m, 4H). mp 105-106°C.  $R_f$ =0.30 (10% ethyl acetate/n-hexane).

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### EXAMPLE 159



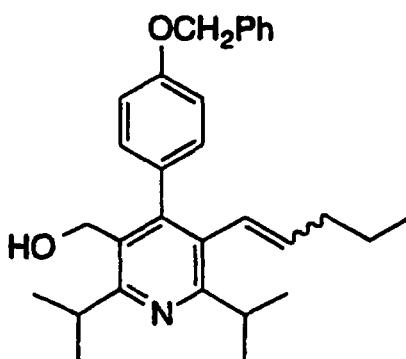
### 2,6-Diisopropyl-3-hydroxymethyl-4-(3,4-difluorophenyl)-5-pentyl-pyridine

20 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3,4-difluorophenyl)-5-(pent-1-enyl)pyridine (Example 158) by the procedure described in Example 126.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.81 (t,  $J$ =7.0 Hz, 3H), 1.12 (m, 4H), 1.30 (m, 14H), 2.27 (m, 2H), 3.24 (m, 1H), 3.41 (m, 1H), 4.32 (d,  $J$ =4.0 Hz, 2H), 6.95 (m, 1H), 7.06 (m, 1H), 7.25 (m, 1H). mp 106-107°C.  $R_f$  0.30 (10% ethyl acetate/n-hexane).

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EXAMPLE 1602,6-Diisopropyl-3-hydroxymethyl-4-(4-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

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Step A: Diethyl 1,4-dihydro-2,6-diisopropyl-4-(4-benzyloxyphenyl)-3,5-pyridinedicarboxylate

To 4-benzyloxybenzaldehyde (24.3 g, 114 mmol) and ethyl isobutyryl acetate (37.8 g, 239 mmol) were added ethanol (50 mL), acetic acid (1 mL), and piperidine (1.7 mL). The mixture was stirred under an argon atmosphere at 25°C for 12 hours. Freshly prepared sodium ethoxide in ethanol (15%, 15 mL) was then added and the reaction mixture was stirred at 25°C for 2 hours. To this mixture was added a solution of ammonium acetate (13.1 g, 171 mmol) in acetic acid (100 mL). The reaction was heated at reflux for 14 h and was then cooled to 25°C, during which time a white precipitate developed. To the mixture was added a 40% (v/v) solution of 2-propanol in water. The mixture was stirred for 0.5 hours at 25°C and was then cooled to -20°C for 2 hours. The white solid was collected by filtration with vacuum and washed with a 50% (v/v) solution of isopropanol in water to provide the product (41.8 g, 85 mmol, 75%) as a pure white solid (mp 140-141°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.14-1.29 (m, 18H), 4.10 (q, J = 6.9 Hz, 4H), 4.19 (sept, J = 6.9 Hz, 2H), 4.95 (s, 1H), 5.01 (s, 2H), 6.12 (s, 1H), 6.82 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 7.27-7.45 (m, 5H).

Step B: Diethyl 2,6-diisopropyl-4-(4-benzyloxyphenyl)-3,5-pyridine-dicarboxylate

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To a solution of the intermediate obtained in Step A (39.72 g, 81 mmol) in acetone (400 mL) stirred under argon at 25°C was added an aqueous solution of ammonium cerium(IV) nitrate ("CAN") (1M, 162 mL). The mixture was stirred at 25°C for 0.5 hours and the acetone was then removed under reduced pressure. The resultant mixture was diluted with dichloromethane (400 mL) and poured into

30

- 0 water (100 mL). The organic layer was saved and the aqueous layer is extracted with dichloromethane (100 mL). The combined organic layer was washed with a saturated solution of sodium chloride (100 mL), dried over sodium sulfate, and concentrated under reduced pressure to afford the product as a white powder (39.51 g, 100%) (mp 87°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.96 (t, J = 6.9 Hz, 6H),  
5 1.31 (d, J = 6.6 Hz, 12H), 3.10 (sept, J = 6.6 Hz, 2H), 4.01 (q, J = 7.5 Hz, 4H), 5.09 (s, 2H), 6.95 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 8.7 Hz, 2H), 7.32-7.46 (m, 5H).

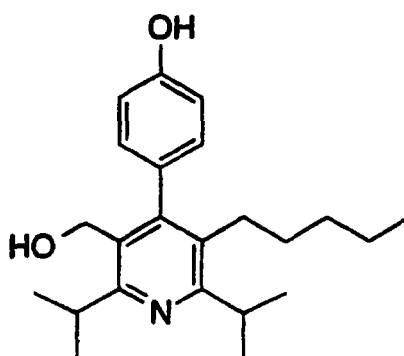
Step C: Ethyl 2,6-diisopropyl-4-(4-benzyloxyphenyl)-5-(pent-1-enyl)-3-pyridinecarboxylate

- 10 Prepared from the intermediate obtained in Step B by the procedure described in Example 1, Steps D-F. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.21-1.34 (m, 14H), 1.96 (q, J = 7.2 Hz, 2H), 3.05 (septet, J = 6.6 Hz, 1H), 3.42 (septet, J = 6.6 Hz, 1H), 3.94-4.03 (m, 2H), 5.06-5.12 (m, 2H), 5.32-5.42 (m, 1H), 6.03-6.15 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 7.10 (d, J = 9.0 Hz,  
15 2H), 7.34-7.47 (m, 5H).

Step D: 2,6-Diisopropyl-3-hydroxymethyl-4-(4-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

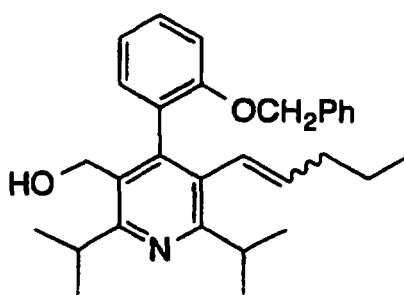
- 20 The intermediate obtained in Step C (6 g, 12.35 mmol) was dissolved in anhydrous tetrahydrofuran ("THF") (130 mL) under argon and treated dropwise at room temperature with lithium aluminum hydride ("LAH") (1.0 M in THF, 24.7 mL, 24.7 mmol). The reaction mixture was stirred at reflux for 3 hr, cooled to room temperature and quenched by the addition of 0.9 mL H<sub>2</sub>O, 0.9 mL 20% aqueous NaOH, and 2.7 mL H<sub>2</sub>O. The resulting suspension was filtered through a cake of  
25 Celite and the filtrate concentrated and purified by chromatography through silica (20% ethyl acetate/hexane) to afford 4.76 g of the title compound as a colorless wax. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.73-0.83 (m, 3H), 1.37-1.70 (m, 14H), 1.56 (s, 1H), 1.92 (dq, J = 0.90, 6.90 Hz, 2H), 3.41 (δ, J = 6.60, 13.20, 24.60 Hz, 2H), 4.43 (d, J = 5.1 Hz, 2H), 5.10 (s, 2H), 5.27-5.37 (m, 1H), 5.97 (d, J = 15.90 Hz, 1H), 6.97-7.09 (m,  
30 4H), 7.35-7.48 (m, 5H).

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EXAMPLE 1612,6-Diisopropyl-3-hydroxymethyl-4-(4-hydroxyphenyl)-5-pentylpyridine

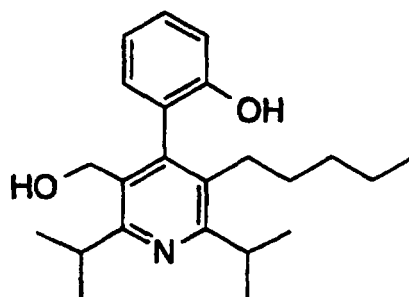
5        2,6-Diisopropyl-3-hydroxymethyl-4-(4-benzyloxyphenyl)-5-(pent-1-enyl)pyridine (Example 160) (500 mg, 1.13 mmol) was dissolved in absolute ethanol (10 mL) under argon, treated with 10% palladium on carbon (15 mg), then stirred under a hydrogen atmosphere for 14 h. After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed and the residue is purified by flash chromatography (5% methanol-methylene chloride) to yield 371 mg of the title compound as a waxy solid (mp 158.5°C). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.79 (t, J = 6.6 Hz, 3H), 1.06-1.36 (m, 21H), 2.24-2.31 (m, 2H), 3.22 (sept, J = 6.6 Hz, 1H), 3.40 (sept, J = 6.6 Hz, 1H), 4.36 (d, J = 5.4 Hz, 2H), 4.85 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H).

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EXAMPLE 1622,6-Diisopropyl-3-hydroxymethyl-4-(2-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

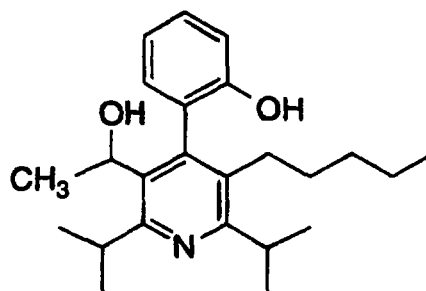
20        The title compound was prepared as a waxy solid from 2-benzyloxybenzaldehyde by the procedures described in Example 160. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.69-0.74 (m, 3H), 1.07-1.38 (m, 14H), 1.69-1.79 (m, 1H) 1.84-1.99 (m, 2H), 3.26-3.54 (m, 2H) 4.28-4.46 (m, 2H), 4.90-5.09 (m, 2H), 5.26-5.47 (m, 1H), 25        6.00 (dd, J = 15.9, 1.2 Hz, 1H), 7.05-7.10 (m, 5H), 7.24-7.36 (m, 4H).

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**EXAMPLE 163****5    2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-pentylpyridine**

The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(2-benzyloxyphenyl)-5-(pent-1-enyl)pyridine (Example 162) by the method detailed in Example 161. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75-0.73 (m, 3H), 1.09-1.15 (m, 4H), 1.30-1.37 (m, 14H), 1.70-1.73 (m, 1H), 2.16-2.28 (m, 1H), 2.32-2.42 (m, 1H), 3.22-3.32 (m, 1H), 3.39-3.51 (m, 1H), 4.29-4.35 (m, 1H), 4.48-4.54 (m, 1H), 5.14 (br s, 1H), 7.02-7.05 (m, 3H), 7.28-7.36 (m, 1H). FAB-MS: calcd for (C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub>) 355, found 356 (M + 1). Anal. calc. for C<sub>23</sub>H<sub>33</sub>NO<sub>2</sub>: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.63; H, 9.12; N, 3.75. mp 125.5°C.

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**EXAMPLE 164****20    2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-pentylpyridine****Step A:    2,6-Diisopropyl-(2-benzyloxyphenyl)-5-pentyl-3-pyridine-carboxaldehyde**

2,6-Diisopropyl-3-hydroxymethyl-4-(2-benzyloxyphenyl)-5-(pent-1-enyl)pyridine (Example 162) (680 mg, 1.53 mmol) was dissolved in 15 mL of methylene chloride under an argon atmosphere and treated with a mixture of Celite (661 mg) and pyridinium chlorochromate ("PCC") (661 mg, 2 eq). The reaction was stirred at

25

0 room temperature for 1.5 h. The suspension was filtered through a pad of silica and the pad was washed with 50 mL CH<sub>2</sub>Cl<sub>2</sub> and the filtrate was combined and concentrated *in vacuo* to afford 572.4 mg of product (84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.70 (t, J = 7.2 Hz, 3H), 1.08-1.35 (m, 15H), 1.85-1.93 (m, 1H), 3.26-3.45 (m, 1H), 3.87-3.97 (m, 1H), 4.97-5.06 (m, 2H), 5.27-5.50 (m, 1H), 6.01-6.10 (m, 1H), 6.94-  
5 7.34 (m, 9H), 9.82 (d, J = 3.6 Hz, 1H).

Step B: 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-benzyloxyphenyl)-5-(pent-1-enyl)pyridine

Prepared as a separable mixture of two diastereomers from the intermediate  
10 from Step A by the method detailed in Example 101, Step B. The two diastereomers were separated by flash chromatography on silica eluting with 10% ethyl acetate-hexane.

Diastereomer 1: colorless oil, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.68-1.91 (m 23H), 3.19-3.40 (m, 1H), 3.77 (sept, J = 6.6 Hz, 1H), 4.69-4.79 (m, 1H), 4.94 (dd, J =  
15 12.3, 3.9 Hz, 1H), 5.05 (d, J = 12.3 Hz, 1H), 5.20-5.43 (m, 1H), 5.90-6.05 (m, 1H), 6.94-7.38 (m, 9H). FAB-MS: calcd for (C<sub>31</sub>H<sub>39</sub>NO<sub>2</sub>) 457, found 458 (M + 1).

Diastereomer 2: colorless oil, <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.69 (t, J = 7.2 Hz, 3H), 1.05-1.40 (m, 17H), 1.67-1.73 (m, 1H), 1.80-1.88 (m, 2H), 3.18-3.41 (m, 1H),  
20 3.68-3.80 (m, 1H), 4.84-5.08 (m, 3H), 5.25-5.42 (m, 1H), 5.86-6.08 (m, 1H), 6.90-7.38 (m, 9H). FAB-MS: calcd for (C<sub>31</sub>H<sub>39</sub>NO<sub>2</sub>) 457, found 458 (M + 1).

Step C: 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-pentylpyridine

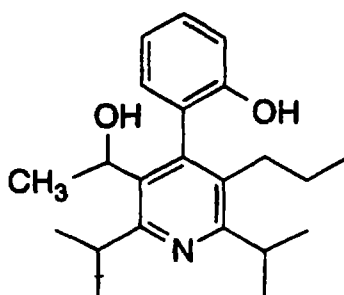
The diastereomeric mixture of intermediates from Step B (39 mg) was  
25 dissolved in absolute ethanol (1.5 mL) under argon, treated with 10% palladium on carbon (4 mg), then stirred under a hydrogen atmosphere for 8 hr. After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed and the product dried *in vacuo* to afford 32 mg of the title compound as a colorless solid. Preparative thin layer chromatography  
30 ("prep TLC") using a 20% ethyl acetate-hexane mixture as the eluent provided the two diastereomers.

Diastereomer 1 (D1) (11.2 mg): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.68 (t, J = 7.30 Hz, 3H), 0.99-1.03 (m, 4H), 1.19-1.34 (m, 17H), 1.62 (d, J = 3.60 Hz, 1H), 1.97-2.07 (m, 1H), 2.16-2.26 (m, 1H), 3.14 (septet, J = 7.30 Hz, 1H), 3.67 (septet, J = 7.30  
35 Hz, 1H), 4.72 (br s, 1H), 4.83 (dq, J = 4.20, 6.60 Hz, 1H), 6.89-6.97 (m, 3H), 7.19-7.25 (m, 1H). FAB-MS: calcd for (C<sub>24</sub>H<sub>35</sub>NO<sub>2</sub>) 369, found 370 (M + 1).

Diastereomer 1 (D1) could be resolved into the constituent enantiomers as follows. A Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 2% (1% acetic acid, 99% ethanol) and 98% hexane at a flow rate of 175 mL/min. The sample was dissolved in mobile phase (20 mg/mL) and 5 mL aliquots were injected at 30 minute intervals. The effluent was monitored at 280 nm and two fractions (corresponding to the enantiomers) were collected at (15-17 min, 100% ee) and (19-26 min, >99% ee), respectively.

Diastereomer 2 (D2) (11.8 mg):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.68 (t,  $J$  = 6.60 Hz, 3H), 0.99-1.03 (m, 4H), 1.16-1.32 (m, 17H), 1.86 (br s, 1H), 2.00-2.10 (m, 1H), 2.19-2.29 (m, 1H), 3.14 (septet,  $J$  = 6.60 Hz, 1H), 3.67 (septet,  $J$  = 6.60 Hz, 1H), 4.57 (q,  $J$  = 6.60 Hz, 1H), 4.76 (br s, 1H), 6.84-6.93 (m, 3H), 7.19-7.24 (m, 1H). FAB-MS: calcd for ( $\text{C}_{24}\text{H}_{35}\text{NO}_2$ ) 369, found 370 ( $\text{M}+1$ ).

### EXAMPLE 165



### 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-propylpyridine

Step A: Diethyl-2,6-diisopropyl-4-(2-benzyloxyphenyl)-3,5-pyridine-dicarboxylate

Prepared from 2-benzyloxybenzaldehyde by the methods detailed in Example 160, Steps A-B.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.87 (t,  $J$  = 6.9 Hz, 6H), 1.32 (d,  $J$  = 6.6 Hz, 6H), 1.33 (d,  $J$  = 6.6 Hz, 6H), 3.19 (sept,  $J$  = 6.6 Hz, 2H), 3.97 (q,  $J$  = 7.2 Hz, 4H), 5.01 (s, 2H), 6.88 (d,  $J$  = 8.1 Hz, 1H), 6.94 (dt,  $J$  = 7.2, 0.6 Hz, 1H), 7.16 (dd,  $J$  = 7.8, 1.8 Hz, 1H), 7.14-7.30 (m, 6H).

Step B: 5-Ethoxycarbonyl-2,6-diisopropyl-4-(2-benzyloxyphenyl)-3-pyridinecarboxaldehyde

Prepared from the intermediate from Step A by the methods detailed in Example 1, Steps D-E.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.91 (t,  $J$  = 6.6 Hz, 3H), 1.30-

- 0 1.39 (m, 12H), 3.18 (septet,  $J = 6.0$  Hz, 1H), 3.91-4.03 (m, 3H), 5.04 (dd,  $J = 6.6, 12.6$  Hz, 2H), 6.96-7.05 (m, 2H), 7.17-7.28 (m, 6H), 7.34-7.40 (m, 1H).

Step C: 2,6-Diisopropyl-4-(2-benzyloxyphenyl)-3-ethoxycarbonyl-5-(prop-1-enyl)pyridine

- 5 Ethyltriphenylphosphonium bromide (4.01 g, 10.8 mmol) was suspended in anhydrous THF (130 mL) under argon and stirred at  $-78^{\circ}\text{C}$ . A 1.6 M solution of *n*-butyllithium in hexanes (6.75 mL, 10.8 mmol) was added dropwise. The reaction mixture was allowed to come to  $0^{\circ}\text{C}$  and stirred at that temperature for 1 hr. The resulting brightly colored solution was cooled again to  $-78^{\circ}\text{C}$  and treated dropwise  
10 with a solution of the intermediate obtained in Step B (4.0 g, 9.0 mmol) in THF (20 mL). The reaction mixture was allowed to stir at  $25^{\circ}\text{C}$  for 3 hrs, then quenched by the addition of water (5 mL). The THF was removed *in vacuo*, the residue partitioned between ethyl ether (200 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over  $\text{MgSO}_4$  and concentrated. Flash  
15 chromatography through silica (5% ethyl acetate/hex) afforded 4.1 g of the product (E, Z mixture) as a viscous oil.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.86-0.92 (m, 3H), 1.40-1.21 (m, 15H), 3.06-3.28 (m, 2H), 3.91-4.01 (m, 2H), 5.00 (br s, 2H), 5.29-5.56 (m, 1H), 6.10-6.19 (m, 1H), 6.89-6.97 (m, 2H), 7.08-7.12 (m, 1H), 7.15-7.19 (m, 2H), 7.22-7.29 (m, 4H).

20

Step D: 2,6-Diisopropyl-3-hydroxymethyl-4-(2-benzyloxyphenyl)-5-(prop-1-enyl)pyridine

- Prepared from the intermediate from Step C by the method detailed in Example 160, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.21-1.60 (m, 15H), 1.90-1.95  
25 (m, 1H), 3.18-3.53 (m, 2H), 4.26-4.58 (m, 2H), 4.87-4.94 (m, 1H), 5.06 (d,  $J = 12.3$  Hz, 1H), 5.27-5.57 (m, 1H), 5.95-6.05 (m, 1H), 7.00-7.06 (m, 5H), 7.22-7.37 (m, 4H).

Step E: 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-propylpyridine

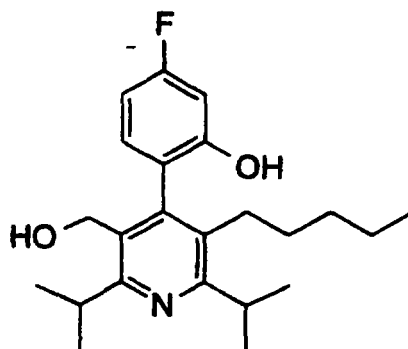
- 30 The intermediate from Step D was converted into the title compound by the methods detailed in Example 164, Steps A-C. The diastereomers were separated by radial band chromatography using a gradient eluent of 100% hexane to 5% ethyl acetate-hexane.

- Diastereomer 1 (D1):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.66 (t,  $J = 7.50$  Hz, 3H),  
35 1.15-1.34 (m, 15H), 1.59 (br s, 1H), 1.96-2.06 (m, 1H), 2.15-2.25 (m, 1H), 3.15 (sept,  $J = 6.60$  Hz, 1H), 3.56 (sept,  $J = 6.60$  Hz, 1H), 4.70 (br s, 1H), 4.81-4.87 (m, 1H), 6.90-6.97 (m, 3H), 7.19-7.26 (m, 1H). FAB-MS: calcd for ( $\text{C}_{22}\text{H}_{31}\text{NO}_2$ ) 341, found 342 ( $M+1$ ).

Diastereomer 1 (D1) was resolved into its constituent enantiomers as follows. A Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column (BRB-9466AD; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 25% hexane and 75% of a mixture of (15% THF in heptane) at 150 mL/min. The sample was dissolved in mobile phase (10 mg/mL) and 5 mL aliquots were injected at 35 min intervals. The effluent was monitored at 280 nm. Peaks overlapped and were thus shaved. Mixed fractions were then evaporated and reinjected. The collected enantiomers were assayed off line on an analytical column (BRB-9705A) at 1.5 mL/min with a mobile phase of 1% (1% acetic acid in ethanol) and 99% hexane. The low  $R_t$  enantiomer from the preparative column was the high  $R_t$  enantiomer on the analytical column with  $R_t$  = 8.80 min; 98.8% ee. The high  $R_t$  enantiomer from the preparative column was the low  $R_t$  enantiomer on the analytical column with  $R_t$  = 3.71 min; 81% ee.

Diastereomer 2 (D2):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.72 (t,  $J$  = 7.50 Hz, 3H), 1.22-1.36 (m, 15H), 2.03-2.15 (m, 1H), 2.23-2.33 (m, 1H), 2.56 (d,  $J$  = 3.0 Hz, 1H), 3.21 (septet,  $J$  = 6.60 Hz, 1H), 3.73 (septet,  $J$  = 6.60 Hz, 1H), 4.56-4.63 (dq,  $J$  = 3.0, 6.0 Hz, 1H), 5.66 (br s, 1H), 6.88-6.99 (m, 3H), 7.25-7.28 (m, 1H). FAB-MS: calcd for ( $\text{C}_{22}\text{H}_{31}\text{NO}_2$ ) 341, found 342 ( $M+1$ ).

#### EXAMPLE 166



#### 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-2-hydroxy)phenyl]-5-pentylpyridine

##### 25 Step A: 2-Benzyloxy-4-fluorobromobenzene

To a solution containing 2-bromo-5-fluorophenol (50 g, 0.26 mol) in 500 mL acetone was added potassium carbonate (54.2 g, 0.39 mmol) and benzyl bromide (34.3 mL, 0.288 mol). The reaction was heated at reflux under an argon atmosphere for 2 h and then allowed to cool to 25°C. The acetone was removed under reduced pressure and the residue was taken up in ether (400 mL). The organic layer was

0 washed with water (5 x 100 mL) and brine (1 x 100 mL) and then dried (MgSO<sub>4</sub>). The solution was then concentrated under reduced pressure and subjected to flash chromatography using hexane as the eluent. In this manner, 2-benzyloxy-4-fluorobenzene was obtained as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 5.14 (s, 2H), 6.57-6.63 (m, 1H), 6.69 (dd, J = 2.7, 10.2 Hz, 1H), 7.32-7.52 (m, 6H).

5

Step B: 2-Benzyloxy-4-fluorobenzaldehyde

To a slurry of magnesium (9.52 g, 0.39 mol) in THF (25 mL) in a 1 L round bottom flask fitted with a condenser was added the intermediate obtained in Step A (1 g). A vigorous reflux commenced at once. To this refluxing mixture was added  
10 a solution of the intermediate from Step A (109 g) at a rate which maintained reflux. After completion of addition the reaction was allowed to proceed until it cooled to 25°C and was then heated at reflux for 1 h. The reaction was allowed to cool to 25°C and DMF (48 mL) was then added portionwise. The reaction was allowed to  
15 cool to 25°C and was then filtered through a plug of Celite. The THF was removed under reduced pressure and the residue was dissolved in ethyl acetate (500 mL) and washed sequentially with water (100 mL), 10% HCl (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The resultant residue was  
20 purified by flash chromatography (10% ethyl acetate-hexane) to provide 77.3 g of 2-benzyloxy-4-fluorobenzaldehyde. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 5.16 (s, 2H), 6.70-6.76 (m, 2H), 7.34-7.44 (m, 5H), 7.87-7.92 (m, 1H), 10.43 (s, 1H). FAB-MS: calcd for (C<sub>14</sub>H<sub>11</sub>O<sub>2</sub>F) 230; found 231 (M+1).

25 Step C: 2,6-Diisopropyl-3-hydroxymethyl-4-[(2-benzyloxy-4-fluoro)phenyl]-5-(pent-1-enyl)pyridine

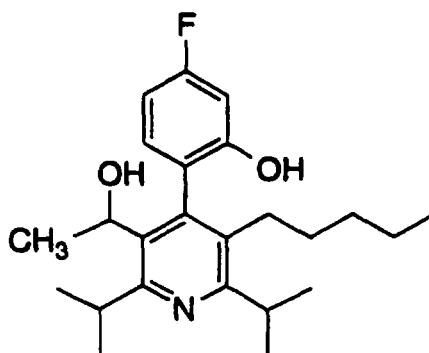
Prepared from the intermediate obtained in Step B by the methods described in Example 160, Steps A-D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.73 (t, J = 7.4 Hz, 3H), 1.09-1.36 (m, 14H), 1.63-1.73 (m, 2H), 1.89 (q, J = 6.9 Hz, 1H), 3.25 (septet, J = 6.6 Hz, 1H), 3.46 (d septet, J = 2.7, 6.6 Hz, 1H), 4.29-4.42 (m, 2H), 4.89-5.06 (m, 2H),  
30 5.24-5.47 (m, 1H), 5.95-6.00 (m, 1H), 6.70-6.79 (m, 3H), 7.00-7.07 (m, 5H). FAB-MS: calcd for (C<sub>30</sub>H<sub>36</sub>NO<sub>2</sub>F) 461, found 462.

Step D: 2,6-Diisopropyl-3-(hydroxymethyl)-4-[(4-fluoro-2-hydroxy)phenyl]-5-pentylpyridine

35 The title compound was prepared as a racemate from the intermediate obtained in Step C by the method detailed in Example 161. <sup>1</sup>H NMR (300 MHz,

- 0 CDCl<sub>3</sub>):  $\delta$  0.78 (t,  $J$  = 6.6 Hz, 3H), 1.09-1.35 (m, 18H), 1.65 (t,  $J$  = 5.0 Hz, 1H), 2.13-2.23 (m, 1H), 2.28-2.38 (m, 1H), 3.24 (sept,  $J$  = 6.6 Hz, 1H), 3.39 (sept,  $J$  = 6.6 Hz, 1H), 4.29 (dd,  $J$  = 11.1, 5.0 Hz, 1H), 4.52 (dd,  $J$  = 11.1, 5.1 Hz, 1H), 5.45 (bs, 1H), 6.71-6.78 (m, 2H), 6.95-7.00 (m, 1H). FAB-MS: calcd for (C<sub>23</sub>H<sub>32</sub>NO<sub>2</sub>F) 373, found 374 (M + 1).  $R_f$  = 0.15 (20% ether-hexanes). mp 152°C.

5

EXAMPLE 167

10 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-[(4-fluoro-2-hydroxy)phenyl]-5-pentylpyridine

- The title compound was prepared as two separable diastereomers from 2,6-diisopropyl-3-hydroxymethyl-4-[(2-benzyloxy-4-fluoro)phenyl]-5-(pent-1-enyl)pyridine (Example 166, Step C) by the methods detailed in Example 164, Steps A-C. The diastereomers were separated by radial band chromatography using a gradient eluent of 100% hexane to 20% ether-hexane.

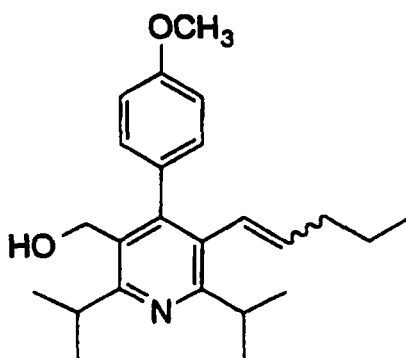
- 15 Diastereomer 1 (D1): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  0.80 (t,  $J$  = 6.6 Hz, 3H), 1.10-1.42 (m, 21H), 1.64 (d,  $J$  = 3.6 Hz, 1H), 2.03-2.13 (m, 1H), 2.21-2.31 (m, 1H), 3.15-3.26 (septet, 1H), 3.54-3.65 (septet, 1H), 4.89-4.98 (m, 1H), 4.99 (br s, 1H), 6.69-6.75 (m, 2H), 6.94-6.99 (d,  $J$  = 2.7, 6.5, 6.5 Hz, 1H). FAB-MS: calcd for (C<sub>24</sub>H<sub>34</sub>NO<sub>2</sub>F) 387, found 388 (M + 1).  $R_f$  = 0.41 (40% ether-hexanes). mp 124-126°C.

- Diastereomer 1 (D1) was resolved into its constituent enantiomers as follows. A Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 2% (1% acetic acid, 99% ethanol) and 98% hexane at a flow rate of 175 mL/min. The sample was dissolved in mobile phase (50 mg/mL) and 5 mL aliquots were injected at 30 min intervals. The effluent was monitored at 280 nm and two fractions (corresponding to the two enantiomers) were collected at (13-18 min, 100% ee) and (18.5-27 min, >99% ee), respectively.

30

- 0 Diastereomer 2 (D2):  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.78 (t,  $J$  = 6.5 Hz, 3H), 1.06-1.40 (m, 21H), 1.75 (d,  $J$  = 3.6 Hz, 1H), 2.06-2.16 (m, 1H), 2.26-2.37 (m, 1H), 3.21 (septet,  $J$  = 6.6 Hz, 1H), 3.74 (septet,  $J$  = 6.6, 1H), 4.59-4.67 m, 1H), 4.83 (br s, 1H), 6.68-6.75 (m, 2H), 6.86-6.91 ( $\delta$ ,  $J$  = 3.0, 6.6, 6.6 Hz, 1H); FAB-MS: calcd for ( $\text{C}_{24}\text{H}_{34}\text{NO}_2\text{F}$ ) 387, found 388 ( $M + 1$ ).  $R_f$  = 0.24 (40% ether-hexanes). mp 157-  
5 159°C.

### EXAMPLE 168



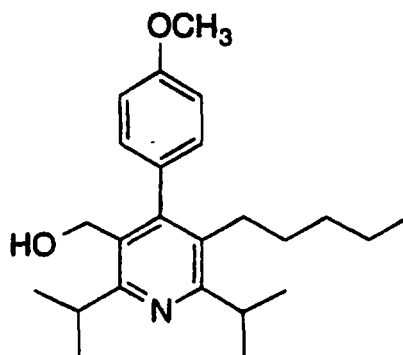
10

#### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methoxyphenyl)-5-(pent-1-enyl)pyridine

- The title compound was prepared from 4-methoxybenzaldehyde by the methods detailed in Example 125.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.76 and 0.81 (t,  $J$  = 7.2 Hz, 3H), 1.12-1.39 (m, 14H), 1.60-1.80 (bs, 1H), 1.86-1.97 (m, 2H), 3.33-3.50 (m, 2H), 3.85 (s, 3H), 4.43 (m, 2H), 5.27-5.48 (m, 1H), 5.93-6.05 (m, 1H), 6.92 (d,  $J$  = 8.4 Hz, 2H), 7.07 (d,  $J$  = 8.4 Hz, 2H). FAB-MS: calcd for ( $\text{C}_{24}\text{H}_{33}\text{NO}_2$ ) 367, found 368 ( $M+1$ ).
- 15

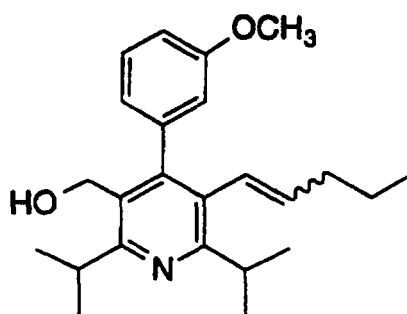
### EXAMPLE 169

20

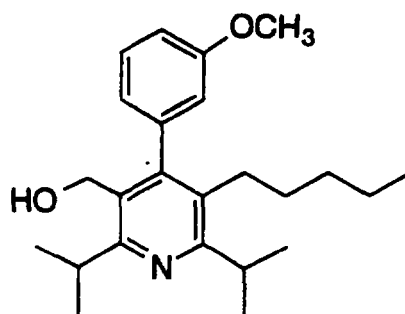


#### 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methoxyphenyl)-5-pentylpyridine

- 0 The title compound was prepared as a white solid from 2,6-diisopropyl-3-hydroxymethyl-4-(4-methoxyphenyl)-5-(pent-1-enyl)pyridine (Example 168) by the methods detailed in Example 126. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.80 (t, J = 6.6 Hz, 3H), 1.08-1.19 (m, 4H), 1.24-1.38 (m, 15H), 2.27-2.33 (m, 2H), 3.24 (sept, J = 6.6 Hz, 1H), 3.42 (sept, J = 6.6 Hz, 1H), 3.87 (s, 3H), 4.35 (d, J = 5.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.7 Hz, 2H). FAB-MS: calcd for (C<sub>24</sub>H<sub>35</sub>NO<sub>2</sub>) 369, found 370 (M + 1). mp 47-49°C.

EXAMPLE 1702,6-Diisopropyl-3-hydroxymethyl-4-(3-methoxyphenyl)-5-(pent-1-enyl)pyridine

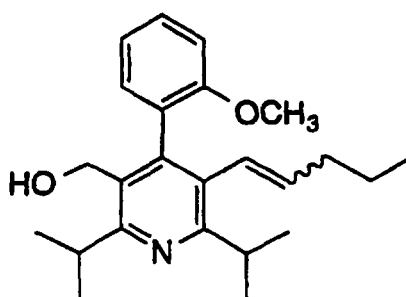
- 15 The title compound was prepared from 3-methoxybenzaldehyde by the methods detailed in Example 125. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 7.5 Hz, 3H), 1.17-1.41 (m, 14H), 1.65 (s, 1H), 1.97 (δ, J = 14.0, 7.2, 1.5 Hz, 2H), 3.39-3.55 (m, 2H), 3.81 (s, 3H), 4.45 (s, 2H), 5.35-5.50 (m, 1H), 6.01-6.09 (m, 1H), 6.73-6.77 (m, 2H), 6.89 (δ, J = 8.1, 2.1, 0.9 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H). FAB-MS: calcd for (C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub>) 367, found 368 (M + 1). mp 71-75°C.

EXAMPLE 1712,6-Diisopropyl-3-hydroxymethyl-4-(3-methoxyphenyl)-5-pentylpyridine

- 25 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-

- 0 (3-methoxyphenyl)-5-(pent-1-enyl)pyridine (Example 170) by the methods detailed  
in Example 126.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.79 (t,  $J$  = 6.6 Hz, 3H), 1.09-1.33 (m,  
7H), 1.30 (d,  $J$  = 6.6 Hz, 6H), 1.33 (d,  $J$  = 6.6 Hz, 6H), 2.25-2.31 (m, 2H), 3.23 (sept,  $J$  =  
6.6 Hz, 1H), 3.42 (sept,  $J$  = 6.6 Hz, 1H), 3.82 (s, 3H), 4.35 (d,  $J$  = 6.0 Hz, 2H), 6.73 (dd,  
5  $J$  = 2.4, 1.5 Hz, 1H), 6.76 (dt,  $J$  = 7.5, 1.4 Hz), 6.93 (d,  $J$  = 8.4, 3.6, 1.2 Hz, 1H), 7.34 (t,  $J$   
= 8.1 Hz, 1H). FAB-MS: calcd for  $(\text{C}_{24}\text{H}_{35}\text{NO}_2)$  369, found 370 ( $M + 1$ ). mp 65-66°.

### EXAMPLE 172

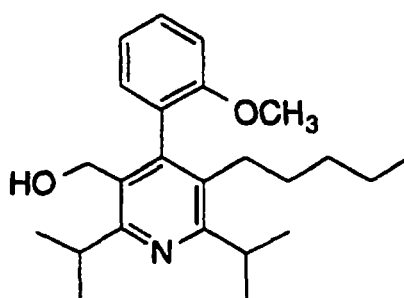


10

#### 2,6-Diisopropyl-3-hydroxymethyl-4-(2-methoxyphenyl)-5-(pent-1-enyl)pyridine

- The title compound was prepared from 2-methoxybenzaldehyde by the  
methods detailed in Example 125.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.82 and 0.72 (t,  $J$   
= 7 Hz, 3H), 1.05-1.47 (m, 15H), 1.80-2.00 (m, 1H), 2.05 (bs, 1H), 3.21-3.60 (m, 2H),  
15 3.75 and 3.76 (s, 3H), 4.27 (d,  $J$  = 11.4 Hz, 1H), 4.43 (d,  $J$  = 11.4 Hz, 1H), 5.25-5.44 (m,  
1H), 6.01-6.07 (m, 1H), 6.93-7.03 (m, 3H), 7.29-7.37 (m, 1H).

### EXAMPLE 173



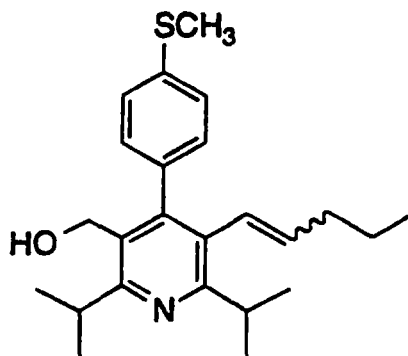
20

#### 2,6-Diisopropyl-3-hydroxymethyl-4-(2-methoxyphenyl)-5-pentylpyridine

- The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-  
(2-methoxyphenyl)-5-(pent-1-enyl)pyridine (Example 172) by the methods detailed  
25 in Example 126.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.77 (t,  $J$  = 6.6 Hz, 3H), 1.06-1.11 (m,  
4H), 1.22-1.38 (m, 14H), 1.87 (dd,  $J$  = 9.3, 3.3 Hz, 1H), 2.14 -2.40 (m, 2H), 3.25 (sept,  $J$

0 = 6.6 Hz, 1H), 3.46 (sept,  $J = 6.6$  Hz, 1H), 3.76 (s, 3H), 4.19 (dd,  $J = 11.7, 3.0$  Hz, 1H), 4.39 (dd,  $J = 11.7, 9.0$  Hz), 7.00-7.08 (m, 3H), 7.35-7.42 (m, 1H).

### EXAMPLE 174



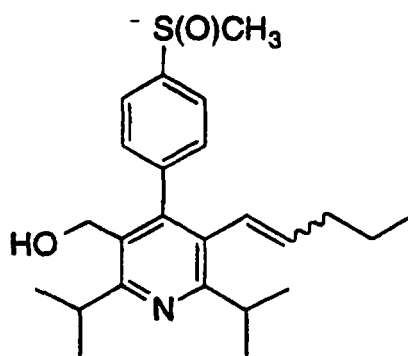
5

### 2,6-Diisopropyl-3-hydroxymethyl-4-[4-(methylthio)phenyl]-5-(pent-1-enyl)pyridine

The title compound was prepared as a thick colorless oil from 4-(methylthio)benzaldehyde by the methods detailed in Example 125.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.66 and 0.72 (t,  $J = 7.5$  Hz, 3H), 1.05-1.32 (m, 14H), 1.51-1.70 (bs, 1H), 1.80-1.89 (m, 2H), 2.43 (s, 3H), 3.12-3.41 (m, 2H), 4.32 (bs, 2H), 5.17-5.40 (m, 1H), 5.85-5.97 (m, 1H), 6.99 (d,  $J = 8.1$  Hz), 7.18 (d,  $J = 8.1$  Hz, 2H).

10

### EXAMPLE 175



15

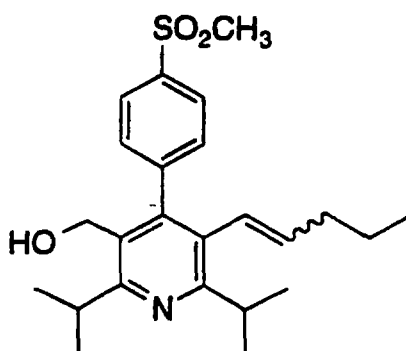
### 2,6-Diisopropyl-3-hydroxymethyl-4-[4-(methylsulfinyl)phenyl]-5-(pent-1-enyl)pyridine

2,6-Diisopropyl-3-hydroxymethyl-4-[4-(methylthio)phenyl]-5-(pent-1-enyl)pyridine (100 mg, 0.261 mmol) (Example 174) was dissolved in methylene chloride (1.5 mL) and stirred at  $0^\circ\text{C}$  under an argon atmosphere. To this mixture was added a solution containing 3-chloroperoxybenzoic acid ("mCPBA") (85%, 53 mg, 0.261 mmol) in methylene chloride (1 mL). The mixture was stirred for 1.5 h at  $0^\circ\text{C}$  and is quenched with the addition of a saturated aqueous solution of  $\text{NaHSO}_3$

20

0 (3 mL). The reaction mixture was further diluted through the addition of water (5 mL) and then extracted with methylene chloride (3 x 10 mL). The combined organic layer was washed sequentially with a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resultant residue was purified by flash chromatography to  
 5 yield the title compound (52 mg, 50%) as a white solid, mp 133-135°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 and 0.69 (t, J = 7.5 Hz, 3H), 1.08-1.36 (m, 14H), 1.70-1.92 (m, 3H), 2.75 and 2.76 (s, 3H), 3.19-3.51 (m, 2H), 4.32-4.40 (m, 2H), 5.20-5.45 (m, 1H), 5.93-6.00 (m, 1H), 7.31-7.38 (m, 2H), 7.59-7.70 (m, 2H). Anal. calc. for C<sub>24</sub>H<sub>33</sub>NO<sub>2</sub>S: C, 71.86; H, 8.29; N, 3.39; S, 7.73. Found: C, 72.14; H, 8.32; N, 3.51; S, 8.02.

10

EXAMPLE 176

15

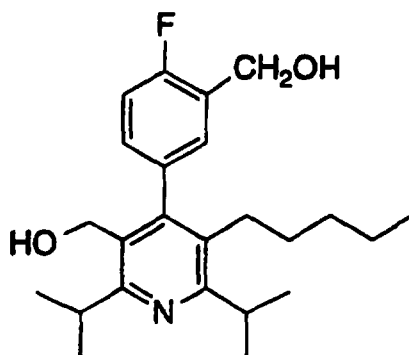
2,6-Diisopropyl-3-hydroxymethyl-4-[4-(methylsulfonyl)phenyl]-5-(pent-1-enyl)pyridine

2,6-Diisopropyl-3-hydroxymethyl-4-[4-(methylsulfonyl)phenyl]-5-(pent-1-enyl)pyridine (100 mg, 0.261 mmol) (Example 174) was dissolved in methylene  
 20 chloride (1.5 mL) and stirred at 0°C under an argon atmosphere. To this mixture was added a solution containing 3-chloroperoxybenzoic acid ("mCPBA") (85%, 53 mg, 0.261 mmol) in methylene chloride (1 mL). The mixture was stirred for 1.5 h at 0°C and quenched with the addition of a saturated aqueous solution of NaHSO<sub>3</sub> (3 mL). The reaction mixture was further diluted through the addition of water (5  
 25 mL) and is then extracted with methylene chloride (3 x 10 mL). The combined organic layer was washed sequentially with a saturated aqueous solution of sodium bicarbonate (10 mL) and brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resultant residue was purified by flash chromatography to  
 30 yield the title compound (31.1 mg, 29%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.69 and 0.79 (t, J = 7.2 Hz, 3H), 1.08-1.37 (m, 14H), 1.45 (t, J = 4.2 Hz, 1H), 1.86-1.93 (m, 2H),

- 0 3.10 and 3.11 (s, 3H), 3.25-3.50 (m, 2H), 4.34-4.36 (m, 2H), 5.20-5.50 (m, 1H), 5.93-6.00 (m, 1H), 7.41 (d,  $J = 8.4$  Hz, 2H), 7.96 (d,  $J = 8.4$  Hz, 2H). Anal. calc. for  $C_{24}H_{33}NO_3S$ : C, 69.28; H, 7.91; N, 3.18; S, 7.50. Found: C, 69.36; H, 8.00; N, 3.37; S, 7.71.

### EXAMPLE 177

5



### 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-hydroxymethyl)phenyl]-5-pentylpyridine

10

#### Step A: 2,6-Diisopropyl-3-[(t-butyl-dimethylsiloxy)methyl]-4-(4-fluorophenyl)-5-pentylpyridine

- To a solution of 2,6-diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine (3.14 g, 8.78 mmol) (Example 1, Step H) in methylene chloride (45 mL) were added imidazole (0.9 g, 13.17 mmol, 1.5 eq) and t-butyl-dimethylsilyl chloride (2.0 g, 13.17 mmol, 1.5 eq). A white precipitate began to form immediately. The mixture was stirred for 14 h at 25°C and was then diluted with methylene chloride (100 mL) and washed sequentially with 10% hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL), and brine (20 mL). The organic layer was concentrated under reduced pressure and the resultant residue was recrystallized from methanol to provide the product (3.27 g, 79%) as a white fluffy crystalline solid.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  -0.10 (s, 6H), 0.79 (t,  $J = 6.9$  Hz, 3H), 0.83 (s, 9H), 1.07-1.20 (m, 4H), 1.29-1.32 (m, 14H), 2.23-2.30 (m, 2H), 3.21 (sept,  $J = 6.6$  Hz, 1H), 3.35 (sept,  $J = 6.6$  Hz, 1H), 4.24 (s, 2H), 7.05-7.18 (m, 4H). Anal. calc. for  $C_{29}H_{46}NOFSi$ : C, 73.83; H, 9.83; N, 2.97. Found: C, 73.82; H, 9.95; N, 2.86.

#### Step B: 2,6-Diisopropyl-3-[(t-butyl-dimethylsiloxy)methyl]-4-[(4-fluoro-3-hydroxymethyl)phenyl]-5-pentylpyridine

- 30 To a solution of the intermediate from Step A (5.4 g, 11.4 mmol) in THF (80

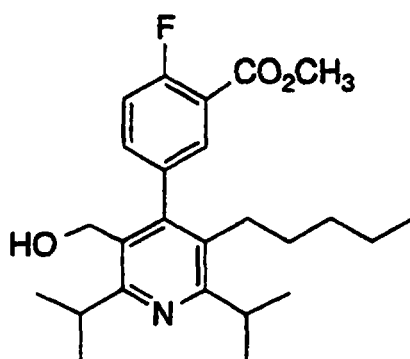
0 mL) was added *sec*-butyllithium (1.3 M, 26.4 mL, 3 eq) at -78°C under an argon atmosphere. The yellow solution was stirred for 1 h at -78°C and quenched through the addition of water (50 mL). The mixture was allowed to warm to 25°C and extracted with ethyl acetate (3 x 50 mL) and the organic layer was washed with water (50 mL) and brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under  
5 reduced pressure to afford the crude intermediate. (6.41 g).

