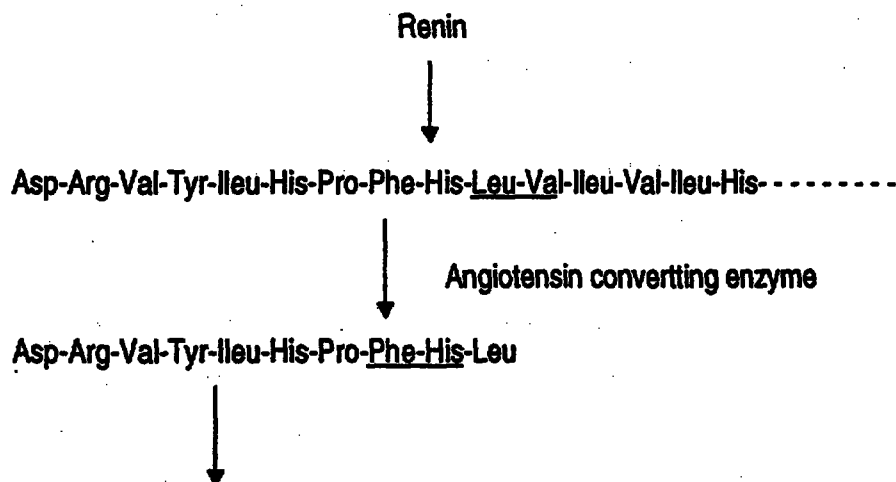


Synthesis of Prototypes for Renin Inhibitors

This invention relates to the field of biological activity relating to enzymatic and similar specific chemical breakdown of angiotensinogen by scission to angiotensin-I, then to angiotensin-II, which engages receptors initiating biological activity as is well known.

It is long known to use compounds of similar chemical properties and general stereochemical conformation either as substitutes for activators to produce positive effects or to block specific receptors to prevent negative effects. In practice despite massive advances in knowledge of conformational structure of chemical compounds, neither the exact conformation of a particular compound, nor its chemical synthesis, nor its biological properties are confidently predictable. In the present invention the compounds envisaged are important intermediates for the manufacture of prototype Renin-inhibitors. Renin inhibitors prevent the production of angiotensin-II, a potent vasoconstrictor and therefore are potent antihypertensives. The basic action of renin is as shown hereinafter, wherein angiotensinogen is first cleaved to provide a specific fragment (angiotensin I), then subcleaved to a second specific fragment (angiotensin II), which engages the appropriate receptor to initiate biological activity:



Asp-Arg-Val-Tyr-Ileu-His-Pro-Phe

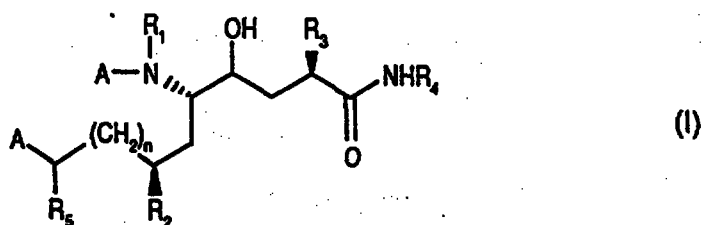


A-II receptor



Biological activity

The present invention contemplates novel stereoselective chemical synthesis of compounds as of the general formula I



Although the invention will be described and referred to specifically as it relates to such compounds and their processes of principles of this invention are equally applicable to similar compounds and processes and accordingly, it will be understood that the invention is not limited to such compounds and processes.

BACKGROUND & PRIOR ART

The background is that of stereospecific synthetic organic chemistry, a voluminous and ever expanding field, in which it is a full time occupation to keep abreast of general trends, especially in areas relating to human medical application.

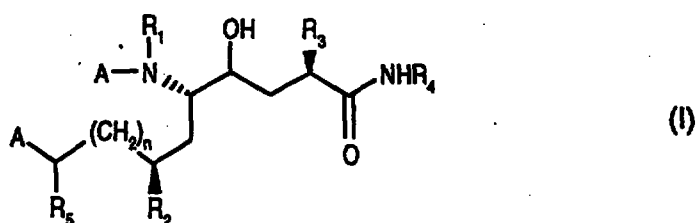
Applicant is not aware of any prior art related to the specific subject matter described herein.

A principal object of the invention is to develop novel compounds suitable as prototypes for renin inhibitors. It is a related principal object to synthesize said novel compounds by novel chemical processes. It is a subsidiary object to devise practical synthetic schemes to prepare the novel compounds. It is a further subsidiary object to prepare the novel compounds as stereoisomerically pure as practicable. It is a further object to characterize all the

compounds so prepared as fully as possible. Other objects would be readily apparent to skilled practitioners in the art, from the following specification, appended claims, and accompanying schemes and figures.

DESCRIPTION OF INVENTION

In one broad aspect the invention is directed to a chemical compound having the structure



where n is 0-3 inclusive, A are either both hydrogen atoms or together are a single carbon-nitrogen bond, R₁ is hydrogen, or hydrocarbylcarboxy wherein the hydrocarbyl entity is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R₂ and R₃ or independently alkyl of 1 to 4 carbon atoms, R₄ is alkyl of 1 to 6 carbon atoms or a substituent of aliphatic character, R₅ is selected from aromatics, substituted aromatics and heteroaromatics, substituted or unsubstituted cycloalkyls, cycloalkenes having 3 to 8 carbon atoms, with substituents selected from alkyl, alkoxy of 3 to 10 carbon atoms and alkoxy derivatives, primary and secondary amides and alkyl derivatives. Alkyl derivatives of primary and secondary amides are, for example, primary and secondary carbamoylalkyl groups. Preferably n is 0.

Substituents of aliphatic character are, for example, butyl, 2-morpholinoethyl or 2-carbamoyl-2-methyl-propyl. Alkoxy derivatives are, for example, alkoxyalkoxy groups such as 3-methoxy-propyloxy.

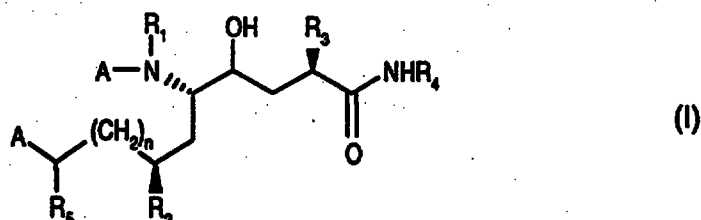
Both A taken together may form a single carbon nitrogen bond. In one variation R₁ is preferably alkylcarboxy and the alkyl group has 1 to 6 carbon atoms. A preferred compound is (1'S,2S,3R,3'R,5S)-5-[(3'-Butylcarbamoyl)-1'hydroxy-butyl]-3-methyl-2-phenyl-pyrrolidine-

1-carboxylic acid tert-butyl ester. Another preferred compound is (1'S,2S,3R,3'R,5S)-5-[(3'-Butylcarbamoyl)-1'hydroxy-butyl]-3-methyl-2-phenyl-pyrrolidine.

In a second variation R₁ is preferably aralkylcarboxy and the aralkyl group has 7 to 10 carbon atoms. A preferred compound is (1'S,2S,3R,3'R,5S)-5-[(3'-Butylcarbamoyl)-1'hydroxy-butyl]-3-methyl-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester.

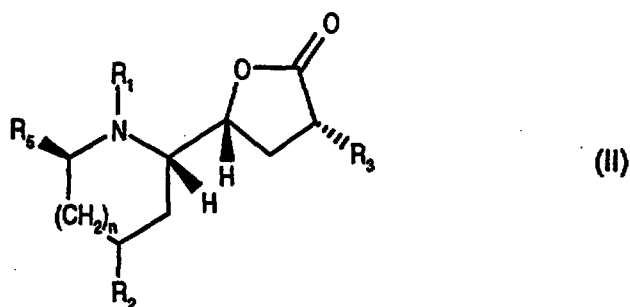
Both A may be hydrogen, when R₁ is preferably alkylcarboxy and the aralkyl group has 1 to 7 carbon atoms. A preferred compound is (2R,4S,5S,7R)-5-[[1,1-Dimethylethoxy)carbonyl]amino]-4-hydroxy 2,7-dimethyl-8-phenyl octanoic acid butyl amide. Another preferred compound is (2R,4S,5S,7R)-5-amino-4-hydroxy-2,7-dimethyl-8-phenyl octanoic acid butyl amide.

In another broad aspect the invention is directed to processes of preparation of a first chemical compound of structure



where n is 0-3 inclusive, A are either both hydrogen atoms or form a single carbon-nitrogen bond, R₁ is hydrogen, or hydrocarbylcarboxy wherein said hydrocarbyl is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R₂ and R₃ are independently alkyl of 1 to 4 carbon atoms, R₄ is alkyl of 1 to 6 carbon atoms or a substituent of aliphatic character such as, for example, butyl, 2-morpholinoethyl or 2-carbamoyl-2-methyl-propyl, R₅ is selected from aromatics, substituted aromatics and heteroaromatics, substituted or unsubstituted cycloalkyls, cycloalkenes having 3 to 8 carbon atoms, with substituents selected from alkyl, alkoxy or 3 to 10 carbon atoms and alkoxy derivatives such as 3-Methoxy-propyloxy, primary and secondary amides, alkyl derivatives. The processes include a step selected from the group consisting of (a) hydrogenolysis of a second compound of the above formula wherein both A together form a single carbon

nitrogen bond and R_1 is alkylcarboxy wherein said alkyl has 1 to 6 carbon atoms, in the presence of $\text{Pd}(\text{OH})_2/\text{C}$; (b) hydrogenolysis of a third compound of the above formula wherein both A together form a single carbon nitrogen bond and R_1 is aralkylcarboxy wherein said aralkyl has 7 to 10 carbon atoms, in the presence of $\text{Pd}(\text{PH})_2/\text{C}$, and dialkyl dicarbonate wherein both said dicarbonate alkyl groups are identical and have 1 to 6 carbon atoms; and (c) treating a fourth compound having the structure



where n is 0-3 inclusive, R_1 is hydrocarbylcarboxy wherein said hydrocarbyl is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R_2 and R_3 are independently alkyl of 1 to 4 carbon atoms, with $R_4\text{NHAIme}_2$ where R_4 is alkyl of 1 to 6 carbon atoms. Preferably n is zero, in both formulae. A preferred process of claim 14, comprises the step of hydrogenolysis of said second compound. Another preferred process, comprises the step of hydrogenolysis of said third compound. A further preferred process comprises the step of treating said fourth compound, where in a preferred step R_1 is alkylcarboxy, said alkyl group having 1 to 6 carbon atoms. Alternatively R_1 may be aralkylcarboxy, said aralkyl having 7 to 10 carbon atoms.

