Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1955–1963

Synthetic route towards (5*R*,2′*S*,5′*S*,6′*S*)-ribosyl-diazepanone, an analogue core of the liposidomycins

Bruno Drouillat, Yann Bourdreux, Delphine Perdon and Christine Greck*

Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles St-Quentin-en-Yvelines, 45, Avenue des Etats Unis, 78035 Versailles Cédex, France

Received 10 July 2007; accepted 25 July 2007

Abstract—The synthesis of (5*R*,2′*S*,5′*S*,6′*S*)-ribosyl-diazepanone, an analogue core of liposidomycins is described. The core ribosyl seven-membered heterocycle of nucleoside antibiotic liposidomycins was formed by reductive amination of an α-ribosylamino ester derived from D-ribose, and an amino aldehyde derived from methyl 4-triisopropylsilyloxy-3-oxobutanoate, followed by a peptidic coupling reaction.
© 2007 Elsevier Ltd. All rights reserved.

1. Introduction

The liposidomycins are a family of complex nucleoside antibiotics that can be isolated from *Streptomyces griseosporeus*.[1] They act by inhibiting phospho-*N*-acetyl-muramyl-pentapeptide-transferase (translocase I), an enzyme involved in the lipid cycle of the biosynthesis of bacterial peptidoglycan.[2] The liposidomycin core structure was elucidated by NMR and mass spectra studies of their degradation products, which revealed the presence of a 5′-substituted uridine, a 5-amino-5-deoxyribose and a disubstituted 1,4-diazepan-3-one.[3] The liposidomycins B and C are the major members of this family (Fig. 1). They display only minor peripheral structural differences in their lipidic side chain. The determination of the absolute configuration of the ribosyl-diazepanone core, although initially uncertain, has been the subject of various synthetic approaches.[4] Knapp et al.[5] suggested that the unassigned stereogenic centres for the ribosyl-diazepanone of liposidomycins presented a (*S*)-configuration. The X-ray crystal analysis of caprazol,[6] the core structure of the caprazamycins, which are nucleoside antibiotics structurally and biologically related to the liposidomycins and recently synthesized by Matsuda,[7] confirmed the stereochemical assignments for the liposidomycin core structure.

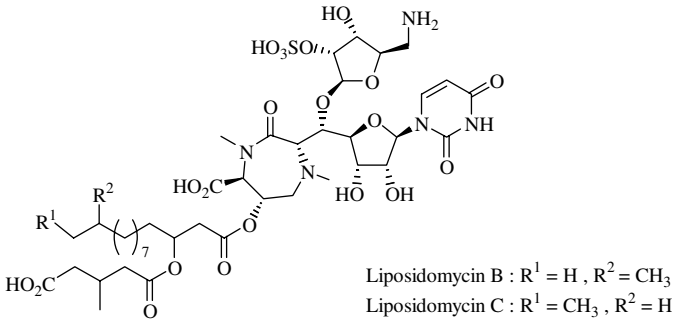


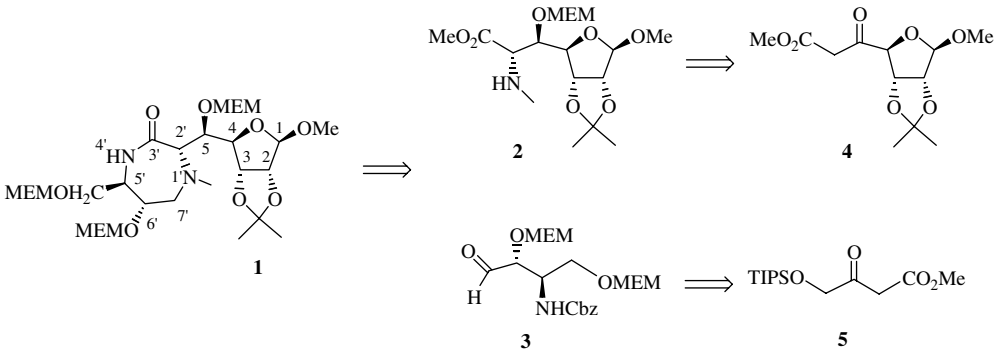
Figure 1. Structures of liposidomycins B and C.

The liposidomycins are potential lead compounds for the design of novel antibiotics acting on peptidoglycan biosynthesis. We designed a convergent synthesis of liposidomycin core analogues using the same methodology to control the stereochemistry at each of the stereocentres of the two intermediates necessary for the synthesis of the ribosyl seven-membered heterocycle. We have used this pathway to synthesize (5*R*,2′*S*,5′*S*,6′*S*)-ribosyl-diazepanone **1**, the 5-*epi* analogue core of the liposidomycins.

Retrosynthetic analysis (Scheme 1) shows that the core can be divided into two key intermediates **2** and **3**. Each precursor was obtained with complete *anti* selectivity at C_2–C_3 from the corresponding β-ketoesters **4** and **5** by asymmetric hydrogenation in the presence of a chiral ruthenium

* Corresponding author. Tel.: +33 139254474; fax: +33 139254452; e-mail: greck@chimie.uvsq.fr

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.07.023



Scheme 1. Retrosynthetic analysis of the 5-*epi* analogue of the ribosyl diazepanone core of the liposidomycins.

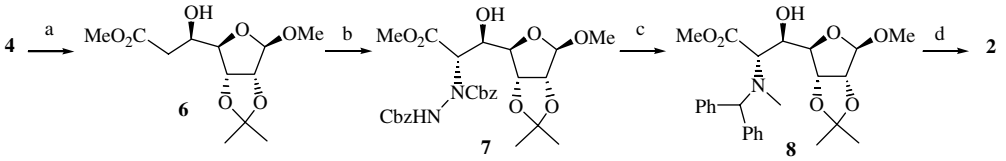
catalyst, followed by electrophilic amination[8] of the resulting β-hydroxyester.

2. Results and discussion

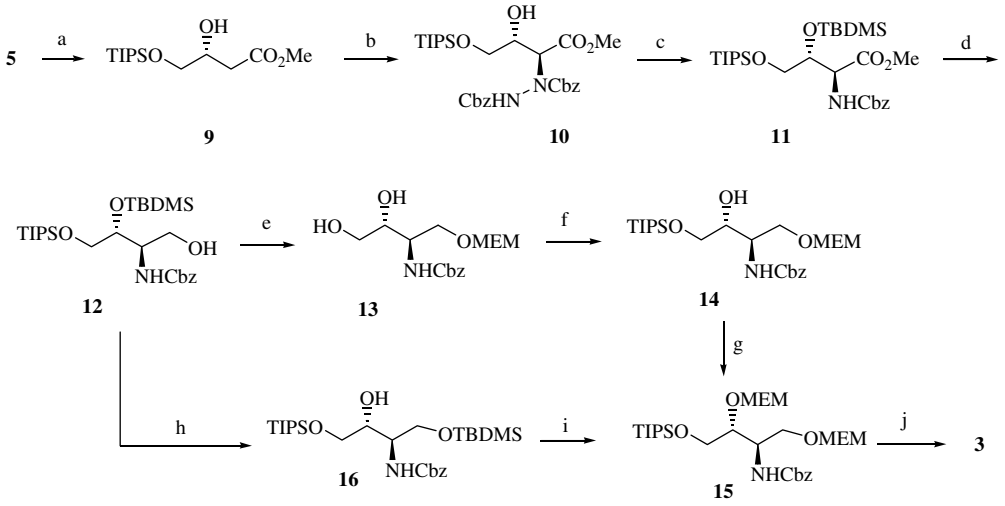
β-Ketoester **4** derived from D-ribose was hydrogenated in methanol at 40 °C under an atmospheric pressure in the presence of 2 mol % of (*S*)-BinapRuBr$_2$ to afford the corresponding β-hydroxyester **6** in quantitative yield as a 95/5 diastereomeric mixture. Compound **6** was separated by flash chromatography and isolated in 94% yield as a single diastereomer. The catalyst, prepared in situ from commercially available Ru(Cod)(2-methylallyl)$_2$,[9] was shown to control the stereochemistry at the created hydroxyl centre.[10] Electrophilic amination of the zinc enolate of **6** was performed at −78 °C with dibenzyl azodicarboxylate to produce *anti*-diastereoisomer **7** in 56% yield and with complete diastereoselectivity. Catalytic hydrogenolysis of the benzyl carbamates and of the N–N bond under atmospheric pressure occurred simultaneously in the presence of Raney Ni. The benzophenone Schiff base of the resulting α-amino-β-hydroxyester, formed by transimination with benzophenone imine in the presence of methanolic HCl, was reduced with sodium cyanoborohydride.[11] Reductive N-methylation with a formaldehyde aqueous solution[12] afforded **8** in 94% yield from **7**. Crystallographic analysis of a *tert*-butyldimethylsilyl ether derivative of **8** shows an *anti*-relationship between the two adjacent aminated and hydroxylated carbons with C-5 (*R*) and C-6 (*S*) absolute configurations.[10] Protection of the hydroxyl function of **8** with a methoxyethoxymethyl group followed by hydrogenolysis of the benzhydryl group in ethanol with Pd/C as catalyst gave α-ribosylamino ester **2** in 58% yield (Scheme 2).