This intermediate (3.2 g) was dissolved in THF (50 mL) and stirred at 0°C as lithium aluminum hydride ("LAH") (1M in THF, 25.7 mL, 25.7 mmol) was added to it. The resultant mixture was stirred at 0°C for 1.5 h and quenched through the sequential addition of water (1 mL), 1N aqueous sodium hydroxide (1 mL), and  
10 water (3 mL). The resultant mixture was filtered and the precipitate rinsed with ether (100 mL). The combined organic layer was washed with water (25 mL) and brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resultant residue was subjected to flash chromatography using a 10% ether-hexane mixture as the eluent. In this manner, 1.1 g of the product was obtained. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ -0.09 (s, 6H), 0.83 (s, 9H), 1.07-1.20 (m, 4H), 1.29-1.33 (m, 17H),  
15 1.96-2.02 (m, 1H), 2.22-2.31 (m, 2H), 3.23 (sept, J = 6.6 Hz, 1H), 3.36 (sept, J = 6.6 Hz, 1H), 4.22-4.32 (m, 2H), 4.70-4.90 (m, 2H), 7.09-7.12 (m, 2H), 7.23-7.28 (m, 1H).

20 Step C: 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-hydroxy-methyl)phenyl]-5-pentylpyridine

To a solution of the intermediate from Step B (123 mg, 0.245 mmol) in THF (3 mL) was added tetrabutylammonium fluoride (1M in THF, 0.7 mL, 0.7 mmol) at 25°C under an argon atmosphere. The mixture was stirred for 14 h at 25°C and is then diluted with water (5 mL) and extracted with methylene chloride (3 x 5 mL).  
25 The combined organic layer was washed with brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 40% ethyl acetate-hexane mixture as the eluent. In this manner, the title compound (79 mg, 83%) was produced as a colorless oil. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 6.6 Hz, 3H), 1.10-1.17 (m, 4H), 1.24-1.35 (m, 14H),  
30 2.10-2.40 (m, 2H), 2.73 (bs, 1H), 3.22 (sept J = 6.6 Hz, 1H), 3.34 (sept, J = 6.6 Hz, 1H), 3.85 (bs, 1H), 4.06 (d, J = 11.4 Hz, 1H), 4.35 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 14.1 Hz, 1H), 4.73 (d, J = 14.1 Hz, 1H), 7.00-7.06 (m, 2H), 7.25 (d, J = 7.2 Hz, 1H).

0

EXAMPLE 178

5

2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-methoxycarbonyl)phenyl]-5-pentylpyridine

Step A: 2,6-Diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine

To a solution of 2,6-diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-hydroxymethyl)phenyl]-5-pentylpyridine (Example 177, Step B) (1.09 g, 2.18 mmol) in methylene chloride (100 mL) was added a mixture of PCC (0.94 g, 4.35 mmol, 2 eq) and Celite (0.94 g). The resultant mixture was stirred for 2 h at 25°C and then filtered through a pad of silica gel. The silica gel pad was rinsed with a 10% ethyl acetate-hexane mixture (200 mL) and the combined organic layer was concentrated to afford the crude product (0.78 g) as a white waxy solid.

Step B: 2,6-Diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-methoxycarbonyl)phenyl]-5-pentylpyridine

To a solution of the intermediate from Step A (82 mg, 0.164 mmol) in methanol (3 mL) were added potassium cyanide (53 mg, 0.82 mmol) and activated manganese dioxide (71 mg, 5 eq). The mixture was stirred at 25°C for 14 h and is then filtered through a pad of Celite. The Celite pad was rinsed with ethyl acetate (25 mL) and the combined organic layer was washed with brine (5 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resultant residue was purified by flash chromatography to provide the intermediate (70 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ -0.13 (s, 6H), 0.75 (t, J = 6.6 Hz, 3H), 1.06-1.40 (m, 27H), 2.20-2.35 (m, 2H), 3.20 (sept, J = 6.6 Hz, 1H), 3.32 (sept, J = 6.6 Hz, 1H), 4.15 (d, J = 10.8 Hz, 1H), 4.25 (d, J = 10.8 Hz, 1H), 7.15-7.25 (m, 1H), 7.40-7.50 (m, 1H), 7.69 (dd, J = 6.6, 2.4 Hz, 1H), 10.41 (s, 1H). FAB-MS: calcd for (C<sub>30</sub>H<sub>46</sub>NO<sub>2</sub>FSi) 499, found 500 (M+1).

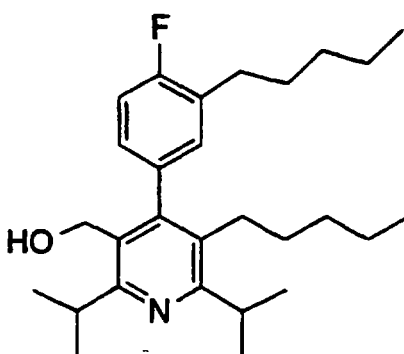
0

**Step C:** 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-methoxy-carbonyl)phenyl]-5-pentylpyridine

The title compound was prepared from the intermediate obtained in Step B by the method detailed in Example 177, Step C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 6.6 Hz, 3H), 1.08-1.16 (m, 4H), 1.23-1.34 (m, 15H), 2.20-2.30 (m, 2H), 3.22 (sept, J = 6.6 Hz, 1H), 3.40 (sept, J = 6.6 Hz, 1H), 3.93 (s, 3H), 4.25-4.39 (m, 2H), 7.12 (dd, J = 10.3, 8.5 Hz, 1H), 7.28 (d, J = 8.5, 4.8, 2.2 Hz, 1H), 7.69 (dd, J = 6.6, 2.2 Hz, 1H).

10

**EXAMPLE 179**



2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-pentyl)phenyl]-5-pentylpyridine

**Step A:** 2,6-Diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-(pent-1-enyl))phenyl]-5-pentylpyridine

To a solution of 2,6-diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (Example 178, Step A) (200 mg, 0.40 mmol) in THF (10 mL) was added a butyltriphenylphosphonium bromide/sodium amide mixture (Fluka, 0.55 g, 3 eq) under an argon atmosphere. The reaction was stirred at 25°C for 1.5 h and is quenched by dropwise addition of water (3 mL) and further diluted with brine (5 mL). The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. The resultant residue was subjected to flash chromatography to yield the intermediate (205 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ -0.13 (s, 6H), 0.75-1.47 (m, 35H), 2.13-2.33 (m, 4H), 3.21 (septet, J = 6.6 Hz, 1H), 3.34 (septet, J = 6.6 Hz, 1H), 2.7 (d, J = 2.7 Hz, 2H), 5.75-6.31 (m, 1H), 6.41-6.59 (m, 1H), 6.98-7.09 (m, 3H). FAB-MS: calcd for (C<sub>34</sub>H<sub>54</sub>NOFSi) 539, found 540 (M + 1).

30

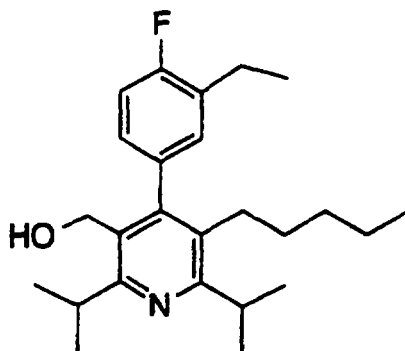
0 Step B: 2,6-Diisopropyl-3-[(t-butyl dimethylsiloxy)methyl]-4-[(4-fluoro-3-pentyl)phenyl]-5-pentylpyridine

5 The intermediate from Step A (200 mg) was dissolved in ethanol (10 mL) and the mixture purged with argon. A quantity of 10% Pd-C (20 mg) was then added and the mixture was purged with hydrogen and stirred under a hydrogen atmosphere at 25°C for 16 h. The mixture was then filtered through a pad of silica and the silica pad is rinsed with ethanol (25 mL). The organic layer was concentrated under reduced pressure and the resultant residue was subjected to flash chromatography using hexane as the eluent to afford the intermediate (150 mg, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ -0.11 (s, 6H), 0.76-1.65 (m, 39H), 2.17-2.33 (m, 2H), 2.51-2.78 (m, 2H), 3.21 (septet, J = 6.6 Hz, 1H), 3.35 (septet, J = 6.6 Hz, 1H), 4.42 (dd, J = 10.2, 16.2, 2H), 6.92-7.05 (m, 3H). FAB-MS: calcd for (C<sub>34</sub>H<sub>56</sub>NOFSi) 541, found 542 (M+1).

15 Step C: 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-pentyl)-phenyl]-5-pentylpyridine

The title compound was prepared as a colorless oil from the intermediate from Step B by the method detailed in Example 177, Step C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J = 6.9 Hz, 3H), 0.88 (t, J = 6.9 Hz, 3H), 1.08-1.34 (m, 24H), 1.57-1.65 (m, 1H), 2.22-2.29 (m, 2H), 2.57-2.75 (m, 2H), 3.21 (sept, J = 6.6 Hz, 1H), 3.40 (sept, J = 6.6 Hz, 1H), 4.33 (dd, J = 5.6, 1.4 Hz, 2H), 6.93-7.09 (m, 3H). FAB-MS: calcd for (C<sub>28</sub>H<sub>42</sub>NOF) 427, found 428 (M + 1). R<sub>f</sub> = 0.42 (20% ether-hexanes).

EXAMPLE 180

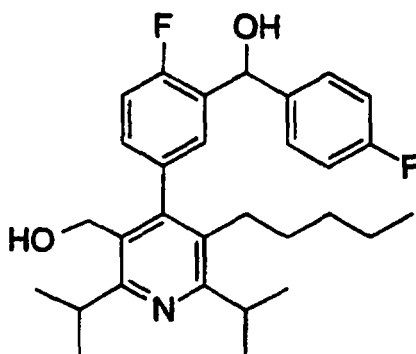


25 2,6-Diisopropyl-3-hydroxymethyl-4-[(4-fluoro-3-ethyl)phenyl]-5-pentylpyridine

The title compound was prepared as a white wax from 2,6-diisopropyl-3-[(t-butyl dimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (Example 178, Step A) (200 mg, 0.40 mmol) and an ethyltriphenylphosphonium

- 0 bromide/sodium amide mixture (Fluka) by the methods detailed in Example 179, Steps A-C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.77 (t,  $J$  = 6.9 Hz, 3H), 1.10-1.33 (m, 22H), 2.17-2.33 (m, 2H), 2.60-2.80 (m, 2H), 3.21 (sept,  $J$  = 6.6 Hz, 1H), 3.40 (sept,  $J$  = 6.6 Hz, 1H), 4.34 (dd,  $J$  = 5.7, 1.8 Hz, 2H), 6.94-7.09 (m, 3H). FAB-MS: calcd for ( $\text{C}_{25}\text{H}_{36}\text{NOF}$ ) 385, found 386 ( $M+1$ ).  $R_f$  = 0.38 (20% ether-hexanes).

5

EXAMPLE 181

- 10 2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-( $\alpha$ -hydroxy-4-fluorobenzyl)]-5-pentylpyridine

Step A: 2,6-Diisopropyl-3-(*t*-butyldimethylsilyloxymethyl)-4-[4-fluoro-3-( $\alpha$ -hydroxy-4-fluorobenzyl)phenyl]-5-pentyl-pyridine

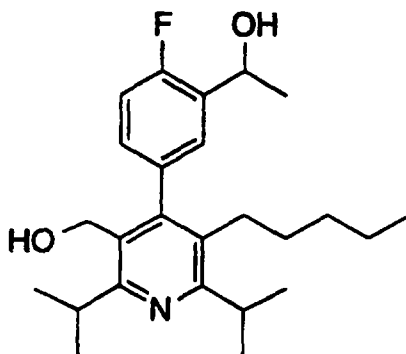
- 15 To a solution of 2,6-diisopropyl-3-[(*t*-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (160 mg, 0.321 mmol) (Example 178, Step A) in THF (10 mL) was added 4-fluorophenyl magnesium bromide (1.0 M in THF, 0.4 mL, 2.5 eq) under an argon atmosphere at 25°C. The mixture was stirred for 30 min and then quenched by the dropwise addition of water (5 mL). The mixture
- 20 was extracted with ether (2 x 10 mL) and the combined organic layer was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using a 10% ether-hexane mixture as the eluent to provide 150 mg of the intermediate.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  -0.19 (d, 6.3 Hz, 3H), -0.10 (d,  $J$  = 7.2 Hz, 3H), 0.71-1.30 (m, 30 H), 2.17-2.28 (m, 3H), 3.18 (septet,  $J$  = 6.6 Hz, 1H), 3.25-3.40 (m, 1H), 4.04-4.38 (m, 2H), 6.14 (dd,  $J$  = 4.4, 17.9 Hz, 1H), 6.97-7.38 (m, 7H). FAB-MS: calcd for ( $\text{C}_{36}\text{H}_{51}\text{NOF}_2\text{Si}$ ) 595, found 596 ( $M+1$ ).
- 25

Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-( $\alpha$ -hydroxy-4-fluorobenzyl)phenyl]-5-pentylpyridine

30

- 0 The title compound was prepared from the intermediate from Step A by the method detailed in Example 177, Step C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.72-1.45 (m, 22H), 2.13-2.36 (m, 2H), 2.65 (d, J = 4.2 Hz, 1H), 3.21 (sept, J = 6.6 Hz, 1H), 3.39 (sept, J = 6.6 Hz, 1H), 4.21-4.39 (m, 2H), 6.14-6.17 (m, 1H), 6.98-7.12 (m, 4H), 7.35-7.42 (m, 3H). FAB-MS: calcd for (C<sub>30</sub>H<sub>37</sub>NO<sub>2</sub>F<sub>2</sub>) 481, found 482 (M + 1). R<sub>f</sub> = 0.21,
- 5 0.51 (50% ether-hexanes). mp 118-120°C.

### EXAMPLE 182

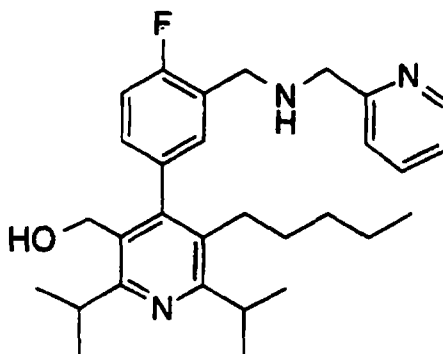


10

### 2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-(1-hydroxyethyl)phenyl]-5-pentylpyridine

- The title compound was prepared as an oil from 2,6-diisopropyl-3-[(*t*-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine
- 15 (Example 178, Step A) and methylmagnesium bromide by the methods detailed in Example 181, Steps A-B. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.76 (t, J = 6.0 Hz, 3H), 1.09-1.53 (m, 21H), 1.84 (br s, 1H), 2.18-2.27 (m, 2H), 2.87 (br s, 1H), 3.20 (septet, J = 6.6 Hz, 1H), 3.37 (septet, J = 6.6 Hz, 1H), 4.16 (d, J = 11.4 Hz, 1H), 4.28-4.35 (m, 1H), 5.16-5.19 (m, 1H), 7.01-7.07 (m, 2H), 7.25-7.34 (m, 1H). FAB-MS: calcd for
- 20 (C<sub>25</sub>H<sub>36</sub>NO<sub>2</sub>F) 401, found 402 (M + 1). R<sub>f</sub> = 0.32 and 0.20 (50% ether-hexanes).

### EXAMPLE 183



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2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-((N-((pyridin-2-yl)-methyl)amino)methyl)]phenyl-5-pentylpyridine

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Step A: 2,6-Diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[4-fluoro-3-((N-((pyridin-2-yl)methyl)amino)methyl)]phenyl-5-pentylpyridine

To a solution of 2,6-diisopropyl-3-[(t-butyldimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (500 mg, 1 mmol) (Example 178, Step A) in methanol (10 mL) and ether (2 mL) was added 2-methylaminopyridine (0.42 mL, 4 mmol, 4 eq) under an argon atmosphere at 25°C. To this solution were added ZnCl<sub>2</sub> (68.1 mg, 0.5 eq) and sodium cyanoborohydride (62.8 mg, 1 eq) in methanol (6 mL). The reaction was allowed to stir for 20 h and was then quenched with the addition of aqueous sodium hydroxide (0.1N, 7 mL). The methanol was removed under reduced pressure and the aqueous residue was extracted with ethyl acetate (3 x 30 mL). The organic layer was washed with water (10 mL) and brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated under reduced pressure. The resultant residue was subjected to flash chromatography using a 60% ether-hexane mixture as the eluent to provide the intermediate (260 mg, 44%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ - 0.12 (s, 6H), 0.72-0.81 (m, 12H), 1.80 (br s, 1H), 1.07-1.15 (m, 4H), 1.27-1.31 (m, 14H), 2.23-2.29 (m, 2H), 3.20 (septet, J = 6.6 Hz, 1H), 3.34 (septet, J = 6.6 Hz, 1H), 3.83-4.03 (m, 4H), 4.25 (dd, J = 10.5, 27.6 Hz, 2H), 7.06-7.33 (m, 5H), 7.64 (δ, J = 1.8, 7.5, 7.5 Hz, 1H), 8.54-8.56 (m, 1H). FAB-MS: calcd for (C<sub>36</sub>H<sub>54</sub>N<sub>3</sub>OFSi) 591, found 592 (M + 1).

25

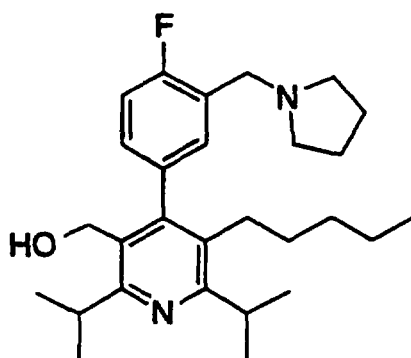
Step B: 2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-((N-((pyridin-2-yl)methyl)amino)methyl)]phenyl-5-pentylpyridine

30

The title compound was prepared as a colorless oil from the intermediate obtained in Step A by the method detailed in Example 177, Step C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J = 6.9 Hz, 3H), 1.07-1.36 (m, 18H), 1.75 (bs, 2H), 2.19-2.36 (m, 2H), 3.20 (sept, J = 6.6 Hz, 1H), 3.47 (sept, J = 6.6 Hz, 1H), 3.74 (d, J = 14.1 Hz, 1H), 3.79 (d, J = 13.5 Hz, 1H), 3.89 (d, J = 13.5 Hz, 1H), 4.07 (d, J = 14.1 Hz, 1H), 4.20 (d, J = 11.4 Hz, 1H), 4.41 (d, J = 11.4 Hz, 1H), 7.02-7.25 (m, 4H), 7.38 (d, J = 7.8 Hz, 1H), 7.66 (δ, J = 7.5, 7.5, 1.8 Hz, 1H), 8.47 (m, 1H). FAB-MS: calcd for (C<sub>30</sub>H<sub>40</sub>N<sub>3</sub>OF) 477, found 478 (M + 1). R<sub>f</sub> = 0.4 (ethyl acetate).

35

0

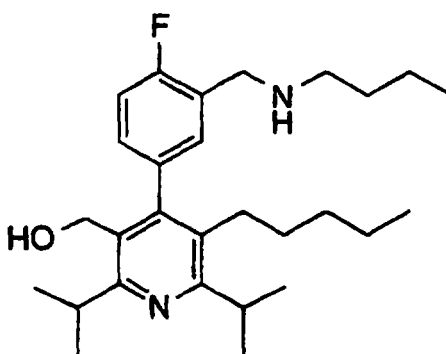
EXAMPLE 184

5

2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-(pyrrolidin-1-yl)methyl]phenyl-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-[(t-butyl-dimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (Example 178, Step A) by the methods detailed in Example 183, Steps A-B. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J = 6.6 Hz, 3H), 1.05-1.31 (m, 18 H), 1.75-1.85 (m, 5 H), 2.23-2.29 (m, 2H), 2.50-3.50 (m, 4H), 3.20 (sept, J = 6.6 Hz, 1H), 3.41 (sept, J = 6.6 Hz, 1 H), 3.71 (d, J = 12.9 Hz, 1H), 3.82 (d, J = 12.9 Hz, 1H), 4.29 (dd, J = 11.7, 20.4 Hz, 2H), 7.03-7.13 (m, 2H), 7.26-7.30 (m, 1H). FAB-MS: calcd for (C<sub>28</sub>H<sub>41</sub>N<sub>2</sub>OF) 440, found 441 (M + 1). R<sub>f</sub> = 0.2 (ethyl acetate).

15

EXAMPLE 185

20

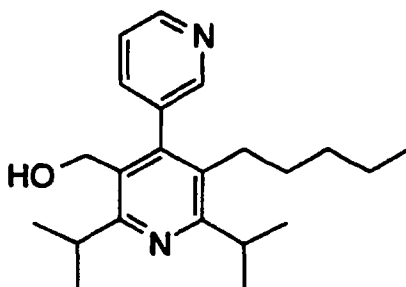
2,6-Diisopropyl-3-hydroxymethyl-4-[4-fluoro-3-(butylamino)methyl]phenyl-5-pentylpyridine

The title compound was prepared from 2,6-diisopropyl-3-[(t-butyl-dimethylsiloxy)methyl]-4-[(4-fluoro-3-formyl)phenyl]-5-pentylpyridine (Example 178, Step A) by the methods detailed in Example 183, Steps A-B. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.79 (t, J = 6.8 Hz, 3 H), 0.91 (t, J = 7.4 Hz, 3 H), 1.10-1.61 (m, 24 H),

- 0 2.25-2.31 (m, 2 H), 2.62 (t,  $J = 7.2$  Hz, 2 H), 3.23 (sept,  $J = 6.6$  Hz, 1 H), 3.42 (sept,  $J = 6.6$  Hz, 1H), 3.89 (s, 2H), 4.32 (dd, 11.7 Hz, 2H), 7.04-7.20 (m, 3 H). FAB-MS: calcd for  $(C_{28}H_{43}N_2O)$  442, found 443 ( $M+1$ ).  $R_f = 0.33$  (ethyl acetate).

### EXAMPLE 186

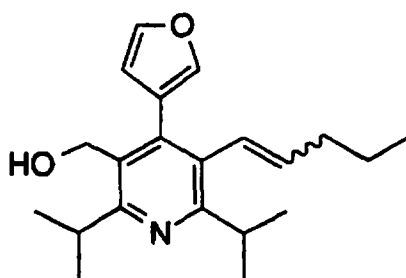
5



### 2,6-Diisopropyl-3-hydroxymethyl-4-(pyridin-3-yl)-5-pentylpyridine

- 10 The title compound was prepared as an oil from ethyl isobutyryl acetate, ammonium acetate and pyridine-3-carboxaldehyde in 0.56% yield by the methods described in Example 125. FAB-MS: calculated for  $C_{22}H_{32}N_2O$  340; found 341 ( $M+1$ ).  $^1H$ -NMR (300 MHz,  $CD_3OD$ ):  $\delta$  0.77 (t,  $J = 6.5$  Hz, 3H), 1.08-1.32 (m, 18H), 2.27-2.33 (m, 2H), 3.28 (septet,  $J = 6.6$  Hz, 1H), 3.48 (septet,  $J = 6.6$  Hz, 1H), 4.25 (s, 2H), 7.52-7.57 (m, 1H), 7.73-7.76 (m, 1H), 8.42-8.43 (m, 2H), 8.59 (dd,  $J = 5.1, 1.5$  Hz, 1H). Anal. calc for  $C_{22}H_{32}N_2O$ : C, 77.60; H, 9.47; N, 8.23. Found: C, 75.96; H, 9.32; N, 7.88.  $R_f = 0.40$  (diethyl ether).
- 15

### EXAMPLE 187



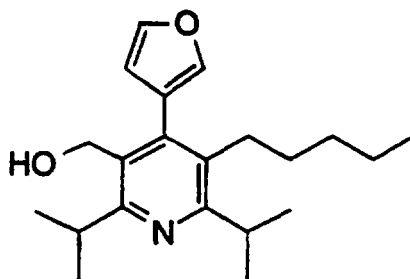
20

### 2,6-Diisopropyl-3-hydroxymethyl-4-(3-furyl)-5-(pent-1-enyl)pyridine

- 25 Substituting 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) for ceric ammonium nitrate (CAN) to oxidize the dihydropyridine intermediate to the phenyl pyridine, the title compound was prepared as a mixture of *E* and *Z* isomers (4.5:1, *E:Z*) from ethyl isobutyryl acetate, ammonium acetate and furan-3-carboxaldehyde in 10% yield by the methods described in Example 125. FAB-MS:

- 0 calculated for  $C_{21}H_{29}NO_2$  327; found 328 (M+1).  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  0.84 (t,  $J = 7.4$  Hz, 3H), 1.17-1.38 (m, 14H), 2.01-2.04 (m, 2H), 3.39 (septet,  $J = 6.6$  Hz, 1H), 3.47 (septet,  $J = 6.6$  Hz, 1H), 4.44 (s, 2H), 5.40-5.58 (m, 2H), 6.11-6.25 (m, 1H), 6.38-6.40 (m, 1H), 7.41-7.54 (m, 2H).

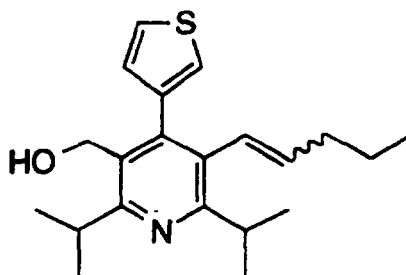
5

EXAMPLE 1882,6-Diisopropyl-3-hydroxymethyl-4-(3-furyl)-5-pentylpyridine

- 10 The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-(3-furyl)-5-(pent-1-enyl)pyridine (Example 187) in 6% yield by the methods described in Example 125. FAB-MS: calculated for  $C_{21}H_{31}NO_2$  329; found 330 (M+1).  $^1H$  NMR (300 MHz,  $CD_3OD$ ):  $\delta$  0.83 (t,  $J = 6.8$  Hz, 3H), 1.19-1.36 (m, 19H), 2.42-2.48 (m, 2H), 3.25 (septet,  $J = 6.6$  Hz, 1H), 3.45 (septet,  $J = 6.6$  Hz, 1H), 4.38 (s, 2H), 6.42 (m, 1H), 7.45-7.46 (m, 1H), 7.61-7.62 (t,  $J = 1.7$  Hz, 1H). Anal. calc for  $C_{21}H_{31}NO_2$ : C, 76.55; H, 9.48; N, 4.25. Found: C, 76.41; H, 9.76; N, 4.24.  $R_f = 0.59$  (20% EtOAc/hex). mp 98-100°C.
- 15

EXAMPLE 189

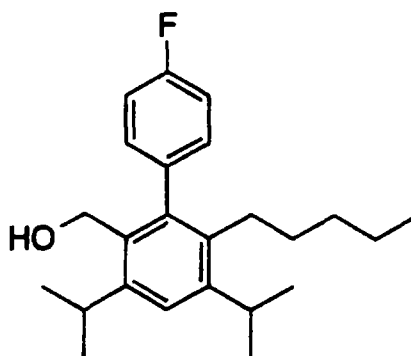
20

2,6-Diisopropyl-3-hydroxymethyl-4-(thiophen-3-yl)-5-(pent-1-enyl)-pyridine

- 25 The title compound was prepared as a mixture of E and Z isomers (5.5:1, E:Z) from ethyl isobutyrylacetate, ammonium acetate and thiophene-3-carboxaldehyde in 7% yield by the methods described in Example 125. FAB-MS:

- 0 calculated for  $C_{21}H_{29}NOS$  343; found 344 ( $M+1$ ).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  0.78-0.84 (m, 3H), 1.22-1.37 (m, 15H), 1.96-2.00 (m, 2H), 3.37-3.50 (m, 2H), 4.47 (d,  $J$  = 5.7 Hz, 2H), 5.32-5.43 (m, 1H), 6.02-6.12 (m, 1H), 6.95-6.97 (m, 1H), 7.12-7.13 (m, 1H), 7.35-7.38 (m, 1H). Anal. calc for  $C_{21}H_{29}NOS$ : C, 73.43; H, 8.52; N, 4.08; S, 9.32. Found: C, 73.38; H, 8.75; N, 3.97; S, 9.03.  $R_f$  = 0.65 (20% EtOAc/hex). mp 85-87°C.

5

EXAMPLE 19010 3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl

Step A: 1-(2-Methoxyethoxy)methoxymethyl-2,4-diisopropyl-5-hydroxymethylbenzene

- A mixture of 1,5-bis(hydroxymethyl)-2,4-diisopropylbenzene (0.947 g, 4.26 mmol) (prepared by the method of Fey, *et al.* U.S. Patent 5,138,090), methoxyethoxymethyl chloride (0.49 mL, 4.29 mmol), and diisopropylethylamine (1.1 mL, 6.31 mmol) in  $CH_2Cl_2$  (9.6 mL) was stirred overnight. The mixture was diluted with water (50 mL) and extracted with  $CH_2Cl_2$  (3 x 50 mL). Silica gel chromatography (67:33 hexanes/ethyl acetate) provided a colorless oil (0.679 g, 51%).  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta$  7.31 (s, 1H), 7.29 (s, 1H), 4.83 (s, 2H), 4.72 (s, 2H), 4.66 (s, 2H), 3.76 (m, 2H), 3.60 (m, 2H), 3.43 (s, 3H), 3.26 (m, 2H), 1.27 (d, 7.0 Hz, 12H). EI-MS: calculated for  $C_{18}H_{30}O_4$  310; found 292 ( $M-H_2O$ , 24%), 221 (100%).

25 Step B: 3-(2-Methoxyethoxy)methoxymethyl-4,6-diisopropylbenzaldehyde

- Prepared from the intermediate obtained in Step A by the procedure described in Example 1, Step E.  $^1H$  NMR ( $CDCl_3$ , 300 MHz):  $\delta$  10.29 (s, 1H), 7.80 (s, 1H), 7.39 (s, 1H), 4.83 (s, 2H), 4.70 (s, 2H), 3.98 (sept, 6.8 Hz, 1H), 3.76 (m, 2H), 3.59 (m, 2H), 3.42 (s, 3H), 3.26 (sept, 6.8 Hz, 1H), 1.30 (d, 7.0 Hz, 6H), 1.28 (d, 7.0 Hz, 6H). FAB-MS: calculated for  $C_{18}H_{28}O_4$  308; found 309 ( $M+H$ ).

0

**Step C:**     N-Phenyl 3-(2-methoxyethoxy)methoxymethyl-4,6-diisopropylbenzidine

A mixture of the intermediate from Step B (2.35 g, 7.62 mmol), aniline (700 mL, 7.68 mmol), *p*-toluenesulfonic acid (58.8 mg, 309 mmol), and molecular sieves (20.7 g) in toluene was refluxed overnight. The mixture was cooled to room temperature and filtered. The filtrate was diluted with ethyl acetate (65 mL) and washed with saturated aqueous NaHCO<sub>3</sub> solution (50 mL) and water (50 mL), dried (MgSO<sub>4</sub>), and concentrated to give an orange oil (2.78 g, 96%). The product was used in the next step without purification. <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz): δ 8.70 (s, 1H), 8.48 (s, 1H), 7.31 (s, 1H), 7.17 (m, 4H), 7.00 (m, 1H), 4.61 (s, 2H), 4.60 (s, 2H), 3.56 (m, 2H), 3.46 (sept, 6.8 Hz, 1H), 3.29 (m, 2H), 3.20 (sept, 6.8 Hz, 1H), 3.07 (s, 3H), 1.17 (d, 7.0 Hz, 6H), 1.12 (d, 7.0 Hz, 6H).

**Step D:**     Bis[(2-N-phenylmethylimino)-3,5-diisopropyl-6-(2-methoxyethoxy)methoxymethylphenyl]dipalladium

A mixture of the intermediate from Step C (2.78 g, 7.27 mmol) and Pd(OAc)<sub>2</sub> (1.63 g, 7.26 mmol) in acetic acid (34 mL) was refluxed for 1 h. The mixture was cooled to rt, poured into water (135 mL), and filtered through a medium porosity fritted funnel. The filtrate was lyophilized. The residue was dissolved in ethyl acetate (100 mL) and washed with saturated aqueous NaHCO<sub>3</sub> (50 mL) and saturated aqueous NaCl (50 mL), dried (MgSO<sub>4</sub>), and concentrated to give a brown solid. The solid was mixed with 50:50 petroleum ether/ethyl acetate (17 mL) and cooled in the freezer. The resulting precipitate was collected and dried to give a brown solid (0.951 g, 27%). <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz): δ 7.70 (s, 1H), 7.65 (s, 1H), 7.63 (s, 1H), 7.11 (s, 1H), 7.08 (s, 1H), 6.99 (m, 1H), 6.73 (s, 1H), 5.33 (s, 2H), 5.08 (s, 2H), 4.19 (m, 2H), 3.35 (m, 2H), 3.04 (s, 3H), 2.68 (sept, 6.8 Hz, 1H), 2.15 (sept, 6.8 Hz, 1H), 1.01 (d, 7.0 Hz, 6H), 0.96 (d, 7.0 Hz, 6H). FAB-MS: calculated for C<sub>48</sub>H<sub>64</sub>N<sub>2</sub>O<sub>6</sub>Pd<sub>2</sub> 976; found 488 (M/2).

**Step E:**     3,5-Diisopropyl-2-formyl-6-(2-methoxyethoxy)methoxymethyl-4'-fluoro-1,1'-biphenyl

A mixture of 1,2-dibromoethane (80 mL) and magnesium turnings (0.349 g, 14.4 mmol) in diethyl ether (1 mL) was heated to reflux for several minutes. The mixture was diluted with diethyl ether and a solution of 1-bromo-4-fluorobenzene (950 mL, 8.65 mmol) and 1,2-dibromoethane (160 mL) in diethyl ether (3 mL) was added over several minutes. The reflux was continued for 1 h then the mixture was cooled to room temperature. The supernatant liquid was added via cannula to a

0 solution of the intermediate obtained in Step D (0.951 g, 973 mmol) and triphenylphosphine (2.02 g, 7.71 mmol) in benzene (19 mL) and the mixture stirred overnight. Aqueous 6N HCl (6 mL) was added and the mixture stirred for 2 h. The mixture was filtered and the solids washed with diethyl ether (75 mL). The combined filtrates were washed with saturated aqueous sodium chloride solution  
5 (50 mL). Silica gel chromatography provided a colorless solid (0.413 g, 53%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 9.70 (s, 1H), 7.50 (s, 1H), 7.26 (m, 2H), 7.11 (m, 2H), 4.59 (s, 2H), 4.30 (s, 2H), 3.89 (sept, 6.8 Hz, 2H), 3.55 (m, 2H), 3.44 (m, 2H), 3.37 (s, 3H), 1.33 (d, 6.6 Hz, 6H), 0.96 (d, 7.0 Hz, 6H). FAB-MS: calculated for C<sub>24</sub>H<sub>31</sub>FO<sub>4</sub> 402; found 403 (M+H).

10

Step F: 3,5-Diisopropyl-2-(2-methoxyethoxy)methoxymethyl-6-(pent-1-enyl)-4'-fluoro-1,1'-biphenyl

Prepared from the intermediate obtained in Step E by the procedure described in Example 1, Step F. The olefin was a mixture of cis and trans isomers in  
15 a ratio of 9:91. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.32 (s, 1H), 7.12 (m, 2H), 7.01 (m, 2H), 5.95 (d, 16.2 Hz, 1H), 5.23 (dt, 16.2 Hz, 7.0 Hz, 1H), 4.57 (s, 2H), 4.29 (s, 2H), 3.53 (m, 2H), 3.43 (m, 2H), 3.37 (s, 3H), 3.31 (m, 2H), 1.89 (m, 2H), 1.32 (d, 6.6 Hz, 6H), 1.23 (d, 7.0 Hz, 6H), 1.2 (m, 2H), 0.74 (t, 7.4 Hz, 3H). FAB-MS: calculated for C<sub>28</sub>H<sub>39</sub>FO<sub>3</sub> 442; found 442 (M<sup>+</sup>).

20

Step G: 3,5-Diisopropyl-2-(2-methoxyethoxy)methoxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl

Prepared from the intermediate obtained in Step F by the procedure described in Example 1, Step H. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.29 (s, 1H), 7.19  
25 (m, 2H), 7.07 (m, 2H), 4.52 (s, 2H), 4.21 (s, 2H), 3.51 (m, 2H), 3.41 (m, 2H), 3.37 (s, 3H), 3.27 (sept, 6.8 Hz, 1H), 3.16 (sept, 6.8 Hz, 1H), 2.27 (m, 2H), 1.30 (d, 7.0 Hz, 6H), 1.27 (m, 2H), 1.23 (d, 7.0 Hz, 6H), 1.10 (m, 4H), 0.77 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>28</sub>H<sub>41</sub>FO<sub>3</sub> 444; found 445 (M+H).

30 Step H: - 3,5-Diisopropyl-2-acetoxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl

Chlorotrimethylsilane (110 mL, 867 mmol) was added to a cooled (0°C) mixture of the intermediate from Step G (62.4 mg, 140 mmol) and NaI (132 mg, 880 mmol) in CH<sub>3</sub>CN (1.4 mL). After 25 min. the mixture was filtered through silica gel (5:1 hexanes/ethyl acetate) and the filtrate concentrated. A mixture of the  
35 residue and sodium acetate (122 mg, 1.49 mmol) in dimethyl formamide (2.3 mL) was heated to 80°C overnight. The solvent was removed and the residue dissolved in water (15 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 15 mL). Silica gel

0 chromatography (95:5 hexane/ethyl acetate) provided a colorless oil (38.2 mg, 69%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.31 (s, 1H), 7.15 (m, 2H), 7.07 (m, 2H), 4.76 (s, 2H), 3.18 (sept, 6.8 Hz, 1H), 3.12 (sept, 6.8 Hz), 2.28 (m, 2H), 1.97 (s, 3H), 1.29 (d, 6.6 Hz, 6H), 1.29 (m, 2H), 1.29 (d, 6.6 Hz, 6H), 1.14 - 1.07 (m, 4H), 0.78 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>26</sub>H<sub>35</sub>FO<sub>2</sub> 398; found 338 (M-AcOH).

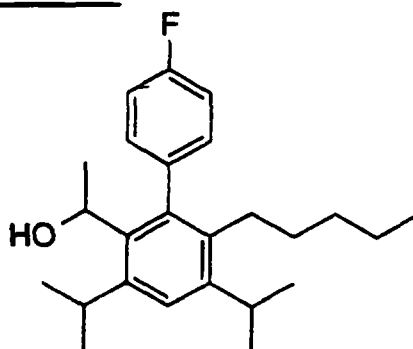
5

Step I: 3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl

A solution of the intermediate obtained in Step H (11.2 mg, 28.1 mmol) and potassium hydroxide (109 mg, 1.65 mmol) in methanol (2 mL) was heated at 50°C for 3 h. The solvent was removed, and the residue dissolved in saturated aqueous ammonium chloride (15 mL) and extracted with diethyl ether (3 x 15 mL). Silica gel chromatography (5:1 hexane/ethyl acetate) provided the title compound as a colorless crystalline solid (12.0 mg, 120%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.30 (s, 1H), 7.19 (m, 2H), 7.11 (m, 2H), 4.32 (s, 2H), 3.37 (sept, 6.9 Hz, 1H), 3.16 (sept, 6.9 Hz, 1H), 2.26 (m, 2H), 1.31 (d, 6.6 Hz, 6H), 1.29 (m, 2H), 1.28 (d, 7.0 Hz, 6H), 1.17 - 1.03 (m, 4H), 0.77 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>24</sub>H<sub>33</sub>FO 356; found 356 (M<sup>+</sup>). R<sub>f</sub> = 0.33 (83:17 hexanes/ethyl acetate). Anal. calculated for C<sub>24</sub>H<sub>33</sub>FO: C, 80.85; H, 9.33 Found: C, 80.63; H, 9.40. mp 98-99°C.

15

EXAMPLE 191



20

3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl

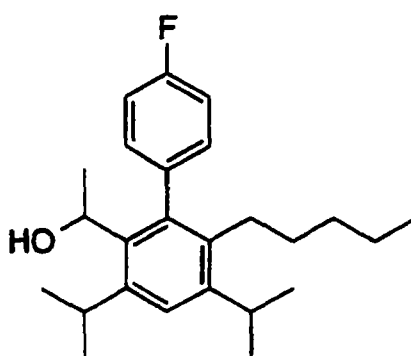
Step A: 3,5-Diisopropyl-2-formyl-6-pentyl-4'-fluoro-1,1'-biphenyl

25 Prepared from 3,5-diisopropyl-2-hydroxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl (Example 190) by the procedure described in Example 1, Step E. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 9.70 (s, 1H), 7.42 (s, 1H), 7.23-7.10 (m, 4H), 3.88 (sept, 6.8 Hz, 1H), 3.23 (sept, 6.8 Hz, 1H), 2.34 (m, 2H), 1.31 (d, 6.6 Hz, 6H), 1.29 (d, 7.0 Hz, 6H), 1.28 (m, 2H), 1.14 (m, 4H), 0.79 (t, 6.6 Hz, 3H). FAB-MS: calculated for C<sub>24</sub>H<sub>31</sub>FO 354; found 355 (M+H).

30

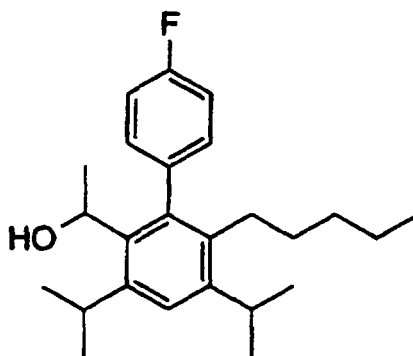
**Step B: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl**

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 101, Step B. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.32 (s, 1H), 7.19-7.06 (m, 4H), 4.70 (dq, 7.0 Hz, 2.9 Hz, 1H), 3.88 (sept, 6.8 Hz, 1H), 3.13 (sept, 6.8 Hz, 1H), 2.20 (m, 2H), 1.63 (d, 2.9 Hz, 1H), 1.40 (d, 6.6 Hz, 3H), 1.30 (d, 7.0 Hz, 6H), 1.3 (m, 2H), 1.27 (d, 7.0 Hz, 6H), 1.08 (m, 4H), 0.78 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>FO 370; found 370 (M<sup>+</sup>). R<sub>f</sub> = 0.36 (83:17 hexanes/ethyl acetate). mp 126°C.

**EXAMPLE 192****3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl**

In a separate experiment, the title compound was prepared by the methods described in Example 191. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.76 - 0.80 (m, 3H), 1.04 - 1.31 (m, 19H), 1.40 (d, J = 6.6 Hz, 3H), 2.17 - 2.22 (m, 2H), 3.11 - 3.16 (m, 1H), 3.86 - 3.90 (m, 1H), 4.66 - 4.73 (m, 1H), 7.06 - 7.22 (m, 4H), 7.32 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.87, 22.01, 23.37, 24.22, 24.55, 24.61, 25.08, 28.66, 28.94, 29.91, 31.02, 32.22, 68.89, 114.65 - 115.15 (2d, 2C), 124.25, 130.33 - 131.28 (2d, 2C), 135.51, 136.96, 137.72, 139.00, 145.80 (2C), 161.67 (d, J = 245.7 Hz, 1C). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>OF 370; found 370 (M<sup>+</sup>). Anal. calc for C<sub>25</sub>H<sub>35</sub>OF: C, 81.03; H, 9.52. Found: C, 81.05; H, 9.70. R<sub>f</sub> = 0.37 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 75% - 100 %B over 30 min; 254 nm, 1 mL/min): R.T. 20.0 min. (91.1 area %); (Daicel Chiralcel OD-H; isocratic 99:1 hexanes:methyl *t*-butyl ether; 254 nm, 1.5 mL/min); R.T. = 5.83 min (49.0 area %), 7.67 min. (51 area %). mp 124.0-125.0°C.

0

EXAMPLE 193(+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl

5 Step A: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl,  
hemi-phthalate ester

A solution of 1.90 g (5.36 mmol) of 3,5-diisopropyl-2-formyl-6-pentyl-4'-fluoro-1,1'-biphenyl (Example 191, Step A) in 36 mL of tetrahydrofuran at -78°C under an argon atmosphere was treated with a dropwise addition of 4.6 mL (6.43 mmol) of a 1.4 M solution of methyllithium in ether. The reaction mixture was allowed to warm to room temperature over one hour. 1.03 g (6.97 mmol) of phthalic anhydride was then added as a solid and stirring was continued for another hour. The reaction was quenched with 30 mL saturated aqueous ammonium chloride and extracted with 60 mL ethyl acetate. Separated organic phase was washed again with 30 mL saturated aqueous ammonium chloride. Combined aqueous portions were extracted with several portions of 20 mL of ethyl acetate. Combined organic portions were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude mixture was purified by flash column chromatography on silica using hexanes:ethyl acetate:acetic acid (75:24:1) as eluent to provide 2.55 g (4.94 mmol, 97 %) of the product. FAB-MS: calculated for C<sub>33</sub>H<sub>39</sub>O<sub>4</sub>F 518; found 519 (M+H). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.77 (t, J = 7.0 Hz, 3H), 1.03 - 1.30 (m, 18H), 1.53 (d, J = 7.0 Hz, 3H), 2.16 - 2.22 (m, 2H), 3.05 - 3.20 (m, 1H), 3.53 - 3.65 (m, 1H), 5.87 - 5.93 (m, 1H), 7.05 - 7.37 (m, 4H), 7.54 - 8.06 (m, 5H). R<sub>f</sub> = 0.47 (75:24:1 hexanes:ethyl acetate:acetic acid).

25

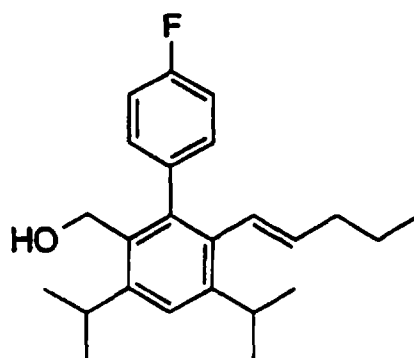
Step B: (+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-  
biphenyl

A solution of 2.54 g (4.90 mmol) of the hemi-phthalate ester from Step A in 50 mL of hexane and 0.5 mL of methanol at reflux was treated with 0.63 mL (4.90 mmol) of (R)-(+)-α-methylbenzylamine. Reflux was continued until solids began to

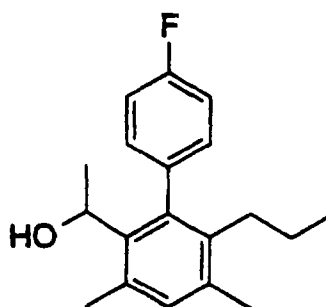
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0 precipitate. At this point, the flask was removed from the hot plate and allowed to cool. Further cooling was achieved by placing the flask in a freezer (-25°C) overnight. Crystals were harvested via filtration and washed with hexane. The amine salt crystals were then suspended in hexane and methanol was added at reflux until the crystals dissolved. Reflux was continued until solids began to  
5 precipitate. At this point, the flask was removed from the hot plate and allowed to cool. Further cooling was not necessary and the salt crystals were harvested as above. The salts were crystallized a third time via the second method described, and the harvested crystals were placed in a vacuum oven overnight at 50°C to afford 0.57 g (0.89 mmol, 18 %) of crystalline amine salt. A solution of 0.57 g (0.89  
10 mmol) of the amine salt in 5 mL dioxane was treated with a 20% solution (w/v) of NaOH/H<sub>2</sub>O and was held at reflux for 3.5 hours. After cooling to room temperature, the reaction mixture was diluted with 20 mL of ethyl acetate. The separated aqueous phase was extracted with ethyl acetate (2 x 10 mL). Combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The crude oil was  
15 purified by flash column chromatography on silica using hexanes:ethyl acetate (19:1) and the resulting material placed in a vacuum oven overnight (at 50°C) to afford 0.26 g (0.70 mmol, 79%) of the title compound as a white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 - 0.80 (m, 3H), 1.02 - 1.31 (m, 19H), 1.40 (d, J = 6.6 Hz, 3H), 2.17 - 2.22 (m, 2H), 3.08 - 3.18 (m, 1H), 3.83 - 3.92 (m, 1H), 4.66 - 4.73 (m, 1H), 7.05 -  
20 7.23 (m, 4H), 7.32 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.88, 22.02, 23.38, 24.23, 24.56, 24.63, 25.09, 28.68, 28.96, 29.92; 31.04, 32.23, 68.91, 114.66 - 115.16 (2d, 2C), 124.27, 130.34 - 131.30 (2d, 2C), 135.53, 136.98, 137.74, 139.02, 145.82 (2C), 161.68 (d, J = 245.4 Hz, 1C). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>OF 370; found 370 (M<sup>+</sup>). Anal. calc for C<sub>25</sub>H<sub>35</sub>OF: C, 81.03; H, 9.52. Found: C, 81.15; H, 9.68. R<sub>f</sub> = 0.36 (9:1  
25 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 75%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 20.0 min (93.9 area %), (Daicel Chiralcel OD-H; isocratic 99:1 hexanes:methyl *t*-butyl ether; 254 nm, 1.5 mL/min); R.T. 5.23 min.(98.0 area %), 8.37 min. (0.89 area %); 98.2 % e.e. [α]<sub>D</sub> = +26.9° (c = 0.00196 g/mL, CH<sub>2</sub>Cl<sub>2</sub>).  
30 mp 95.0-96.0°C.

