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Procédé de préparation pour les dérivés de taxanes

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09155673.8 / 2 077 264**08157617.5 / 1 980 557****03747971.4 / 1 537 093**(73) Proprietor: **Indena S.p.A.****20139 Milano (IT)**

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WO-A-02/12215 WO-A-94/22856**US-A- 5 821 363**

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Description**DISCLOSURE**

5 [0001] The present application is a divisional of European patent application No. 03747971.4 filed on 5 September 2003 and published as EP 1537093 A2.

[0002] The present invention relates to novel 13-ketobaccatin III and taxane derivatives and to the processes for the preparation thereof.

10 **TECHNOLOGICAL BACKGROUND**

[0003] WO 94/22856 discloses 14-hydroxy-taxanes having improved antitumor properties compared with conventional taxanes. One of said 14-hydroxy derivatives, referred to as IDN 5109, is at present under advanced clinical development. Said 14-hydroxylated derivatives can be easily prepared from natural 14-hydroxybaccatin.

15 [0004] It has now been found that IDN 5109 analogues bearing different substituents than the hydroxy group at the 14- position have surprising biological activity, as they are effective not only against taxane-resistant tumors but also against MDR cell lines.

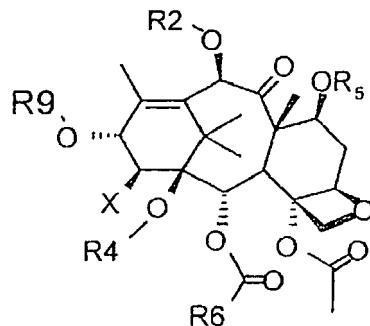
20 [0005] The derivatives of EP 1 537 093 A2 can be obtained by enolization of 13-ketobaccatin III and treatment with suitable electrophiles which can be converted into the desired group. Subsequent reduction of the C 13 carbonyl and esterification with isoserine chains afford the compounds of EP 1 537 093 A2, as defined below.

25 [0006] 7-Protected 13-ketobaccatin III is a very interesting compound as a key intermediate to 12,13-isotaxanes (Wicnienski et al., US 5,821,363), to novel taxanes modified at the 13- position (Menichincheri et al., WO9614308) and at the C and D ring (Dubois et al., Tetrahedr. Lett. 2000, 41, 3331-3334; Uoto et al., Chem. Pharm. Bull. 1997, 45(12), 2093-2095). 7-Protected 13-ketobaccatin III is an important intermediate in the studies on total synthesis of taxol and analogues (Nicolaou et al., J. Am. Chem. Soc. 1995, 117, 624-633; Nicolaou et al. 1995, 117, 2409-2420; Nicolaou et al., US 5,504,222). Some modifications of 7-protected 13-ketobaccatin III have also been reported, such as formation of hydrazones and oximes (Menichincheri et al., WO9614308; Menichincheri et al., Med. Chem. Res. (1996), 6(4), 264-292), direct treatment with oxidizing agents (Bombardelli et al., WO0212215; Harriman et al., Tetrahedr. Lett. 1995, 36(49), 8909-8912; or with reducing agents (Marder et al., Tetrahedr. 1995, 51(7), 1985-1994). Reactions of 13,14-enolization have not been described insofar, while rearrangement reactions in bases have been disclosed (Pinciroli et al., Tetrahedr. Lett. 1996, 37(52), 9365-9368; Yu and Liu, Tetrahedr. Lett. 1997, 38(23), 4133-4136).

30 [0007] According to a further aspect, the invention of EP 1 537 093 A2 relates to a process for the 13,14 enolization of 13-ketobaccatin III to give intermediates sufficiently stable for further elaboration.

35 **DETAILED DISCLOSURE OF THE INVENTION**

[0008] The compounds described in EP 1 537 093 A2 of the invention have the following general formula III



III

55 wherein

X is $-N_3$, $-NH_2$, $-NH-R_3$, $=CH-R_8$, or $-O-R_3$ when R_6 is different from phenyl,

R_2 is hydrogen or acyl;

R_3 is C_1-C_4 alkoxy carbonyl or, taken together with R_4 , forms a carbonyl, thiocarbonyl, SO , SO_2 group;

5 R₄ is hydrogen or, taken together with R₃ or R₈, forms the groups specified in the respective definitions of R₃ and R₈;

R₅ is hydrogen or an alcohol-protecting group;

R₆ is aryl, substituted aryl, heteroaryl, with the proviso that it is different from phenyl when X is -O-R₃;

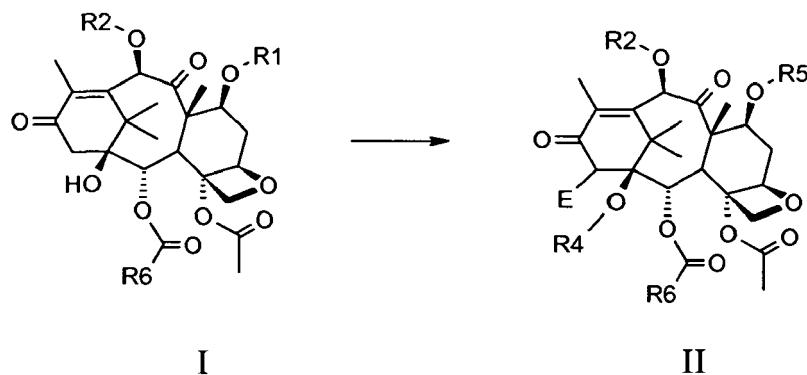
R₈ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy carbonyl or, taken together with R₄, forms a carbonyl group;
R₉ is an acyl or hydroxyaminoacyl group.

[0009] The compounds of formula III can be prepared from compounds of formula II, in turn obtainable by conversion of 13-ketobaccatin III derivatives of formula I:

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[0010] In formulae I and II,

R₁ is an alcohol-protecting group;

R₂ is an acyl group or an alcohol-protecting group;

E is -OH, -O-R₃, =N₂, -N₃, -NH₂, -NH-R₃, -NH-NH₂, -NH-N=N-Ts, -NH-N=N-Boc, -N(CO₂R₇)NHCO₂R₇, =CH-R₈;

30

Ts is p-toluenesulfonyl;

R₃ is C₁-C₄ alkoxy carbonyl or, taken together with R₄, forms a carbonyl, thiocarbonyl, SO, SO₂ group;

R₄ is hydrogen or, taken together with R₃ or R₈, forms the groups specified in the respective definitions of R₃ and R₈;

R₅ is hydrogen or an alcohol-protecting group;

R₆ is aryl, substituted aryl, heteroaryl;

35

R₇ is a C₁-C₄ alkyl, aryl or arylalkyl group;

R₈ is hydrogen, C₁-C₄ alkyl, C₁-C₄ alkoxy carbonyl or, taken together with R₄, forms a carbonyl group.

[0011] The compounds of formula III are useful for the treatment of neoplasias of various origin, in particular of tumors of such organs as ovary, breast, lung, colon, brain, as well as for the treatment of leukemias and melanoma.

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[0012] In compounds of formulae I, II and III, an acyl group is preferably a straight or branched C₂-C₆ aliphatic acyl group, or a benzoyl group optionally substituted with one or more C₁-C₄ alkyl groups, C₁-C₄ alkoxy groups, halogens; aryl is preferably phenyl; substituted aryl is preferably phenyl substituted with one or more C₁-C₄ alkyl groups, C₁-C₄ alkoxy groups, halogens; heteroaryl is preferably 2-,3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl; arylalkyl is preferably benzyl; a hydroxyaminoacyl group is preferably a β-isobutylisoserine or phenylisoserine residue substituted at the amino group with benzoyl or C₁-C₄ alkoxy carbonyl groups.

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[0013] According to EP 1 537 093 A2, compounds of formula II wherein E is -OH, =N₂, -N₃, -NH-N=N-Ts, -NH-N=N-Boc, -N(CO₂R₇)NHCO₂R₇, =CH-R₈, can be obtained from suitable 13-ketobaccatin III protected derivatives of formula I through a process which is shown in the following scheme and involves:

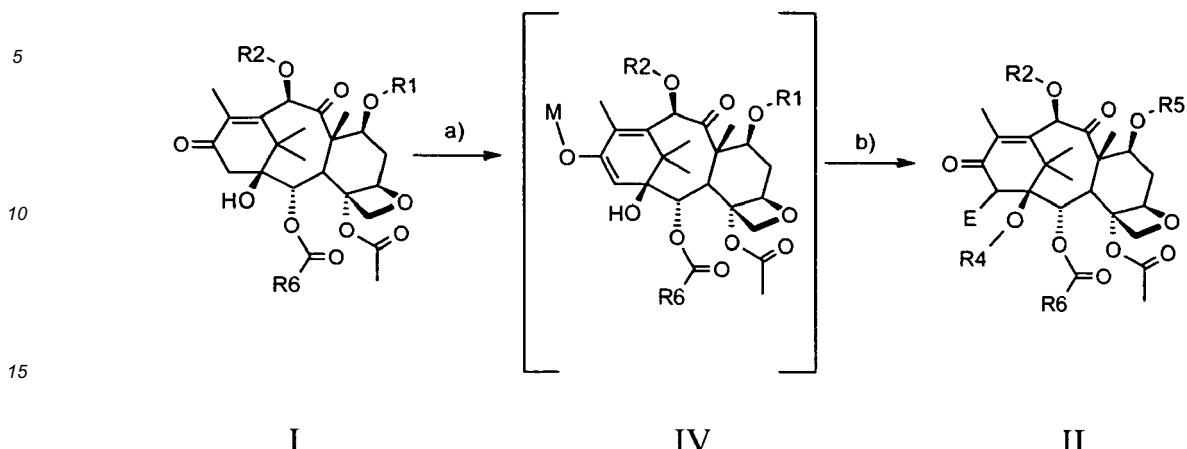
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a) treatment with bases to form an enolate of formula IV, wherein M is an alkali metal;

b) treatment of enolate IV with a suitable electrophile which can be converted to an E group to give a compound of formula II.

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Scheme



20 [0014] Formation of enolate in step a) can be easily obtained by treatment of protected 13-ketobaccatin III with a base such as potassium t-butoxide, potassium bis(trimethylsilyl)amide, lithium diisopropyl amine in inert solvents such as tetrahydrofuran or diethyl ether, also in admixture with hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2[1H]-pyrimidinone (DMPU). The reaction is suitably carried out in a range of temperatures from -40 to -78°C.

25 [0015] Particularly preferred protective groups are silyl ethers, acetals, ethers, carbonates and carbamates.

[0016] Starting 13-ketobaccatin III (formula I) is easily obtainable from the appropriate protected baccatin by reaction with conventional oxidizers, as described in literature.

[0017] 7-Protected 13-ketobaccatin III having different benzoate groups at the 2- position can be prepared according to the method by Ojima et al. (J. Am. Chem. Soc. 2000, 122, 5343-5353).

30 [0018] In the reported examples, R₁ is usually *tert*-butoxycarbonyl (Boc), triethylsilyl (TES) or 2-methoxypropane (MOP), and R₂ is usually acetyl, but other equivalent groups can be conveniently used to prepare similar compounds.

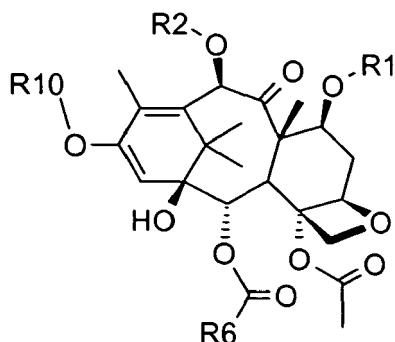
[0019] According to the scheme above, in step b) enolate IV is treated *in situ* with electrophiles such as oxaziridines (e.g. N-benzenesulfonyl phenyl oxaziridine, N-benzenesulfonyl m-nitrophenyl oxaziridine and camphorsulfonyloxaziridine), diazadicarboxylates (e.g. di-*tert*-butyl diazadicarboxylate and dibenzyl diazadicarboxylate), p-toluenesulfonylazide, t-butoxycarbonylazide, aldehydes (e.g. acetaldehyde, ethylglyoxylate) to give 13-ketobaccatin III of formula II wherein E is -OH, -NH-N=N-Ts, -NH-N=N-Boc, -N(CO₂R₇)NHCO₂R₇, =CH-R₈.

35 [0020] When p-toluenesulfonylazide is used as the electrophile, the product wherein E is NH-N=N-Ts (or the N=N-NHTs tautomer) is obtained, besides decomposition products wherein E is N₃ or N₂. The quenching conditions of the reaction may be modulated to direct the reaction mainly to only one of the products. Thus, the tosylazido derivative can be recovered from the crude product by extraction with polar aprotic solvents such as dichloromethane or ethyl acetate. The diazo derivative is obtained upon stirring the reaction crude in polar aprotic solvents for reasonably long times, optionally under heating. The azido derivative is obtained by treating the reaction crude with protic agents, such as mixtures of acetic acid in THF with DMPU or HMPA, immediately after addition of the azide donor.

40 [0021] When ethyl glyoxylate is used as the electrophile, crotonic condensation with concomitant closure of the carbethoxy group at the C1 hydroxyl group takes place, to give an α,β -unsaturated γ -lactone.

45 [0022] In all cases, diastereoselection of the reaction is such that the E group is introduced mainly in 14 β configuration.

[0023] Alternatively, enolate IV can be treated with silylating (e.g. tri-*i*-propyl silyl chloride), acylating (e.g. di-*tert*-butylpyrocyanate), alkylating (e.g. dimethyl sulfate or methyl iodide) or phosphorylating agents thereby obtaining enol derivatives of formula V



wherein

R₁₀ is acyl, alkyl, trialkylsilyl or phosphate, and

R₁, R₂ and R₆ are as defined above.

[0024] Compounds V can also be easily obtained by enolization of ketone of formula II with particularly weak bases such as triethylamine or pyridine in aprotic solvents such as methylene chloride, toluene or mixtures thereof.

[0025] Compounds V can afford compounds of formula II by treatment with electrophiles in suitable conditions.

[0026] The groups introduced at the 14- position with the procedure described above can be further transformed to obtain other 13-ketobaccatin III derivatives functionalized at the 14- position.

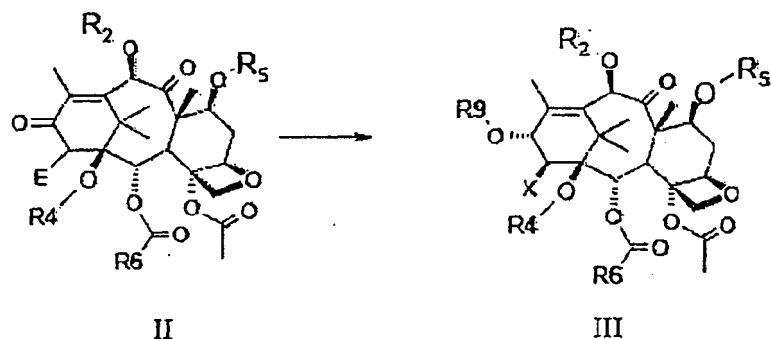
[0027] Thus, compounds of formula II wherein E is -N(CO₂R₇)NHCO₂R₇ can be converted in the corresponding hydrazino derivatives (wherein E is -NH-NH₂) by decarboxylation according to conventional methods.

[0028] Compounds of formula II wherein E is -N₃ are easily reduced to amine (E = NH₂) by means of reductive systems such as triphenylphosphine in aqueous medium or H₂-Pd/C in a suitable solvent.

[0029] Compounds of formula II wherein E is -OH or -NH₂ can be treated with carbonating (e.g. carbonyldiimidazole, phosgene or triphosgene), thiocarbonating (e.g. thiocarbonyl diimidazole, thiophosgene) or sulfonylating agents (e.g. sulfonyl chloride or thionyl chloride), to obtain compounds of formula II wherein E is -OR₃ or -NHR₃. The reaction can be conveniently carried out in chlorinated solvents in the presence of a base (e.g. pyridine or triethylamine) in a range of temperatures from -40°C to 70°C.

[0030] Alternatively, compounds of formula II wherein E is -OH or -NH₂ can be alkylated with such agents as alkyl halides or benzyl halides in the presence of weak bases.

[0031] Compounds of formula II are key intermediates for the synthesis of compounds of formula III. In particular, compounds III are obtainable from compounds of formula II wherein E is -O-R₃, -N₃, -NH-R₃, =CH-R₈, and R₂, R₄, R₅, R₆ are as defined above;

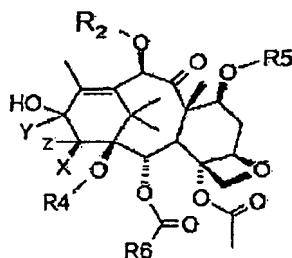


through a process which comprises:

a) reduction of the C13 carbonyl to give compounds of formula VII

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VII

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wherein

X is -O-R₃, -N₃, -NH-R₃, -CH₂-R₈;Y and Z are hydrogen or, when X is -CH₂-R₈, are taken together to form a double bond;

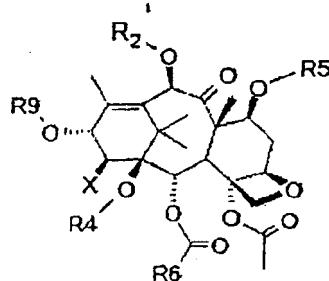
and the other groups are defined as above;

b) esterification at the 13- position with derivatives of acids of formula IX to give compounds of formula VIII

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VIII

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wherein

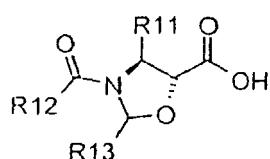
R₄, R₅, R₆, R₉ are as defined above;X is -O-R₃, -N₃, -NH-R₃, -CH₂-R₈;

c) optional cleavage of the protective groups.

40 [0032] Reduction of C13 ketone of step a) is carried out with suitable hydrides such as sodium borohydride, lithium borohydride, tetrabutylammonium borohydride, tetraethylammonium borohydride, sodium triacetoxy borohydride. The reaction can be carried out in a stoichiometric amount of reducing agent, although an excess is usually preferred. Depending on the used reducing agent, the reaction is carried out in alcohols, ethers, mixtures of alcohols and ethers or inert solvents, at temperatures ranging from -50 to 0°C.

45 [0033] C13 Esterification of step b) is usually carried out by action of carboxylic acids, or the corresponding salts, of formula IX

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55

IX

wherein

R_{11} and R_{13} , which can be the same or different, are C_1 - C_6 alkyl, aryl, or heteroaryl;
 R_{12} is C_1 - C_6 alkyl, aryl, heteroaryl or C_1 - C_4 alkoxy;

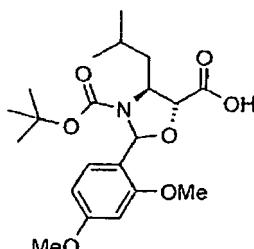
5 in the presence of condensing agents such as carbodiimides (e.g. dicyclohexylcarbodiimide or ethyl dimethylaminopropyl carbodiimide). Other known methods for the esterification at the 13- position of 7-protected baccatin III can also be successfully used.

