

Description

1,4-Benzothiazepine-1,1-dioxide derivatives substituted by sugar residues,
process for their preparation, pharmaceuticals comprising these
5 compounds, and their use

The invention relates to substituted 1,4-benzothiazepine-1,1-dioxide
derivatives, their physiologically tolerable salts and physiologically
functional derivatives.

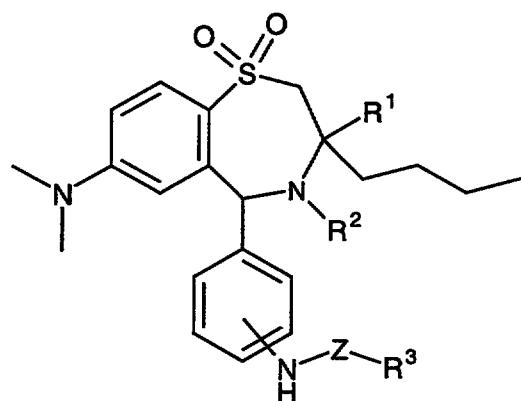
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1,4-Benzothiazepine-1,1-dioxide derivates and their use for the treatment
of hyperlipidemia and also arteriosclerosis and hypercholesterolemia have
already been described [cf. PCT Application No. PCT/GB 95/01884,
Publication No. WO 96/05188].

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The invention is based on the object of making available further
compounds which display a therapeutically valuable hypolipidemic action.
In particular, the object consists in finding novel compounds which cause a
higher excretion of bile acid, even at a lower dosage, compared with the
20 compounds described in the prior art.

The invention therefore relates to compounds of the formula I



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in which

R¹ is methyl, ethyl, propyl, butyl;

30 R² is H, OH;

R^3 is a sugar residue, disugar residue, trisugar residue, tetrasugar residue, the sugar residue, disugar residue, trisugar residue or tetrasugar residue optionally being mono- or polysubstituted by a sugar protective group;

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Z is $-(C=O)_n-C_0-C_{16}-alkyl-$, $-(C=O)_n-C_0-C_{16}-alkyl-NH-$, $-(C=O)_n-C_0-C_{16}-alkyl-O-$, $-(C=O)_n-C_1-C_{16}-alkyl-(C=O)_m$, a covalent bond;

10 n is 0 or 1;

m is 0 or 1;

15 and their pharmaceutically tolerable salts and physiologically functional derivatives.

Preferred compounds of the formula I are those in which one or more radical(s) has or have the following meaning:

20 R^1 is ethyl, propyl, butyl;

R^2 is H, OH;

25 R^3 is a sugar residue, disugar residue, the sugar residue or disugar residue optionally being mono- or polysubstituted by a sugar protective group;

30 Z is $-(C=O)_n-C_0-C_{16}-alkyl-$, $-(C=O)_n-C_0-C_{16}-alkyl-NH-$, $-(C=O)_n-C_0-C_{16}-alkyl-O-$, $-(C=O)_n-C_1-C_{16}-alkyl-(C=O)_m$, a covalent bond;

n is 0 or 1;

m is 0 or 1;

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and their pharmaceutically tolerable salts.

Particularly preferred compounds of the formula I are those in which one or more radical(s) has or have the following meaning:

R^1 is ethyl, butyl;

R^2 is H, OH;

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R^3 is a sugar residue, the sugar residue optionally being mono- or polysubstituted by a sugar protective group;

Z is $-(C=O)-C_0-C_4$ -alkyl, a covalent bond;

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and their pharmaceutically tolerable salts.

On account of their higher water solubility compared with the starting or base compounds, pharmaceutically tolerable salts are particularly suitable for medicinal applications. These salts must have a pharmaceutically tolerable anion or cation. Suitable pharmaceutically tolerable acid addition salts of the compounds according to the invention are salts of inorganic acids, such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric, sulfonic and sulfuric acids and also organic acids, such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isothionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic, tartaric and trifluoroacetic acids. For medicinal purposes, the chlorine salt is particularly preferably used. Suitable pharmaceutically tolerable basic salts are ammonium salts, alkali metal salts (such as sodium and potassium salts) and alkaline earth metal salts (such as magnesium and calcium salts).

Salts with a nonpharmaceutically tolerable anion are likewise included in the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically tolerable salts and/or for use in nontherapeutic, for example in-vitro, applications.

The term "physiologically functional derivative" used here designates any physiologically tolerable derivative of a compound according to the invention, e.g. an ester which on administration to a mammal, such as, for example, man, is able (directly or indirectly) to form such a compound or an active metabolite thereof.

A further aspect of this invention is prodrugs of the compounds according to the invention. Such prodrugs can be metabolized in vivo to give a compound according to the invention. These prodrugs can themselves be active or inactive.

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The compounds according to the invention can also be present in various polymorphic forms, e.g. as amorphous and crystalline polymorphic forms. All polymorphic forms of the compounds according to the invention are included in the scope of the invention and are a further aspect of the

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Below, all references to "compound(s) according to formula (I)" relate to compound(s) of the formula (I) as described above, and to their salts, solvates and physiologically functional derivatives as described herein.

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The amount of a compound according to formula (I) which is necessary in order to achieve the desired biological effect is dependent on a number of factors, e.g. the chosen specific compound, the intended use, the manner of administration and the clinical condition of the patient. In general, the daily dose lies in the range from 0.1 mg to 100 mg (typically from 0.1 mg and 50 mg) per day per kilogram of body weight, e.g. 0.1-10 mg/kg/day. Tablets or capsules can contain, for example, from 0.01 to 100 mg, typically from 0.02 to 50 mg. In the case of pharmaceutically tolerable salts, the abovementioned weight data relate to the weight of the

25 benzothiazepine ion derived from the salt. For the prophylaxis or therapy of the abovementioned conditions, the compounds according to formula (I) can be used themselves as the compound, but they are preferably present with a tolerable carrier in the form of a pharmaceutical composition. The carrier must of course be tolerable, in the sense that it is compatible with

30 the other constituents of the composition and is not harmful to the health of the patient. The carrier can be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet, which can contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances can likewise be

35 present, including further compounds according to formula (I). The pharmaceutical compositions according to the invention can be prepared by one of the known pharmaceutical methods, which essentially consist in mixing the constituents with pharmacologically tolerable carriers and/or excipients.