35

EXAMPLE 1943,5-Diisopropyl-2-hydroxymethyl-6-(pent-1-enyl)-4'-fluoro-1,1'-biphenyl

The title compound was prepared from the intermediate obtained in Example 190, Step F by the procedures described in Example 190, Steps H and I. The olefin was a mixture of cis and trans isomers in a ratio of 17:83.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.33 (s, 1H), 7.15-7.02 (m, 4H), 5.95 (d, 16.2 Hz, 1H), 5.24 (dt, 16.2 Hz, 7.0 Hz, 1H), 4.40 (s, 2H), 3.41 (sept, 6.8 Hz, 1H), 3.30 (sept, 6.8 Hz, 1H), 1.89 (dt, 7.2 Hz, 7.2 Hz, 2H), 1.33 (d, 6.6 Hz, 6H), 1.24 (d, 7.0 Hz, 6H), 1.2 (m, 2H), 0.74 (t, 7.4 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{31}\text{FO}$  354; found 354 ( $\text{M}^+$ ).  $R_f$  = 0.36 (83:17 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{24}\text{H}_{31}\text{FO}$ : C, 81.31; H, 8.81 Found: C, 81.04; H, 8.65. mp 85-95°C.

EXAMPLE 1953,5-Dimethyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenylStep A: 2-Allyloxy-4,6-dimethylacetophenone

A solution of 2-hydroxy-4,6-dimethylacetophenone (4.99 g, 30.4 mmol) in dimethylformamide (31 mL) was added to a cooled (0°C) suspension of sodium hydride (0.772 g, 32.1 mmol) in dimethylformamide (8 mL). The mixture was warmed to room temperature for 2.5 h. The mixture was recooled to 0°C and allyl

0 bromide (5.4 mL, 62.4 mmol) added. The mixture was warmed to room temperature and stirred 25 h. The mixture was diluted with saturated aqueous sodium chloride solution (150 mL) and extracted with diethyl ether (250 mL + 2 x 125 mL). The combined organic phase was washed with 1 N KOH (2 x 125 mL) and saturated aqueous sodium chloride solution. Silica gel chromatography provided a colorless oil (5.74 g, 92%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.64 (s, 1H), 6.56 (s, 1H), 6.03 (ddt, 17.3 Hz, 10.7 Hz, 5.2 Hz, 1H), 5.38 (d, 17.3 Hz, 1H), 5.27 (d, 10.7 Hz, 1H), 4.55 (d, 5.0 Hz, 2H), 2.51 (s, 3H), 2.31 (s, 3H), 2.22 (s, 3H).

**Step B: 2-Hydroxy-3-(prop-2-enyl)-4,6-dimethylacetophenone**

10 A solution of the intermediate obtained in Step A (6.30 g, 30.8 mmol) and 2,6-di-*t*-butyl-4-methylphenol (71.9 mg, 326 mmol) in xylenes was degassed by three freeze-pump-thaw cycles. The mixture was heated in an oil bath at 225°C for 8 h. The mixture was cooled to room temperature and concentrated in vacuo. Silica gel chromatography provided a yellow oil (5.47 g, 87%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 13.09 (s, 1H), 6.56 (s, 1H), 5.93 (m, 1H), 4.95 (m, 2H), 3.42 (d, 6.0 Hz, 2H), 2.65 (s, 3H), 2.55 (s, 3H), 2.27 (s, 3H). EI MS: 204 (M<sup>+</sup>, 70), 189 (100).

**Step C: 2-Acetyl-3,5-dimethyl-6-(prop-2-enyl)phenyltriflate**

20 A solution of triflic anhydride (1.10 mL, 6.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (3.8 mL) was added to a cooled (-10°C) solution of pyridine (0.58 mL, 6.54 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9.6 mL). After 35 min. a solution of the intermediate obtained in Step B (0.271 g, 1.33 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6.4 mL) was added and the mixture allowed to warm to room temperature. After 5 h the mixture was poured into ice water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 x 15 mL). Silica gel chromatography provided a yellow oil (0.426 g, 95%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.09 (s, 1H), 5.86 (m, 1H), 5.09 (d, 10.3 Hz, 1H), 4.93 (d, 17.1 Hz, 1H), 3.51 (d, 5.6 Hz, 2H), 2.52 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H).

**Step D: 3,5-Dimethyl-2-acetyl-6-(prop-2-enyl)-4'-fluoro-1,1'-biphenyl**

30 A mixture of the intermediate obtained in Step C (3.25 g, 9.68 mmol), 4-fluorophenylboronic acid (2.06 g, 14.7 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (1.13 g, 976 μmol), K<sub>3</sub>PO<sub>4</sub> (4.10 g, 19.3 mmol), and KBr (1.97 g, 16.6 mmol) in 1,4-dioxane (50 mL) was heated at 85°C for 16.5 h. The mixture was poured into saturated aqueous ammonium chloride (100 mL) and extracted with diethyl ether (100 mL + 2 x 75 mL). Silica gel chromatography (95:5 hexanes/ethyl acetate) provided a yellow oil (1.03 g, 38%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.18 (m, 2H), 7.06 (m, 3H), 5.76 (m, 1H), 4.97 (d, 10.2 Hz, 1H), 4.72 (d, 17.0 Hz, 1H), 3.15 (d, 5.5 Hz, 2H), 2.32 (s, 3H), 2.24 (s, 3H), 1.91 (s, 3H).

0

**Step E: 3,5-Dimethyl-2-acetyl-6-propyl-4'-fluoro-1,1'-biphenyl**

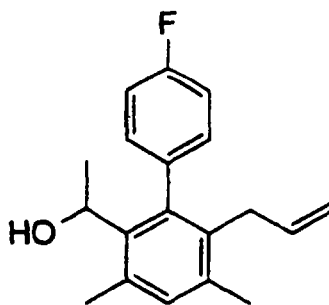
Prepared from the intermediate obtained in Step D by the procedure described in Example 1, Step H.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.19 (m, 2H), 7.07 (m, 3H), 2.36 (m, 5H), 2.22 (s, 3H), 1.91 (s, 3H), 1.32 (m, 2H), 0.75 (t, 7.2 Hz, 3H). FAB-MS: calculated for  $\text{C}_{19}\text{H}_{21}\text{FO}$  284; found 285 (M+H).

5

**Step F: 3,5-Dimethyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl**

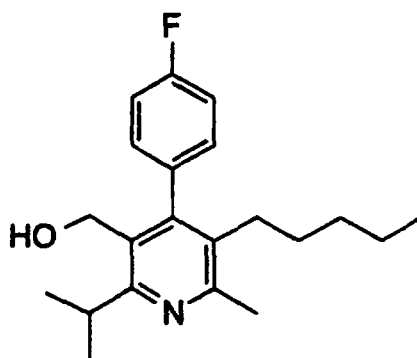
A mixture of the intermediate obtained in Step E (21.0 mg, 73.8  $\mu\text{mol}$ ) and lithium aluminum hydride (31.0 mg, 0.818 mmol) in tetrahydrofuran (2 mL) was refluxed overnight. Aqueous hydrochloric acid (5%, 1 mL) was added and the mixture stirred 1h. The mixture was diluted with 5% aqueous hydrochloric acid (25 mL) and extracted with diethyl ether (3 x 15 mL). Silica gel chromatography provided the title compound as a colorless crystalline solid (15.7 mg, 74%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.19-7.01 (m, 5H), 4.71 (dq, 6.7 Hz, 3.2 Hz, 1H), 2.56 (s, 3H), 2.32 (s, 3H), 2.20 (m, 2H), 1.52 (d, 3.3 Hz, 1H), 1.38 (d, 7.0 Hz, 3H), 1.28 (m, 2H), 0.73 (t, 7.2 Hz). EI-MS: calculated for  $\text{C}_{19}\text{H}_{23}\text{FO}$  286; found 286 ( $\text{M}^+$ , 29), 225 (100).  $R_f$  = 0.31 (83:17 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{19}\text{H}_{23}\text{FO}$ : C, 79.68; H, 8.10 found: C, 79.46; H, 7.95. mp 98-99°C.

20

**EXAMPLE 196****3,5-Dimethyl-2-(1-hydroxyethyl)-6-(prop-2-enyl)-4'-fluoro-1,1'-biphenyl**

The title compound was prepared from the intermediate obtained in Example 195, Step D by the procedure described in Example 195, Step F.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.16-7.02 (m, 5H), 5.66 (m, 1H), 4.90 (d, 10.2 Hz, 1H), 4.75-4.62 (m, 2H), 2.99 (d, 5.5 Hz, 2H), 2.57 (s, 3H), 2.28 (s, 3H), 1.50 (d, 3.7 Hz, 1H), 1.38 (d, 7.0 Hz, 3H).  $R_f$  = 0.27 (83:17 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{19}\text{H}_{21}\text{FO}$ : C, 80.25; H, 7.44 Found: C, 80.14; H, 7.36. mp 92°C.

30

**EXAMPLE 197****2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-methylpyridine****Step A: 2-Isopropyl-3-carboethoxy-4-(4-fluorophenyl)-5-carbomethoxy-6-methyl-1,4-dihydropyridine**

A mixture of methyl 3-aminocrotonate (13 g, 114 mmol) and 4-carboethoxy-5-(4-fluorophenyl)-2-methylpent-4-en-2-one (30 g, 114 mmol) (prepared by the method of Angerbauer, et al. U.S. Patent 5,169,857) in absolute ethanol (300 mL) was refluxed overnight. The mixture was concentrated in vacuo and the crude product taken to the next step without purification.

**Step B: 2-Isopropyl-3-carboethoxy-4-(4-fluorophenyl)-5-(pent-1-enyl)-6-methylpyridine**

Prepared from the intermediate obtained in Step A by the procedures described in Example 1, Steps C-F. The olefin was obtained as a mixture of cis and trans isomers in a ratio of 34:66.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.16 (m, 2H), 7.04 (m, 2H), 6.02 (m, 1H), 5.46 (m, 1H), 4.01 (m, 2H), 3.06 (m, 1H), 2.61 (s, 3H, major isomer), 2.50 (s, 3H, minor isomer), 1.99 (m, 1H), 1.67 (m, 1H), 1.4 - 1.15 (m, 8H), 0.98 (m, 3H), 0.79 (m, 3H).

**Step C: 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(pent-1-enyl)-6-methylpyridine**

A mixture of 1.25 g (3.38 mmol) the intermediate obtained in Step B and lithium aluminum hydride (0.28 g, 6.8 mmol) in tetrahydrofuran (50 mL) was refluxed for 2.5 h. The mixture was quenched with water (10 mL) and extracted with ethyl acetate to provide a colorless crystalline solid (1.0 g, 90%). The olefin was obtained as a mixture of cis and trans isomers in a ratio of 19:81.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.10 (m, 4H), 5.88 (d, 16.2 Hz, 1H), 5.39 (dt, 16.2 Hz, 7.0 Hz, 1H),

0 4.39 (d, 5.5 Hz, 2H), 3.44 (sept, 7.0 Hz, 1H), 2.57 (s, 3H, major isomer), 2.46 (s, 3H, minor isomer), 1.92 (m, 2H), 1.4 - 1.15 (m, 4H), 1.33 (d, 6.6 Hz, 6H), 0.75 (t, 7.4 Hz, 3H). FAB-MS: calculated for  $C_{21}H_{26}FNO$  310; found 326 ((M-H)<sup>+</sup>).  $R_f$  = 0.44 (80:20 hexanes/ethyl acetate). Anal. calculated for  $C_{21}H_{26}FNO$ : C, 77.03; H, 8.00; F, 5.80; N, 4.28. Found: C, 77.02; H, 8.14; F, 5.99; N, 4.22. mp 106-108°C.

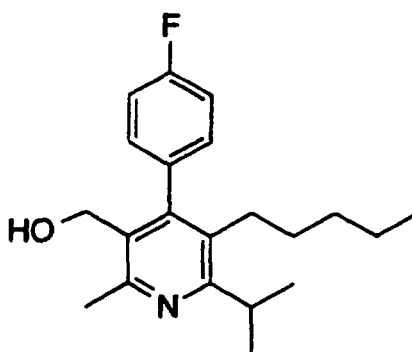
5

Step D: 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-methylpyridine

10 A mixture of the intermediate obtained in Step C (1.3 g) and 10% Pd/C (0.1 g) in absolute ethanol (50 mL) was stirred under an atmosphere of hydrogen overnight. The mixture was filtered through a pad of silica gel and the pad washed with ethyl acetate. Silica gel chromatography (80:20 hexanes/ethyl acetate) followed by recrystallization from ethyl acetate afforded the title compound as colorless crystals (650 mg, 50%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.25 (s, 2H), 7.23 (s, 2H), 4.43 (d, 5.5 Hz, 2H), 3.53 (sept, 7.0 Hz, 1H), 2.69 (s, 3H), 2.35 (m, 2H), 1.44 (d, 6.6 Hz, 6H), 1.4 (m, 2H), 1.2 (m, 4H), 0.88 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $C_{21}H_{28}FNO$  310; found 328 ((M-H)<sup>+</sup>).  $R_f$  = 0.43 (80:20 hexanes/ethyl acetate). Anal. calculated for  $C_{21}H_{28}FNO$ : C, 76.56; H, 8.57; F, 5.77; N, 4.25. Found: C, 76.71; H, 8.60; F, 6.04; N, 4.21. mp 83-85°C.

20

EXAMPLE 198



2-Isopropyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-methylpyridine

25

Step A: 2-Isopropyl-3-carboethoxy-4-(4-fluorophenyl)-5-hydroxymethyl-6-methylpyridine

30 Prepared from the intermediate obtained in Example 197, Step A by the procedures described in Example 1, Steps C and D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.25 (m, 2H), 7.09 (m, 2H), 4.44 (d, 5.1 Hz, 2H), 3.97 (q, 7.1 Hz, 2H), 3.04 (sept, 6.8

- 0 Hz, 1H), 2.71 (s, 3H), 1.53 (t, 5.2 Hz, 1H), 1.30 (d, 6.6 Hz, 6H), 0.96 (t, 7.2 Hz, 3H). EI-MS: calculated for C<sub>19</sub>H<sub>22</sub>FNO<sub>3</sub> 331; found 331.

**Step B:** 2-Isopropyl-3-carboethoxy-4-(4-fluorophenyl)-5-(*t*-butyl-dimethylsiloxy)methyl-6-methylpyridine

- 5 A solution of the intermediate obtained in Step A (3.41 g, 10.3 mmol) *t*-butyldimethylsilylchloride (1.86 g, 1.2 equiv), and imidazole (1.75 g, 2.5 equiv) in dimethylformamide (6 mL) was stirred overnight. The mixture was diluted with water and extracted with ethyl acetate. Silica gel chromatography (95:5 hexanes/ethyl acetate) provided a colorless solid (3.5 g, 76%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.30 (m, 2H), 7.20 (m, 2H), 4.49 (s, 2H), 4.03 (q, 7 Hz, 2H), 3.1 (sept, 1H),  
10 2.72 (s, 3H), 1.34 (d, 7.0 Hz, 6H), 1.01 (t, 7.0 Hz, 3H), 0.90 (s, 9H), 0.00 (s, 6H). FAB-MS: calculated for C<sub>25</sub>H<sub>36</sub>FNO<sub>3</sub>Si 331; found 446 (M+H).

**Step C:** 2-Isopropyl-3-(pent-1-enyl)-4-(4-fluorophenyl)-5-(*t*-butyl-dimethylsiloxy)methyl-6-methylpyridine

- 15 Prepared from the intermediate obtained in Step B by the procedures described in Example 1, Steps D, E, and F. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.2-7.0 (m, 4H), 5.99 (d, 16.2 Hz, 1H), 5.28 (dt, 15.6 Hz, 7.2 Hz, 1H), 4.30 (s, 2H), 3.38 (m, 1H), 2.67 (m, 3H), 1.92 (m, 2H), 1.4-1.2 (m, 8H), 0.85 (s, 9H), 0.75 (t, 7.4 Hz, 3H), -  
20 0.06 (s, 6H).

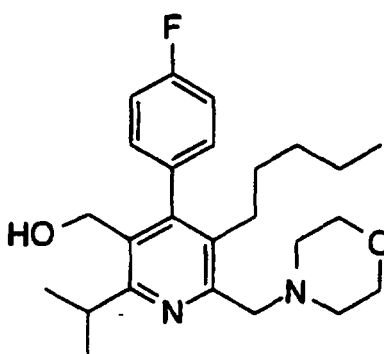
**Step D:** 2-Isopropyl-3-(pent-1-enyl)-4-(4-fluorophenyl)-5-hydroxymethyl-6-methylpyridine

- 25 Tetrabutylammonium fluoride (1 mL of 1.0 M solution in tetrahydrofuran, 2.5 equiv) was added to a solution of the intermediate obtained in Step C (200 mg, 0.45 mmol) in tetrahydrofuran (10 mL). After 2 h the mixture was concentrated in vacuo. The residue was dissolved in water and extracted with ethyl acetate. Silica gel chromatography (80:20 hexanes/ethyl acetate) provided a colorless solid (120 mg, 81%). The olefin was obtained as a mixture of *cis* and *trans* isomers in a ratio  
30 of 8:92. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.09 (m, 4H), 5.96 (d, 16.2 Hz, 1 H), 5.27 (dt, 16.2 Hz, 1H), 4.38 (d, 5.5 Hz, 2H), 3.36 (sept, 1H), 2.69 (s, 3H), 1.90 (m, 2H), 1.4 - 1.1 (m, 4H), 1.25 (d, 6.6 Hz, 6H), 0.73 (t, 7.4 Hz, 3H). FAB-MS: calculated for C<sub>21</sub>H<sub>26</sub>FNO 327; found 327 (M<sup>+</sup>). R<sub>f</sub> = 0.23 (80:20 hexanes/ethyl acetate). Anal. calculated for C<sub>21</sub>H<sub>26</sub>FNO: C, 77.03; H, 8.00; F, 5.80; N, 4.28. Found: C, 76.92; H,  
35 8.07; F, 5.92; N, 4.15. mp 119-120°C.

0 **Step E:** **2-Isopropyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-**  
**methylpyridine**

The title compound was obtained as a colorless solid in 86% yield from the intermediate obtained in Step D by the procedure described in Example 1, Step H. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.2 (m, 4H), 4.29 (d, 5.5 Hz, 2H), 3.24 (sept, 6.6 Hz, 1H), 2.65 (s, 3H), 2.26 (m, 2H), 1.29 (d, 6.6 Hz, 6H), 1.25 (m, 4H), 1.1 (m, 4H), 0.76 (t, 7.0 Hz, 3H). FAB-MS: calculated for C<sub>21</sub>H<sub>28</sub>FNO 329; found 328 ((M-H)<sup>+</sup>). R<sub>f</sub> = 0.20 (80:20 hexanes/ethyl acetate). Anal. calculated for C<sub>21</sub>H<sub>28</sub>FNO: C, 76.56; H, 8.57; F, 5.77; N, 4.25. Found: C, 76.49; H, 8.55; F, 5.78; N, 4.21. mp 110-112°C.

10 EXAMPLE 199



15 2-Morpholinomethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-  
isopropylpyridine

**Step A:** 2-Isopropyl-3-(*t*-butyldiphenylsiloxy)methyl-4-(4-fluorophenyl)-5-pentyl-6-methylpyridine

A solution of the intermediate from Example 197, Step D (50 mg, 0.15 mmol), *t*-butyldiphenylsilylchloride (50 mg, 1.2 equiv), and imidazole (25 mg, 2.5 equiv) in dimethylformamide (0.5 mL) was stirred for 2 h. The mixture was diluted with water and extracted with ethyl acetate. Silica gel chromatography (95:5 hexanes/ethyl acetate) provided a colorless solid (64 mg, 75%). <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.41 (m, 6H), 7.33 (m, 4H), 7.05 (m, 4H), 4.25 (s, 2H), 3.13 (sept, 6.8 Hz, 1H), 2.57 (s, 3H), 2.23 (m, 2H), 1.3 (m, 2H), 1.17 (d, 6.6 Hz, 6H), 1.15 (m, 4H), 0.99 (s, 9H), 0.78 (t, 6.4 Hz, 3H).

**Step B:** 2-Isopropyl-3-(*t*-butyldiphenylsiloxy)methyl-4-(4-fluorophenyl)-5-pentyl-6-methylpyridine *N*-oxide

30 A mixture of the intermediate from Step A (60 mg, 0.11 mmol) and 3-

- 0 chloroperoxybenzoic acid (52 mg, 1.4 equiv) in chloroform (5 mL) was refluxed for 15 min. The mixture was diluted with ethyl acetate (30 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 25 mL). The organic phase was filtered through a shoroom temperature pad of silica gel and concentrated to give a yellow solid (54 mg, 84%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.31 (m, 6H), 7.24 (m, 4H), 6.96 (m, 4H), 4.13 (s, 2H), 3.16 (br s, 1H), 2.47 (s, 3H), 2.18 (m, 2H), 1.33 (d, 6.6 Hz, 6H), 1.25 (m, 2H), 1.05 (m, 4H), 0.93 (s, 9H), 0.70 (t, 6.4 Hz, 3H).

Step C: 2-Chloromethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

- 10 Phosphorus oxychloride (9.5 g) and triethyl amine (8.6 mL) were added simultaneously to a refluxing solution of the intermediate obtained in Step B (15 g, 25.8 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL). After 3 h, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL) and washed with saturated aqueous sodium bicarbonate solution (3 x 100 mL). Silica gel chromatography (90:10 hexanes/ethyl acetate) provided a solid (9.4 g, 61%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41 (m, 6H), 7.32 (m, 4H), 7.06 (m, 4H), 4.75 (s, 2H), 4.27 (s, 2H), 3.15 (sept, 6.8 Hz, 1H), 2.39 (m, 2H), 1.35 (m, 2H), 1.18 (d, 6.6 Hz, 6H), 1.12 (m, 4H), 1.00 (s, 9H), 0.79 (t, 6.6 Hz, 3H).

Step D: 2-Morpholinomethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

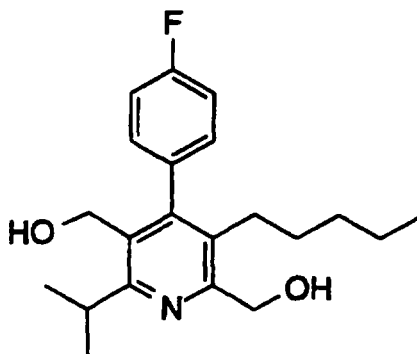
- 20 A mixture of the intermediate prepared in Step C (0.5 g, 0.83 mmol), morpholine (0.108 g, 1.5 equiv), and 4-dimethylaminopyridine (0.172 g, 1.7 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was refluxed for 2 h. The mixture was washed with saturated aqueous sodium chloride solution. Silica gel chromatography (90:10 hexanes/ethyl acetate) provided a yellow oil (170 mg, 30%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41 (m, 6H), 7.34 (m, 4H), 7.05 (m, 4H), 4.26 (s, 2H), 3.71 (m, 4H), 3.67 (s, 2H), 3.13 (sept, 6.8 Hz, 1H), 2.61 (m, 4H), 2.35 (m, 2H), 1.15 (d, 6.6 Hz, 6H), 1.1 (m, 4H), 0.99 (s, 9H), 0.9 (m, 2H), 0.78 (t, 7.0 Hz, 3H).

- 30 Step E: 2-Morpholinomethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

- The title compound was prepared from the intermediate obtained in Step D by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.17 (m, 4H), 4.36 (d, 5.1 Hz, 2H), 3.68 (m, 6H), 3.42 (sept, 6.6 Hz, 1H), 2.59 (m, 4H), 2.39 (m, 2H), 1.32 (d, 6.6 Hz, 6H), 1.25 (m, 2H), 1.1 (m, 4H), 0.78 (t, 6.6 Hz, 3H). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>2</sub> 414; found 415 (M+H). Anal. calculated for

0 C<sub>25</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>2</sub>: C, 72.43; H, 8.51; F, 4.58; N, 6.76. Found: C, 72.49; H, 8.42; F, 4.71; N, 7.05.

### EXAMPLE 200



#### 2,5-Bis(hydroxymethyl)-3-pentyl-4-(4-fluorophenyl)-6-isopropylpyridine

##### Step A: 2-Acetoxymethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

A mixture of the intermediate obtained in Example 199, Step B (4.8 g, 7.97 mmol) and acetic anhydride (20 mL) was heated to 100°C for 20 min. The mixture was poured onto ice and the aqueous phase extracted with ethyl acetate (3 x 30 mL). The combined organic phase was washed with saturated aqueous sodium bicarbonate solution (3 x 50 mL), and saturated aqueous sodium chloride solution (3 x 50 mL). Silica gel chromatography provided a yellow oil (4.4 g, 90%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40 (m, 6H), 7.31 (m, 4H), 7.06 (m, 4H), 5.29 (s, 2H), 4.26 (s, 2H), 3.14 (sept, 6.8 Hz, 1H), 2.2 (m, 2H), 2.18 (s, 3H), 1.2 (m, 2H), 1.16 (d, 6.6 Hz, 6H), 1.05 (m, 4H), 0.99 (s, 9H), 0.77 (t, 6.8 Hz, 3H).

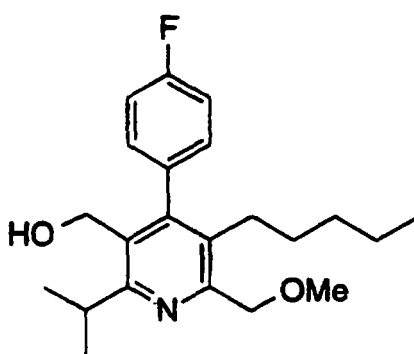
##### Step B: 2-Hydroxymethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

A mixture of the intermediate obtained in Step A (60 mg, 0.096 mmol) and potassium carbonate (5 equiv) in methanol (8 mL) and water (2 mL) was refluxed for 1.5 h. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium chloride solution. Concentration of the organic phase provided a colorless solid (60 mg, 100%) that was used in the next step without purification. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.4-7.2 (m, 10H), 7.11 (m, 4H), 4.90 (s, 2H), 4.39 (s, 2H), 3.34 (sept, 7.0 Hz, 1H), 2.34 (m, 2H), 1.25 (d, 7.0 Hz, 6H), 1.2 (m, 2H), 1.04 (m, 4H), 0.90 (s, 9H), 0.68 (t, 7.0 Hz, 3H).

**Step C:**     2,5-Bis(hydroxymethyl)-3-pentyl-4-(4-fluorophenyl)-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Step B by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>OD): δ 7.21 (m, 4H), 4.70 (s, 2H), 4.30 (s, 2H), 3.54 (sept, 6.6 Hz, 1H), 2.28 (m, 2H), 1.32 (d, 6.6 Hz, 6H), 1.25 (m, 2H), 1.1 (m, 4H), 0.75 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>21</sub>H<sub>28</sub>FNO<sub>2</sub> 345; found 346 (M+H). Anal. calculated for C<sub>21</sub>H<sub>28</sub>FNO<sub>2</sub>: C, 73.01; H, 8.17; F, 5.50; N, 4.05. Found: C, 72.89; H, 8.25; F, 5.21; N, 4.41. mp 135-136°C.

**EXAMPLE 201**



**2-Methoxymethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine**

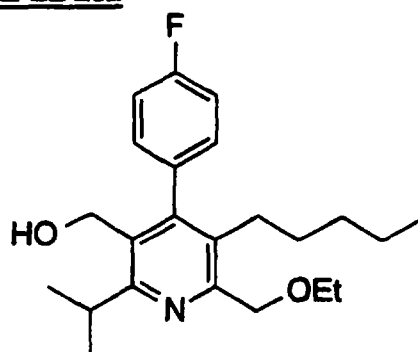
**Step A:**     2-Methoxymethyl-3-pentyl-4-(4-fluorophenyl)-5-(t-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

A mixture of the intermediate obtained in Example 200, Step B (0.1 g, 0.17 mmol), methyl iodide (0.013 mL, 1.2 equiv), and sodium hydride (8 mg of a 60% dispersion in mineral oil, 1.2 equiv) in tetrahydrofuran (1 mL) was heated at 40°C for 3 h. The mixture was diluted with water and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was washed with saturated aqueous sodium chloride solution (3 x 10 mL). Silica gel chromatography provided a colorless solid (40 mg, 40%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41 (m, 6H), 7.32 (m, 4H), 7.06 (m, 4H), 4.62 (s, 2H), 4.27 (s, 2H), 3.48 (s, 3H), 3.15 (sept, 6.6 Hz, 1H), 2.36 (m, 2H), 1.27 (m, 2H), 1.18 (d, 6.6 Hz, 6H), 1.12 (m, 2H), 1.00 (s, 9H), 0.87 (m, 2H), 0.78 (t, 6.6 Hz, 3H).

0    Step B:        2-Methoxymethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-  
                          isopropylpyridine

          The title compound was prepared from the intermediate obtained in Step A  
 by the procedure described in Example 198, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$   
 7.14 (m, 4H), 4.62 (s, 2H), 4.36 (d, 5.2 Hz, 2H), 3.46 (s, 3H), 3.44 (sept, 6.6 Hz, 1H),  
 5    2.38 (m, 2H), 1.34 (d, 7.0 Hz, 6H), 1.23 (m, 2H), 1.12 (m, 4H), 0.77 (t, 6.8 Hz, 3H).  
 FAB-MS: calculated for  $\text{C}_{22}\text{H}_{30}\text{FNO}_2$  359; found 360 (M+H). Anal. calculated for  
 $\text{C}_{22}\text{H}_{30}\text{FNO}_2$ : C, 73.51; H, 8.41; F, 5.28; N, 3.90. Found: C, 73.40; H, 8.47; F, 5.19;  
 N, 3.91.

EXAMPLE 202

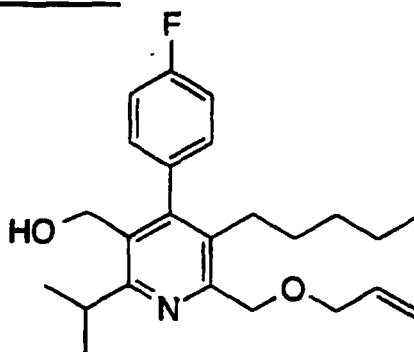


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2-Ethoxymethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

          The title compound was prepared from the intermediate obtained in  
 15    Example 200, Step B by the procedures described in Example 201, Step A, and  
 Example 198, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 (m, 4H), 4.68 (s, 2H), 4.35  
 (d, 4.4 Hz, 2H), 3.65 (q, 7.0 Hz, 2H), 3.44 (sept, 6.6 Hz, 1H), 2.40 (m, 2H), 1.4 (m, 2H),  
 1.34 (d, 6.6 Hz, 6H), 1.26 (t, 7.0 Hz, 3H), 1.13 (m, 4H), 0.78 (t, 6.6 Hz, 3H). FAB-MS:  
 calculated for  $\text{C}_{23}\text{H}_{32}\text{FNO}_2$  373; found 374 (M+H). Anal. calculated for  
 20     $\text{C}_{23}\text{H}_{32}\text{FNO}_2$ : C, 73.96; H, 8.64; F, 5.09; N, 3.75. Found: C, 73.97; H, 8.83; F, 5.33;  
 N, 3.52.

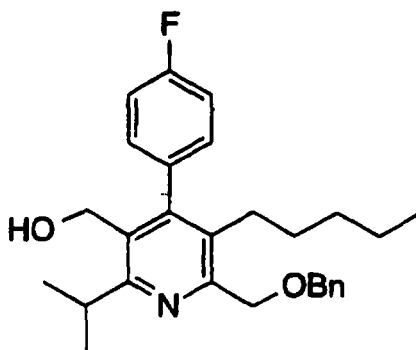
EXAMPLE 203



2-(Prop-2-enyloxy)methyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Example 200, Step B by the procedures described in Example 201, Step A, and Example 198, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (m, 4H), 5.97 (ddt, 17.1 Hz, 10.5 Hz, 6 Hz, 2H), 5.33 (d, 17.3 Hz, 1H), 5.21 (d, 10.3 Hz, 1H), 4.68 (s, 2H), 4.34 (s, 2H), 4.12 (d, 5.5 Hz, 2H), 3.44 (sept, 6.8 Hz, 1H), 2.39 (m, 2H), 1.33 (d, 6.6 Hz, 6H), 1.29 (m, 2H), 1.10 (m, 4H), 0.77 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{32}\text{FNO}_2$  385; found 386 (M+H). Anal. calculated for  $\text{C}_{24}\text{H}_{32}\text{FNO}_2$ : C, 74.8; H, 8.37; F, 4.93; N, 3.63. Found: C, 75.2; H, 8.54; F, 4.90; N, 3.52.

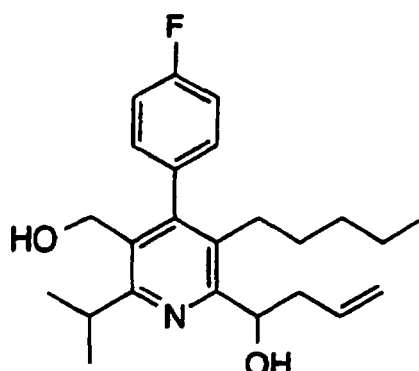
EXAMPLE 204



2-Benxyloxymethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Example 200, Step B by the procedures described in Example 201, Step A, and Example 198, Step D.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.43-7.30 (m, 5H), 7.17 (m, 4H), 4.73 (s, 2H), 4.66 (s, 2H), 4.36 (s, 2H), 3.46 (sept, 6.6 Hz, 1H), 2.38 (m, 2H), 1.36 (d, 6.6 Hz, 6H), 1.25 (m, 2H), 1.05 (m, 4H), 0.75 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{32}\text{FNO}_2$  435; found 436 (M+H). Anal. calculated for  $\text{C}_{28}\text{H}_{34}\text{FNO}_2$ : C, 77.21; H, 7.87; F, 4.36; N, 3.22. Found: C, 77.26; H, 7.84; F, 4.42; N, 3.11. mp 110-112°C.

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EXAMPLE 205

2-(1-Hydroxybut-3-enyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-  
isopropylpyridine

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Step A: 2-Formyl-3-pentyl-4-(4-fluorophenyl)-5-(t-butyldiphenyl-  
siloxymethyl)-6-isopropylpyridine

Prepared from 2-hydroxymethyl-3-pentyl-4-(4-fluorophenyl)-5-  
 [(t-butyldiphenylsiloxy)methyl]-6-isopropylpyridine (Example 200, Step B) by the  
 procedure described in Example 1, Step E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 10.20 (s,  
 1H), 7.41 (m, 6H), 7.33 (m, 4H), 7.04 (m, 4H), 4.33 (s, 2H), 3.23 (sept, 6.6 Hz, 1H),  
 2.66 (m, 2H), 1.3-1.1 (m, 6H), 1.22 (d, 6.6 Hz, 6H), 1.01 (s, 9H), 0.79 (t, 7.0 Hz, 3H).  
 FAB-MS: calculated for C<sub>37</sub>H<sub>44</sub>FN<sub>2</sub>O<sub>2</sub>Si 581; found 582 (M+H).

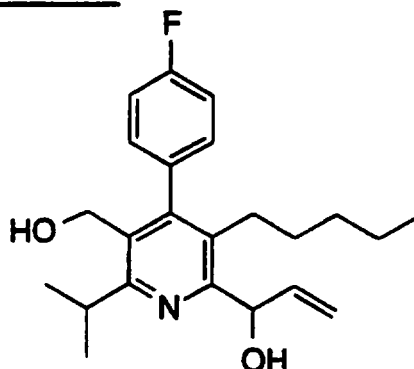
Step B: 2-(1-Hydroxybut-3-enyl)-3-pentyl-4-(4-fluorophenyl)-5-  
(t-butyldiphenylsiloxy)methyl-6-isopropylpyridine

A mixture of the intermediate obtained in Step A (0.2 g, 0.34 mmol) and  
 allylmagnesium bromide (1 mL of 1.0 M solution in tetrahydrofuran, 3 equiv) in  
 tetrahydrofuran (10 mL) was refluxed for 1.5 h. The mixture was concentrated in  
 vacuo. The residue was dissolved in ethyl acetate and washed with saturated  
 aqueous sodium chloride solution. Silica gel chromatography (97:3 hexanes/ethyl  
 acetate) provided a yellow oil (110 mg, 52%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.42  
 (m, 6H), 7.2 (m, 4H), 7.06 (m, 4H), 5.94 (m, 1H), 5.14-5.08 (m, 2H), 4.99-4.90 (m, 2H),  
 4.28 (d, 2.2 Hz, 2H), 3.16 (sept, 6.8 Hz, 1H), 2.55 (m, 1H), 2.45-2.15 (m, 3H), 1.3 (m,  
 2H), 1.20 (d, 6.6 Hz, 3H), 1.15 (d, 6.6 Hz, 3H), 1.1 (m, 4H), 0.76 (t, 6.6 Hz, 3H).

Step C: 2-(1-Hydroxybut-3-enyl)-3-pentyl-4-(4-fluorophenyl)-5-  
hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Step B  
 by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ

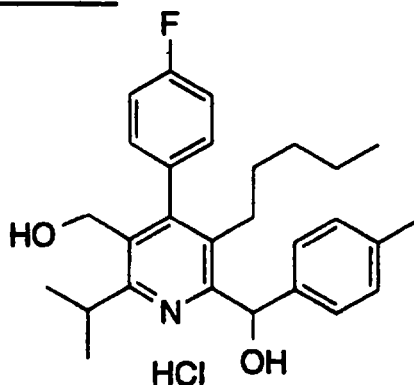
- 0 7.16 (m, 4H), 5.94 (m, 1H), 5.13 (d, 7.7 Hz, 1H), 5.08 (s, 1H), 4.92 (s, 2H), 4.38 (m, 2H), 3.47 (sept, 6.7 Hz, 1H), 2.51 (m, 1H), 2.4-2.1 (m, 3H), 1.35 (d, 6.6 Hz, 3H), 1.34 (d, 6.6 Hz, 3H), 1.29 (m, 2H), 1.10 (m, 4H), 0.77 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $C_{24}H_{32}FNO_2$  385; found 386 (M+H).  $R_f$  = 0.15 (85:15 hexanes/ethyl acetate). Anal. calculated for  $C_{24}H_{32}FNO_2$ : C, 74.77; H, 8.37; F, 4.93; N, 3.63. Found: C, 74.85; H, 8.53; F, 4.99; N, 3.50.
- 5

EXAMPLE 206

10 2-(1-Hydroxyprop-2-enyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Prepared from the intermediate in Example 205, Step A by the procedures described in Example 205, Step B, and Example 198, Step D.  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.16 (m, 4H), 5.89 (d, 17.0 Hz, 10.0 Hz, 7.1 Hz, 1H), 5.66 (d, 5.5 Hz, 1H),

- 15 5.37 (d, 16.9 Hz, 1H), 5.26 (t, 5.7 Hz, 1H), 5.20 (d, 9.9 Hz, 1H), 4.38 (d, 4.8 Hz, 2H), 3.49 (sept, 6.7 Hz, 1H), 2.33 (m, 1H), 2.13 (m, 2H), 1.35 (d, 6.6 Hz, 3H), 1.34 (d, 6.6 Hz, 3H), 1.2 (m, 2H), 1.10 (m, 4H), 0.76 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $C_{23}H_{30}FNO_2$  371; found 372 (M+H).  $R_f$  = 0.15 (85:15 hexanes/ethyl acetate). MP = 113-115°C. Anal. calculated for  $C_{23}H_{30}FNO_2$ : C, 74.36; H, 8.14; F, 5.11; N, 3.77.
- 20 Found: C, 74.16; H, 8.28; F, 5.11; N, 3.60.

EXAMPLE 207

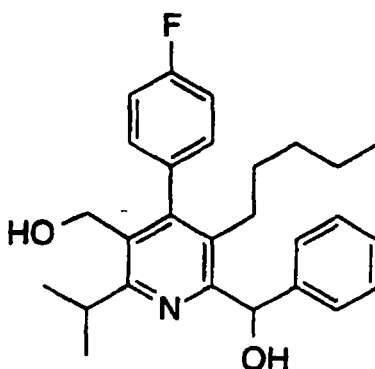
0

2-(Hydroxy-*p*-tolyl)methyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine, hydrochloride

Prepared from the intermediate in Example 205, Step A by the procedures described in Example 205, Step B, and Example 198, Step D. <sup>1</sup>H NMR (CD<sub>3</sub>OD, 300 MHz): δ 7.28 (m, 6H), 7.21 (m, 2H), 6.90 (d, 7.7 Hz, 1H), 6.43 (s, 1H), 4.48 (d, 11.8 Hz, 1H), 4.41 (d, 11.8 Hz, 1H), 3.96 (sept, 6.8 Hz, 1H), 2.46 (s, 3H), 2.19 (m, 2H), 1.61 (d, 7.0 Hz, 3H), 1.58 (d, 7.0 Hz, 3H), 1.0-0.6 (m, 5H), 0.57 (t, 7.0 Hz, 3H), 0.3 (m, 1H). FAB-MS: calculated for C<sub>28</sub>H<sub>34</sub>FNO<sub>2</sub> 435; found 436 (M+H). Anal. calculated for C<sub>28</sub>H<sub>34</sub>FNO<sub>2</sub>·HCl: C, 71.25; H, 7.47; Cl, 7.51; F, 4.02; N, 2.97. Found: C, 71.43; H, 7.49; Cl, 7.48; F, 4.10; N, 2.87. mp 178-180°C.

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EXAMPLE 208



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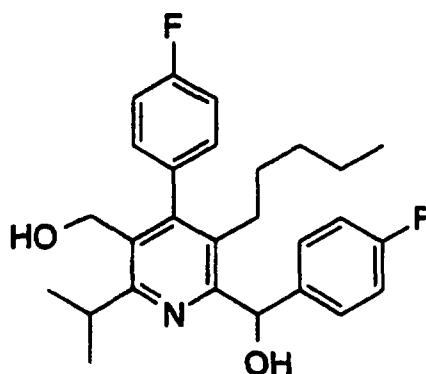
2-(a-Hydroxy)benzyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Prepared from the intermediate in Example 205, Step A by the procedures described in Example 205, Step B, and Example 198, Step D. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.30 (m, 5H), 7.17 (m, 4H), 6.43 (d, 6.6 Hz, 1H), 5.79 (d, 6.6 Hz, 1H), 4.40 (m, 2H), 3.55 (sept, 6.6 Hz, 1H), 2.21-2.09 (m, 2H), 1.45 (d, 6.6 Hz, 3H), 1.43 (d, 6.6 Hz, 3H), 1.32 (m, 1H), 1.14-0.88 (m, 6H), 0.69 (t, 3H). FAB-MS: calculated for C<sub>27</sub>H<sub>32</sub>FNO<sub>2</sub> 421; found 422 (M+H). R<sub>f</sub> = 0.10 (85:15 hexanes/ethyl acetate). Anal. calculated for C<sub>27</sub>H<sub>32</sub>FNO<sub>2</sub>: C, 76.93; H, 7.65; F, 4.51; N, 3.32. Found: C, 76.70; H, 7.86; F, 4.45; N, 3.14.

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EXAMPLE 209

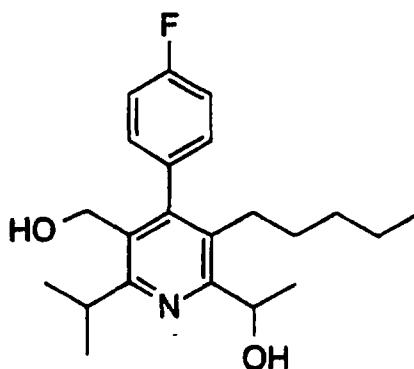
5

2-(4-Fluorophenyl)hydroxymethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

10

Prepared from the intermediate in Example 205, Step A by the procedures described in Example 205, Step B, and Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.24 (m, 2H), 7.15 (m, 4H), 6.98 (m, 2H), 6.40 (d, 5.9 Hz, 1H), 5.77 (d, 5.5 Hz, 1H), 4.40 (m, 2H), 3.55 (sept, 6.6 Hz, 1H), 2.13 (m, 2H), 1.43 (d, 6.3 Hz, 3H), 1.41 (d, 6.6 Hz, 3H), 1.08 (m, 1H), 0.99 (m, 6H), 0.69 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{27}\text{H}_{31}\text{F}_2\text{NO}_2$  439; found 440 ( $\text{M}+\text{H}$ ).  $R_f$  = 0.15 (85:15 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{27}\text{H}_{31}\text{F}_2\text{NO}_2$ : C, 73.78; H, 7.11; F, 8.64; N, 3.19. Found: C, 73.49; H, 7.23; F, 8.45; N, 3.01.

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EXAMPLE 210

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2-(1-Hydroxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Step A: 2-(1-Hydroxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

0 Prepared from the intermediate in Example 205, Step A by the procedure described in Example 205, Step B.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.42 (m, 6H), 7.32 (m, 4H), 7.05 (m, 4H), 5.16 (d, 7.7 Hz, 1H), 4.99 (m, 1H), 4.28 (s, 2H), 3.16 (sept, 6.8 Hz, 1H), 2.25 (m, 2H), 1.45 (d, 6.3 Hz, 2H), 1.19 (d, 6.6 Hz, 3H), 1.16 (d, 6.6 Hz, 3H), 1.10 (m, 6H), 0.76 (t, 6.8 Hz, 3H).

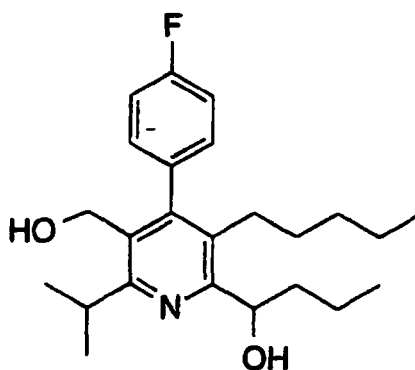
5

Step B: 2-(1-Hydroxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate in Step A by the procedure described in Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.19-7.15 (m, 4H), 5.12 (d, 7.0 Hz, 1H), 4.99 (t, 1H), 4.38 (d, 5.5 Hz, 2H), 3.48 (sept, 6.8 Hz, 1H), 2.27 (m, 2H), 1.43 (d, 6.3 Hz, 1H), 1.35 (d, 6.6 Hz, 6H), 1.30 (m, 2H), 1.09 (m, 7H), 0.76 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{22}\text{H}_{30}\text{FNO}_2$  359; found 360 (M+H).  $R_f$  = 0.15 (85:15 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{22}\text{H}_{30}\text{FNO}_2$ : C, 73.51; H, 8.41; F, 5.28; N, 3.90. Found: C, 73.24; H, 8.40; F, 5.41; N, 3.85. mp 125-127°C.