[0034] Protective groups in step c) are removed under the conditions described in literature for the concerned protective group.

[0035] The most preferred carboxylic acid is the N -Boc-isobutyrylisoserine derivative of formula X

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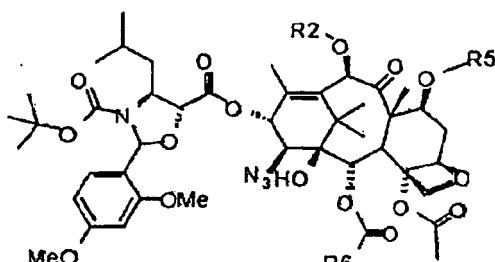
X

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[0036] In this case, coupling with compounds of formula VII under the conditions illustrated in the examples yields compounds of formula XI

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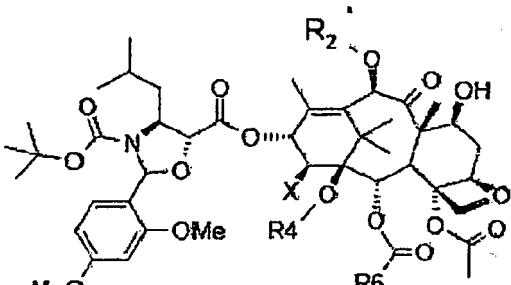
XI

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which by selective deprotection at the 7- position afford compounds of formula XII

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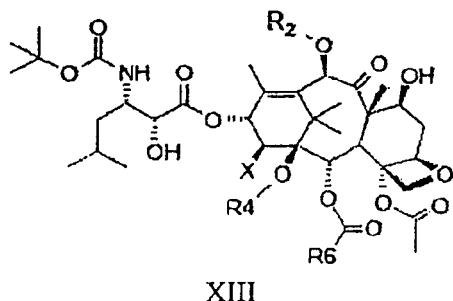
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XII

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which are subjected to opening of the oxazolidine ring, to yield compounds of formula XIII

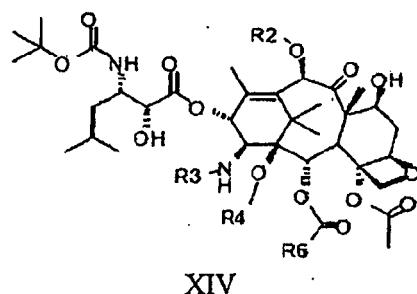


15 wherein X, R₂, R₄, and R₆ are as defined above.

[0037] In case C13 esterification is carried out with the carboxylic acid of formula X, C7 deprotection is preferably effected before opening the oxazolidine.

[0038] Derivative of formula XI wherein X is -N₃ is particularly interesting, in that it is an useful intermediate for the preparation of compounds of formula XIV

20



35 wherein

R₂ is an acyl group or an alcohol-protecting group;

R₃ is hydrogen, acyl, alkyl or, taken together with R₄, forms a C=O, C=S, SO, SO₂ group;

R₄ is hydrogen or, taken together with R₃, forms a C=O, C=S, SO, SO₂ group;

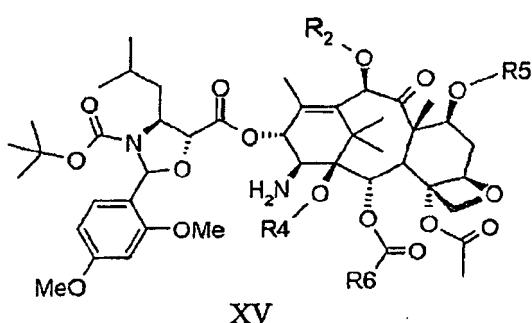
R₅ is aryl, substituted aryl, heteroaryl;

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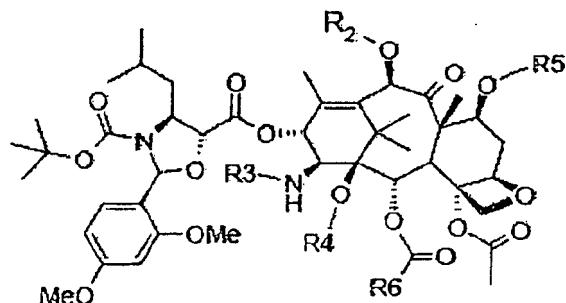
according to an alternative preparation process to that described above, comprising:

a) reduction of the 14-azido group to give compounds of formula XV

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b) optional treatment with an acylating or alkylating agent to give compounds of formula XVI



XVI

c) cleavage of the C7 protective group and opening of the oxazolidine to give compounds of formula XIV.

[0039] In the formulae XV and XVI, R₂, R₃, R₄, R₅ and R₆ have the same meanings as defined above.

[0040] For the envisaged therapeutical uses, compounds of formula III will be administered in the form of suitable pharmaceutical formulations, mainly through the parenteral route and at dosages in principle similar to those already used for some time in clinical practice with commercially available taxane derivatives (Paclitaxel and Docetaxel, for example).

[0041] The following examples illustrate the invention in greater detail.

Example 1

7-Boc-13-ketobaccatin III

[0042] A solution of 13-ketobaccatin III (1.10 g, 1.9 mmol) in CH₂Cl₂ (0.5 mL) at 20°C is added with carbon tetrachloride (14 ml). Partial precipitation of the baccatin derivative takes place. Subsequently, 1-methylimidazole (23 μ L, 0.28 mmol) and di-*tert*-butyl-dicarbonate (1.03 g, 4.7 mmol) are added, under stirring and argon stream. After 8 hours, further 1-methyl-imidazole (16.0 μ L, 0.20 mmol) is added. The solution is left at 25°C for 24 hours, then solvent is evaporated off under reduced pressure. The oily residue is dissolved in a 1:1 acetone/water mixture (10 mL) and left at 20°C for about 16 hours. The precipitate is filtered, washed with *n*-pentane and dried to give 1.12 g of the title product. Chromatography of mother liquors affords a further 0.12 g of product (SiO₂, *n*-hexane/EtOAc, 1.5:1.0). 1.24 g of product are thereby obtained (1.81 mmol, 95%). $[\alpha]_D^{20} = -35.6^\circ$ (c 1.05, CHCl₃); IR (CDCl₃, cm⁻¹): 3483, 1731, 1676, 1371, 1274; ¹H-NMR (CDCl₃, 400 MHz): δ = 1.20 (s, 3H, Me), 1.22 (s, 3H, Me), 1.47 (s, 9H, 3Me), 1.76 (s, 3H, Me), 1.91 (m, 1H, H-6, J_1 = 10.4 Hz, J_2 = 14.8 Hz, J_3 = 2.0 Hz), 1.92 (b, 1H, OH), 2.17 (s, 3H, Me), 2.19 (s, 3H, Me), 2.20 (s, 3H, Me), 2.64 (m, 1H, H-6, J_1 = 7.2 Hz, J_2 = 14.8 Hz, J_3 = 9.5 Hz), 2.66 (d, 1H, H-14, J = 19.6 Hz), 2.94 (d, 1H, H-14, J = 19.6 Hz), 4.02 (d, 1H, H-3, J = 6.8 Hz), 4.09 (d, 1H, H-20, J = 9.0 Hz), 4.32 (d, 1H, H-20, J = 9.0 Hz), 4.94 (d, 1H, H-5, J_1 = 9.5 Hz, J_2 = 2.0 Hz), 5.39 (m, 1H, H-7, J_1 = 10.4 Hz, J_2 = 7.2 Hz), 5.67 (d, 1H, H-2, J = 6.8 Hz), 6.57 (s, 1H, H-10), 7.44-7.50 (m, 2H, arom), 7.61-7.64 (m 1H, arom), 8.30 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): β = 10.7, 14.0, 18.4, 21.0, 21.9, 27.9, 33.1, 33.6, 42.7, 46.7, 57.3, 72.8, 74.7, 76.3, 76.5, 77.4, 78.7, 80.5, 83.4, 84.0, 128.9, 129.0, 130.3, 134.3, 141.0, 152.4, 152.5, 167.0, 168.3, 170.3, 198.4, 200.5. Anal. Calc. C₃₆H₄₄O₁₃: C. 63.15; H. 6.48. Found: C. 63.39; H. 6.60.

Example 2

7-TES-13-ketobaccatin III

[0043] 13-Ketobaccatin III (5 g, 8.5 mmol), triethyl silyl chloride (3.6 mL, 21.4 mmol, 2.5 eq) and N-methylimidazole (2.73 mL, 34.3 mmol, 4 eq) are dissolved in anhydrous methylene chloride (25 mL). The solution is left under stirring for 1.5 h at room temperature, then quenched by carefully pouring it in a 2M NaHSO₄ solution (25 mL). The aqueous phase is repeatedly extracted with DCM (2x10 mL) and the combined organic phases are washed with brine (2x20 mL). The organic phase is dried over sodium sulfate and the solvent is evaporated off to give 4.7 g of the title product which is

used directly in the subsequent step without further purification. M.p.: 212°C. TLC: cHex-AcOEt 1:1, Rf=0.57. ¹H-NMR (200 MHz, CDCl₃): δ 0.58-0.66 (m, 6H, Si-CH₂), 0.90-0.98 (t, J=8.4, 9H, CH₂CH₃), 1.21 (s, 3H, 17-Me), 1.27 (s, 3H, 16-Me), 1.69 (s, 3H, 19-Me), 1.83-1.96 (m, 1H, 6-H), 2.20 (s, 3H, 18-Me), 2.21 (s, 3H, 10-OAc), 2.25 (s, 3H, 4-OAc), 2.48-2.65 (m, 1H, 6-H), 2.81 (ABq, 2H, 14-H), 3.93 (d, J=6.6, 1H, 3-H), 4.25 (ABq, 2H, 20-H), 4.51 (dd, J=10.6, 7.0, 1H, 7-H), 4.94 (d, J=7.7, 1H, 5-H), 5.72 (d, J=7.0, 1H, 2-H), 6.61 (s, 1H, 10-H), 7.52 (t, J=6.2, 2H, Bz), 7.64 (t, J=6.2, 1H, Bz), 8.10 (dd, J=7.4, 1.1, 2H, Bz).

Example 3

10 **14 β -azido-7-Boc-13-ketobaccatin III**

[0044] A solution of 7-Boc-13-ketobaccatin III (0.149 g, 0.22 mmol) in THF (1.8 mL) and DMPU (0.8 mL) is added in 2 minutes to a suspension of potassium *tert*-butoxide (0.064 g, 0.568 mmol) in anhydrous THF (1.5 mL) at -75°C, under nitrogen stream and strong stirring. After 15 min, 0.063 g (0.33 mmol) of tosylazide dissolved in 0.7 ml of THF are added in two minutes at -75°C. After two hours, temperature has raised to -50°C, the reaction is quenched by addition of 0.057 mL (1.00 mmol) of glacial acetic acid. Temperature is slowly raised to 20°C and after 19 hours the reaction mixture is diluted with 15 ml of Et₂O and extracted with 10 ml of a NH₄Cl aqueous saturated solution. The organic phases are washed three times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 1.7:1.0) affords 0.080 g (0.10 mmol, 50%) of the title product. IR (KBr, cm⁻¹): 2976, 2935, 2122, 1731, 1272; ¹H-NMR (CDCl₃, 400 MHz): δ = 1.01 (s, 3H, Me), 1.22 (s, 3H, Me), 1.47 (s, 9H, 3Me), 1.81 (s, 3H, Me), 1.96 (m, 1H, H β -6, J₁ = 2.0 Hz, J₂ = 10.8 Hz, J₃ = 14.0 Hz), 2.19 (s, 3H, Me), 2.20 (s, 3H, Me), 2.24 (s, 3H, Me), 2.62 (m, 1H, H α -6, J₁ = 7.2 Hz, J₂ = 9.6 Hz, J₃ = 14.0 Hz), 3.11 (s, 1H, OH), 3.98 (d, 1H, H-3, 6.8 Hz), 4.24 (d, 1H, H-20, J = 8.4 Hz), 4.26 (s, 1H, H-14), 4.33 (d, 1H, H-20, J = 8.4 Hz), 4.93 (d, 1H, H-5, J₁ = 2.0 Hz, J₂ = 9.6 Hz), 5.37 (m, 1H, H-7, J₁ = 10.8 Hz, J₂ = 7.2 Hz), 5.81 (d, 1H, H-2, J = 6.8 Hz), 6.56 (s, 1H, H-10), 7.48-7.52 (m, 2H, arom), 7.60-7.66 (m 1H, arom), 8.02-8.05 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 10.8, 14.4, 19.2, 20.9, 21.9, 27.9, 33.5, 33.7, 43.3, 45.8, 54.0, 57.2, 65.4, 72.5, 74.4, 75.5, 75.8, 76.1, 81.0, 83.5, 83.7, 129.1, 129.2, 130.0, 134.1, 138.8, 152.5, 153.8, 165.4, 168.2, 170.0, 196.6, 199.8. Anal. Calc C₃₆H₄₃N₃O₁₃: C, 59.58; H, 5.97. Found : C, 59.81; H, 5.85. MS m/z 725.1 (M⁺ calc C₃₆H₄₃N₃O₁₃ 725.7), 687.1, 670.0.

30 Example 4

14-diazo-7-Boc-13-ketobaccatin III and 14 β -(1-p-toluenesulfonyl)triazenyl-7-Boc-13-ketobaccatin III

[0045] A solution of 7-Boc-13-ketobaccatin III (0.03 g, 0.04 mmol) in THF (0.7 mL) and HMPA (0.2 mL) is added in 2 minutes to a suspension of potassium *tert*-butoxide (0.013 g, 0.04 mmol) in anhydrous THF (0.7 mL) at -75°C, under nitrogen stream and strong stirring. After 15 min, 0.013 g (0.07 mmol) of tosylazide dissolved in 0.2 ml of THF are added in two minutes at -75°C. After two hours, and after temperature has raised to -50°C, the reaction is quenched by addition of 5.0 ml of a NH₄Cl saturated solution. Temperature is slowly raised to 20°C and the reaction mixture is diluted with 3.0 ml of Et₂O and extracted with 6.0 ml of a NH₄Cl aqueous saturated solution. The organic phases are washed three times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 1.7:1.0) affords 0.080 g (0.10 mmol, 45%) of 7-Boc-14-diazo-13-ketobaccatin III and 14 β -(1-p-toluenesulfonyl)triazenyl-7-Boc-13-ketobaccatin III (0.025 g, 0.028 mmol, 13%) as a 3:1 mixture of tautomers.

[0046] *14-diazo-7-Boc-13-ketobaccatin III*: IR (KBr, cm⁻¹): 3500-3100, 2982, 2935, 2095, 1734, 1656, 1633, 1272; ¹H-NMR (CDCl₃, 400 MHz): δ = 1.23 (s, 3H, Me), 1.31 (s, 3H, Me), 1.48 (s, 9H, 3Me), 1.77 (s, 3H, Me), 1.92 (m, 1H, H β -6, J₁ = 1.5 Hz, J₂ = 10.8 Hz, J₃ = 14.0 Hz), 2.18 (s, 3H, Me), 2.19 (s, 3H, Me), 2.22 (s, 3H, Me), 2.63 (m, 1H, H α -6, J₁ = 6.8 Hz, J₂ = 8.0 Hz, J₃ = 14.0 Hz), 4.04 (d, 1H, H-3, 6.4 Hz), 4.08 (d, 1H, H-20, J = 8.4 Hz), 4.36 (d, 1H, H-20, J = 8.4 Hz), 4.95 (d, 1H, H-5, J₁ = 1.5 Hz, J₂ = 8.0 Hz), 5.41 (m, 1H, H-7, J₁ = 10.8 Hz, J₂ = 6.8 Hz), 5.85 (d, 1H, H-2, J = 7.2 Hz), 6.50 (s, 1H, H-10), 7.48-7.54 (m, 2H, arom), 7.62-7.68 (m 1H, arom), 8.40-8.80 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 11.1, 14.4, 18.7, 21.0, 27.9, 32.9, 33.5, 43.0, 46.1, 56.6, 65.4, 73.7, 74.5, 76.2, 76.3, 79.5, 80.4, 83.5, 84.0, 128.3, 129.1, 130.4, 134.5, 141.1, 145.7, 152.5, 167.3, 168.3, 170.4, 184.1, 200.9. Anal. Calc. C₃₆H₄₂N₂O₁₃: C, 60.84; H, 5.96. Found : C, 60.71; H, 5.95. MS m/z 710.2 (M⁺ calcd for C₃₆H₄₂N₂O₁₃ 710.7), 687.1, 670.0.

[0047] *14 β -(1-p-toluenesulfonyl)triazenyl-7-Boc-13-ketobaccatin III*: ¹H-NMR (CDCl₃, 400 MHz, 21°C): δ = 1.26 (s, 3H, Me), 1.29 (s, 3H, Me), 1.43 (s, 9H, 3Me, minor), 1.46 (b, 9H, 3Me, major), 1.54 (s, 3H, Me), 1.67 (s, 3H, Me), 1.85 (m, 1H, H β -6, J₁ = 1.5 Hz, J₂ = 10.0 Hz, J₃ = 14.0 Hz), 2.05-2.18 (b, 9H, 3Me), 2.86 (m, 1H, H α -6, J₁ = 7.0 Hz, J₂ = 8.0 Hz, J₃ = 14.0 Hz), 3.98 (d, 1H, H-3, J = 11.0 Hz, minor), 4.10 (d, 1H, H-3, J = 10.8 Hz, major), 4.39 (d, 1H, H-20, J = 8.4 Hz), 4.61 (d, 1H, H-20, J = 8.4 Hz), 4.87 (s, 1H), 4.95 (d, 1H, H-5, J₁ = 1.5 Hz, J₂ = 8.0 Hz), 5.34 (s, 1H), 5.51 (m, 1H, H-7, J₁ = 10.8 Hz, J₂ = 7.0 Hz), 5.78-5.88 (m, 1H, H-2, major, J = 10.8 Hz and 1H, H-2, minor), 6.42-6.46 (b, 1H, H-10, major), 6.46-6.50 (b, 1H, H-10, minor), 7.28-7.32 (m, 2H, arom), 7.48-7.54 (m, 2H, arom), 7.62-7.68 (m 1H, arom),

7.79-7.82 (m, 2H, arom), 8.26-8.30 (d, 2H, arom).