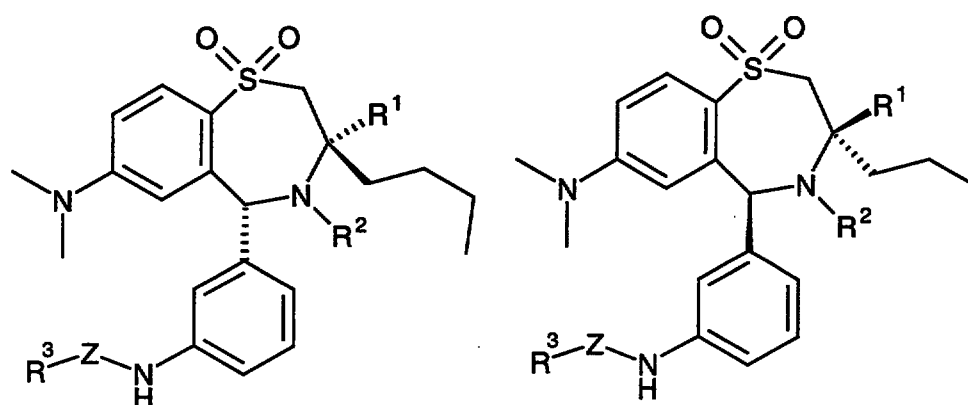
Pharmaceutical compositions according to the invention are those which are suitable for oral and peroral (e.g. sublingual) administration, even if the most suitable manner of administration in each individual case is dependent on the nature and the severity of the condition to be treated and on the type of the compound according to formula (I) used in each case. Sugar-coated formulations and sugar-coated sustained release formulations are also included in the scope of the invention. Acid-resistant and enteric formulations are preferred. Suitable enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration can be present in separate units, such as, for example, capsules, cachets, lozenges or tablets, which in each case contain a certain amount of the compound according to formula (I); as powders or granules; as a solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. These compositions can be prepared, as already mentioned, according to any suitable pharmaceutical method which comprises a step in which the active compound and the carrier (which can consist of one or more additional constituents) are brought into contact. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely divided solid carrier, after which the product, if necessary, is shaped. Thus, for example, a tablet can be prepared by compressing or shaping a powder or granules of the compound, if appropriate with one or more additional constituents. Pressed tablets can be prepared by tableting the compound in free-flowing form, such as, for example, a powder or granules, if appropriate mixed with a binder, lubricant, inert diluent and/or a (a number) of surface-active/dispersing agent(s) in a suitable machine. Shaped tablets can be prepared by shaping the pulverulent compound, moistened with an inert liquid diluent, in a suitable machine.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges, which contain a compound according to the formula (I) with a flavoring, customarily sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

The invention furthermore relates both to isomeric mixtures of the formula I and to the pure stereoisomers of the formula I, and also to diastereomer mixtures of the formula I and the pure diastereomers. The separation of the mixtures is carried out chromatographically.

Racemic and enantiomerically pure compounds of the formula I having the following structure are preferred:



Sugar residues are understood as meaning compounds which are derived from aldoses and ketoses having 3 to 7 carbon atoms, which can belong to the D or L series; these also include amino sugars, sugar alcohols or sugar acids. Examples which may be mentioned are glucose, mannose, fructose, galactose, ribose, erythrose, glyceraldehyde, sedoheptulose, glucosamine, galactosamine, glucuronic acid, galacturonic acid, gluconic acid, galactonic acid, mannonic acid, glucamine, 3-amino-1,2-propanediol, glucaric acid and galactaric acid.

Disugars are intended to mean saccharides which consist of two sugar units. Di-, tri- or tetrasaccharides are formed by acetal-like bonding of 2 or more sugars. The bonds can occur here in the α or β form. Examples which may be mentioned are lactose, maltose and cellobiose.

If the sugar is substituted, the substitution preferably takes place on the hydrogen atom of an OH group of the sugar.

The following protective groups are essentially suitable for the hydroxyl groups of the sugars: benzyl, acetyl, benzoyl, pivaloyl, trityl, tert-butyl-

dimethylsilyl, benzylidene, cyclohexylidene or isopropylidene protective groups.

5 The compounds of the formula I and their pharmaceutically tolerable salts and physiologically functional derivatives are ideal pharmaceuticals for the treatment of lipid metabolism disorders, in particular of hyperlipidemia. The compounds of the formula I are likewise suitable for influencing the serum cholesterol level and for preventing and treating arteriosclerotic symptoms. The compounds can optionally also be administered in combination with
10 statins, such as, for example, simvastatin, fluvastatin, pravastatin, cerivastatin, lovastatin or atorvastatin. The following findings confirm the pharmacological activity of the compounds according to the invention.

15 The biological testing of the compounds according to the invention was carried out by means of the perfusion test. This test investigates the action of the compounds according to the invention on the bile acid transport in the ileum. The diastereomer mixtures of the compounds were tested.

The perfusion test was carried out as follows:

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Experimental set-up

Male Wistar rats (weight range 250-350 g) were anesthetized with urethane (1.5 g/kg i.p.) and the bile duct was cannulated with a polyethylene tube.
25 Eight cm proximally to the ileocecal flap, an incision was made into the ileum and a silicone adapter for tubes was sewn in. A second incision with implantation of a corresponding silicone adapter was made in the cecum. Silicone tubes were attached to the adapter in order to perfuse the ileum in an orthograde and open manner (nonrecirculating) with perfusion buffer at
30 a perfusion rate of 1 ml/min.

The perfusion tubes were filled with perfusion buffer (137 mM NaCl, 0.9 mM CaCl₂, 0.51 mM MgCl₂, 8.1 mM Na₂HPO₄, 2.7 mM KCl, 1.47 mM KH₂PO₄) (pH 7.4), 1% (v/v) ethanol + 1% DMSO. The perfusion buffer
35 contained the test compounds in concentrations as indicated or the vehicle. The buffer was preheated to 37°C. The perfusion buffer contained 3 mM taurocholic acid (TCA), which in turn was labeled with 1000 dpm/ μ l of ³H TCA as a marker.

Study design and evaluation of the results

An experimental batch was chosen which allowed the determination of the inhibition of bile acid transport in the individual animal. The bile was
5 collected at 10 min intervals over a period of 90 min (in the case of a following wash-out phase for testing the reversibility over a period of up to 160 min. The perfusion of the vehicle-containing buffer solution over a period of 40 min (pre-test substance) was followed by a perfusion with
10 perfusion buffer which contained the test compound in the concentration to be tested (to 90 min).