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EXAMPLE 211



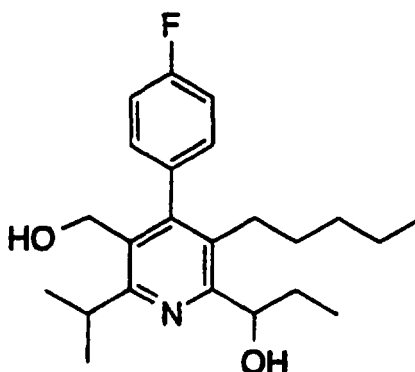
20

2-(1-Hydroxybutyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Prepared from the compound obtained in Example 205 by the procedure described in Example 1, Step H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.17 (m, 4H), 4.92 (br s, 2H), 4.85 (br s, 2H), 4.37 (d, 5.2 Hz, 2H), 3.47 (sept, 6.6 Hz, 1H), 2.29-2.23 (m, 2H), 1.62-1.53 (m, 5H), 1.35 (d, 6.6 Hz, 3H), 1.34 (d, 6.6 Hz, 3H), 1.3 (m, 1H), 1.11 (m, 5H), 0.94 (t, 7.0 Hz, 3H), 0.77 (t, 6.4 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$  387; found 388 (M+H). Anal. calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$ : C, 74.38; H, 8.84; F, 4.90; N, 3.61. Found: C, 74.11; H, 8.93; F, 4.96; N, 3.51.

30

0

EXAMPLE 212

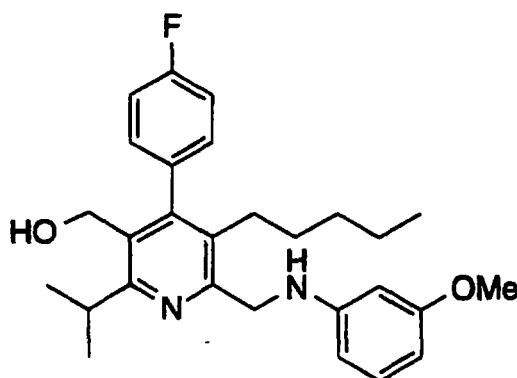
5

2-(1-Hydroxypropyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

10

The title compound was prepared from the intermediate obtained in Example 206 by the procedure described in Example 1, Step H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.18 (m, 4H), 4.94 (br s, 1H), 4.82 (br s, 1H), 4.39 (d, 4.8 Hz, 2H), 3.48 (sept, 6.6 Hz, 1H), 2.3-2.1 (m, 2H), 1.82 (m, 1H), 1.36 (d, 5.5 Hz, 3H), 1.34 (d, 6.3 Hz, 3H), 1.11 (m, 8H), 1.02 (t, 7.4 Hz, 3H), 0.78 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{23}\text{H}_{32}\text{FNO}_2$  373; found 374 ( $\text{M}+\text{H}$ ).  $R_f$  = 0.15 (85:15 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{23}\text{H}_{32}\text{FNO}_2$ : C, 73.96; H, 8.64; F, 5.09; N, 3.75. Found: C, 73.88; H, 8.57; F, 5.17; N, 3.53. mp 89-90°C.

15

EXAMPLE 213

20

2-N-(2-Methoxyphenyl)aminomethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

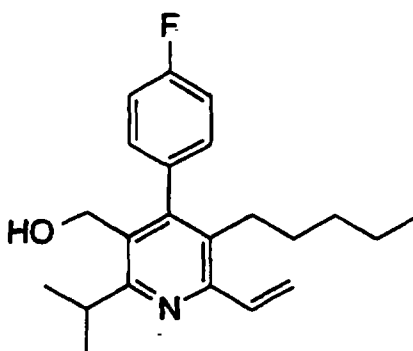
Step A: 2-N-(2-Methoxyphenyl)aminomethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

0 A mixture of the intermediate from Example 205, Step A (60 mg, 0.10 mmol) and *m*-anisidine (50 mg, 4 equiv) in methanol (10 mL) was treated with a mixture of zinc chloride (7 mg, 0.5 equiv) and sodium cyanoborohydride (6 mg, 1 equiv) in methanol (15 mL). After stirring at room temperature overnight the mixture was quenched with water and extracted with ethyl acetate (3 x 15 mL). The combined  
 5 organic phase was washed with saturated aqueous sodium chloride solution (3 x 15 mL). Silica gel chromatography provided a colorless solid (70 mg, 99%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.43 (m, 6H), 7.32 (m, 4H), 7.16 (m, 1H), 7.06 (m, 4H), 6.43 (m, 1H), 6.32 (m, 2H), 5.98 (br s, 1H), 4.38 (s, 2H), 4.29 (s, 2H), 3.83 (s, 3H), 3.19 (sept, 6.6 Hz, 1H), 2.28 (m, 2H), 1.25 (m, 2H), 1.22 (d, 6.6 Hz, 6H), 1.14 (m, 2H), 0.99 (s, 9H),  
 10 0.80 (t, 6.8 Hz, 3H).

Step B: 2-N-(2-Methoxyphenyl)aminomethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

15 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 5H), 6.43 (m, 1H), 6.32 (m, 2H), 4.40 (s, 2H), 4.39 (s, 2H), 3.83 (s, 3H), 3.50 (sept, 6.6 Hz, 1H), 2.32 (m, 2H), 1.39 (d, 6.6 Hz, 6H), 1.31 (m, 2H), 1.16 (m, 4H), 0.80 (t, 6.4 Hz, 3H). FAB-MS: calculated for C<sub>28</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>2</sub> 450; found 451 (M+H). Anal. calculated for C<sub>28</sub>H<sub>35</sub>FN<sub>2</sub>O<sub>2</sub>: C, 74.64; H, 7.83; N, 6.22. Found: C, 74.44; H, 7.75;  
 20 N, 6.03. mp 109-110°C.

EXAMPLE 214



2-Ethenyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Step A: 2-Ethenyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

30 *n*-Butyl lithium (0.03 mL of 1.6 M solution in hexanes) was added to a cooled

0 (0°C) solution of methyltriphenylphosphonium bromide (18 mg) in tetrahydrofuran (3 mL). After 2 h, a solution of 2-formyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine (Example 205, Step A) in tetrahydrofuran (1 mL) was added and the mixture warmed to room temperature. After 30 min. the mixture was quenched with water and extracted with ethyl acetate. Silica gel chromatography (95:5 hexanes/ethyl acetate) afforded a colorless solid (20 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.44-7.36 (m, 6H), 7.34-7.27 (m, 4H), 7.08-6.98 (m, 5H), 6.59 (dd, 16.7 Hz, 2.7 Hz, 1H), 5.48 (dd, 10.5 Hz, 2.8 Hz, 1H), 4.26 (s, 2H), 3.16 (sept, 6.6 Hz, 1H), 2.29 (m, 2H), 1.4-1.2 (m, 2H), 1.19 (d, 6.6 Hz, 6H), 1.15 (m, 4H), 0.98 (s, 9H), 0.78 (t, 6.8 Hz, 3H).

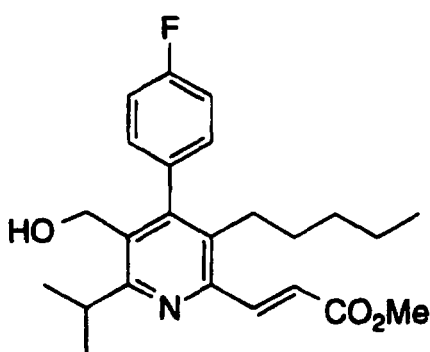
10

Step B: 2-Ethenyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Step / by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.17 (s, 2H), 7.14 (s, 2H), 7.04 (dd, 16.7 Hz, 10.5 Hz, 1H), 6.61 (dd, 16.7 Hz, 2.8 Hz, 1H), 5.51 (dd, 10.5 Hz, 2.8 Hz, 1H), 4.36 (s, 2H), 3.45 (sept, 6.7 Hz, 1H), 2.32 (m, 2H), 1.37 (d, 6.6 Hz, 6H), 1.34 (m, 2H), 1.15 (m, 4H), 0.80 (t, 6.6 Hz, 3H). FAB-MS: calculated for C<sub>22</sub>H<sub>28</sub>FNO 341; found 342 (M+H). Anal. calculated for C<sub>22</sub>H<sub>28</sub>FNO: C, 77.38; H, 8.27; N, 4.10. Found: C, 77.15; H, 7.98; N, 4.06.

20

EXAMPLE 215



25 2-(2-Carbomethoxyethenyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

Step A: 2-(2-Carbomethoxyethenyl)-3-pentyl-4-(4-fluorophenyl)-5-(t-butyldiphenylsiloxy)methyl-6-isopropylpyridine

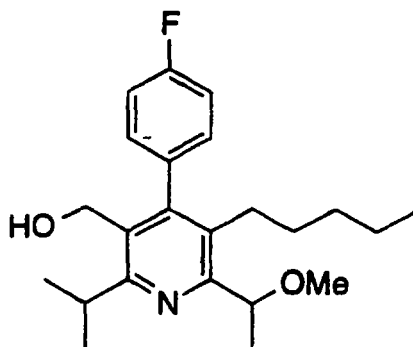
30 A mixture of the intermediate obtained in Example 205, Step A (50 mg, 85

mmol) and methyl (triphenylphosphoranylidene)acetate (31 mg, 1.1 equiv) in toluene (5 mL) was heated to reflux for 5 h. The mixture was cooled to rt and concentrated in vacuo. Silica gel chromatography provided a yellow oil (60 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.96 (d, 15.1 Hz, 1H), 7.42 (m, 6H), 7.34-7.21 (m, 5H), 7.05 (s, 2H), 7.03 (s, 2H), 4.28 (s, 2H), 3.84 (s, 3H), 3.17 (sept, 6.8 Hz, 1H), 2.38 (m, 2H), 1.31 (m, 2H), 1.19 (d, 6.6 Hz, 6H), 1.14 (m, 4H), 1.00 (s, 9H), 0.79 (t, 6.6 Hz, 3H).

**Step B:** 2-(2-Carbomethoxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.95 (d, 15.1 Hz, 1H), 7.25 (d, 15.1 Hz, 1H), 7.17 (s, 2H), 7.15 (s, 2H), 4.37 (d, 3.7 Hz, 2H), 3.84 (s, 3H), 3.45 (sept, 6.6 Hz, 1H), 2.40 (m, 2H), 1.35 (d, 6.6 Hz, 6H), 1.3 (m, 4H), 1.14 (m, 4H), 1.00 (s, 9H), 0.79 (t, 6.6 Hz, 3H). EI-MS: calculated for C<sub>24</sub>H<sub>30</sub>FNO<sub>3</sub> 399; found 399 (M<sup>+</sup>). Anal. calculated for C<sub>24</sub>H<sub>30</sub>FNO<sub>3</sub>: C, 72.16; H, 7.57; N, 3.51. Found: C, 71.79; H, 7.50; N, 3.32. mp 82-83°C.

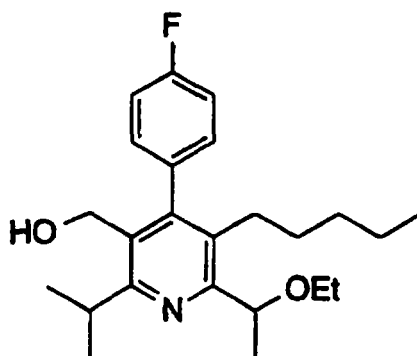
**EXAMPLE 216**



2-(1-Methoxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

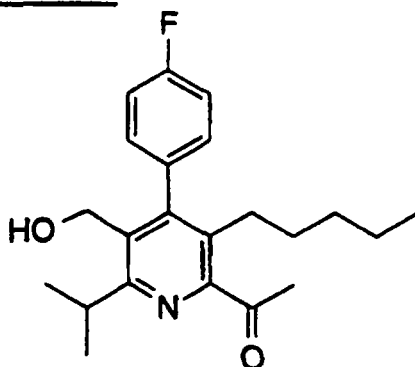
The title compound was prepared from the intermediate obtained in Example 210, Step A by the procedures described in Example 201, Step A, and Example 198, Step D. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.15 (m, 4H), 4.75 (q, 6.3 Hz, 1H), 4.35 (d, 3.7 Hz, 2H), 3.44 (sept, 6.4 Hz, 1H), 3.31 (s, 3H), 2.4-2.2 (m, 2H), 1.58 (d, 6.3 Hz, 3H), 1.35 (d, 6.3 Hz, 3H), 1.34 (d, 6.6 Hz, 3H), 1.27 (m, 2H), 1.11 (m, 4H), 0.78 (t, 6.6 Hz, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>32</sub>FNO<sub>2</sub> 373; found 374 (M+H). Anal. calculated for C<sub>23</sub>H<sub>32</sub>FNO<sub>2</sub>: C, 73.96; H, 8.64; F, 5.09; N, 3.75. Found: C, 73.92; H, 8.75; F, 4.93; N, 3.60.

0

EXAMPLE 217

5 2-(1-Ethoxyethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-  
isopropylpyridine

The title compound was prepared from the intermediate obtained in Example 210, Step A by the procedures described in Example 201, Step A, and  
 10 Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.16 (m, 4H), 4.83 (q, 6.5 Hz, 1H), 4.34 (d, 4.4 Hz, 2H), 3.5-3.2 (m, 3H), 2.4-2.2 (m, 2H), 1.57 (d, 6.6 Hz, 3H), 1.34 (d, 6.6 Hz, 3H), 1.33 (d, 6.6 Hz, 3H), 1.27 (m, 2H), 1.10 (m, 4H), 1.20 (t, 7.2 Hz, 3H), 0.77 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$  387; found 388 (M+H).  
 Anal. calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$ : C, 74.38; H, 8.84; F, 4.90; N, 3.61. Found: C,  
 15 74.67; H, 9.00; F, 5.14; N, 3.27.

EXAMPLE 218

20 2-Acetyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

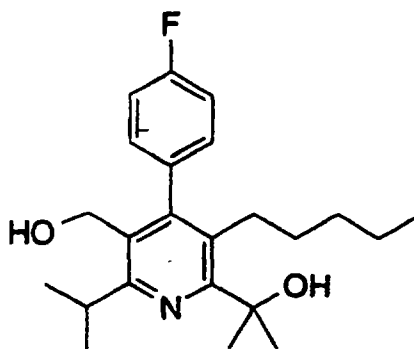
Step A: 2-Acetyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-  
6-isopropylpyridine

- 0 A mixture of the intermediate obtained in Example 210, Step A (210 mg, 0.35 mmol), pyridinium chlorochromate (113 mg, 1.5 equiv), and Celite (110 mg) in CH<sub>2</sub>Cl<sub>2</sub> (13 mL) was stirred overnight. The mixture was filtered through a short pad of silica gel. Silica gel chromatography (95:5 hexanes/ethyl acetate) afforded a colorless solid (120 mg, 57%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.41 (m, 6H), 7.34 (m, 4H), 7.06 (s, 2H), 7.03 (s, 2H), 4.29 (s, 2H), 3.18 (sept, 6.6 Hz, 1H), 2.75 (s, 3H), 2.54 (m, 2H), 1.3 (m, 2H), 1.19 (d, 6.6 Hz, 6H), 1.15 (m, 4H), 1.00 (s, 9H), 0.77 (m, 3H).

Step B: 2-Acetyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

- 10 The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 198, Step D. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.17 (s, 2H), 7.15 (s, 2H), 4.39 (d, 5.2 Hz, 2H), 3.48 (sept, 6.8 Hz, 3H), 2.74 (s, 3H), 2.55 (m, 2H), 1.35 (d, 6.6 Hz, 6H), 1.3 (m, 2H), 1.1 (m, 4H), 0.77 (t, 6.6 Hz, 3H). FAB-MS: calculated for C<sub>22</sub>H<sub>28</sub>FNO<sub>2</sub> 357; found 358 (M+H). Anal. calculated for C<sub>22</sub>H<sub>28</sub>FNO<sub>2</sub>: C, 73.92; H, 7.90; N, 3.92. Found: C, 73.89; H, 8.14; N, 3.88. mp 69-70°C.

EXAMPLE 219



20

2-(1-Hydroxy-1-methylethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

- 25 Step A: 2-(1-Hydroxy-1-methylethyl)-3-pentyl-4-(4-fluorophenyl)-5-(t-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

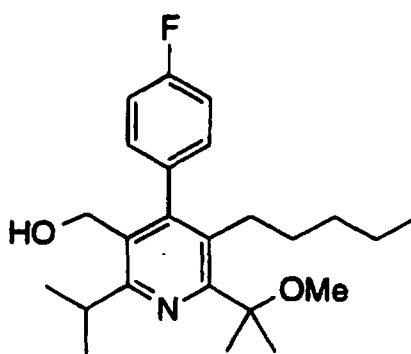
- Prepared from the intermediate obtained in Example 218, Step A by the procedure described in Example 205, Step B. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.41 (m, 6H), 7.32 (m, 4H), 7.08 (m, 4H), 4.25 (s, 2H), 3.13 (sept, 6.8 Hz, 1H), 2.44 (m, 2H), 1.62 (s, 6H), 1.2 (m, 2H), 1.17 (d, 6.6 Hz, 6H), 1.03 (m, 4H), 1.01 (s, 9H), 0.72 (t, 6.8 Hz, 3H).

30

**Step B:** 2-(1-Hydroxy-1-methylethyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

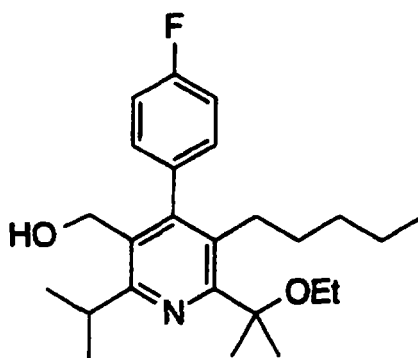
The title compound was prepared from the intermediate obtained in Step A by the procedure described in Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.19 (m, 4H), 4.36 (d, 5.5 Hz, 2H), 3.48 6(sept, 6.6 Hz, 1H), 2.47 (m, 2H), 1.60 (s, 6H), 1.35 (d, 6.6 Hz, 6H), 1.25 (m, 2H), 1.05 (m, 4H), 0.72 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{23}\text{H}_{32}\text{FNO}_2$  373; found 374 (M+H). Anal. calculated for  $\text{C}_{23}\text{H}_{32}\text{FNO}_2$ : C, 73.96; H, 8.63; F, 5.09; N, 3.75. Found: C, 73.88; H, 8.64; F, 4.81; N, 3.59. mp 180-182°C.

**EXAMPLE 220**



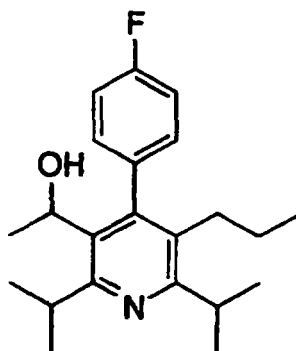
2-(1-Methoxy-1-methyl)ethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Example 219, Step A by the procedures described in Example 201, Step A, and Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.26-7.12 (m, 4H), 4.34 (d, 5.5 Hz, 2H), 3.40 (sept, 6.5 Hz, 1H), 3.12 (s, 3H), 2.76 (m, 2H), 1.67 (s, 6H), 1.31 (d, 6.6 Hz, 6H), 1.3-0.9 (m, 6H), 0.72 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$  387; found 388 (M+H). Anal. calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}_2$ : C, 74.38; H, 8.84; N, 3.61. Found: C, 74.64; H, 8.97; N, 3.61. mp 57-59°C.

EXAMPLE 221

2-(1-Ethoxy-1-methyl)ethyl-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

The title compound was prepared from the intermediate obtained in Example 219, Step A by the procedures described in Example 201, Step A, and Example 198, Step D.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.23-7.11 (m, 4H), 4.33 (d, 5.1 Hz, 2H), 3.39 (sept, 6.6 Hz, 1H), 3.28 (q, 7.0 Hz, 2H), 2.80 (m, 2H), 1.67 (s, 6H), 1.30 (d, 6.6 Hz, 6H), 1.15 (t, 7.0 Hz, 3 H), 1.15-0.9 (m, 6H), 0.71 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{25}\text{H}_{36}\text{FNO}_2$  401; found 402 (M+H). Anal. calculated for  $\text{C}_{25}\text{H}_{36}\text{FNO}_2$ : C, 74.78; H, 9.04; N, 3.49. Found: C, 74.89; H, 9.22; N, 3.24.

EXAMPLE 222

(+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

Step A: (±)-2,6-Diisopropyl-3-[1-hydroxy-2-(S)-toluylsulfoxyethyl]-4-(4-fluorophenyl)-5-propylpyridine

A solution of lithium diisopropylamide was prepared by the addition of *n*-butyllithium (15 mL, 23 mmol, 1.6 M/hexane) to a solution of diisopropylamine (3 mL, 23 mmol) in anhydrous tetrahydrofuran (100 mL) at 0 °C. To this was added a

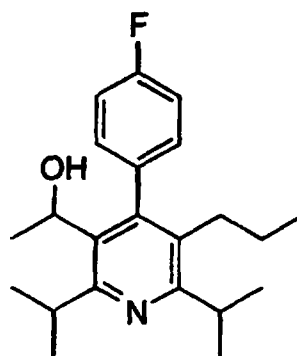
0 solution of (S)-(-)-methyl *p*-tolylsulfoxide (3.6 g, 23 mmol) in anhydrous tetrahydrofuran (20 mL) dropwise, with stirring. The mixture was stirred at 0 °C for 2 hr, then treated with a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-5-propyl-3-pyridinecarboxaldehyde (Example 101, Step A) (3.8 g, 11 mmol) in anhydrous tetrahydrofuran (50 mL) dropwise and with stirring. After stirring 15 min at 0 °C, the reaction mixture was quenched by the addition of saturated NH<sub>4</sub>Cl (5 mL). The solvent was removed *in vacuo* and the residue partitioned between CHCl<sub>3</sub> (300 mL) and water (100 mL). The organic phase was washed with saturated NaHCO<sub>3</sub> (100 mL), water (100 mL) and brine (50 mL), dried over MgSO<sub>4</sub> and concentrated. The crude product consisted of a 1.3:1 ratio of diastereomers which were separated by flash chromatography (step gradient 5%-15%-20% ethyl acetate/hexane), which afforded 1.5 g of the faster diastereomer (I), followed by 2.7 g of the slower diastereomer (II) and 0.83 g of a mixed fraction. Diastereomer II is recrystallized once from ethanol/hexane to afford fine white needles (1.7 g, 3.5 mmol, 30% yield). I: mp 225-227 °C; R<sub>f</sub> = 0.4 (30% ethyl acetate/hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.23 (m, 4 H), 6.95 (m, 2 H), 6.63 (m, 1 H), 6.55 (m, 1 H), 5.03 (d, *J* = 11.0 Hz, 1 H), 4.53 (s, 1 H), 3.79 (m, 2 H), 3.11 (sept, *J* = 6.6 Hz, 1 H), 2.46 (s, 3 H), 2.30 (dd, *J* = 1.9, 14.1 Hz, 1 H), 2.01 (m, 2 H), 1.25 (m, 12 H), 1.16 (m, 2 H), 0.64 (t, *J* = 7.3 Hz, 3 H). FAB-MS: calcd for C<sub>29</sub>H<sub>36</sub>FNO<sub>2</sub>S, 481, found 482 (M+H). II: mp 205-206 °C; R<sub>f</sub> = 0.2 (30% ethyl acetate/hexane); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.38 (d, *J* = 8.2 Hz, 2 H), 7.24 (m, 2 H), 7.05 (m, 1 H), 7.03 (m, 1 H), 6.97 (m, 1 H), 6.87 (m, 1 H), 4.84 (dt, *J* = 2.7, 10.8 Hz, 1 H), 3.69 (sept, *J* = 6.6 Hz, 1 H), 3.49 (dd, *J* = 10.8, 13.1 Hz, 1 H), 3.14 (sept, *J* = 6.6 Hz, 1 H), 3.00 (d, *J* = 2.5 Hz, 1 H), 2.68 (dd, *J* = 2.5, 13.1 Hz, 1 H), 2.41 (s, 3 H), 2.10 (m, 2 H), 1.23 (m, 14 H), 0.69 (t, *J* = 7.3 Hz, 3 H). FAB-MS calcd for C<sub>29</sub>H<sub>36</sub>FNO<sub>2</sub>S, 481, found 482 (M+H).

25 **Step B:** (+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

A suspension of Raney nickel (20 g) in methanol (50 mL) was stirred under a hydrogen atmosphere for 1 hr. The suspension was cooled to 0 °C and treated with a solution of the intermediate II obtained in Step A (1.6 g, 3.3 mmol) in methanol (50 mL). The suspension was stirred vigorously under hydrogen at 0 °C for 16 hr. After purging with argon, the methanolic solution was decanted from the catalyst, the catalyst washed and decanted 3 more times with methanol. The combined decanted solution was filtered through celite and concentrated. Flash chromatography through a plug of silica (10% ethyl acetate/hexane) afforded the title compound (99% e.e.) as a white solid (1.1 g, 3.2 mmol, 96%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.11 (m, 3 H), 7.04 (m, 1 H), 4.64 (dq, *J* = 3.7, 6.6 Hz, 1 H), 3.73 (sept, *J*

0 = 6.6 Hz, 1 H), 3.18 (sept,  $J = 6.6$  Hz, 1 H), 2.15 (m, 2 H), 1.56 (d,  $J = 3.7$  Hz, 1 H), 1.39 (d,  $J = 6.6$  Hz, 3 H), 1.28 (m, 14 H), 0.73 (t,  $J = 7.35$  Hz, 3 H). FAB-MS calcd for  $C_{22}H_{30}FNO$ , 343, found 344 (M+H). Anal. Calcd for  $C_{22}H_{30}FNO$ : C, 76.93; H, 8.80; N, 4.08; F, 5.53. Found: C, 76.98; H, 8.71; N, 3.76; F, 5.73.  $[\alpha]_D = +41.5^\circ$  ( $CHCl_3$ ). mp 101-103°C.  $R_f = 0.3$  (10% ethyl acetate/hexane).

5

EXAMPLE 223(+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

10

Step A: 2,6-Diisopropyl-4-(4-fluorophenyl)-5-propyl-3-[(1-oxo-2-toluylsulfoxy)ethyl]pyridine

To a solution of diisopropylamine (4.8 mL, 36.7 mmol) in anhydrous tetrahydrofuran (160 mL) was added n-butyllithium (23 mL, 33.4 mmol, 1.45 M/THF) at 0°C. To the reaction mixture was added a solution of (S)-(-)-methyl p-tolylsulfoxide (5.65 g, 36.7 mmol) in anhydrous tetrahydrofuran (30 mL). The mixture was stirred for 1.5 hours, then treated with a solution of 2,6-diisopropyl-4-(4-fluorophenyl)-5-propyl-3-pyridinecarboxaldehyde (Example 101, Step A) (8.0 g, 24.4 mmol) in anhydrous tetrahydrofuran (100 mL) at 0°C. After stirring 15 minutes at 0°C, the reaction was quenched by addition of saturated ammonium chloride solution (8 mL). The solvent was removed in vacuo and the residue dissolved in chloroform (480 mL). The organic phase was washed with water (2 x 160 mL) and brine (160 mL), dried over magnesium sulfate and concentrated. The residue was dissolved in dichloromethane (800 mL) and manganese(IV) dioxide (40 g, 464 mmol) is added. The suspension was stirred vigorously with a mechanical stirrer and refluxed for 16 hours. The manganese(IV) dioxide was removed by filtration through celite, washed with dichloromethane (100 mL) and the solvent removed in vacuo. Filtration through a pad of silica gel (7.5% diethyl ether-dichloromethane) afforded a white solid (10.2 g, 21.3 mmol, 87%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.39 (m, 2 H), 7.26 (m, 2 H), 7.05 (m, 4 H), 3.72 (d,  $J = 16$  Hz, 1 H),

0 3.38 (d,  $J = 16$  Hz, 1 H), 3.24 (sept,  $J = 6.6$  Hz, 1 H), 2.59 (sept,  $J = 6.6$  Hz, 1 H), 2.42 (s, 3 H), 2.32 (m, 2 H), 1.27 (m, 8 H), 1.20 (m, 8 H), 0.75 (t,  $J = 7.35$  Hz, 3 H). FAB-MS: calculated for  $C_{29}H_{34}FNO_2S$ , 479, found 480 (M+H). mp 140-142°C.  $R_f = 0.2$  (20% ethyl acetate/hexane).

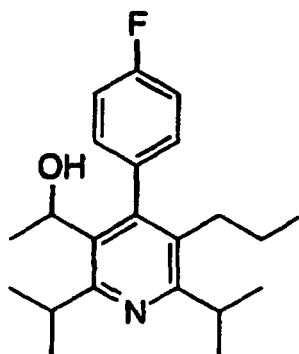
5 **Step B:** 2,6-Diisopropyl-3-(1-hydroxy-2-(S)-toluylsulfoxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

To a solution of the intermediate obtained in Step A (5.8 g, 12.1 mmol) in anhydrous tetrahydrofuran (145 mL) at -78°C was added rapidly a solution of lithium aluminum hydride (169 mL, 169 mmol, 1.0 M/THF). After 15 minutes the  
 10 reaction mixture became turbid and was slowly quenched at -78°C with water (6 mL), 20% aqueous sodium hydroxide solution (6 mL) and water (18 mL). The reaction mixture was allowed to warm to room temperature and the resulting suspension was filtered through a pad of celite. The solvent was evaporated and the residue purified by silica gel chromatography (10% diethyl  
 15 ether/dichloromethane) to afford a white solid (4.8 g, 10 mmol, 83%).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.41 (d,  $J = 8.5$  Hz, 2 H), 7.27 (m, 2 H), 7.06 (d,  $J = 7$  Hz, 2 H), 7.00 (m, 1 H), 6.89 (m, 1 H), 4.85 (dt,  $J = 2.2, 11$  Hz, 1 H), 3.71 (sept,  $J = 6.6$  Hz, 1 H), 3.51 (dd,  $J = 11, 13$  Hz, 1 H), 3.16 (sept,  $J = 6.6$  Hz, 1 H), 3.02 (d,  $J = 2.2$  Hz, 1 H), 2.70 (dd,  $J = 2.2, 13$  Hz, 1 H), 2.43 (s, 3 H), 2.12 (m, 2 H), 1.25 (m, 14 H), 0.71 (t,  $J = 7.35$   
 20 Hz, 3 H). FAB-MS calculated for  $C_{29}H_{36}FNO_2S$ , 481, found 482 (M+H). mp 204-206°C.  $R_f = 0.2$  (30% ethyl acetate/hexane).

**Step C:** (+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

25 A suspension of Raney nickel (40 g, washed with 3 x 100mL ethanol) in ethanol (80 mL) was stirred under hydrogen atmosphere for 1.5 hours. The suspension was treated with a solution of the intermediate obtained in Step B (4.1 g, 8.5 mmol) in ethanol (180 mL) at room temperature and stirred vigorously for 5 hours. The suspension was carefully filtered through celite and concentrated.  
 30 Filtration through silica gel ( $CH_2Cl_2$ ) afforded the title compound (99% e.e.) as a white solid (2.74 g, 8 mmol, 94 %).  $^1H$  NMR (300 MHz,  $CDCl_3$ ):  $\delta$  7.11 (m, 3 H), 7.04 (m, 1 H), 4.64 (dq,  $J = 3.7, 6.6$  Hz, 1 H), 3.73 (sept,  $J = 6.6$  Hz, 1 H), 3.18 (sept,  $J = 6.6$  Hz, 1 H), 2.15 (m, 2 H), 1.56 (d,  $J = 3.7$  Hz, 1 H), 1.39 (d,  $J = 6.6$  Hz, 3 H), 1.28 (m, 14 H), 0.73 (t,  $J = 7.35$  Hz, 3 H). FAB-MS calculated for  $(C_{22}H_{31}FNO, M+H)$  344, found 344. Anal. Calcd for  $C_{22}H_{30}FNO$ : C, 76.93; H, 8.80; N, 4.08; F, 5.53; Found: C, 77.20; H, 8.97; N, 4.01; F, 5.60.  $[a]_D = +39.4^\circ$  ( $CH_2Cl_2$ ). mp 104-106°C.  $R_f = 0.4$  ( $CH_2Cl_2$ ).

0

EXAMPLE 2245 (+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridineStep A: 2,6-Diisopropyl-3-(1-oxoethyl)-4-(4-fluorophenyl)-5-propylpyridine

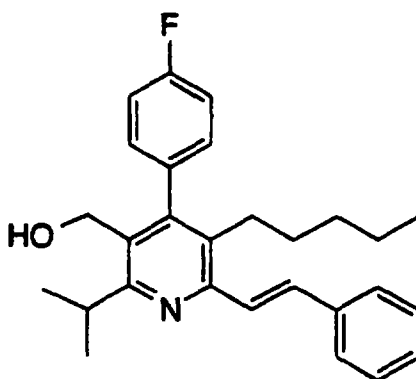
To (±)-2,6-diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine (Example 101) (8.03 g, 23.4 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (600 mL) was added  
 10 pyridinium chlorochromate (10.08 g, 46.76 mmol) and celite (10.1 g) under argon. The reaction was stirred at room temperature for 16 hours. The reaction was added to a 1:1 mixture of diethyl ether/hexane (1 L), then filtered through a plug of silica. The pad was washed with 150 mL of diethyl ether and the combined filtrates were concentrated in vacuo to afford a white solid (7.95 g, 23.3 mmol, 98%). <sup>1</sup>H  
 15 NMR (300 MHz, CDCl<sub>3</sub>): δ 7.12 (m, 4 H), 3.26 (septet, J = 6.6 Hz, 1 H), 2.85 (septet, J = 6.6 Hz, 1 H), 2.36 (m, 2 H), 1.97 (s, 3 H), 1.33 (m, 14 H), 0.774 (t, J = 7.4 Hz, 3 H). FAB-MS calcd for (C<sub>22</sub>H<sub>28</sub>NOF) 341, found 342 (M+H). mp 131-133°C. R<sub>f</sub> = 0.5 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

20 Step B: (+)-2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine

To a solution of (1S,2R)-(+)-N-methylephedrine (31.1 g, 0.174 mol) in ether (208 mL) was added lithium aluminum hydride (1M/diethyl ether, 1.5 eq., 174 mL) dropwise at 0°C under argon. The reaction was refluxed for 1.5 h, turning from a  
 25 clear solution to a white milky solution. The reaction was cooled to room temperature and then -78°C. The intermediate obtained in Step A (39.53g, 0.116 mmol) was dissolved in 400 mL of dry diethyl ether and cooled to 0°C for a dropwise addition to the reaction mixture (~2 mL/min., the temperature should not rise above -60°C). The reaction was kept at -78°C for 4.0 hours and then  
 30 allowed to warm overnight. The reaction was quenched at 0°C with isopropanol

- 0 (70 mL) and diluted with ether (700 mL), washed with water (4 x 500 mL), 10% HCl (2 x 500 mL), brine (2 x 500 mL) and dried with MgSO<sub>4</sub>. Filtration and concentration afforded a residue which was filtered through a pad of silica (600 g, 10% diethyl ether/hexane) to give the title compound (97% e.e.) as a white solid (36.67 g, 107 mmol, 92%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.11 (m, 4 H), 4.67 (dq, J = 3.3, 6.6 Hz, 1 H), 3.74 (septet, J = 6.6 Hz, 1 H), 3.20 (septet, J = 6.6 Hz, 1 H), 2.17 (m, 2 H), 1.61 (d, J = 2.9 Hz, 1 H), 1.40 (d, J = 7.0 Hz, 3 H), 1.30 (m, 14 H), 0.741 (t, J = 7.4 Hz, 3 H). FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>NOF) 343, found 344 (M+H). mp 102-104°C. R<sub>f</sub> = 0.2 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

10

EXAMPLE 225

15

2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-(2-trans-phenylethyl)pyridine

Step A: 2-Bromomethyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

- 20 Prepared from the intermediate obtained in Example 200, Step B by the procedure described in Example 47, Step B. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.40 (m, 6H), 7.32 (m, 4H), 7.04 (m, 4H), 4.64 (s, 2H), 4.26 (s, 2H), 3.14 (sept, 6.8 Hz, 1H), 2.38 (m, 2H), 1.34 (m, 2H), 1.17 (d, 7.0 Hz, 6H), 1.12 (m, 4H), 1.00 (s, 9H), 0.78 (t, 6.6 Hz, 3H).

25

Step B: 2-(Diethylphosphono)methyl-3-pentyl-4-(4-fluorophenyl)-5-(*t*-butyldiphenylsiloxy)methyl-6-isopropylpyridine

- 30 A mixture of diethylphosphite (280 mg) and sodium metal (50 mg) in benzene (5 mL) was stirred overnight. A mixture of the sodium diethylphosphite solution (1 mL) and the intermediate obtained in Step A (110 mg, 0.17 mmol) in benzene (5 mL) was refluxed for 2 h. The mixture was concentrated in vacuo. The

- 0 residue was dissolved in ethyl acetate (30 mL) and washed with saturated aqueous sodium chloride solution (3 x 10 mL). Silica gel chromatography (70:30 hexanes/ethyl acetate) provided a yellow oil (80 mg, 67%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.41 (m, 6H), 7.32 (m, 4H), 7.04 (m, 4H), 4.25 (s, 2H), 4.15 (dq, 7.2 Hz, 4H), 3.49 (d, 22.4 Hz, 2H), 3.14 (sept, 6.8 Hz, 1H), 2.38 (m, 2H), 1.30 (t, 7.2 Hz, 6H),  
5 1.25 (m, 2H), 1.16 (d, 6.6 Hz, 6H), 1.10 (m, 4H), 0.99 (s, 9H), 0.77 (t, 6.8 Hz, 3H).

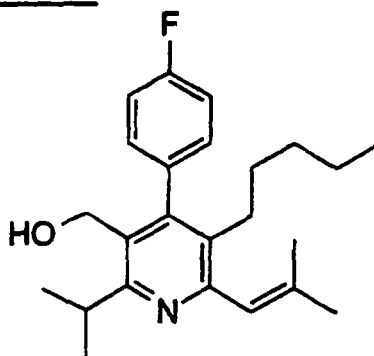
**Step C:** 2-(trans-2-Phenylethenyl)-3-pentyl-4-(4-fluorophenyl)-5-(t-butyl-diphenylsiloxy)methyl-6-isopropylpyridine

- 10 Sodium hydride (8 mg) was added to a mixture of the intermediate obtained in Step B (90 mg, 128 μmol) and benzaldehyde (20 mg) in THF (2.7 mL). After 15 min. the mixture was diluted with ethyl acetate and washed with saturated aqueous sodium chloride solution. Silica gel chromatography (97:3 hexanes/ethyl acetate) provided a yellow oil (100 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.00 (d, 15.4 Hz, 1H), 7.61 (m, 2H), 7.45-7.27 (m, 14H), 7.04 (m, 4H), 4.29 (s, 2H), 3.20 (sept, 6.4 Hz, 1H),  
15 2.38 (m, 2H), 1.40 (m, 2H), 1.25 (d, 6.6 Hz, 6H), 1.18 (m, 4H), 1.00 (s, 9H), 0.81 (m, 3H).

**Step D:** 2-(trans-2-Phenylethenyl)-3-pentyl-4-(4-fluorophenyl)-5-hydroxymethyl-6-isopropylpyridine

- 20 The title compound was prepared from the intermediate obtained in Step C by the procedure described in-Example 198, Step D. Silica gel chromatography (94:6 hexanes/ethyl acetate) provided a yellow oil (24 mg, 38%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.02 (d, 15.5 Hz, 1H), 7.63 (m, 2H), 7.43-7.31 (m, 4H), 7.16 (m, 4H), 4.38 (s, 2H), 3.48 (sept, 6.6 Hz, 1H), 2.41 (m, 2H), 1.42 (d, 6.6 Hz, 6H),  
25 1.4 (m, 2H), 1.19 (m, 4H), 0.82 (t, 6.8 Hz, 3H). FAB-MS: calculated for C<sub>28</sub>H<sub>32</sub>FNO 417; found 418 (M+H). R<sub>f</sub> = 0.13 (90:10 hexanes/ethyl acetate). Anal. calculated for C<sub>28</sub>H<sub>32</sub>FNO: C, 80.54; H, 7.72; N, 3.35. Found: C, 80.34; H, 7.79; N, 3.10. mp 98-100°C.

**EXAMPLE 226**

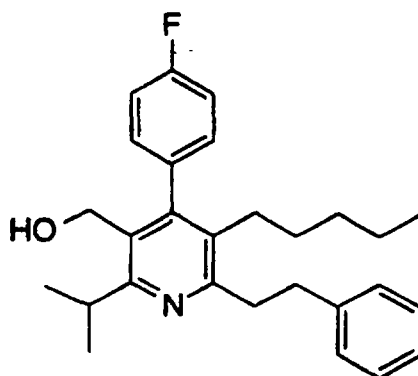


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2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-(2-methylpropenyl)pyridine

The title compound was prepared as a yellow oil from the intermediate obtained in Example 225, Step B by the procedure described in Example 225, Step C and Example 198, Step D. The product was obtained as an inseparable mixture of the title compound and the corresponding deconjugated olefin in a ratio of 84:16.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.16 (m, 4H), 6.43 (s, 1H), 4.82 (s, 1H, minor isomer), 4.60 (s, 1H, minor isomer), 4.36 (s, 2H), 3.58 (s, 2H, minor isomer), 3.46 (sept, 6.6 Hz, 1H), 2.26 (m, 2H), 2.07 (s, 3H), 1.99 (s, 3H), 1.82 (s, 3H, minor isomer), 1.35 (d, 7.0 Hz, 6H), 1.28 (m, 2H), 1.13 (m, 4H), 0.79 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{32}\text{FNO}$  369; found 370 ( $\text{M}+\text{H}$ ).  $R_f$  = 0.16 (90:10 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{24}\text{H}_{32}\text{FNO}$ : C, 78.01; H, 8.73; N, 3.79. Found: C, 77.73; H, 8.86; N, 3.97.

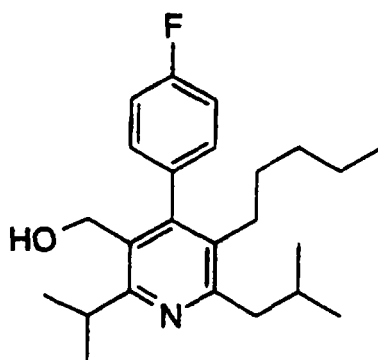
15

EXAMPLE 227

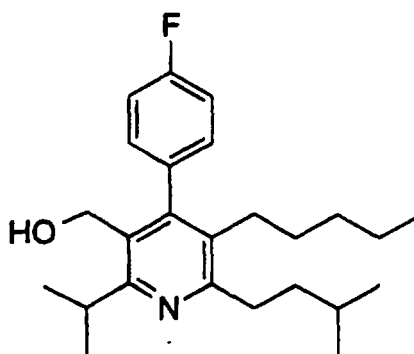
20

2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-(2-phenylethyl)pyridine

The title compound was prepared as a yellow oil from the intermediate obtained in Example 225, Step D by the procedure described in Example 1, Step H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.29-7.19 (m, 5H), 7.14 (s, 2H), 7.12 (s, 2H), 4.34 (s, 2H), 3.44 (sept, 6.6 Hz, 1H), 3.18-3.10 (m, 4H), 2.20 (m, 2H), 1.35 (d, 6.6 Hz, 6H), 1.22 (m, 2H), 1.08 (m, 4H), 0.76 (t, 6.8 Hz, 3H). FAB-MS: calculated for  $\text{C}_{28}\text{H}_{34}\text{FNO}$  419; found 420 ( $\text{M}+\text{H}$ ).  $R_f$  = 0.21 (90:10 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{28}\text{H}_{34}\text{FNO}$ : C, 80.18; H, 8.17; N, 3.34. Found: C, 80.12; H, 8.15; N, 3.24.

EXAMPLE 2282-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-(2-methylpropyl)pyridine

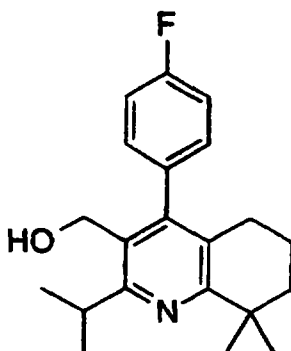
The title compound was prepared as a colorless crystalline solid from the intermediate obtained in Example 226 by the procedure described in Example 1, Step H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.15 (m, 4H), 4.33 (d, 5.2 Hz, 2H), 3.41 (sept, 6.6 Hz, 1H), 2.67 (d, 7.0 Hz, 2H), 2.34 (m, 2H), 2.25 (m, 2H), 1.32 (d, 6.6 Hz, 6H), 1.20 (m, 2H), 1.12 (m, 4H), 0.99 (d, 6.6 Hz, 6H), 0.78 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}$  371; found 372 ( $\text{M}+\text{H}$ ).  $R_f$  = 0.77 (90:10 hexanes/ethyl acetate). Anal. calculated for  $\text{C}_{24}\text{H}_{34}\text{FNO}$ : C, 77.59; H, 9.22; N, 3.77. Found: C, 77.49; H, 9.20; N, 3.73.

EXAMPLE 2292-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentyl-6-(3-methylbutyl)pyridine

The title compound was prepared as a yellow oil from the intermediate obtained in Example 225, Step B by the procedures described in Example 225, Steps C and D, and Example 1, Step H.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.14 (m, 4H), 4.34

- 0 (d, 3.7 Hz, 2H), 3.41 (sept, 6.8 Hz, 1H), 2.80 (m, 2H), 2.26 (m, 2H), 1.68 (m, 3H), 1.33 (d, 6.6 Hz, 6H), 1.29 (m, 2H), 1.12 (m, 4H), 0.98 (d, 6.3 Hz, 6H), 0.79 (t, 6.6 Hz, 3H). FAB-MS: calculated for  $C_{25}H_{36}FNO$  385; found 386 (M+H).  $R_f$  = 0.15 (90:10 hexanes/ethyl acetate). Anal. calculated for  $C_{25}H_{36}FNO$ : C, 77.88; H, 9.41; N, 3.63. Found: C, 77.62; H, 9.13; N, 3.42.

5

EXAMPLE 230

10 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline

Step A: 2-[(4-Fluorophenyl)methylene]-4-methyl-3-oxopentanoic acid

- 15 To a solution of ethyl isobutyryl acetate (30 g, 0.190 mol) in ethanol (75 mL) was added cyclohexane (120 mL), acetic acid (0.6 mL), piperidine (0.6 mL), and 4-fluorobenzaldehyde (20.35 mL, 0.190 mol). The reaction was heated at reflux with a Dean-Starck trap for 5 hours. The mixture was poured into 200 mL of diethyl ether and washed with brine (1 x 75 mL). The organic layer was dried with  $MgSO_4$ , filtered, and concentrated to afford an orange oil. The product was taken directly
- 20 to the next step without any further purification.  $R_f$  = 0.1 (50%  $CH_2Cl_2$ /hexane).