Aldehyde precursor **3** was obtained from prochiral β-ketoester **5** using *anti*-2-amino-1,3,4-butanetriol intermediates (Scheme 3).[13] The first step was the hydrogenation of β-ketoester **5** in methanol at 40 °C under a pressure of 10 bar in the presence of 2 mol % of (*S*)-BinapRuBr$_2$. Under these conditions, β-hydroxyester **9** was obtained in 92% yield and complete enantioselectivity as confirmed by europium-complex NMR studies by comparison with the racemic mixture.[14] The zinc enolate of **9** was generated using methyl zinc bromide and lithium diisopropylamide at −78 °C before reaction with dibenzyl azodicarboxylate to give *anti* diastereoisomer **10** in 70% yield and with complete diastereoselectivity. In order to shorten the synthesis of **3**, we tried initially to protect the secondary alcohol of compound **10** with a methoxyethoxymethyl group. Unfortunately, this protection was not successful under sufficiently mild conditions. The hydroxyl function was protected as a *tert*-butyldimethylsilyl ether because degradation products were formed during N–N bond cleavage of the free alcohol. One-pot deprotection and cleavage of the deprotected hydrazine derivative was achieved under an atmospheric pressure of hydrogen by successively adding Pd/C and Raney Ni as catalysts to the reaction mixture. The resulting α-amino ester was protected with a benzyloxycarbonyl group to afford **11** in 70% yield from **10**. Reduction of the ester function of **11** to 2-aminobutanetriol proceeded in high yield and without detectable epimerization by using calcium borohydride.[15]

At this point, two synthetic pathways were used to obtain aldehyde **3**. The first route involves the hydroxyl protection of **12** as a methoxyethoxymethyl ether, followed by desilylation of the two silyl ethers by TBAF in THF afforded diol **13** in 85% yield. This full desilylation was necessary as it is



Scheme 2. Reagents and conditions: (a) H_2 (1 atm), (*S*)-Binap $RuBr_2$ 2%, MeOH, 40 °C, 16 h (94%); (b) (i) MeZnBr (1.1 equiv), THF, 1 h, 0 °C; (ii) LDA (2.2 equiv), THF, 1 h, 78 °C; (iii) CbzN=NCbz (2 equiv), THF, 1.5 h, −78 °C; (iv) satd aq NH_4Cl (56%, de >95%); (c) (i) H_2 1 atm, Raney Ni, MeOH, 18 h; (ii) Ph_2C=NH (1.5 equiv), DCM, MeOH satd HCl, 18 h; (iii) MeCN, AcOH (9 equiv), $NaBH_3CN$ (4 equiv), 1.5 h, then aqueous HCHO (50 equiv), 1 h, 0 °C (94%); (d) (i) DIPEA (5 equiv), MEMCl (5 equiv), DCM, 72 h; (ii) H_2 1 atm, Pd/C, EtOH, 18 h (58%).



Scheme 3. Reagents and conditions: (a) H_2 (10 bar), (*S*)-Binap $RuBr_2$ 2%, MeOH, 40 °C, 16 h (92%, ee >95%); (b) (i) MeZnBr (1.1 equiv) THF, 1 h, 0 °C; (ii) LDA (2.2 equiv), THF, 1 h, −78 °C; (iii) CbzN=NCbz (2 equiv), THF, 1.5 h, −78 °C; (iv) satd aq NH_4Cl; (70%, de >95%); (c) (i) TBDMSOTf (1.5 equiv), 2,6-lutidine (2 equiv), DCM, 2 h, −78 °C; (ii) H_2 (1 atm), Pd/C, MeOH, 1 h, then Raney Ni, 1 h; (iii) CbzCl (1.2 equiv), DMAP (1.2 equiv), MeCN, 12 h (70%); (d) $Ca(BH_4)_2$ (7 equiv), THF/EtOH 1/1.2, −20 °C, 15 min to rt, 18 h (91%); (e) (i) DIPEA (2.5 equiv), MEMCl (2.5 equiv), DCM, 16 h; (ii) TBAF (3 equiv), THF, 30 min, 0 °C (85%); (f) TIPSOTf (1.05 equiv), imidazole (2.6 equiv), DMF, 16 h (87%); (g) DIPEA (5 equiv), MEMCl (5 equiv), DCM, 48 h (70%); (h) NaH (4.5 equiv), DMF, 30 min, −20 °C (42%); (i) (i) PTSA·H_2O (0.1 equiv), EtOH/THF 2/1, 3 h; (ii) DIPEA (10 equiv), MEMCl (10 equiv), DCM, 16 h (72%); (j) (i) TBAF (1.5 equiv), THF, 10 min, 0 °C; (ii) DMSO (3 equiv), $(COCl)_2$ (1.1 equiv), DCM, 1 h, −78 °C then NEt_3 (7.5 equiv), 15 min, −78 °C (81%).

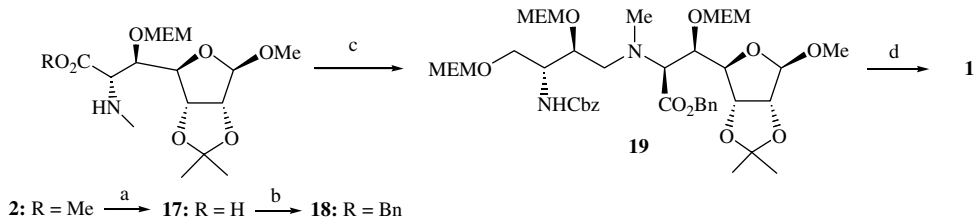
not possible to selectively cleave a primary triisopropylsilyl ether in the presence of a secondary *tert*-butyldimethylsilyl ether.[16a] The primary alcohol of **13** was regioselectively silylated in 87% yield using 1.05 equiv of triisopropylsilyl triflate in the presence of imidazole in DMF. Compound **14** was reacted with methoxyethoxymethyl chloride in the presence of diisopropylethylamine to afford **15** in 70% yield.

A second pathway was developed to shorten the synthesis of **15**. We exploited the ability of the *tert*-butyldimethylsilyl group to migrate under basic conditions[16b] and the possible cleavage of a primary TBDMS ether in the presence of a primary TIPS ether. We previously noticed that the benzylation of compound **12** under classical conditions (NaH, BnBr) occurred with migration of the silyl ether from the secondary to the primary alcohol and the corresponding product was isolated in 80% yield.[13] Treatment of **12** with sodium hydride in DMF at −20 °C resulted in the migration of the TBDMS group to the primary alcohol. Compound **16** was isolated in 42% yield and the remaining starting material **12** was recycled. After selective cleavage of the *tert*-butyldimethylsilyl ether of **16** using 0.1 equiv of *p*-toluenesulfonic acid monohydrate in THF/EtOH,[16c] the resulting diol was reacted with methoxyethoxymethyl chloride in the presence of diisopropylethylamine to afford **15** in 72% yield.

Removal of the triisopropylsilyl ether group of **15** by TBAF in THF followed by Swern oxidation of the primary alcohol yielded aldehyde **3** in 81% yield.

Having completed the synthesis of the two compounds **2** and **3** with high enantio- and diastereoselectivities, we had to accomplish the coupling of the two intermediates. First, we accomplished the coupling of **2** and **3** using reductive amination conditions. However, ester deprotection under basic conditions of the resulting adduct was troublesome as noticed before by us[17] and by Matsuda[7] for the synthesis of caprazol. Thus, we first performed the basic hydrolysis of the ester of **2**. This reaction was quantitative within 3 h at room temperature in the presence of potassium hydroxide in a mixture H_2O/MeOH 1/1. After acidification, the reaction mixture was lyophilized to give α-ribosylamino acid **17**. Following our previously described synthesis of two liposidomycin ribosyl-diazepanone C-6′ deoxy derivatives, we treated **17** with an excess of aldehyde **3** in the presence of sodium borohydride in acetonitrile.[17] Unfortunately, these reaction conditions led only to the reduction of aldehyde **3** to the corresponding primary alcohol with no reductive amination product.