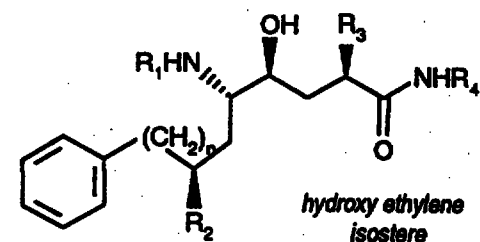
BRIEF DESCRIPTION OF THE APPENDED FIGURES AND SCHEMES

Scheme 1 indicates a first synthetic route of the invention;

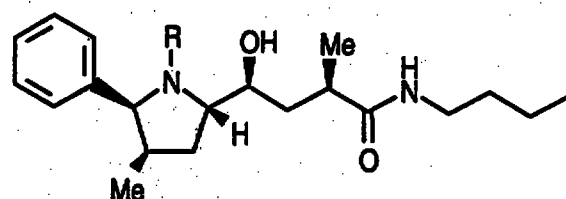
DESCRIPTION OF THE PREFERRED EMBODIMENTS

The chemical formulae of some compounds of the invention are depicted hereinafter:

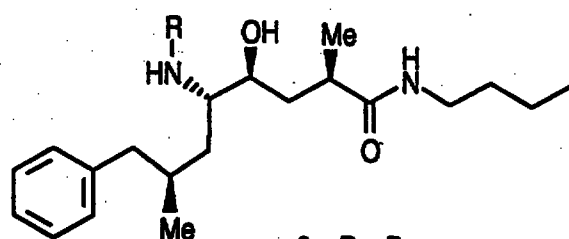
- 6 -



hydrophobic domain

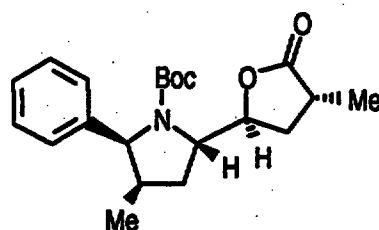
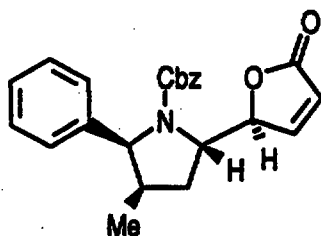


2a, R = Boc; 2b, Cbz
2c, R = H

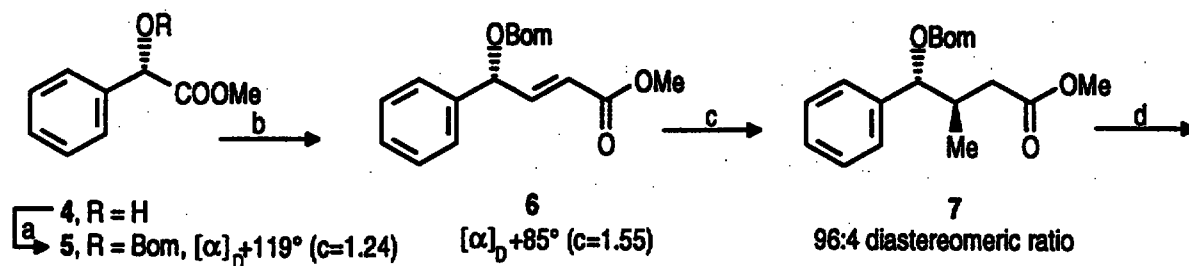


3a, R = Boc
3b, R = H

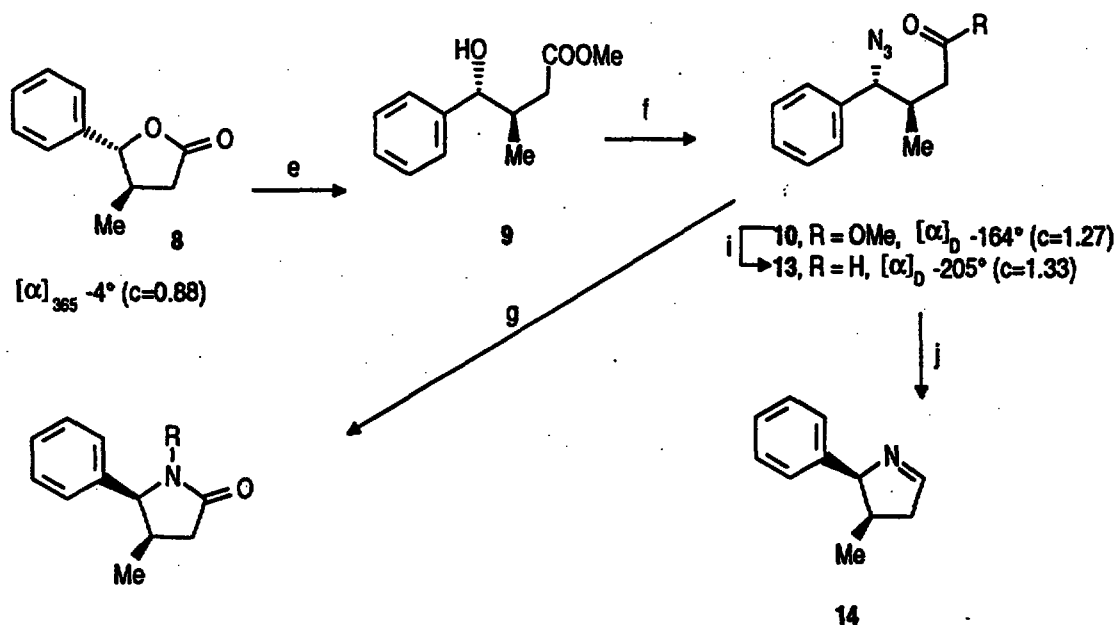
The chemical formula of a first and a second compound of the invention are depicted hereinafter:



The detailed steps of a synthetic route from (S) methyl mandelate 4 to starting precursors (2S,3R)-3-Methyl-5-oxo-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 12, and (2S,3R)-3-Methyl-2-phenyl-3,4-dihydro-2H-pyrrole 14 are as follows:



- 7 -

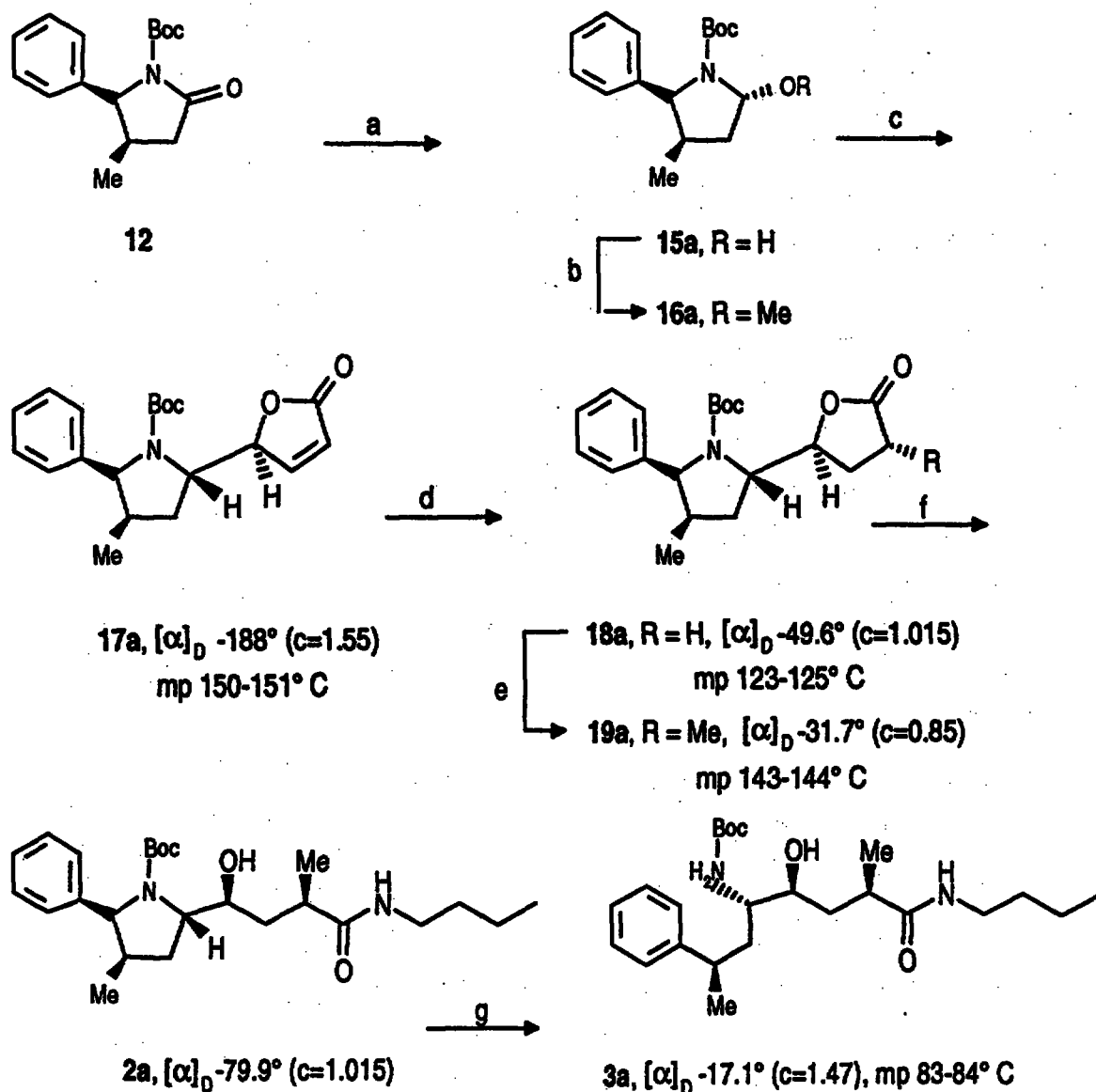


- a) $\text{PhCH}_2\text{OCH}_2\text{Cl}$ (Bom-Cl), $i\text{-Pr}_2\text{EtN}$, CH_2Cl_2 , , 100 h, 83%;
 (b) i, DIBAL-H, toluene, -78°C , 3.5 h; ii, MeOH, -78°C , 30 min; iii, methyl triphenylphosphoranylidene acetate, rt, 20 min, 75% trans, 6% cis;
 (c) $\text{Me}_2\text{CuLi}_2 \cdot 3\text{TMSCl}$, THF, -78°C , 2 h;
 d) TMSBr, CH_2Cl_2 , -23°C to rt, 72% for steps (c) and (d);
 e) i, 0.5N NaOH, MeOH, 0°C to rt, 2 h; ii, 1N HCl; iii $\text{CH}_2\text{N}_2\text{-Et}_2\text{O}$, EtOAc, 0°C , 98%;
 f) $(\text{PhO})_2\text{P(O)N}_3$, DEAD, PPh_3 , THf, 0° to rt, 16 h, 89%;
 g) 1,3-propanediol, $i\text{-Pr}_2\text{EtN}$, MeOH, rt, 18 h, 86%;
 h) $(\text{Boc})_2\text{O}$, $i\text{-Pr}_2\text{EtN}$, DMPA, CH_2Cl_2 , rt, 24 h, 99%;
 i) i DIBAL-H, toluene, -78°C , 1 h, ; ii, MeOH, -78°C , 20 min, 77%;
 j) PPh_3 , toluene, 16 h.

This route starts from methyl mandelate 4, wherein the hydroxyl is protected by forming a Brom (benzyloxymethyl) acetal 5 in 83 % yield. The carbon chain is then extended to give the phenyl trans-2-butenic acid 6 homolog by effective insertion of a trans double bond, in 75 % yield, with 6 % of *cis* isomer 6 was then methylated to give 7 unpurified as a mixture of 94:6 of the diastereoisomers including 5 % of the deconjugated product crude yield approximately 96 %. Crude 7 was cyclized to lactone 8, phenyl methyl dihydrofuranone, in 72 % yield (from 6). 8 was converted to the equivalent hydroxymethyl ester 9 by hydrolysis

and methylation in 98 % yield. **9** was converted to the equivalent azido ester **10** in 89 % yield as 96:4 diastereoisomeric mixture. **10** in one avenue is cyclized to lactam **11**, methyl phenyl pyrrolidinone in 86 % yield, followed by protection of the amino- hydrogen with carboxybutyl ester to give **12** in 99 % yield. In an alternate avenue **10** was converted to the equivalent azido-aldehyde **13** in 77 % yield, then cyclized to imine **14**, methyl phenyl dihydro H pyrrole.

Detailed steps of a subsequent synthetic route starting from **12** to (2R,4S,5S,7R)-5-[[1,1-Dimethylethoxy)carbonyl]amino]-4-hydroxy-2,7-dimethyl-8-phenyl octanoic acid butyl amide **3a** are depicted hereinafter.

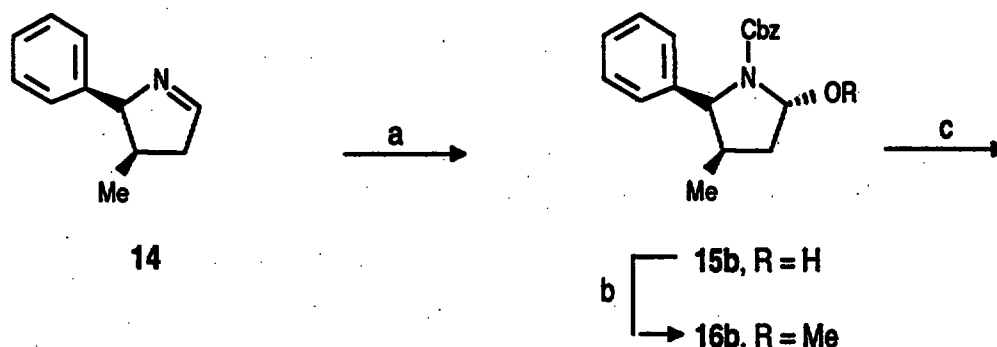


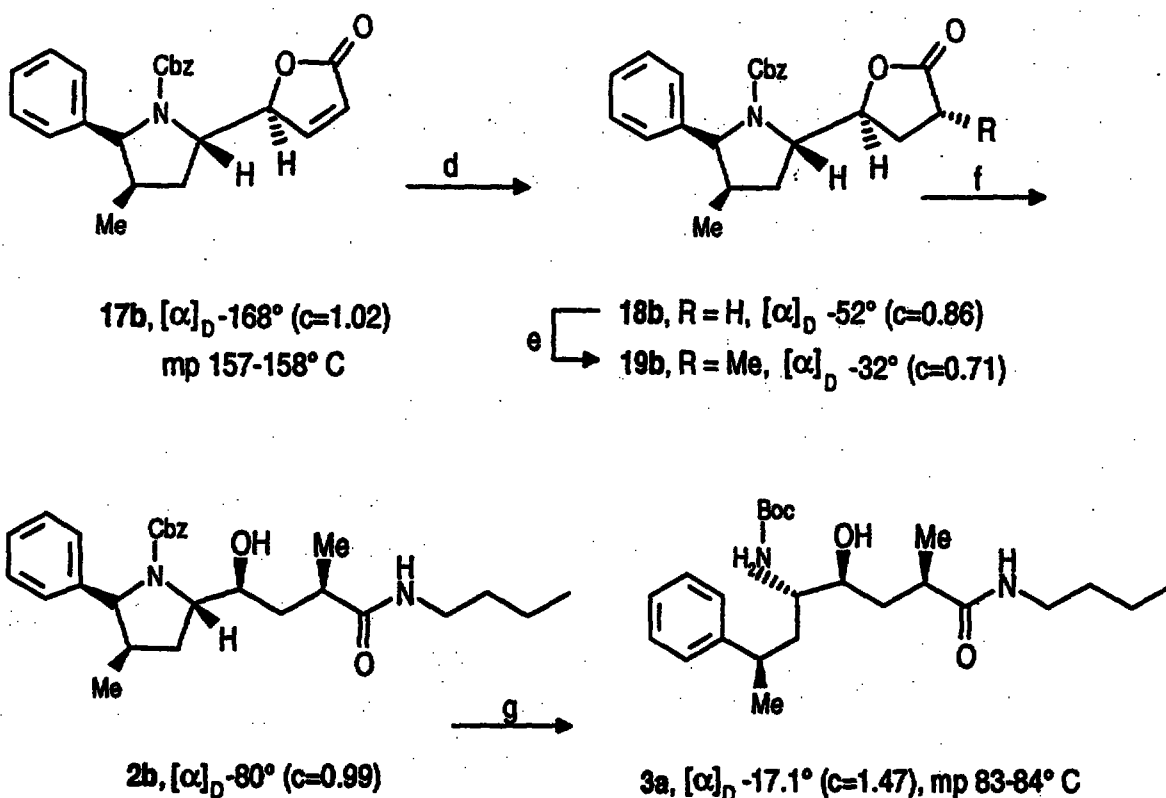
- 9 -

- a), i, DIBAL-H, toluene, -78° C, 4 h; ii, MeOH, -78° C, 30 min, 72%;
 b) CSA, MeOH, rt, 1 h, 100%;
 c) 2-(trimethylsilyloxy)furan, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; CH_2Cl_2 , -78° C, 1 h, threo:erythro = 6:1, 98%;
 d) 10% Pd-C, H_2 (1 atm), EtOAc, rt, 1 h, 93%;
 e) i, $(\text{TMS})_2\text{NLi}$, THF, -78° C, 40 min; ii, MeJ, -78° C, 90 min, -50° C, 1 h; iii, AcOH-THF, 67%;
 f) BuNHAlMe_2 , CH_2Cl_2 , rt, 7 h, 76%;
 g) 20% $\text{Pd}(\text{OH})_2$; H_2 ; (56 psi), EtOH/EtOAc (2:3), rt, 48 h, 73%.

This route starts with protected lactam **12**, whose amido-carbonyl is effectively reduced to hydroxyl to hemiaminal **15a**, as a mixture anomers and rotamers in 72 % yield. This was then methylated to give **16a**, as a mixture of four isomers, in 100 % yield. This compound was then treated effectively displacing/replacing methoxy, with the substituted furan, to form an unsaturated lactone ring, to give **17a**, in 98 % yield of 6:1 threo:erythro isomeric ratio. Pure erythro **17a** was crystallized as a mixture of rotamers. **17a** was hydrogenated saturating the double furan/lactone bond to give 93 % yield of **18a** as a mixture of two rotamers. The saturated lactone ring of **18a** was methylated, 67 % of the desired mono-methyl **19a**, and 15 % of the dimethyl lactone were obtained. Crystalline **19a** was X-ray analyzed. The lactone ring was opened by formation of the butyl amide to give **2a** in 76 % yield. Then the pyrrolidine ring was hydrogenolyzed to give **3a** in 73 % yield.