For the calculation of the percentage inhibition by the test compound, the dpms (disintegrations per min of $^3\text{H-TCA}$) in the bile from 80-90 min (end of the perfusion with the test substance) were related to the collection period
15 30-40 min during the preliminary phase, when the excretion of the $^3\text{H-TCA}$ in the control phase had reached its maximum and plateau. The EC_{50} (= effective concentration 50) was calculated as the effective concentration between the inhibitory values of different concentration which inhibited the maximum bile acid excretion by 50%.

Results

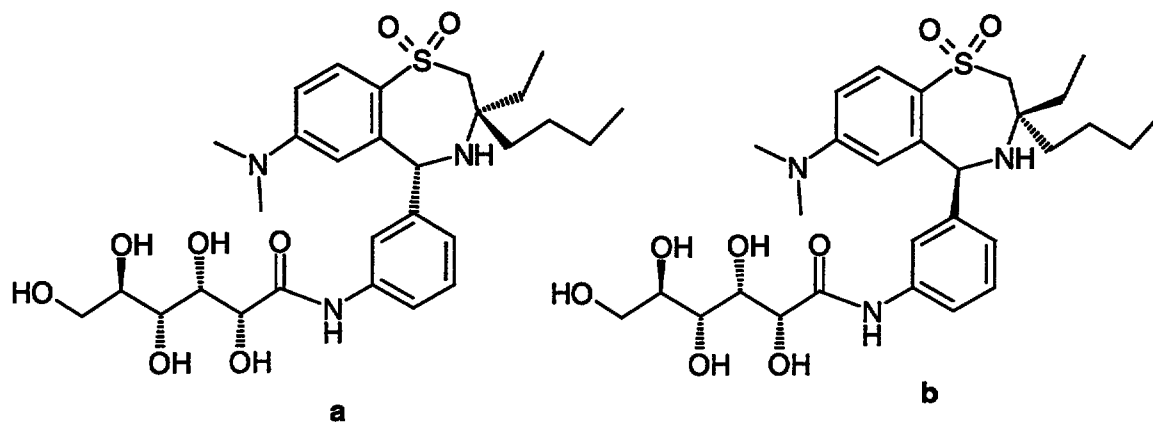
Table 1:

Compounds from Example	EC ₅₀ Ileum perfusion (μ M)
1	0.09
2	0.15
3	0.22
4	0.72
5	0.4
6	0.09
7	1.4
Comparison Example	
1	9.8

- 5 From the measured data, it can be seen that the compounds of the formula I according to the invention have an action which is better by the factor 7 to 100 relative to the compounds described in the prior art.

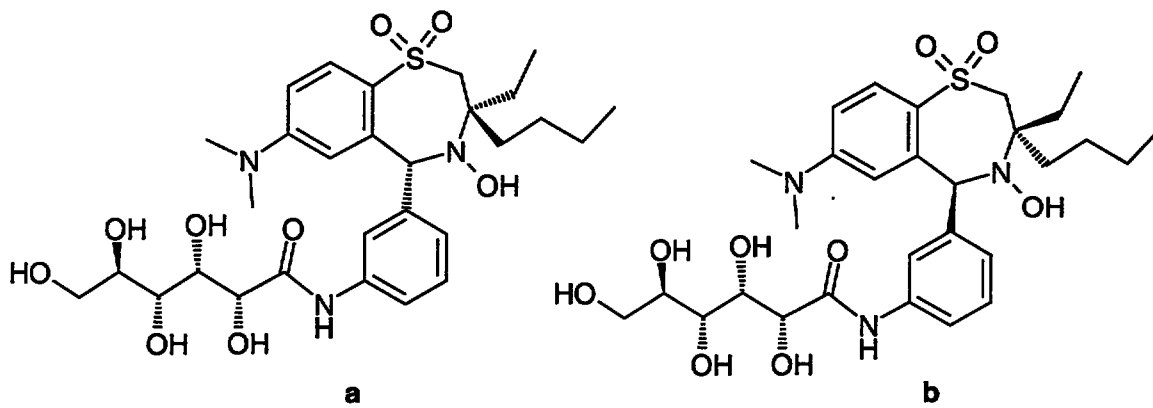
- 10 The following examples serve to illustrate the invention in greater detail, without restricting same to products and embodiments described in the examples.

Example 1



5 $C_{29}H_{43}N_3O_8S$ (593.74). MS $(M + H)^+ = 594.3$

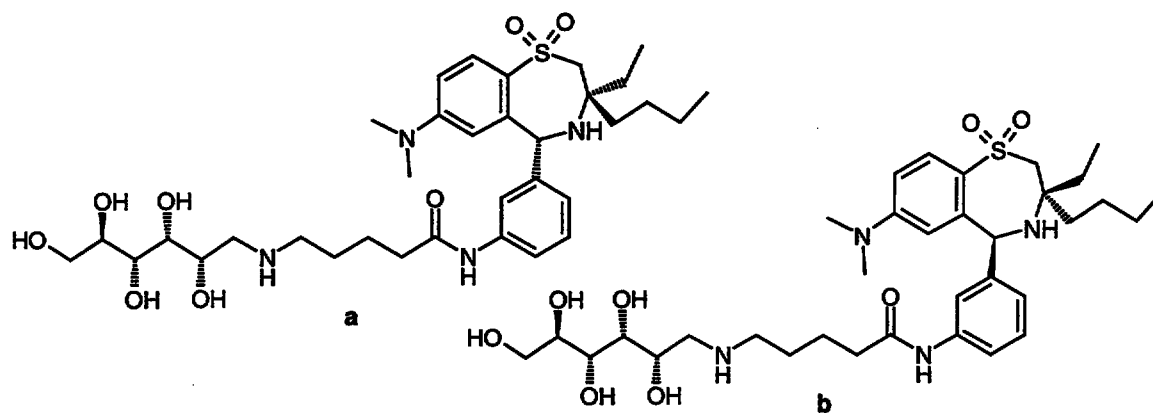
Example 2



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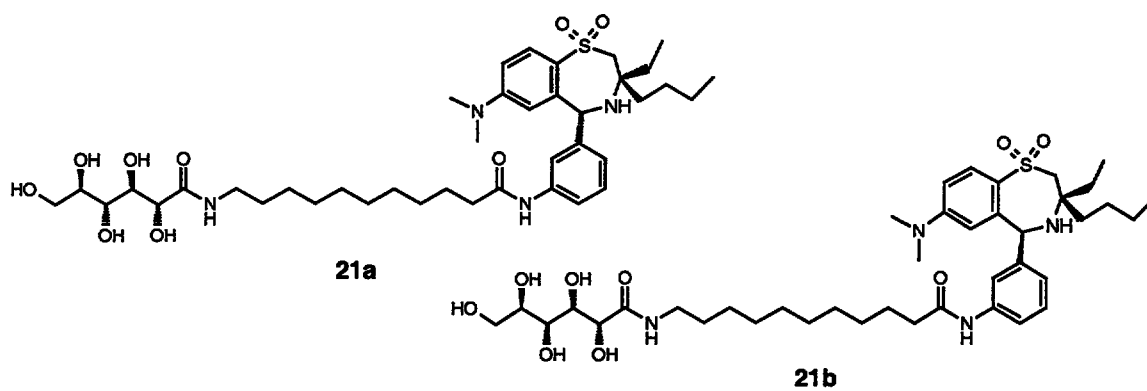
$C_{29}H_{43}N_3O_9S$ (609.74), MS $(M + H)^+ = 610.4$