We decided to attempt the reductive amination using the benzyl ester of **17**, which can later be hydrogenolyzed together with the benzyl carbamate group. Treatment of the crude ribosylamino acid **17** with an excess of benzyl alcohol and hydroxybenzotriazole (HOBt) in the presence of dimethylaminopyridine and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) in DCM gave benzyl ester **18** in 55% yield from **2**. At this point, we used a stepwise reductive amination procedure where amine **18** and an excess of **3** were first mixed together in dichloroethane in the presence of 3 Å-MS and acetic acid. The resulting imine was reduced using sodium triacetoxyborohydride[18] to give compound **19** in 45% yield. Simultaneous hydrogenolysis of the benzyl ester and of the benzylcarbamate of **19** in the presence of catalytic Pd/C in EtOH/H_2O followed by intramolecular peptidic coupling with an excess of EDC and HOBt in the presence of dimethylaminopyridine in DMF, led to the expected



Scheme 4. Reagents and conditions: (a) KOH (3 equiv), MeOH/H_2O 1/1, 3 h (quantitative yield); (b) BnOH (10 equiv), HOBt (2 equiv), DMAP (0.2 equiv), EDC·HCl (2.5 equiv), DCM, 4 days (55%); (c) **3** (2 equiv), 3 Å-MS, AcOH, DCE, 24 h then $NaBH(OAc)_3$ (2 equiv), 40 h then **3** (1.4 equiv), 48 h, then $NaBH(OAc)_3$ (2 equiv), 18 h (45%); (d) (i) H_2 (5 bar), Pd/C cat., EtOH/H_2O 1/1, 5 h (quantitative yield); (ii) HOBt (3 equiv), DMAP (0.4 equiv), EDC (3.5 equiv), DMF, 16 h (28%).

lactam **1** in 28% isolated yield from **19** (Scheme 4). This yield is comparable to those obtained by Le Merrer[4c] for the macrolactamization step or by Matsuda[7] for the macrocyclization step by reductive amination.

3. Conclusion

We designed a convergent synthetic approach to the 5-*epi* liposidomycin ribosyl-diazepanone analogue derivative **1** using the same strategy to control the stereochemistry at each of the stereocentres of the ribosyl seven-membered heterocycle. This methodology, based on the catalytic hydrogenation of a β-ketoester followed by electrophilic amination of the resulting β-hydroxyester to give an α-amino-β-hydroxy ester with excellent *anti* stereoselectivity, could be extended to generate other diastereomers of the diazepanone of the liposidomycins by coupling different *anti*-precursors. An approach to the synthesis of the natural ribosyl-diazepanone core is currently in progress.

4. Experimental

4.1. General experimental methods

Solvents were distilled according to the literature.[19] Flash column chromatographic separations were carried out over Merck silica gel 60 (0.035–0.070 mm). The solvent system is given v/v. NMR spectra were recorded on a Bruker AC-200 or Avance 300 spectrometer, and reported in parts per million (δ) relative to tetramethylsilane (0.00 ppm) as the internal standard. Coupling constant (J) was reported in Hertz (Hz). Abbreviations of multiplicity were as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Assignment was based on 1H–1H COSY and HMQC NMR spectra. Optical rotations were recorded at 25 °C on a Perkin–Elmer 241 polarimeter (1 dm cell). Melting points were measured by means of a capillary tube immersed in an oil bath (Tottoli apparatus, Büchi). Infrared spectra were recorded on a Nicolet Impact 400 D spectrometer in KBr discs or films. Routine mass spectra were recorded on HP MS Engin 5989B mass spectrometer by Vincent Steinmetz (ILV, Versailles). High-resolution mass spectra were performed on a Q-TOF Ultima Bruker mass spectrometer (Université d'Amiens, France). Elemental analyses were performed by the Service de Microanalyses of ICSN, Gif-sur-Yvette, France.

4.1.1. Methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-5-oxo-β-D-*ribo*-heptafuranosid)uronate 4. Compound **4** was prepared according to Masamune's procedure.[20] Carbonyldiimidazole (8.6 g, 53.0 mmol) was added to a solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranosiduronic acid[21] (8.5 g, 39.0 mmol) in dry THF (150 mL). The reaction mixture was stirred for 7 h before adding the magnesium salt of monomethylmalonate (13.5 g, 52.3 mmol). After stirring for 16 h, the solution was concentrated under vacuum. The residue was treated with a 1 M aqueous solution of HCl (250 mL) cooled to 0 °C. The aqueous layer (pH 1) was extracted with ethyl acetate (5 × 100 mL). The ethyl acetate extract was washed with a saturated aqueous solution of sodium bicarbonate (50 mL), dried over sodium sulfate and concentrated. The crude product was crystallized from diisopropyl ether giving 7.5 g (27.4 mmol, 70% yield) of the title compound as white crystals. In $CDCl_3$, 7% of the enol form was detected by ^1H and ^{13}C NMR. Mp 56 °C; $[\alpha]_D^{25} = -119$ (c 1.1, CH_2Cl_2); IR (KBr): 2940, 1730, 1700, 1570, 1360, 1320, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.45 (s, 3H, OCH_3), 3.52 (d, 1H, H-6a, $J_{6a,6b} = 16.55$ Hz), 3.75 (s, 3H, $COOCH_3$), 3.77 (d, 1H, H-6b, $J_{6a,6b} = 16.55$ Hz), 4.51 (d, 1H, H-2, $J_{2,3} = 5.88$ Hz), 4.65 (s, 1H, H-4), 5.03 (s, 1H, H-1), 5.22 (d, 3H, H-3, $J_{2,3} = 5.88$ Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 24.91, 26.35, 44.96, 52.42, 56.52, 80.50, 84.29, 89.65, 110.42, 112.66, 167.52, 201.69; MS (ESI^+): $m/z = 275$ $[M+H]^+$; Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.57. Found: C, 52.52; H, 6.75.

4.1.2. Methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-*allo*-heptafuranosid)uronate 6. The (*S*)-BinapRuBr$_2$ catalyst was prepared under argon according to the literature.[8a] To bis-(2-methylallyl)-cycloocta-1,5-diene-ruthenium(II) complex (16 mg, 0.050 mmol, 0.020 equiv) and (*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (34 mg, 0.055 mmol, 0.022 equiv) in degassed acetone (2 mL) was added a methanolic solution of hydrogen bromide (0.15–0.18 M, 0.044 equiv). The reaction mixture was stirred for 1 h and the solution then concentrated under vacuum. A solution of **4** (0.685 g, 2.50 mmol) in degassed methanol (5 mL) was canulated into the (*S*)-BinapRuBr$_2$ (2 mol %). The reaction mixture was purged three times with hydrogen and vigorously stirred at rt. After 16 h, the solution was concentrated under vacuum and the residue was purified by flash chromatography (Et_2O/pentane 25/75) to afford 0.648 g (2.35 mmol, 94% yield) of the title compound

as a solid. A sample was crystallized from diisopropyl ether/pentane 1/9 giving white needles. Mp 32 °C; $[\alpha]_D^{25} = -45$ (*c* 1.0, CH_2Cl_2); IR (KBr): 3400, 2920, 1720, 1360, 1200, 1100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.33 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.52 (dd, 1H, H-6a, $J_{6a,6b} = 16.08$ Hz, $J_{5,6a} = 7.92$ Hz), 2.66 (dd, 1H, H-6b, $J_{6a,6b} = 16.08$ Hz, $J_{5,6b} = 3.63$ Hz), 3.41 (s, 3H, OCH_3), 3.62 (d, 1H, O*H*, $J_{5,OH} = 10.01$ Hz), 3.72 (s, 3H, COOCH_3), 4.07 (m, 1H, H-5), 4.10 (s, 1H, H-4), 4.59 (d, 1H, H-2, $J_{2,3} = 6.24$ Hz), 4.88 (d, 1H, H-3, $J_{2,3} = 6.24$ Hz), 4.98 (s, 1H, H-1); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 24.48, 26.09, 37.77, 51.61, 55.70, 68.26, 80.36, 85.22, 89.57, 109.70, 111.97, 171.90; MS (ESI^+): $m/z = 277$ $[M+H]^+$; Anal. Calcd for $C_{12}H_{20}O_7$: C, 52.17; H, 7.24. Found: C, 52.11; H, 7.44.