Detailed steps of a subsequent synthetic route starting from **14** to **3** are depicted hereinafter:





- a) i, $\text{PhCH}_2\text{C}(\text{O})\text{Cl}$, toluene, -78°C , 1 h; ii, 2N HCl, -78°C to rt; 67%;
- b) CSA, MeOH, rt, 1 h, 89%;
- c) 2-(trimethylsilyloxy)furan, $\text{BF}_3 \cdot \text{Et}_2\text{O}$; CH_2Cl_2 , -78°C , 2 h, threo:erythro = 5:1, 78%;
- d) 5% Pd-C, H_2 (1 atm), benzene, rt, 30 min, 90%;
- e) i, $(\text{TMS})_2\text{NLi}$, MeJ, THF, -78°C , 40 min; ii, saturated NaHCO_3 , 57%;
- f) BuNHAlMe_2 , CH_2Cl_2 , rt, 2 h, 52%;
- g) $(\text{Boc})_2\text{O}$, 20% $\text{Pd}(\text{OH})_2$; H_2 (60 psi), EtOH/EtOAc (2:3), rt, 72 h, 46%.

This route is generally analogous to scheme 2, starting with cyclized imine 14, and protecting the imino nitrogen with a carboxybenzyl group rather than a carboxybutyl group, to yield 67 % (from 13) of 15b as a mixture of anomers and rotamers. Thereafter the steps are closely similar giving 89 % of 16b, 78 % of 17b, as 5:1 threo:erythro isomeric ratio. Pure erythro 17b was crystallized as a mixture of rotamers. Crystalline 17b was X-ray analyzed. Continuing gave 90 % of 18b, 56 % of 19b, 52 % of 2b, which was directly converted to 3a, in 46 % yield.

EXAMPLES

(S)-(Benzyloxy-methoxy)-phenyl acetic acid methyl ester 5:

To the solution of 6.5 g (39.9 mmol) of (*S*)-methyl in 90 mL of anhydrous THF were added successively 12.0 mL (69 mmol) of *i*-Pr₂EtN, 8.2 mL (59.5 mmol) of benzyl chloromethyl ether and 1.46 g (3.95 mmol) of Bu₄N-I-. After the reaction was stirred at room temperature overnight. 4.0 mL (23.0 mmol) of *i*-Pr₂EtN and 2.7 mL (19.65 mmol) of benzyl chloromethyl ether were added. The reaction was stirred at room temperature for 40 h and 2.0 mL (11.5 mmol) of *i*-Pr₂EtN and 1.35 mL (9.8 mmol) of the alkylating agent were added and stirred at room temperature for another 44 h. Methanol (1.5 mL) was added to consume the excess alkylating agent. After 30 min the reaction was partitioned between 150 mL of water and 250 mL of EtOAc. The organic layer was washed with 0.5 N HCl, pH 7 phosphate buffer, then with brine, dried over MgSO₄ and concentrated. Purification of the residue by column chromatography (silica gel, 15 % EtOAc/hexanes), gave 9.25 g (83 %), of the ester 5 as a colorless syrup.

$[\alpha]_D + 119^\circ$ (c 1.24, CHCl₃); IR (thin film) 1730, 1445, 1260, 1200, 1160, 1040 cm⁻¹;

¹H NMR (CDCl₃, 300 MHz) δ 7.50-7.27 (m, 10H, ArH), 5.25 (s, 1H, PhCHO), 4.92 and 4.84 (AB quartet, 2H, *J* = 7Hz, OCH₂O), 4.69 and 4.59 (AB quartet, 2H, *J* = 12Hz, OCH₂Ph), 3.7 (s, 3H, OCH₃); ¹³C (CDCl₃, 75 MHz) δ 171.1, 137.3, 135.9, 128.7, 128.6, 128.3, 127.8, 127.7, 127.3, 93.2, 70.0, 52.2; exact mass calculated for C₁₇H₁₉O₄ 287.128334, found 287.130.

(2*E*, 4*R*)-4-(Benzyloxy-methoxy)-4-phenyl-but-2-enoic acid methyl ester 6:

To a cooled (-78°C) solution of 8.5 g (29.7 mmol) of the ester 5 in 100 mL of anhydrous toluene was added a cold (-78°C) solution of DIBAL-H (33 mL, 1M in toluene, 33 mmol) in anhydrous toluene (20 mL) via canula dropwise over a period of 30 min. The reaction was stirred at -78°C for another 3 h. Methanol (3.6 mL, 89 mmol) was added dropwise and the resulting solution was stirred at -78°C for 30 min. The cooling bath was removed and the reaction was allowed to warm to room temperature. Methyl triphenylphosphoranylidene acetate (15.0 g, 44.8 mmol) was added to the reaction mixture and stirred for 20 min. The aluminum complex was filtered and the solvent evaporated. Ether was added and the insoluble PPh₃O and excess reagent filtered. Solvent was evaporated and the residue purified by column chromatography (silica gel, 12 % EtOAc/hexanes), to yield 0.7 g (6 % for 2 steps), of the *cis* ester and 8.5 g (75 % for 2 steps), of the *trans* ester 6 as a colorless syrup; $[\alpha]_D + 85^\circ$ (c 1.55, CHCl₃); IR (thin film) 1710, 1645, 1440, 1290, 1260, 1010 cm⁻¹;

¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.27 (m, 10H, ArH), 7.0 (dd, 1H, *J* = 5Hz, 16Hz, CHCH=), 6.13 (dd, 1H, *J* = 2Hz, =CHCO₂Me), 4.81 and 4.74 (AB quartet, 2H, *J* = 7Hz, OCH₂O), 4.64 and 4.56 (AB quartet, 2H, *J* = 12Hz, OCH₂Ph), 3.74 (s, 3H, OCH₃); ¹³C (CDCl₃, 75 MHz) δ 166.6, 147.1, 138.4, 138.3, 128.6, 128.3, 128.2, 127.9, 127.7, 127.3, 120.4, 91.9, 76.3, 69.7, 51.5; exact mass calculated for C₁₉H₂₁O₄ 313.143984, found 313.1433.

(3*R*, 4*R*)-4-(Benzyloxy-methoxy)-3-methyl-4-phenyl-butyric acid methyl ester (7):

Methyl lithium (116.6 mL, 1.4 M in ether, 163.2 mmol) was added to the -78°C suspension of 15.54 g (81.6 mmol) of CuI in 400 mL of anhydrous THF. The mixture was warmed to 0°C, held at that temperature for 10 min, and then re-cooled to -78°C. This mixture was treated with TMS-Cl (31 mL, 244.8 mmol) followed by a solution of the unsaturated ester 6 (8.49 g 27.2 mmol) in anhydrous THF (40 mL). The reaction was stirred at -78°C for 2 h and then quenched with 15 mL of 1:15 % aqueous NH₄OH and saturated aqueous NH₄Cl solution. The cooling bath was removed and the reaction allowed to warm to room temperature. Aqueous 10 % NH₄OH (50 mL) and ether (300 mL) were then added and the resulting mixture was stirred until a homogenous organic phase and a dark blue aqueous phase were obtained. The two layers were separated, the organic phase was washed with water, brine, dried over MgSO₄ and concentrated to yield an inseparable mixture of 7 as a 94:6 diastereomeric mixture and the deconjugated product (5 % by ¹H NMR). ¹H NMR (CDCl₃, 300 MHz) δ 7.39-7.23 (m, 10H, ArH), 4.68 and 4.46 (AB quartet, 2H, *J* = 12Hz, OCH₂O), 4.67 and 4.58 (AB quartet, 2H, *J* = 7Hz, OCH₂Ph), 4.42 (d, 1H, *J* = 8Hz, PhCHO), 3.67 (s, 3H, OCH₃), 2.73 (dd, 1H, *J* = 5Hz, 15Hz, one of CH₂CO₂CH₃), 2.42 (m, 1H, CHCH₃), 2.24 (dd, 1H, *J* = 9Hz, 15Hz, one of CH₂CO₂CH₃), 0.83 (d, 3H, *J* = 7Hz, CHCH₃); mass spectrum *m/e* 329 (M⁺ + H).

(4*R*, 5*R*)-4-Methyl-5-phenyl-dihydro-furan-2-one 8:

To the cooled (-23°C) solution of the unpurified ester 7 from the above reaction (8.55 g, theoretical yield 26.1 mmol) in 260 mL of anhydrous CH₂Cl₂ was added 10.3 mL (78.3 mmol) of TMS-Br and the solution was gradually allowed to warm to room temperature overnight. The reaction was diluted with more CH₂Cl₂ (100 mL), washed with saturated aqueous NaHCO₃ (2x 50 mL), water, brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (silica gel, 24 % EtOAc/hexanes), to yield 3.45 g 72 % for 2 steps) of 8 as a crystalline solid, mp 53-54°C; [α]_D²⁵ -4° (c 0.88, CHCl₃); IR

(CHCl₃) 1780, 1280, 1150, 1005 cm⁻¹; ¹H (CDCl₃, 300 MHz) δ 7.44-7.27 (m, 5H, ArH), 4.95 (d, 1H, J = 8Hz, PhCHO), 2.81 (dd, 1H, J = 7Hz, 17Hz, one of CH₂CO), 2.49 (m, 1H, CHCH₃); 2.3 (dd, 1H, J = 10Hz, 17Hz, one of CH₂CO), 1.21 (d, 3H, J = 6Hz, CHCH₃) ¹³C (CDCl₃, 75 MHz) δ 176.0, 137.8, 128.6, 125.8, 88.0, 39.7, 37.1, 16.3; exact mass calculated for C₁₁H₁₃O₂ 177.091555, found 177.0909.