Step B: 2-Isopropyl-3-carboethoxy-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline

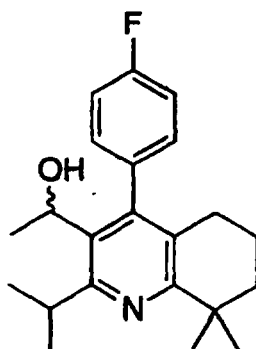
- 25 To a solution of lithium bis(trimethylsilyl)amide (1.0 M/THF, 2 eq. 13.6 mL) in THF (15 mL) was added 2,2-dimethylcyclohexanone (1.88 mL, 13.6 mmol) at -78°C. The reaction was stirred for 15 minutes, and then the intermediate obtained in Step A (3 g, 11.4 mmol) was added dropwise. The reaction was stirred overnight and allowed to warm to room temperature. To the crude product was added acetic acid (19.4 mL), ammonium acetate (2.62 g, 34.0 mmol) and copper acetate (5.14 g, 28.3 mmol). The reaction mixture was heated at 100°C and the THF was removed
- 30

by distillation. The reaction was heated to 130°C and allowed to reflux for 24 hours. Ethyl acetate (100 mL) was added and washed with sodium bicarbonate (2 x 30 mL), water (2 x 20 mL), brine (2 x 20 mL), dried with MgSO<sub>4</sub>, filtered, and concentrated to afford an oil. Flash chromatography (5 % ethyl acetate/hexane) afforded a white solid (1.36 g, 3.7 mmol, 32%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.17 (m, 2 H), 7.08 (m, 2 H), 3.98 (q, *J* = 7.4 Hz, 2 H), 3.03 (septet, *J* = 7.0 Hz, 1 H), 2.35 (t, *J* = 5.9 Hz, 2 H), 1.70 (m, 4 H), 1.36 (s, 6 H), 1.31 (d, *J* = 4.1 Hz, 6 H), 0.965 (t, *J* = 7.4 Hz, 3 H). FAB-MS: calculated for (C<sub>23</sub>H<sub>28</sub>FNO) 369, found 370 (M+H). mp 124-126°C. R<sub>f</sub> = 0.6 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

**Step C: 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline**

To the intermediate obtained in Step B (1.32 g, 3.6 mmol) in THF (35 mL) was added lithium aluminum hydride (1 M/THF, 2 eq., 7.2 mL) dropwise. The reaction was refluxed for 1.5 hours and cooled to room temperature. Then the reaction was quenched with water and the THF was evaporated. The residue was partitioned between diethyl ether (150 mL) and water (100 mL). The organic layer was washed with brine (1 x 100 mL), dried with MgSO<sub>4</sub>, filtered, and concentrated to afford a solid. Flash chromatography (40% CH<sub>2</sub>Cl<sub>2</sub>/hexane) afforded the title compound as a white solid (808 mg, 2.5 mmol, 70%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13 (d, *J* = 7.0 Hz, 4 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 3.42 (septet, *J* = 6.6 Hz, 1 H), 2.24 (t, *J* = 5.5 Hz, 2 H), 1.67 (m, 4 H), 1.32 (m, 13 H). FAB-MS: calculated for (C<sub>21</sub>H<sub>26</sub>FNO) 327, found 328 (M+H). mp 146-149°C. R<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

**EXAMPLE 231**



**2-Isopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline**

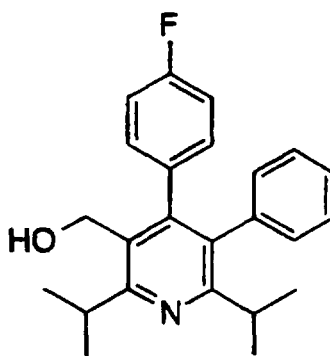
**Step A:**     2-Isopropyl-3-carboxaldehyde-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline

To a solution of 2-isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline (Example 230) (765 mg, 2.34 mmol) in dichloromethane (30 mL) was added Celite (1.01 g) and pyridinium chlorochromate (1.01 g, 4.69 mmol). The reaction was stirred at room temperature for 2 hours and then added to a 1:1 diethyl ether/hexane solution (500 mL). The solution was passed through a pad of silica and washed several times with diethyl ether. Concentration yielded a white solid (568 mg, 1.75 mmol, 75%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 9.78 (s, 1 H), 7.15 (m, 4 H), 3.86 (septet, *J* = 6.6 Hz, 1 H), 2.31 (t, *J* = 5.9 Hz, 2 H), 1.70 (m, 4 H), 1.37 (s, 6 H), 1.30 (m, 6 H). FAB-MS: calculated for (C<sub>21</sub>H<sub>24</sub>FNO) 325, found 326 (M+H). mp 94-96°C. R<sub>f</sub> = 0.7 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

**Step B:**     2-Isopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5,6,7,8-tetrahydro-8,8-dimethylquinoline

To the intermediate obtained in Step A (508 mg, 1.56 mmol) in THF (20 mL) was added methylmagnesium bromide (0.57 mL, 3.0 M/ether, 1.1 eq.) dropwise at -78°C. After 2 hours, the reaction was quenched with saturated ammonium chloride (30 mL) and diluted with dichloromethane (100 mL). The solid was filtered and the mother liquor was washed with water (1 x 50 mL), brine (1 x 50 mL), dried with MgSO<sub>4</sub>, filtered, and concentrated to afford a white solid. Flash chromatography (50% dichloromethane/hexane) gave a white solid (205 mg, 0.6 mmol, 39%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.13 (m, 3 H), 7.01 (m, 1 H), 4.73, 4.71 (dq, *J* = 3.7, 6.6 Hz, 1 H), 3.74 (septet, *J* = 6.6 Hz, 1 H), 2.13 (q, *J* = 4.4 Hz, 2 H), 1.64 (m, 3 H), 1.31 (m, 17 H). FAB-MS: calculated for (C<sub>22</sub>H<sub>27</sub>FNO) 341, found 342 (M+H). mp 56.5-58.5°C. R<sub>f</sub> = 0.2 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

**EXAMPLE 232**

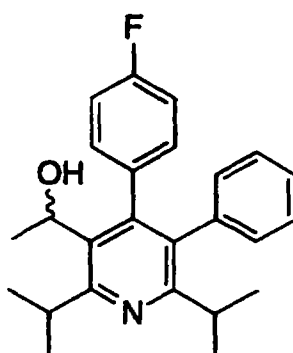


0 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-(1-butenyl)pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4-fluorobenzaldehyde and 3-methyl-1-phenyl-2-butanone according to the procedures described in Example 230. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 3 H), 6.91 (m, 6 H), 4.45 (d, *J* = 5.1 Hz, 2 H), 3.52 (sept., *J* = 6.6 Hz, 1 H), 2.86 (sept., *J* = 6.6 Hz, 1 H), 1.55 (s, 1 H), 1.36 (m, 6 H), 1.17 (d, *J* = 6.6 Hz, 6 H). FAB-MS: calculated for (C<sub>24</sub>H<sub>26</sub>FNO) 363, found 364 (M+H). mp 115-117°C. R<sub>f</sub> = 0.3 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

10

EXAMPLE 233

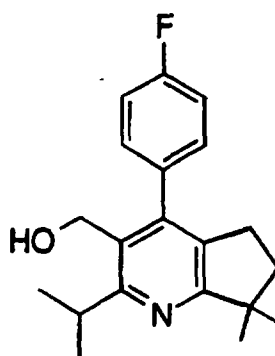


15 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-phenylpyridine

The title compound was prepared according to the procedures described in Example 231. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.14 (m, 3 H), 6.88 (m, 6 H), 4.80 (dq, *J* = 7.0, 3.7 Hz, 1 H), 3.84 (sept., *J* = 6.6 Hz, 1 H), 2.79 (sept., *J* = 6.6 Hz, 1 H), 1.66 (d, *J* = 3.7 Hz, 1 H), 1.48 (d, *J* = 7.0 Hz, 3 H), 1.39 (m, 6 H). FAB-MS: calculated for (C<sub>25</sub>H<sub>28</sub>FNO) 377, found 378 (M+H). mp 155-157°C. R<sub>f</sub> = 0.4 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

20

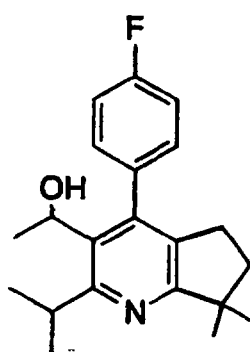
EXAMPLE 234



0 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-7,7-dimethyl-5H-cyclo-  
penta[b]pyridine

The title compound was prepared from ethyl isobutyrylacetate, 4 fluorobenzaldehyde and 2,2-dimethylcyclopentanone according to the procedures described in Example 230. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.29 (m, 2 H), 7.14 (m, 2 H), 4.49 (d, J = 5.2 Hz, 2 H), 3.46 (sept., J = 6.6 Hz, 1 H), 2.56 (t, J = 7.0 Hz, 2 H), 1.90 (t, J = 7.0 Hz, 2 H), 1.34 (m, 13 H). FAB-MS: calculated for (C<sub>20</sub>H<sub>24</sub>FNO) 313, found 314 (M+H). mp 141-143°C. R<sub>f</sub> = 0.1 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

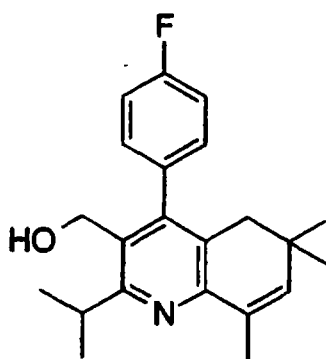
10 EXAMPLE 235



15 2-Isopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-7,7-dimethyl-5H-cyclo-  
penta[b]pyridine

The title compound was prepared according to the procedures described in Example 231. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.15 (m, 4 H), 4.95 (dq, J = 6.6, 3.7 Hz, 1 H), 3.77 (sept., J = 6.6 Hz, 1 H), 2.44 (m, 2 H), 1.88 (t, J = 7.4 Hz, 2 H), 1.62 (d, J = 3.7 Hz, 1 H), 1.48 (d, J = 7.0 Hz, 3 H), 1.32 (m, 12 H). FAB-MS: calculated for (C<sub>21</sub>H<sub>26</sub>FNO) 327, found 328 (M+H). mp 90-92°C. R<sub>f</sub> = 0.1 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

20 EXAMPLE 236

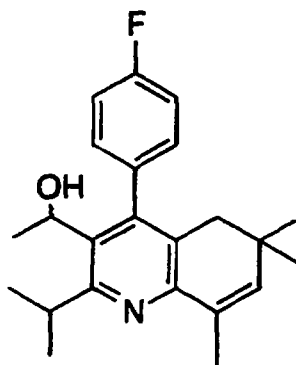


0 2-Isopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5,6-dihydro-6,6,8-  
trimethylquinoline

The title compound was prepared from ethyl isobutyrylacetate, 4 fluorobenzaldehyde and 2,4,4-trimethyl-2-cyclohexen-1-one according to the procedures described in Example 230. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.16 (m, 4 H),

5 5.81 (s, 1 H), 4.41 (d, *J* = 5.2 Hz, 2 H), 3.45 (sept., *J* = 6.6 Hz, 1 H), 2.29 (s, 2 H), 2.16 (s, 3 H), 1.58 (s, 1 H), 1.35 (d, *J* = 6.6 Hz, 6 H), 0.95 (s, 6 H). FAB-MS: calculated for (C<sub>22</sub>H<sub>26</sub>FNO) 339, found 340 (M+H). mp 112-114°C. R<sub>f</sub> = 0.2 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

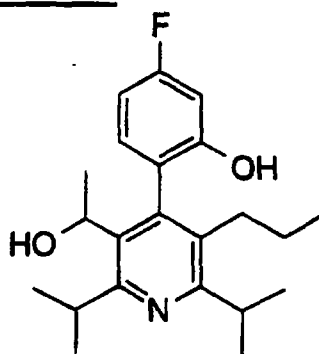
10 EXAMPLE 237



15 2-Isopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5,6-dihydro-6,6,8-  
trimethylquinoline

The title compound was prepared according to the procedures described in Example 231. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.14 (m, 3 H), 7.00 (m, 1 H), 5.78 (s, 1 H), 4.77 (dq, *J* = 6.6, 3.7 Hz, 1 H), 3.76 (sept., *J* = 6.6 Hz, 1 H), 2.18 (s, 2 H), 2.14 (s, 3 H), 1.61 (d, *J* = 3.7 Hz, 1 H), 1.43 (d, *J* = 6.6 Hz, 3 H), 1.33 (m, 6 H), 0.91 (s, 6 H). FAB-MS: calculated for (C<sub>23</sub>H<sub>28</sub>FNO) 353, found 354 (M+H). mp 117-119°C. R<sub>f</sub> = 0.3 (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane).

20 EXAMPLE 238



2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluoro-2-hydroxyphenyl)-5-propylpyridineStep A: 2,6-Diisopropyl-3-hydroxymethyl-4-[(2-benzyloxy-4-fluoro)phenyl]-5-prop-1-enylpyridine

Prepared from the intermediate obtained in Example 166, Step B by the methods described in Example 160, Steps A-D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.20-1.34 (m, 12H), 1.56-1.59 (m, 3H), 1.68-1.74 (m, 1H), 3.13-3.50 (m, 2H), 4.23-4.42 (m, 2H), 4.87-5.05 (m, 2H), 5.25-5.56 (m, 1H), 5.23-6.03 (m, 1H), 6.69-6.77 (m, 2H), 6.95-7.08 (m, 3H), 7.22-7.27 (m, 3H). FAB-MS: calcd for (C<sub>28</sub>H<sub>32</sub>NO<sub>2</sub>F) 433; found 434 (M + 1). R<sub>f</sub> = 0.30 (10% ethyl acetate-hexane).

Step B: 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluoro-2-hydroxyphenyl)-5-propylpyridine

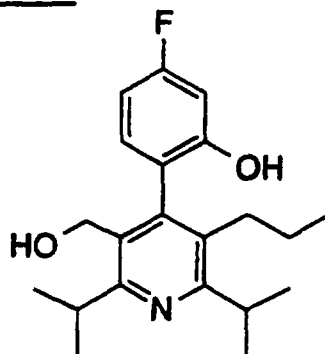
The title compound was prepared as two separable diastereomers from the intermediate obtained in Step A by the methods described in Example 164, Steps A-C. The diastereomers were separated by radial band chromatography using a gradient eluent of 100% hexane to 20% ether-hexane.

Diastereomer 1: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J = 7.2 Hz, 3H), 1.27-1.40 (m, 17H), 1.66 (br s, 1H), 2.02-2.12 (m, 1H), 2.20-2.31 (m, 1H), 3.21 (sept, J = 6.6 Hz, 1H), 3.60 (sept, J = 6.6 Hz, 1H), 4.94 (m, 1H), 5.03 (br s, 1H), 6.70-6.76 (m, 2H), 6.94-7.00 (m, 1H); FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>NO<sub>2</sub>F) 359, found 360 (M + 1). R<sub>f</sub> = 0.29 (20% ethyl acetate-hexane). mp 152-153°C.

Diastereomer 1 was resolved into its constituent enantiomers as follows. A Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 1% (1% acetic acid, 99% ethanol) and 99% hexane at a flow rate of 150 mL/min. The sample was dissolved in chloroform (50 mg/mL) and 5 mL aliquots were injected at 40 min intervals. The effluent was monitored at 280 nm and two fractions (corresponding to the two enantiomers) were collected at (17-23 min, 100% ee) and (23-32 min, 98% ee), respectively.

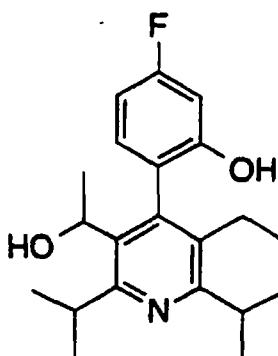
Diastereomer 2: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 (t, J = 7.2 Hz, 3H), 1.26-1.31 (m, 14H), 1.38 (d, J = 6.9 Hz, 3H), 1.84-1.87 (m, 1H), 2.05-2.14 (m, 1H), 2.24-2.34 (m, 1H), 3.20 (septet, J = 6.6 Hz, 1H), 3.72 (septet, J = 6.6, 1H), 4.58-4.65 (m, 1H), 5.06 (br s, 1H), 6.67-6.74 (m, 2H), 6.85-6.90 (m, 1H); FAB-MS: calcd for (C<sub>22</sub>H<sub>30</sub>NO<sub>2</sub>F) 359, found 360 (M + 1). R<sub>f</sub> = 0.19 (20% ether-hexanes). mp 157-159°C.

0

EXAMPLE 2392,6-Diisopropyl-3-(1-hydroxymethyl)-4-(4-fluoro-2-hydroxyphenyl)-5-propylpyridine

5        The title compound was prepared from 2,6-diisopropyl-3-hydroxymethyl-4-  
 [(2-benzyloxy-4-fluoro)phenyl]-5-(prop-1-enyl)pyridine (Example 238, Step A) by  
 the method described in Example 161, Step A (mp 138-141°C). <sup>1</sup>H NMR (300 MHz,  
 CDCl<sub>3</sub>): δ 0.76 (t, J = 7.2 Hz, 3H), 1.24-1.35 (m, 14H), 1.82 (br s, 1H), 2.12-2.22 (m,  
 1H), 2.27-2.37 (m, 1H), 3.24 (sept, J = 6.6 Hz, 1H), 3.39 (sept, J = 6.6 Hz, 1H), 4.29 (d, J  
 10 = 11.4 Hz, 1H), 4.52 (d, J = 10.8 Hz, 1H), 5.72 (br s, 1H), 7.70-6.77 (m, 2H), 6.94-7.00  
 (m, 1H). FAB-MS: calcd for (C<sub>21</sub>H<sub>28</sub>NO<sub>2</sub>F) 345; found 346 (M + 1). R<sub>f</sub> = 0.30 (10%  
 ethyl acetate-hexane).

15        The racemate was resolved into its constituent enantiomers as follows. A  
 Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column  
 (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase  
 consisting of 1% (1% acetic acid, 99% ethanol) and 99% hexane at a flow rate of 100  
 mL/min. The sample was dissolved in mobile phase (5 mg/mL) and 3 mL aliquots  
 were injected at 30 min intervals. The effluent was monitored at 280 nm and two  
 fractions (corresponding to the two enantiomers) were collected at (24-36 min, 100%  
 20 ee) and (26-30 min, 95.5% ee), respectively.

EXAMPLE 240

2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluoro-2-hydroxyphenyl)-5-ethylpyridine

Step A: 2,6-Diisopropyl-3-hydroxymethyl-4-[(2-benzyloxy-4-fluoro)phenyl]-5-ethenyl)pyridine

Prepared from the intermediate obtained in Example 166, Step B by the methods described in Example 160, Steps A-D. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25-1.33 (m, 12H), 1.66-1.70 (m, 1H), 3.34-3.50 (m, 2H), 4.28-4.41 (m, 2H), 4.89-5.18 (m, 4H), 6.29-6.39 (m, 1H), 6.67-6.78 (m, 2H), 7.23-7.25 (m, 3H). FAB-MS: calcd for (C<sub>27</sub>H<sub>30</sub>NO<sub>2</sub>F) 419; found 420 (M + 1). R<sub>f</sub> = 0.29 (10% ethyl acetate-hexane).

Step B: 2,6-Diisopropyl-3-carboxaldehyde-4-[(2-benzyloxy-4-fluoro)phenyl]-5-ethenyl)pyridine

Prepared from the intermediate obtained in Step A by the method described in Example 164, Step A. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25-1.33 (m, 12H), 3.24 (sept, 1H, J = 6.6 Hz), 3.89 (sept, 1H, J = 6.6 Hz), 4.93-5.04 (m, 3H), 5.23 (dd, 1H, J = 1.5, 11.4 Hz), 6.40 (dd, 1H, J = 11.4, 17.7 Hz), 6.70-7.04 (m, 2H), 6.99-7.04 (m, 1H), 7.10-7.14 (m, 2H), 7.24-7.29 (m, 3H), 9.82 (s, 1H). FAB-MS: calcd for (C<sub>27</sub>H<sub>28</sub>NO<sub>2</sub>F) 417; found 418 (M + 1). R<sub>f</sub> = 0.68 (10% ethyl acetate-hexane).

Step C: 2,6-Diisopropyl-3-(2-hydroxyethyl)-4-[(2-hydroxy-4-fluoro)phenyl]-5-ethyl)pyridine

To an oven-dried 250 mL three-neck round bottom flask equipped with a thermometer were added copper(I) iodide (3.21 g, 16.9 mmol) and toluene (40 mL) under an argon atmosphere. The slurry was cooled to an internal temperature of 0°C. Methyllithium (1.4M in ether, 25 mL, 0.03314 mol) was added at a rate to maintain reaction temperature <5°C. The reaction was then allowed to stir at 0°C for 50 min. At the end of this time the intermediate from Step B (1.33 g, 3.19 mmol) in 10 mL toluene was added via syringe at a rate to maintain reaction temperature <5°C. The syringe was rinsed with an additional 4 mL toluene and this rinse was added to the reaction mixture at a rate to maintain reaction temperature <5°C. The reaction was stirred at 0°C for 35 min. The reaction was then quenched by the addition of a saturated solution of ammonium chloride (20 mL) and was allowed to stir for 36 h at 25°C. The reaction mixture was poured into a separatory funnel and was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was then concentrated to yield the crude intermediate (1.4 g, yellow oil, 9:1 ratio of diastereomers). The crude intermediate was dissolved in a mixture of ethanol (30 mL) and tetrahydrofuran (10 mL) under argon, treated with 10% palladium on

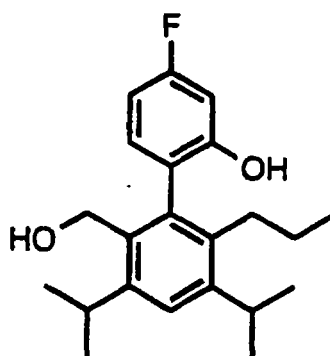
0 carbon (140 mg), and was then stirred under a hydrogen atmosphere for 14 h. After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed and the residue was purified by flash chromatography (12-15% ethyl acetate-hexane) to yield 1.0 g of the title compound as two separate diastereomers.

5 Diastereomer 1:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.91 (t,  $J = 7.4$  Hz, 3H), 1.28-1.40 (m, 15H), 1.70 (d,  $J = 3.9$  Hz, 1H), 2.12-2.24 (m, 1H), 2.29-2.41 (m, 1H), 3.24 (sept,  $J = 6.6$  Hz, 1H), 3.61 (sept,  $J = 6.6$  Hz, 1H), 4.89-5.00 (m, 1H), 5.10 (br s, 1H), 6.70-6.76 (m, 2H), 6.96-7.01 (m, 1H); FAB-MS: calcd for ( $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{F}$ ) 345, found 346 ( $M + 1$ ).  $R_f = 0.43$  (30% ether-hexane). mp 190-191°C.

10 Diastereomer 1 was resolved into its constituent enantiomers as follows. A Waters Prep LC 2000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 1% (1% acetic acid, 99% ethanol) and 99% hexane at a flow rate of 100 mL/min. The sample (1 g) was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (40 mL), ethanol  
15 (1 mL), and 10 mL of the mobile phase. The mixture was injected and the effluent was monitored at 280 nm and two fractions (corresponding to the two enantiomers) were collected at (27-29 min, 99.8% ee) and (37-57 min, 99.4% ee), respectively. Fraction 1 (27-29 min):  $[\alpha]^{25}_{\text{D}} +4.7^\circ$  ( $c = 0.54$ ,  $\text{CH}_2\text{Cl}_2$ ).

20 Diastereomer 2:  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.89 (t,  $J = 7.5$  Hz, 3H), 1.26-1.38 (m, 15H), 1.92 (d,  $J = 3$  Hz, 1H), 2.12-2.25 (m, 1H), 2.31-2.43 (m, 1H), 3.23 (septet,  $J = 6.6$  Hz, 1H), 3.72 (septet,  $J = 6.6$ , 1H), 4.56-4.63 (m, 1H), 5.14 (br s, 1H), 6.68-6.74 (m, 2H), 6.85-6.91 (m, 1H); FAB-MS: calcd for ( $\text{C}_{21}\text{H}_{28}\text{NO}_2\text{F}$ ) 345, found 346 ( $M + 1$ ).  $R_f = 0.27$  (30% ether-hexane). mp 201-202°C.

25

EXAMPLE 241

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl

30

0 **Step A:** Dimethyl 4,6-diethyl-2-hydroxy-1,3-benzenedicarboxylate

A mixture of dimethyl 1,3-acetonedicarboxylate (200 g, 1.15 mol), 3,5-heptanedione (140 g, 1.09 mol) and sodium methoxide (70 g, 1.25 mol) in methanol (1.5 L) was held at reflux overnight. Methanol was removed via rotary evaporation and the resulting orange sludge was partitioned between diethyl ether (1 L) and 10 % aqueous hydrochloric acid (1 L). The separated aqueous layer was extracted with diethyl ether (0.5 L x 2). The combined organic portions were washed with saturated aqueous sodium chloride (0.1 L), dried over sodium sulfate, filtered through a pad of silica (40 mm x 100 mm) and concentrated in vacuo. The crude oil was purified via vacuum distillation at 0.25 Torr to afford the clean product as translucent yellow oil (bp: 125-145°C, 202 g, 70 %): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.20 (t, J = 7.4 Hz, 6H), 2.71 - 2.80 (m, 4H), 3.95 (s, 6H), 6.64 (s, 1H), 11.67 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 15.42, 28.31, 52.27, 115.22, 121.91, 148.63, 159.71, 169.86. EI-MS: calculated for C<sub>14</sub>H<sub>18</sub>O<sub>5</sub> 266; found 266 (M<sup>+</sup>). Anal. calc for C<sub>14</sub>H<sub>18</sub>O<sub>5</sub>: C, 63.15; H, 6.81. Found: C, 63.23; H, 6.92. R<sub>f</sub> = 0.38 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A=0.05 % aqueous trifluoroacetic acid, B=CH<sub>3</sub>CN; linear gradient: 50%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 14.4 min (100.0 area %).

**Step B:** Dimethyl 4,6-diethyl-2-methoxy-1,3-benzenedicarboxylate

20 A mixture of the crude intermediate obtained in Step A (241.6 g, 0.91 mol), potassium carbonate (204 g, 1.48 mol) and dimethyl sulfate (129 mL, 1.37 mol) in acetone (1 L) was stirred vigorously overnight. After six hours at reflux, the reaction was cooled to room temperature, additional dimethyl sulfate (43 mL, 0.46 mol) was added, and reflux was continued overnight. The mixture was filtered  
25 through a pad of Celite, diethyl ether (1 L) was used to wash the Celite pad, and the combined filtrates were concentrated in vacuo. The resulting crude oil was purified via vacuum distillation to afford the pure product as a translucent yellow oil (bp: 180-190°C, 178.1 g, 58 % (2 steps)): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.16-1.25 (m, 6H), 2.55-2.66 (m, 4H), 3.81 (s, 3H), 3.91 (s, 6H), 6.89 (s, 1H). R<sub>f</sub> = 0.34 (9:1 hexanes:ethyl  
30 acetate).

**Step C:** Dimethyl 4,6-diisopropyl-2-methoxy-1,3-benzenedicarboxylate

A solution of diisopropylamine (26.7 mL, 0.20 mol) in dry tetrahydrofuran (0.2 L) at -78°C under an argon atmosphere was treated with slow  
35 addition of n-butyllithium (2.47M in hexanes, 85.0 mL, 0.20 mol). After the reaction stirred for fifteen minutes, a solution of the intermediate from Step B (58.0 g, 0.16 mol) in dry tetrahydrofuran (0.2 L) was added to the solution of LDA over 45

0 minutes. Stirring was continued for 80 minutes while the internal temperature was held at -76°C. Neat iodomethane (13.2 mL, 0.21 mol) was added to the reaction mixture via syringe; two-thirds of the charge was transferred at the outset, the reaction was allowed to stir for 30 minutes, then the final third of the charge was added, followed by another 30 minutes of stirring. A second pot of LDA (0.2 mol) in dry tetrahydrofuran (0.2 L) was produced by the above procedure and was transferred to the reaction mixture via cannula over 45 minutes. Stirring was continued for 80 minutes at -76 °C then a second portion of neat iodomethane (13.2 mL, 0.21 mol) was added to the reaction mixture using the addition sequence described above. The cooling bath was removed and the reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.4 L). The mixture was extracted with diethyl ether (3 x 0.4 L) and the combined organic portions were dried over magnesium sulfate, filtered through a plug of silica gel and concentrated in vacuo to afford the clean product as an off-white solid (60.2 g, 98 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.24 (d, J = 6.6 Hz, 12H), 2.84-2.96 (m, 2H), 3.82 (s, 3H), 3.92 (s, 6H), 7.04 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 23.72, 31.36, 52.30, 63.56, 117.95, 125.66, 148.68, 153.76, 168.36. FAB-MS: calculated for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub> 308; found 309 ((M+H)<sup>+</sup>). Anal. calc for C<sub>17</sub>H<sub>24</sub>O<sub>5</sub>: C, 66.21; H, 7.84. Found: C, 66.22; H, 7.94. R<sub>f</sub> = 0.3 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A=0.05 % aqueous trifluoroacetic acid, B=CH<sub>3</sub>CN; linear gradient: 50%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 16.2 min (97.6 area%). mp 70.5-71.5 °C.

Step D: Diisopropyl 4,6-diisopropyl-2-methoxy-1,3-benzenedicarboxylate

Isopropanol (50 mL) was cautiously added to a flask charged with sodium hydride (95%, 0.33 g, 13.8 mmol). A solution of the intermediate obtained in Step C (8.5 g, 27.6 mmol) in isopropanol (100 mL) was added and the resulting mixture was held at reflux overnight. Additional sodium hydride (95%, 0.33 g, 13.8 mmol) and isopropanol (50 mL) were added to push the reaction to completion. Reflux was continued for five hours then the reaction mixture was cooled to ambient temperature and quenched with 10 % aqueous hydrochloric acid (60 mL). Isopropanol was removed in vacuo and the residual aqueous layer was extracted with diethyl ether (2 x 150 mL). The combined ethereal extracts were dried over magnesium sulfate, concentrated in vacuo, and chromatographed on silica (300 g) using dichloromethane:hexanes (1:1) as eluent to provide the clean product as a colorless crystalline solid (8.5 g, 85 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.25 (d, J = 7.0 Hz, 12H), 1.37 (d, J = 6.3 Hz, 12H), 2.90-2.98 (m, 2H), 3.85 (s, 3H), 5.30 (septet, J = 6.3 Hz, 2H), 7.02 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 21.77, 23.74, 31.12, 63.59, 68.92, 117.78, 126.44, 148.08, 153.20, 167.40. FAB-MS: calculated for C<sub>21</sub>H<sub>32</sub>O<sub>5</sub> 364; found

0 365 ((M+H)+). Anal. calc for C<sub>21</sub>H<sub>32</sub>O<sub>5</sub>: C, 69.20; H, 8.85. Found: C, 69.23; H, 8.86. R<sub>f</sub> = 0.42 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A=0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 50%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 24.4 min (96.6 area %). mp 68.0-69.0°C.

5 Step E:        Diisopropyl 3,5-diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-  
                         dicarboxylate

10 A dry flask containing freshly ground magnesium turnings (2.88 g, 120 mmol) and a crystal of iodine was heated until a dark purple iodine atmosphere had formed. The flask was cooled to ambient temperature and a solution of 2-bromo-5-fluorophenyl benzyl ether (33.8 g, 120 mmol, Example 166, Step A) in dry tetrahydrofuran (60 mL) was added in several portions over 40 minutes at a rate sufficient to maintain reflux. Reflux was continued for 45 minutes, then the reaction was cooled to room temperature. This solution of Grignard reagent was transferred via syringe to a second flask containing a solution of the intermediate from Step D (11.0 g, 30.2 mmol) in dry benzene (66 mL). The reaction mixture was held at reflux for one hour, quenched with 10% aqueous hydrochloric acid (300 mL) and extracted with diethyl ether (3 x 300 mL). The combined extracts were dried over magnesium sulfate and concentrated in vacuo to give a brown oil which was subjected to flash column chromatography on silica (80 mm x 19.5") using a stepwise gradient elution of dichloromethane:hexanes (1:3, 1:2, 1:1, 4L each). The fractions containing the product were combined and concentrated to afford an inseparable mixture of the product and an unidentified side product in about a 1:1 ratio as a pale yellow gum (5.3 g, 33% mass balance). This material was not fully characterized and was used without further purification.

25

Step F:        Isopropyl 3,5-diisopropyl-6-hydroxymethyl-2'-benzyloxy-4'-fluoro-  
                         1,1'-biphenyl-2-carboxylate

30 A mixture of the intermediate from Step E (5.83 g, 10.9 mmol) and Red-Al (3.3 mL, 10.9 mmol) in dry tetrahydrofuran (100 mL) was held at reflux for 2.5 hours. Additional Red-Al was added (in 3.3 mL aliquots) and reflux maintained until the lower R<sub>f</sub> spot disappeared (21 hours, total 8 eq. Red-Al; i.e. the by-product from the previous step reacted faster than the desired diester). The reaction mixture was cooled to 0 °C, carefully quenched with water (14 mL), and vigorously stirred for 2 hours. The precipitated solids were removed via vacuum filtration through paper and the collected solids were washed with ethyl acetate (3 x 100 mL) and refiltered. The combined filtrates were washed with a 1:1 mixture of water and saturated aqueous sodium chloride (100 mL), followed by water (75 mL) and

35

0 saturated aqueous sodium chloride (50 mL). The organic portion was separated,  
 dried over sodium sulfate and concentrated in vacuo. Purification by flash column  
 chromatography on silica (80 mm x 6") using hexanes:ethyl acetate (19:1) as eluent  
 gave pure diisopropyl 3,5-diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-  
 5 dicarboxylate (2.63 g, 4.92 mmol). This was resubjected to the reaction conditions  
 with Red-Al (2.95 mL, 9.84 mmol) in dry tetrahydrofuran (45 mL). Additional Red-  
 Al was added (in 2.95 mL aliquots) and reflux maintained until the reaction was  
 complete (30 hours, total 12 eq. Red-Al). Worked up as above and subjected crude  
 product to flash column chromatography on silica (40 mm x 7") using hexanes:ethyl  
 acetate (19:1) as eluent to provide the desired product as a translucent colorless oil  
 10 (1.25 g, 55 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.91 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 6.3  
 Hz, 3H), 1.20-1.33 (m, 9H), 1.35 (d, J = 7.0 Hz, 3H), 1.91-2.00 (br s, 1H), 2.94-3.07 (m,  
 1H), 3.37-3.50 (m, 1H), 4.24-4.46 (m, 2H), 4.84-5.06 (m, 3H), 6.73-6.87 (m, 2H), 7.01-  
 7.08 (m, 2H), 7.14-7.29 (m, 4H), 7.39 (s, 1H). FAB-MS: calculated for C<sub>30</sub>H<sub>35</sub>O<sub>4</sub>F  
 478; found 479 ((M+H)+). R<sub>f</sub> = 0.23 (9:1 hexanes:ethyl acetate).

15

**Step G: Isopropyl 3,5-diisopropyl-6-formyl-2'-benzyloxy-4'-fluoro-1,1'-  
 biphenyl-2-carboxylate**

A chilled (0°C) mixture of the intermediate from Step F (0.73 g, 1.52 mmol),  
 Celite (1.46 g), and pyridinium chlorochromate (0.61 g, 2.84 mmol) in dry  
 20 dichloromethane (30 mL) was stirred for 5 hours, while warming to room  
 temperature. The mixture was diluted with ethyl acetate (30 mL) and hexane (60  
 mL) and filtered through a plug of silica (30 mm x 3"). Elution was continued with  
 ethyl acetate:hexanes (1:1 mixture, 2 x 120 mL). The combined filtrates were  
 concentrated in vacuo to afford the desired product as a clear colorless oil (0.72 g,  
 25 99 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.90 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.3 Hz,  
 3H), 1.23-1.36 (m, 12H), 2.99-3.10 (m, 1H), 3.92-4.02 (m, 1H), 4.85-5.06 (m, 3H), 6.65-  
 6.76 (m, 2H), 7.15-7.30 (m, 6H), 7.46 (s, 1H), 9.84 (s, 1H). FAB-MS: calculated for  
 C<sub>30</sub>H<sub>33</sub>O<sub>4</sub>F 476; found 477 ((M+H)+). R<sub>f</sub> = 0.47 (9:1 hexanes:ethyl acetate).

30 **Step H: Isopropyl 3,5-diisopropyl-6-(prop-1-enyl)-2'-benzyloxy-4'-fluoro-1,1'-  
 biphenyl-2-carboxylate**

A chilled (-70°C) suspension of (ethyl)triphenylphosphonium bromide (0.88  
 g, 2.37 mmol) in dry tetrahydrofuran (6 mL) was treated with dropwise addition of  
 n-butyllithium (2.47M in hexanes, 1.04 mL, 2.56 mmol). The mixture was  
 35 immediately warmed to 0 °C, stirred for 90 minutes at 0 °C, and recooled to -70 °C.  
 A solution of the intermediate from Step G (0.94 g, 1.97 mmol) in dry  
 tetrahydrofuran (6 mL) was added to the solution of ylide over several minutes

0 and the reaction mixture was warmed again to 0 °C and stirred for one hour. The reaction was quenched with water (3 mL) and diluted with ethyl acetate (25 mL). The organic portion was washed with saturated aqueous sodium chloride solution (2 x 15 mL). The combined aqueous portions were back-extracted with ethyl acetate (10 mL). The combined organic portions were dried over sodium sulfate  
5 and concentrated in vacuo to provide the crude solid which was subjected to flash column chromatography on silica (30 mm x 6") using hexanes:ethyl acetate (19:1) as eluent. The clean fractions were combined and concentrated in vacuo to afford the desired product as a pale yellow oil (0.81 g, 84 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.84-0.92 (m, 3H), 1.02-1.59 (m, 18H), 2.96-3.31 (m, 2H), 4.82-4.97 (m, 1H), 4.98 (s,  
10 2H), 5.19-5.52 (m, 1H), 6.07- 6.19 (m, 1H), 6.57-6.69 (m, 2H), 7.05-7.31 (m, 7H). FAB-MS: calculated for C<sub>32</sub>H<sub>37</sub>O<sub>3</sub>F 488; found 489 (M+H)<sup>+</sup>. R<sub>f</sub> = 0.58 (9:1 hexanes:ethyl acetate).

15 Step I: 3,5-Diisopropyl-2-hydroxymethyl-6-(prop-1-enyl)-2'-benzyloxy-4'-fluoro-1,1'-biphenyl

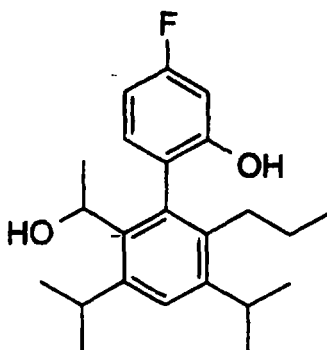
A reaction flask was charged with a suspension of lithium aluminum hydride (95%, 0.14 g, 3.3 mmol) in dry tetrahydrofuran (5 mL) and heated to reflux. A solution of the intermediate from Step H (0.80 g, 1.64 mmol) in dry tetrahydrofuran (10 mL) was added to the refluxing suspension dropwise from a  
20 syringe. The reaction mixture was held at reflux for 23 hours, cooled to ambient temperature and quenched using saturated aqueous sodium sulfate solution which was added dropwise until gas evolution stopped. The mixture was then diluted with ethyl acetate (15 mL), stirred for several minutes and filtered through a pad of Celite. The pad was washed copiously with additional ethyl acetate. The combined  
25 filtrates were concentrated in vacuo and subjected to flash column chromatography on silica (30 mm x 3") to afford the clean product as a clear oil (0.53 g, 75 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.05-1.46 (m, 15H), 1.68-1.78 (br s, 1H), 3.07-3.49 (m, 2H), 4.27-4.47 (m, 2H), 4.85-5.05 (m, 2H), 5.25-5.52 (m, 1H), 5.92-6.08 (m, 1H), 6.68-6.76 (m, 2H), 6.98-7.13 (m, 3H), 7.18-7.29 (m, 3H), 7.35 (s, 1H). FAB-MS: calculated for C<sub>29</sub>H<sub>33</sub>O<sub>2</sub>F 432; found 432 (M)<sup>+</sup>. R<sub>f</sub> = 0.29 (9:1 hexanes:ethyl acetate).  
30

Step J: 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl

A mixture of the intermediate from Step I (0.53 g, 1.23 mmol), and 10%  
35 Pd/C (53 mg) in methanol (12 mL) was stirred under one atmosphere of hydrogen gas for 18 hours. The reaction mixture was then filtered through a pad of Celite and the pad was rinsed thoroughly with methanol (100 mL). The combined

- 0 filtrates were concentrated in vacuo and subjected to flash column chromatography on silica (20 mm x 4") using hexanes:ethyl acetate (9:1) as eluent. In this manner, the pure product was obtained as a clear oil which slowly solidified to provide the title compounds as a white solid (0.37 g, 87 %).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.76 (t,  $J = 7.4$  Hz, 3H), 1.16-1.36 (m, 15H), 2.11-2.42 (m, 2H), 3.12-3.25 (m, 1H), 3.30-3.43 (m, 1H), 4.29-4.47 (m, 2H), 6.69-6.80 (m, 2H), 7.00-7.07 (m, 1H), 7.36 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  14.65, 24.29, 24.34, 24.50, 24.58, 29.21, 32.18, 59.61, 103.6 (d,  $J = 24.4$  Hz), 107.6 (d,  $J = 22.0$  Hz), 123.50, 123.67 (d,  $J = 2.4$  Hz), 131.21 (d,  $J = 9.8$  Hz), 134.07, 134.66, 137.42, 146.30, 148.12, 154.26 (d,  $J = 12.2$  Hz), 163.01 (d,  $J = 244.2$  Hz). FAB-MS: calculated for  $\text{C}_{22}\text{H}_{29}\text{O}_2\text{F}$  344; found 344 (M)+. Anal. calc for  $\text{C}_{22}\text{H}_{29}\text{O}_2\text{F}$ : C, 76.71; H, 8.49. Found: C, 76.66; H, 8.34.  $R_f = 0.41$  (4:1 hexanes:ethyl acetate). HPLC: (C-18, A=0.05 % aqueous trifluoroacetic acid, B= $\text{CH}_3\text{CN}$ ; linear gradient: 50%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 17.1 min (97.5 area %). mp 127.5 - 129.0°C.

15

EXAMPLE 2423,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl

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Step A: 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-fluoro-2'-benzyloxy-1,1'-biphenyl

- 25 A mixture of the racemic compound prepared in Example 241 (293 mg, 851  $\mu\text{mol}$ ), benzyl bromide (110  $\mu\text{L}$ , 925  $\mu\text{mol}$ ), and potassium carbonate (303 mg, 2.19 mmol) in acetone (29 mL) was heated to reflux for 3 h. The mixture was diluted with saturated aqueous ammonium chloride solution (50 mL) and extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). Silica gel chromatography (90:10 hexane/ethyl acetate) provided a colorless oil (0.369 g, 100%).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.34 (s, 1H), 7.23 (m, 3H), 7.12 (m, 1H), 7.03 (m, 2H), 6.84-6.75 (m, 2H), 5.04 (d, 12.1 Hz, 1H), 4.94 (d, 12.1

30

0 Hz, 1H), 4.38 (dd, 11.4 Hz, 8.5 Hz, 1H), 4.25 (dd, 11.4 Hz, 3.3 Hz, 1H), 3.39 (sept, 6.9 Hz, 1H), 3.18 (sept, 6.9 Hz, 1H), 2.30-2.40 (m, 1H), 2.09-2.20 (m, 1H), 1.65 (dd, 8.5 Hz, 3.3 Hz, 1H), 1.26-1.34 (m, 14H), 0.72 (t, 7.4 Hz, 3H).

5 Step B: 3,5-Diisopropyl-2-formyl-6-propyl-4'-fluoro-2'-benzyloxy-1,1'-biphenyl

Prepared from the intermediate obtained in Step A by the procedure described in Example 218, Step A. Silica gel chromatography (95:5 hexane/EtOAc) provided a colorless crystalline solid (0.323 g, 88%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 9.74 (s, 1H), 7.41 (s, 1H), 7.22-7.28 (m, 3H), 7.06-7.13 (m, 3H), 6.72-6.80 (m, 2H), 5.00 (s, 2H), 3.91 (sept, 6.8 Hz, 1H), 3.23 (sept, 6.7 Hz, 1H), 2.37-2.46 (m, 1H), 2.17-2.27 (m, 1H), 1.20-1.36 (m, 14H), 0.73 (t, 7.4 Hz, 3H). FAB-MS: calculated for C<sub>29</sub>H<sub>33</sub>FO<sub>2</sub> 432; found 433 (M+H).

15 Step C: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-2'-benzyloxy-1,1'-biphenyl

Methyl lithium (2.7 mL of 1.4 M solution in Et<sub>2</sub>O, 3.78 mmol) was added dropwise over five minutes to a cooled (ice-water bath) suspension of CuI (715 mg, 3.75 mmol, purified by extraction with THF) in toluene (10.8 mL) such that the internal temperature of the mixture was ≤3°C. The addition produced first a yellow-orange suspension and then a colorless solution. After 25 minutes the mixture was again a yellow-orange suspension. A solution of the intermediate obtained in Step B (306 mg, 707 μmol) in toluene (1 mL) was added dropwise over four minutes such that the internal temperature of the mixture was ≤2°C. After 30 minutes 1/3 saturated aqueous NH<sub>4</sub>OH solution (40 mL) was added. After an additional 60 minutes the mixture was diluted with saturated aqueous NH<sub>4</sub>Cl solution (40 mL) and extracted with Et<sub>2</sub>O (3 x 40 mL). Silica gel chromatography (83:17 hexane/EtOAc) provided a colorless solid (0.290 g, 91%). The product was a mixture of diastereomers in a ratio of 93:7 as judged by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, only peaks corresponding to the major diastereomer were visible): δ 7.35 (s, 1H), 7.22-7.24 (m, 3H), 7.11 (dd, 8.1 Hz, 7.0 Hz, 1H), 7.04 (m, 2H), 6.70-6.78 (m, 2H), 4.99 (d, 2.6 Hz, 2H), 4.83 (qd, J<sub>q</sub>=6.8 Hz, J<sub>d</sub>=2.8 Hz, 1H), 3.84 (sept, 6.8 Hz, 1H), 3.14 (sept, 6.9 Hz, 1H), 2.29 (m, 1H), 2.07 (m, 1H), 1.74 (d, 2.9 Hz, 1H), 1.25-1.35 (m, 17H), 0.70 (t, 7.4 Hz, 3H). EI-MS: calculated for C<sub>30</sub>H<sub>37</sub>FO<sub>2</sub> 448; found 448 (M<sup>+</sup>).

35 Step D: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl

0       The title compound was prepared from the intermediate obtained in Step C by the procedure described in Example 1, Step H. Silica gel chromatography (83:17 hexane/EtOAc) provided two colorless solids (0.229 g, 99%).

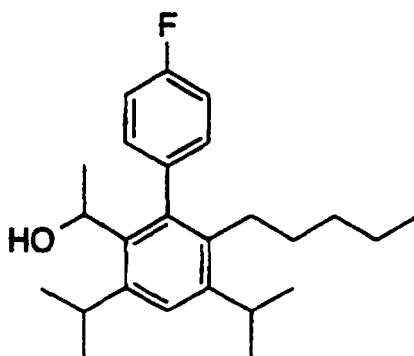
Diastereomer 1 was obtained as a colorless crystalline solid (0.214 g, 92%).  
5       <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.37 (s, 1H), 7.03 (m, 1H), 6.72 (m, 2H), 4.80-4.89 (m, 2H), 3.79 (sept, 6.8 Hz, 1H), 3.14 (sept, 6.8 Hz, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.64 (d, 3.3 Hz, 1H), 1.41 (d, 7.0 Hz, 3H), 1.26-1.31 (m, 14H), 0.74 (t, 7.4 Hz, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>31</sub>FO<sub>2</sub> 358; found 341 (M-OH). mp 149-150°C. R<sub>f</sub> = 0.25 (83:17 hexane/ethyl acetate).