4.1.3. Methyl (methyl 6-deoxy-6-*N*,*N*′-dibenzyloxycarbonyl-hydrazino-2,3-*O*-isopropylidene-D-*glycero*-β-D-*allo*-heptafuranosid)uronate 7. To a solution of **6** (0.641 g, 2.32 mmol) in dry THF (2.3 mL) at 0 °C was added dropwise a solution of MeZnBr (2.55 mmol) prepared from zinc bromide (0.575 g, 2.55 mmol) in dry THF (2.6 mL) and methyllithium (1.65 mL, 2.64 mmol, 1.6 M sol in Et_2O). After stirring for 1 h, the reaction mixture was cooled to −78 °C and a solution of lithiumdiisopropylamide (5.10 mmol) in THF (5.2 mL) was added dropwise. After a further 1 h at −78 °C, a solution of dibenzyl azodicarboxylate (1.38 g, 4.64 mmol) in THF (5 mL) was added dropwise, the reaction mixture was stirred for 1.5 h, hydrolyzed at −78 °C with a saturated aqueous solution of ammonium chloride (50 mL), warmed to rt, extracted into ethyl acetate (3 × 70 mL), dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography (Et_2O/pentane 60/40) affording 0.746 g (1.30 mmol, 56% yield) of the title compound as a solid. A sample was crystallized from ether/pentane 8/2 giving white crystals. Mp 110 °C; $[\alpha]_D^{25} = -10$ (*c* 1.0, CH_2Cl_2); IR (KBr): 3380, 2940, 1700, 1200, 1170, 1150 cm^{-1}; ^1H NMR (300 MHz, toluene-d_8, 353 K) δ (ppm): 1.31 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.36 (s, 3H, OCH_3), 3.37 (s, 1H, OH), 3.55 (s, 3H, COOCH_3), 4.45 (m, 1H, H-5), 4.66 (d, 1H, H-2, $J_{2,3} = 5.91$ Hz), 4.81 (d, 1H, H-4, $J_{4,5} = 8.19$ Hz), 5.05 (d, 1H, H-4, $J_{2,3} = 5.91$ Hz), 5.15 (m, 3H, H-1 and PhCH_2), 5.52 (d, 1H, H-6, $J_{5,6} = 2.97$ Hz), 6.97 (s, 1H, N*H*), 7.19 (m, 10H, Ar-*H*); ^{13}C NMR (75 MHz, toluene-d_8, 353 K) δ (ppm): 24.25, 25.75, 50.62, 54.32, 62.84, 66.88, 67.76, 71.85, 81.56, 84.93, 86.87, 109.90, 111.44, 127.41, 128.62, 135.61, 135.47, 155.38, 168.88; MS (ESI^+): $m/z = 575$ $[M+H]^+$; Anal. Calcd for $C_{28}H_{34}N_2O_{11}$: C, 58.53; H, 5.96; N, 4.88. Found: C, 58.41; H, 5.99; N, 4.88.

4.1.4. Methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-6-[(*N*-benzhydryl-*N*-methyl)amino]-D-*glycero*-β-D-*allo*-heptafuranosid)uronate 8. A solution of **7** (3 g, 5.22 mmol) in dry methanol (115 mL) containing Raney Ni (1 g) was vigorously stirred for 18 h under hydrogen. After filtering, the solution was concentrated under vacuum. To the residue dissolved in dry dichloromethane (21 mL) was added benzophenone imine (1.31 mL, 7.83 mmol) and a saturated methanolic solution of HCl (0.9 mL). The reaction mixture was stirred for 18 h. The mixture was filtered and the white solid residue was washed with dichloromethane (3 × 5 mL). The filtrate was concentrated under vacuum and to the resulting residue dissolved in dry acetonitrile (25 mL) was added sodium cyanoborohydride (1.31 g, 20.81 mmol) and acetic acid (2.7 mL, 47 mmol). After 1.5 h, the solution was cooled to 0 °C before adding a 37% aqueous solution of formaldehyde stabilized with 10–15% methanol (19 mL, 261 mmol). After 1 h, a saturated aqueous solution of sodium bicarbonate (50 mL) was slowly added to the reaction mixture. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (EtOAc/pentane 30/70) affording 2.32 g (4.92 mmol, 94% yield) of the title compound as a white solid. Mp 134 °C; $[\alpha]_D^{25} = -105$ (*c* 1.2, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.25 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.44 (s, 3H, OCH_3), 3.47 (d, 1H, H-6, $J_{5,6} = 10.29$ Hz), 3.78 (s, 3H, COOCH_3), 4.09 (s, 1H, O*H*), 4.24 (d, 1H, H-5, $J_{5,6} = 10.29$ Hz), 4.52 (m, 3H, H-2, H-3, H-4), 4.99 (s, 1H, H-1), 5.14 (s, 2H, H-1, $(Ph)_2CH$), 7.15-7.29 (m, 6H, Ar-*H*), 7.46 (m, 4H, Ar-*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 24.47, 26.41, 36.13, 50.95, 55.71, 63.39, 71.03, 74.83, 79.96, 86.03, 88.23, 110.69, 111.68, 126.55, 127.02, 127.29, 127.58, 127.81, 128.53, 142.05, 142.82, 170.34; MS (ESI^+): $m/z = 472$ $[M+H]^+$; Anal. Calcd for $C_{26}H_{33}NO_7$: C, 66.22; H, 7.05; N, 2.97. Found: C, 66.07; H, 7.23; N, 2.98.

4.1.5. Methyl (methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(2-methoxyethoxymethyl)-6-*N*-methylamino-D-*glycero*-β-D-*allo*-heptafuranosid)uronate 2. To a solution of **8** (0.835 g, 1.77 mmol) in dichloromethane (10 mL) containing diisopropylethylamine (1.55 mL, 8.86 mmol) was added 2-methoxyethoxymethyl chloride (1 mL, 8.86 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 72 h. The reaction mixture was hydrolyzed with a saturated aqueous solution of sodium chloride (20 mL) and extracted with ethyl acetate (4 × 20 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 1/1) affording 0.813 g of the expected compound as an oil. A solution of this oil (0.813 g, 1.45 mmol) in ethanol (35 mL) containing 10% Pd/C (20 mg) was vigorously stirred under hydrogen for 18 h. After filtering, the solution was concentrated under vacuum and the residue was purified by flash chromatography (EtOAc) affording 0.403 g (1.025 mmol, 58% yield) of the title compound as a colourless oil. $[\alpha]_D^{25} = +1$ (*c* 0.9, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.39 (s, 3H, NCH_3), 3.33 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3), 3.60 (m, 4H, H-6, OCH_aCH_2O), 3.76 (m, 5H, H-5, COOCH_3 and OCH_bCH_2O), 4.25 (d, 1H, H-4, $J_{4,5} = 9.90$ Hz), 4.57 (d, 1H, H-2, $J_{2,3} = 6.00$ Hz), 4.72 (d, 1H, OC$H_{a'}$O, $J = 7.20$ Hz), 4.76 (d, 1H, H-3, $J_{2,3} = 6.00$ Hz), 4.89 (d, 1H, OC$H_{b'}$O, $J = 7.20$ Hz), 4.98 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 24.97, 26.49, 35.13, 51.80, 55.82, 59.10, 64.29, 67.92, 71.64, 82.01, 83.28, 85.05, 85,91, 97.52, 110.06, 112.38, 171.98; MS (ESI^+): $m/z = 394$ $[M+H]^+$; Anal. Calcd for $C_{17}H_{31}NO_9$: C, 51.90; H, 7.94; N, 3.56. Found: C, 52.07; H, 7.86; N, 3.40.