Example 5

5 **14 β -amino-7-Boc-13-ketobaccatin III**

[0048] A solution of 0.04 g (0.05 mmol) of 14 β -azido-7-Boc-13-ketobaccatin III in 1.5 ml of 7:3 acetonitrile-water is added with 0.013 g (0.05 mmol) of triphenylphosphine. After two hours the reaction mixture is concentrated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 1.4:1.0) yields 0.024 g (0.03 mmol, 71%) of the title product. IR (KBr, cm⁻¹): 3500-3100, 3053, 2960, 1726, 1478, 1434, 1090; ¹H-NMR (CDCl₃, 400 MHz): 0.89 (s, 3H, Me), 1.25 (s, 3H, Me), 1.48 (s, 9H, 3Me), 1.84 (s, 3H, Me), 1.98 (m, 1H, H β -6, J₁ = 2.1 Hz, J₂ = 10.8 Hz, J₃ = 14.4 Hz), 2.14 (s, 3H, Me), 2.19 (s, 3H, Me), 2.22 (s, 3H, Me), 2.61 (m, 1H, H α -6, J₁ = 7.0 Hz, J₂ = 9.6 Hz, J₃ = 14.4 Hz), 3.58 (s, 1H, C14-H), 4.01 (d, 1H, H-3, 6.4 Hz), 4.26 (d, 1H, H-20, J = 8.4 Hz), 4.33 (d, 1H, H-20, J = 8.4 Hz), 4.94 (d, 1H, H-5, J₁ = 2.1 Hz, J₂ = 9.6 Hz), 5.40 (m, 1H, H-7, J₁ = 10.8 Hz, J₂ = 7.2 Hz), 5.86 (d, 1H, H-2, J = 6.8 Hz), 6.55 (s, 1H, H-10), 7.44-7.50 (m, 2H, arom), 7.58-7.63 (m 1H, arom), 7.8-8.15 (d, 2H, arom); Anal. Calc C₃₆H₄₅NO₁₃: C, 61.79; H, 6.48. Found : C, 61.89; H, 6.42.

Example 6

20 **14 β -azido-7-TES-13-ketobaccatin III**

[0049] A solution of 1.40 g (2.0 mmol) of 7-TES-13-ketobaccatin III in 7.5 ml of THF and 3.7 ml of DMPU, under nitrogen stream, is added with 5.2 ml of a 1.0 M solution of potassium *tert*-butoxide in THF at -78°C in two minutes and under strong stirring. After 10 min, 0.70 g (3.6 mmol) of tosylazide dissolved in 5.8 ml of THF is added very slowly at the same temperature. The reaction is quenched after 1 hour 30 minutes by addition of 0.5 mL (9.2 mmol) of acetic acid. Temperature spontaneously reaches room temperature. After 24 hours, the reaction mixture is diluted with 50 ml of Et₂O and extracted with 50 ml of a NH₄Cl aqueous saturated solution. The resulting organic phases are washed three times with H₂O, dried, filtered and concentrated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc/Et₂O, 1.8:0.7:0.4) affords 1.12 g (1.5 mmol, 76%) of the title product. IR (KBr, cm⁻¹): 3600-3100, 2956, 2878, 2117, 1730, 1370, 1238; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.59 (m, 6H, 3 CH₂), 0.93 (m, 9H, 3Me), 1.00 (s, 3H, Me), 1.27 (s, 3H, Me), 1.72 (s, 3H, Me), 1.91 (m, 1H, H β -6, J₁ = 2.2 Hz, J₂ = 10.7 Hz, J₃ = 14.2 Hz), 2.19 (s, 3H, Me), 2.22 (s, 3H, Me), 2.25 (s, 3H, Me), 2.54 (m, 1H, H α -6, J₁ = 6.7 Hz, J₂ = 9.7 Hz, J₃ = 14.2 Hz), 3.09 (s, 1H, OH), 3.86 (d, 1H, H-3, J = 6.7 Hz), 4.24 (d, 1H, H-20, J = 8.6 Hz), 4.25 (s, 1H, CHN₃), 4.33 (d, 1H, H-20, J = 8.6 Hz), 4.46 (m, 1H, H-7, J₁ = 10.7 Hz, J₂ = 6.7 Hz), 4.92 (d, 1H, H-5, J₁ = 2.0 Hz, J₂ = 9.5 Hz), 5.82 (d, 1H, H-2, J = 6.9 Hz), 6.53 (s, 1H, H-10), 7.47-7.53 (m, 2H, arom), 7.60-7.65 (m 1H, arom), 8.02-8.04 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 5.6, 7.2, 10.1, 14.4, 19.4, 21.2, 22.1, 34.0, 37.4, 43.4, 45.7, 59.6, 65.5, 72.5, 72.8, 75.5, 75.6, 76.3, 81.3, 84.0, 129.0, 129.2, 129.9, 134.0, 138.2, 155.4, 165.3, 169.0, 169.9, 196.5, 199.5. Anal. Calc. C₃₇H₄₉N₃O₁₁Si: C, 60.06; H, 6.68. Found : C, 59.87; H, 6.79. MS (m/z) 740.0 (M⁺ calc. C₃₇H₄₉N₃O₁₁Si 739.9), 700.2, 621.0, 242.3.

40 Example 7

14-diazo-7-TES-13-ketobaccatin III and 14 β -(1-*p*-toluenesulfonyl)triazenyl-7-TES-13-ketobaccatin III

[0050] A solution of 0.22 g (0.32 mmol) of 7-TES-13-ketobaccatin III in 3.5 ml of THF and 0.6 ml of DMPU is slowly added, under strong stirring, with 0.8 ml of a 1.0 M solution of potassium *tert*-butoxide in THF at -78°C. After 15 min 0.11 g (0.58 mmol) of tosylazide dissolved in 0.9 ml of THF is added with a syringe at -70°C. Temperature is brought to -50°C in 20 minutes. The reaction is quenched after 1 hour by addition of 4 ml of a NH₄Cl aqueous saturated solution. Temperature is brought to 20°C, the reaction mixture is diluted with 3 ml of Et₂O and extracted with 2 ml of NH₄Cl aqueous saturated solution. The organic phases are washed three times with H₂O, dried, filtered and concentrated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 2.1:1.0) affords 0.092 g (0.13 mmol, 40%) of 7-TES-13-keto-14-diazo-baccatin III and 0.062 g (0.07 mmol, 23%) of 7-TES-13-keto-14 β -(1-*p*-toluenesulfonyl)triazenyl-baccatin III as a tautomeric mixture.

[0051] *14-diazo-7-TES-13-ketobaccatin III*: IR (KBr, cm⁻¹): 3600-3100, 2956, 2881, 2098, 1727, 1629, 1370, 1270; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.57 (m, 6H, 3 CH₂), 0.91 (m, 9H, 3Me), 1.26 (s, 3H, Me), 1.28 (s, 3H, Me), 1.65 (s, 3H, Me), 1.85 (m, 1H, H β -6, J₁ = 2.2 Hz, J₂ = 10.7 Hz, J₃ = 14.2 Hz), 2.16 (s, 3H, Me), 2.20 (s, 3H, Me), 2.21 (s, 3H, Me), 2.53 (m, 1H, H α -6, J₁ = 6.7 Hz, J₂ = 9.7 Hz, J₃ = 14.2 Hz), 3.89 (d, 1H, H-3, J = 6.8 Hz), 4.07 (d, 1H, H-20, J = 8.2 Hz), 4.33 (d, 1H, H-20, J = 8.2 Hz), 4.47 (m, 1H, H-7, J₁ = 10.5 Hz, J₂ = 6.7 Hz), 4.92 (d, 1H, H-5, J₁ = 2.2 Hz, J₂ = 9.7 Hz), 5.84 (d, 1H, H-2, J = 7.2 Hz), 6.50 (s, 1H, H-10), 7.42-7.50 (m 2H, arom), 7.59-7.62 (m 1H, arom), 8.10-8.20 (d, 2H,

arom); ^{13}C -NMR (CDCl₃, 100 MHz): 5.7, 7.2, 10.4, 14.4, 18.9, 21.2, 22.0, 33.1, 37.4, 43.0, 45.9, 59.1, 69.6, 72.3, 74.0, 76.0, 76.5, 79.5, 80.6, 84.2, 127.7, 128.3, 129.0, 130.2, 130.4, 134.3, 140.4, 146.4, 167.0, 168.9, 170.3, 183.9, 200.6. Anal. Calc C₃₇H₄₈N₂O₁₁Si: C, 61.31; H, 6.67. Found : C, 61.39; H, 6.75.

[0052] 14 β -(1-*p*-toluenesulfonyl)triazenyl-7-TES-13-ketobaccatin III: IR (KBr, cm⁻¹): 3600-3100, 2957, 1728, 1625, 1615; ^1H -NMR (CDCl₃, 400 MHz, 60°C) relevant resonances at: δ = 0.57-0.64 (m, 6H, 3 CH₂), 0.90-0.96 (m, 9H, 3Me), 1.34 (s, 3H, Me), 1.44 (s, 3H, Me), 1.45 (s, 3H, Me), 1.89 (m, 1H, H β 6, J_1 = 3.3 Hz, J_2 = 10.8 Hz, J_3 = 13.9 Hz), 2.06-2.10 (b, 3H, Me), 2.10-2.14 (b, 3H, Me), 2.16-2.18 (b, 3H, Me), 2.39-2.44 (b, 3H, Me), 2.58 (m, 1H, H α -6, J_1 = 6.3 Hz, J_2 = 9.5 Hz, J_3 = 13.9 Hz), 3.80-4.02 (b, 1H, H-3), 4.35 (d, 1H, H-20, J = 8.8 Hz), 4.62 (d, 1H, H-20, J = 8.8 Hz), 4.78 (m, 1H, H-7, J_1 = 10.8 Hz, J_2 = 6.3 Hz), 4.80 (s, 1H, H-14), 4.94 (d, 1H, H-5, J_1 = 3.3 Hz, J_2 = 9.5 Hz), 5.12-5.30 (b, 1H, NH), 5.80 (d, 1H, H-2, J = 10.8 Hz), 6.66-6.70 (b, 1H, H-10), 7.24-7.30 (m, 2H, arom), 7.46-7.50 (m, 2H, arom), 7.58-7.60 (m 1H, arom), 7.78-7.82 (d, 2H, arom), 8.24-8.28 (d, 2H, arom); ^{13}C -NMR (CDCl₃, 100 MHz) relevant resonances of the major tautomer at: 5.8 (3 CH₂, minor), 6.1 (3 CH₂, major), 7.04 (3 Me, minor), 7.1 (3 Me, major), 9.1, 20.8, 21.7, 21.8, 25.4, 26.5, 37.5, 42.7, 71.5, 74.7, 74.8, 78.3, 79.2, 84.3, 126.6, 127.5, 128.5, 128.9, 129.3, 129.7, 130.0, 130.7 (2 CH), 133.7, 164.7, 168.5, 170.7, 202.2, 203.8.

Example 8

14 β -azido-7-TES-baccatin III

[0053] A solution of 0.46 g (0.63 mmol) of 14 β -azido-7-TES-13-ketobaccatin III in 0.7 ml of THF and 12 ml of ethanol is added with 0.47 g (12.5 mmol) of sodium borohydride in small portions at -40°C and under strong stirring. Temperature spontaneously raises to -28°C. After 4 days, the reaction is quenched by addition of 2 ml of acetic acid and extracted three times with 15 ml of ethyl acetate. The organic phases are dried, filtered and evaporated under reduced pressure. Chromatography of the crude (SiO₂, *n*-hexane/EtOAc, 2.1:1.0) affords 0.33 g (0.44 mmol, 70%) of the title product. IR (KBr, cm⁻¹): 3600-3300, 2956, 2881, 2112, 1728, 1371, 1233; ^1H -NMR (CDCl₃, 400 MHz): δ = 0.59 (m, 6H, 3 CH₂), 0.93 (m, 9H, 3Me), 0.98 (s, 3H, Me), 1.24 (s, 3H, Me), 1.71 (s, 3H, Me), 1.90 (m, 1H, H β -6, J_1 = 2.1 Hz, J_2 = 10.7 Hz, J_3 = 14.2 Hz), 2.18 (s, 3H, Me), 2.20 (m, 3H, Me), 2.34 (s, 3H, Me), 2.53 (m, 1H, H α -6, J_1 = 6.6 Hz, J_2 = 9.7 Hz, J_3 = 14.2 Hz), 2.82 (b, 1H, OH), 3.00 (s, 1H, OH), 3.82 (d, 1H, H-3, J = 7.1 Hz), 3.98 (d, 1H, CHN₃, J = 7.3 Hz), 4.23 (d, 1H, H-20, J = 8.4 Hz), 4.33 (d, 1H, H-20, J = 8.4 Hz), 4.46 (m, 1H, H-7, J_1 = 10.4 Hz, J_2 = 6.5 Hz), 4.80 (m, 1H, C13-H), 4.97 (d, 1H, H-5, J_1 = 1.9 Hz, J_2 = 9.5 Hz), 5.82 (d, 1H, H-2, J = 7.1 Hz), 6.41 (s, 1H, H-10), 7.44-7.50 (m, 2H, arom), 7.58-7.62 (m 1H, arom), 8.07-8.1 (d, 2H, arom); ^{13}C -NMR (CDCl₃, 100 MHz): 5.7, 7.2, 10.4, 15.2, 21.3, 22.1, 22.8, 26.6, 30.1, 37.5, 43.3, 46.8, 59.0, 68.8, 72.5, 74.6, 75.4, 75.7, 76.6, 76.9, 81.3, 84.3, 128.8, 129.4, 130.1, 133.8, 134.3, 140.9, 165.8, 169.4, 170.4, 201.4. Anal. Calc. C₃₇H₅₁N₃O₁₁Si: C, 59.90; H, 6.93. Found : C, 60.16; H, 6.89.

Example 9

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-14 β -azido-7-TES-baccatin III

[0054] A solution of 0.074 g (0.18 mmol) of N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine acid in 5 ml of toluene, cooled to 0°C, is added under nitrogen stream and stirring, with 0.08 g (0.11 mmol) of 7-TES-14 β -azido-baccatin III, 0.04 g (0.18 mmol) of dicyclohexylcarbodiimide (DCC), 0.01 g (0.12 mmol) of dimethylaminopyridine (DMAP), and 0.003 g (0.02 mmol) of *p*-toluenesulfonic acid (PTSA). After 1 hour a 70°C the reaction mixture is cooled and filtered and the solid is washed three times with dichloromethane; the combined organic phases are subsequently evaporated under reduced pressure. Chromatography of the reaction crude (SiO₂, *n*-hexane/EtOAc, 2.2:1.0) affords 0.089 g (0.08 mmol, 72%) of the title product. IR (KBr, cm⁻¹): 3491, 2957, 2111, 1731, 1614, 1508, 1368; ^1H -NMR (CDCl₃, 400 MHz) relevant resonances at: δ = 0.59 (m, 6H, 3 CH₂), 0.93 (m, 9H, 3Me), 1.71 (s, 3H, Me), 1.91 (m, 1H, H β -6, J_1 = 2.0 Hz, J_2 = 11.2 Hz, J_3 = 14.0 Hz), 2.11 (s, 3H, Me), 2.19 (s, 3H, Me), 2.33 (s, 3H, Me), 2.52 (m, 1H, H α -6, J_1 = 6.8 Hz, J_2 = 9.6 Hz, J_3 = 14.0 Hz), 3.83 (d, 1H, H-3), 3.83 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.04 (d, 1H, H-14, J = 8.8 Hz), 4.24 (d, 1H, H-20, J = 8.0 Hz), 4.32 (d, 1H, H-20), 4.94 (m, 1H, H-5), 5.88 (d, 1H, H-2, J = 7.6 Hz), 6.25 (d, 1H, H-13, J = 8.8 Hz), 7.44-7.50 (m, 2H, arom), 7.58-7.62 (m 1H, arom), 8.07-8.1 (d, 2H, arom). Anal. Calc. C₅₈H₈₀N₄O₁₇Si: C, 61.47; H, 7.11. Found : C, 60.89; H, 7.34.

Example 10

13-(N-Boc- β -isobutylisoserinoyl)-14 β -azido-baccatin III

[0055] A solution of 0.080 g (0.07 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-14 β -azido-7-TES-baccatin III in 2 ml of acetonitrile and 2 ml of pyridine is added, at 0°C, with 0.8 mL (0.1 mL/10 mg of

substrate) of hydrofluoric acid-pyridine. After half an hour, the temperature is brought to 25°C. After three hours the reaction is quenched by addition of 4 ml of a NH₄Cl saturated solution and extracted three times with 8 ml of AcOEt. The organic phases are washed three times with a CuSO₄ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The resulting reaction crude (dissolved in 1.5 ml of dichloromethane) is added at 0°C with 0.7 ml of a 0.1 M solution of acetyl chloride in MeOH. After three hours the reaction is quenched by addition of 3 ml of a NH₄Cl aqueous saturated solution. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography (SiO₂, *n*-hexane/EtOAc, 1.0:1.2) yields 0.04 g (0.05 mmol, 70%) of the title product. IR (KBr, cm⁻¹): 3461, 2110, 1734, 1636, 1373, 1242, 1048; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.97 (t, 6H, 2Me), 1.19 (s, 3H, Me), 1.20 (s, 3H, Me), 1.38-1.4 (br s., 11H), 1.68-1.74 (m, 1H, H-5'), 1.71 (s, 3H, Me), 1.88 (s, 3H, Me), 1.91 (m, 1H, H β -6, J_1 = 2.3 Hz, J_2 = 10.7 Hz, J_3 = 14.8 Hz), 2.24 (s, 3H, Me), 2.43 (s, 3H, Me), 2.46-2.52 (b, 1H, OH), 2.57 (m, 1H, H α -6, J_1 = 6.6 Hz, J_2 = 9.6 Hz, J_3 = 14.9 Hz), 3.76 (d, 1H, H-3, J = 7.1 Hz), 3.85 (d, 1H, OH), 4.04 (d, 1H, H-14, J = 8.8 Hz), 4.08 (m, 1H, H-3'), 4.26 (d, 1H, H-20, J = 8.8 Hz), 4.35 (d, 1H, H-20), 4.39 (m, 1H, H-7), 4.72 (d, 1H, H-2'), 4.98 (m, 1H, H-5, J_1 = 2.3 Hz, J_2 = 9.6 Hz), 5.88 (d, 1H, H-2, J = 7.1 Hz), 6.07 (d, 1H, H-13, J = 8.8 Hz), 6.28 (s, 1H, H-10), 7.44-7.50 (m, 2H, arom), 7.58-7.62 (m 1H, arom), 8.07-8.1 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 10.0, 15.3, 21.3, 22.3, 22.7, 23.6, 23.7, 25.1, 27.1, 28.6, 35.9, 40.8, 43.5, 45.3, 52.0, 59.0, 65.5, 72.3, 74.1, 74.8, 75.5, 76.5, 77.2, 77.6, 80.5, 81.6, 84.5, 128.9, 129.1, 130.1, 133.9, 134.9, 139.1, 156.2, 165.7, 170.0, 171.1, 173.4, 202.9. Anal. Calc. C₃₉H₅₃NO₁₁Si: C, 62.70; H, 7.34. Found : C, 62.36; H, 7.49.