(3R,4R)-4-Hydroxy-3-methyl-4-phenyl-butyric acid methyl ester 9:

To the cooled (0°C) solution of 2.43 g (13.8 mmol) of the lactone 8 in methanol (40 mL) was added 41 mL of 0.5 N aqueous NaOH. The reaction was warmed to room temperature and stirred for 2 h. Methanol was removed in vacuo and the residue diluted to 140 mL with water. The reaction mixture was cooled and the pH adjusted to 4 using 1N aqueous HCl. Solid NaCl was added and the mixture allowed to warm to room temperature. It was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine, dried over MgSO₄ and concentrated. The residue was dissolved in EtOAc and methylated with diazomethane in ether. Evaporation of the solvent afforded 2.82 g (98 %), of the hydroxy ester 9 which was used in the next step without further purification, IR (thin film) 3600-3260, 1740, 1725, 1460, 1170, 1020 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.37-7.27 (m, 5H, ArH), 4.43 (d, 1H, J = 7Hz, PhCHOH), 3.66 (s, 3H, OCH₃), 2.63 (dd, 1H, J = 5Hz, 15Hz, one of CH₂CO₂CH₃), 2.38 (br. s. 1H, OH), 2.36 (m, 1H, CHCH₃), 2.26 (dd, 1H, J = 8Hz, 15Hz, one of CH₂CO₂CH₃), 0.85 (d, 3H, J = 7Hz, CHCH₃); mass spectrum m/e 209 (M⁺ + H).

(3R,4R)-4-Azido-3-methyl-4-phenylbutyric acid methyl ester 10:

Triphenylphosphine (5.33 g, 20.3 mmol) was added to the solution of 2.82 g (13.56 mmol) of the hydroxyester 9 in 70 mL of anhydrous THF and cooled to 0°C. DEAD was added dropwise followed by the dropwise addition of (PhO)₂P(O)N₃. The reaction was gradually allowed to warm to room temperature overnight. THF was removed and the residue purified by column chromatography (silica gel, 12 % EtOAc/hexanes), to yield 2.8 g (89 %), of the azido ester 10 as a 96:4 diastereomeric mixture, [α]_D-164° (c 1.27, CHCl₃); IR (thin film) 2100, 1740, 1450, 1250, 1165 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.42-7.26 (m, 5H, ArH), 4.48 (d, 1H, J = 6Hz, PhCHN₃), 3.65 (s, 3H, OCH₃) 2.37 (m, 2H, CHCH₃, one of CH₂CO₂CH₃), 2.09 (dd, 1H, J = 10Hz, 17Hz one of CH₂CO₂CH₃), 0.99 (d, 3H, J = 6Hz, CHCH₃); ¹³C(CDCl₃, 75 MHz) δ 172.6, 137.9, 128.5, 128.1, 127.1, 10.2, 51.4, 37.9, 36.0, 15.6; exact mass calculated for C₁₂H₁₆N₃O₂ 234.124252, found 234.125.

(4*R*, 5*S*)-4-Methyl-5-phenyl-pyrrolidine-2-one 11:

To the solution of 2.5 g (10.73 mmol) of the azidoester 10 in methanol (55 mL) at room temperature, was added successively 14 mL (80.48 mmol) of *i*-Pr₂EtN and 5.39 mL (53.65 mmol) of 1,3-propanedithiol and stirred for 48 h. Methanol was removed in vacuo and the residue diluted with EtOAc. It was washed with 0.5 N aqueous NaOH (80 mL x 2), water, brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (silica gel, 25 % EtOAc/hexanes initially and then 20 % acetone/CHCl₃), to yield 1.62 g (86 %), of the lactam 11 as a colorless solid, mp 105-106°C; [α]_D²⁷ (c 1.055, CHCl₃); IR (CHCl₃) 3460, 1710, 1450, 1340 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.4-7.17 (m, 5H, ArH), 6.12 (br, s, 1H, NH), 4.79 (d, 1H, *J* = 8Hz, PhCHN), 2.86 (m, 1H, CHCH₃), 2.53 (dd, 1H, *J* = 8Hz, 17Hz, one of CH₂CO), 2.13 (dd, 1H, *J* = 8Hz, 17Hz, one of CH₂CO), 0.66 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 178.1, 138.6, 128.4, 127.7, 126.5, 61.5, 37.6, 34.2, 16.2; exact mass calculated for C₁₁H₁₃NO 175.09972, found 175.10029.

(2*S*,3*R*)-3-Methyl-5-oxo-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl 12:

To a solution of 1.37 g (7.83 mmol) of the lactam 11 in anhydrous CH₂Cl₂ (32 mL) was added successively the solution of 3.76 g (17.2 mmol) of di-tert-butyl dicarbonate in CH₂Cl₂ (5 mL), 3.4 mL (19.58 mmol) of *i*-Pr₂EtN and 96 mg (0.78 mmol) of DMAP and stirred at room temperature for 24 h. The initially colorless reaction mixture turned dark brown at the end of the reaction. Solvent was removed in vacuo and the residue purified by column chromatography (silica gel, 30 % EtOA/hexanes), to yield 2.12 g (99 %) of the compound 12 as a colorless solid, mp 74-75°C; [α]_D⁴ (c 0.835, CHCl₃); IR (CHCl₃) 1780, 1740, 1720, 1460, 1340, 1150 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.38-7.10 (m, 5H, ArH), 5.10 (d, 1H, *J* = 8Hz PhCHN), 2.75 (m, 1H, CHCH₃), 2.58 (dd, 1H, *J* = 8Hz, 17Hz, one of CH₂CO), 2.37 (dd, 1H, *J* = 12Hz, 17Hz, one of CH₂CO), 1.27 (s, 9H, C(CH₃)₃), 0.69 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C CDCl₃, 75 MHz) δ 174.3, 149.3, 137.0, 128.3, 127.6, 126.2, 82.5, 65.5, 38.8, 30.8, 27.5, 15.7; exact mass calculated for C₁₆H₂₁NO₃ 275.15213, found 275.15394.

(2*S*,3*R*,5*R*,5*S*)-5-Hydroxy-3-methyl-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 15a:

To a cooled (-78°C) solution of 1.1 g (4 mmol) of the compound 12 in 10 mL of anhydrous toluene was added DIBAL-H (4.4 mL, 1M in toluene, 4.4 mmol) dropwise and stirred for

4 h. Methanol (1.5 mL) was added and the reaction mixture stirred at -78°C for 30 min. The reaction mixture was warmed to room temperature and 50 mL of ether and a drop of water were added. The aluminum complex was filtered and solvent evaporated. The residue was purified by column chromatography (silica gel, 20 % EtOAc/hexanes), to yield 800 mg (72 %), of 15a as a mixture of nanomers and rotamers, 240 mg of the starting material. ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.2 (m, 16H, 4 x ArH), 7.02 (m, 4H, 4 x ArH), 5.94, 5.82 and 5.83-5.56 (m, 4H, 4 x CHOH), 4.89, 4.82, 4.74 (3 x d, 4H, $J = 8\text{Hz}$, PhCHN), 4.47, 3.74, 3.52 and 3.21 (4 x br, s, 4H, 4 x OH), 2.98-2.86 and 2.56-2.40 (2 x m, 4H, 4 x CHCH₃), 2.33-1.64 (m, 8Hz, 4 x CH₂CHOH), 1.2 and 1.18 (2 x s, 36H, 4 x C(CH₃)₃), 0.64 and 0.63 (2 x d, 12H $J = 7\text{Hz}$, 4 x CH₂CH₃); mass spectrum m/e 260 ($\text{M}^+ - \text{OH}$).

(2S,3R,5R,5S)-5-Methoxy-3-methyl-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 16a:

To the solution of 745 mg (2.69 mmol) of the hemiaminal 15a, in 20 mL of methanol was added 31 mg (0.133 mmol) of CSA and stirred at room temperature for 1 h. Et₃N (10 drops) was added and methanol removed under reduced pressure. The residue was purified by column chromatography (silica gel, 20 % EtOAc/hexanes), to yield 780 mg (100 %) of 16a as an anomeric and rotameric mixture of four isomers, ^1H NMR (CDCl_3 , 300 MHz) δ 7.33-7.21 (m, 12H, 4 x ArH), 7.02 and 7.0 (2 x d, $J = 8\text{Hz}$ 4 x ArH), 5.42 and 5.20 2 x d, 2H, $J = 5\text{Hz}$, 2 x CHOCH₃), 5.26 (br, s, 2H, 2 x CHOCH, 4.92 (br, s, 2H, 2 x PhCHN), 4.88 and 4.78 (2 x d, 2H, $J = 8\text{Hz}$, 2 x PhCHN), 3.54, 3.48 and 3.43 (3 x s, 12H, 4 x OCH₃), 2.93-1.63 (m, 12H, 4 x CHCH₃ and 4 x CH₂CHOHCH₃), 1.44 and 1.08 (2 x s, 36H, 4 x C(CH₃)₃), 0.67, 0.59 and 0.57 (3 x d, 12H, $J = 7\text{Hz}$, 4 x CHCH₃); mass spectrum m/e 290 ($\text{M}^+ - \text{H}$).

(2S,2'S,3R,5S)-3-Methyl-5-oxo-(5'-oxo-2',5'-dihydro-furan -2-yl)-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 17a:

To a cooled (-78°C) solution of 740 mg (2.54 mmol) of 16a in 26 mL of anhydrous CH₂Cl₂ was added successively 0.64 mL (3.81 mmol) of 2-(trimethylsiloxy)-furan and 0.19 mL (1.52 mmol) of BF₃.Et₂O and the solution was stirred for 1 h. The reaction mixture was quenched with 10 mL of 2 N aqueous HCl and warmed to room temperature. The mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄ and concentrated to yield 860 mg (98 %), of a 6:1 (by ^1H NMR) of threo:erythro isomers. The pure threo isomer 17a was obtained, as a mixture of rotamers, by fractional crystallization from 30 %

EtOAc/hexanes, mp 150-151°C; $[\alpha]_D^{25}$ -188° (c 1.115, CHCl₃); IR (CHCl₃) 1755, 1685, 1450, 1370, 1165, 1085 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.68 and 7.58 (2 x dd, 2H, *J* = 2Hz, 2 x OCHCH=), 7.31-7.17 (m, 6H, 2 x ArH), 7.0 and 6.97 (2 x d, 4H, *J* = 7Hz, 2 x ArH), 6.24 and 6.08 (2 x dd, 2H, *J* = 2Hz, 6Hz, 2 x CH-CHCO), 5.55 (dt, 1H, *J* = 2Hz, 4Hz, CHO), 5.40 (dt, 1H, *J* = 2Hz, 3Hz, CHO), 4.88 and 4.71 (2 x d, 2H, *J* = 8Hz, 2 x PhCHN), 4.66 (dt, 1H, *J* = 3Hz, 4Hz, CHN), 4.62 (m, 1H, CHN), 2.77 and 2.35 (2 x m, 2H, CHCH₃), 2.05-1.83 (m, 2H, CH₂CHN), 1.76 (dd, 1H, *J* = 8Hz, 13Hz, one of CH₂CHN), 1.60 (dd, 1H, *J* = 7Hz, 13Hz, one of CH₂CHN), 1.44 and 1.02 (2 x s, 18H, 2 x C(CH₃)₃), 0.55 and 0.53 (2 x d, 6H, *J* = 7Hz, 2 x CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 173.1, 154.8, 154.7, 141.2, 127.8, 126.7, 126.3, 120.3, 84.7, 79.7, 66.7, 58.0, 36.1, 32.5, 27.5, 15.3; exact mass calculated for C₂₀H₂₆NO₄ 344.18619, found 344.1867.