Example 3



5 $C_{34}H_{54}N_4O_8S$ (678.89). MS $(M + H)^+ = 679.4$

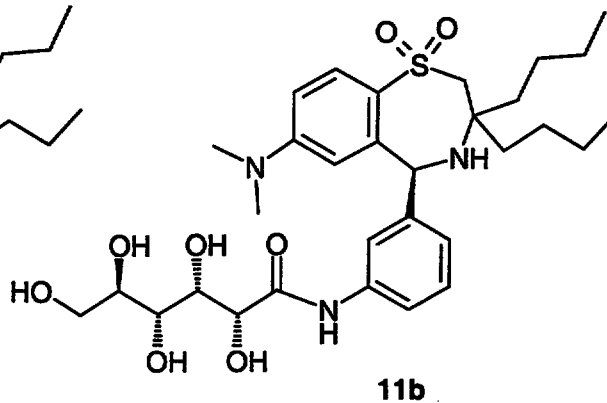
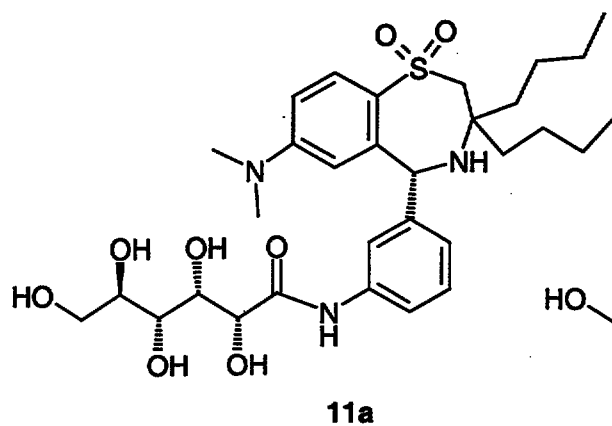
Example 4



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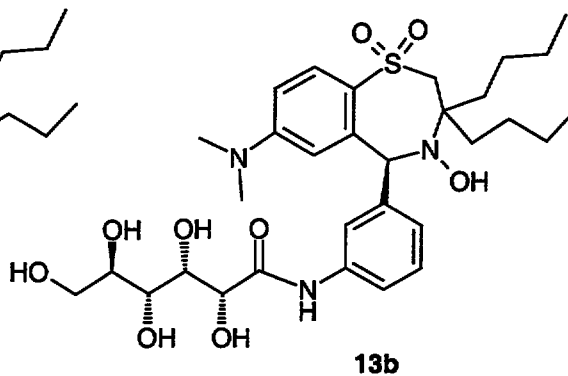
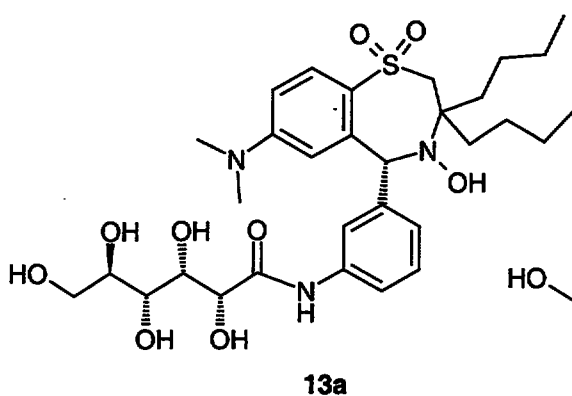
$C_{41}H_{64}N_4O_9S$ (777.03). MS $(M + H)^+ = 777.6$

Example 5



5 $C_{31}H_{47}N_3O_8S$ (621.79). MS $(M + H)^+ = 622.4$

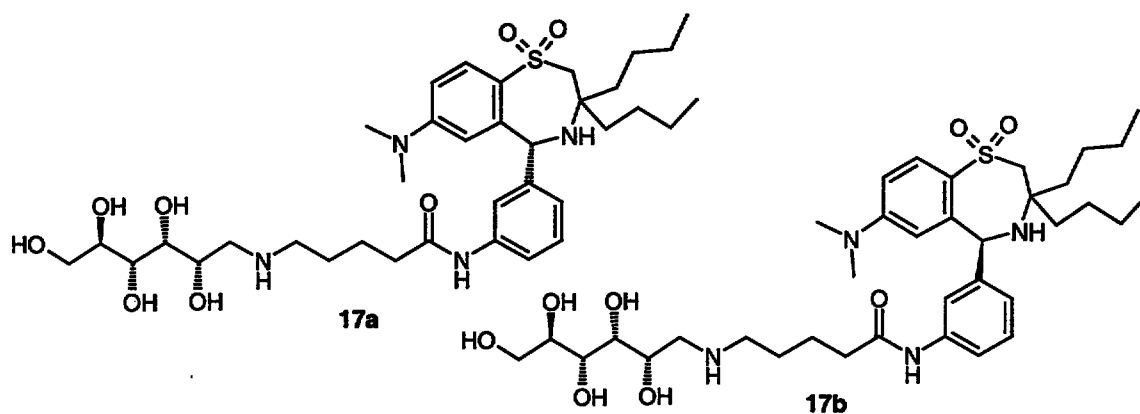
Example 6



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$C_{31}H_{47}N_3O_9S$ (637.79). MS $(M + H)^+ = 638.5$

Example 7

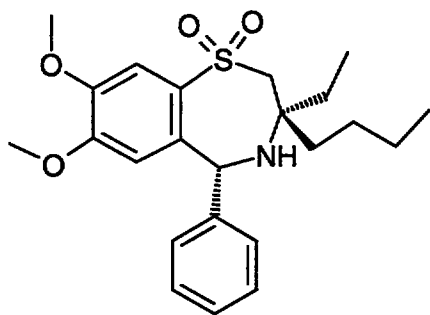


5 $C_{36}H_{58}N_4O_8S$ (706.94). MS $(M + H)^+ = 707.6$

Comparison example from WO 96/05188 (Example No. 20, 264W94(Glaxo Wellcome)):