Example 11

14 β -amino-7-TES-13-ketobaccatin III

[0056] A solution of 0.08 g (0.11 mmol) of 14 β -azido-7-TES-13-ketobaccatin III in 3.2 ml of an acetonitrile/water 9/1 mixed solution is added with 0.03 g (0.12 mmol) of triphenylphosphine. The reaction is cooled at 5°C, and after 18 hours is evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc/Et₂O, 1.8:0.7:0.3) affords 0.07 g (0.11 mmol, 97%) of the title product: IR (KBr, cm⁻¹): 3500-3100, 3053, 1730, 1438, 1239, 1063; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.58 (m, 6H, 3 CH₂), 0.84 (s, 3H, Me), 0.93 (m, 9H, 3Me), 1.27 (s, 3H, Me), 1.73 (s, 3H, Me), 1.90 (m, 1H, H β -6, J_1 = 2.0 Hz, J_2 = 11.2 Hz, J_3 = 14.0 Hz), 2.12 (s, 3H, Me), 2.19 (m, 3H, Me), 2.21 (s, 3H, Me), 2.52 (m, 1H, H α -6, J_1 = 6.4 Hz, J_2 = 9.2 Hz, J_3 = 14.0 Hz), 3.57 (s, 1H, H-14), 3.84 (d, 1H, H-3, J = 6.8 Hz), 4.24 (d, 1H, H-20, J = 8.8 Hz), 4.30 (d, 1H, H-20, J = 8.8 Hz), 4.47 (m, 1H, H-7, J_1 = 10.4 Hz, J_2 = 6.4 Hz), 4.89 (d, 1H, H-5, J_1 = 2 Hz, J_2 = 9.6 Hz), 5.86 (d, 1H, H-2, J = 6.8 Hz), 6.50 (s, 1H, H-10), 7.43-7.45 (m, 2H, arom), 7.61-7.66 (m 1H, arom), 7.99-8.01 (d, 2H, arom); Anal. Calc. C₄₃H₅₈N₄O₁₅Si: C, 59.30; H, 6.71. Found : C, 60.3; H, 7.19.

Example 12

14 β -Amino-7-TES-13-ketobaccatin III 14,1-carbamate

[0057] A solution of 0.18 g (0.26 mmol) of 14 β -amino-7-TES-13-ketobaccatin III in 6 mL of CH₂Cl₂ at -78°C is added with 0.13 mL (0.26 mmol) of a 1.93 M solution of phosgene in toluene and 0.04 mL (0.51 mmol) of pyridine under stirring. After 1 hour the reaction mixture is quenched by addition of 5 ml of water and extracted with 10 ml of dichloromethane; the organic phases are washed three times with brine, dried, filtered, and evaporated under reduced pressure. Chromatography (SiO₂, *n*-hexane/EtOAc/Et₂O, 1.8:0.7:0.3) affords 0.16 g (0.22 mmol, 86%) of the title product. IR (KBr, cm⁻¹): 3342, 2955, 1731, 1452, 1238, 1090; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.60 (m, 6H, 3 CH₂), 0.93 (m, 9H, 3Me), 1.14 (s, 3H, Me), 1.34 (s, 3H, Me), 1.73 (s, 3H, Me), 1.92 (m, 1H, H β -6, J_1 = 2.4 Hz, J_2 = 10.8 Hz, J_3 = 14.0 Hz), 2.15 (s, 3H, Me), 2.20 (m, 3H, Me), 2.22 (s, 3H, Me), 2.52 (m, 1H, H α -6, J_1 = 6.6 Hz, J_2 = 9.7 Hz, J_3 = 14.0 Hz), 3.83 (d, 1H, H-3, J = 6.8 Hz), 4.17 (s, 1H, H-14), 4.23 (d, 1H, H-20, J = 8.8 Hz), 4.32 (d, 1H, H-20, J = 8.8 Hz), 4.46 (m, 1H, H-7, J_1 = 10.7 Hz, J_2 = 6.5 Hz), 4.90 (d, 1H, H-5, J_1 = 1.9 Hz, J_2 = 9.5 Hz), 6.02 (s, 1H, N-H), 6.06 (d, 1H, H-2, J = 6.9 Hz), 6.48 (s, 1H, H-10), 7.42-7.45 (m, 2H, arom), 7.58-7.61 (m 1H, arom), 7.96-7.98 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 5.7, 7.2, 10.4, 14.2, 19.8, 21.1, 22.1, 30.1, 32.9, 37.3, 42.6, 45.4, 59.2, 59.3, 69.7, 72.3, 74.9, 76.3, 80.9, 84.2, 86.2, 128.4, 129.0, 129.9, 134.2, 138.9, 151.1, 155.7, 164.6, 168.9, 170.1, 195.6, 199.3. Anal. Calc. C₃₉H₅₁NO₁₂Si: C, 62.13; H, 6.82. Found : C, 60.16; H, 6.89.

Example 13

14 β -amino-7-TES-baccatin III 14,1-carbamate

[0058] A solution of 0.07 g (0.1 mmol) of 14 β -amino-7-TES-13-ketobaccatin III 14,1-carbamate in 4 ml of ethanol at -40°C is added, under stirring, with 0.056 g (1.49 mmol) of sodium borohydride. Temperature is brought to -18°C then,

after 4 hours, a further 0.04 g (1.0 mmol) of sodium borohydride is added. After 18 hours, the reaction mixture is quenched by addition of 2 ml of acetic acid and extracted with 10 ml of ethyl acetate. The organic phases are dried, filtered, and evaporated under reduced pressure. $^1\text{H-NMR}$ spectrum of the residue shows the presence of 14 β -amino-7-TES-baccatin III 14,1-carbamate and of its 13 β epimer in an $\alpha/\beta=62/38$ ratio. Chromatography of the mixture (SiO_2 , dichloromethane/EtOAc, 1.0:0.9) yields 0.04 g (0.06 mmol, 62%) of the title product. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 0.58 (m, 6H, 3 CH_2), 0.93 (m, 9H, 3Me), 1.08 (s, 3H, Me), 1.26 (s, 3H, Me), 1.70 (s, 3H, Me), 1.88 (m, 1H, $\text{H}\beta$ -6, J_1 = 2.0 Hz, J_2 = 10.0 Hz, J_3 = 13.2 Hz), 2.15 (s, 3H, Me), 2.17 (m, 3H, Me), 2.19 (s, 3H, Me), 2.52 (m, 1H, $\text{H}\alpha$ -6, J_1 = 7.2 Hz, J_2 = 9.6 Hz, J_3 = 14.0 Hz), 3.66 (b, 1H, OH), 3.75 (d, 1H, H-3, J = 7.2 Hz), 3.98 (d, 1H, H-14, J = 6.0 Hz), 4.15 (d, 1H, H-20, J = 8.4 Hz), 4.23 (d, 1H, H-20, J = 8.4 Hz), 4.44 (m, 1H, H-7, J_1 = 10.0 Hz, J_2 = 6.0 Hz), 4.66 (m, 1H, H-13), 4.93 (d, 1H, H-5, J_1 = 2.0 Hz, J_2 = 8 Hz), 5.98 (d, 1H, H-2, J = 7.2 Hz), 6.42 (s, 1H, H-10), 7.41-7.45 (m, 2H, arom), 7.58-7.61 (m 1H, arom), 7.98-8.01 (d, 2H, arom); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): 5.7, 7.2, 10.6, 15.1, 21.3, 22.1, 22.6, 26.2, 30.1, 37.4, 42.2, 46.5, 58.9, 61.1, 71.1, 72.3, 73.4, 75.4, 80.7, 84.3, 88.9, 128.8, 128.9, 129.9, 132.5, 134.0, 143.1, 158.2, 165.3, 169.2, 170.3, 201.3. Anal. Calc. $\text{C}_{39}\text{H}_{53}\text{NO}_{12}\text{Si}$: C, 61.97; H, 7.07. Found : C, 62.3; H, 6.93.

15 Example 14

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-14 β -amino-7-TES-baccatin III 14,1-carbamate

20 [0059] A solution of 0.124 g (0.30 mmol) of N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine in 6 ml of toluene, cooled at 0°C, is added with 0.102 g (0.14 mmol) of 7-TES-14 β -amino-baccatin III 14,1-carbamate, 0.06 g (0.30 mmol) of dicyclohexylcarbodiimide (DCC), 0.02 g (0.15 mmol) of dimethylaminopyridine (DMAP), and 0.005 g (0.03 mmol) of *p*-toluenesulfonic acid (PTSA), under stirring and nitrogen stream. After 2 hours at 70°C, a further 0.045 g (0.11 mmol) of N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine and 0.022 g (0.11 mmol) of DCC are added. After 25 a further 3 hours, the reaction is cooled and filtered. The solid is washed three times with dichloromethane; the combined organic phases are subsequently concentrated under reduced pressure. Chromatography of the reaction mixture (SiO_2 , n-hexane/EtOAc/ CH_2Cl_2 , 1.0:0.6:0.6) yields 0.136 g (0.12 mmol, 86%) of the title product. IR (KBr, cm^{-1}): 3435, 2956, 1735, 1454, 1369, 1235; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz) relevant resonances: δ = 0.58 (m, 6H, 3 CH_2), 0.93 (m, 9H, 3Me), 1.75 (s, 3H, Me), 2.19 (s, 3H, Me), 2.26 (s, 3H, Me), 2.52 (m, 1H, $\text{H}\alpha$ -6, J_1 = 6.4 Hz, J_2 = 10.0 Hz, J_3 = 14.4 Hz), 3.87 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.22 (d, 1H, H-20, J = 7.6 Hz), 4.26 (d, 1H, H-20), 4.90 (m, 1H, H-5, J = 7.2 Hz), 6.05 (d, 1H, H-2, J = 7.2 Hz), 7.40-7.44 (m, 2H, arom), 7.56-7.60 (m 1H, arom), 7.98-7.99 (d, 2H, arom). Anal. Calc. $\text{C}_{59}\text{H}_{80}\text{N}_2\text{O}_{18}\text{Si}$: C, 62.53; H, 7.11. Found : C, 63.3; H, 6.99.

35 Example 15

13-(N-Boc- β -isobutylisoserinoyl)-14 β -amino-baccatin III 14,1-carbamate

40 [0060] A solution of 0.114 g (0.10 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-14 β -amino-7-TES-baccatin III 14,1-carbamate in 1.6 ml of dichloromethane is added, at 0°C, with 1.02 ml of a 0.01 M acetyl chloride solution in methanol. After 24 hours at 5°C, the reaction mixture is quenched by addition of 7 ml of a NH_4Cl aqueous saturated solution and extracted with 10 ml of AcOEt. The combined organic phases are subsequently dried and concentrated under reduced pressure. The chromatographic purification (SiO_2 , n-hexane/EtOAc/ Et_2O 1:0.7:0.3) affords 0.06 g (0.061 mmol, 66%) of the title compound. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 0.97 (t, 6H, 2Me), 1.25-1.31 (b, 8H, 2Me and 2H of H-4'), 1.37 (s, 9H, 3Me), 1.69-1.72 (s, 4H, Me, H-5'), 1.78-1.96 (m, 4H, $\text{H}\beta$ -6, Me), 2.25 (s, 3H, Me), 2.33 (s, 3H, Me), 2.55 (m, 1H, $\text{H}\alpha$ -6), 3.05 (d, 1H, OH, J = 6.4 Hz), 3.76 (d, 1H, H-3, J = 7.2 Hz), 4.15 - 4.22 (m, 3H, H-14, H-2', H3'), 4.28 (d, 1H, H-20), 4.35 (d, 1H, H-20), 4.38 (m, 1H, H-7), 4.73 (d, 1H, N'-H, J = 9.6 Hz), 4.94 (m, 1H, H-5, J_1 = 0.8 Hz, J_2 = 7.6 Hz), 6.02 (d, 1H, H-2, J = 7.6 Hz), 6.11 (d, 1H, H-13, J = 6.8 Hz, J = 1.6 Hz), 6.26 (s, 1H, H-10), 7.42-7.45 (m, 2H, arom), 7.54-7.58 (m 1H, arom), 8.02-8.1 (d, 2H, arom); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz) relevant resonances: 10.2, 15.4, 21.2, 21.8, 22.9, 23.4, 23.8, 25.0, 26.3, 28.7, 30.1, 35.8, 41.8, 42.5, 44.9, 51.8, 57.8, 58.8, 71.2, 72.1, 73.0, 75.3, 76.4, 81.2, 81.7, 84.4, 128.7, 128.9, 130.0, 134.0, 134.1, 140.1, 156.4, 164.9, 173.5, 202.5; Anal. Calc. $\text{C}_{44}\text{H}_{58}\text{N}_2\text{O}_{16}$: C, 60.68; H, 6.71. Found : C, 61.2; H, 6.99.

55 Example 16

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III

50 [0061] A catalytic amount of palladium on charcoal is added to a solution of 0.052 g (0.05 mmol) 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-14 β -azido-7-TES-baccatin III in 2.0 ml of MeOH, then gas hydrogen is

bubbled therein. After 18 hours at room temperature, the reaction mixture is filtered through celite bed, and the solid is washed with 6 ml of ethyl acetate. The resulting organic phases are heated to 45°C for 20 minutes and subsequently evaporated under reduced pressure. Chromatography of the residue (SiO₂, n-hexane/EtOAc/CH₂Cl₂ 0.7:0.3:1.0) yields 0.72 g (0.064 mmol, 70%) of the title product. IR (KBr, cm⁻¹): 3449, 2957, 1726, 1617, 1368, 1237, 1105; ¹H-NMR (CDCl₃, 400 MHz) relevant resonances at δ = 0.58 (m, 6H, 3CH₂), 0.94 (m, 9H, 3Me), 1.07 (m, 10H), 1.72 (s, 3H, Me), 2.12 (s, 3H, Me), 2.18 (s, 3H, Me), 2.30 (s, 3H, Me), 2.51 (m, 1H, H α -6), 3.35 (d, 1H, J = 8.8 Hz), 3.83 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.26 (m, 2H, 2H-20), 4.53 (m, 3H), 4.93 (d, 1H, H-5), 5.85 (d, 1H, H-2, J = 7.2 Hz), 6.06 (d, 1H, H-13), 6.45-6.51 (m, 3H), 6.59 (s, 1H, H-10), 7.42-7.45 (m, 2H, arom), 7.54-7.60 (m 1H, arom), 8.00-8.02 (d, 2H, arom). Anal. Calc. C₅₈H₈₂N₂O₁₇Si: C, 62.91; H, 7.46. Found : C, 63.4; H, 6.87.

Example 17

13-(N-Boc- β -isobutylisoserinoyl)-14 β -amino-baccatin III

[0062] A solution of 0.107 g (0.09 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III in 2.7 ml of acetonitrile and 2.7 ml of pyridine is added, at 0°C, with 10.7 mL (0.1 mL/10 mg of substrate) hydrofluoric acid-pyridine. After half an hour the temperature is brought to 25°C. After three hours, the reaction is quenched by addition of 6 ml of a NH₄Cl aqueous saturated solution and extracted three times with 8 ml of AcOEt. The organic phases are washed three times with a CuSO₄ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The resulting reaction crude is dissolved in 3.5 ml of dichloromethane, then added, at 0°C, with 1.15 ml of a 0.1 M acetyl chloride solution in MeOH. After three hours, the reaction is quenched by addition of 5 ml of a NH₄Cl aqueous saturated solution and extracted with 8 ml of AcOEt. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography (SiO₂, n-hexane/EtOAc, 1.0:1.2) yields 0.05 g (0.06 mmol, 70%) of the title product. ¹H-NMR (CDCl₃, 400 MHz): δ = 1.00 (m, 6H, 2Me), 1.14 (s, 3H, Me), 1.19 (s, 3H, Me), 1.32 (s, 9H, 3Me), 1.62-1.78 (s, 4H, Me, H-5'), 1.84-1.94 (m, 4H, H β -6, Me), 2.24 (s, 3H, Me), 2.39 (s, 3H, Me), 2.55 (m, 1H, H α -6, J ₁ = 6.4 Hz, J ₂ = 9.6 Hz, J ₃ = 14.8 Hz), 3.09 (b, 1H, OH), 3.35 (d, 1H, J = 9.2 Hz), 3.74 (d, 1H, J = 7.2 Hz), 4.18 - 4.33 (m, 4H, H-2', H β -2', 2H-20), 4.41 (m, 1H, H-7), 4.70 (d, 1H, N'-H, J = 9.6 Hz), 4.95 (m, 1H, H-5, J ₁ = 2 Hz, J ₂ = 9.6 Hz), 5.81 (d, 1H, H-2, J = 7.6 Hz), 5.90 (d, 1H, H-13, J = 9.2 Hz, J = 1.2 Hz), 6.27 (s, 1H, H-10), 7.42-7.46 (m, 2H, arom), 7.52-7.61 (m 1H, arom), 8.0-8.06 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 10.1, 15.3, 21.3, 22.3, 23.0, 23.7, 24.4, 25.1, 26.8, 28.6, 30.1, 35.8, 42.2, 43.3, 45.0, 51.4, 53.5, 58.7, 72.3, 72.9, 75.1, 75.3, 75.7, 80.6, 81.5, 84.5, 128.8, 129.8, 130.0, 133.4, 135.0, 138.8, 156.1, 165.6, 169.8, 171.4, 203.3, MS (mz) (M⁺ calc. C₄₃H₆₀N₂O₁₅ 844.4), 845.4, 789.5, Anal. Calc. C₄₃H₆₀N₂O₁₅: C, 61.12; H, 7.16. Found : C, 62.3; H, 6.99.