4.1.6. Methyl (3*R*)-3-hydroxy-4-(triisopropylsilyloxy)butanoate 9. Methyl 4-triisopropysilyloxy-3-oxobutanoate (3.420 g, 11.86 mmol) was dissolved under argon in degassed methanol (24 mL). This solution was canulated into the (*S*)-BinapRuBr$_2$ complex (2 mol %), prepared as previously described for **6**. The reaction mixture was placed in an autoclave, which was purged three times with hydrogen and brought to a pressure of 10 bar. The autoclave was heated to 40 °C. After 16 h, magnetic stirring was stopped and the autoclave was cooled to rt. The solution was concentrated under vacuum and the residue was purified by flash chromatography (Et$_2$O/cyclohexane 20/80) affording 3.163 g (10.91 mmol, 92% yield) of the title compound as a pale yellow oil. $[\alpha]_D^{25} = +16$ (*c* 1.3, EtOH); IR (film): 3405, 2945, 2863, 1741, 881 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.06 (s, 21H, Si(C*H*(CH_3)$_2$)$_3$), 2.50 (dd, 1H, H-2a, $J_{2a,2b} = 16$ Hz, $J_{2a,3} = 7.4$ Hz), 2.59 (dd, 1H, H-2b, $J_{2a,2b} = 16$ Hz, $J_{2b,3} = 5.3$ Hz), 2.94 (br s, 1H, O*H*), 3.70 (m, 5H, CO_2CH_3 and H-4), 4.10 (m, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 11.81, 17.93, 37.84, 51.77, 66.41, 68.74, 172.52; MS (ESI$^+$): $m/z = 291$ [M+H]$^+$; Anal. Calcd for $C_{14}H_{30}O_4Si$: C, 57.89; H, 10.41. Found: C, 58.14; H, 10.58.

4.1.7. Methyl (2*S*,3*R*)-2-*N*,*N*′-dibenzyloxycarbonylhydrazino-3-hydroxy-4-(triisopropylsilyloxy)butanoate 10. To a solution of **9** (3.23 g, 11.13 mmol) in dry THF (11 mL) at 0 °C was added dropwise a solution of MeZnBr (12.23 mmol) prepared from zinc bromide (2.75 g, 12.23 mmol) in dry THF (11 mL) and methyllithium (8.8 mL, 14.08 mmol, 1.6 M sol in Et$_2$O). After stirring for 1 h, the reaction mixture was cooled to −78 °C and a solution of lithiumdiisopropylamide (24.46 mmol) in THF (25 mL) was added dropwise. After a further 1 h at −78 °C, a solution of dibenzyl azodicarboxylate (6.63 g, 22.24 mmol) in THF (7 mL) was added dropwise, the reaction mixture was stirred for 1.5 h, hydrolyzed at −78 °C with a saturated aqueous solution of ammonium chloride (110 mL), warmed to rt, extracted into ethyl acetate, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography (EtOAc/pentane 5/95) to afford 4.58 g (7.79 mmol, 70% yield) of the title compound as an oil. $[\alpha]_D^{25} = +2$ (*c* 1.7, EtOH); IR (film): 3472, 3088, 3062, 3032, 2934, 2863, 1755, 1712, 881 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.07 (s, 21H, Si(C*H*(CH_3)$_2$)$_3$), 3.05 (s, 1H, O*H*), 3.71 (s, 3H, CO_2CH_3), 3.89 (m, 2H, H-4), 4.23 (m, 1H, H-3), 5.02 (m, 1H, H-2), 5.16 (m, 4H, 2 × CO_2CH_2Ph), 7.08 (s, 1H, N*H*), 7.30 (m, 10H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.91, 17.83, 52.14, 62.20, 64.17, 67.83, 68.62, 71.14, 127.81, 128.02, 128.21, 128.34, 128.44, 128.51, 135.51, 135.60, 155.91, 156.20, 170.23; MS (ESI$^+$): $m/z = 611$ [M+Na]$^+$; Anal. Calcd for $C_{30}H_{44}N_2O_8Si$: C, 61.20; H, 7.53; N, 4.76. Found: C, 60.99; H, 7.63; N, 4.64.

4.1.8. Methyl (2*S*,3*R*)-2-*N*-benzyloxycarbonylamino-4-triisopropylsilyloxy-3-(*tert*-butyldimethylsilyloxy)butanoate 11. *tert*-Butyldimethylsilyl triflate (2.15 mL, 9.34 mmol) was added dropwise in 15 min at −78 °C to a solution of **10** (3.63 g, 6.17 mmol) in dichloromethane (11 mL) containing 2,6-lutidine (1.45 mL, 12.44 mmol). The reaction mixture was stirred for 2 h at −78 °C, after which methanol (75 mL) was added and the mixture was warmed to rt. The solution was concentrated under vacuum and the residue was immediately purified by flash chromatography (EtOAc/pentane 10/90) affording 4.25 g of the expected compound as a colourless oil. A solution of this oil (4.25 g, 6.04 mmol) in dry methanol (115 mL) containing 10% Pd/C (300 mg) was stirred under hydrogen for 1 h. Raney Ni (4 g) was added to the reaction mixture, which was vigorously stirred under hydrogen until TLC monitoring showed complete transformation of the intermediate hydrazine (about 1 h). After filtering, the solution was concentrated under vacuum and the residue was purified by flash chromatography (Et$_2$O/pentane 15/85) affording 2.02 g of the expected compound as a colourless oil. To a solution of this oil (2.02 g, 4.82 mmol) in acetonitrile (25 mL) containing 4-dimethylaminopyridine (647 mg, 5.30 mmol) was added benzyl chloroformate (0.76 mL, 5.30 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 12 h before adding methanol (50 mL). The solution was concentrated under vacuum and the residue was purified by flash chromatography (Et$_2$O/cyclohexane 5/95) affording 2.39 g (4.32 mmol, 70% yield) of the title compound as an oil. $[\alpha]_D^{25} = +24$ (*c* 2.1, CH_2Cl_2); IR (film): 3431, 3092, 3064, 3029, 2945, 2858, 1726, 1506, 892, 786 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.07 (s, 6H, Si(CH_3)$_2$), 0.87 (s, 9H, SiC(CH_3)$_3$), 1.07, 1.08 (2s, 21H, Si(C*H*(CH_3)$_2$)$_3$), 3.73 (m, 5H, CO_2CH_3 and H-4), 4.09 (m, 1H, H-3), 4.49 (dd, 1H, H-2, $J_{2,NH} = 8.0$ Hz, $J_{2,3} = 3.1$ Hz), 5.12 (s, 2H, OCH_2Ph), 5.85 (d, 1H, N*H*, $J_{2,NH} = 8.0$ Hz), 7.34 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): −5.12, −4.63, 11.87, 17.94, 18.07, 25.63, 52.03, 57.62, 65.34, 66.77, 73.54, 127.81, 127.97, 128.42, 136.54, 155.92, 170.41; MS (ESI$^+$): $m/z = 576$ [M+Na]$^+$; Anal. Calcd for $C_{28}H_{51}NO_6Si_2$: C, 60.72; H, 9.28; N, 2.53. Found: C, 60.42; H, 9.39; N, 2.39.

4.1.9. (2*R*,3*R*)-2-*N*-Benzyloxycarbonylamino-3-*O*-*tert*-butyldimethylsilyl-4-*O*-(triisopropylsilyl)butane-1,3,4-triol 12. A solution of **11** (2.52 g, 4.55 mmol) in dry ethanol (30 mL) was canulated into a 500 mL round bottom flask containing a suspension of calcium chloride (3.51 g, 31.62 mmol) in dry THF (25 mL). Sodium borohydride (2.06 g, 54.45 mmol) was added slowly to the solution cooled to −20 °C. After stirring at −20 °C for 1 h, the reaction mixture was warmed to rt and stirred for 18 h. The reaction mixture was hydrolyzed at 0 °C with a saturated aqueous solution of ammonium chloride (300 mL). The organic layer was extracted with ethyl acetate (4 × 150 mL). The ethyl acetate extract was washed with a saturated aqueous solution of sodium chloride (200 mL), dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et$_2$O/pentane 30/70) affording 2.18 g (4.15 mmol, 91% yield) of the title compound as an oil. $[\alpha]_D^{25} = +7$ (*c* 2.1, CH_2Cl_2); IR (film): 3416, 3092, 3064, 3029, 2868, 1705, 1506, 898, 785 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.08 (s, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, SiC(CH_3)$_3$), 1.06, 1.07 (2s, 21H, Si(C*H*(CH_3)$_2$)$_3$), 3.66–3.82 (m, 3H, H-1 and H-4a), 3.93 (m, 1H, H-2), 4.01–4.07 (m, 2H, H-3 and H-4b), 5.12 (s, 2H, OCH_2Ph), 5.67 (d, 1H, N*H*, $J_{2,NH} = 7.81$ Hz), 7.35 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): −5.11, −4.69, 11.81, 17.86, 17.93, 25.71, 53.52, 62.48, 65.10, 66.65,

74.55, 127.97, 128.00, 128.45, 129.14, 136.58, 156.29; MS (ESI^+): $m/z = 548$ $[M+Na]^+$; Anal. Calcd for $C_{27}H_{51}NO_5Si_2$: C, 61.67; H, 9.78; N, 2.66. Found: C, 61.66; H, 9.92; N, 2.63.