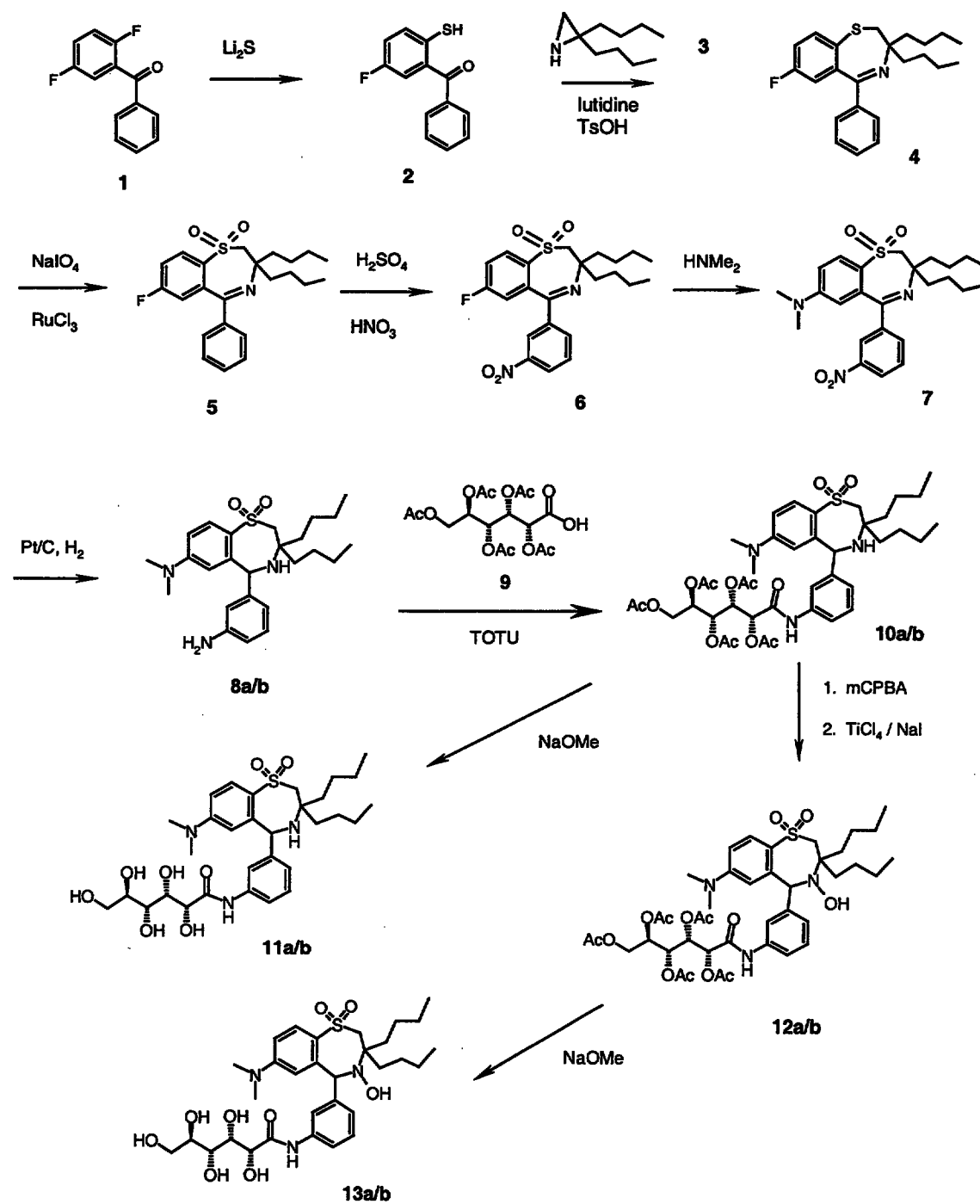
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Comparison Example 1

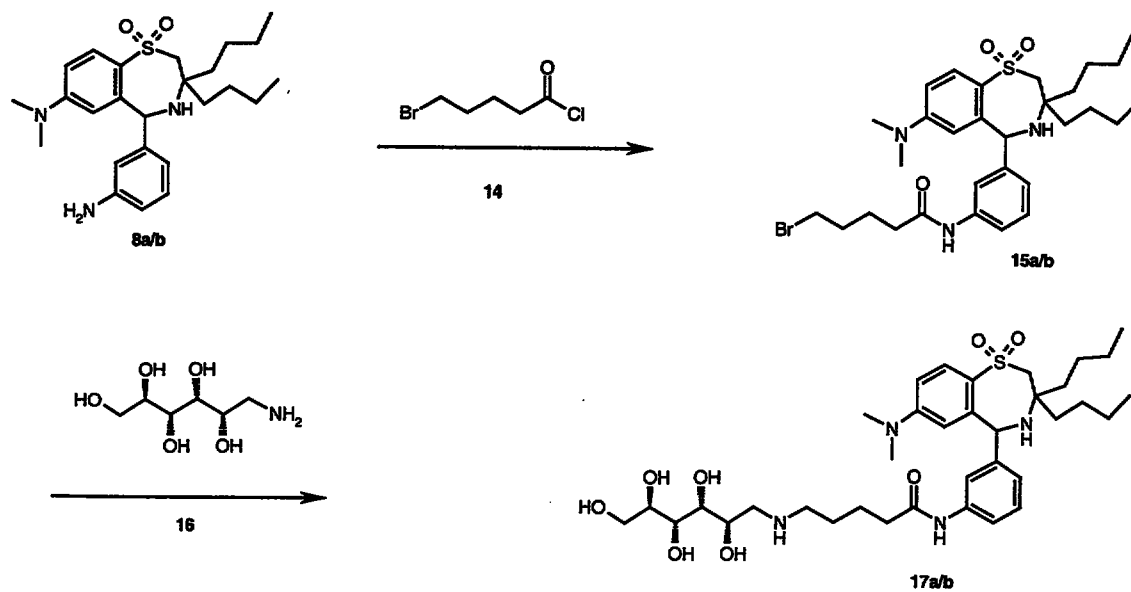


The examples were prepared as follows:

Reaction Scheme 1

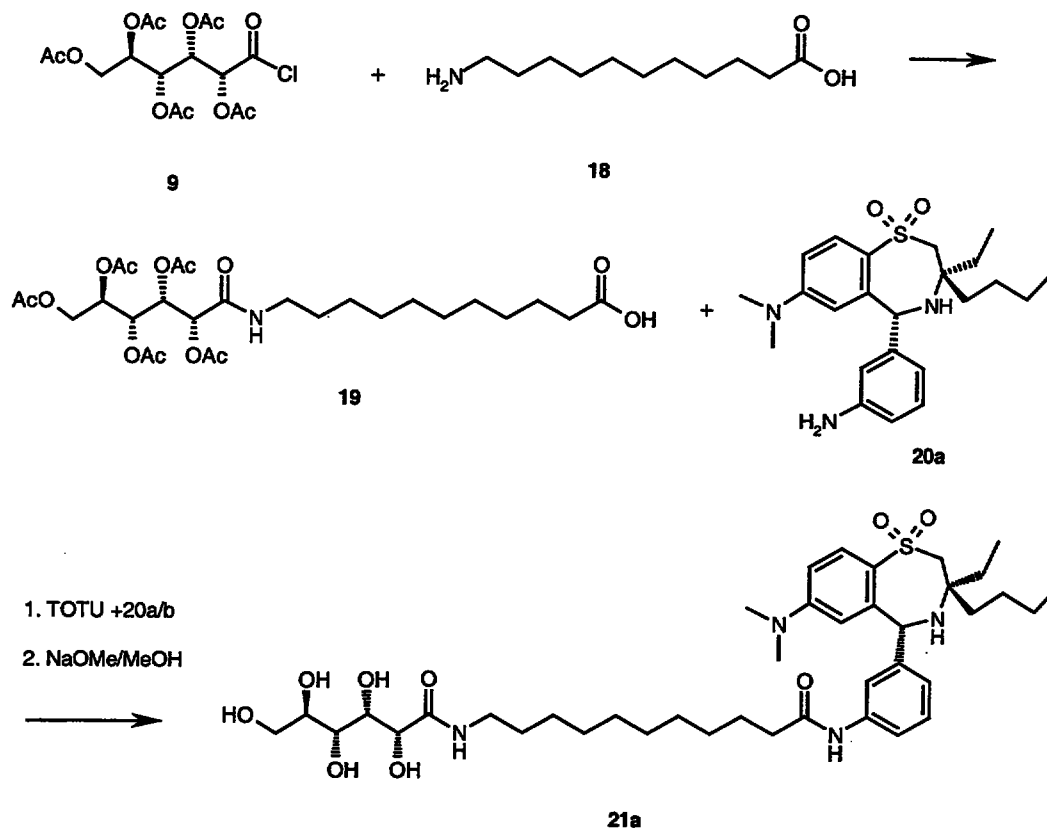


Reaction Scheme 2



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Reaction Scheme 3



Synthesis of compound 2:

20g (91.6 mmol) of 2,5-difluorobenzophenone **1** (Fluka) are dissolved in 400 ml of DMSO. 7.0 g (150 mmol) of lithium sulfide (Fluka) are added under argon. After three hours at 120°C, the mixture is allowed to cool to RT. It is shaken with 200 ml of 2 M HCl aq. and 500 ml of ethyl acetate. The organic phase is washed a further two times with NaCl soln., dried over MgSO₄, filtered and concentrated. 24 g of crude product **2** are obtained as a reddish oil. TLC (n-heptane/ethyl acetate 3:1). R_f = 0.3, starting material **1** R_f = 0.4. C₁₃H₉FOS (232.28). MS (M+H)⁺ = 233.1.

Synthesis of compound 4:

7 g of crude product **2**, 2.5g (16 mmol) of dibutylaziridine **3** (R. Gauthier et al., J. Organomet. Chem. 140 (1977) 245 - 255) and 300mg of p-toluenesulfonic acid are dissolved in 100 ml of lutidine. The reaction solution is boiled in a water separator for three hours. It is then concentrated and the residue is purified by flash chromatography. Yield 3.6g (61%) of **4** as a colorless oil. TLC (n-heptane/ethyl acetate 9:1). R_f = 0.5. C₂₃H₂₈FNS (369.55). MS (M+H)⁺ = 370.3.

Synthesis of compound 5:

3.6 g (9.7 mmol) of **4** and 6.0 g of NaIO₄ are suspended in 100 ml of acetonitrile, 50 ml of methylene chloride and 30 ml of water. After addition of 200 mg of RuCl₃, the mixture is stirred vigorously at room temperature for 2 hours. The solution is diluted with 200 ml of ethyl acetate and washed 2x with NaCl soln. After drying over MgSO₄, it is concentrated and purified by flash chromatography. Yield 3.47 g (89%) of **5** as an amorphous solid. TLC (n-heptane/ethyl acetate 4:1). R_f = 0.5, starting material **4** R_f = 0.6. C₂₃H₂₈FNO₂S (401.55). MS (M+H)⁺ = 402.2.

Synthesis of compound 6:

3.47 g (8.6 mmol) of **5** are dissolved in 24 ml of nitrating acid (from 14 ml of HNO₃ and 10 ml of H₂SO₄). The reaction temperature is kept at 20°C by cooling. After 30 minutes, the solution is poured onto a mixture of 700 g of ice and 200 ml of ethyl acetate. The aqueous phase is separated off and

washed carefully four times with 150 ml of saturated NaHCO_3 soln. It is then dried over MgSO_4 , concentrated and purified by flash chromatography. Yield 3.0 g (78%) of **6** as an amorphous solid. TLC (n-heptane/ethyl acetate 4:1). $R_f = 0.4$. $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_4\text{SF}$ (446.54). MS (M+H)⁺ = 447.2.

Synthesis of compound 7:

3.0 g (6.7 mmol) of **6** are dissolved in 50 ml of 33% strength HNMe_2 in ethanol (Fluka) and the solution is stirred at 50°C for one hour. It is then allowed to cool to RT and the resulting product is filtered. Yield 2.86 g (90%) of **7**, yellowish crystals m.p. 188°C. TLC (n-heptane/ethyl acetate 2:1). $R_f = 0.5$, starting material **7** $R_f = 0.6$. $\text{C}_{52}\text{H}_{33}\text{N}_3\text{O}_4\text{S}$ (471.62). MS (M+H)⁺ = 472.3.