Example 18

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -t-butoxycarbamoyl-baccatin III 14,1-carbamate

[0063] A solution of 0.11 g (0.10 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III in 3 ml of dichloromethane is added with 0.04 g (0.20 mmol) of BOC₂O, 0.03 mL (0.21 mmol) of triethylamine and 0.006 g (0.05 mmol) of dimethylaminopyridine, at room temperature. After 3 hours the reaction is quenched by addition of 4 ml of a NH₄Cl aqueous saturated solution and extracted three times with 6 ml of dichloromethane. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography (SiO₂, n-hexane/EtOAc/CHCl₃, 8.0:3.0:5.0) affords 0.09 g (0.06 mmol, 69%) of the title product. IR (KBr, cm⁻¹): 3450, 2961, 1803, 1733, 1370, 1239, 1089; ¹H-NMR (CDCl₃, 400 MHz) relevant resonances at δ = 0.59 (m, 6H, 3CH₂), 0.94 (m, 9H, 3Me), 1.37 (s, 9H), 1.72 (s, 3H, Me), 2.19 (s, 3H, Me), 2.23 (s, 3H, Me), 2.46 (s, 3H, Me), 2.52 (m, 1H, H α -6), 3.82 (s, 3H, OMe), 3.88 (s, 3H, OMe), 4.18 (d, 1H, H-20, J = 8 Hz), 4.24 (d, 1H, H-20, J = 8 Hz), 4.56 (m, 3H), 4.76 (d, 1H, J = 7.2 Hz), 4.93 (d, 1H, H-5), 6.01 (d, 1H, H-2, J = 7.2 Hz), 6.36 (s, 1H, H-10), 6.42 (d, 1H), 6.47-6.51 (m, 3H), 7.32-7.42 (m, 2H, arom), 7.51-7.58 (m 1H, arom), 7.92-7.98 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz) relevant resonances: 5.7, 7.2, 10.7, 15.5, 21.2, 22.2, 22.4, 22.9, 23.7, 26.7, 28.1, 28.6, 37.4, 42.1, 43.7, 46.3, 55.5, 55.7, 58.7, 59.8, 71.3, 72.1, 74.1, 74.7, 76.2, 80.2, 84.4, 84.8, 104.5, 128.5, 129.0, 129.9, 133.9, 134.1, 139.5, 150.4, 151.2, 159.2, 164.6, 171.0, 200.7; Anal. Calc. C₆₄H₉₄N₂O₁₉Si: C, 62.8; H, 7.74. Found : C, 61.3; H, 6.64.

Example 19

13-(N-Boc- β -isobutylisoserinoyl)-14 β -t-butoxycarbamoyl-baccatin III 14,1-carbamate

[0064] A solution of 0.08 g (0.07 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-

14 β -t-butoxycarbamoyl-baccatin III 14,1-carbamate in 2.1 ml of acetonitrile and 2.1 ml of pyridine is added, at 0°C, with 0.8 mL (0.1 mL/10 mg of substrate) of hydrofluoric acid-pyridine. After half an hour temperature is brought to 25°C. After three hours, the reaction is quenched by addition of 6 ml of a NH₄Cl aqueous saturated solution and extracted three times with 7 ml of AcOEt. The organic phases are washed three times with a CuSO₄ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The resulting reaction crude is dissolved in 3 ml of dichloromethane, then added with 0.82 ml of a 0.1 M solution of acetyl chloride in MeOH, at 0°C. After three hours the reaction is quenched by addition of 7 ml of a NH₄Cl aqueous saturated solution and extracted with 8 ml of AcOEt. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography of the resulting mixture (SiO₂, n-hexane/EtOAc, 1.0:1.2) yields 0.03 g (0.06 mmol, 46%) of the title product. IR (KBr, cm⁻¹): 3450, 2961, 1803, 1733, 1506, 1370, 1239, 1089, 732; ¹H-NMR (CDCl₃, 400 MHz) relevant resonances at δ = 0.98 (m, 6H, 2Me), 1.28 (s, 3H, Me), 1.31 (s, 3H, Me), 1.38 (s, 9H, 3Me), 1.43 (s, 9H, 3Me), 1.66 (m, 1H, H-5'), 1.72 (s, 3H, Me), 1.91 (m, 4H, H β -6, Me), 2.25 (s, 3H, Me), 2.53 (m, 4H, Me, H α -6), 3.82 (d, 1H, H-3, J = 7.2 Hz), 3.95 (b, 1H, OH), 4.07 (m, 1H, H-3'), 4.25 (m, 3H, 2H-20, H-2'), 4.42 (m, H, H-7), 4.74 (d, 1H, H-14, J = 7.6 Hz), 4.89 (d, 1H, N-H, J = 8.8 Hz), 4.96 (m, 1H, H-5, J_2 = 7.6 Hz), 6.01 (d, 1H, H-2, J = 7.2 Hz), 6.26 (m, 2H, H-10, H-13), 7.38-7.42 (m, 2H, arom), 7.54-7.58 (m 1H, arom), 7.95-7.97 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 10.2, 16.0, 21.2, 22.6, 23.3, 23.5, 25.3, 27.0, 28.1, 28.7, 35.9, 42.0, 45.2, 51.6, 58.9, 59.5, 71.2, 72.1, 74.2, 75.3, 76.3, 80.7, 84.6, 85.4, 128.4, 129.0, 129.9, 133.3, 134.0, 141.4, 150.2, 155.9, 164.4, 169.5, 171.0, 171.2, 172.1, 202.5; Anal. Calc. C₄₈H₆₈N₂O₁₇: C, 61.00; H, 7.25. Found : C, 61.3; H, 6.64.

Example 20

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III 14,1-thiocarbamate

[0065] A solution of 0.171 g (0.15 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III in 7 ml of acetonitrile is added, at room temperature, with 0.14 g (0.61 mmol) of di-2-pyridyl-thionocarbonate. After two hours, the reaction mixture is quenched by addition of 4 ml of water and extracted three times with 6 ml of dichloromethane. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO₂, n-hexane/EtOAc/CH₂Cl₂, 7.0:5.0:8.0) affords 0.13 g (0.11 mmol, 69%) of the title product. IR (KBr, cm⁻¹): 3446, 2958, 1732, 1694, 1595, 1278, 1167; ¹H-NMR (CDCl₃, 400 MHz, 55°C) relevant resonances at: δ = 0.60 (m, 6H, 2 CH₃), 0.95 (m, 9H, 3Me), 1.08 (m, 6 H), 1.18-1.48 (m, 18H), 1.73 (s, 3 H, Me), 2.13 (s, 3H, Me), 2.19 (s, 3H, Me), 2.23 (s, 3H, Me), 2.51 (m, 1H, H α -6, J_1 = 6.6 Hz, J_2 = 9.7 Hz, J_3 = 14.3 Hz), 3.78 (d, 1H, H-14, J_1 = 7.4Hz), 3.82 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.23-4.29 (m, 3H, H-3, 2H-20, J = 7.2 Hz), 4.44 (m, 2H, H-7, H-3'), 4.90 (m, 1H, H-5, J = 9.8 Hz), 6.09 (d, 1H, H-13, J = 7.1 Hz), 6.13 (d, 1H, H-2, J = 7.2 Hz), 6.48 (m, 4H, arom), 7.37-7.41 (m, 2H, arom), 7.54-7.57 (m 1H, arom), 7.96-7.98 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): 5.69, 7.17, 10.7, 15.0, 21.1, 22.3, 22.6, 22.8, 25.7, 26.2, 28.5, 37.3, 42.7, 46.4, 55.6, 55.7, 58.8, 62.8, 70.6, 72.1, 74.6, 75.7, 76.2, 80.7, 84.3, 86.9, 98.7, 104.3, 128.8, 128.8, 129.1, 129.9, 133.8, 134.7, 137.9, 159.0, 161.6, 164.8, 169.2, 169.9, 171.5, 187.9, 200.4; Anal. Calc. C₆₀H₈₄N₂O₁₇SSi: C, 61.83; H, 7.26. Found : C, 61.2; H, 7.3.

Example 21

13-(N-Boc- β -isobutylisoserinoyl)-14 β -amino-baccatin III 14,1-thiocarbamate

[0066] A solution of 0.11 g (0.10 mmol) of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-14 β -amino-baccatin III 14,1-thiocarbamate in 2.7 ml of acetonitrile and 2.7 ml of pyridine is added, at 0°C, with 1.1 mL hydrofluoric acid-pyridine. After half an hour temperature is raised to 25°C. After two hours, the reaction is quenched by addition of 6 ml of a NH₄Cl aqueous saturated solution and extracted three times with 11 ml of AcOEt. The organic phases are washed three times with a CuSO₄ aqueous saturated solution, dried, filtered, and evaporated under reduced pressure. The resulting reaction crude (dissolved in 4 ml of dichloromethane) is added, at 0°C, with 1.2 ml of a 0.1 M solution of acetyl chloride in MeOH. After three hours the reaction is quenched by addition of 7 ml of a NH₄Cl aqueous saturated solution and extracted with 8 ml of AcOEt. The organic phases are dried, filtered, and evaporated under reduced pressure. Chromatography of the residue (SiO₂, EtOAc/n-hexane, 1.4:1) yields 0.03 g (0.05 mmol, 62%) of the title product. IR (KBr, cm⁻¹): 3343, 2960, 1735, 1686, 1514, 1239, 1088, 733; ¹H-NMR (CDCl₃, 400 MHz): δ = 0.99 (m, 6H, 2Me), 1.29 (s, 3H, Me), 1.41 (s, 9H, 3Me), 1.73 (s, 3H, Me), 1.74-1.94 (m, 10H, H β -6, H-5', H-4', 2Me), 2.24 (s, 3H, Me), 2.31 (s, 3H, Me), 2.48 (m, 1H, H α -6, J_1 = 6.4 Hz, J_2 = 9.0 Hz, J_3 = 15.0 Hz), 3.72 (d, 1H, H-3, J = 7.2 Hz), 4.10 - 4.18 (m, 2H, H-2', H3'), 4.28 (m, 2H, H-20), 4.36 (m, 2H, H-7, H-20), 4.78 (d, 1H, N'-H, J = 9.2 Hz), 4.94 (m, 1H, H-5, J_1 = 2.4 Hz, J_2 = 9.6 Hz), 6.09 (d, 2H, H-2, H-13, J = 7.6 Hz), 6.26 (s, 1H, H-10), 7.40-7.45 (m, 2H, arom), 7.49-7.52 (m 1H, arom), 7.99-8.01 (d, 2H, arom), 9.33 (s, 1H, NH); ¹³C-NMR (CDCl₃, 100 MHz): 10.2, 15.3, 21.2, 21.9, 23.1, 23.7, 25.0, 26.2, 28.7, 35.9, 41.6, 42.7, 45.3, 52.0, 58.9, 62.0, 70.7, 72.0, 72.8, 75.3, 76.4, 76.7, 81.2, 82.1, 84.4, 94.8, 128.8,

129.8, 130.0, 133.9, 134.1, 139.9, 156.2, 164.8, 169.5, 171.0, 173.5, 202.3; Anal. Calc. C₄₄H₅₈N₂O₁₅S: C, 59.58; H, 6.59. Found : C, 61.3; H, 6.64.

Example 22

5

7-TES-14-(Boc)-triazenyl-13-ketobaccatin III

[0067] (0.06 g, 0.52 mmol), of potassium *tert*-butoxide are suspended at -75°C, under nitrogen stream and strong stirring, in 1.5 mL of anhydrous THF. After 10 minutes a solution of 0.13 g (0.19 mmol) of 7-TES-13-ketobaccatin III in 1.0 ml of THF and 0.7 ml of DMPU is added in 3 minutes at the same temperature. After 15 min, 0.06 g (0.41 mmol) of *tert*Boc-azide dissolved in 1 ml of THF is added in two minutes at -70°C. After two hours, and after temperature has raised to -50°C, the reaction is quenched by addition of 5.0 ml of a NH₄Cl saturated aqueous solution. Temperature is slowly raised to 20°C and the reaction mixture is diluted with 3.0 ml of Et₂O and extracted with 6.0 ml of a NH₄Cl aqueous saturated solution. The organic phases are washed three times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 2.3:1.0) affords 0.022 g (0.26 mmol, 50%) of the title product. IR (KBr, cm⁻¹): 3500-3100, 2962, 1731, 1374, 1238; ¹H-NMR (CDCl₃, 400 MHz): ¹H-NMR (CDCl₃, 400 MHz): relevant resonances δ = 0.58 (m, 6H, 3CH₂), 0.91 (m, 9H, 3Me), 1.11 (s, 3H, Me), 1.31 (s, 3H, Me), 1.55 (s, 9H, 3Me), 1.71 (s, 3H, Me), 1.88 (m, 1H, H β -6), 2.20 (s, 3H, Me), 2.21 (s, 3H, Me), 2.22 (s, 3H, Me), 2.52 (m, 1H, H α -6), 3.91 (d, 1H, H-3), 4.23 (s, 2H, 2H-20), 4.47 (m, 2H, H-7, H-14), 4.92 (d, 1H, H-5), 5.80 (d, 1H, CH₂), 6.54 (s, 1H, H-10), 6.89 (S, 1H), 7.38-7.60 (m, 4H, arom), 7.96-7.99 (m, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): δ = 5.5, 7.0, 10.0, 14.3, 19.2, 21.0, 22.0, 28.3, 33.8, 37.3, 43.1, 45.1, 59.3, 72.5, 73.5, 73.9, 75.6, 76.4, 76.7, 80.8, 83.3, 84.0, 128.9, 129.0, 129.2, 130.3, 130.4, 133.7, 138.6, 150.4, 152.1, 165.7, 169.2, 171.0, 194.7, 200.3; MS (m/z) (M⁺ calc. C₄₂H₅₉N₃O₁₃Si 841.4), 842.4, 714, 652, 574; Anal. Calc. C₄₂H₅₉N₃O₁₃Si: C, 59.91; H, 7.06. Found: C, 58.9; H, 6.57.

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Example 23

14-[N,N'-bis-(benzyloxycarbonyl)hydrazino]-7-Boc-13-ketobaccatin III

[0068] 0.16 g (1.47 mmol) of potassium *tert*-butoxide are suspended, under nitrogen stream and strong stirring, in 3.0 ml of anhydrous THF at -72°C. The mixture is added, in two minutes and at the same temperature, with 0.37 g (0.54 mmol) of 7-Boc-13-ketobaccatin III in 2.5 ml of THF and 1.8 ml of DMPU. After 15 minutes, 0.32 g (1.19 mmol) di-*tert*-benzyl-azodicarboxylate dissolved in 3.0 ml of THF and 0.2 ml of DMPU are slowly added at -68°C. Temperature is raised -50°C, and after 8 hours the reaction mixture is quenched by addition of 2 mL (0.03 mmol) of acetic acid diluted with 10 ml of ethyl ether and extracted with 10 ml of a NH₄Cl aqueous saturated solution. The organic phases are washed three times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 1.3:5.0) affords 0.30 g (0.29 mmol, 55%) of the title product. ¹H-NMR (CDCl₃, 400 MHz): δ = 0.86 (s, 3H, Me), 1.23 (s, 3H, Me), 1.47 (s, 9H, 3Me), 1.82 (s, 3H, Me), 1.97 (m, 1H, H β -6, J₁ = 2.5 Hz, J₂ = 10.9 Hz, J₃ = 14.3 Hz), 2.13 (s, 3H, Me), 2.18 (s, 3H, Me), 2.19 (s, 3H, Me), 2.59 (m, 1H, H α -6, J₁ = 7.2 Hz, J₂ = 9.5 Hz, J₃ = 14.3 Hz), 4.14 (d, 1H, H-3, 6.2 Hz), 4.24 (d, 1H, H-20, J = 8.6 Hz), 4.37 (d, 1H, H-20, J = 8.6 Hz), 4.90 (s, 1H, H-14), 4.92 (d, 1H, H-5, J₁ = 2.5 Hz, J₂ = 9.5 Hz), 4.99 (d, 1H, CH₂, J = 12.5 Hz), 5.06 (d, 1H, CH₂, J = 12.5 Hz), 5.12 (d, 1H, CH₂, J = 12.5 Hz), 5.18 (d, 1H, CH₂, J = 12.5 Hz), 5.41 (m, 1H, H-7, J₁ = 10.8 Hz, J₂ = 6.9 Hz), 5.62 (s, 1H), 5.97 (d, 1H, H-2, J = 6.2 Hz), 6.56 (s, 1H, H-10), 6.89 (s, 1H), 7.15-7.30 (m, 10H, arom), 7.34-7.40 (m, 2H, arom), 7.50-7.55 (m 1H, arom), 8.25 (d, 2H, arom); ¹³C-NMR (CDCl₃, 100 MHz): δ = 10.9, 14.4, 20.1, 21.0, 22.0, 27.9, 33.6, 43.5, 45.9, 57.2, 66.1, 68.8, 69.5, 73.6, 74.4, 75.2, 75.8, 76.8, 80.9, 83.3, 84.2, 127.5, 128.3, 128.5, 128.6, 128.7, 128.8, 128.9, 129.2, 131.1, 133.6, 135.0, 135.3, 138.4, 152.6, 153.3, 157.0, 158.0, 166.2, 168.4, 171.7, 196.4, 200.2; Anal. Calc. C₅₂H₅₈N₂O₁₇: C, 63.53; H, 5.95. Found : C, 62.5; H, 6.02.

Example 24

50

14-[N,N'-bis-(Boc)hydrazino]-7-Boc-13-ketobaccatin III

[0069] 0.16 g of potassium *tert*-butoxide (1.47 mmol) are suspended, under nitrogen stream and strong stirring, in 3.0 ml of anhydrous THF at -72°C. The mixture is added, in two minutes and at the same temperature, with 0.37 g (0.54 mmol) of 7-Boc-13-ketobaccatin III in 2.5 ml of THF and 1.8 ml of DMPU. After 15 minutes, 0.27 g (1.19 mmol) di-*tert*-butyl azodicarboxylate dissolved in 3.0 ml of THF and 0.2 ml of DMPU are slowly added at -68°C. After 1 hour the reaction is quenched by addition of 2 mL (0.03 mmol) of acetic acid diluted with 10 ml of ethyl ether and extracted with a NH₄Cl aqueous saturated solution. The organic phases are washed three times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO₂, *n*-hexane/EtOAc, 1.3:5.0) affords 0.35 g (0.37 mmol,

70%) of the title product. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 1.00 (s, 3H, Me), 1.26 (s, 3H, Me), 1.35 (s, 9H, 3Me), 1.40 (s, 9H, 3Me), 1.46 (s, 9H, 3Me), 1.82 (s, 3H, Me), 1.97 (m, 1H, $\text{H}\beta$ -6, J_1 = 2.6 Hz, J_2 = 10.7 Hz, J_3 = 14.3 Hz), 2.17 (s, 3H, Me), 2.18 (s, 3H, Me), 2.21 (s, 3H, Me), 2.59 (m, 1H, $\text{H}\alpha$ -6, J_1 = 7.0 Hz, J_2 = 9.7 Hz, J_3 = 14.3 Hz), 4.15 (d, 1H, H-3, 6.3 Hz), 4.23 (d, 1H, H-20, J = 8.4 Hz), 4.35 (d, 1H, H-20, J = 8.4 Hz), 4.90 (d, 1H, H-5, J_1 = 2.2 Hz, J_2 = 9.7 Hz), 5.14 (s, 1H, H-14), 5.41 (m, 1H, H-7, J_1 = 10.7 Hz, J_2 = 6.9 Hz), 5.58 (s, 1H), 5.97 (d, 1H, H-2, J = 6.4 Hz), 6.53 (s, 1H, H-10), 6.58 (s, 1H), 7.38-7.42 (m, 2H, arom), 7.50-7.55 (m 1H, arom), 8.29 (d, 2H, arom); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 10.9, 14.3, 20.1, 21.0, 21.9, 27.9, 28.1, 28.2, 33.7, 34.6, 43.6, 45.9, 57.3, 65.1, 73.4, 74.5, 75.0, 76.1, 76.8, 80.9, 82.7, 83.2, 83.3, 84.2, 128.4, 129.4, 131.2, 133.3, 138.5, 152.6, 153.2, 155.8, 157.3, 166.2, 168.4, 171.7, 196.9, 200.4; Anal. Calc. $\text{C}_{46}\text{H}_{62}\text{N}_2\text{O}_{19}$: C, 58.34; H, 6.60. Found : C, 60.3; H, 6.64.