4.1.10. (2*R*,3*R*)-2-*N*-Benzyloxycarbonylamino-1-*O*-(2-methoxyethoxymethyl)butane-1,3,4-triol 13. To a solution of **12** (0.350 g, 0.666 mmol) in dichloromethane (4 mL) containing diisopropylethylamine (0.31 mL, 1.666 mmol) was added 2-methoxyethoxymethyl chloride (0.20 mL, 1.666 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 16 h. The reaction mixture was hydrolyzed with a saturated aqueous solution of sodium chloride (20 mL) and extracted with ethyl acetate (4 × 20 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 4/6) affording 373 mg of the expected compound as a colourless oil. To a solution of this oil (0.361 g, 0.588 mmol) in THF (5 mL) at 0 °C was slowly added a 1 M solution of tetrabutylammonium fluoride in THF (1.8 mL, 1.8 mmol). After 30 min, the reaction mixture was hydrolyzed with a saturated aqueous solution of sodium chloride (20 mL). The aqueous layer was extracted with ethyl acetate (4 × 25 mL). The ethyl acetate extract was dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (EtOAc/pentane 50/50) affording 0.195 g (0.569 mmol, 85%) of the title compound as a white solid. Mp 46 °C; $[\alpha]_D^{25} = -2$ (*c* 2.6, CH_2Cl_2); IR (KBr): 3742, 3064, 3029, 2924, 1700, 1531 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.04 (s, 1H, O*H*), 3.37 (s, 3H, CH_3), 3.54–3.78 (m, 9H, H-1a, H-2, H-3, H-4, and OCH_2CH_2O), 4.10 (dd, 1H, H-1b, $J_{1a,1b} = 9.76$ Hz, $J_{1b,2} = 2.56$ Hz), 4.71 (s, 2H, OCH_2O), 5.10 (d, 1H, OC*H*′Ph, $J_{H',H''} = 12.14$ Hz), 5.16 (d, 1H, OC*H*″Ph, $J_{H',H''} = 12.14$ Hz), 5.55 (d, 1H, N*H*, $J_{2,NH} = 8.10$ Hz), 7.35 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 52.06, 58.94, 62.96, 66.79, 67.14, 67.26, 70.74, 71.74, 95.48, 128.15, 128.31, 128.58, 136.09, 157.39; MS (ESI^+): $m/z = 366$ $[M+Na]^+$; Anal. Calcd for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34; N, 4.08. Found: C, 56.14; H, 7.34; N, 3.91.

4.1.11. (2*R*,3*R*)-2-*N*-Benzyloxycarbonylamino-1-*O*-(2-methoxyethoxymethyl)-4-*O*-(triisopropylsilyl)butane-1,3,4-triol 14. To a solution of **13** (173 mg, 0.504 mmol) in *N*,*N*-dimethylformamide (2 mL) containing imidazole (0.072 g, 1.310 mmol) was added triisopropylsilyl triflate (0.117 mL, 0.529 mmol) at 0 °C. The reaction mixture was warmed and stirred for 16 h at rt. Methanol (1 mL) was added at 0 °C and the mixture was warmed to rt. After adding ethyl acetate (25 mL), the organic layer was washed with a saturated aqueous solution of sodium chloride (2 × 10 mL), dried over sodium sulfate and concentrated under vacuum. The residue was purified by flash chromatography (Et_2O/pentane 75/25) affording 0.218 g (0.437 mmol, 87%) of the title compound as a colourless oil. $[\alpha]_D^{25} = -11$ (*c* 2.1, CH_2Cl_2); IR (film): 3400, 3092, 3064, 3029, 2939, 2863, 1721, 1521, 886, 786 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.05, 1.07 (2s, 21H, Si(CH(CH_3)$_2$)$_3$), 3.37 (s, 3H, CH_3), 3.54 (m, 2H, OCH_2), 3.68 (m, 3H, H-1a and OCH_2), 3.78 (m, 3H, H-3 and H-4), 3.90 (m, 1H, H-2), 3.98 (dd, 1H, H-1b, $J_{1a,1b} = 10.02$ Hz, $J_{1b,2} = 3.66$ Hz), 4.72 (s, 2H, OCH_2O), 5.07 (d, 1H, OC*H*′Ph, $J_{H',H''} = 12.33$ Hz), 5.15 (d, 1H, OC*H*″Ph, $J_{H',H''} = 12.33$ Hz), 5.56 (d, 1H, N*H*, $J_{2,NH} = 8.48$ Hz), 7.35 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 11.79, 17.91, 52.57, 58.96, 64.97, 66.69, 67.07, 67.37, 71.53, 71.69, 95.75, 127.99, 128.04, 128.46, 136.52, 156.18; MS (ESI^+): $m/z = 522$ $[M+Na]^+$; Anal. Calcd for $C_{25}H_{45}NO_7Si$ C, 60.09; H, 9.08; N, 2.80. Found: C, 59.96; H, 9.18; N, 2.67.

4.1.12. (2*R*,3*R*)-1-*O*-*tert*-Butyldimethylsilyl-2-*N*- benzyloxycarbonylamino-4-*O*-(triisopropylsilyl)butane-1,3,4-triol 16. To a solution of **12** (2.18 g, 4.15 mmol) in *N*,*N*-dimethylformamide (19 mL) cooled to −20 °C was added sodium hydride (448 mg, 18.63 mmol) over 30 min. After addition, the reaction mixture was hydrolyzed at −20 °C with a saturated aqueous solution of ammonium chloride (60 mL) and extracted with ethyl acetate (4 × 40 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 20/80) affording 0.913 g (1.74 mmol, 42% yield) of the title compound as an oil and 0.719 g (1.36 mmol, 33%) of the starting material. $[\alpha]_D^{25} = +11$ (*c* 1.3, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 0.06, 0.07 (2s, 6H, Si(CH_3)$_2$), 0.83 (s, 9H, SiC(CH_3)$_3$), 1.12, 1.14 (2s, 21H, Si(CH(CH_3)$_2$)$_3$), 3.08 (s, 1H, O*H*), 3.73–3.90 (m, 5H, H-2, H-3, H-4a and H-1), 4.02 (d, 1H, H-4b, $J_{4a,4b} = 8.85$ Hz), 5.17 (s, 2H, OCH_2Ph), 5.47 (d, 1H, N*H*, $J_{2,NH} = 7.32$ Hz), 7.33 (m, 5H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): −5.62, 11.86, 17.98, 18.22, 25.87, 53.51, 62.51, 65.15, 66.64, 74.63, 128.58, 128.12, 128.03, 136.67, 156.15; MS (ESI^+): $m/z = 548$ $[M+Na]^+$; Anal. Calcd for $C_{27}H_{51}NO_5Si_2$: C, 61.67; H, 9.78; N, 2.66. Found: C, 61.79; H, 9.64; N, 2.66.

4.1.13. (2*R*,3*R*)-2-*N*-Benzyloxycarbonylamino-1,3-*O*-bis(2-methoxyethoxymethyl)-4-*O*-(triisopropylsilyl)butane-1,3,4-triol 15. Synthesis of **15** from **14**: to a solution of **14** (0.210 g, 0.420 mmol) in dichloromethane (5 mL) containing diisopropylethylamine (0.36 mL, 2.104 mmol) was added 2-methoxyethoxymethyl chloride (0.24 mL, 2.104 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 48 h. The reaction mixture was hydrolyzed with a saturated aqueous solution of sodium chloride (20 mL) and extracted with ethyl acetate (4 × 20 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 4/6) affording 173 mg (0.294 mmol, 70%) of the title compound as a colourless oil. Synthesis of **15** from **16**: compound **16** (103 mg, 0.196 mmol) was dissolved in a 0.02 M *p*-toluenesulfonic acid monohydrate 2.3:1 solution of EtOH and THF (1 mL, 0.020 mmol) at rt. The reaction was stirred for 3 h before adding a 5% aqueous solution of sodium hydrogenocarbonate (0.5 mL) and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 20/80) affording 0.061 g of the expected compound as a colourless oil. To a solution of this oil (0.061 g, 0.147 mmol) in dichloromethane (2 mL) containing diisopropylethylamine (0.26 mL, 1.48 mmol) was added 2-methoxyethoxymethyl chloride (0.17 mL, 1.48 mmol) at 0 °C. The reaction mixture was warmed to rt and stirred for 16 h. The reaction