Synthesis of compound 8a/b as an enatiomer mixture:

1.05 g (2.2 mmol) of **7** are suspended in 30 ml of toluene and 500 mg of platinum on active carbon (10% strength) are added. The mixture is hydrogenated in a shaking autoclave for 30 hours at 150 bar hydrogen pressure and 100°C. For work-up, the mixture is filtered through silica gel, which is washed with 100 ml of methanol, the filtrate is concentrated and the residue is purified by flash chromatography. Yield 495 mg (48%) of **8a/b** as an amorphous solid. TLC (n-heptane/ethyl acetate 1:1). $R_f = 0.3$. $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_2\text{S}$ (443.65). MS (M+H)⁺ = 444.3.

Synthesis of compound 10a/b as a diastereomer mixture:

80 mg (0.18 mmol) of **8a/b** and 100 mg (0.24 mmol) of penta-O-acetyl-D-gluconic acid (Org. Synth. Vol. 5, 887) are dissolved in 4 ml of DMF (dimethylformamide). 100 mg (0.3 mmol) of TOTU (Fluka), 35 mg (0.24 mmol) of oxime (ethyl hydroxyiminocyanoacetate; Fluka) and 0.1 ml (0.78 mmol) of NEM (4-ethylmorpholine) are added successively. After one hour at room temperature, the mixture is diluted with 20 ml of ethyl acetate and washed three times with water. The organic phase is dried over MgSO_4 , filtered and concentrated. The residue is purified by means of flash chromatography (ethyl acetate/n-heptane 2:1) and 130 mg (86%) of **10a/b** are obtained as an amorphous solid. TLC (ethyl acetate/n-heptane 2:1)

$R_f = 0.3$. The product **10a/b** has the same retention as the starting material **8a/b**, but colors differently with 2 M sulfuric acid. $C_{41}H_{57}N_3O_{13}S$ (131.97), MS $(M + H)^+ = 832.6$.

5 Synthesis of compound **11a/b** as a diastereomer mixture:

130 mg (0.16 mmol) of **10a/b** are dissolved in 5 ml of methanol. After addition of 0.2 ml of a methanolic 1 M sodium methoxide solution, the mixture is allowed to stand at room temperature for one hour. It is then
10 neutralized using methanolic HCl solution and concentrated. The residue is purified by flash chromatography (methylene chloride/methanol/conc. ammonia 30/10/3) and 78 mg (80%) of **10a/b** are obtained as an amorphous solid. TLC (methylene chloride/methanol/conc. ammonia 30/10/3). $R_f = 0.4$. $C_{31}H_{47}N_3O_8S$ (621.80). MS $(M + H)^+ = 622.4$.

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Synthesis of compound **12a/b** as a diastereomer mixture:

618 mg (0.74 mmol) of **10a/b** are dissolved in 30 ml of methylene chloride and 385 mg (2.23 mmol) of 70% strength m-chloroperbenzoic acid (Fluka)
20 are added. After 30 minutes at room temperature, the mixture is diluted with 100 ml of ethyl acetate and washed three times with $NaHCO_3$ soln. After drying using $MgSO_4$, the mixture is concentrated and 700 mg of crude product are obtained. This crude product is dissolved in 28 ml of a 0.05 M $TiCl_4$ /acetonitrile soln. After addition of 300 mg of solid NaI, the
25 mixture is stirred for 15 minutes. For work-up, it is diluted with 150 ml of ethyl acetate and washed with 100 ml of 2 M of sodium thiosulfate solution. The organic phase is dried over $MgSO_4$ and concentrated, and the residue is purified by flash chromatography. Yield 550 mg (87% over 2 stages) of **12a/b** as an amorphous solid. TLC (n-heptane/ethyl acetate 1:2). $R_f = 0.3$,
30 starting material **10a/b** $R_f = 0.35$. $C_{41}H_{57}N_3O_{14}S$ (847.99). MS $(M+H)^+ = 848.5$.

Synthesis of compound **13a/b** as a diastereomer mixture:

35 550 mg (0.65 mmol) of **12a/b** are dissolved in 20 ml of methanol. After addition of 0.3 ml of a methanolic 1 M sodium methoxide solution, the mixture is allowed to stand at room temperature for one hour. It is then neutralized using methanolic HCl solution and concentrated. The residue is

purified by flash chromatography (methylene chloride/methanol/conc. ammonia 30/10/3) and 370 mg (89%) of **13a/b** are obtained as an amorphous solid. TLC (methylene chloride/methanol/conc. ammonia 30/10/3). $R_f = 0.4$. $C_{31}H_{47}N_3O_9S$ (637.80). MS $(M + H)^+ = 638.4$.

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Synthesis of compound **15a/b** as a diastereomer mixture:

719 mg (1.6 mmol) of **8a/b** are dissolved in 30 ml of methylene chloride and 2 ml of triethylamine. 0.5 ml (3.7 mmol) of **14** is added dropwise to this solution and it is allowed to stand at room temperature for 15 minutes. The solution is then filtered through silica gel and washed with 100 ml of ethyl acetate. After concentration, the residue is purified by flash chromatography. Yield 950 mg (95%) of **15a/b** as an amorphous solid. TLC (n-heptane/ethyl acetate 1:1). $R_f = 0.4$. $C_{30}H_{44}BrN_3O_3S$ (606.67). MS $(M+H)^+ = 607.3$.

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Synthesis of compound **17a/b** as a diastereomer mixture:

897mg (1.47 mmol) of **15a/b** are dissolved in 20 ml of DMF. After addition of 1.3 g (7.1 mmol) of **16** (glucamine, Fluka), the mixture is heated at 80°C for two hours. It is then diluted with 50 ml of ethyl acetate and washed three times with water. The organic phase is dried over $MgSO_4$, filtered and concentrated. The residue is purified by means of flash chromatography (methylene chloride/methanol/conc. ammonia 30/10/3) and 700 mg (67%) of **17a/b** are obtained as an amorphous solid. TLC (methylene chloride/methanol/conc. ammonia 30/10/3). $R_f = 0.4$. $C_{36}H_{58}N_4O_8S$ (706.95). MS $(M + H)^+ = 707.4$.

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Synthesis of compound **19**:

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8.0 g (18.8 mmol) of **9** (penta-O-acetyl-D-gluconoyl chloride; Org. Synth. Vol. 5, 887) are added to a suspension of 8.0 g (40 mmol) of **18** (Fluka) in 150 ml of anhydrous DMF. This suspension is vigorously stirred at room temperature for 20 hours. 500 ml of ethyl acetate and 200 ml of water are then added. The aqueous phase is extracted again with 250 ml of ethyl acetate. The combined organic phase is washed three times with sodium chloride solution, dried over $MgSO_4$, filtered and concentrated. Yield 9.5 g (86%) of **19** as a colorless oil. TLC (methylene chloride/methanol/conc. ammonia 30/10/3). $R_f = 0.8$. $C_{27}H_{43}NO_{13}$ (589.64). MS $(M + H)^+ = 590.4$.