10       Diastereomer 1 (212 mg) was resolved into its constituent enantiomers as follows: a Waters Prep LC 4000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 × 50 cm ID). The system was equilibrated with a mobile phase consisting of 1% butanol and 99% heptane at a flow rate of 100 mL/min. The sample was dissolved in dichloromethane (70 mg/mL) and 1 mL aliquots were injected at 40 min intervals. The effluent was monitored at 285 nm and two  
15       fractions (corresponding to the two enantiomers) were collected at (19-23 min, 100% ee) and (30-37 min, ≥98% ee), respectively.

Enantiomer 1 was obtained as a colorless solid (78 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.37 (s, 1H), 7.02 (m, 1H), 6.71 (m, 2H), 4.77-4.89 (m, 2H), 3.77 (m, 1H), 3.14 (sept, 6.8 Hz, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 1.63 (d, 2.9 Hz, 1H), 1.41 (d, 6.6  
20       Hz, 3H), 1.26-1.31 (m, 14H), 0.74 (t, 7.2 Hz, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>31</sub>FO<sub>2</sub> 358; found 341 (M-OH).

Enantiomer 2 was obtained as a colorless solid (74 mg). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.38 (s, 1H), 7.03 (m, 1H), 6.72 (m, 2H), 4.80-4.90 (m, 2H), 3.79 (sept, 6.6  
25       Hz, 1H), 3.14 (sept, 6.7 Hz, 1H), 2.30 (m, 1H), 2.07 (m, 1H), 1.63 (d, 3.3 Hz, 1H), 1.41 (d, 6.6 Hz, 3H), 1.26-1.31 (m, 14H), 0.74 (t, 7.2 Hz, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>31</sub>FO<sub>2</sub> 358; found 341 (M-OH).

Diastereomer 2 was obtained as a colorless crystalline solid (15.3 mg, 7%).  
30       <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.37 (s, 1H), 6.92 (m, 1H), 6.70 (m, 2H), 5.1 (br s, 1H), 4.64 (q, 6.7 Hz, 1H), 3.85 (sept, 6.7 Hz, 1H), 3.14 (sept, 6.8 Hz, 1H), 2.32 (m, 1H), 2.09 (m, 1H), 1.8 (br s, 1H), 1.37 (d, 6.6 Hz, 3H), 1.24-1.30 (m, 14H), 0.74 (t, 7.2 Hz, 3H). FAB-MS: calculated for C<sub>23</sub>H<sub>31</sub>FO<sub>2</sub> 358; found 341 (M-OH). mp 179-180°C.

**EXAMPLE 243****(+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl****Step A: 3,5-Diisopropyl-2-(1-oxoethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl**

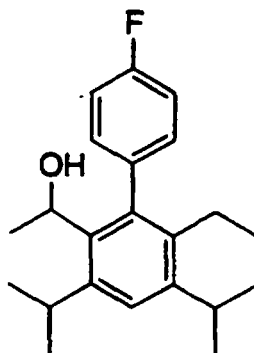
A mixture of 3,5-diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl (Example 192, 13.7 g, 37.1 mmol), Celite (26 g), and pyridinium chlorochromate (14.9 g, 69.3 mmol) in dichloromethane (750 mL) was stirred for 45 minutes. The mixture was diluted with ethyl acetate (750 mL) and hexane (1.5 L) and filtered through a plug of silica (100 mm x 2") topped with Celite (100 mm x 0.5"). Elution was continued with ethyl acetate:hexanes (1:1 mixture, 3L x 2). The combined filtrates were concentrated *in vacuo* to afford the desired product as a white solid (13.5 g, 99 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.75 - 0.80 (m, 3H), 1.06 - 1.31 (m, 18H), 1.95 (s, 3H), 2.33 - 2.39 (m, 2H), 2.78 (septet, J = 7.0 Hz, 1H), 3.18 (septet, J = 7.0 Hz, 1H), 7.03 - 7.09 (m, 2H), 7.17 - 7.22 (m, 2H), 7.26 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.75, 22.02, 24.32, 24.37, 28.99, 29.10, 29.28, 30.60, 31.04, 32.06, 33.03, 114.85 (d, J = 20.8 Hz, 2C), 122.06, 132.03 (d, J = 7.3 Hz, 2C), 135.52 (d, J = 2.4 Hz, 1C), 135.58, 135.76, 140.13, 140.85, 147.66, 161.99 (d, J = 246.6 Hz, 1C), 208.23. EI-MS: calculated for C<sub>25</sub>H<sub>33</sub>OF 368; found 368 (M<sup>+</sup>). Anal. calc for C<sub>25</sub>H<sub>33</sub>OF: C, 80.86; H, 8.96. Found: C, 81.04; H, 9.06. R<sub>f</sub> = 0.65 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 75%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 22.7 min (94.0 area %). mp 123.0-124.5°C.

**Step B: (+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl**

A mixture of (1S,2R)-(+)-N-methylephedrine (13.9 g, 77.3 mmol) in diethyl ether (225 mL) at 0 °C under an argon atmosphere was treated with slow addition of lithium aluminum hydride (1M in diethyl ether, 77.3 mL, 77.3 mmol). The

0 mixture was held at reflux for one hour and then cooled to -75 °C. A solution of  
the intermediate from Step A (13.5 g, 36.7 mmol) in diethyl ether (500 mL, 50 mL  
rinse) was then added to the reaction mixture in such a manner that the internal  
temperature did not rise above -68 °C. The reaction stirred for 3 hours at -75 °C  
and was warmed to ambient temperature overnight. The reaction was cooled to 0  
5 °C, quenched by adding water (500 mL), and diluted with diethyl ether (750 mL).  
The aqueous portion was separated and back-extracted with diethyl ether (200 mL).  
The combined organic portions were washed with water (2 x 500 mL), 10 %  
aqueous hydrochloric acid (500 mL), and saturated aqueous sodium chloride (2 x  
500 mL), dried over sodium sulfate, filtered through a pad of silica (80 mm x 1.25")  
10 and concentrated *in vacuo*. The resulting solid was recrystallized from  
ethanol:water (2:1) and dried *in vacuo* with several minutes of heating to provide  
the title compound as a fine white powder (11.08 g, 82 %). <sup>1</sup>H NMR (300 MHz,  
CDCl<sub>3</sub>): δ 0.75 - 0.80 (m, 3H), 1.02 - 1.31 (m, 19H), 1.40 (d, J = 6.6 Hz, 3H), 2.17 - 2.22  
(m, 2H), 3.08 - 3.18 (m, 1H), 3.83 - 3.92 (m, 1H), 4.66 - 4.73 (m, 1H), 7.05 - 7.23 (m,  
15 4H), 7.32 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.88, 22.02, 23.38, 24.23, 24.56,  
24.63, 25.09, 28.68, 28.96, 29.92, 31.04, 32.23, 68.91, 114.80 (d, J = 20.8 Hz, 1C), 115.02  
(d, J = 20.8 Hz, 1C), 124.27, 130.40 (d, J = 8.5 Hz, 1C), 131.25 (d, J = 7.3 Hz, 1C),  
135.53, 136.98, 137.73 (d, J = 2.4 Hz, 1C), 139.02, 145.82 (2C), 161.68 (d, J = 245.4 Hz,  
1C). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>O 370; found 370 (M<sup>+</sup>). Anal. calc for  
20 C<sub>25</sub>H<sub>35</sub>O: C, 81.03; H, 9.52. Found: C, 81.15; H, 9.68. R<sub>f</sub> = 0.36 (9:1 hexanes:ethyl  
acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear  
gradient: 75%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 22.6 min (98.3 area %),  
(Daicel Chiralcel OD-H; isocratic 99:1 hexanes:methyl *t*-butyl ether; 254 nm, 1.5  
mL/min); R.T. 6.20 min. (97.2 area %), 8.37 min. (0.36 area %); 99.5 % e.e. [α]<sub>D</sub> =  
25 +26.9° (c = 0.00196 g/mL, CH<sub>2</sub>Cl<sub>2</sub>). mp 108.5-109.5°C.

#### EXAMPLE 244



30 (+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl

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**Step A:**     Dimethyl 4,6-diethyl-2-trifluoromethanesulfonyloxy-1,3-benzenedicarboxylate

A solution of 90 g (338 mmol) of dimethyl 4,6-diethyl-2-hydroxy-1,3-benzenedicarboxylate (Example 241, Step A) in dichloromethane (1 L) was treated with pyridine (109 mL, 1.35 mol). The mixture was stirred under argon at 0°C and treated dropwise with triflic anhydride (83 mL, 507 mmol). The reaction mixture was warmed to room temperature and stirred for 3 hours. Then was washed with 5% HCl (1.5 L), water (1 L), saturated sodium bicarbonate (2 x 500 mL), and dried with MgSO<sub>4</sub>. Filtration and concentration afforded a dark oil (129.7 g, 326 mmol, 96%). R<sub>f</sub> = 0.4 (10% ethyl acetate/hexane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.20 (s, 1 H), 3.93 (s, 6 H), 2.74 (q, J = 7.4 Hz, 4 H), 1.22 (t, J = 4.8 Hz, 6 H). FAB-MS: calculated for (C<sub>15</sub>H<sub>27</sub>F<sub>3</sub>O<sub>7</sub>) 398, found 399 (M+H).

**Step B:**     3,5-Diethyl-2,6-dicarboxymethyl-4'-fluoro-1,1'-biphenyl

To a solution of the intermediate obtained in Step A (129.7 g, 326 mmol) in dioxane (2.5 L) was added 4-fluorobenzene boronic acid (68.4 g, 492 mmol), potassium phosphate (145 g, 683 mmol), potassium bromide (58.1 g, 488 mmol), tetrakis(triphenylphosphine)palladium (18.8 g, 16.3 mmol), and water (20 mL). The reaction mixture was stirred under argon at reflux for 24 hrs. The reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The oily residue was filtered twice through a pad of silica (700 g, 40% dichloromethane/hexane) to afford a yellow solid. Recrystallization from hexane afforded a white solid (52.6 g, 153 mmol, 47%). mp = 98-99°C. R<sub>f</sub> = 0.4 (10% ethyl acetate/hexane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.26 (m, 2 H), 7.17 (s, 1 H), 7.04 (m, 2 H), 3.49 (s, 6 H), 2.67 (q, J = 7.7 Hz, 4 H), 1.25 (t, J = 7.7 Hz, 6 H). FAB-MS: calculated for (C<sub>20</sub>H<sub>21</sub>FO<sub>4</sub>) 344, found 345 (M+H).

**Step C:**     3,5-Diisopropyl-2,6-dicarboxymethyl-4'-fluoro-1,1'-biphenyl

A solution of diisopropylamine (22.7 mL, 0.174 mol) in dry tetrahydrofuran (0.2 L) at -78°C under an argon atmosphere was treated with slow addition of n-butyllithium (2.5M in hexanes, 70 mL, 0.174 mol). After the reaction stirred for fifteen minutes, a solution of the intermediate from Step B (46.0 g, 0.133 mol) in dry tetrahydrofuran (0.2 L) was added to the solution of LDA over 15 minutes. Stirring was continued for 30 minutes while the temperature was held at -78°C. Neat iodomethane (11.2 mL, 0.180 mol) was added to the reaction mixture via syringe; two-thirds of the charge was transferred at the outset, the reaction was allowed to stir for 20 minutes, then the final third of the charge was added, followed by

0 another 10 minutes of stirring. A second pot of LDA (0.174 mol) in dry tetrahydrofuran (0.2 L) was produced by the above procedure and was transferred to the reaction mixture via cannula over 15 minutes. Stirring was continued for 30 minutes at -78 °C then a second portion of neat iodomethane (11.2 mL, 0.180 mol) was added to the reaction mixture using the addition sequence described above.

5 The cooling bath was removed and the reaction mixture was quenched with saturated aqueous ammonium chloride solution (0.4 L). The mixture was extracted with diethyl ether (3 x 0.4 L) and the combined organic portions were dried over magnesium sulfate and concentrated in vacuo to afford an oil, which crystallized upon standing. The white solid was washed with a small portion of hexane (41.7 g, 84 %). mp 128-130°C.  $R_f$  = 0.5 (10% ethyl acetate/hexane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33 (s, 1 H), 7.26 (m, 2 H), 7.03 (m, 2 H), 3.49 (s, 6 H), 2.97 (sept,  $J$  = 6.6 Hz, 2 H), 1.29 (d,  $J$  = 7.0 Hz, 6 H). FAB-MS: calculated for ( $\text{C}_{22}\text{H}_{25}\text{FO}_4$ ) 372, found 373 (M+H).

15 Step D: 3,5-Diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl

To a solution of the intermediate obtained in Step C (37.3 g, 100 mmol) in anhydrous tetrahydrofuran (350 mL) stirred under argon at 0°C was added a solution of 3.4M of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al) (105 mL, 204 mmol, 65 wt% in toluene) via syringe over 20 min. The reaction mixture was allowed to stir at room temperature for 24 hr, then cooled again to 0°C and carefully quenched by the dropwise addition of water. The solution was decanted from the solid which forms and the solvent removed in vacuo. The residue was purified by flash chromatography (500 g silica) via step

20 gradient. Elution with 5% diethyl ether/hexane affords 9.8 g (26.3 mmol, 28%) of recovered starting material and elution with 40% diethyl ether( $\text{Et}_2\text{O}$ )/hexane affords the desired product as a white solid (26.8 g, 77.8 mmol, 78%). mp 124-126°C.  $R_f$  = 0.2 (10% ethyl acetate/hexane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.35 (s, 1 H), 7.27 (m, 2 H), 7.08 (m, 2 H), 4.44 (d,  $J$  = 5.5 Hz, 2 H), 3.43 (m, 4 H), 2.92 (sept,  $J$  = 6.6 Hz, 1 H), 1.59 (s, 1 H), 1.28 (m, 12 H). FAB-MS: calculated for ( $\text{C}_{21}\text{H}_{25}\text{FO}_3$ ) 344, found 345 (M+H).

30 Step E: 3,5-Diisopropyl-2-carboxaldehyde-6-carboxymethyl-4'-fluoro-1,1'-biphenyl

35 To a solution of the intermediate obtained in Step D (26.8 g, 77.8 mmol) in dichloromethane (400 mL) was added celite (33.6 g). The suspension was stirred at room temperature and treated with pyridinium chlorochromate (PCC) (33.6 g, 15.6

0 mmol) in three portions. The suspension was stirred at room temperature for 2 hr, then poured into 1:1 diethyl ether/hexane (1 L), filtered through a pad of silica, the pad was washed with diethyl ether (600 mL) and the combined eluent concentrated to afford a gummy oil (23.3 g, 68.1 mmol, 87%):  $R_f$  = 0.4 (10% ethyl acetate/hexane).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.87 (s, 1 H), 7.36 (s, 1 H), 7.28 (m, 2 H), 7.15 (m, 2 H), 3.48 (s, 3 H), 3.89 (sept,  $J$  = 6.6 Hz, 1 H), 3.10 (sept,  $J$  = 6.6 Hz, 1 H), 1.35 (m, 12 H); FAB-MS calcd for  $(\text{C}_{21}\text{H}_{23}\text{FO}_3)$  342, found 343 (M+H).

Step F: 3,5-Diisopropyl-2-carboxymethyl-6-ethenyl-4'-fluoro-1,1'-biphenyl

10 Methyltriphenylphosphonium bromide (15.5 g, 43.4 mmol) was suspended in anhydrous THF (250 mL) under argon and stirred at  $-78^\circ\text{C}$ . A 1.6 M solution of *n*-butyllithium in hexanes (25 mL, 40.2 mmol) was added dropwise. The reaction mixture was allowed to come to  $0^\circ\text{C}$  and was stirred at that temperature for 1.5 hr. The resulting brightly colored solution was cooled again to  $-78^\circ\text{C}$  and treated dropwise with a solution of the intermediate obtained in Step E (11.4 g, 33.3 mmol) 15 in THF (100 mL). The reaction mixture was allowed to stir at  $0^\circ\text{C}$  for 1 hr, then quenched by the addition of water (30 mL). The THF was removed *in vacuo*, the residue partitioned between diethyl ether (400 mL) and water (400 mL). The organic layer was washed with brine (100 mL), dried over  $\text{MgSO}_4$  and concentrated. Flash chromatography through silica (5% diethyl ether/hexane) 20 affords a solid (10.3 g, 30.3 mmol, 91%) (E, Z mixture).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.31 (s, 1 H), 7.16 (m, 2 H), 7.02 (m, 2 H), 6.10 (dd,  $J$  = 6.3, 11.4 Hz, 1 H), 6.04 (dd,  $J$  = 1.8, 13.6 Hz, 1 H), 5.48 (dd,  $J$  = 1.8, 19.9 Hz, 1 H), 3.46 (s, 3 H), 3.35 (sept,  $J$  = 6.6 Hz, 1 H), 2.93 (sept,  $J$  = 6.6 Hz, 1 H), 1.29 (m, 12 H). EI-MS calculated for  $(\text{C}_{22}\text{H}_{25}\text{FO}_2)$  340, found 340 (M+). mp  $58-61^\circ\text{C}$ .  $R_f$  = 0.6 (10% ethyl acetate/hexane).

25

Step G: 3,5-Diisopropyl-2-hydroxymethyl-6-ethenyl-4'-fluoro-1,1'-biphenyl

The intermediate obtained in Step F (10.0 g, 29.4 mmol) was dissolved in anhydrous THF (150 mL) under argon and treated dropwise at room temperature with lithium aluminum hydride (1.0 M in THF, 41 mL, 41 mmol). The reaction 30 mixture was stirred at reflux for 2 hours, cooled to room temperature and quenched by the addition of 30 mL  $\text{H}_2\text{O}$ . The THF was removed *in vacuo*, the residue partitioned between diethyl ether (400 mL) and water (3 x 400 mL). The organic layer was washed with brine (300 mL), dried over  $\text{MgSO}_4$  and concentrated. Flash chromatography through silica (5% diethyl ether/hexane) 35 affords a solid (7.7 g, 24.7 mmol, 84%).  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (s, 1 H), 7.14 (m, 4 H), 6.35 (dd,  $J$  = 6.3, 11.4 Hz, 1 H), 5.20 (dd,  $J$  = 1.8, 13.6 Hz, 1 H), 4.98 (dd,  $J$  = 1.8, 19.9 Hz, 1 H), 4.40 (d,  $J$  = 5.5 Hz, 2 H), 3.39 (m, 2 H), 1.29 (m, 12 H). FAB-MS

- 0 calculated for (C<sub>21</sub>H<sub>25</sub>FO) 312, found 312 (M<sup>+</sup>). mp 97-99°C. R<sub>f</sub> = 0.1 (50% dichloromethane/hexane).

Step H: 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-fluoro-1,1'-biphenyl

- 5 The intermediate obtained in Step G (7.7 g, 24.7 mmol) was dissolved in absolute ethanol (200 mL) under argon, treated with 10% palladium on carbon (610 mg, 0.1 eq), then stirred under a hydrogen atmosphere for 2 hr. After purging the system with argon, the catalyst was removed by filtration through a pad of Celite. The solvent was removed and the product dried *in vacuo* to afford the title compound as a white solid (7.7 g, 25 mmol, 99%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ
- 10 7.32 (s, 1 H), 7.15 (m, 4 H), 4.33 (m, 2 H), 3.39 (septet, *J* = 7 Hz, 1 H), 3.32 (septet, *J* = 7 Hz, 1 H), 2.37 (q, *J* = 7.7 Hz, 2 H), 1.29 (m, 13 H), 0.92 (t, *J* = 7.7 Hz, 3 H). FAB-MS calculated for (C<sub>21</sub>H<sub>27</sub>FO) 314, found 314 (M<sup>+</sup>). mp 106-108°C. R<sub>f</sub> = 0.1 (50% dichloromethane /hexane).

15 Step I: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl

- The intermediate obtained in Step H (7.65 g, 24.3 mmol) was dissolved in dichloromethane (250 mL), treated with celite (10.5 g). The suspension was stirred at room temperature and treated with pyridinium chlorochromate (PCC) (10.5 g, 48.7 mmol). Stirring was continued at room temperature for 2 hrs. The suspension
- 20 was poured into 1:1 diethyl ether/hex (1 L), filtered through a pad of silica, the pad washed with diethyl ether (600 mL) and the combined eluent concentrated to afford a solid (7.25 g, 23.2 mmol, 95%).

- The intermediate (7.25 g, 23.2 mmol) was dissolved in THF (75 mL) at 0°C under argon atmosphere and treated dropwise with Methyl magnesium bromide
- 25 (3 M, 1.3 eq, 10.1 mL). The reaction was stirred for 1 hr. The reaction was quenched with saturated ammonium chloride (7 mL) and the THF was evaporated *in vacuo* to afford an oil. The product was partitioned between water (100 mL) and diethyl ether (250 mL) and the organic layer was dried with MgSO<sub>4</sub>, filtered, and concentrated to yield a white solid. Flash chromatography using silica gel (60% CH<sub>2</sub>Cl<sub>2</sub>/hexane) afforded a white solid (7.2 g, 22 mmol, 99%). mp 138-140°C; R<sub>f</sub> =
- 30 0.1 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (s, 1 H), 7.15 (m, 4 H), 4.69 (dq, *J* = 2.9, 7 Hz, 1 H), 3.88 (septet, *J* = 7 Hz, 1 H), 3.17 (septet, *J* = 6.6 Hz, 1 H), 2.28 (q, *J* = 7.4 Hz, 2 H), 1.64 (d, *J* = 2.9 Hz, 1 H), 1.39 (d, *J* = 6.6 Hz, 3 H), 1.27 (m, 12 H), 0.89 (t, *J* = 7.4 Hz, 3 H); FAB-MS calcd for (C<sub>22</sub>H<sub>29</sub>FO) 328, found 328
- 35 (M<sup>+</sup>).

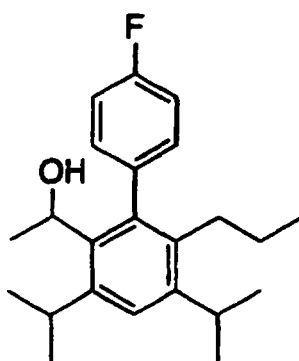
0 **Step J:** 3,5-Diisopropyl-2-(1-oxoethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl

The intermediate obtained in Step I (7.23 g, 22 mmol) in dichloromethane (100 mL) was added pyridinium chlorochromate (9.49 g, 44 mmol) and celite (9.49 g) under argon. The reaction was stirred at room temperature for 24 hours. The reaction was added to a 1:1 mixture of diethyl ether/hexane (1 L), then filtered  
5 through a plug of silica. The pad was washed with 650 mL of diethyl ether and the combined filtrates were concentrated in vacuo to afford a white solid (7.18 g, 22 mmol, 99%). mp 121-23°C;  $R_f$  = 0.3 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.27 (s, 1 H), 7.21 (m, 2 H), 7.07 (m, 2 H), 3.22 (septet,  $J$  = 7 Hz, 1 H), 2.78 (septet,  $J$  = 7 Hz, 1 H), 2.43 (q,  $J$  = 7.4 Hz, 2 H), 1.96 (s, 3 H), 1.28 (m, 12 H), 0.930 (t,  $J$  = 7.7 Hz, 3 H); FAB-MS calcd for (C<sub>22</sub>H<sub>27</sub>FO) 326, found 327 (M+H).  
10

**Step K:** (+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl

To a solution of (1S,2R)-(+)-N-methylephedrine (6.29 g, 35.1 mol) in diethyl ether (45 mL) was added lithium aluminum hydride (1M/diethyl ether, 1.5 eq., 35 mL) dropwise at 0°C under argon. The reaction was refluxed for 1.5 h. turning  
15 from a clear solution to a white milky solution. The reaction was cooled to room temperature and then -78°C. The intermediate obtained in Step J (6.64 g, 20.3 mmol) was dissolved in 60 mL of dry diethyl ether for a dropwise addition to the reaction mixture (~2 mL/min., the temperature should not rise above -60°C). The  
20 reaction was kept at -78°C for 2.0 hours and then allowed to warm overnight. The reaction was quenched at 0°C with water (30 mL) and diluted with diethyl ether (250 mL), washed with water (3 x 200 mL), brine (100 mL) and dried with MgSO<sub>4</sub>. Filtration and concentration afford a residue which was filtered through a pad of silica (400 g, 80% dichloromethane/hexane) to give the titled compound (99% e.e.)  
25 as a white solid (5.85 g, 17.8 mmol, 88%). mp 143-145°C;  $R_f$  = 0.1 (50% CH<sub>2</sub>Cl<sub>2</sub>/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.34 (s, 1 H), 7.15 (m, 4 H), 4.68 (dq,  $J$  = 3.3, 7 Hz, 1 H), 3.88 (septet,  $J$  = 7 Hz, 1 H), 3.18 (septet,  $J$  = 7 Hz, 1 H), 2.29 (q,  $J$  = 7.7 Hz, 2 H), 1.68 (s, 1 H), 1.37 (d,  $J$  = 4.8 Hz, 3 H), 1.26 (m, 12 H), 0.890 (t,  $J$  = 7.4 Hz, 3 H); FAB-MS calcd for (C<sub>22</sub>H<sub>29</sub>FO) 328, found 328 (M+); Anal. Calcd for C<sub>22</sub>H<sub>29</sub>FO: C, 80.45; H, 8.90; F, 5.78. Found: C, 80.19; H, 8.77; F, 5.84;  $[\alpha]_D^{22}$  = +26.6.  
30

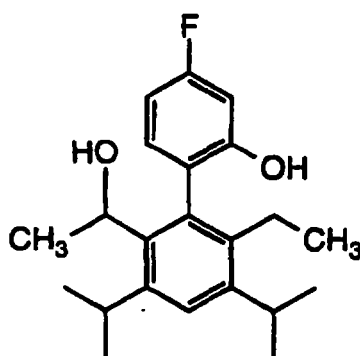
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EXAMPLE 245(+)-3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl

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The title compound (99% ee) was prepared from the intermediate obtained in Step E, Example 244 and ethyl triphenylphosphonium bromide according to the procedures described in Example 244, Steps F-K.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33 (s, 1 H), 7.14 (m, 4 H), 4.70 (dq,  $J = 2.9, 7$  Hz, 1 H), 3.88 (septet,  $J = 6.62$  Hz, 1 H), 3.14 (septet,  $J = 6.62$  Hz, 1 H), 2.18 (m, 2 H), 1.67 (d,  $J = 2.9$  Hz, 1 H), 1.37 (d,  $J = 7$  Hz, 3 H), 1.29 (m, 14 H), 0.719 (t,  $J = 7$  Hz, 3 H); FAB-MS calcd for  $(\text{C}_{23}\text{H}_{31}\text{FO})$  342, found 342 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{23}\text{H}_{31}\text{FO}$ : C, 80.66; H, 9.12; F, 5.55. Found: C, 80.71; H, 8.99; F, 5.34;  $[\alpha]^{22} = +23.8$ . mp 114-116°C;  $R_f = 0.1$  (50%  $\text{CH}_2\text{Cl}_2$ /hexane).

15

EXAMPLE 2463,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-2'-hydroxy-1,1'-biphenylStep A: Di-tert-butyl 4,6-diethyl-2-hydroxy-1,3-benzenedicarboxylate

A mixture of di-tert-butyl 1,3-acetonedicarboxylate (10 g, 38.7 mmol), 3,5-heptanedione (6.5 g, 50.3 mmol) and sodium methoxide (2.7 g, 50.3 mmol) in

0 methanol (100 mL) was stirred at room temperature overnight. Methanol was removed via rotary evaporation and the resulting orange sludge was partitioned between diethyl ether (100 mL) and 10 % aqueous hydrochloric acid (100 mL). The separated aqueous layer was extracted with diethyl ether (50 mL x 2). The combined organic portions were washed with saturated aqueous sodium chloride  
5 (20 mL), dried over sodium sulfate, filtered through a pad of silica (20 mm x 40 mm) and concentrated in vacuo to yield a yellow oil (13.23 g, 97 %): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.20 (t, 6H), 1.60 (s, 18H) 2.74 (q, 4H), 6.55 (s, 1H), 11.73 (s, 1H).

10 Step B: Di-tert-butyl 3,5-diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-dicarboxylate

The title compound was prepared from the intermediate obtained in Step A by the methods described in Example 241, Steps B, C, and E. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.15 (s, 18H), 1.27 (dd, J=5.15, 1.65 Hz, 12 H), 3.06 (m, 2H), 4.95 (s 2H), 6.65 (m, 2H), 7.27 (m, 7H).

15 Step C: 3,5-Diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-dicarboxylate

To a solution of 14.37 g (25.53 mmol) of the intermediate obtained in Step B in dichloromethane (150 mL) at 0°C was added trifluoroacetic acid (20 mL, 259.60 mmol). This reaction mixture was allowed to warm to room temperature  
20 overnight. The reaction mixture was concentrated to dryness and the residue was partitioned between diethyl ether and aqueous sodium hydroxide. The organic layer was removed, washed with aqueous sodium hydroxide and the two aqueous layers were combined. The combined aqueous layers were washed with diethyl ether (1x) then made acidic by addition of HCl (10%) and extracted with diethyl  
25 ether (3x). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to yield an off-white solid. The crude product was taken directly to the next step without any further purification.

30 Step D: Dimethyl 3,5-diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-dicarboxylate

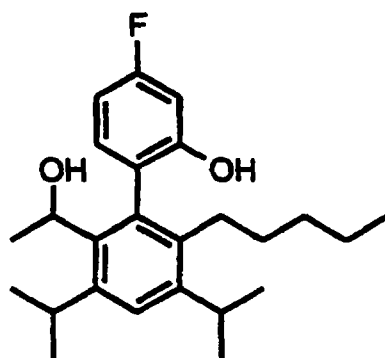
To a suspension of 7.17 g (15.93 mmol) of the intermediate obtained in Step C in dichloromethane (200 mL) at 0°C was added solid potassium carbonate (10.05 g, 72.71 mmol) followed by iodomethane (5.0 mL, 80.31 mmol). The mixture was allowed to warm to room temperature. After stirring for 1 day the mixture was  
35 diluted with water and extracted with diethyl ether (3x). The combined extracts were washed with brine (1x), dried over magnesium sulfate, filtered and concentrated to yield an off-white solid. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 1.22 (dd,

- 0 J=4.41, 2.4 Hz, 12H), 2.94 (m, 2H), 3.39 (s, 6H), 4.93 (s, 2H), 6.55 (m, 2H), 7.05 (m, 1H), 7.18 (m, 6H).

**Step E: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl**

- 5 The title compound was prepared from the intermediate obtained in Step D by the methods described in Example 241 steps F-I (using ethyl triphenylphosphonium bromide in Step H) followed by Example 242 steps B-D. Silica gel chromatography (90% hexane/10% EtOAc) provided two colorless solids (1.129g, 84%).
- 10 Diastereomer 1 was obtained as a colorless crystalline solid (1.029g, 77%). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.89 (t, J=7.36 Hz, 3H), 1.28 (m, 12H), 1.40 (d, J=6.62 Hz, 3H), 1.63 (bs, 1H), 2.29 (m, 2H), 3.17 (m, 1H), 3.78 (m, 1H), 4.84 (m, 1H), 6.70 (m, 2H), 7.03 (m, 1H), 7.38 (s, 1H). FAB-MS: calculated for C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>F, 344; found 367 [M+Na]. mp 174-175°C.
- 15 Diastereomer 1 (1.029 g) was resolved into its constituent enantiomers as follows: a Waters Prep LC 4000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 0.75% butanol and 99.25% hexane at a flow rate of 100 mL/min. The sample was dissolved in dichloromethane (20 mg/mL) and the sample was
- 20 injected in one injection. The effluent was monitored at 285 nm and two fractions (corresponding to the two enantiomers) were collected at (26-32 min, ≥98% ee) and (34-48 min, ≥99% ee), respectively.
- Enantiomer 1 was obtained as a colorless solid (480 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.89 (t, J=7.54 Hz, 3H), 1.28 (m, 12H), 1.40 (d, J=5.14 Hz, 3H), 1.65
- 25 (bs, 1H), 2.19 (m, 1H), 2.35 (m, 1H), 3.17 (m, 1H), 3.78 (m, 1H), 4.85 (m, 1H), 6.71 (m, 2H), 7.03 (m, 1H), 7.38 (s, 1H). mp condenses at 57-59°C.
- Enantiomer 2 was obtained as a colorless solid (483 mg). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.89 (t, J=7.36 Hz, 3H), 1.28 (m, 12H), 1.39 (d, J=6.99 Hz, 3H), 1.63
- 30 (bs, 1H), 2.29 (m, 2H), 3.17 (m, 1H), 3.78 (m, 1H), 4.84 (m, 1H), 6.70 (m, 2H), 7.03 (m, 1H), 7.38 (s, 1H). FAB-MS: calculated for C<sub>22</sub>H<sub>29</sub>O<sub>2</sub>F, 344; found 367 [M+Na]. mp condenses at 57-59°C.
- Diastereomer 2 was obtained as a colorless crystalline solid (100 mg, 7%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 0.88 (t, J=7.54 Hz, 3H), 1.27 (m, 12H), 1.36 (d, J=6.62 Hz, 3H), 1.8 (bs, 1H), 2.19 (m, 1H), 2.39 (m, 1H), 3.16 (m, 1H), 3.84 (m, 1H), 4.63 (q, J=6.62 Hz, 1H), 5.09 (bs, 1H), 6.69 (m, 2H), 6.92 (t, J=7.35 Hz, 1H), 7.37 (s, 1H). mp
- 35 183-184°C.

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EXAMPLE 2473,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl5 Step A: 3,5-Diisopropyl-2-hydroxymethyl-6-(pent-1-enyl)-2'-benzyloxy-4'-fluoro-1,1'-biphenyl

The desired compound was prepared from dimethyl 3,5-diisopropyl-2'-benzyloxy-4'-fluoro-1,1'-biphenyl-2,6-dicarboxylate (Example 246, Step D) by the procedure described in Example 241, Steps F - I (using pentyl triphenylphosphonium bromide in Step H). The pure product obtained was a clear oil (4.73 g, 52 % over 4 steps). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.67 - 0.78 (m, 3H), 1.09 - 1.34 (m, 14H), 1.66 - 1.88 (m, 3H), 3.16 - 3.46 (m, 2H), 4.29 - 4.44 (m, 2H), 4.88 - 5.04 (m, 2H), 5.27 - 5.41 (m, 1H), 5.94 - 6.01 (m, 1H), 6.69 - 6.78 (m, 2H), 7.00 - 7.06 (m, 3H), 7.22 - 7.26 (m, 3H), 7.35 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 14.18, 14.52, 22.89, 23.05, 24.39, 24.64, 24.94, 25.11, 25.38, 29.73, 30.50, 30.66, 31.68, 35.85, 60.78, 71.07, 71.45, 102.25, 102.59, 108.08, 108.37, 122.33, 122.54, 127.11, 127.22, 127.92, 128.11, 128.51, 129.16, 132.70, 132.83, 133.39, 134.06, 135.96, 136.96, 137.29, 137.35, 147.48, 147.63, 147.79, 156.90, 156.93, 163.26 (d, J = 246.6 Hz, 1C). FAB-MS: calculated for C<sub>31</sub>H<sub>37</sub>O<sub>2</sub>F 460; found 460 (M<sup>+</sup>). Anal. calc for C<sub>31</sub>H<sub>37</sub>O<sub>2</sub>F: C, 80.83; H, 8.10. Found: C, 80.91; H, 8.01. R<sub>f</sub> = 0.34 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 80%-100% B over 20 min; 254 nm, 1 mL/min): R.T. 14.8 min (37.7 area %), 15.2 min (56.0 area %); 93.7 % purity (cis- and trans-).

25 Step B: 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-2'-hydroxy-1,1'-biphenyl

The title compound was prepared from the intermediate obtained in Step A utilizing the procedures outlined in Example 242, Steps B-D. The crude product was subjected to flash column chromatography on silica (50 mm x 6") using  
30 hexanes:ethyl acetate (19:1 and 9:1) as eluent to separate the diastereomers (2.19 g,

0 90 %, 75 % over 3 steps).

Diastereomer 1 was obtained as a white solid (2.03 g, 83 %). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 6.6 Hz, 3H), 0.96 - 1.23 (m, 19H), 1.41 (d, J = 7.0 Hz, 3H), 2.04 - 2.37 (m, 2H), 3.09 - 3.19 (m, 1H), 3.74 - 3.84 (m, 1H), 4.81 - 4.90 (m, 2H), 6.68 - 6.75 (m, 2H), 6.99 - 7.06 (m, 1H), 7.37 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.83, 21.94, 23.83, 24.27, 24.38, 24.50, 24.88, 28.70, 29.05, 29.80, 30.76, 32.20, 68.21, 102.98 (d, J = 24.4 Hz, 1C), 107.33 (d, J = 20.8 Hz, 1C), 123.58 (d, J = 2.4 Hz, 1C), 125.45, 130.70 (d, J = 9.8 Hz, 1C), 131.78, 137.45, 138.55, 146.48, 146.94, 154.29 (d, J = 6.1 Hz, 1C), 163.04 (d, J = 244.2 Hz, 1C). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>O<sub>2</sub>F 386; found 409 (M+Na)<sup>+</sup>. Anal. calc for C<sub>25</sub>H<sub>35</sub>O<sub>2</sub>F: C, 77.68; H, 9.13. Found: C, 77.38; H, 9.20. R<sub>f</sub> = 0.30 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 70%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 12.9 min (91.3 area %); (silica, A = hexanes, B = isopropanol, isocratic run: 3 % B over 15 min; 254 nm, 1 mL/min): R.T. 5.1 min (100 area %). mp 122.5-124.0°C.

Diastereomer 1 (1.92 g) was resolved into its constituent enantiomers as follows: a Waters Prep LC 4000 HPLC system was equipped with a chiral HPLC column (BRB-9668A; 6 x 50 cm ID). The system was equilibrated with a mobile phase consisting of 0.75% butanol and 99.25% hexane at a flow rate of 100 mL/min. The sample was dissolved in dichloromethane (40 mg/mL) and the sample was loaded in two injections. The effluent was monitored at 285 nm and two fractions (corresponding to the two enantiomers) were collected.

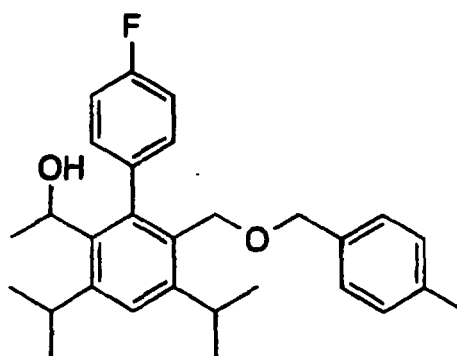
Enantiomer 1 was obtained as a white crystalline solid (0.78 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 6.6 Hz, 3H), 0.96 - 1.23 (m, 19H), 1.41 (d, J = 7.0 Hz, 3H), 2.04 - 2.37 (m, 2H), 3.09 - 3.19 (m, 1H), 3.74 - 3.84 (m, 1H), 4.81 - 4.90 (m, 2H), 6.68 - 6.75 (m, 2H), 6.99 - 7.06 (m, 1H), 7.37 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 13.83, 21.94, 23.83, 24.27, 24.38, 24.50, 24.88, 28.70, 29.05, 29.80, 30.76, 32.20, 68.21, 102.98 (d, J = 24.4 Hz, 1C), 107.33 (d, J = 20.8 Hz, 1C), 123.58 (d, J = 2.4 Hz, 1C), 125.45, 130.70 (d, J = 9.8 Hz, 1C), 131.78, 137.45, 138.55, 146.48, 146.94, 154.29 (d, J = 6.1 Hz, 1C), 163.04 (d, J = 244.2 Hz, 1C). FAB-MS: calculated for C<sub>25</sub>H<sub>35</sub>O<sub>2</sub>F 386; found 409 (M+Na)<sup>+</sup>. Anal. calc for C<sub>25</sub>H<sub>35</sub>O<sub>2</sub>F: C, 77.68; H, 9.13. Found: C, 77.74; H, 9.00. R<sub>f</sub> = 0.30 (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B = CH<sub>3</sub>CN; linear gradient: 70%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 12.8 min (94.9 area %); (BRB-9668, 99 % (1 % butanol in hexanes), 5 min, 285 nm, 2mL/min): R.T. 2.6 min (100 area %, 100 % e.e.). [α]<sub>D</sub> = -14.3° (c = 0.00200 g/mL, CH<sub>2</sub>Cl<sub>2</sub>). mp 105.0-106.5°C.

Enantiomer 2 was obtained as a white flaky solid (0.73 g). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 0.78 (t, J = 6.6 Hz, 3H), 0.96 - 1.23 (m, 19H), 1.41 (d, J = 7.0 Hz, 3H), 2.04 - 2.37 (m, 2H), 3.09 - 3.19 (m, 1H), 3.74 - 3.84 (m, 1H), 4.81 - 4.90 (m, 2H), 6.68 -

0 6.75 (m, 2H), 6.99 - 7.06 (m, 1H), 7.37 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.83, 21.94, 23.83, 24.27, 24.38, 24.50, 24.88, 28.70, 29.05, 29.80, 30.76, 32.20, 68.21, 102.98 (d,  $J = 24.4$  Hz, 1C), 107.33 (d,  $J = 20.8$  Hz, 1C), 123.58 (d,  $J = 2.4$  Hz, 1C), 125.45, 130.70 (d,  $J = 9.8$  Hz, 1C), 131.78, 137.45, 138.55, 146.48, 146.94, 154.29 (d,  $J = 6.1$  Hz, 1C), 163.04 (d,  $J = 244.2$  Hz, 1C). FAB-MS: calculated for  $\text{C}_{25}\text{H}_{35}\text{O}_2\text{F}$  386; found 409 (M+Na) $^+$ . Anal. calc for  $\text{C}_{25}\text{H}_{35}\text{O}_2\text{F}$ : C, 77.68; H, 9.13. Found: C, 77.64; H, 9.06.  $R_f = 0.30$  (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B =  $\text{CH}_3\text{CN}$ ; linear gradient: 70%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 12.8 min (94.7 area %); (BRB-9668, 99 % (1 % butanol in hexanes), 5 min, 285 nm, 2 mL/min): R.T. 1.7 min (0.51 area %), 2.9 min (0.97 area %), 4.0 min (98.5 area %, 98 % e.e.).  $[\alpha]_D = +16.0^\circ$  ( $c = 0.00200$  g/mL,  $\text{CH}_2\text{Cl}_2$ ). mp 103.5-105.5°C.

5 Diastereomer 2 was obtained as a white solid (0.16 g, 7 %).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  0.78 (t,  $J = 6.6$  Hz, 3H), 0.96 - 1.33 (m, 19H), 1.37 (d,  $J = 6.6$  Hz, 3H), 2.05 - 2.38 (m, 2H), 3.09 - 3.19 (m, 1H), 3.80 - 3.89 (m, 1H), 4.61 - 4.68 (m, 1H), 4.75 - 5.25 (br s, 1H), 6.66 - 6.74 (m, 2H), 6.90 - 6.96 (m, 1H), 7.37 (s, 1H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.83, 21.94, 23.43, 24.08, 24.48, 24.56, 24.98, 28.70, 29.04, 29.80, 30.76, 32.19, 68.89, 102.80 (d,  $J = 24.4$  Hz, 1C), 107.36 (d,  $J = 22.0$  Hz, 1C), 123.24 (d,  $J = 2.4$  Hz, 1C), 125.64, 131.25 (d,  $J = 9.8$  Hz, 1C), 131.56, 137.08, 138.44, 146.81, 146.84, 154.37 (d,  $J = 12.2$  Hz, 1C), 163.03 (d,  $J = 244.2$  Hz, 1C). FAB-MS: calculated for  $\text{C}_{25}\text{H}_{35}\text{O}_2\text{F}$  386; found 409 (M+Na) $^+$ . Anal. calc for  $\text{C}_{25}\text{H}_{35}\text{O}_2\text{F}$ : C, 77.68; H, 9.13. Found: C, 77.70; H, 9.12.  $R_f = 0.17$  (9:1 hexanes:ethyl acetate). HPLC: (C-18, A = 0.05 % aqueous trifluoroacetic acid, B =  $\text{CH}_3\text{CN}$ ; linear gradient: 70%-100% B over 30 min; 254 nm, 1 mL/min): R.T. 17.6 min (86.9 area %); (silica, A = hexanes, B = isopropanol, isocratic run: 3 % B over 15 min; 254 nm, 1 mL/min): R.T. 4.9 min (100 area %). mp 148.0-150.0°C.

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EXAMPLE 248

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(+)-3,5-Diisopropyl-2-[(p-methylbenzyloxy)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

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**Step A:** 3,5-Diisopropyl-2-[(*p*-methylbenzyloxy)methyl]-6-hydroxymethyl-4'-fluoro-1,1'-biphenyl

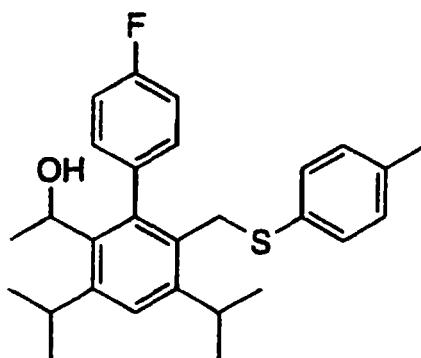
To a solution of 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D) (4.09 g, 11.9 mmol) in THF (70 mL) was added at room temperature sodium hydride (0.85 g, 35.4 mmol) in portions. The reaction mixture was stirred for 10 min. and then treated with  $\alpha$ -bromo-*p*-xylene (2.64 g, 14.3 mmol). The reaction mixture was heated at reflux for 24 hrs then cooled to room temperature and quenched with water (30 mL). The solvent was removed *in vacuo* and the residue partitioned between diethyl ether (300 mL) and water (200 mL). The ether layer was dried (MgSO<sub>4</sub>) and concentrated, the residue was purified through silica (70% CH<sub>2</sub>Cl<sub>2</sub>/hexane) which afforded a white solid (4.5 g, 10.3 mmol, 84%). The product was dissolved in THF (40 mL) was treated with lithium aluminum hydride (19.8 mL, 19.8 mmol, 1.0M in THF). The reaction mixture was heated at reflux for 2 hrs then allowed to cool to room temperature. The mixture was quenched with water (6 mL), and the solvent was removed *in vacuo*. The residue was partitioned between diethyl ether (200 mL) and water (300 mL). The organic layer was washed with water (3 X 300mL), brine (100 mL), dried (MgSO<sub>4</sub>), filtered and concentrated. The residue was filtered through a cake of silica (CH<sub>2</sub>Cl<sub>2</sub>, 1L) and evaporated to afford a white solid (3.26 g, 7.7 mmol, 78%). mp 99-101°C; R<sub>f</sub> = 0.07 (80% CH<sub>2</sub>Cl<sub>2</sub>/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.38 (s, 1 H), 7.24 (m, 2 H), 7.09 (m, 6 H), 4.36 (d, *J* = 5.5 Hz, 2 H), 4.27 (s, 2 H), 4.11 (s, 2 H), 3.42 (septet, *J* = 6.6 Hz, 1 H), 3.32 (septet, *J* = 6.6 Hz, 1 H), 2.35 (s, 3 H), 1.60 (s, 1 H), 1.22 (m, 12 H); FAB-MS calcd for (C<sub>28</sub>H<sub>33</sub>FO<sub>2</sub>) 420, found 403 (M-OH).