mixture was hydrolyzed with a saturated aqueous solution of sodium chloride (5 mL) and extracted with ethyl acetate (4 × 5 mL). The ethyl acetate extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (Et_2O/pentane 1/1) affording 83 mg (0.141 mmol, 72% yield) of the title compound as a colourless oil. $[\alpha]_D^{25} = +18$ (*c* 1.2, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.04, 1.05 (2s, 21H, Si(C*H*(CH_3)$_2$)$_3$), 3.31 (s, 3H, CH_3), 3.37 (s, 3H, CH_3), 3.51 (m, 4H, 2 × OCH_2), 3.66 (m, 5H, H-1a, 2 × OCH_2), 3.80 (m, 4H, H-1b, H-3 and H-4), 4.08 (m, 1H, H-2), 4.69 (s, 2H, OCH_2O), 4.79 (m, 2H, OCH_2O), 5.09 (s, 2H, OCH_2Ph), 5.99 (dl, 1H, N*H*, $J_{2,NH} = 13.98$ Hz), 7.34 (m, 5H, Ar-*H*). ^{13}C NMR, (75 MHz, $CDCl_3$) δ (ppm): 11.70, 17.92, 51.84, 58.97, 64.54, 66.45, 66.87, 67.42, 71.67, 71.72, 79.23, 95.54, 95.95, 127.81, 127.94, 128.38, 136.77, 156.34; MS (ESI^+): $m/z = 610$ $[M+Na]^+$; Anal. Calcd for $C_{29}H_{53}NO_9Si$: C, 59.25; H, 9.09; N, 2.38. Found: C, 59.15; H, 9.01; N, 2.15.

4.1.14. (2*R*,3*R*)-3-*N*-Benzyloxycarbonylamino-2,4-bis(2-methoxyethoxymethoxy)butanal 3. To a solution of **15** (1.25 g, 2.13 mmol) in THF (40 mL) at 0 °C was slowly added a 1 M solution of tetrabutylammonium fluoride in THF (3.2 mL, 3.2 mmol). After 10 min, the solution was concentrated under vacuum and the residue was purified by flash chromatography (EtOAc/cyclohexane 50/50) affording 0.901 g of the expected compound as a colourless oil. To a solution of DMSO (0.44 mL, 6.27 mmol) in dry dichloromethane (5.4 mL) cooled to −78 °C was added dropwise a solution of oxalyl chloride (0.20 mL, 2.30 mmol) in dichloromethane (5.4 mL). After 10 min, a solution of the previous oil (0.901 g, 2.09 mmol) in dry dichloromethane (9 mL) was added dropwise at −78 °C to the reaction mixture. After 1 h at −78 °C, triethylamine (2.2 mL, 15.7 mmol) was added. After stirring at −78 °C for 15 min, a saturated aqueous solution of ammonium chloride (40 mL) was added to the reaction mixture. The organic layer was extracted with ethyl acetate (4 × 40 mL). The ethyl acetate extract was dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography (EtOAc/cyclohexane 50/50) affording 0.749 g (1.75 mmol, 82% yield) of the title compound as a colourless oil. $[\alpha]_D^{25} = +14$ (*c* 1.3, EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.23 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.55 (m, 4H, 2 × OCH_2), 3.66 (m, 4H, 2 × OCH_2), 3.70 (m, 3H, H-3 and H-4), 4.10 (d, 1H, H-2, $J_{2,3} = 4.2$ Hz), 4.71 (s, 2H, OCH_2O), 4.75 (m, 2H, OCH_2O), 5.03 (s, 2H, OCH_2Ph), 5.69 (d, 1H, NH, $J_{3,NH} = 9.0$ Hz), 7.26 (m, 5H, Ar-*H*), 9.53 (s, 1 H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 51.39, 59.02, 65.49, 66.99, 67.19, 68.08, 71.52, 71.69, 83.89, 96.61, 128.54, 128.20, 128.17, 136.37, 156.02, 199.36; HR-MS (ESI^+) calcd for $C_{20}H_{31}NO_9Na$: 452.1897 $[M+Na]^+$, found: 452.1906 $[M+Na]^+$.

4.1.15. Benzyl (methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(2-methoxyethoxymethyl)-6-*N*-methylamino-D-*glycero*-β-D-*allo*-heptafuranosid)uronate 18. A solution of **2** (83 mg, 0.21 mmol) in a 1/1 mixture of methanol/water (2 mL) containing potassium hydroxide (35 mg, 0.63 mmol) was stirred for 3 h. After acidification to pH 1 at 0 °C with a 0.01 M aqueous solution of HCl, the solution was lyophilized. To a suspension of the residue in dichloromethane (6 mL) at 0 °C was added benzyl alcohol (0.22 mL, 2.1 mmol), hydroxybenzotriazole (57 mg, 0.42 mmol), 2,5-dimethylaminopyridine (5 mg, 0.041 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100 mg, 0.53 mmol). The reaction mixture was stirred for 4 days at rt and concentrated under vacuum. The residue was purified by flash chromatography (methanol/dichloromethane 5/95 containing 1% NEt_3) affording 0.055 g (0.117 mmol, 55% yield) of the title compound as an oil. $[\alpha]_D^{25} = -19$ (*c* 1.3, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.39 (s, 3H, NCH_3), 3.34 (s, 3H, OCH_3), 3.38 (s, 3H, OCH_3), 3.52 (m, 3H, OCH_aCH_2), 3.56 (d, 1H, H-6, $J_{5,6} = 1.7$ Hz), 3.76 (m, 2H, H-5 and OCH_bCH_2O), 4.30 (d, 1H, H-4, $J_{4,5} = 10.2$ Hz), 4.56 (d, 1H, H-2, $J_{2,3} = 6.1$ Hz), 4.70 (d, 1H, OC$H_{a'}$O, $J_{Ha',Hb'} = 7.3$ Hz), 4.76 (d, 1H, H-3, $J_{2,3} = 7.3$ Hz), 4.86 (d, 1H, OC$H_{b'}O$, $J_{Ha',Hb'} = 7.3$ Hz), 4.97 (s, 1H, H-1). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.18, 26.53, 35.13, 55.69, 59.03, 64.47, 66.52, 67.84, 71.57, 81.95, 83.66, 85.00, 85.99, 97.50, 109.76, 112.37, 128.06, 128.10, 128.32, 128.42, 135.74, 171.51; HR-MS (ESI^+) calcd *m*/*z* for $C_{23}H_{35}NO_9Na$: 492.2210 $[M+Na]^+$, found: 492.2210 $[M+Na]^+$.

4.1.16. Benzyl (methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-(2-methoxyethoxymethyl)-6-*N*,*N*-{methyl[(2′*S*,3′*R*)-3′-*N*-benzyloxycarbonylamino-2′-(2-methoxyethoxymethoxy)-4′-(2-methoxyethoxymethoxy)butyl]amino}-D-*glycero*-β-D-*allo*-heptafuranosid)uronate 19. A solution of **18** (58 mg, 0.123 mmol) and **3** (107 mg, 0.25 mmol) in toluene (10 mL) was stirred for 15 min before concentrating under vacuum. To the residue dissolved in dichloroethane (12 mL) was added 3 Å-MS (2 g) and acetic acid (0.3 mL). The solution was stirred for 24 h before adding sodium triacetoxyborohydride (53 mg, 0.25 mmol). After 40 h, **3** (76 mg, 0.18 mmol) was added and the solution was stirred for 48 h before adding sodium triacetoxyborohydride (38 mg, 0.18 mmol). After 18 h, the reaction mixture was filtered, diluted with dichloromethane (10 mL) and quenched by adding 5% aqueous solution of sodium bicarbonate (10 mL). The product was extracted with dichloromethane (2 × 10 mL). The organic extract was dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (methanol/dichloromethane 3/97) affording 49 mg (0.055 mmol, 45% yield) of the title compound as a colourless oil. $[\alpha]_D^{25} = -16$ (*c* 0.5, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.26 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 2.36 (s, 3H, NCH_3), 2.59 (dd, 1H, H-1′a, $J_{1'a,1'b} = 13.89$ Hz, $J_{1'a,2'} = 4.23$ Hz), 2.75 (dd, 1H, H-1′b, $J_{1'a,1'b} = 13.89$ Hz, $J_{1'b,2'} = 7.71$ Hz,), 3.35-3.37 (m, 13H, 4 × OCH_3, H-3′), 3.49-3.75 (m, 16H, 3 × O(CH_2)$_2$O, H-5, H-6, H-4′), 3.98 (m, 1H, H-2′), 4.47 (d, 1H, H-4, $J_{4,5} = 6.07$ Hz), 4.66-4.84 (m, 7H, H-2, 3 × OCH_2O), 4.91 (s, 1H, H-1), 4.93 (m, 1H, H-3), 5.08 (m, 2H, OCH_2Ph), 5.16 (m, 2H, OCH_2Ph), 6.01 (d, 1H, N*H*, $J_{3',NH} = 8.67$ Hz), 7.34 (m, 10H, Ar-*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.03, 26.68, 39.77, 56.16, 58.91, 66.06, 66.54, 66.78, 67.37, 67.42, 67.55, 67.69, 71.56, 71.69, 67.84, 79.16, 79.77, 85.34, 86.32, 85.34, 85.45, 97.74, 110.38, 112.71, 127.91, 128.07, 128.18,

128.37, 128.47, 135.86, 156.35, 169.56; HR-MS (ESI^+) calcd for $C_{43}H_{66}N_2O_{17}Na$: 905.4259 $[M+Na]^+$, found: 905.4246 $[M+Na]^+$.