Example 25

13-Ketobaccatin III 13,14-triisopropylsilyl enoether

[0070] A solution of 0.07 g (0.10 mmol) of 7-TES-13-ketobaccatin III in 2 ml of anhydrous THF is added with 0.25 mL (0.25 mmol) of a potassium *tert*-butoxide solution 1.0 M solution, under stirring and nitrogen stream, at -75°C. After 12 minutes, 0.04 mL (0.17 mmol) of triisopropylsilyl chloride is added very slowly with a syringe at the same temperature. After 45 minutes, the reaction is quenched by addition of 7 ml of a NH_4Cl aqueous saturated solution and extracted three times with 15.0 ml of Et_2O . The organic phases are washed four times with water, dried, filtered and evaporated under reduced pressure. Chromatography of the residue (SiO_2 , *n*-hexane/ EtOAc / Et_2O , 1.8:0.7:0.5) affords 0.035 g (0.04 mmol, 43%) of the title compound. IR (KBr, cm^{-1}): 3474, 2948, 1725, 1369, 1239, 1108, 732; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 0.58 (m, 6H, 3 CH_2), 0.92 (m, 9H, 3Me), 1.05 (s, 3H, Me), 1.14 (m, 18 H, 6Me), 1.25 (s, 3H, Me), 1.70 (s, 3H, Me), 1.88 (m, 1H, $\text{H}\beta$ -6, J_1 = 1.2 Hz, J_2 = 11.2 Hz, J_3 = 14 Hz), 2.10 (s, 3H, Me), 2.19 (m, 3H, Me), 2.23 (s, 3H, Me), 2.50 (m, 1H, $\text{H}\alpha$ -6, J_1 = 1.2 Hz, J_2 = 9.5 Hz, J_3 = 14.0 Hz), 3.74 (d, 1H, H-3, J = 7.6 Hz), 4.16 (d, 1H, H-20, J = 8.4 Hz), 4.27 (d, 1H, H-20, J = 8.4 Hz), 4.46 (m, 1H, H-7, J_1 = 6.4 Hz, J_2 = 11.2 Hz), 4.82 (s, 1H, H-14), 4.94 (d, 1H, H-5, J_1 = 1.2 Hz, J_2 = 8 Hz), 5.76 (d, 1H, H-2, J = 7.2 Hz), 6.40 (s, 1H, H-10), 7.43-7.47 (m, 2H, arom), 7.57-7.60 (m 1H, arom), 8.07-8.09 (d, 2H, arom); $^{13}\text{C-NMR}$ (CDCl_3 , 100 MHz): δ = 5.71, 7.2, 10.7, 13.0, 14.2, 18.1, 18.4, 18.5, 19.8, 21.4, 22.3, 28.5, 30.1, 37.5, 41.0, 45.6, 58.4, 72.2, 74.2, 76.2, 75.5, 80.8, 81.9, 84.4, 110.6, 128.7, 129.7, 130.2, 133.6, 134.7, 137.8, 153.5, 166.7, 169.3, 170.0, 201.7. MS (*m/z*) (M $^+$ calc. $\text{C}_{47}\text{H}_{72}\text{O}_{10}\text{Si}_2$ 854.5), 855.5, 795.5, 735.5, 673.4; Anal. Calc. $\text{C}_{47}\text{H}_{72}\text{O}_{10}\text{Si}_2$: C, 66.16; H, 8.51. Found : C, 67.5; H, 8.64.

Example 26

7-TES-13-ketobaccatin III 13,14-diethylphosphoenolate

[0071] A solution of 7-TES-13-ketobaccatin III (258 mg, M.W.=698 g/mol, 0.37 mmol) in anhydrous THF (7.5 ml) is added drop by drop with a 0.5M solution of KHMDS (1.7 ml, 0.85 mmol, 2.3 eq.) in toluene, under nitrogen and at -78°C. After stirring at -78°C for 1 hour, diethylchlorophosphosphate (80 μl , M.W.=172.55 g/mol, 0.55 mmol, 1.2 g/ml, 1.5 eq.) is added thereto. The mixture is left under stirring at -78°C for 30 minutes, at 0°C for 1.5 hours and at room temperature overnight, then added with water (15 ml) and extracted with AcOEt (3 x 15 ml). The crude (300 mg) is purified by flash silica gel chromatography (AcOEt : hexane 1:1) to obtain the desired product (150 mg, M.W.=834 g/mol, 0.18 mmol) in a 48% yield. TLC (AcOEt : hexane 1:1) R_f = 0.26

Example 27

7-Boc-13-ketobaccatin III 13,14-Boc-enol ester

[0072] A solution of 13-ketobaccatin III (0.525 g, 0.9 mmol) and DMAP (9 mg, 70 mmol) in methylene chloride (5.0 mL) is added with Boc anhydride (0.236 g, 1.10 mmol) under stirring. The solution is left under stirring at room temperature overnight. The solvent is removed under reduced pressure and the oily residue is dissolved in 50% aqueous acetone (10 mL) and left under stirring for 1 hour. The solution is extracted with methylene chloride and the combined organic phases are dried over sodium sulfate and then evaporated. The residue is chromatographed on silica to give 0.36 g of the title product (0.52 mmol, 58%), 80 mg of unreacted product and 50 mg of 7-Boc-13-ketobaccatin III.

[0073] $[\alpha]_D^{20} = -35.6^\circ$ (c 1.05, CHCl_3); IR (CDCl_3 , cm^{-1}): 3483, 1731, 1676, 1371, 1274; $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ = 1.20 (s, 3H, Me), 1.22 (s, 3H, Me), 1.47 (s, 9H, 3Me), 1.76 (s, 3H, Me), 1.91 (m, 1H, $\text{H}\beta$ -6, J_1 = 10.4 Hz, J_2 = 14.8 Hz, J_3 = 2.0 Hz), 1.92 (b, 1H, OH), 2.17 (s, 3H, Me), 2.19 (s, 3H, Me), 2.20 (s, 3H, Me), 2.64 (m, 1H, $\text{H}\alpha$ -6, J_1 = 7.2 Hz, J_2 = 14.8 Hz, J_3 = 9.5 Hz), 2.66 (d, 1H, H-14, J = 19.6 Hz), 2.94 (d, 1H, H-14, J = 19.6 Hz), 4.02 (d, 1H, H-3, J = 6.8 Hz), 4.09 (d, 1H, H-20, J = 9.0 Hz), 4.32 (d, 1H, H-20, J = 9.0 Hz), 4.94 (d, 1H, H-5, J_1 = 9.5 Hz, J_2 = 2.0 Hz), 5.39 (m,

1H, H-7, J_1 = 10.4 Hz, J_2 = 7.2 Hz), 5.67 (d, 1H, H-2, J = 6.8 Hz), 6.57 (s, 1H, H-10), 7.44-7.50 (m, 2H, arom), 7.61-7.64 (m 1H, arom), 8.30 (d, 2H, arom); ^{13}C -NMR (CDCl₃, 100 MHz): δ = 10.7, 14.0, 18.4, 21.0, 21.9, 27.9, 33.1, 33.6, 42.7, 46.7, 57.3, 72.8, 74.7, 76.3, 76.5, 77.4, 78.7, 80.5, 83.4, 84.0, 128.9, 129.0, 130.3, 134.3, 141.0, 152.4, 152.5, 167.0, 168.3, 170.3, 198.4, 200.5. Anal. Calcd for C₃₆H₄₄O₁₃: C. 63.15; H. 6.48. Found : C. 63.39; H. 6.60.

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Example 28

7-TES-13-keto-14-(N,N'-bis-(benzyloxycarbonyl)hydrazino)-baccatin III

10 [0074] A solution of 13-keto-7-TES-baccatin III (450 mg, 0.64 mmol) in anhydrous THF (12 mL) and DMPU (2.5 mL) under stirring is cooled to -70°C under nitrogen, then added drop by drop with potassium *tert*-butoxide (1.61 mL, 1M in THF, 1.61 mmol). The solution is stirred at -65°C for 45 minutes, then added with dibenzylazadicarboxylate (276 mg, 90%, 0.82 mmol), checking the reaction by TLC: after 2 hours the conversion is still uncompleted, therefore further dibenzylazadicarboxylate (69 mg, 0.20 mmol) is added. After 1h the reaction is treated with acetic acid (0.15 mL, 40% in THF) and left to warm at room temperature, then diluted with a NaCl aqueous saturated solution (10 mL) and extracted with AcOEt (2 x 10 mL). The organic phase is washed with a NaCl aqueous saturated solution (10 mL), dried (Na₂SO₄) and evaporated. The residue is purified by column chromatography (silica, 1→2% AcOEt in CH₂Cl₂) to obtain the title product (451 mg, 70%) and 13-keto-7-TES-baccatin III (45 mg, 10%). R_f = 0.6 (silica, 50% AcOEt in cyclohexane); m.p. 181-182°C (Et₂O/EtP); ^1H -NMR (200 MHz, CDCl₃) δ 8.29 (d, J = 7.0 Hz, 2 H, Bz), 7.19-7.55 (m, 13 H, Bz, Ar), 6.87 (s, 1 H, NH), 6.53 (s, 1 H, 10-H), 5.99 (d, J = 6.6 Hz, 1 H, 2-H), 5.63 (s, 1 H, 14-H), 5.16 (d, J = 3.3 Hz, 2 H, CH₂Ph), 5.04 (d, J = 4.8 Hz, 2 H, CH₂Ph), 4.88 (d, J = 4.0 Hz, 1 H, 5-H), 4.51 (dd, J = 6.6, 4.0 Hz, 1 H, 7-H), 4.32 (Abq, 2 H, 20-H), 4.01 (d, J = 6.6 Hz, 1 H, 3-H), 2.42-2.61 (m, 1 H, 6-H), 2.23 (s, 3 H, 4-OAc), 2.22 (s, 3 H, 10-OAc), 2.15 (s, 3 H, 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.74 (s, 3 H, 19-Me), 1.29 (s, 3 H, 16-Me), 1.28 (s, 3 H, 17-Me), 0.90-0.98 (t, J = 8.7 Hz, 9 H, Si(CH₂CH₃)₃), 0.58-0.66 (m, 6 H, Si(CH₂CH₃)₃); ^{13}C -NMR (300 MHz, CDCl₃) δ 200.1, 196.7, 171.9, 169.3, 166.3, 158.1, 157.1, 138.0, 135.5, 135.2, 133.6, 131.3, 129.5, 129.0, 128.9, 128.7, 128.5, 127.7, 84.6, 81.3, 75.8, 75.3, 74.0, 72.5, 69.6, 68.9, 66.3, 59.6, 46.0, 43.7, 37.6, 34.8, 22.2, 21.1, 20.2, 14.2, 10.2, 7.1, 5.6.

Example 29

7-TES-13-keto-14-hydrazino-baccatin III

30 [0075] A solution of 13-keto-7-TES-14-(N,N'-bis-(benzyloxycarbonyl)-hydrazino)-baccatin (564 mg, 0.55 mmol) in AcOEt (45 mL) is hydrogenated with 10% Pd/C as catalyst (557 mg) for 45 minutes. The catalyst is filtered off through Celite, then the solvent is evaporated off under reduced pressure without heating to obtain the title product (386 mg, 96%). This compound is unstable in various conditions (chromatographic column) and solvents (CDCl₃). R_f = 0.2 (silica, 5% AcOEt in CH₂Cl₂); ^1H -NMR (200 MHz, CDCl₃) δ 8.21 (d, J = 7.3 Hz, 2 H, Bz), 7.41-7.61 (m, 3 H, Bz), 6.54 (s, 1 H, 10-H), 5.85 (d, J = 6.6 Hz, 1 H, 2-H), 5.37 (s, 1 H), 5.18 (s, 1 H), 4.92 (d, J = 8.1 Hz, 1 H, H-5), 4.51 (dd, J = 6.6, 4.1 Hz, 1 H, H-7), 4.29 (s, 2 H, H-20), 3.92 (d, J = 7.0 Hz, 1 H, H-3), 2.47-2.62 (m, 1 H, H-6), 2.25 (s, 3 H, 4-OAc), 2.23 (s, 3 H, 10-OAc), 2.06 (s, 3 H, 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.74 (s, 3 H, 19-Me), 1.31 (s, 3 H, 16-Me), 1.28 (s, 3 H, 17-Me), 0.90-0.98 (t, J = 8.7 Hz, 9 H, Si(CH₂CH₃)₃), 0.58-0.66 (m, 6 H, Si(CH₂CH₃)₃).

Example 30

7-TES-13-keto-baccatin III [14,1-d]-3,4-dehydrofuran-2-one

45 [0076] A solution of 13-keto-7-TES-baccatin (600 mg, 0.86 mmol) in anhydrous THF (20 mL) under stirring is cooled to -70°C under nitrogen, then added drop by drop with potassium *tert*-butoxide (2.16 mL, 1M in THF, 2.16 mmol) and stirred at -65°C for 45 minutes. Ethyl glyoxylate (0.36 mL, 50% in toluene, 1.29 mmol) is then added checking the reaction by TLC: after 2 hours the conversion is still uncompleted, therefore further dibenzylazadicarboxylate (0.12 mL, 0.43 mmol) is added. After 1h the reaction is treated with anhydrous citric acid (290 mg) and left to warm at room temperature, then immediately purified by column chromatography (silica, 10→20% AcOEt in cyclohexane) to obtain the title product (503 mg, 79%) as a yellow solid. R_f = 0.55 (silica, 50% AcOEt in cyclohexane); m.p. 252-253°C (Et₂O/Etp); ^1H -NMR (200 MHz, CDCl₃) δ 7.97 (d, J = 8.4 Hz, 2 H, Bz), 7.43-7.62 (m, 3 H, Bz), 6.87 (s, 1 H, 21-H), 6.66 (s, 1 H, 10-H), 6.16 (d, J = 6.9 Hz, 1 H, 2-H), 4.88 (d, J = 8.8 Hz, 1 H, 5-H), 4.50 (dd, J = 6.6, 3.6 Hz, 1 H, 7-H), 4.13-4.24 (Abq, 2 H, 20-H), 3.98 (d, J = 6.9 Hz, 1 H, 3-H), 2.49-2.64 (m, 1 H, 6-H), 2.39 (s, 3 H, 4-OAc), 2.27 (s, 3 H, 10-OAc), 2.14 (s, 3 H, 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.75 (s, 3 H, 19-Me), 1.45 (s, 3 H, 16-Me), 1.27 (s, 3 H, 17-Me), 0.91-0.99 (t, J = 8.4 Hz, 9 H, Si(CH₂CH₃)₃), 0.56-0.68 (m, 6 H, Si(CH₂CH₃)₃); ^{13}C (300 MHz, CDCl₃) δ 199.4, 182.9, 171.0, 169.5, 165.2, 158.7, 156.3, 143.1, 134.7, 130.5, 129.4, 128.7, 127.4, 94.3, 84.4, 77.3, 77.1, 76.4, 72.8, 68.6, 60.8, 47.3, 45.2, 32.9, 22.3,

21.4, 20.8, 14.6, 10.3, 7.4, 5.3; $[\alpha]^{20}_D +72$ (c 1, CHCl_3).

Example 31

5 **7-TES-13,14-dehydro-baccatin III [14,1-d]-furan-2-one**

[0077] A solution of 13-keto-7-TES-baccatin [14,1-d]-3,4-dehydrofuran-2-one derivative (90 mg, 0.12 mmol) in AcOEt (10 mL) is hydrogenated with 10% Pd/C as the catalyst (90 mg) for 45 minutes. The catalyst is filtered off through Celite, then the solvent is evaporated off and the residue is purified through a column (silica, 20→50% AcOEt in cyclohexane) to obtain the title product (67 mg, 75%) as a white solid. $R_f = 0.2$ (silica, 50% AcOEt in cyclohexane); m.p. 235-236°C (EtOAc/hexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.01 (d, $J = 6.9$ Hz, 2 H, Bz), 7.44-7.62 (m, 3 H, Bz), 6.43 (s, 1 H, 10-H), 6.10 (d, $J = 6.6$ Hz, 1 H, 2-H), 4.98 (d, $J = 5.9$ Hz, 1 H, 5-H), 4.44 (dd, $J = 6.6, 3.6$ Hz, 1 H, 7-H), 4.17-4.39 (Abq, 2 H, 20-H), 3.76 (d, $J = 7.0$ Hz, 1 H, 3-H), 3.13-3.41 (Abq, 2 H, 21-H), 2.49-2.64 (m, 1 H, 6-H), 2.23 (s, 3 H, 4-OAc), 2.22 (s, 3 H, 10-OAc), 2.20 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.74 (s, 3 H, 19-Me), 1.27 (s, 3 H, 16-Me), 1.16 (s, 3 H, 17-Me), 0.90-0.98 (t, $J = 8.1$ Hz, 9 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.56-0.68 (m, 6 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$); ^{13}C (300 MHz, CDCl_3) δ 201.5, 175.0, 170.1, 169.6, 164.9, 148.7, 136.8, 134.9, 133.8, 129.6, 128.8, 128.7, 102.2, 92.4, 84.1, 80.8, 76.1, 75.9, 72.2, 70.4, 58.4, 45.0, 39.6, 37.3, 32.0, 28.1, 21.3, 20.9, 19.6, 13.5, 10.0, 6.7, 5.3.

20 Example 32

20 **7-TES-baccatin [14,1-d]-3,4-dehydrofuran-2-one**

[0078] A solution of Bu_4NBH_4 (180 mg, 0.7 mmol) in MeOH (10 mL) under stirring is cooled to -30°C, then dropped into a solution of 7-TES-13-ketobaccatin [14,1-d]-3,4-dehydrofuran-2-one (200 mg, 0.28 mmol) in THF (1 mL). After 30 minutes the reaction mixture is treated with citric acid (180 mg) and left to warm at room temperature. After addition of water (10 mL), the mixture is extracted with AcOEt (2 x 10 mL) and the organic phase is washed with water (5 mL), dried over Na_2SO_4 and evaporated. The residue is purified by silica gel chromatography (20→30% AcOEt in cyclohexane) to obtain 7-TES-13,14-dehydro-baccatin [14,1-d]-furan-2-one (103 mg, 52%) and the title product (52 mg, 26%) as white solids.