**Step B:** (+)-3,5-Diisopropyl-2-[(*p*-methylbenzyloxy)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

The title compound was prepared by subjecting the intermediate obtained in Step A to the procedures described in Example 244, Steps I-K. mp 84-86°C; R<sub>f</sub> = 0.1 (80% CH<sub>2</sub>Cl<sub>2</sub>/hexane); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.39 (s, 1 H), 7.27 (m, 2 H), 7.09 (m, 6 H), 4.76 (dq, *J* = 1.5, 7 Hz, 1 H), 4.22 (s, 2 H), 4.03 (s, 2 H), 3.89 (septet, *J* = 6.6 Hz, 1 H), 3.26 (septet, *J* = 6.6 Hz, 1 H), 2.35 (s, 3 H), 1.66 (s, 1 H), -1.40 (d, *J* = 6.6 Hz, 3 H), 1.26 (m, 12 H); FAB-MS calcd for (C<sub>29</sub>H<sub>35</sub>FO<sub>2</sub>) 434, found 417 (M-OH); Anal. Calcd for C<sub>29</sub>H<sub>35</sub>FO<sub>2</sub>: C, 80.15; H, 8.12; F, 4.37. Found: C, 80.10; H, 8.30; F, 4.24; [ $\alpha$ ]<sub>D</sub><sup>22</sup> = +30.7.

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EXAMPLE 249

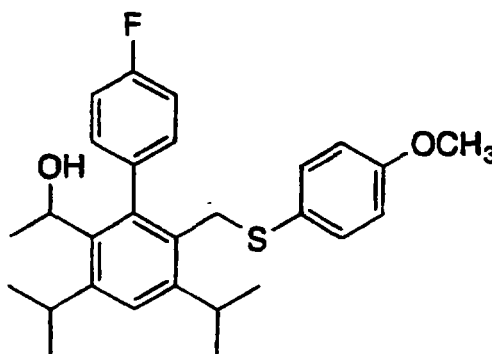
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(+)-3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

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The title compound was prepared from *p*-thiocresol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.36$  (70%  $\text{CH}_2\text{Cl}_2/\text{hexane}$ );  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.40 (s, 1 H), 7.28 (m, 2 H), 7.11 (m, 6 H), 4.76 (dq,  $J = 1.8, 7$  Hz, 1 H), 3.92 (septet,  $J = 6.6$  Hz, 1 H), 3.78 (s, 2 H), 3.26 (septet,  $J = 6.6$  Hz, 1 H), 2.36 (s, 3 H), 1.66 (s, 1 H), 1.40 (d,  $J = 6.6$  Hz, 3 H), 1.28 (m, 12 H); FAB-MS calcd for  $(\text{C}_{28}\text{H}_{33}\text{FOS})$  436, found 436 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{29}\text{H}_{35}\text{FOS}$ : C, 77.02; H, 7.62; S, 7.34; F, 4.35. Found: C, 76.90; H, 7.77; S, 7.30; F, 4.37;  $[\alpha]^{22} = +32.2$ .

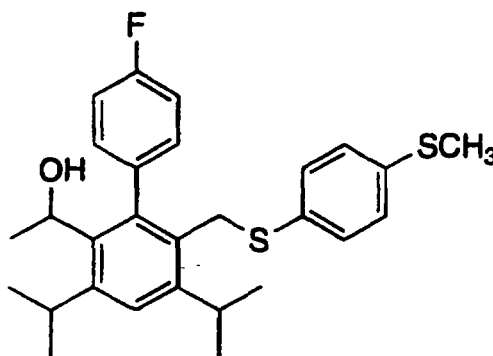
EXAMPLE 250

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(+)-3,5-Diisopropyl-2-[(4-methoxythiophenyl)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

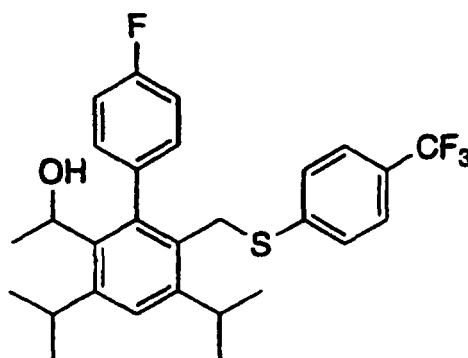
The title compound was prepared from 4-methoxy thiophenol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.23$  (70%  $\text{CH}_2\text{Cl}_2$ /hexane); mp  $140-2^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.36 (s, 1 H), 7.30 (m, 2 H), 7.08 (m, 4 H), 6.75 (m, 2 H), 4.72 (q,  $J = 7$  Hz, 1 H), 3.89 (septet,  $J = 7$  Hz, 1 H), 3.78 (s, 3 H), 3.68 (m, 2 H), 3.38 (septet,  $J = 7$  Hz, 1 H), 1.57 (m, 1 H), 1.40 (d,  $J = 6.6$  Hz, 3 H), 1.31 (m, 12 H); FAB-MS calcd for  $(\text{C}_{28}\text{H}_{33}\text{FO}_2\text{S})$  452, found 452 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{33}\text{FO}_2\text{S}$ : C, 74.30; H, 7.35; S, 7.08; F, 4.20. Found: C, 74.06; H, 7.46; S, 6.87; F, 4.09;  $[\alpha]^{22} = +24.5$ .

### EXAMPLE 251



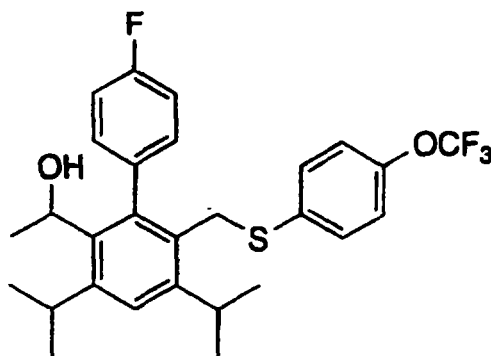
### 15 (+)-3,5-Diisopropyl-2-[(4-thiomethylthiophenyl)-methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

The title compound was prepared from 4-(methylthio)phenol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.52$  (90%  $\text{CH}_2\text{Cl}_2$ /hexane); mp  $157-9^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (s, 1 H), 7.30 (m, 2 H), 7.12 (m, 6 H), 4.71 (q,  $J = 7$  Hz, 1 H), 3.90 (septet,  $J = 7$  Hz, 1 H), 3.75 (d,  $J = 11$  Hz, 1 H), 3.70 (d,  $J = 11$  Hz, 1 H), 3.33 (septet,  $J = 7$  Hz, 1 H), 2.46 (s, 3 H), 1.58 (s, 1 H), 1.40 (d,  $J = 6.6$  Hz, 3 H), 1.29 (m, 12 H); EI-MS calcd for  $(\text{C}_{28}\text{H}_{33}\text{FOS}_2)$  468, found 468 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{33}\text{FOS}_2$ : C, 71.76; H, 7.10; S, 13.68; F, 4.05. Found: C, 71.54; H, 7.22; S, 13.26; F, 4.17;  $[\alpha]^{22} = +40.6$ .

EXAMPLE 252

(+)-3,5-Diisopropyl-2-[(4-trifluoromethylthiophenyl)-methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

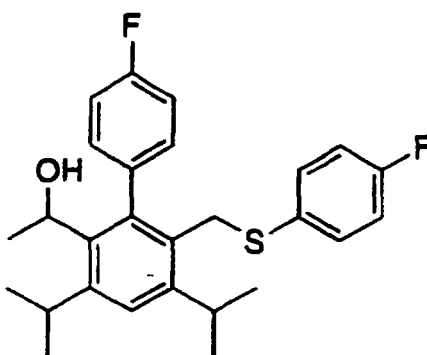
The title compound was prepared from 4-(trifluoromethyl)benzene thiol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.39$  (80%  $\text{CH}_2\text{Cl}_2$ /hexane); mp  $171-3^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.45 (s, 1 H), 7.42 (s, 1 H), 7.39 (s, 1 H), 7.30 (m, 1 H), 7.09 (m, 5 H), 4.72 (q,  $J = 7$  Hz, 1 H), 3.91 (septet,  $J = 7$  Hz, 1 H), 3.83 (d,  $J = 11$  Hz, 1 H), 3.78 (d,  $J = 11$  Hz, 1 H), 3.28 (septet,  $J = 7$  Hz, 1 H), 1.60 (s, 1 H), 1.41 (d,  $J = 6.6$  Hz, 3 H), 1.29 (m, 12 H); FAB-MS calcd for  $(\text{C}_{28}\text{H}_{30}\text{F}_4\text{OS})$  490, found 490 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{30}\text{F}_4\text{OS}$ : C, 68.55; H, 6.16; S, 6.53; F, 15.49. Found: C, 68.67; H, 6.15; S, 6.56; F, 15.33;  $[\alpha]^{22}_D = +25.6$ .

EXAMPLE 253

(+)-3,5-Diisopropyl-2-[(4-trifluoromethoxythiophenyl)-methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

The title compound was prepared from 4-(trifluoromethoxy)benzene thiol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.39$  (80%  $\text{CH}_2\text{Cl}_2$ /hexane); mp  $124-6^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.38 (s, 1 H), 7.30 (m, 2 H), 7.09 (m, 6 H), 4.73 (q,  $J = 7$  Hz, 1 H), 3.91 (septet,  $J = 7$  Hz, 1 H), 3.78 (d,  $J = 11$  Hz, 1 H), 3.73 (d,  $J = 11$  Hz, 1 H), 3.31 (septet,  $J = 7$  Hz, 1 H), 1.60 (s, 1 H), 1.41 (d,  $J = 7$  Hz, 3 H), 1.28 (m, 12 H); FAB-MS calcd for  $(\text{C}_{28}\text{H}_{30}\text{F}_4\text{O}_2\text{S})$  506, found 506 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{30}\text{F}_4\text{O}_2\text{S}$ : C, 66.39; H, 5.97; S, 6.33; F, 15.00. Found: C, 66.71; H, 6.06; S, 6.22; F, 15.24;  $[\alpha]^{22} = +25.8$ .

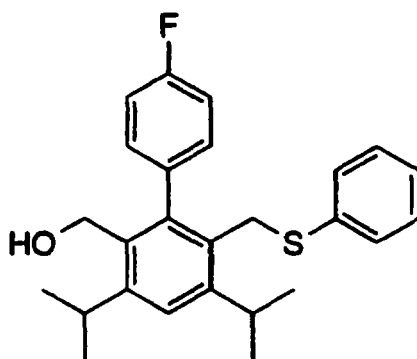
#### EXAMPLE 254



#### 15 (+)-3,5-Diisopropyl-2-[(4-fluorothiophenyl)-methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl

The title compound was prepared from 4-fluorothiophenol and 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D), according to the procedures described in Example 47, Steps B and C, followed by the procedures described in Example 244, Steps I-K.  $R_f = 0.35$  (70%  $\text{CH}_2\text{Cl}_2$ /hexane); mp  $138-140^\circ\text{C}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.37 (s, 1 H), 7.30 (m, 2 H), 7.05 (m, 4 H), 6.90 (m, 2 H), 4.71 (q,  $J = 7$  Hz, 1 H), 3.90 (septet,  $J = 6.6$  Hz, 1 H), 3.72 (m, 2 H), 3.33 (septet,  $J = 6.6$  Hz, 1 H), 1.52 (s, 1 H), 1.39 (d,  $J = 6.6$  Hz, 3 H), 1.27 (m, 12 H); FAB-MS calcd for  $(\text{C}_{28}\text{H}_{30}\text{FO}_2\text{S})$  506, found 506 ( $\text{M}^+$ ); Anal. Calcd for  $\text{C}_{28}\text{H}_{30}\text{FO}_2\text{S}$ : C, 74.30; H, 7.35; S, 7.08; F, 4.20. Found: C, 74.06; H, 7.46; S, 6.87; F, 4.09;  $[\alpha]^{22} = +17.6$ .

0

EXAMPLE 2553,5-Diisopropyl-2-(thiophenylmethyl)-6-(hydroxymethyl)-4'-fluoro-1,1'-biphenyl

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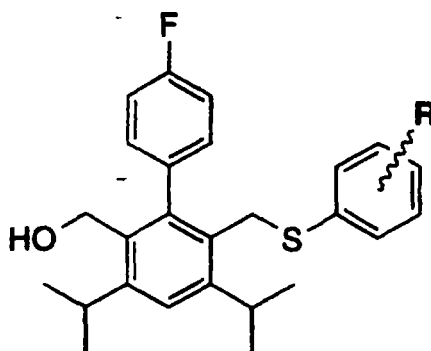
- A suspension of Wang-resin (100 g, 1.09 mmol/g hydroxylated) was suspended in 1 L of a solution of 4N HCl in dioxane and gently stirred at room temperature for two days. After filtration, the chlorinated resin was washed 6 times with each of the following solvents; dioxane, isopropanol and finally THF. The resin was then dried at 60°C overnight. From this resin, 2.5 g (2.2 mmol based on the chlorine content detected by elemental analysis) was suspended in DMF (25 mL) and stirred at room temperature for 5 minutes, then the DMF was decanted off for the addition of a solution of 3,5-diisopropyl-2-hydroxymethyl-6-carboxymethyl-4'-fluoro-1,1'-biphenyl (Example 244, Step D) (1.13 g, 3.3 mmol) in DMF (25 mL), followed by a solution of sodium hydride (60 % in mineral oil, 170 mg, 3.3 mmol) in DMF (12.5 mL). The suspension was stirred at room temperature for two days under an argon atmosphere. The suspension was then filtered and the resulting resin was successively washed 10 times with each of the following solvents; DMF, a mixture THF/water (1:1), THF and finally with CH<sub>2</sub>Cl<sub>2</sub>.
- The resin residue was then treated with a solution of lithium aluminum hydride (1 M in THF, 15 mL, 15 mmol) and heated at reflux for 2 days. The suspension was filtered and the resulting residue was washed successively 10 times with each of the following solvents; THF, a mixture of THF/water (1:1), a mixture of THF/water (2:1), THF and finally with CH<sub>2</sub>Cl<sub>2</sub>.
- The residue was suspended in THF (25 mL) and slowly treated with PBr<sub>3</sub> (835 µL, 8.7 mmol) at room temperature. The resin was filtered out and washed 10 times with each of the following solvents; THF, mixture of THF/1N sodium bicarbonate (1:1), THF/water (1:1), THF and finally CH<sub>2</sub>Cl<sub>2</sub>, then dried at 60°C overnight which afforded 2.25 g of resin (0.62 mmol/g based on the bromine content detected by elemental analysis).

30

- 0 To 25 mg of this intermediate coupled with a resin was added thiophenol (26.4 mg, 0.24 mmol) in dry THF (500  $\mu$ L) and N-methylmorpholine (26  $\mu$ L, 0.24 mmol), then the suspension was refluxed for 8 hours. After filtration, the resin was washed successively 10 times with each of the following solvents; THF, a mixture of THF/water (1:1) and THF. The resin was then suspended in a mixture of TFA and CH<sub>2</sub>Cl<sub>2</sub> (1:1) and stirred at room temperature for one hour. The resin was filtered off and the solvent recovered then evaporated. The residue was dissolved in a mixture of methanol and acetonitrile (1:1) and one drop of diisopropylethylamine, then stirred for one hour; HPLC: 12.5 min (Hypersil BDS-C18, 5 $\mu$ m, 125 x 2 mm/Hewlett Packard, Flow 0.5 mL, 0-13 min 30-90%C, 13-15 min 90%C, Solvent A: Water/0.1% TFA; Solvent B: Acetonitrile). After evaporation of the solvent, the remaining residue was transferred in a microtiterplate for testing.

The compounds identified in the following Table as Examples 256-288 were prepared analogously to the compound of Example 255.

Table of Exemplary Compounds 255-288



| Example | R                 | HPLC<br>R.T. (method) | Est.'d Purity<br>(%) |
|---------|-------------------|-----------------------|----------------------|
| 255     | H                 | 12.5 (I)              | 60-70                |
| 256     | 4-tBu             | 14.9 (I)              | 90                   |
| 257     | 4-OMe             | 12.2 (I)              | 60-70                |
| 258     | 4-Me              | 13.2 (I)              | 50-60                |
| 259     | 4-ipr             | 14.4 (I)              | 50-60                |
| 260     | 4-F               | 12.5 (I)              | 90                   |
| 261     | 4-Et              | 15.1 (I)              | 90                   |
| 262     | 4-CF <sub>3</sub> | 13.4 (I)              | 70-80                |

| Example | R                   | HPLC<br>R.T. (method) | Est.'d Purity<br>(%) |
|---------|---------------------|-----------------------|----------------------|
| 263     | 4-Br                | 13.9 (I)              | 90                   |
| 264     | 3-Me                | 13.2 (I)              | 90                   |
| 265     | 3-F                 | 13.0 (I)              | 70-80                |
| 266     | 3-Cl                | 13.5 (I)              | 90                   |
| 267     | 3-CF <sub>3</sub>   | 13.4 (I)              | 90                   |
| 268     | 2-Me                | 13.2 (I)              | 90                   |
| 269     | 2-F                 | 12.4 (I)              | 60-70                |
| 270     | 2-Cl                | 12.9 (I)              | 50-60                |
| 271     | 2,3-Me              | ND                    | ND                   |
| 272     | 2,3-Cl              | 6.8 (III)             | 50-60                |
| 273     | 2,4-Me              | 13.9 (I)              | 50-60                |
| 274     | 2,4-Cl              | 14.2 (I)              | 60-70                |
| 275     | 2,4-F               | 12.6 (I)              | 60-70                |
| 276     | 2-Me-4-Cl           | 14.2 (I)              | 90                   |
| 277     | 2-Cl-4-F            | 13.3 (I)              | 80-90                |
| 278     | 2,5-Cl              | 14.0 (I)              | 60-70                |
| 279     | 2,6-Cl              | 13.7 (II)             | 50                   |
| 280     | 3,4-Me              | 15.0 (I)              | 90                   |
| 281     | 3,4-Cl              | 14.3 (I)              | 90                   |
| 282     | 3-Cl-4-F            | 13.5 (I)              | 90                   |
| 283     | 3,5-Me              | 13.9 (I)              | 90                   |
| 284     | 3,5-CF <sub>3</sub> | 14.4 (I)              | 90                   |
| 285     | 3,5-Cl              | 14.8 (I)              | 90                   |
| 286     | 2,3,5,6-F-4-Me      | 14.0 (I)              | 80-90                |
| 287     | 2,3,5,6-F-4-Cl      | 14.0 (I)              | 60-70                |
| 288     | 2,3,5,6-F           | 12.9 (I)              | 60-70                |

HPLC: The Retention times (R.T.) for the compounds shown in the above table of exemplary compounds 255-290 were measured in minutes according to one of the three methods described below:

(I) Hypersil BDS-C18, 5 $\mu$ m, 125 x 2 mm/Hewlett Packard, Flow 0.5 mL, 0-13 min 30-90%C, 13-15 min 90% C, Solvent A: Water/0.1% TFA; Solvent B: Acetonitrile.

0 (II) Hypersil BDS-C18, 5 $\mu$ m, 125 x 2 mm/Hewlett Packard, Flow 0.5 mL, 0-13 min 30-90%C, 13-25 min 90% C, Solvent A: Water/0.1% TFA; Solvent B: Acetonitrile.

(III) NPS ODS-1, 1.5mm, 33 x 4.6 mm/Micra, Flow 1.0 mL, 0-8 min 15-70% C, Solvent A: Water/0.1% TFA; Solvent B: Acetonitrile.

5 The estimated purity numbers were determined by comparison of peak areas, not by reference to standards.

10 The pharmaceutical utility of compounds of this invention is indicated by the following assay for glucagon receptor activity.

The affinity for the glucagon receptor of compounds of the present invention is determined by the glucagon receptor binding assay. Membranes were prepared from Chinese Hamster Ovary cells expressing the glucagon receptor (CHO-HGR) by scraping the cells into hypotonic lysis buffer (10 mM Tris, pH 7.4, 2 mM EDTA, 5 mM MgCl<sub>2</sub> and 1 mM PMSF) and subjecting the material to Polytron homogenization. Nuclei were removed by a 15-min 800 x g centrifugation step conducted at 4°C. Membranes containing the receptor were collected by centrifugation at 15,000 x g for 15 min at 4°C. The membranes were washed once in lysis buffer and suspended in 0.25 M sucrose, 10 mM Tris, 5 mM EDTA, pH 7.4. The membranes were used in ligand binding studies as reported (Yoo-Warren, H., Willse, A.G., Hancock, N., Hull, J., McCaleb, M., and Livingston, J. Regulation of Rat Glucagon Receptor Expression. *Biochem. Biophysical Res. Commun.* 1994, 205, 347-353). In brief, 10 ug of membrane protein was incubated in 130  $\mu$ l of binding buffer that consisted of 20 mM Tris, pH 7.4, 1 mM EDTA, 1 mg/ml BSA, and 1 mg/ml bacitracin. The membrane suspension was placed in each well of a 96-well filtration plate (glass fiber type C, Millipore). Twenty  $\mu$ l of test compound was added to each well to give final concentrations ranging from 2 nM to 20  $\mu$ M. Following the addition of test compound, 50  $\mu$ l of <sup>125</sup>I-glucagon (9 fmol) (NEN) was added to each well. Control wells contained membranes, 0.5% DMSO (solvent for test compounds), radiolabeled glucagon without and with excess native glucagon (1  $\mu$ M) to establish nonspecific binding. The plates were incubated for 60 min at room temperature, and then filtered on a Millipore vacuum apparatus. Following a wash step with ice-cold PBS/0.1% BSA, the filters were punched into test tubes, and the membrane bound radioactivity was determined. An IC<sub>50</sub> value (the concentration of test compound needed to reduce membrane binding of radiolabelled glucagon by 50%) was calculated for each compound. If 20  $\mu$ M

- 0 compound did not reduce glucagon binding by 50%, the % reduction at 20  $\mu$ M was reported in place of an IC<sub>50</sub> value. The binding characteristics for compounds of this invention are shown in Table I(C).

Table I(C)

5

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 1       | 0.6                            |                              |
| 2       |                                | 2.73                         |
| 3       |                                | 1.52                         |
| 4       |                                | 1.98                         |
| 5       |                                | 12.42                        |
| 6       |                                | 34.23                        |
| 7       |                                | 42.14                        |
| 8       |                                | 17.02                        |
| 9       |                                | 16.56                        |
| 11      | 8                              |                              |
| 12      | 1.7                            |                              |
| 13      | 3                              |                              |
| 14      | 1.4                            |                              |
| 15      | 1.7                            |                              |
| 16      | 0.85                           |                              |
| 17      | 0.6                            |                              |
| 18      | 0.75                           |                              |
| 19      | 0.7                            |                              |
| 20      | 1.3                            |                              |
| 21      | 0.8                            |                              |
| 22      | 1.1                            |                              |
| 23      | 0.39                           |                              |
| 24      | 0.75                           |                              |
| 25      | 0.4                            |                              |
| 26      | 1                              |                              |
| 27      | 20                             |                              |
| 28      | 1                              |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 29      | 1                              |                              |
| 30      | 0.9                            |                              |
| 31      | 2.6                            |                              |
| 32      | 1.1                            |                              |
| 33      | 1.8                            |                              |
| 34      | 0.6                            |                              |
| 35      | 0.7                            |                              |
| 36      | 1.8                            |                              |
| 37      | 0.75                           |                              |
| 38      | 0.6                            |                              |
| 39      | 1.3                            |                              |
| 40      | 0.75                           |                              |
| 41      | 0.6                            |                              |
| 42      | 0.7                            |                              |
| 43      | 1.8                            |                              |
| 44      | 1.0                            |                              |
| 45      | 1.1                            |                              |
| 46      | 9                              |                              |
| 47      | 1.5                            |                              |
| 48      | 1.8                            |                              |
| 49      | 1.1                            |                              |
| 50      | 0.9                            |                              |
| 51      | 16                             |                              |
| 52      | 20                             |                              |
| 53      | 4.9                            |                              |
| 54      | 1.8                            |                              |
| 55      |                                | 15.66                        |
| 56      | 1.9                            |                              |
| 57      | 1.1                            |                              |
| 58      | 1.5                            |                              |
| 59      | 1                              |                              |
| 60      | 1.6                            |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 61      | 3.4                            |                              |
| 62      | 1.1                            |                              |
| 63      | 1.7                            |                              |
| 64      | 1.1                            |                              |
| 65      | 0.75                           |                              |
| 66      | 1                              |                              |
| 67      | 1.1                            |                              |
| 68      | 13                             |                              |
| 69      |                                | 40.21                        |
| 70      | 12                             |                              |
| 71      |                                | 46.33                        |
| 72      |                                | 42.15                        |
| 73      |                                | 17.46                        |
| 74      |                                | 27.08                        |
| 75      |                                | 34.16                        |
| 76      |                                | 5.18                         |
| 77      | 6                              |                              |
| 78      | 7.5                            |                              |
| 79      | 10                             |                              |
| 80      |                                | 38.76                        |
| 81      | 7.5                            |                              |
| 82      | 1.9                            |                              |
| 83      | 0.65                           |                              |
| 84      | 1.9                            |                              |
| 85      | 1.5                            |                              |
| 86      | 1.1                            |                              |
| 87      | 1.9                            |                              |
| 88      |                                | 24.75                        |
| 89      |                                | 36.03                        |
| 90      |                                | 29.14                        |
| 91      |                                | 14.15                        |
| 92      |                                | 11.59                        |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 93      |                                | 28.33                        |
| 94      |                                | 38.54                        |
| 95      |                                | 26.53                        |
| 96      |                                | 27.84                        |
| 97      |                                | 29.25                        |
| 98      | 14                             |                              |
| 99      |                                | 43.18                        |
| 100     |                                | 39.61                        |
| 101     | 0.22                           |                              |
| 102     | 0.11                           |                              |
| 103     | 1.9                            |                              |
| 104     | 0.25                           |                              |
| 105     | 0.3                            |                              |
| 106     | 0.15                           |                              |
| 107     | 3                              |                              |
| 108     | 0.24                           |                              |
| 109     | 0.12                           |                              |
| 110     | 2                              |                              |
| 112     |                                | 4.17                         |
| 113     | 0.6                            |                              |
| 114     |                                | 38.49                        |
| 115     |                                | 21.12                        |
| 116     |                                | 17.03                        |
| 117     |                                | 45.14                        |
| 118     | 13                             |                              |
| 119     |                                | 30.2                         |
| 120     |                                | 37.01                        |
| 121     |                                | 26.19                        |
| 122     |                                | 7.54                         |
| 123     |                                | 49.22                        |
| 124     | 12                             |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 125     |                                | 31.62                        |
| 126     |                                | 35.29                        |
| 127     |                                | 45.53                        |
| 128     | 3                              |                              |
| 129     | 1.5                            |                              |
| 130     | 1                              |                              |
| 131     |                                | 37.27                        |
| 132     |                                | 42.48                        |
| 133     |                                | 35.46                        |
| 134     |                                | 34.41                        |
| 135     |                                | 4.64                         |
| 136     |                                | 2.37                         |
| 137     | 11                             |                              |
| 138     | 9                              |                              |
| 139     | 17                             |                              |
| 140     |                                | 46.28                        |
| 141     |                                | 34.05                        |
| 142     |                                | 33.11                        |
| 143     | 0.9                            |                              |
| 144     | 0.8                            |                              |
| 145     |                                | 41.44                        |
| 146     |                                | 48.78                        |
| 148     |                                | 7.78                         |
| 149     |                                | 39.03                        |
| 150     | 4.5                            |                              |
| 151     | 10.5                           |                              |
| 152     |                                | 25.35                        |
| 153     | 6                              |                              |
| 154     |                                | 20.71                        |
| 155     |                                | 25.25                        |
| 156     |                                | 26.05                        |
| 157     |                                | 32.6                         |

| Example  | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|----------|--------------------------------|------------------------------|
| 158      | 1.8                            |                              |
| 159      | 1.1                            |                              |
| 160      |                                | 21.03                        |
| 161      |                                | 23.99                        |
| 162      |                                | 13.88                        |
| 163      | 0.5                            |                              |
| 164 - D1 | 0.045                          |                              |
| 164 - D2 | 0.1                            |                              |
| 165 - D1 | 0.04                           |                              |
| 165 - D2 | 1.1                            |                              |
| 166      | 0.19                           |                              |
| 167 - D1 | 0.03                           |                              |
| 167 - D2 | 2.2                            |                              |
| 169      |                                | 37.06                        |
| 170      |                                | 45.45                        |
| 171      |                                | 48.37                        |
| 173      |                                | 27.4                         |
| 174      |                                | 33.38                        |
| 175      |                                | 40.88                        |
| 176      |                                | 13.83                        |
| 177      | 19                             |                              |
| 178      |                                | 25.98                        |
| 179      |                                | 26.79                        |
| 180      |                                | 38.21                        |
| 181      |                                | 45.96                        |
| 182      |                                | 49.07                        |
| 183      |                                | 13.23                        |
| 184      |                                | 28.93                        |
| 185      |                                | 41.22                        |
| 186      | 20                             |                              |
| 187      | 12                             |                              |
| 188      | 10.5                           |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 189     | 12                             |                              |
| 190     | 0.3                            |                              |
| 191     | 0.13                           |                              |
| 192     | 0.13                           |                              |
| 193     | 0.086                          |                              |
| 194     | 1                              |                              |
| 195     | 12                             |                              |
| 196     |                                | 40.32                        |
| 197     | 7                              |                              |
| 198     | 17                             |                              |
| 199     |                                | 8.67                         |
| 200     |                                | 32.77                        |
| 201     |                                | 46.67                        |
| 202     | 9                              |                              |
| 203     | 6.3                            |                              |
| 204     | 1.8                            |                              |
| 205     | 18                             |                              |
| 206     |                                | 44.57                        |
| 207     |                                | 43.97                        |
| 208     | 19                             |                              |
| 210     | 18                             |                              |
| 211     | 19                             |                              |
| 212     | 14                             |                              |
| 213     | 7                              |                              |
| 214     | 5                              |                              |
| 215     | 19                             |                              |
| 217     | 8                              |                              |
| 218     | 6.5                            |                              |
| 219     |                                | 5.11                         |
| 220     | 1.3                            |                              |
| 221     | 1.3                            |                              |
| 222     | 0.11                           |                              |

| Example   | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|-----------|--------------------------------|------------------------------|
| 223       | 0.11                           |                              |
| 224       | 0.11                           |                              |
| 225       | 7                              |                              |
| 226       | 3                              |                              |
| 227       | 1.3                            |                              |
| 228       | 2                              |                              |
| 229       | 0.8                            |                              |
| 230       | 0.9                            |                              |
| 231       | 0.5                            |                              |
| 232       | 1.2                            |                              |
| 233       | 0.6                            |                              |
| 234       | 8                              |                              |
| 235       | 3.1                            |                              |
| 236       | 4                              |                              |
| 237       | 1.2                            |                              |
| 238       | 0.01                           |                              |
| 239 - rac | 0.08                           |                              |
| 239 - E1  | 2.5                            |                              |
| 239 - E2  | 0.05                           |                              |
| 240       | 0.016                          |                              |
| 241       | 0.11                           |                              |
| 242       | 0.005                          |                              |
| 243       | 0.086                          |                              |
| 244       | 0.18                           |                              |
| 245       | 0.3                            |                              |
| 246       | 0.011                          |                              |
| 247       | 0.006                          |                              |
| 248       | 0.31                           |                              |
| 249       | 0.13                           |                              |
| 250       | 0.2                            |                              |
| 251       | 0.4                            |                              |
| 252       | 0.18                           |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 253     | 0.18                           |                              |
| 254     | 0.11                           |                              |
| 255     | 3                              |                              |
| 256     | 7                              |                              |
| 257     | 7.3                            |                              |
| 258     | 7                              |                              |
| 259     | 6                              |                              |
| 260     | 2.5                            |                              |
| 261     | 5.4                            |                              |
| 262     | 1.7                            |                              |
| 263     | 4.4                            |                              |
| 264     | 3.4                            |                              |
| 265     | 3                              |                              |
| 266     | 2                              |                              |
| 267     | 1.7                            |                              |
| 268     | 4.1                            |                              |
| 269     | 3.4                            |                              |
| 270     | 5                              |                              |
| 271     | 12                             |                              |
| 272     | 2.6                            |                              |
| 273     | 5                              |                              |
| 274     | 12                             |                              |
| 275     | 3                              |                              |
| 276     | 20                             |                              |
| 277     | 2                              |                              |
| 278     | 10                             |                              |
| 279     | 20                             |                              |
| 280     | 10                             |                              |
| 281     | 5.4                            |                              |
| 282     | 1.7                            |                              |
| 283     | 12                             |                              |
| 284     | 7                              |                              |

| Example | IC <sub>50</sub><br>( $\mu$ M) | % Inhibition<br>(20 $\mu$ M) |
|---------|--------------------------------|------------------------------|
| 285     | 9                              |                              |
| 286     | 18                             |                              |
| 287     | 20                             |                              |
| 288     | 2                              |                              |

0

Preferred phenyl pyridine compounds of general formula (IC) and more particularly of general formula 1B are shown in the following list:

- 5 2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-ethylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-ethylpyridine;
- 10 2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-propylpyridine;
- 15 2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-butylpyridine;
- 20 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine;
- 25 2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-pentylpyridine;

- 0 2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-hexylpyridine;
- 5 2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-phenyl-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-fluorophenyl)-5-hydroxymethyl-  
pyridine;
- 10 2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-chlorophenyl)-5-hydroxymethyl-  
pyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-methylphenyl)-5-hydroxymethyl-  
pyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxyphenyl)-5-hydroxymethyl-  
pyridine;
- 15 2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-  
hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-phenyl-5-hydroxymethyl-  
pyridine;
- 20 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-fluorophenyl)-5-  
hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-chlorophenyl)-5-  
hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-methylphenyl)-5-  
hydroxymethyl-pyridine;
- 25 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxyphenyl)-5-  
hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-  
hydroxymethyl-pyridine;
- 30 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-ethylpyridine;

- 0 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-propylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-propylpyridine;
- 5 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-propylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-propylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-propylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-butylpyridine;
- 10 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-butylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-butylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-butylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-butylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-butylpyridine;
- 15 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-pentylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-pentylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-pentylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-pentylpyridine;
- 20 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-pentylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-hexylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-hexylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-hexylpyridine;
- 25 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-hexylpyridine;  
 2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-hexylpyridine;  
 2,6-Diisopropyl-3-[(p-tolylthio)methyl]-4-phenyl-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(p-tolylthio)methyl]-4-(4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;
- 30 2,6-Diisopropyl-3-[(p-tolylthio)methyl]-4-(4-chlorophenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(p-tolylthio)methyl]-4-(4-methylphenyl)-5-(1-hydroxyethyl)-pyridine;

- 0 2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxyphenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-phenyl-5-(1-hydroxyethyl)-  
 5 pyridine;  
 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-chlorophenyl)-5-(1-hydroxyethyl)-pyridine;  
 10 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-methylphenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxyphenyl)-5-(1-hydroxyethyl)-pyridine;  
 2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-  
 15 (1-hydroxyethyl)-pyridine.

Preferred biphenyl compounds of general formula (IC) and more particularly of general formula 1D are shown in the following list:

- 20 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-2'-hydroxy-1,1'-biphenyl;  
 25 3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-methyl-1,1'-biphenyl;  
 30 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-propyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-butyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-fluoro-1,1'-biphenyl;

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- 0 3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-chloro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-methyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-butyl-2'-hydroxy-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-butyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-1,1'-biphenyl;  
5 3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-chloro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-methyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-2'-hydroxy-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
10 3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-fluoro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-chloro-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-methyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-2'-hydroxy-1,1'-biphenyl;  
15 3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-4'-fluoro-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-4'-chloro-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-4'-methyl-1,1'-biphenyl;  
20 3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-2'-hydroxy-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(p-tolylthio)methyl]-6-hydroxymethyl-2'-hydroxy-4'-fluoro-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-1,1'-biphenyl;  
3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-4'-fluoro-1,1'-  
25 biphenyl;  
3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-4'-chloro-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-4'-methyl-1,1'-  
biphenyl;  
30 3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-2'-hydroxy-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[(4-fluorophenyl)thio)methyl]-6-hydroxymethyl-2'-hydroxy-4'-  
fluoro-1,1'-biphenyl;

- 0 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-2'-hydroxy-1,1'-biphenyl;  
 5 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-methyl-1,1'-biphenyl;  
 10 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-chloro-1,1'-biphenyl;  
 15 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl;  
 20 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-1,1'-biphenyl;  
 25 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 30 3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-1,1'-biphenyl;  
 3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-methyl-1,1'-biphenyl;

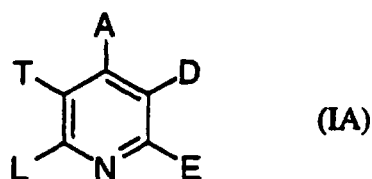
- 0 3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-4'-fluoro-  
1,1'-biphenyl;  
3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-1,1'-biphenyl];  
5 3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-4'-chloro-1,1'-  
biphenyl;  
3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-4'-methyl-1,1'-  
10 biphenyl;  
3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-  
1,1'-biphenyl;  
3,5-Diisopropyl-2-[[[(4-fluorophenyl)thio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-4'-  
fluoro-1,1'-biphenyl.

15

Other embodiments of the invention will be apparent to the skilled in the art  
from a consideration of this specification or practice of the invention disclosed  
herein. It is intended that the specification and examples be considered as  
20 exemplary only, with the true scope and spirit of the invention being indicated by  
the following claims.

0 We claim:

1. Substituted pyridines of the general formula (IA),



5

in which

10 A stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula  $-NR^1R^2$ ,

wherein

15

$R^1$  and  $R^2$  are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 6 carbon atoms,

20

D stands for straight-chain or branched alkyl with up to 8 carbon atoms, which is substituted by hydroxy,

25

E and L are either identical or different and stand for straight-chain or branched alkyl with up to 8 carbon atoms, which is optionally substituted by cycloalkyl with 3 to 8 carbon atoms, or stands for cycloalkyl with 3 to 8 carbon atoms,

or

30

E has the above-mentioned meaning

and

L in this case stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or

0 differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy,  
or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7  
carbon atoms each, or by a group of the formula  $-NR^3R^4$ ,

wherein

5

$R^3$  and  $R^4$  are identical or different and have the meaning given  
above for  $R^1$  and  $R^2$ ,

or

10

E stands for straight-chain or branched alkyl with up to 8 carbon atoms,  
or

15

stands for aryl with 6 to 10 carbon atoms, which is optionally  
substituted up to 3 times in an identical manner or differently by  
halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-  
chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms  
each, or by a group of the formula  $-NR^5R^6$ ,

wherein

20

$R^5$  and  $R^6$  are identical or different and have the meaning given  
above for  $R^1$  and  $R^2$ ,

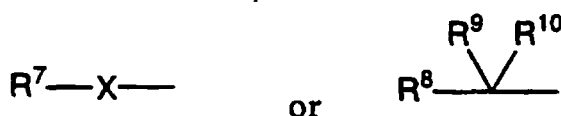
and

25

L in this case stands for straight-chain or branched alkoxy with up to 8  
carbon atoms or for cycloalkyloxy with 3 to 8 carbon atoms,

T stands for a radical of the formula

30



wherein

0             $R^7$  and  $R^8$  are identical or different and denote cycloalkyl with 3 to 8  
              carbon atoms, or aryl with 6 to 10 carbon atoms,  
              or denote a 5- to 7-member aromatic, optionally benzo-  
              condensed, heterocyclic compound with up to 3 heteroatoms  
 5            from the series S, N and/or O, which are optionally substituted  
              up to 3 times in an identical manner or differently by  
              trifluoromethyl, trifluoromethoxy, halogen, hydroxy, carboxyl,  
              by straight-chain or branched alkyl, acyl, alkoxy, or  
              alkoxycarbonyl with up to 6 carbon atoms each, or by phenyl,  
              phenoxy, or thiophenyl, which can in turn be substituted by  
 10            halogen, trifluoromethyl, or trifluoromethoxy,

             and/or the rings are substituted by a group of the formula -  
               $NR^{11}R^{12}$ ,

15            wherein

$R^{11}$  and  $R^{12}$  are identical or different and have the meaning  
              given above for  $R^1$  and  $R^2$ ,

20            X        denotes a straight or branched alkyl chain or alkenyl chain with  
              2 to 10 carbon atoms each, which are optionally substituted up  
              to 2 times by hydroxy,

$R^9$         denotes hydrogen,

25            and

$R^{10}$         denotes hydrogen, halogen, azido, trifluoromethyl, hydroxy,  
              mercapto, trifluoromethoxy, straight-chain or branched alkoxy  
 30            -        with up to 5 carbon atoms, or a radical of the formula -  
               $NR^{13}R^{14}$ ,

             wherein

35             $R^{13}$  and  $R^{14}$  are identical or different and have the meaning  
              given above for  $R^1$  and  $R^2$ ,

0 or

R<sup>9</sup> and R<sup>10</sup> form a carbonyl group together with the carbon atom,  
and the salts thereof.

5

2. Substituted pyridines of the formula according to claim 1, in which

10 A stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each, or by a group of the formula -NR<sup>1</sup>R<sup>2</sup>,

wherein

15

R<sup>1</sup> and R<sup>2</sup> are identical or different and denote hydrogen, phenyl, or straight-chain or branched alkyl with up to 4 carbon atoms,

20

D stands for straight-chain or branched alkyl with up to 6 carbon atoms, which is substituted by hydroxy,

25

E and L are either identical or different and stand for straight-chain or branched alkyl with up to 6 carbon atoms, which is optionally substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl,

or

30

E has the above-mentioned meaning

and

35

L in this case stands for naphthyl or phenyl, which are optionally substituted up to 3 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy

0 with up to 6 carbon atoms each, or by a group of the formula  
-NR<sup>3</sup>R<sup>4</sup>,

wherein

5 R<sup>3</sup> and R<sup>4</sup> are identical or different and have the meaning given  
above for R<sup>1</sup> and R<sup>2</sup>,

or

10 E stands for straight-chain or branched alkyl with up to 5 carbon atoms,  
or  
stands for naphthyl or phenyl, which are optionally substituted up to  
3 times in an identical manner or differently by fluorine, chlorine  
bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-  
15 chain or branched alkyl, acyl, or alkoxy with up to 6 carbon atoms  
each, or by a group of the formula -NR<sup>5</sup>R<sup>6</sup>,

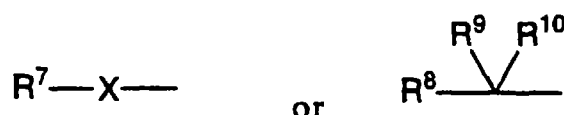
wherein

20 R<sup>5</sup> and R<sup>6</sup> are identical or different and have the meaning given  
above for R<sup>1</sup> and R<sup>2</sup>,

and

25 L in this case stands for straight-chain or branched alkoxy with up to 6  
carbon atoms, or for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy,  
cyclohexyloxy, or cycloheptyloxy,

30 T stands for a radical of the formula



wherein

0           R<sup>7</sup> and R<sup>8</sup> are identical or different and denote cyclopropyl,  
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl,  
or  
denote naphthyl, phenyl, pyridyl, quinolyl, indolyl,  
benzothiazolyl, or benzoxazolyl, which are optionally  
5           substituted up to 3 times in an identical manner or differently  
by trifluoromethyl, trifluoromethoxy, fluorine, chlorine,  
bromine, hydroxy, carboxyl, by straight-chain or branched  
alkyl, alkoxy, or alkoxycarbonyl with up to 5 carbon atoms  
each, or by phenyl, phenoxy, or thiophenyl, which can in turn  
10          by substituted by fluorine, chlorine, bromine, trifluoromethyl,  
or trifluoromethoxy,

and/or the rings are optionally substituted by a group of the  
formula -NR<sup>11</sup>R<sup>12</sup>,

15           wherein

—           R<sup>11</sup> and R<sup>12</sup> are identical or different and have the meaning  
given above for R<sup>1</sup> and R<sup>2</sup>,

20           X       denotes a straight or branched alkyl chain or alkenyl chain with  
2 to 8 carbon atoms each, which are optionally substituted up  
to 2 times by hydroxy,

25           R<sup>9</sup>       denotes hydrogen,

and

30           R<sup>10</sup>       denotes hydrogen, fluorine, chlorine, bromine, azido,  
trifluoromethyl, hydroxy, mercapto, trifluoromethoxy,  
straight-chain or branched alkoxy with up to 4 carbon atoms,  
or a radical of the formula -NR<sup>13</sup>R<sup>14</sup>,

wherein

35           R<sup>13</sup> and R<sup>14</sup> are identical or different and have the meaning  
given above for R<sup>1</sup> and R<sup>2</sup>,

0

or

R<sup>9</sup> and R<sup>10</sup> form a carbonyl group together with the carbon atom,

5

and the salts thereof.

3. Substituted pyridines of the formula according to claim 1, in which

10

A stands for phenyl, which is optionally substituted up to 2 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 5 carbon atoms each,

15

D stands for straight-chain or branched alkyl with up to 5 carbon atoms, which is substituted by hydroxy,

20

E and L are either identical or different and stand for straight-chain or branched alkyl with up to 5 carbon atoms, which is optionally substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl,

or

25

E has the above-mentioned meaning

and

30

L in this case stands for phenyl, which is optionally substituted up to 2 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 5 carbon atoms each,

or

35

E stands for straight-chain or branched alkyl with up to 4 carbon atoms, or

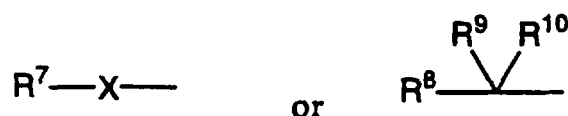
stands for phenyl, which is optionally substituted up to 2 times in an identical manner or differently by fluorine, chlorine, bromine, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 5 carbon atoms each,

and

L in this case stands for straight-chain or branched alkoxy with up to 5 carbon atoms, or for cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, or cycloheptyloxy,

10

T stands for a radical of the formula



15

wherein

R<sup>7</sup> and R<sup>8</sup> are identical or different and denote cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or adamantyl, or

20

denote phenyl, pyridyl, quinolyl, indolyl, naphthyl, benzothiazolyl, or benzoxazolyl, which are optionally substituted up to 2 times in an identical manner or differently by trifluoromethyl, trifluoromethoxy, fluorine, chlorine, bromine, hydroxy, carboxyl, by straight-chain or branched alkyl, alkoxy, or alkoxycarbonyl with up to 4 carbon atoms each, or by phenyl, phenoxy, or thiophenyl, which can in turn be substituted by fluorine, chlorine, bromine, trifluoromethyl, or trifluoromethoxy,

25

30

X denotes a straight or branched alkyl chain with 2 to 6 carbon atoms each, which are optionally substituted up to 2 times by hydroxy,

35

R<sup>9</sup> denotes hydrogen,

0 and

R<sup>10</sup> denotes hydrogen, fluorine, chlorine, bromine, azido, amino, trifluoromethyl, hydroxy, mercapto, trifluoromethoxy, straight-chain or branched alkoxy with up to 3 carbon atoms,

5 or

R<sup>9</sup> and R<sup>10</sup> form a carbonyl group together with the carbon atom,

10 and the salts thereof.

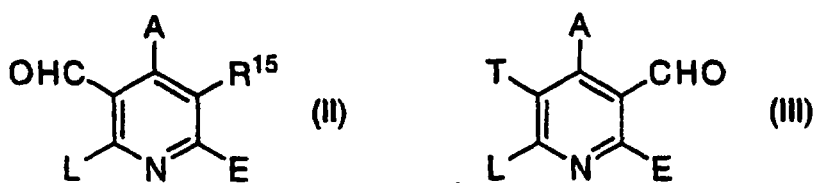
15 4. Substituted pyridines of the formula according to claim 1, in which

A stands for phenyl, which is optionally substituted by fluorine, chlorine, or methyl.

20 5. Substituted pyridines according to claims 1 through 4 for therapeutic use.