4.1.17. Methyl (5*R*)-5-*O*-(2-methoxyethoxymethyl)-5-*C*-[(2′*S*,5′*S*,6′*S*)-6′-(2-methoxyethoxymethoxy)-5′-(2-methoxyethoxymethoxymethyl)-1′-methyl-3′-oxo-1′,4′-diazepan-2′-yl]-2,3-*O*-isopropylidene-β-D-ribofuranoside 1. A solution of **19** (49 mg, 0.055 mmol) in a 1/1 mixture of ethanol/water (8 mL) containing Pd/C (25 mg) was stirred vigorously at 25 °C for 6 h under 5 bar hydrogen. After filtering, the solution was concentrated under vacuum. To the residue dissolved in dry *N*,*N*-dimethylformamide (3 mL) cooled to 0 °C was added hydroxybenzotriazole (22 mg, 0.162 mmol), 2,5-dimethylaminopyridine (3 mg, 0.024 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (37 mg, 0.193 mmol). The reaction mixture was stirred for 16 h at 25 °C before adding methanol (1 mL). After 1 h, the solution was concentrated under vacuum and the residue was purified by flash chromatography (16 M ammonia solution/methanol/dichloromethane 0.25/2.5/100) affording 10 mg (0.016 mmol, 28% yield) of the title compound as a colourless oil. $[\alpha]_D^{25} = -10$ (*c* 0.6, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 1.31 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 2.53 (s, 3H, NCH_3), 3.11 (m, 2H, H-7′), 3.37–3.41 (m, 12H, $4\times$OCH_3), 3.56–3.91 (m, 14H, $3\times$O(CH_2)$_2$O, H-2′, H-6′), 4.07 (m, 1H, H-5), 4.23 (m, 1H, H-5′), 4.34 (d, 1H, H-4, $J_{4,5} = 9.84$ Hz), 4.59 (d, 1H, H-2, $J_{2,3} = 6.36$ Hz) 4.70–4.86 (m, 6H, $3\times$OCH_2O), 4.98–5.01 (m, 2H, H-1, H-3), 6.35 (s, N*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 25.16, 26.52, 37.17, 55.71, 56.08, 59.01, 59.07, 63.45, 64.71, 65.67, 67.34, 67.51, 67.53, 67.74, 68.12, 70.02, 82.11, 85.74, 86.23, 110.27, 112.29, 177.72; HR-MS (ESI^+) calcd for $C_{28}H_{52}N_2O_{14}Na$: 663.3316 $[M+Na]^+$, found: 663.3293 $[M+Na]^+$.

Acknowledgement

Funding for this work was provided by the Ministère de la Recherche through a grant to Y.B.

References

1. Isono, K.; Uramoto, M.; Kusakabe, H.; Kimura, K.; Izaki, K.; Nelson, C. C.; McCloskey, J. A. *J. Antibiot.* **1985**, *38*, 1617–1621.
2. (a) Silver, L. L. *Curr. Opin. Microbiol.* **2003**, *6*, 431–438; (b) Kimura, K.; Bugg, T. D. H. *Nat. Prod. Rep.* **2003**, *20*, 252–273; (c) Brandish, P. E.; Kimura, K.; Inukai, M.; Southgate, R.; Lonsdale, J. T.; Bugg, T. D. H. *Antimicrob. Agents Chemother.* **1996**, *40*, 1640–1644.
3. (a) Ubukata, M.; Isono, K.; Kimura, K.; Nelson, C. C.; McCloskey, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 4416–4417; (b) Ubukata, M.; Kimura, K.; Isono, K.; Gregson, J. M.; McCloskey, J. A. *J. Org. Chem.* **1992**, *57*, 6392–6403.
4. (a) Spada, M. R.; Ubukata, M.; Isono, K. *Heterocycles* **1992**, *34*, 1147–1167; (b) Kim, K. S.; Ahn, Y. H. *Tetrahedron: Asymmetry* **1998**, *9*, 3601–3605; (c) Le Merrer, Y.; Gravier-Pelletier, C.; Gerrouache, M.; Depezay, J.-C. *Tetrahedron Lett.* **1998**, *39*, 385–388; (d) Gravier-Pelletier, C.; Milla, M.; Le Merrer, Y.; Depezay, J.-C. *Eur. J. Org. Chem.* **2001**, *16*, 3089–3096; (e) Sarabia, F.; Martin-Ortiz, L.; Lopez-Herrera, F. *Org. Lett.* **2003**, *5*, 3927–3930.
5. Knapp, S.; Moriello, G. J.; Doss, G. A. *Org. Lett.* **2002**, *4*, 603–606.
6. Miyake, T.; Igarashi, M.; Shidara, T.; Takahashi, Y. JP WO 2004-067544A1, 2004.
7. Hirano, S.; Ichikawa, S.; Matsuda, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1854–1856.
8. (a) Greck, C.; Bischoff, L.; Ferreira, F.; Pinel, C.; Piveteau, E.; Genêt, J. P. *Synlett* **1993**, 475–477; (b) Greck, C.; Drouillat, B.; Thomassigny, C. *Eur. J. Org. Chem.* **2004**, *7*, 1377–1385, and references cited therein.
9. (a) Genêt, J. P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano De Andrade, M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665–674; (b) Genêt, J. P.; Ratovelomanana-Vidal, V.; Caño de Andarade, C.; Pfister, X.; Guerreiro, P.; Lenoir, J. Y. *Tetrahedron Lett.* **1995**, *36*, 4801–4804; (c) Ratovelomanana-Vidal, V.; Genêt, J. P. *J. Organomet. Chem.* **1998**, *567*, 163–171.
10. Drouillat, B.; Poupardin, O.; Bourdreux, Y.; Greck, C. *Tetrahedron Lett.* **2003**, *44*, 2781–2783.
11. O'Donnel, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666.
12. Chruma, J. J.; Sames, D.; Polt, R. *Tetrahedron Lett.* **1997**, *38*, 5085–5086.
13. Bourdreux, Y.; Drouillat, B.; Greck, C. *Synlett* **2005**, 2086–2088.
14. In the presence of the NMR shift complex tris[3-(trifluoromethylhydroxymethylene)-D-camphorato]-europium (molar ratio β-hydroxyester/europium complex = 8/1; CCl_4/$CDCl_3$ = 70/30), the methyl ester chemical shifts of the racemic mixture obtained by reduction of **5** with sodium borohydride were at 3.82 and 3.79 ppm using ^1H NMR analysis. Under the same analytical conditions, a single methyl ester chemical shift at 3.82 ppm was observed for **9** obtained by hydrogenation of **5** in the presence of (*S*)-Binap$RuBr_2$ catalyst.
15. Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507–5510.
16. (a) Crouch, R. D. *Tetrahedron: Asymmetry* **2004**, *28*, 5833–5871; (b) *Protective Groups in Organic Synthesis*; Greene, T. W., Wuts, P. G. M., Eds., 3rd ed.; John Wiley & Sons: New York, 1999; (c) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, *9*, 1031–1069.
17. Bourdreux, Y.; Drouillat, B.; Greck, C. *Lett. Org. Chem.* **2006**, *3*, 368–370.
18. Abdel-Magid, A. F.; Caron, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849–3862.
19. *Purification of Laboratory Chemicals*, 4th ed.; Aramarego, W. L. F., Perrin, D. D., Eds.; Butterworth Heinemann, 1996.
20. Brooks, D. W.; Lu, L. D. L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *1*, 72–74.
21. Hampton, A.; Perini, F.; Harper, P. J. *Carbohydr. Res.* **1974**, *37*, 359–367.