(2*S*,2'*S*,3*R*,5*S*)-3-Methyl-5-(5'-oxo-tetrahydro-furan-2'-yl)-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 18a:

To the solution of 250 mg (0.73 mmol) of 17a in 3 mL of EtOAc was added 30 mg of 10 % Pd/C and the mixture was stirred under a H₂ atmosphere for 1 h. The catalyst was filtered through a pad of celite and the solvent evaporated to yield 230 mg (93 %), of 18a as a mixture of two rotamers, mp 123-125°C; $[\alpha]_D^{25}$ -49.6° (1.015, CHCl₃); IR (CHCl₃) 1760, 1675, 1400, 1350, 1150 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.31 and 7.21 (m, 6H, 2 x ArH), 7.0 (d, 4H, *J* = 8Hz, 2 x ArH), 4.80 (dt, 2H, *J* = 3Hz, 7Hz, 2 x CHO), 4.91 and 4.76 (2 x d, 2H, *J* = 8Hz, 2 x PhCHN), 4.53 (dd, 1H, *J* = 3Hz, 7Hz, CHN), 4.41 (t, 1H, *J* = 7Hz, CHN), 2.86 (m 1H, CHCH₃), 2.68-2.22 (m, 4H, CH₂CH₂CO), 1.96-1.90 (m, 2H, CH₂CHN), 2.86-1.79 (m, 7H, CHCH₃, CH₂CH₂CO, CH₂CHN), 1.42 and 1.05 (2 x s, 18H, 2 x C(CH₃)₃), 0.58 and 0.56 (2 x d, 6H, *J* = 7Hz, 2 x CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 177.0, 155.3, 141.5, 127.7, 126.5, 126.2, 82.4, 79.4, 67.0, 58.7, 35.9, 33.4, 28.3, 27.5, 24.6, 15.4; exact mass calculated for C₂₀H₂₆NO₄ 346.20184, found 346.20230.

(2*S*,2'*S*,3*R*,4'*R*,5*S*)-3-Methyl-5-(4'-methyl-5'-oxo-tetrahydro-furan-2'-yl)-2-phenyl-pyrrolidine-1-carboxylic acid tert-butyl ester 19a:

To a cooled (-78°C) solution of (TMS)₂NLi (0.27 mL, 1M in THF, 0.27 mmol) was added the solution of 18a (85 mg, 0.25 mmol) in 1 mL of anhydrous THF over a period of 3 min. via canula and the solution was stirred for 40 min. MeI (0.16 mL, 2.5 mmol) was added and the solution was stirred at -78°C for 90 min. after which the reaction mixture was warmed to

-50°C and stirred for another 1 h. The reaction mixture was quenched with a solution of AcOH (0.15 mL) in 0.4 mL anhydrous THF and allowed to warm to temperature, then diluted with EtOAc, washed with water, brine, dried over MgSO₄ and concentrated. Purification of the residue by column chromatography (silica gel, 25 % EtOAc/hexanes), afforded, 14 mg (15 %) of the dimethylated lactone and 59 mg (67 %), of the monomethylated product 19a as a mixture of rotamers, mp 143-144°C; [α]_D-31.7° (c 0.85, CHCl₃); IR (CHCl₃) 1750, 1680, 1440, 1355, 1150, 1000 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.31-7.18 (m, 6H, 2 x ArH), 7.0 and 6.98 (2 x d, 4H, *J* = 7Hz, 2 x ArH), 4.91 and 4.73 (2 x d, 2H, *J* = 8Hz, 1 x PhCHN), 4.65 (dt, 1H, *J* = 4Hz, 7Hz, CHO), 4.59 (dt, 1H, *J* = 4Hz, 8Hz, CHO), 4.5 (dd, 1H, *J* = 4Hz, 8Hz, CHN), 4.32 (t, 1H, *J* = 8Hz, CHN), 2.94-2.62 (m, 5H, 2 x CHCH₃CO, one of OCHCH₂CHCH₃), 2.62-2.29 (m, 1H, one of OCHCH₂), 2.03-1.81 (m, 5H, 3 x one of CH₂CHN, 2 x one of the OCHCH₂), 1.70 (dd, 1H, *J* = 6Hz, 13Hz, one of CH₂N), 1.31 and 1.27 (2 x d, 6H, *J* = 7Hz, CHCH₃CO), 1.39 and 1.03 (2 x s, 18H, 2 x C(CH₃)₃), 0.54 and 0.57 (2 x d, 6H, *J* = 7Hz, 2 x CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 180.2, 155.6, 141.7, 128.0, 127.8, 126.6, 126.4, 80.8, 79.6, 67.2, 59.3, 35.9, 35.1, 34.2, 33.7, 33.3, 32.7, 28.0, 27.6, 16.0, 15.5; exact mass calculated for C₂₁H₃₀NO₄ 360.2175, found 360.2159.

(1'S,2S,3R,3'R,5S)-5-(3'-Butylcarbamoyl-1'-hydroxy-butyl)-3-methyl-2-phenyl-pyrrolidine-1--carboxylic acid tert-butyl ester 2a:

To the solution of 56 mg (0.156 mmol) of 19a in 0.9 mL of anhydrous CH₂Cl₂ was added BuNHAME₂ (0.28 mL, 0.67 M in CH₂Cl₂, 0.23 mmol) and stirred at room temperature for 7 h. The reaction mixture was cooled to 0°C and quenched with 2 mL of 1 N aqueous HCl, then diluted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated. Purification of the residue by column chromatography (silica gel, 10 % acetone/CHCl₃), afforded 51 mg (76 %), of the amide 2a as a syrup. [α]_D-79.9° (c 1.015 CHCl₃); IR (CHCl₃) 3480, 3500-3300, 1665, 1465, 1415, 1155 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.30-7.19 (m, 3H, ArH), 6.98 (d, 2H, *J* = 7Hz, ArH), 6.0 (br, t, 1H, *J* = 5Hz, NH), 4.78 (d, 1H *J* = 6Hz, OH), 4.71 (d, 1H, *J* = 8Hz, PhCHN), 4.12 (t, 1H, *J* = 8Hz, CHN), 3.50 (m, 1H, CHOH), 3.35-3.15 (m, 2H, CH₂NH), 2.74-2.49 (m, 2H, CHCH₃, CHCH₃CO), 1.94-1.70 (m, 3H), 1.54-1.21 (m, 5H), 1.17 (d, 3H, *J* = 7Hz, CHCH₃CO), 1.06 (s, 9H, C(CH₃)₃), 0.93 (t, 3H, *J* = 7Hz, CH₂CH₃), 0.55 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 176.1, 158.0, 141.0, 127.8, 126.6, 80.3, 74.5, 63.4, 40.9, 38.9, 37.1, 35.7, 32.9, 31.7, 27.7, 20.0, 18.5, 15.0, 13.7; mass spectrum *m/e* 433 (M⁺ + H).

(2*R*,4*S*,5*S*,7*R*)-5-[[1,1-Dimethylethoxy)carbonyl]amino]-4-hydroxy-2,7-dimethyl-8-phenyl-octanoic acid butyl amide 3a:

To the solution of 40 mg (0.93 mmol) of the amide 2a in 1 mL of 40 % EtOH/EtOAc was added 10 mg of Pearlmen's catalyst (20 % Pd(OH)₂/c) and the suspension was stirred under 56 psi H₂ pressure for 2 days. The catalyst was filtered and the solvent evaporated. Purification of the residue using PTLC (10 % acetone/CHCl₃), afforded 4 mg of the starting material and 29 mg (73 %) of 3, mp 83-84°C; [α]_D-17.1° (c 1.47 CHCl₃), IR (CHCl₃); 3460, 3400-3300, 1710, 1660, 1500, 1370, 1170 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.29-7.15 (m, 5H, ArH), 5.82 (br, s, CH₂NH), 4.75 (d, 1H, *J* = 8Hz, NHBoc), 3.72-3.61 (m, 2H, CHOH, CHNHBoc), 3.33-3.17 (m, 2H, CH₂N), 2.86 (dd, 1H, *J* = 5Hz, one of PhCH₂), 2.55 (m, 1H, CHCH₃CO), 2.26 (dd, 1H, *J* = 9Hz, 13Hz, one of PhCH₂), 1.80 (m, 1H, CHCH₃), 1.68 (t, 2H, *J* = 6Hz), 1.55-1.23 (m, 6H), 1.47 (s, 9H, C(CH₃)₃), 1.20 (d, 3H, *J* = 7Hz, CHCH₃CO), 0.93 (t, 3H, *J* = 7Hz CH₂CH₃), 0.87 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 176.8, 156.4, 141.1, 129.1, 127.9, 125.6, 79.1, 70.1, 52.1, 42.6, 40.0, 39.1, 38.4, 37.6, 31.9, 31.6, 28.3, 19.9, 19.8, 17.0, 13.6; mass spectrum *m/e* 435 (M⁺ + H).