[0079] $R_f = 0.15$ (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.02 (d, $J = 6.9$ Hz, 2 H, Bz), 7.40-7.63 (m, 3 H, Bz), 6.47 (s, 1 H, 21-H), 6.25 (s, 1 H, 10-H), 6.12 (d, $J = 8.1$ Hz, 1 H, 2-H), 5.14 (m, 1 H, 13-H), 4.92 (d, $J = 8.1$ Hz, 1 H, 5-H), 4.55 (dd, $J = 7.0, 3.6$ Hz, 1 H, 7-H), 4.15-4.30 (Abq, 2 H, 20-H), 4.07 (d, $J = 8.0$ Hz, 1 H, 3-H), 2.49-2.56 (m, 1 H, 6-H), 2.28 (s, 3 H, 4-OAc), 2.22 (s, 3 H, 10-OAc), 2.13 (s, 3 H; 18-Me), 1.84-1.97 (m, 1 H, 6-H), 1.80 (s, 3 H, 19-Me), 1.35 (s, 3 H, 16-Me), 1.27 (s, 3 H, 17-Me), 0.90-0.99 (t, $J = 8.1$ Hz, 9 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.58-0.65 (m, 6 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$).

35 Example 33

40 **13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]-7-TES-baccatin [14,1-d]-3,4-dehydrofuran-2-one**

Preparation of N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine

[0080] N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine sodium salt (72 mg, 0.168 mmol) is dissolved in water (5 mL) and added with CH_2Cl_2 (3 mL). An NaHSO_4 aqueous solution (2M, 0.15 mL) is dropped therein to adjust pH to 3.0. After stirring for some minutes, the organic phase is separated and the aqueous phase is extracted with CH_2Cl_2 (2 mL). The combined organic extracts are washed with water (5 mL) and with a NaCl saturated solution (5 mL), dried over Na_2SO_4 and evaporated to obtain the free acid (68 mg, 100%) as a white solid.

50 *Esterification*

[0081] 7-TES-13,14-dehydro-baccatin [14,1-d]-furan-2-one (100 mg, 0.14 mmol) is suspended in toluene (4 mL) and added drop by drop with N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserine (68 mg, 0.168 mmol) dissolved in CH_2Cl_2 (2 mL), then with N,N-dimethylaminopyridine (DMAP) (7 mg) and dicyclohexylcarbodiimide (DCC) (35 mg, 0.168 mmol). The reaction mixture is heated at 70°C for 3 hours, then left to cool and kept at room temperature until complete precipitation of DCU. The precipitate is filtered (DCU) and washed with toluene (2 x 3 mL), then the filtrate is washed with saturated NaHCO_3 (5 mL), then with 0.4 M HCl (10 mL) to remove DMAP and finally with saturated NaHCO_3 (5 mL). The organic phase is dried over Na_2SO_4 and evaporated to dryness. The residue is purified by column chroma-

tography (20→30% AcOEt in cyclohexane) to obtain a first fraction containing the title product (88 mg, 56%). R_f = 0.55 (silica, 20% AcOEt in cyclohexane); m.p. 150-153°C (iPR₂O/EtP); ¹H-NMR (200 MHz, CDCl₃) δ 7.97 (d, J = 7.0 Hz, 2 H, Bz), 7.42-7.60 (m, 3 H, Bz), 7.19-7.25 (m, 1 H,), 6.68 (s, 1 H, 10-H), 6.46-6.54 (m, 2 H,), 6.03 (s, 1 H,), 5.98 (d, J = 5.1 Hz, 1 H, 2-H), 5.81 (s, 1 H,), 5.05-5.13 (m, 1 H, 4.91 (d, J = 7.0 Hz, 1 H, 5-H), 4.42 (m, 1 H, 7-H), 4.28 (s, 2H, 20-H), 3.95 (d, J = 5.5 Hz, 1 H, 3-H), 3.89 (s, 3 H, O-Me), 3.85 (s, 3 H, O-Me), 2.81 (s, 1 H, 13-H), 2.49-2.64 (m, 1 H, 6-H), 2.34 (s, 3 H, 4-OAc), 2.22 (s, 3 H, 10-OAc), 2.08 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.69 (s, 3 H, 19-Me), 1.27 (s, 3 H, 16-Me), 1.24 (s, 3 H, 17-Me), 1.03-1.13 (, 9 H, N-Boc), 0.90-0.97 (t, J = 7.7 Hz, 9 H, Si(CH₂CH₃)₃), 0.54-0.62 (m, 6 H, Si(CH₂CH₃)₃); ¹³C (300 MHz, CDCl₃) δ 203.5, 170.6, 170.2, 168.8, 164.5, 161.7, 159.1, 155.7, 139.0, 138.5, 133.9, 130.0, 129.6, 129.0, 128.7, 128.3, 127.8, 118.8, 104.3, 98.6, 90.0, 87.0, 84.3, 81.3, 80.8, 79.5, 75.0, 73.6, 72.9, 72.1, 67.7, 60.1, 58.9, 56.9, 55.4, 50.9, 50.1, 45.4, 43.7, 39.3, 38.3, 37.4, 29.7, 29.1, 28.2, 26.9, 25.5, 22.8, 22.6, 22.5, 21.1, 19.8, 15.9, 9.5, 6.8, 5.6; $[\alpha]^{20}_D$ +44 (c 0.25, CHCl₃).

Example 34

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-baccatin [14,1-d]-3,4-dehydrofuran-2-one

[0082] A solution of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-7-TES-baccatin [14,1-d]-3,4-dehydrofuran-2-one (63 mg, 0.056 mmol) in acetonitrile (3 mL) and pyridine (3 mL) is stirred in polyethylene container and cooled to 0°C. A solution of HF-pyridine (0.4 mL) is slowly added thereto, then the mixture is left to warm at room temperature and kept under stirring for 24 hours, then poured in cold water (10 mL) and extracted with CH₂Cl₂ (2 x 5 mL). The organic phase is washed with 2M NaHSO₄ to pH 2, then with 5% NaHCO₃ (5 mL) and finally with a NaCl saturated solution (5 mL). The mixture is dried over Na₂SO₄ and the solvent is evaporated off. The residue is purified by column chromatography (25→35% AcOEt in cyclohexane) to obtain the title product (45 mg, 80%) as a white solid. R_f = 0.3 (silica, 50% AcOEt in cyclohexane); ¹H-NMR (200 MHz, CDCl₃) δ 7.95 (d, J = 7.5 Hz, 2 H, Bz), 7.43-7.59 (m, 3 H, Bz), 7.22-7.27 (m, 1 H,), 6.66 (s, 1 H, 21-H), 6.51-6.54 (m, 2 H,), 5.99 (d, J = 5.5 Hz, 1 H, 2-H), 5.84 (s, 1 H,), 5.57 (s, 1 H, 10-H), 5.05-5.13 (m, 1 H,), 4.90 (d, J = 7.0 Hz, 1 H, 5-H), 4.70(=), 4.42 (m, 1 H, 7-H), 4.30-4.32 (ABq, 2H, 20-H), 3.89 (s, 3 H, O-Me), 3.86 (d, J = 5.5 Hz, 1 H, 3-H), 3.84 (s, 3 H, O-Me), 3.03 (s, 1 H, 13-H), 2.49-2.64 (m, 1 H, 6-H), 2.34 (s, 3 H, 4-OAc), 2.27 (s, 3 H, 10-OAc), 1.88 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.69 (s, 3 H, 19-Me), 1.27 (s, 3 H, 16-Me), 1.25 (s, 3 H, 17-Me), 1.07-1.12 (9 H, N-Boc). ¹³C (300 MHz, CDCl₃) δ 205.6, 172.2, 171.2, 170.1, 169.0, 164.9, 162.1, 159.4, 155.6, 153.5, 139.2, 137.6, 134.3, 130.3, 129.3, 129.1, 128.5, 127.9, 119.0, 114.2, 104.6, 98.9, 90.5, 87.2, 84.7, 81.6, 81.2, 79.8, 76.8, 72.0, 68.3, 59.2, 58.4, 57.5, 55.9, 55.8, 44.0, 39.4, 38.1, 35.8, 30.0, 29.3, 28.5, 25.8, 23.2, 22.9, 22.8, 21.3, 20.8, 16.3, 9.5; $[\alpha]^{20}_D$ +82 (c 0.9, CHCl₃).

Example 35

13-(N-Boc-β-isobutylisoserinoyl)-baccatin [14,1-d]-3,4-dehydrofuran-2-one

[0083] A solution of 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)-β-isobutylisoserinoyl]-baccatin [14,1-d]-3,4-dehydrofuran-2-one derivative (44 mg, 0.04 mmol) in CH₂Cl₂ (4 mL) under stirring is cooled to 0°C. A solution of acetyl chloride in methanol (0.01 M, 0.7 mL) is dropped into the mixture, which is left to warm at room temperature, checking the reaction by TLC: after 18 hours the starting product is still partly present, therefore a further amount of acetyl chloride solution (0.3 mL) is added. After 3 hours a NH₄Cl saturated solution (4 mL) is added and the organic phase is dried over Na₂SO₄ and evaporated. The residue is purified by column chromatography (25→35% AcOEt in cyclohexane) to obtain the title product (30 mg, 85%) as a white solid. R_f = 0.2 (silica, 50% AcOEt in cyclohexane); m.p. 149-154°C (CH₂Cl₂/iPR₂O); ¹H-NMR (200 MHz, CDCl₃) δ 7.95 (d, J = 7.4 Hz, 2 H, Bz), 7.42-7.60 (m, 3 H, Bz), 6.16 (s, 1 H, 21-H), 5.99 (d, J = 5.5 Hz, 1 H, 2-H), 5.57 (s, 1 H, 10-H), 4.90 (dd, J = 3.7, 6.2 Hz, 1 H, 5-H), 4.77 (d, J = 10.2 Hz, 1 H, NH), 4.30-4.47 (m, 4 H, 2'-H, 7-H, 20-H, 3'-H), 3.81 (d, J = 5.5 Hz, 1 H, 3-H), 3.00 (s, 1 H, 13-H), 2.49-2.61 (m, 1 H, 6-H), 2.45 (s, 3 H, 4-OAc), 2.27 (s, 3 H, 10-OAc), 1.84-1.97 (m, 1 H, 6-H), 1.83 (s, 3 H; 18-Me), 1.69 (s, 3 H, 19-Me), 1.44 (s, 9 H, N-Boc), 1.27 (s, 3 H, 16-Me), 1.24 (s, 3 H, 17-Me), 1.01-1.07 (m, 8 H,); ¹³C (300 MHz, CDCl₃) δ 205.4, 172.0, 171.6, 171.3, 170.0, 164.8, 156.1, 154.8, 139.7, 136.3, 134.0, 130.3, 128.9, 128.4, 115.5, 90.1, 84.6, 81.2, 81.0, 77.8, 76.7, 73.3, 71.9, 68.1, 58.3, 57.4, 51.2, 42.3, 39.1, 38.1, 35.7, 29.9, 29.1, 28.5, 25.0, 23.4, 22.4, 21.2, 20.6, 16.4, 9.3.

Example 36

13-Carbethoxy-7-TES-13,14-dehydro-baccatin

[0084] A solution of 13-keto-7-TES-baccatin (150 mg, 0.21 mmol) in anhydrous THF (5 mL) and DMPU (1 mL) under stirring is cooled to -70°C under nitrogen. Potassium *tert*-butoxide (0.54 mL, 1M in THF, 0.54 mmol) is dropped therein

and the mixture is kept under stirring at -65°C for 45 minutes, then added with ClCOOEt (31L, 0.31 mmol), checking the reaction by TLC: after 2h30min, acetic acid (0.05 mL, 40% in THF) is dropped in the mixture, which is left to warm at room temperature. After dilution with a NaCl saturated solution (5 mL), the reaction mixture is extracted with AcOEt (2 x 5 mL) and the organic phase is washed with a NaCl saturated solution (5 mL), dried (Na_2SO_4) and evaporated. The residue is purified by chromatography on silica (1→5% AcOEt in CH_2Cl_2) to obtain the title product (136 mg, 82%).

[0085] $R_f = 0.55$ (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.09 (d, $J = 7.0$ Hz, 2 H, Bz), 7.45-7.62 (m, 3 H, Bz), 6.45 (s, 1 H, 10-H), 5.83 (d, $J = 7.4$ Hz, 1 H, 2-H), 5.38 (s, 1 H, 14-H), 4.98 (d, $J = 8.4$ Hz, 1 H, 5-H), 4.46 (dd, $J = 6.9, 3.7$ Hz, 1 H, 7-H), 4.16-4.35 (m, 4 H, 20-H, $\text{COOCH}_2\text{CH}_3$), 3.76 (d, $J = 5.5$ Hz, 1 H, 3-H), 2.47-2.62 (m, 1 H, 6-H), 2.28 (s, 3 H, 4-OAc), 2.20 (s, 3 H, 10-OAc), 2.04 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.72 (s, 3 H, 19-Me), 1.46 (s, 3 H, 16-Me), 1.37 (s, 3 H, 17-Me), 1.33 (m, 3 H, $\text{COOCH}_2\text{CH}_3$), 0.90-0.98 (t, $J = 8.7$ Hz, 9 H, Si(CH_2CH_3)₃), 0.57-0.65 (m, 6 H, Si(CH_2CH_3)₃); $^{13}\text{C-NMR}$ (300 MHz, CDCl_3) δ 201.5, 170.3, 169.3, 166.5, 153.0, 151.2, 136.9, 134.6, 133.7, 130.0, 129.3, 128.6, 119.1, 84.0, 80.6, 80.5, 75.3, 73.0, 72.2, 65.3, 58.3, 44.8, 41.0, 37.2, 27.6, 21.7, 21.0, 18.9, 14.2, 13.5, 10.0, 6.8, 5.3.

Example 37

13-carbobenzyloxy-7-TES-13,14-dehydro-baccatin III

[0086] A solution of 13-keto-7-TES-baccatin III (150 mg, 0.21 mmol) in anhydrous THF (5 mL) and DMPU (1 mL) under stirring is cooled to -70°C under nitrogen. Potassium *tert*-butoxide (0.54 mL, 1M in THF, 0.54 mmol) is dropped in the mixture, which is kept under stirring at -65°C for 45 minutes, then added with $\text{ClCOOCH}_2\text{Ph}$ (49 μ L, 0.31 mmol), checking the reaction by TLC: after 2h30 min acetic acid (0.05 mL, 40% in THF) is dropped into the reaction, which is left to warm at room temperature. After dilution with a NaCl saturated solution (5 mL), the reaction mixture is extracted with AcOEt (2 x 5 mL) and the organic phase is washed with a NaCl saturated solution (5 mL), dried (Na_2SO_4) and evaporated. The residue is purified by chromatography on silica (1→3% AcOEt in CH_2Cl_2) to obtain the title product (117 mg, 67%).

[0087] $R_f = 0.6$ (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.09 (d, $J = 7.0$ Hz, 2 H, Bz), 7.37-7.62 (m, 8 H, Bz, Ar), 6.44 (s, 1 H, 10-H), 5.83 (d, $J = 7.4$ Hz, 1 H, 2-H), 5.39 (s, 1 H, 14-H), 5.25 (s, 2 H, CH_2), 4.97 (d, $J = 8.0$ Hz, 1 H, 5-H), 4.45 (dd, $J = 7.0, 3.7$ Hz, 1 H, 7-H), 4.15-4.30 (Abq, 2H, 20-H), 3.74 (d, $J = 7.4$ Hz, 1 H, 3-H), 2.47-2.62 (m, 1 H, 6-H), 2.25 (s, 3 H, 4-OAc), 2.20 (s, 3 H, 10-OAc), 2.01 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.72 (s, 3 H, 19-Me), 1.44 (s, 3 H, 16-Me), 1.28 (s, 3 H, 17-Me), 0.90-0.98 (t, $J = 8.7$ Hz, 9 H, Si(CH_2CH_3)₃), 0.57-0.65 (m, 6 H, Si(CH_2CH_3)₃); $^{13}\text{C-NMR}$ (300 MHz, CDCl_3) δ 201.5, 170.3, 169.3, 166.5, 153.0, 151.3, 137.0, 134.5, 133.7, 130.1, 129.3, 129.0, 128.8, 128.7, 128.6, 119.1, 84.0, 80.6, 80.5, 76.3, 75.3, 73.0, 72.2, 70.7, 58.3, 44.8, 41.0, 37.2, 27.7, 21.7, 21.0, 18.9, 13.5, 10.0, 6.8, 5.3.

Example 38

14-hydroxy-13-keto-7-TES-baccatin III 1,14-sulfite

[0088] A solution of 14-hydroxy-13-keto-7-TES-baccatin (300 mg, 0.42 mmol) in Anhydrous CH_2Cl_2 (3 mL) is dropped into a solution of SOCl_2 (0.092 mL, 1.26 mmol) and triethylamine (0.35 mL, 2.52 mmol) in anhydrous CH_2Cl_2 (6 mL) at 0°C. The reaction mixture is kept under stirring for 20 minutes, then poured into ice-water (10 mL) and the separated organic phase is washed with water (10 mL), dried (Na_2SO_4) and evaporated. The residue is purified by silica chromatography (10→20% AcOEt in cyclohexane) to obtain the two sulfite isomers A (86 mg, 27%) and B (201 mg, 63%) as yellow solids.

[0089] *Isomer A-* $R_f = 0.65$ (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.09 (d, $J = 7.0$ Hz, 2 H, Bz), 7.44-7.65 (m, 3 H, Bz), 6.59 (s, 1 H, 10-H), 6.16 (d, $J = 6.2$ Hz, 1 H, 2-H), 5.16 (s, 1 H, 14-H), 4.92 (d, $J = 8.4$ Hz, 1 H, 5-H), 4.50 (dd, $J = 6.6, 3.6$ Hz, 1 H, 7-H), 4.12-4.38 (Abq, 2H, 20-H), 3.99 (d, $J = 6.6$ Hz, 1 H, 3-H), 2.49-2.64 (m, 1 H, 6-H), 2.25 (s, 3 H, 4-OAc), 2.23 (s, 3 H, 10-OAc), 2.19 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.71 (s, 3 H, 19-Me), 1.39 (s, 3 H, 16-Me), 1.15 (s, 3 H, 17-Me), 0.91-0.99 (t, $J = 8.7$ Hz, 9 H, Si(CH_2CH_3)₃), 0.58-0.66 (m, 6 H, Si(CH_2CH_3)₃); MS: 760 M/Z.