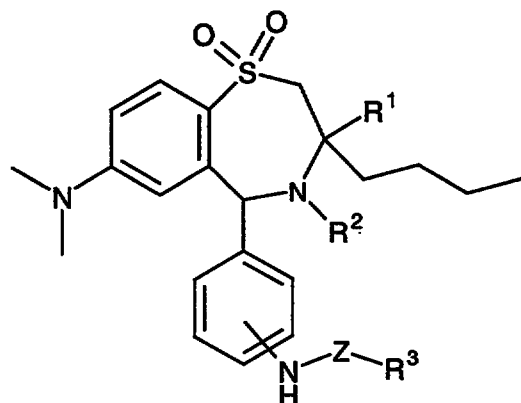
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Synthesis of compound **21a/b** as a diastereomer mixture:

200 mg (0.34 mmol) of **19**, 70 mg (0.17 mmol) of **20a/b** (**20a/b** is prepared
5 analogously to **8a/b** by carrying out the reaction sequence of reaction
scheme 1 with 2-butyl-2-ethylaziridine (R. Gauthier et al., J. Organomet.
Chem. 140 (1977) 245 – 255) and **1**, 240 mg of TOTU, 80 mg of oxime
and 0.3 ml of NEM are reacted in 4 ml of DMF analogously to the
10 procedure for compound **11a/b**. After flash chromatography (methylene
chloride/methanol/conc. ammonia 30/ 5/ 1), 60 mg (46%, over two stages)
of **21a/b** are obtained as an amorphous solid. TLC (methylene
chloride/methanol/conc. ammonia 30/ 5/ 1). $R_f = 0.2$. $C_{40}H_{64}N_4O_9S$
(777.04). MS $(M + H)^+ = 777.8$.

Patent claims

1. A compound of the formula I,



5

in which

10 R^1 is methyl, ethyl, propyl, butyl;

R^2 is H, OH;

15 R^3 is a sugar residue, disugar residue, trisugar residue, tetrasugar residue, the sugar residue, disugar residue, trisugar residue or tetrasugar residue optionally being mono- or polysubstituted by a sugar protective group;

20 Z is $-(C=O)_n-C_0-C_{16}-alkyl-$, $-(C=O)_n-C_0-C_{16}-alkyl-NH-$, $-(C=O)_n-C_0-C_{16}-alkyl-O-$, $-(C=O)_n-C_1-C_{16}-alkyl-(C=O)_m$, a covalent bond;

n is 0 or 1;

25 m is 0 or 1;

or its pharmaceutically tolerable salts and physiologically functional derivatives.

30 2. A compound of the formula I as claimed in claim 1, wherein one or more of the radicals has or have the following meaning:



- R^1 is ethyl, propyl, butyl;
- R^2 is H, OH;
- 5 R^3 is a sugar residue, disugar residue, the sugar residue or disugar residue optionally being mono- or polysubstituted by a sugar protective group;
- 10 Z is $-(C=O)_n-C_0-C_{16}-alkyl-$, $-(C=O)_n-C_0-C_{16}-alkyl-NH-$, $-(C=O)_n-C_0-C_{16}-alkyl-O-$, $-(C=O)_n-C_1-C_{16}-alkyl-(C=O)_m$, a covalent bond;
- n is 0 or 1;
- 15 m is 0 or 1;

or its pharmaceutically tolerable salts.

- 20 3. A compound of the formula I as claimed in claim 1 or 2, wherein one or more of the radicals has or have the following meaning:

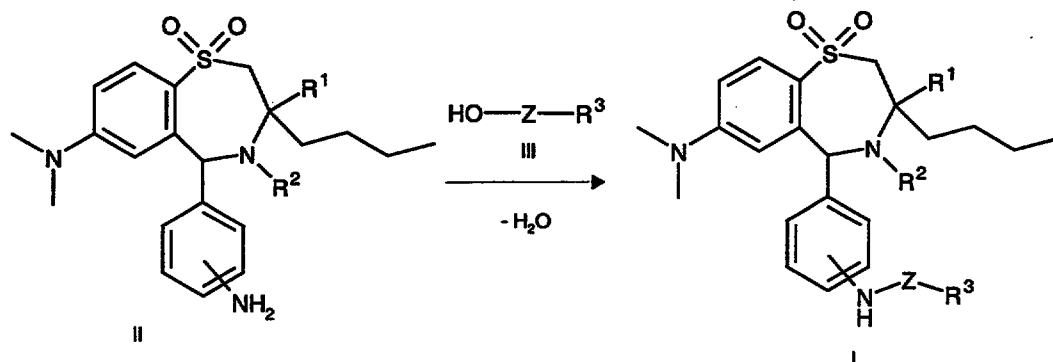
- R^1 is ethyl, butyl;
- 25 R^2 is H, OH;
- R^3 is a sugar residue, the sugar residue optionally being mono- or polysubstituted by a sugar protective group;
- 30 Z is $-(C=O)-C_0-C_4-alkyl$, a covalent bond;

or its pharmaceutically tolerable salts.

- 35 4. A process for the preparation of compounds of the formula I as claimed in one or more of claims 1 to 3, which comprises reacting, according to the following reaction scheme



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- an amine of the formula II, in which R^1 , R^2 and R^3 have the meanings indicated for formula I, with a compound of the formula III, in which R^3 and Z have the meanings indicated for formula I, with removal of water to give a compound of the formula I and optionally converting the compound of the formula I obtained into a physiologically tolerable salt or a physiologically functional derivative.
- 5
- 10 5. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 3.
6. A pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 3 and one or more statins.
- 15 7. A compound as claimed in one or more of claims 1 to 3 for use as a medicament for the treatment of lipid metabolism disorders.
8. A process for the production of a pharmaceutical comprising one or more of the compounds as claimed in one or more of claims 1 to 3, which comprises mixing the active compound with a pharmaceutically suitable carrier and bringing this mixture into a form suitable for administration.
- 20 9. Use of the compounds as claimed in one or more of claims 1 to 3 for the production of a medicament for treating hyperlipidemia.
- 25 10. The use of the compounds as claimed in one or more of claims 1 to 3 for the production of a medicament for influencing the serum cholesterol level.



11. The use of the compounds as claimed in one or more of claims 1 to 3 for the production of a medicament for preventing arteriosclerotic symptoms.