(3*R*,4*S*)-4-Azido-3-methyl-4-phenyl-butyraldehyde 13:

To a cooled (-78°C) solution of 820 g (3.52 mmol) of the compound 10 in 35 mL of anhydrous toluene was added DIBAL-H (3.9 mL, 1 M in toluene, 3.9 mmol) dropwise via canula over a period of 15 min and was stirred for another 45 min. Methanol (0.43 mL, 10.6 mmol) was added and the reaction mixture stirred at -78°C for 20 min. The reaction mixture was allowed to warm to room temperature and ether and a drop of water were added. The aluminum complex was filtered and solvent evaporated. The residue was purified by column chromatography (silica gel, 1 % Et₃N, 14 % EtOAc, 85 % hexanes), to yield 550 mg (77 %) of 13, [α]_D-205° (c 1.33, CHCl₃); IR (thin film) 2100, 1730, 1450, 1245 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 9.66 (s, 1H, CHO), 7.4-7.26 (m, 5H, ArH), 4.46 (d, 1H, *J* = 7Hz, PhCHN₃), 2.48 (m, 2H, CHCH₃, one of CH₂CHO), 2.22 (dd, 1H, *J* = 9Hz, 18Hz one of CH₂CHO), 1.02 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 200.9, 137.7, 128.7, 128.3, 128.2, 70.4, 47.4, 33.9, 16.1; mass spectrum *m/e* 103 (M⁺).

(2*S*,3*R*)-3-Methyl-2-phenyl-4-dihydro 2H-pyrrole 14:

Triphenylphosphine (750 mg, 2.86 mmol) was added to the solution of 527 mg (2.6 mmol) of the azidoaldehyde 13 in 36 mL of anhydrous toluene and stirred for 16 h when the reaction was judged complete by the examination. The above was used in the next step.

(2*S*,3*R*,5*R*,5*S*)-5-Hydroxy-3-methyl-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester 15b:

To the above solution of the imine in toluene at -78°C was added benzyl chloroformate (0.37 mL, 2.6 mmol) and stirred for 1 h. The reaction was quenched by adding 2 N aqueous HCl and allowed to warm to room temperature. The reaction mixture was diluted with EtOAc, washed with unsaturated brine, and brine, dried over MgSO₄ and concentrated. The residue was purified by column chromatography (silica gel, 1 % Et₃N, 29 % EtOAc, 70 % hexanes), to yield 541 mg (67 % for 2 steps) of the hemiaminal 15a as an anomeric and rotameric mixture, ¹H NMR (CDCl₃, 300 MHz) δ 7.4-7.16 (m, 18H, 2 x ArH), 7.37-7.02 (m, 18H, 2 x ArH), 6.9-6.87 (m 2H, 2 x ArH), 6.80 (d, 2H, *J* = 7Hz, 2 x ArH), 5.86 and 5.77 (2 x d, 2H, *J* = 6Hz, 5Hz, 2 x CHOH), 5.68 (t, 2H, *J* = 7Hz, 2 x CHOH), 5.21 and 5.12; 5.08 and 4.98 (2 x AB quartet, 4H, *J* = 13Hz, 2 x CO₂CH₂Ph), 5.22 and 5.11; 5.07 and 4.93 (2 x AB quartet, 4H, *J* = 13Hz, 2 x CO₂CH₂Ph), 4.98 and 4.96 (2 x d, 2H, *J* = 9Hz, 2 x PhCHN), 4.95 and 4.88 (2 x d, 2H, *J* = 8Hz, PhCHN), 4.38, 4.0, 3.52 and 3.26 (4 x br, s, 4H, 4 x OH), 2.96 and 2.51 (2 x m, 4H, CHCH₃), 2.30, 1.73 and 1.99-1.75 (3 x m, 8H, 4 x CH₂CHOH), 0.65, 0.64 and 0.63 (3 x d, 12H, *J* = 7Hz, 4 x CHCH₃); mass spectrum (*m/e*) 310 (M⁺-H).

(2*S*,3*R*,5*R*,5*S*)-5-Methoxy-3-methyl-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester 16b:

To the solution of 540 mg (1.74 mmol) of the hemiaminal 15b, in 9 mL of methanol was added 18 mg (0.078 mmol) of CSA and stirred at room temperature for 1 h. Et₃N (10 drops) was added and methanol removed under reduced pressure. The residue was purified by column chromatography (silica gel, 20 % EtOAc/hexanes), to yield 502 mg (89 %) of 16b as a mixture of anomers and rotamers, ¹H NMR (CDCl₃, 300 MHz) δ 7.37-6.98 (m, 36H, 4 x ArH) 6.82 and 6.6 (2 x d, 4H, *J* = 7Hz, 4 x ArH), 5.46 and 5.30 (2 x d, 2H, *J* = 5Hz, CHOCH₃), 5.34 (br, s, 2H, 2 x CHOCH₃), 5.18 and 5.08; 5.02 and 4.82 (2 x AB quartet, 8H, *J* = 13Hz, 4 x CO₂CH₂Ph), 4.96 and 4.91 (2 x d, 4H, *J* = 7Hz, 4 x PhCHN), 3.56 (br, s, 3H, OCH₃), 3.52, 3.50 and 3.53 (3 x s, 9H, 3 x OCH₃), 2.99-1.66 (m, 12H, 4 x CHCH₃, 4 x CH₂CHOCH₃), 0.68 and 0.61 (2 x d, 12H, *J* = 7Hz, 4 x CHCH₃); mass spectrum *m/e* 324 (M⁺-H).

(2*S*,2'*S*,3*R*,5*S*)-3-Methyl-5-oxo-5'-oxo-2',5'-dihydro-furan-2-yl)-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester 17b:

To a cooled (-78°C) solution of 500 mg (1.54 mmol) of 16b in 15 mL of anhydrous CH₂Cl₂ was added successively 0.38 mL (2.31 mmol) of 2-(trimethylsiloxy)-furan and 0.11 mL (0.92 mmol) of BF₃·Et₂O and the solution was stirred for 2 h. The reaction mixture was quenched with 5 mL of 2 N aqueous HCl and warmed to room temperature. The mixture was diluted with EtOAc, washed with water, brine, dried over MgSO₄ and concentrated to yield 452 mg (78 %) of a 5:1 (by ¹H NMR) of threo:erythro isomers. The pure threo isomer 17b was obtained, as a mixture of rotamers, by fractional crystallization from EtOAc/hexanes, mp 157-158°C; [α]_D²⁰ -168° (c 1.02, CHCl₃); IR (thin film) 1750, 1690, 1390, 1330, 1010 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 7.67 (dd, 2H, *J* = 2Hz, 6Hz, 2 x OCHCH=), 7.41-6.94 (m, 16H, 2 x ArH), 6.6 (d, 4H, *J* = 7Hz, 2 x ArH), 6.08 (dd, 2H, *J* = 2Hz, 2 x CH=CHCO), 5.48 (dt, 2H, *J* = 2Hz, 5Hz, 2 x CHO), 5.16 and 5.07; 4.89 and 4.75 (2 x AB quartet, 4H, *J* = 13Hz, 2 x CO₂CH₂Ph), 4.93 and 4.84 (2 x d, 2H, *J* = 8Hz, 2 x PhCHN), 4.71 (dd, 2H, *J* = 2Hz, 5Hz, 2 x CHN), 2.74 and 2.45 (2 x m, 2H, 2 x CHCH₃), 1.92-1.61 (m, 4H, 2 x CH₂CHN), 0.55 and 0.53 (2 x d, 6H, *J* = 7Hz, 2 x CHCH₃); ¹³C (CDCl₃, 75 MHz) δ 173.0, 154.4, 140.3, 135.7, 128.6, 128.3, 128.2, 128.0, 127.5, 127.2, 127.1, 127.0, 126.1, 120.8, 66.9, 66.4, 58.6, 36.3, 32.2, 15.2; exact mass calculated for C₂₃H₂₃NO₄ 378.170534, found 378.1681.

(2*S*,2'*S*,3*R*,4*S*)-3-Methyl-5-(5'-oxo-tetrahydro-furan-2'-yl)-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester 18b:

To the solution of 210 mg (0.56 mmol) of 17b in 4 mL of benzene was added 20 mg of 5 % Pt/C and the mixture was stirred under a H₂ atmosphere for 1 h. The catalyst was filtered through a pad of celite and the solvent evaporated to yield 190 mg (90 %), of a rotameric mixture of 18b as a syrup, [α]_D²⁰ -52° (0.86, CHCl₃); IR (thin film) 1780, 1700, 1400, 1340, 1160 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 7.33-6.96 (m, 16H, 2 x ArH), 6.66 (d, 4H, *J* = 7Hz, 2 x ArH), 5.1 (AB quartet, 2H, *J* = 12Hz, CO₂CH₂Ph), 4.97 (d, 1H, *J* = 8Hz, PhCHN), 4.90-4.68 (m, 5H, 2 x OCH, PhCHN, CO₂CH₂Ph), 4.58 (m, 1H, CHN), 4.48 (t, 1H, *J* = 7Hz, CHN), 2.88-1.83 (m, 14H), 0.58 and 0.57 (2 x d, 6H, *J* = 7Hz, CHCH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 176.9, 156.0, 140.6, 135.8, 128.2, 128.0, 127.4, 127.3, 126.9, 126.2, 81.8, 66.9, 66.6, 59.3, 36.3, 32.9, 28.5, 24.7, 15.5; exact mass calculated for C₂₃H₂₆NO₄ 380.186184, found 380.1822.