[0090] *Isomer B-* $R_f = 0.60$ (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.03 (d, $J = 7.3$ Hz, 2 H, Bz), 7.49-7.68 (m, 3 H, Bz), 6.55 (s, 1 H, 10-H), 6.13 (d, $J = 6.9$ Hz, 1 H, 2-H), 4.92 (d, $J = 8.4$ Hz, 1 H, 5-H), 4.90 (s, 1 H, 14-H), 4.50 (dd, $J = 6.3, 4.0$ Hz, 1 H, 7-H), 4.12-4.37 (Abq, 2H, 20-H), 3.91 (d, $J = 6.6$ Hz, 1 H, 3-H), 2.49-2.64 (m, 1 H, 6-H), 2.26 (s, 3 H, 4-OAc), 2.25 (s, 3 H, 10-OAc), 2.21 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.75 (s, 3 H, 19-Me), 1.35 (s, 6 H, 16,17-Me), 0.91-0.99 (t, $J = 8.7$ Hz, 9 H, Si(CH_2CH_3)₃), 0.58-0.66 (m, 6 H, Si(CH_2CH_2)₃); MS: 760 M/Z.

Example 39**14-hydroxy-13-keto-7-TES-baccatin III 1,14-sulfate**

5 [0091] *Method A*: a solution of 14-hydroxy-13-keto-7-TES-baccatin III (300 mg, 0.42 mmol) in anhydrous CH_2Cl_2 (3 mL) is dropped into a solution of SO_2Cl_2 (0.1 mL, 1.26 mmol) and triethylamine (0.35 mL, 2.52 mmol) in Anhydrous CH_2Cl_2 (6 mL) at 0°C. The reaction mixture is kept under stirring for 20 minutes, then poured into ice-water (10 mL) and the separated organic phase is washed with water (10 mL), dried (Na_2SO_4) and evaporated. The residue is purified by chromatography on silica (10→20% AcOEt in cyclohexane) to obtain the title product (145 mg, 45%) and a less polar product (53 mg) as yellow solids.

10 [0092] *Method B*: a solution of 14-hydroxy-13-keto-7-TES-baccatin III 1,14-sulfite (isomer B) (91 mg, 0.12 mmol) in CCl_4 (2 mL) and CH_3CN (2 mL) is cooled to 0°C, then added in sequence with RuCl_3 (1 mg), NaIO_4 (38 mg, 0.18 mmol) and finally water (3 mL): the reaction mixture becomes dark and is stirred for 15 minutes, then poured into ethyl ether (10 mL) and the two phases are separated. The aqueous phase is extracted with ethyl ether (5 mL) and the combined 15 organic phases are dried (Na_2SO_4) and evaporated to obtain the title product (90 mg, 97%).

15 [0093] R_f = 0.65 (silica, 50% AcOEt in cyclohexane); $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 8.09 (d, J = 7.0 Hz, 2 H, Bz), 7.46-7.65 (m, 3 H, Bz), 6.59 (s, 1 H, 10-H), 6.18 (d, J = 6.6 Hz, 1 H, 2-H), 5.10 (s, 1 H, 14-H), 4.92 (d, J = 7.6 Hz, 1 H, 5-H), 4.47 (dd, J = 6.9, 3.7 Hz, 1 H, 7-H), 4.08-4.38 (Abq, 2H, 20-H), 3.88 (d, J = 6.6 Hz, 1 H, 3-H), 2.49-2.64 (m, 1 H, 6-H), 2.31 (s, 3 H, 4-OAc), 2.27 (s, 3 H, 10-OAc), 2.24 (s, 3 H; 18-Me), 1.84-1.98 (m, 1 H, 6-H), 1.70 (s, 3 H, 19-Me), 20 1.44 (s, 3 H, 16-Me), 1.36 (s, 3 H, 17-Me), 0.91-0.99 (t, J = 8.4 Hz, 9 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$), 0.58-0.66 (m, 6 H, $\text{Si}(\text{CH}_2\text{CH}_3)_3$).

Example 40**14 β -hydroxy-2-debenzoyl-2-m-methoxybenzoyl-7-TES-13-ketobaccatin III**

25 [0094] A solution 1M in THF of t-BuOK (2.5 ml, 0.86 mmol) cooled to -50°C is dropped into a solution of 2-debenzoyl-2-m-methoxybenzoyl-7-TES-13-ketobaccatin III (670 mg, 0.96 mmol) in anhydrous THF (9 ml) and DMPU (2 ml), cooled at -50°C. The solution is kept under stirring at -60°C for 45 minutes, then added drop by drop with a solution of (\pm)-camphorsulfonyloxaziridine (440 mg, 2 mmol) in anhydrous THF (2 ml). The mixture is stirred for 3 hours at -60°C then treated with a 10% glacial acetic acid solution in anhydrous THF (2 ml). The mixture is left to warm at room temperature, then extracted with DCM (2 x 10 ml). The combined organic phases are washed with water, brine, and dried over Na_2SO_4 . The crude product is used for the subsequent step without further purification. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 0.58-0.66 (m, 6H, Si-CH_2); 0.91-0.99 (t, J = 8.7, 9H, CH_2CH_3); 1.24 (s, 3H, 17-Me); 1.28 (s, 3H, 16,-Me); 1.75 (s, 3H, 19-Me); 1.83-2.05 (m, 1H, 6-H); 2.14 (s, 3H, 18-Me); 2.24 (s, 3H, 10-OAc); 2.26 (s, 3H, 4-OAc); 2.46-2.61 (m, 1H, 6-H); 3.64 (s, 1H, 1-OH); 3.73 (d, J = 1.8, 1H, 14-OH); 3.87 (d, J = 6.9, 1H, 3-H); 4.14 (d, J = 1.8, 1H, 14-H); 4.31 (s, 2H, 20-H); 4.49 (dd, J = 10.7, 6.6, 1H, 7-H); 4.93 (d, J = 7.3, 1H, 5-H); 5.89 (d, J = 7.0, 1H, 2-H); 6.53 (s, 1H, 10-H); 7.54 (2', 1 H, m), 7.13 (4', 1 H, dd, 7.9, 3.0), 7.36 (5', 1 H, t, 7.9 Hz), 7.61 (6', 1 H, d 7.9), 3.85 (OMe, 3 H, s).

Example 41**14 β -hydroxy-2-debenzoyl-2-m-methoxybenzoyl-7-TES-13-ketobaccatin III 1,14-carbonate**

40 [0095] A solution of 14 β -hydroxy-2-debenzoyl-2-m-methoxybenzoyl-7-TES-13-ketobaccatin III (12.2 g) in anhydrous DCM (50 ml) and pyridine (16 ml) is dropped into a 20% phosgene solution in DCM (45 mL, 5 eq) at -10°C. After 2 hours, a 5% NaHCO_3 aqueous solution (100 ml) is dropped therein. The aqueous phase is back-extracted with DCM (3 x 50 ml). The combined organic phases are dried over sodium sulfate and evaporated. The reaction product crude is purified by flash chromatography (silica gel, DCM-AcOEt=50:1) to give the desired compound in 95% yield. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 0.58-0.66 (m, 6H, Si-CH_2); 0.91-0.99 (t, J = 8.7, 9H, CH_2CH_3); 1.21 (s, 3H, 17-Me); 1.39 (s, 3H, 16,-Me); 1.75 (s, 3H, 19-Me); 1.86-2.13 (m, 1H, 6-H); 2.22 (s, 3H, 18-Me); 2.25 (s, 3H, 10-OAc); 2.26 (s, 3H, 4-OAc); 2.48-2.63 (m, 1H, 6-H); 3.83 (d, J = 7.0, 1H, 3-H); 4.30 (ABq, 2H, 20-H); 4.49 (dd, J = 11.0, 7.0, 1H, 7-H); 4.81 (s, 1H, 14-H); 4.93 (d, J = 7.3, 1H, 5-H); 6.15 (d, J = 7.0, 1H, 2-H); 6.54 (s, 1H, 10-H); 7.54 (2', 1 H, m), 7.13 (4', 1 H, dd, 7.9, 3.0), 7.36 (5', 1 H, t, 7.9 Hz), 7.61 (6', 1 H, d 7.9), 3.85 (OMe, 3 H, s).

Example 42**14 β -hydroxy-2-debenzoyl-2-m-methoxybenzoyl-7-TES-baccatin III 1,14-carbonate**

55 [0096] A suspension of tetraethylammonium borohydride (12 eq) in absolute methanol (10 ml) is cooled to -50°C and

added to a solution of 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoyl-7-TES-13-ketobaccatin III 1,14-carbonate (0.5 g, 0.6 mmol) in methanol (10 ml). After disappearance of the starting material (8 h), the reaction is treated with citric acid, then extracted with ethyl acetate. The combined organic phases are dried over sodium sulfate and evaporated. The resulting crude is purified by chromatography to give the desired compound in a 60% yield. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 0.58-0.66 (m, 6H, Si-CH₂); 0.91-0.99 (t, J = 8.7, 9H, CH₂CH₃); 1.16 (s, 3H, 17-Me); 1.28 (s, 3H, 16-Me); 1.74 (s, 3H, 19-Me); 1.85-2.14 (m, 1H, 6-H); 2.06 (s, 3H, 18-Me); 2.21 (s, 3H, 10-OAc); 2.33 (s, 3H, 4-OAc); 2.47-2.65 (m, 1H, 6-H); 3.74 (d, J = 7.4, 1H, 3-H); 4.12-4.35 (m, 2H, 20-H); 4.49 (dd, J = 10.3, 6.6, 1H, 7-H); 4.82 (d, 1H, 14-H); 4.99 (d, J = 7.3, 1H, 5-H); 5.00-5.03 (m, 1H, 13-H); 6.11 (d, J = 7.4, 1H, 2-H); 6.45 (s, 1H, 10-H), 7.54 (2', 1H, m), 7.13 (4', 1H, dd, 7.9, 3.0), 7.36 (5', 1H, t, 7.9 Hz), 7.61 (6', 1H, d 7.9), 3.85 (OMe, 3H, s).

Example 43

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]- 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoyl-7-TES-baccatin III 1,14-carbonate

[0097] The product is obtained from 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoyl-7-TES-baccatin III 1,14-carbonate following the same procedure as described in Example 33. $^1\text{H-NMR}$: (CDCl_3 , 300 MHz) δ 6.17, (H2, d, 8.5 Hz), 3.78, (H3, d, 8.3 Hz), 4.95, (H5, dd, 9.5, 1.1 Hz), 2.54, (H6 α , m), 1.90, (H6 β , m), 3.96, (H7, d, 6.7 Hz), 6.51, (H10, s), 6.49, (H13, m), 4.87, (H14, d, 6.8 Hz), 1.40, (H16, s), 1.35, (H17, s), 2.18, (H18, s), 1.76, (H19, s), 4.29, (H20 α , AB System, 22.6, 8.3 Hz), 6.51, (H2', m), 7.29, (H3', m), 1.65, (H4', m), 1.88, (H5', m), 1.12, (H6', d, 6.3 Hz), 1.12, (H7', d, 6.3 Hz), 2.34, (4 Ac, s), 2.24, (10 Ac, s), 1.40, (Boc, s), 8.06, 6.51, (2,4diMeOPhCH, m), 3.91, (MeO Ph, s), 3.86, (MeO Ph, s), 2.81, (OH, br s), 1.56, (OH, br s), 0.97, (CH₃Tes, t, 8.1), 0.62, (CH₂Tes, q, 8.1 Hz), 7.54 (2', 1H, m), 7.13 (4', 1H, dd, 7.9, 3.0), 7.36 (5', 1H, t, 7.9 Hz), 7.61 (6', 1H, d 7.9), 3.85 (OMe, 3H, s).

Example 44

13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]- 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoylbaccatin III 1,14-carbonate

[0098] The product is obtained from 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]- 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoyl-7-TES-baccatin III 1,14-carbonate following the same procedure as described in Example 34. $^1\text{H-NMR}$: (CDCl_3 , 300 MHz) δ 6.16 (H2, d 7.5 Hz), 3.78 (H3, d 7.4 Hz), 4.98 (H5, dd 9.5, 2.2 Hz), 2.59 (H6 α , ddd 15.0, 9.8, 6.4 Hz), 1.94 (H6 β , ddd 14.9, 11.4, 2.7 Hz), 4.48 (H7, dd 10.9, 6.5 Hz), 6.34 (H10, s), 6.52 (H13, m), 4.87 (H14, d 6.7 Hz), 1.40 (H16, s), 1.33 (H17, s), 2.05 (H18, s), 1.76 (H19, s), 4.33 (H20 α , d 8.3), 4.27 (H20 β , d 8.3 Hz), 6.53 (H2', m), 7.29 (H3', m), 1.65-1.88 (H4', m), 1.77 (H5', m), 1.11 (H6', d 6.2 Hz), 1.11 (H7', d 6.2 Hz), 2.30 (4 Ac, s), 2.34 (10 Ac, s), 1.40 (Boc, s), 6.51-6.57 (2,4 diMeOPhCH, m), 3.91 (MeO Ph, s), 3.86 (MeO Ph, s), 2.81 (OH, br s), 7.54 (2', 1H, m), 7.13 (4', 1H, dd, 7.9, 3.0), 7.36 (5', 1H, t, 7.9 Hz), 7.61 (6', 1H, d 7.9), 3.85 (OMe, 3H, s).

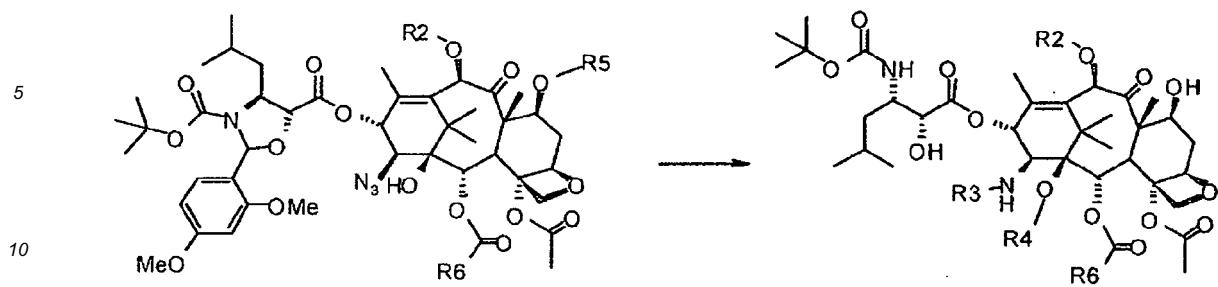
Example 45

13-(N-Boc- β -isobutylisoserinoyl)- 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoylbaccatin III 1,14-carbonate

[0099] The product is obtained from 13-[N-Boc-N,O-(2,4-dimethoxybenzylidene)- β -isobutylisoserinoyl]- 14β -hydroxy-2-debenzoyl-2-*m*-methoxybenzoyl-7-TES-baccatin III 1,14-carbonate following the same procedure as described in Example 35. $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 6.09 (2, 1H, d, 7.3 Hz), 3.68 (3, 1H, d, 7.4 Hz), 4.93 (5, 1H, dd, 9.7, 2.5 Hz), 2.52 (6 α , 1H, ddd, 14.8, 9.8, 6.9 Hz), 1.86 (6 β , 1H, m), 4.37 (7, 1H, m), 6.25 (10, 1H, s), 6.44 (13, 1H, d, broad, 6.9 Hz), 4.83 (14, 1H, d, 6.9 Hz), 1.26 (16, 3H, s), 1.33 (17, 3H, s), 1.88 (18, 3H, d, 1.6 Hz), 1.70 (19, 3H, s), 4.32 (20a, 1H, d, 8.3 Hz), 4.20 (20b, 1H, d, 8.3 Hz), 2.46 (4-CO₂CH₃, 3H, s), 2.23 (10-CO₂CH₃, 3H, s), 4.30 (2', 1H, dd, 6.4, 3.2 Hz), 4.08 (3', 1H, m), 1.21 (4'a, 1H, m), 1.43 (4'b, 1H, m), 1.68 (5', 1H, m), 0.96 (6'a, 3H, d, 6.3 Hz), 0.95 (6'b, 3H, d, 6.3 Hz), 1.34 (Boc, 9H, s), 4.73 (NH, 1H, d, 9.8 Hz), 7.54 (2", 1H, m), 7.13 (4", 1H, dd, 7.9, 3.0), 7.36 (5", 1H, t, 7.9 Hz), 7.61 (6", 1H, d 7.9), 3.85 (OMe, 3H, s).

Claims

1. A process for the preparation of compounds of formula XIV starting from compounds of formula XI

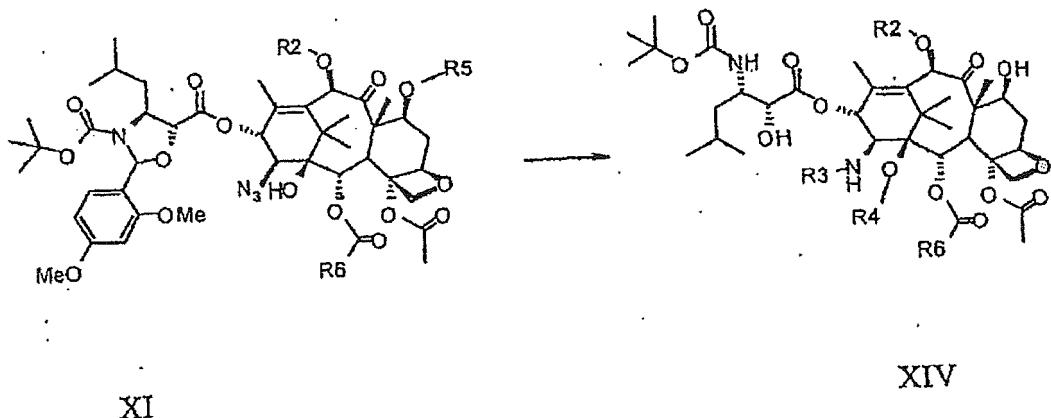


umfassend:

5 a) selektive Reduktion der Azido-Gruppe zur Aminogruppe;
 b) wahlweise Behandlung mit alkylierenden oder acylierenden Mitteln;
 c) Abspaltung der Schutz-Gruppe bei C7;
 d) Öffnen des Oxazolidins.

10 **Revendications**

1. Procédé pour la préparation de composés de formule XIV à partir de composés de formule XI



dans lesquelles

R_2 représente un groupe acyle ou un groupe protecteur d'alcool;
 R_3 représente un hydrogène, un groupe acyle, alkyle ou bien, pris conjointement avec R_4 , il forme un groupe $C = O$, $C = S$, SO , SO_2 ;
 R_4 représente un hydrogène ou bien, pris conjointement avec R_3 , il forme un groupe $C = O$, $C = S$, SO , SO_2 ;
 R_5 représente un hydrogène ou un groupe protecteur d'alcool;
 R_6 représente un groupe aryle, aryle substitué, hétéroaryle;

comportant

a) la réduction sélective du groupe azido en groupe amino ;
 b) Le traitement optionnel avec des agents d'alkylation ou d'acylation ;
 c) le clivage du groupe protecteur du C7 ;
 d) l'ouverture de l'oxazolidine.

REFERENCES CITED IN THE DESCRIPTION

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