6. Process for the production of substituted pyridines according to claims 1 through 4, characterized by the fact that

25 compounds of the general formula (II) or (III)



in which

30

A, E, L, and T have the above-mentioned meanings,

and

0 R15 stands for straight-chain or branched alkoxy carbonyl with up to 4 carbon atoms,

are either first reacted, using the Grignard or Wittig reaction, in an inert solvent, with further derivatization optionally being carried out according to the customary methods, and then are reduced in inert solvents,

or, in the case of compounds with the general formula (III), direct reductions are carried out, optionally via several steps.

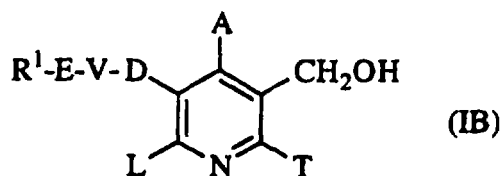
10 7. Pharmaceutical product containing the substituted pyridines according to claims 1 through 4 and, if appropriate, a pharmacologically tolerable formulation adjuvant.

15 8. Pharmaceutical product according to claim 7 for the inhibition of cholesterol ester transfer proteins.

9. Use of the substituted pyridines according to claims 1 through 4 for the production of pharmaceutical products.

20 10. Use of substituted pyridines according to claims 1 through 4 for the production of cholesterol ester transfer protein inhibitors.

11. 3-heteroalkyl-aryl-substituted pyridines of general formula (IB)



25

in which

30 A stands for aryl with 6 to 10 carbon atoms, which is optionally substituted up to 3 times in an identical manner or differently by halogen, hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon atoms each, or by a group of the formula -NR²R³ and/or -WR⁴,

wherein

35

- 0             $R^2$  and  $R^3$  are the same or different and  
             denote hydrogen, phenyl, or straight-chain or branched alkyl  
             with up to 6 carbon atoms,
- 5             $W$        denotes an oxygen or sulfur atom,
- $R^4$        denotes aryl with 6 to 10 carbon atoms, which is optionally  
             substituted up to 3 times in an identical manner or differently  
             by halogen, trifluoromethyl, trifluoromethoxy, hydroxy, or by  
10           straight-chain or branched alkyl or alkoxy with up to 6 carbon  
             atoms each,
- $D$  and  $E$  are identical or different and  
             stand for a straight-chain or branched alkyl chain with up to 8 carbon  
             atoms,
- 15           or
- $E$        stands for a bond,
- 20            $V$        stands for an oxygen or sulfur atom or for a group of the formula  
              $-NR^5-$ ,
- wherein
- 25            $R^5$        denotes hydrogen or straight-chain or branched alkyl with up  
             to 6 carbon atoms or phenyl,
- $R^1$        stands for cycloalkyl with 3 to 6 carbon atoms, or  
             stands for aryl with 6 to 10 carbon atoms or for a 5- to 7-member,  
30           optionally benzo-condensed, saturated or unsaturated, mono-, bi-, or  
             tricyclic heterocyclic compound with up to 4 heteroatoms from the  
             series S, N, and/or O,  
             in which the rings, also via the N function in the case of  
             nitrogen-containing rings, are optionally substituted up to 3 times in  
35           an identical manner or differently by halogen, trifluoromethyl,  
             hydroxy, cyano, carboxyl, trifluoromethoxy, straight-chain or  
             branched acyl, alkyl, alkylthio, alkylalkoxy, alkoxy, or alkoxycarbonyl  
             with up to 6 carbon atoms each, by aryl with 6 to 10 carbon atoms, or  
             by an optionally benzo-condensed, aromatic 5- to 7-member

heterocyclic compound with up to 3 heteroatoms from the series S, N, and/or O,  
and/or are substituted by a group of the formula  $-OR^6$ ,  $-SR^7$ ,  $-SO_2R^8$ ,  
or  $-NR^9R^{10}$ ,

wherein

$R^6$ ,  $R^7$ , and  $R^8$  are identical or different and  
denote aryl with 6 to 10 carbon atoms, which in turn is substituted up  
to 2 times in an identical manner or differently by phenyl or halogen  
or by straight-chain or branched alkyl with up to 4 carbon atoms,

$R^9$  and  $R^{10}$  are identical or different and have the above-indicated  
meaning of  $R^2$  and  $R^3$ ,

L and T are identical or different and

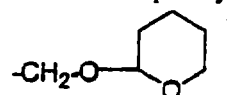
stand for trifluoromethyl or straight-chain or branched alkyl with up  
to 8 carbon atoms, which are optionally substituted by cycloalkyl with  
3 to 7 carbon atoms, or by aryl with 6 to 10 carbon atoms, which in  
turn can be substituted up to 2 times in an identical manner or  
differently by halogen, trifluoromethyl, trifluoromethoxy, or by  
straight-chain or branched alkyl, acyl, or alkoxy with up to 7 carbon  
atoms each,

or

L and/or T stand for cycloalkyl with 3 to 7 carbon atoms or

stand for aryl with 6 to 10 carbon atoms or for a 5- to 7-member,  
saturated, partially unsaturated, or unsaturated heterocyclic  
compound with up to 3 heteroatoms from the series S, N and/or O,  
with binding in the case of a nitrogen atom also being possible via this  
atom, with the rings optionally being substituted up to 3 times in an  
identical manner or differently by halogen, nitro, trifluoromethyl,  
trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or  
alkoxy with up to 7 carbon atoms each,

with the proviso that when L and T are isopropyl and A is 4-fluorophenyl, then  $-D-V-E-R^1$   
is other than  $-CH_2-O-Phenyl$ ,  $-CH_2-O-CH_2-Phenyl$ , or



and the salts thereof.

12. 3-heteroalkyl-aryl-substituted pyridines of the formula according to Claim 11, in which

0           A       stands for naphthyl or phenyl, which are optionally substituted up to  
3 times in an identical manner or differently by fluorine, chlorine,  
hydroxy, trifluoromethyl, trifluoromethoxy, or by straight-chain or  
5           branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each, or by  
a group of the formula  $-NR^2R^3$  and/or by a group of the formula  
 $-W-R^4$ ,

wherein

10            $R^2$  and  $R^3$  are identical or different and  
denote hydrogen, phenyl, or straight-chain or branched alkyl  
with up to 4 carbon atoms,

W       denotes an oxygen or sulfur atom,

15            $R^4$        denotes phenyl or benzyl, which are optionally substituted 1  
to 3 times in an identical manner or differently by fluorine,  
chlorine, trifluoromethyl, trifluoromethoxy, hydroxy, or by  
straight-chain or branched alkyl or alkoxy with up to 5 carbon  
atoms each,

20           D and E are identical or different and  
stand for a straight-chain or branched alkyl chain with up to 6 carbon  
atoms,

25           or

E       stands for a bond,

30           V       stands for an oxygen or sulfur atom or for a group of the formula  
 $-NR^5$ ,

wherein

35            $R^5$        denotes hydrogen or straight-chain or branched alkyl with up  
to 4 carbon atoms or phenyl,

40            $R^1$        stands for cyclopropyl, cyclopentyl, or cyclohexyl, or  
tetrahydropyrimidyl or stands for phenyl, naphthyl, pyridyl,  
tetrazolyl, pyrimidyl, pyrizinyl, pyrrolidinyl, tetrahydropyrimidyl,  
indolyl, morpholinyl, imidazolyl, benzothiazolyl, phenoxathiin-2-yl,  
benzoxazolyl, furyl, quinolyl, pyrazolopyrimidyl, or pyrine-yl,

0 with the rings, also via the N function in the case of  
 nitrogen-containing rings, being optionally substituted up to 3 times  
 in an identical manner or differently by fluorine, chlorine,  
 bromine, trifluoromethyl, hydroxy, cyano, carboxyl,  
 5 trifluoromethoxy, straight-chain or branched acyl, alkyl, alkylthio,  
 alkylalkoxy, alkoxy, or alkoxycarbonyl with up to 4 carbon atoms  
 each, triazolyl, tetrazolyl, benzoxathiazolyl, or phenyl,  
 and/or by a group of the formula  $-OR^6$ ,  $-SR^7$ , or  $-SO_2R^8$ ,

wherein

10  $R^6$ ,  $R^7$ , and  $R^8$  are identical or different and  
 denote phenyl, which in turn is substituted up to 2 times in an  
 identical manner or differently by phenyl, fluorine, chlorine, or  
 by straight-chain or branched alkyl with up to 4 carbon atoms,

15 L and T are identical or different and  
 stand for trifluoromethyl, pyrrolidinyl, or for straight-chain or  
 branched alkyl with up to 7 carbon atoms, which is optionally  
 20 substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,  
 cycloheptyl, naphthyl, or phenyl, which in turn can be substituted up  
 to 2 times in an identical manner or differently by fluorine, chlorine,  
 bromine, trifluoromethyl, trifluoromethoxy, or by straight-chain or  
 branched alkyl, acyl, or alkoxy with up to 6 carbon atoms each,

25 or

L and/or T stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or  
 cycloheptyl, or for naphthyl, phenyl, pyridyl, or furyl, which  
 30 optionally can be substituted up to 3 times in an identical manner or  
 differently by fluorine, chlorine, bromine, nitro, trifluoromethyl,  
 trifluoromethoxy, or by straight-chain or branched alkyl, acyl, or  
 alkoxy with up to 6 carbon atoms each,

and the salts thereof.

35 13. 3-heteroalkyl-aryl-substituted pyridines of the formula according to Claim  
 11, in which

40 A stands for phenyl, which is optionally substituted up to 2 times in an  
 identical manner or differently by fluorine, chlorine, hydroxy,  
 trifluoromethyl, trifluoromethoxy, or by straight-chain or branched

0           alkyl, acyl, or alkoxy with up to 4 carbon atoms each or by benzyloxy,  
which in turn can be substituted by fluorine or chlorine.

5           D and E are identical or different and  
stand for a straight-chain or branched alkyl chain with up to 3 carbon  
atoms,

or

10          E       stands for a bond,

V       stands for an oxygen or sulfur atom or for a group of the formula  
-NR<sup>5</sup>,

15           wherein

R<sup>5</sup>       denotes hydrogen or straight-chain or branched alkyl with up  
to 3 carbon atoms,

20          R<sup>1</sup>       stands for cyclopropyl, cyclopentyl, cyclohexyl, tetrahydropyridyl,  
— phenyl, naphthyl, pyridyl, tetrazolyl, pyrimidyl, pyrazinyl,  
tetrahydropyrimidyl, phenoxathiin-2-yl, indolyl, imidazolyl,  
pyrrolidinyl, morpholinyl, benzothiazolyl, benzoxazolyl, furyl,  
quinolyl, pyrazolopyrimidyl, or purine-yl,  
with the rings, also via the N-function in the case of  
25       nitrogen-containing rings, optionally being substituted up to 3 times  
in an identical manner or differently by fluorine, chlorine,  
trifluoromethyl, hydroxy, cyano, carboxyl, trifluoromethoxy,  
straight-chain or branched alkyl, alkylthio, alkylalkoxy, alkoxy, or  
alkoxycarbonyl with up to 3 carbon atoms each, triazolyl, tetrazolyl,  
30       benzoxathiazolyl, or phenyl,  
and/or substituted by a group of the formula -OR<sup>6</sup>, -SR<sup>7</sup>, or -SO<sub>2</sub>R<sup>8</sup>,

— wherein

35           R<sup>6</sup>, R<sup>7</sup>, and R<sup>8</sup> are identical or different and denote phenyl, which in  
turn is substituted up to 2 times in an identical manner or  
differently by phenyl, fluorine, chlorine, or is substituted by  
straight-chain or branched alkyl with up to 3 carbon atoms,

40          L and T are identical or different and

stand for trifluoromethyl, pyrrolidinyl, or for straight-chain or branched alkyl with up to 6 carbon atoms, which are optionally substituted by cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or phenyl, which in turn may be substituted up to 2 times in an identical manner or differently by fluorine, chlorine, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 4 carbon atoms each,

or

L and/or T stand for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl, or stand for naphthyl, phenyl, or furyl, which are optionally substituted up to 2 times in an identical manner or differently by fluorine, chlorine, trifluoromethyl, trifluoromethoxy, or by straight-chain or branched alkyl or alkoxy with up to 3 carbon atoms each,

and the salts thereof.

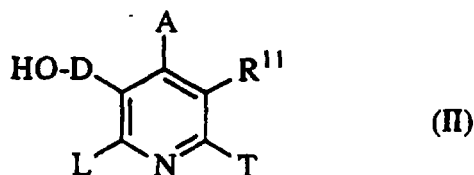
14. 3-heteroalkyl-aryl-substituted pyridines of the formula according to Claim 11, in which

A stands for phenyl, which is optionally substituted up to 2 times in an identical manner or differently by fluorine, chlorine, trifluoromethyl, methoxy, methyl, or by fluorine- or chlorine-substituted benzyloxy.

15. 3-heteroalkyl-aryl-substituted pyridines according to Claims 11 through 14 for therapeutic treatment.

16. Process for the production of 3-heteroalkyl-aryl-substituted pyridines according to Claims 11 through 14, characterized in that

[A] in the case of  $V = O$   
compounds of general formula (II)



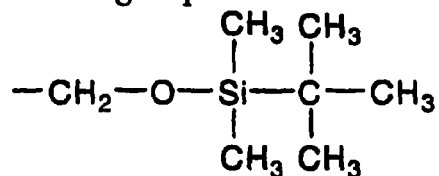
in which

A, D, L, and T have the indicated meaning,

0

and

R<sup>11</sup> stands for straight-chain or branched alkoxycarbonyl with up to 4 carbon atoms or for the group of the formula



5

are reacted with compounds of general formula (III)



10

in which

R<sup>1</sup> and E have the indicated meaning

15

and

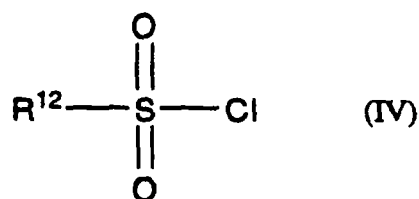
Z— stands for halogen, preferably chlorine or bromine,

20

in inert solvents, optionally in the presence of bases and/or auxiliary agents, and reductive separation is then carried out, depending on the meaning of the group R<sup>11</sup>,

[B] compounds of general formula (II) are next converted by reactions with compounds of general formula (IV)

25

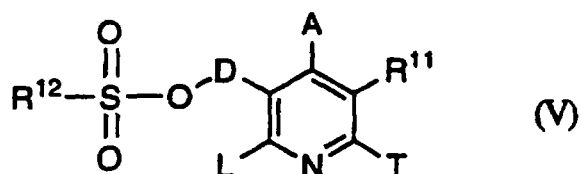


in which

R<sup>12</sup> stands for straight-chain alkyl with up to 4 carbon atoms,

30

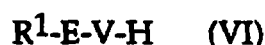
into compounds of general formula (V)



in which

A, D, L, T, R<sup>11</sup>, and R<sup>12</sup> have the indicated meaning,

and these are then reacted with compounds of general formula (VI)



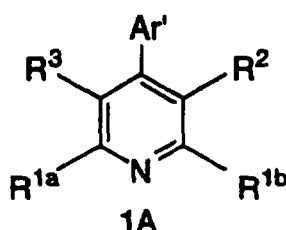
in which

R<sup>1</sup>, E, and V have the indicated meaning,

and reductive separation is carried out,

and optionally, the groups listed under substituents A, L, T, and R<sup>1</sup> are introduced or varied according to customary methods.

17. Pharmaceutical product containing 3-heteroalkyl-aryl-substituted pyridines according to Claims 11 through 14, as well as a pharmacologically safe formulation auxiliary.
18. Pharmaceutical product according to Claim 17 for the treatment of hyperlipoproteinemia.
19. Use of 3-heteroalkyl-aryl-substituted pyridines according to Claims 11 through 14 for the production of pharmaceutical products.
20. Use according to Claim 19 for the production of pharmaceutical products for the treatment of hyperlipoproteinemia.
21. A compound having glucagon receptor antagonistic activity and the structural formula 1A



wherein

$R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkenyl, or (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl;

$R^2$  represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl; the substituents on said substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl  $R^2$  groups being independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2;

$R^4$  and  $R^5$  independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

$R^4$  and  $R^5$  optionally may be joined together to form - (CH<sub>2</sub>)<sub>r</sub>A(CH<sub>2</sub>)<sub>s</sub>- wherein

r and s are independently 1, 2, or 3; and wherein

A represents O, S(O)<sub>n</sub>, CHR<sup>6</sup>, or NR<sup>6</sup>; wherein

n is 0, 1, or 2; and

$R^6$  represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

$R^7$  represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

$R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge containing from 3 to 5 carbon atoms, between the ring carbon atoms to which  $R^2$  and  $R^{1b}$  are attached;

0  $R^3$  represents hydroxy, trifluoroacetyl, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl; the substituents on said substituted alkyl and substituted alkenyl  $R^3$  groups being from 1 to 3 hydroxyl or trifluoromethyl groups; and

5  $Ar'$  represents an optionally mono-, di-, or tri-substituted heteroaromatic ring selected from the group consisting of pyridyls, furanyls, thiophenyls, pyrrolyls, imidazolyls, pyrazolyls, triazolyls, tetrazolyls, oxazolyls, isoxazolyls, thiazolyls and isothiazolyls, wherein the substituents are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano, nitro, trifluoromethyl, -OR<sup>4</sup>, -C(O)R<sup>4</sup>, -OC(O)R<sup>4</sup>, -CO<sub>2</sub>R<sup>4</sup>, -NR<sup>4</sup>R<sup>5</sup>, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2; and

pharmaceutically acceptable salts thereof.

15 22. A compound of claim 21, wherein in structural formula 1A,

$R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, or (C<sub>3</sub>-C<sub>7</sub>)-cycloalkenyl;

20  $R^2$  represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl or substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2;

25  $R^4$  and  $R^5$  independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

$R^6$  represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

30  $R^7$  represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

35  $R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge containing from 3 to 4 carbon atoms, between the ring carbon atoms to which  $R^2$  and  $R^{1b}$  are attached;

0           R<sup>3</sup> represents (C<sub>1</sub>-C<sub>6</sub>) alkanoyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, wherein the substituents are from 1 to 3 hydroxyl groups; and

5           Ar' is selected from the group consisting of pyridyls, furanyls, thiophenyls, pyrazolyls, triazolyls, oxazolyls and thiazolyls, and the optional substituents on Ar' are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl.

10   23.   A compound of claim 21, wherein in structural formula 1A,

          R<sup>1a</sup> and R<sup>1b</sup> independently represent (C<sub>1</sub>-C<sub>6</sub>)-alkyl or (C<sub>2</sub>-C<sub>6</sub>)-alkenyl;

          R<sup>2</sup> represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, or substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 15 3 of halogen or -S(O)<sub>m</sub>R<sup>7</sup> wherein m=0,

          — R<sup>7</sup> represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl;

          R<sup>3</sup> represents substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, wherein the substituents are 1 or 2 hydroxyl groups; and 20

          Ar' is selected from the group consisting of pyridyls, furanyls and thiophenyls, and the optional substituents are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>) alkyl.

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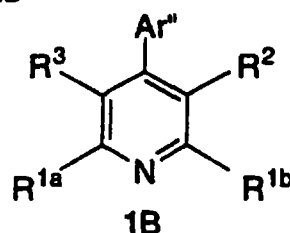
24.   A pharmaceutical composition for use in treating a glucagon-mediated condition, which comprises: a compound of claim 21, and a pharmaceutically acceptable carrier.

30   25.   A method for treating a glucagon-mediated condition which comprises administering to a subject an effective amount of a compound of claim 21.

26.   The method of claim 25, wherein the subject is human, the glucagon-mediated condition is diabetes, and the treatment results in lowering of 35 blood glucose.

0

27. A compound having glucagon receptor antagonistic activity and the structural formula 1B



wherein

5  $R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkenyl, or (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl;

10  $R^2$  represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl; the substituents on said substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl  $R^2$  groups being independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2;

15  $R^4$  and  $R^5$  independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

20  $R^4$  and  $R^5$  optionally may be joined together to form - (CH<sub>2</sub>)<sub>r</sub>A(CH<sub>2</sub>)<sub>s</sub>- wherein

r and s are independently 1, 2, or 3; and wherein

A represents O, S(O)<sub>n</sub>, CHR<sup>6</sup>, or NR<sup>6</sup>; wherein

25  $n$  is 0, 1, or 2; and

$R^6$  represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

30  $R^7$  represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

$R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge containing from 3 to 5 carbon atoms, between the ring carbon atoms to which  $R^2$  and  $R^{1b}$  are attached;

$R^3$  represents hydroxy, trifluoroacetyl,  $(C_1-C_6)$ -alkanoyl, substituted  $(C_1-C_6)$ -alkyl, or substituted  $(C_3-C_6)$ -alkenyl; the substituents on said substituted alkyl and substituted alkenyl  $R^3$  groups being from 1 to 3 hydroxyl or trifluoromethyl groups; and

$Ar$  represents an optionally mono-, di-, or tri-substituted aromatic ring selected from the group consisting of phenyls and naphthyls, wherein the substituents are independently from 1 to 3 of halogen,  $(C_1-C_6)$ -alkyl, substituted  $(C_1-C_6)$ -alkyl,  $(C_2-C_6)$ -alkenyl, substituted  $(C_2-C_6)$ -alkenyl,  $(C_2-C_6)$ -alkynyl, substituted  $(C_2-C_6)$ -alkynyl,  $(C_3-C_7)$ -cycloalkyl, cyano, nitro, trifluoromethyl,  $-OR^4$ ,  $-C(O)R^4$ ,  $-OC(O)R^4$ ,  $-CO_2R^4$ ,  $-NR^4R^5$ ,  $-C(O)NR^4R^5$  or  $-S(O)_mR^7$  wherein  $m$  is 0, 1, or 2; and

pharmaceutically acceptable salts thereof.

28. A compound of claim 27, wherein in structural formula 1B,

$R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl,  $(C_1-C_{10})$ -alkyl, substituted  $(C_1-C_{10})$ -alkyl,  $(C_2-C_{10})$ -alkenyl, substituted  $(C_2-C_{10})$ -alkenyl,  $(C_3-C_7)$ -cycloalkyl, or  $(C_3-C_7)$ -cycloalkenyl;

$R^2$  represents  $(C_1-C_{10})$ -alkyl, substituted  $(C_1-C_{10})$ -alkyl,  $(C_2-C_{10})$ -alkenyl or substituted  $(C_2-C_{10})$ -alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl,  $-C(O)NR^4R^5$ , or  $-S(O)_mR^7$  wherein  $m$  is 0, 1, or 2;

$R^4$  and  $R^5$  independently represent hydrogen,  $(C_1-C_6)$ -alkyl,  $(C_3-C_6)$ -alkenyl,  $(C_3-C_7)$ -cycloalkyl, phenyl, substituted phenyl, phenyl- $(C_1-C_6)$ -alkyl, substituted phenyl- $(C_1-C_6)$ -alkyl, naphthyl, substituted naphthyl, naphthyl- $(C_1-C_6)$ -alkyl, or substituted naphthyl- $(C_1-C_6)$ -alkyl;

$R^6$  represents hydrogen,  $(C_1-C_6)$ -alkyl, phenyl, or phenyl- $(C_1-C_6)$ -alkyl;

$R^7$  represents  $(C_1-C_6)$ -alkyl, phenyl, substituted phenyl, phenyl- $(C_1-C_6)$ -alkyl, substituted phenyl- $(C_1-C_6)$ -alkyl, pyridyl, substituted pyridyl, pyridyl- $(C_1-C_6)$ -alkyl, or substituted pyridyl- $(C_1-C_6)$ -alkyl;

$R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge containing from 3 to 4 carbon atoms, between the ring carbon atoms to which  $R^2$  and  $R^{1b}$  are attached;

0             $R^3$  represents (C<sub>1</sub>-C<sub>6</sub>) alkanoyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, wherein the substituents are from 1 to 3 hydroxyl groups; and

5            Ar" represents a phenyl ring, and the optional substituents on Ar" are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl.

10        29. A compound of claim 27, wherein in structural formula 1B, R<sup>1a</sup> and R<sup>1b</sup> independently represent (C<sub>1</sub>-C<sub>6</sub>)-alkyl or (C<sub>2</sub>-C<sub>6</sub>)-alkenyl;

15            R<sup>2</sup> represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, or substituted (C<sub>2</sub>-C<sub>10</sub>) alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 3 of halogen or -S(O)<sub>m</sub>R<sup>7</sup> wherein m=0;

            R<sup>7</sup> represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl;

            R<sup>3</sup> represents substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, wherein the substituents are 1 or 2 hydroxyl groups; and

20            Ar" represents a phenyl ring, and the optional substituents are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>) alkyl.

25        30. A compound of claim 27, selected from the following group of compounds:

- 2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-ethylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-ethylpyridine;  
 30        2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-ethylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-propylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-propylpyridine;  
 2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-propylpyridine;

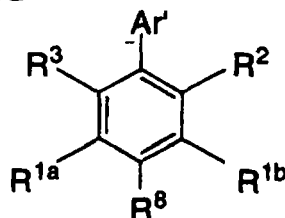
- 0        2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-  
propylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-butylpyridine;  
5        2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-butyl-  
10        pyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-pentylpyridine;  
15        2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-pentylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-pentyl-  
pyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-phenyl-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-fluorophenyl)-5-hexylpyridine;  
20        2,6-Diisopropyl-3-hydroxymethyl-4-(4-chlorophenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(4-methylphenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxyphenyl)-5-hexylpyridine;  
2,6-Diisopropyl-3-hydroxymethyl-4-(2-hydroxy-4-fluorophenyl)-5-hexyl-  
pyridine;  
25        2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-phenyl-5-hydroxymethylpyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-fluorophenyl)-5-hydroxymethyl-  
pyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-chlorophenyl)-5-hydroxymethyl-  
pyridine;  
30        2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-methylphenyl)-5-  
hydroxymethylpyridine;  
2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxyphenyl)-5-  
hydroxymethylpyridine;

- 0        2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-phenyl-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-fluorophenyl)-5-hydroxymethyl-pyridine;  
5        2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-chlorophenyl)-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(4-methylphenyl)-5-hydroxymethyl-pyridine;  
10       2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxyphenyl)-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-[(4-fluorophenyl)thio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-hydroxymethyl-pyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-ethylpyridine;  
15       2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-ethylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-ethylpyridine;  
20       2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-propylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-propylpyridine;  
25       2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-propylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-butylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-butylpyridine;  
30       2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-butylpyridine;  
2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-butylpyridine;

- 0        2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-butylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-pentylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-pentylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-pentylpyridine;  
 5        2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-pentylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-pentylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-pentylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-phenyl-5-hexylpyridine;  
 10       2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-fluorophenyl)-5-hexylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-chlorophenyl)-5-hexylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(4-methylphenyl)-5-hexylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxyphenyl)-5-hexylpyridine;  
           2,6-Diisopropyl-3-(1-hydroxyethyl)-4-(2-hydroxy-4-fluorophenyl)-5-hexylpyridine;  
 15       2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-phenyl-5-(1-hydroxyethyl)-pyridine;  
           2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;  
 20       2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-chlorophenyl)-5-(1-hydroxyethyl)-pyridine;  
           2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(4-methylphenyl)-5-(1-hydroxyethyl)-pyridine;  
           2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxyphenyl)-5-(1-hydroxyethyl)-pyridine;  
 25       2,6-Diisopropyl-3-[(*p*-tolylthio)methyl]-4-(2-hydroxy-4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;  
           2,6-Diisopropyl-3-[(4-fluorophenylthio)methyl]-4-phenyl-5-(1-hydroxyethyl)-pyridine;  
 30       2,6-Diisopropyl-3-[(4-fluorophenylthio)methyl]-4-(4-fluorophenyl)-5-(1-hydroxyethyl)-pyridine;  
           2,6-Diisopropyl-3-[(4-fluorophenylthio)methyl]-4-(4-chlorophenyl)-5-(1-hydroxyethyl)-pyridine;

- 0        2,6-Diisopropyl-3-(((4-fluorophenyl)thio)methyl)-4-(4-methylphenyl)-5-(1-hydroxyethyl)-pyridine;  
       2,6-Diisopropyl-3-(((4-fluorophenyl)thio)methyl)-4-(2-hydroxyphenyl)-5-(1-hydroxyethyl)-pyridine;  
       2,6-Diisopropyl-3-(((4-fluorophenyl)thio)methyl)-4-(2-hydroxy-4-  
 5        fluorophenyl)-5-(1-hydroxyethyl)-pyridine.

31. A pharmaceutical composition for use in treating a glucagon-mediated condition, which comprises: a compound of claim 27, and a pharmaceutically acceptable carrier.
- 10        32. A method for treating a glucagon-mediated condition which comprises administering to a subject an effective amount of a compound of claim 27.
33. The method of claim 32, wherein the subject is human, the glucagon-mediated condition is diabetes, and the treatment results in lowering of  
 15        blood glucose.
34. A compound having glucagon receptor antagonistic activity and the structural formula 1C



1C

20        wherein

- $R^8$  represents hydrogen, halogen, trifluoromethyl, phenyl, substituted phenyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)-alkoxy, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)-alkoxycarbonyl, carboxy, formyl, or -NR<sup>4</sup>R<sup>5</sup>;  
 25        —

- R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted  
 30        naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

0           R<sup>4</sup> and R<sup>5</sup> optionally may be joined together to form -  
(CH<sub>2</sub>)<sub>r</sub>A(CH<sub>2</sub>)<sub>s</sub>- wherein

          r and s are independently 1, 2, or 3, and wherein

          A represents O, S(O)<sub>n</sub>, CHR<sup>6</sup>, or NR<sup>6</sup>; wherein

          n is 0, 1, or 2; and

5           R<sup>6</sup> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, piperidin-1-yl,  
phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

          R<sup>1a</sup> and R<sup>1b</sup> independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl,  
substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl,  
10       (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-  
cycloalkenyl, or (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl;

          R<sup>2</sup> represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-  
alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-  
15       C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>,  
cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl; the substituents on said substituted alkyl,  
substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R<sup>2</sup>  
groups being independently from 1 to 3 of halogen, phenyl, substituted  
phenyl, 1,3-dioxolan-2-yl, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2;

          R<sup>7</sup> represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-  
20       C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl,  
pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl,  
substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-  
C<sub>6</sub>)-alkyl;

          R<sup>2</sup> optionally may be joined to R<sup>1b</sup> to form an alkylene bridge  
25       containing from 3 to 5 carbon atoms, between the ring carbon atoms to  
which R<sup>2</sup> and R<sup>1b</sup> are attached;

          R<sup>3</sup> represents hydroxy, trifluoroacetyl, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, substituted  
(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl; the substituents on said  
substituted alkyl and substituted alkenyl R<sup>3</sup> groups being from 1 to 3  
hydroxyl or trifluoromethyl groups;

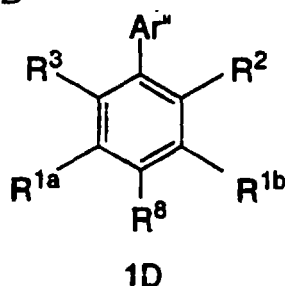
30       Ar' represents an optionally mono-, di-, or tri-substituted  
heteroaromatic ring selected from the group consisting of pyridyls, furanyl,  
thiophenyls, pyrrolyls, imidazolyls, pyrazolyls, triazolyls, tetrazolyls,  
oxazolyls, isoxazolyls, thiazolyls and isothiazolyls, wherein the substituents  
are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted (C<sub>1</sub>-  
35       C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl,  
substituted (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano, nitro,

0 trifluoromethyl,  $-OR^4$ ,  $-C(O)R^4$ ,  $-OC(O)R^4$ ,  $-CO_2R^4$ ,  $-NR^4R^5$ ,  $-C(O)NR^4R^5$ ,  
 or  $-S(O)_mR^7$  wherein m is 0, 1, or 2 and  
 pharmaceutically acceptable salts thereof.

35. A compound of claim 34, wherein in structural formula 1C,  
 5  $R^8$  represents hydrogen, halogen, trifluoromethyl or (C<sub>1</sub>-C<sub>10</sub>) alkyl;  
 $R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl,  
 substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl,  
 (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, or (C<sub>3</sub>-C<sub>7</sub>)-cycloalkenyl;  
 $R^2$  represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-  
 10 alkenyl or substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, wherein the substituents on said  
 substituted alkyl and substituted alkenyl groups are independently from 1 to  
 3 of halogen, phenyl, substituted phenyl,  $-C(O)NR^4R^5$ , or  $-S(O)_mR^7$  wherein  
 m is 0,1,or 2;  
 $R^4$  and  $R^5$  independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-  
 15 alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-  
 alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl,  
 naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;  
 $R^6$  represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-  
 alkyl;  
 20  $R^7$  represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-  
 C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl,  
 pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;  
 $R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge  
 containing from 3 to 4 carbon atoms, between the ring carbon atoms to  
 25 which  $R^2$  and  $R^{1b}$  are attached;  
 $R^3$  represents (C<sub>1</sub>-C<sub>6</sub>) alkanoyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or  
 substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, wherein the substituents are from 1 to 3  
 hydroxyl groups; and  
 $Ar'$  is selected from the group consisting of pyridyls, furanyls,  
 30 thiophenyls, pyrazolyis, triazolyis, oxazolyis and thiazolyis, and the optional  
 substituents on  $Ar'$  are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl,  
 (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano,  $-OR^4$ , or -  
 $OC(O)R^4$ , where  $R^4$  is hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl or  
 substituted phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl.

35

- 0 36. A compound of claim 34, wherein in structural formula 1C,  
 $R^8$  represents hydrogen;  
 $R^{1a}$  and  $R^{1b}$  independently represent (C<sub>1</sub>-C<sub>6</sub>)-alkyl or (C<sub>2</sub>-C<sub>6</sub>)-  
 alkenyl;  
 $R^2$  represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>)-  
 5 alkenyl, or substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, wherein the substituents on said  
 substituted alkyl and substituted alkenyl groups are independently from 1 to  
 3 of halogen or -S(O)<sub>m</sub>R<sup>7</sup> wherein m=0,  
 $R^7$  represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl (C<sub>1</sub>-  
 C<sub>6</sub>)-alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl;  
 10  $R^3$  represents substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted (C<sub>3</sub>-C<sub>6</sub>)-  
 alkenyl; where the substituents are 1 or 2 hydroxyl groups; and  
 $Ar'$  is selected from the group consisting of pyridyls, furanlyls and  
 thiophenyls, and the optional substituents are independently from 1 to 3 of  
 halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is  
 15 hydrogen or (C<sub>1</sub>-C<sub>6</sub>) alkyl.
37. A pharmaceutical composition for use in treating a glucagon-mediated  
 condition, which comprises: a compound of claim 34, and a pharmaceutically  
 acceptable carrier.
- 20 38. A method for treating a glucagon-mediated condition which comprises  
 administering to a subject an effective amount of a compound of claim 34.
39. The method of claim 38, wherein the subject is human, the glucagon-  
 25 mediated condition is diabetes, and the treatment results in lowering c  
 blood glucose.
40. A compound having glucagon receptor antagonistic activity and the  
 structural formula 1D



wherein

0           R<sup>8</sup> represents hydrogen, halogen, trifluoromethyl, phenyl, substituted phenyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)-alkoxy, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyloxy, (C<sub>1</sub>-C<sub>6</sub>)-alkoxycarbonyl, carboxy, formyl, or -NR<sup>4</sup>R<sup>5</sup>;

5           R<sup>4</sup> and R<sup>5</sup> independently represent hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>3</sub>-C<sub>6</sub>)-alkenyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

10           R<sup>4</sup> and R<sup>5</sup> optionally may be joined together to form - (CH<sub>2</sub>)<sub>r</sub>A(CH<sub>2</sub>)<sub>s</sub>- wherein

r and s are independently 1, 2, or 3, and wherein

A represents O, S(O)<sub>n</sub>, CHR<sup>6</sup>, or NR<sup>6</sup>, wherein

n is 0, 1, or 2; and

15           R<sup>6</sup> represents hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, piperidin-1-yl, phenyl, or phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

          R<sup>1a</sup> and R<sup>1b</sup> independently represent trifluoromethyl, (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkenyl, or (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl;

20           R<sup>2</sup> represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>)-alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, substituted (C<sub>2</sub>-C<sub>10</sub>)-alkynyl, (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-cycloalkyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl; the substituents on said substituted alkyl, substituted alkenyl, substituted alkynyl, and substituted cycloalkyl R<sup>2</sup> groups being independently from 1 to 3 of halogen, phenyl, substituted phenyl, 1,3-dioxolan-2-yl, -C(O)NR<sup>4</sup>R<sup>5</sup>, or -S(O)<sub>m</sub>R<sup>7</sup> wherein m is 0, 1, or 2;

25           R<sup>7</sup> represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted phenyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, pyridyl, substituted pyridyl, pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, substituted pyridyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, naphthyl, substituted naphthyl, naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted naphthyl-(C<sub>1</sub>-C<sub>6</sub>)-alkyl;

          R<sup>2</sup> optionally may be joined to R<sup>1b</sup> to form an alkylene bridge containing from 3 to 5 carbon atoms, between the ring carbon atoms to which R<sup>2</sup> and R<sup>1b</sup> are attached;

35           R<sup>3</sup> represents hydroxy, trifluoroacetyl, (C<sub>1</sub>-C<sub>6</sub>)-alkanoyl, substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl; the substituents on said

0 substituted alkyl and substituted alkenyl  $R^3$  groups being from 1 to 3 hydroxyl or trifluoromethyl groups;

5 "Ar" represents an optionally mono-, di-, or tri-substituted aromatic ring selected from the group consisting of phenyls and naphthyls, wherein the substituents are independently from 1 to 3 of halogen,  $(C_1-C_6)$ -alkyl, substituted  $(C_1-C_6)$ -alkyl,  $(C_2-C_6)$ -alkenyl, substituted  $(C_2-C_6)$ -alkenyl,  $(C_2-C_6)$ -alkynyl, substituted  $(C_2-C_6)$ -alkynyl,  $(C_3-C_7)$ -cycloalkyl, cyano, nitro, trifluoromethyl,  $-OR^4$ ,  $-C(O)R^4$ ,  $-OC(O)R^4$ ,  $-CO_2R^4$ ,  $-NR^4R^5$ ,  $-C(O)NR^4R^5$ , or  $-S(O)_mR^7$  wherein m is 0, 1, or 2; and

pharmaceutically acceptable salts thereof.

10

41. A compound of claim 40, wherein in structural formula 1D,

$R^8$  represents hydrogen, halogen, trifluoromethyl or  $(C_1-C_{10})$  alkyl;

15  $R^{1a}$  and  $R^{1b}$  independently represent trifluoromethyl,  $(C_1-C_{10})$ -alkyl, substituted  $(C_1-C_{10})$ -alkyl,  $(C_2-C_{10})$ -alkenyl, substituted  $(C_2-C_{10})$ -alkenyl,  $(C_3-C_7)$ -cycloalkyl, or  $(C_3-C_7)$ -cycloalkenyl;

20  $R^2$  represents  $(C_1-C_{10})$ -alkyl, substituted  $(C_1-C_{10})$ -alkyl,  $(C_2-C_{10})$ -alkenyl or substituted  $(C_2-C_{10})$ -alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 3 of halogen, phenyl, substituted phenyl,  $-C(O)NR^4R^5$ , or  $-S(O)_mR^7$  wherein m is 0, 1, or 2;

$R^4$  and  $R^5$  independently represent hydrogen,  $(C_1-C_6)$ -alkyl,  $(C_3-C_6)$ -alkenyl,  $(C_3-C_7)$ -cycloalkyl, phenyl, substituted phenyl, phenyl- $(C_1-C_6)$ -alkyl, substituted phenyl- $(C_1-C_6)$ -alkyl, naphthyl, substituted naphthyl, naphthyl- $(C_1-C_6)$ -alkyl, or substituted naphthyl- $(C_1-C_6)$ -alkyl;

25  $R^6$  represents hydrogen,  $(C_1-C_6)$ -alkyl, phenyl, or phenyl- $(C_1-C_6)$  alkyl;

$R^7$  represents  $(C_1-C_6)$ -alkyl, phenyl, substituted phenyl, phenyl- $(C_1-C_6)$ -alkyl, substituted phenyl- $(C_1-C_6)$ -alkyl, pyridyl, substituted pyridyl, pyridyl- $(C_1-C_6)$ -alkyl, or substituted pyridyl- $(C_1-C_6)$ -alkyl;

30  $R^2$  optionally may be joined to  $R^{1b}$  to form an alkylene bridge containing from 3 to 4 carbon atoms, between the ring carbon atoms to which  $R^2$  and  $R^{1b}$  are attached;

$R^3$  represents  $(C_1-C_6)$  alkanoyl, substituted  $(C_1-C_6)$ -alkyl, or substituted  $(C_3-C_6)$ -alkenyl, wherein the substituents are from 1 to 3

35 hydroxyl groups; and

0           Ar" represents a phenyl ring, and the optional substituents on Ar" are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, (C<sub>2</sub>-C<sub>6</sub>)-alkynyl, (C<sub>3</sub>-C<sub>7</sub>)-cycloalkyl, cyano, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen, (C<sub>1</sub>-C<sub>6</sub>) alkyl, phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>) alkyl.

5

42. A compound of claim 40, wherein in structural formula 1D,

R<sup>8</sup> represents hydrogen;

R<sup>1a</sup> and R<sup>1b</sup> independently represent (C<sub>1</sub>-C<sub>6</sub>)-alkyl or (C<sub>2</sub>-C<sub>6</sub>)-alkenyl;

10

R<sup>2</sup> represents (C<sub>1</sub>-C<sub>10</sub>)-alkyl, substituted (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>2</sub>-C<sub>10</sub>)-alkenyl, or substituted (C<sub>2</sub>-C<sub>10</sub>) alkenyl, wherein the substituents on said substituted alkyl and substituted alkenyl groups are independently from 1 to 3 of halogen or -S(O)<sub>m</sub>R<sup>7</sup> wherein m=0;

15

R<sup>7</sup> represents (C<sub>1</sub>-C<sub>6</sub>)-alkyl, phenyl, substituted phenyl, phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted phenyl (C<sub>1</sub>-C<sub>6</sub>)-alkyl;

R<sup>3</sup> represents substituted (C<sub>1</sub>-C<sub>6</sub>)-alkyl or substituted (C<sub>3</sub>-C<sub>6</sub>)-alkenyl; where the substituents are 1 or 2 hydroxyl groups; and

20

Ar" represents a phenyl ring, and the optional substituents are independently from 1 to 3 of halogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>2</sub>-C<sub>6</sub>)-alkenyl, -OR<sup>4</sup>, or -OC(O)R<sup>4</sup>, where R<sup>4</sup> is hydrogen or (C<sub>1</sub>-C<sub>6</sub>) alkyl.

43. A compound of claim 40, selected from the following group of compounds:

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-fluoro-1,1'-biphenyl;

25

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-chloro-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-4'-methyl-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-2'-hydroxy-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-ethyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-1,1'-biphenyl; —

30

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-fluoro-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-chloro-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-4'-methyl-1,1'-biphenyl;

3,5-Diisopropyl-2-hydroxymethyl-6-propyl-2'-hydroxy-1,1'-biphenyl;

- 0        3,5-Diisopropyl-2-hydroxymethyl-6-propyl-2'-hydroxy-4'-fluoro-1,1'-  
          biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-butyl-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-fluoro-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-chloro-1,1'-biphenyl;  
5        3,5-Diisopropyl-2-hydroxymethyl-6-butyl-4'-methyl-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-butyl-2'-hydroxy-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-butyl-2'-hydroxy-4'-fluoro-1,1'-  
          biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-1,1'-biphenyl;  
10       3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-fluoro-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-chloro-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-4'-methyl-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-2'-hydroxy-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-pentyl-2'-hydroxy-4'-fluoro-1,1'-  
15       biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-fluoro-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-chloro-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-4'-methyl-1,1'-biphenyl;  
20       3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-2'-hydroxy-1,1'-biphenyl;  
          3,5-Diisopropyl-2-hydroxymethyl-6-hexyl-2'-hydroxy-4'-fluoro-1,1'-  
          biphenyl;  
          3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-1,1'-biphenyl;  
          3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-4'-fluoro-1,1'-  
25       biphenyl;  
          3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-4'-chloro-1,1'-  
          biphenyl;  
          3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-4'-methyl-1,1'-  
          biphenyl;  
30       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-2'-hydroxy-1,1'-  
          biphenyl;  
          3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-hydroxymethyl-2'-hydroxy-4'-  
          fluoro-1,1'-biphenyl;

- 0 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-4'-chloro-1,1'-biphenyl;  
 5 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-2'-hydroxy-1,1'-biphenyl;  
 10 3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-hydroxymethyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-chloro-1,1'-biphenyl;  
 15 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-ethyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-1,1'-biphenyl;  
 20 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-4'-methyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-propyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 25 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-chloro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-4'-methyl-1,1'-biphenyl;  
 30 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-2'-hydroxy-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-butyl-2'-hydroxy-4'-fluoro-1,1'-biphenyl;  
 3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-1,1'-biphenyl;

- 0        3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-fluoro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-chloro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-4'-methyl-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-2'-hydroxy-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-pentyl-2'-hydroxy-4'-fluoro-1,1'-  
 5        biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-fluoro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-chloro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-4'-methyl-1,1'-biphenyl;  
 10       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-2'-hydroxy-1,1'-biphenyl;  
       3,5-Diisopropyl-2-(1-hydroxyethyl)-6-hexyl-2'-hydroxy-4'-fluoro-1,1'-  
       biphenyl;  
       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-1,1'-biphenyl;  
       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-fluoro-1,1'-  
 15       biphenyl;  
       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-chloro-1,1'-  
       biphenyl;  
       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-4'-methyl-1,1'-  
       biphenyl;  
 20       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-1,1'-  
       biphenyl;  
       3,5-Diisopropyl-2-[(*p*-tolylthio)methyl]-6-(1-hydroxyethyl)-2'-hydroxy-4'-  
       fluoro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-[(4-fluorophenylthio)methyl]-6-(1-hydroxyethyl)-1,1'-  
 25       biphenyl;  
       3,5-Diisopropyl-2-[(4-fluorophenylthio)methyl]-6-(1-hydroxyethyl)-4'-  
       fluoro-1,1'-biphenyl;  
       3,5-Diisopropyl-2-[(4-fluorophenylthio)methyl]-6-(1-hydroxyethyl)-4'-  
       chloro-1,1'-biphenyl;  
 30       3,5-Diisopropyl-2-[(4-fluorophenylthio)methyl]-6-(1-hydroxyethyl)-4'-  
       methyl-1,1'-biphenyl;  
       3,5-Diisopropyl-2-[(4-fluorophenylthio)methyl]-6-(1-hydroxyethyl)-2'-  
       hydroxy-1,1'-biphenyl;

0        3,5-Diisopropyl-2-(((4-fluorophenyl)thio)methyl)-6-(1-hydroxyethyl)-2'-  
         hydroxy-4'-fluoro-1,1'-biphenyl.

44.    A pharmaceutical composition for use in treating a glucagon-mediated  
5       condition, which comprises: a compound of claim 40, and a pharmaceutically  
      acceptable carrier.

45.    A method for treating a glucagon-mediated condition which comprises  
      administering to a subject an effective amount of a compound of claim 40.

10    46.   The method of claim 45, wherein the subject is human, the glucagon-  
      mediated condition is diabetes, and the treatment results in lowering of  
      blood glucose.

15    47.   A compound of claim 21, 27, 34, or 40 wherein the substituent shown as R<sup>3</sup> is  
      a hydroxyethyl group having the following stereochemistry