(2*S*,2'*S*,3*R*,4'*R*,5*S*)-3-Methyl-5-(4'-methyl-5'-oxo-tetrahydro-furan 2'-yl)-2-phenyl-pyrrolidine-1-carboxylic acid benzyl ester 19b:

To a cooled (-78°C) solution of (TMS)₂NLi (0.24 mL, 1M in hexanes, 0.24 mmol) in 0.24 mL of anhydrous THF, was added MeI (0.14 mL, 2.19 mmol) followed by the solution of 18b (79 mg, 0.21 mmol) in 1 mL of anhydrous THF and the solution was stirred for 40 min. The reaction mixture was quenched with a saturated aqueous NaHCO₃ solution and allowed to warm to room temperature, then diluted with EtOAc, washed with water, brine, dried over MgSO₄ and concentrated. Purification of the residue by column chromatography (silica gel, 35 % EtOAc/hexanes), afforded 46 mg (56 %), of the monomethylated product 19b as a mixture of rotamers, [α]_D²⁰ (c 1.43, CHCl₃); IR (thin film) 1755, 1675, 1440, 1390, 1225 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 7.39-6.95 (m, 16H, 2 x ArH), 6.65 (d, 4H, *J* = 7Hz, 2 x ArH), 5.07 and 4.82 (2 x AB quartet, 4H, *J* = 12Hz, 2 x CO₂CH₂Ph), 4.97 and 4.87 (2 x d, 2H, *J* = 8Hz, 2 x PhCHN), 4.71 and 4.62 (2 x m, 2H, 2 x CHO), 4.53 (dd, 1H, *J* = 5Hz, CHN), 4.4 (t, 1H, *J* = 7Hz, CHN), 2.9-1.7 (m, 12H), 1.27 and 1.18 (2 x d, 6H *J* x CHCH₃CO), 0.57 and 0.55 (2 x d, 6H, *J* = 7Hz, 2 x CHCH₃); ¹³C NMR (CDCl₃, 75 MHz) δ 179.9, 156.1, 140.6, 135.8, 128.2, 128.0, 127.4, 126.8, 126.1, 80.0, 66.9, 66.6, 59.8, 36.1 33.6, 33.5, 33.1, 15.9, 15.4; exact mass calculated for C₂₄H₂₈NO₄ 394.201834, found 394.20260.

(1'*S*,2*S*,3*R*,3'*R*,5*S*)-5-(3'-Butylcarbamoyl)-1'-hydroxy-butyl)-3-methyl -2-phenyl-pyrrolidine-1-carboxylic acidbenzyl ester 2b:

To the solution of 45 mg (0.11 mmol) of 19b in 0.5 mL of anhydrous CH₂Cl₂ was added BuNHAlMe₂, (0.33 mL, 0.67 M in CH₂Cl₂, 0.22 mmol) and stirred at room temperature for 2 h. The reaction mixture was cooled to 0°C and quenched with 2 mL of 1 N aqueous HCl, then diluted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated.

Purification of the residue by PTLC (10 % acetone/CHCl₃), afforded 22 mg (52 %), of the amide 2b as a syrup, [α]_D²⁰ (c 0.99, CHCl₃); IR (thin film) 3500-3300, 1710, 1670, 1550, 1410, 1340 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz), δ 7.4-6.96 (m, 8H, ArH), 6.63 (d, 2H, *J* = 7Hz, ArH), 5.9 (br, s, 1H, NH), 4.85 (d, 1H, *J* = 7Hz, PhCHN), 4.89 (AB quartet, 2H, *J* = 13Hz, CO₂CH₂Ph), 4.63 (br, s, 1H, OH), 4.17 (dt, 1H, *J* = 2Hz, 9Hz, CHN), 3.56 (dt, 1H, *J* = 2Hz, 9Hz, CHOH), 3.36-3.17 (m, 2H, CH₂NH), 2.75-2.51 (m, 2H, CHCH₃, CHCH₃CO), 1.96-1.72 (m, 3H), 1.55-1.23 (m, 5H), 1.19 (d, 3H, *J* = 7Hz, CHCH₃CO), 0.93 (t, 3H, *J* = 7Hz, CH₂CH₃), 0.57 (d, 3H, *J* = 7Hz, CHCH₃); ¹³C (CDCl₃), 75 MHz) δ 176.0, 158.3, 140.2, 135.8, 128.1,

128.0, 127.4, 127.0, 126.9, 126.3, 74.3, 67.2, 66.2, 64.0, 40.6, 38.9, 37.1, 20.0, 18.4, 14.9, 13.6; exact mass calculated for $C_{28}H_{39}N_2O_4$ 467.290983, found 467.2925.

(2*R*,4*S*,5*S*,7*F*)-5-[[1,1-Dimethylethoxy)carbonyl]amino]-4-hydroxy-2,7-dimethyl-8-phenyl-octanoic acid butyl amide 3a:

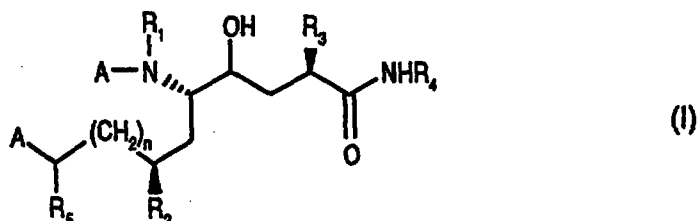
To the mixture of 15 mg (0.023 mmol) of the amide 2b and 28 mg (0.129 mmol) of di-tert-butylidicarbonate in 0.5 mL of 40 mL of 40 % MeOH/EtOAc was added 15 mg of Pearlman's catalyst (20 % $Pd(OH)_2/C$) and the suspension was stirred under 60 psi H_2 pressure for 3 days. The catalyst was filtered and the solvent evaporated. Purification of the residue using PTLC (10 % acetone/ $CHCl_3$), 6.4 mg (46%), of 3a identical to the sample obtained from the hydrogenolysis of the amide 2a.

As those skilled in the art would realize these preferred described details and processes can be subjected to substantial variation, modification, change, alternation, and substitution without affecting or modifying the function of the described embodiments. Although embodiments of the invention have been described above, it is not limited thereto, and it will be apparent to persons skilled in the art that numerous modifications and variations form part of the present invention insofar as they do not depart from the spirit, nature and scope of the claimed and described invention.



CLAIMS:

1. A process of preparation of a first compound having the formula I

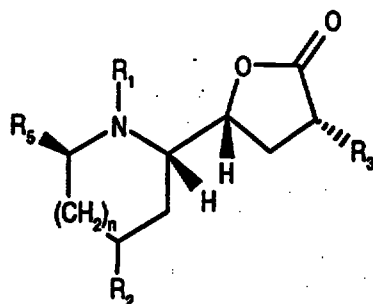


where n is 0-3 inclusive, A are either both hydrogen atoms or together are a single carbon-nitrogen bond, R₁ is hydrogen, or hydrocarbylcarboxy wherein the hydrocarbyl entity is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R₂ and R₃ or independently alkyl of 1 to 4 carbon atoms, R₄ is alkyl of 1 to 6 carbon atoms or a substituent of aliphatic character such as, for example, butyl, 2-morpholinoethyl or 2-carbamoyl-2-methyl-propyl, R₅ is selected from aromatics, substituted aromatics and heteroaromatics, substituted or unsubstituted cycloalkyls, cycloalkenes having 3 to 8 carbon atoms, with substituents selected from alkyl, alkoxy of 3 to 10 carbon atoms and alkoxy derivatives such as 3-methoxy-propyloxy, primary and secondary amides, alkyl derivatives, comprising a step selected from the group consisting of

(a) hydrogenolysis of a second compound of the above formula wherein both A together form a single carbon nitrogen bond and R₁ is alkylcarboxy wherein said alkyl has 1 to 6 carbon atoms, in the presence of Pd(OH)₂/C;

(b) hydrogenolysis of a third compound of the above formula wherein both A together form a single carbon nitrogen bond and R₁ is aralkylcarboxy wherein said aralkyl has 7 to 10 carbon atoms, in the presence of Pd(OH)₂/C, and dialkyl dicarbonate wherein both said dicarbonate alkyl groups are identical and have 1 to 6 carbon atoms;

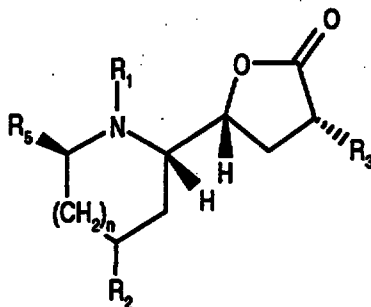
(c) treating a fourth compound having the structure



(II)

where n is 0-3 inclusive, R₁ is hydrocarbylcarboxy wherein said hydrocarbyl is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R₂ and R₃ are independently alkyl of 1 to 4 carbon atoms, with R₄NHAlMe₂ where R₄ is alkyl of 1 to 6 carbon atoms.

2. The process of claim 1, where n is zero, in both formulae.
3. The process of claim 2, comprising the step of hydrogenolysis of said second compound.
4. The process of claim 1, comprising the step of hydrogenolysis of said third compound.
5. The process of claim 1, comprising the step of treating said fourth compound.
6. The process of claim 5, wherein R₁ is alkylcarboxy, said alkyl group having 1 to 6 carbon atoms.
7. The process of claim 5, wherein R₁ is aralkylcarboxy, said aralkyl having 7 to 10 carbon atoms.
8. A compound of the formula compound having the structure

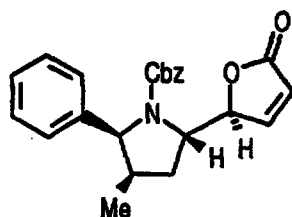


(II)



where n is 0-3 inclusive, R_1 is hydrocarbylcarboxy wherein said hydrocarbyl is selected from the group consisting of alkyl of 1 to 6 carbon atoms or aralkyl of 7 to 10 carbon atoms, R_2 and R_3 are independently alkyl of 1 to 4 carbon atoms, and R_5 is selected from aromatics, substituted aromatics and heteroaromatics, substituted or unsubstituted cycloalkyls, cycloalkenes having 3 to 8 carbon atoms, with substituents selected from alkyl, alkoxy of 3 to 10 carbon atoms alkoxy derivatives alkoxy of 3 to 10 carbon atoms such as 3-methoxypropyloxy, primary and secondary amides and alkyl derivatives, or a salt thereof.

9. A compounds according to claim 8 having the formula



10. A compounds according to claim 8 having the formula

