Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2315–2321

TETRAHEDRON: *ASYMMETRY*

Chiron approach to callipeltin A: first synthesis of fully protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxy heptanoic acid†

S. Chandrasekhar,* T. Ramachandar and B. Venkateswara Rao

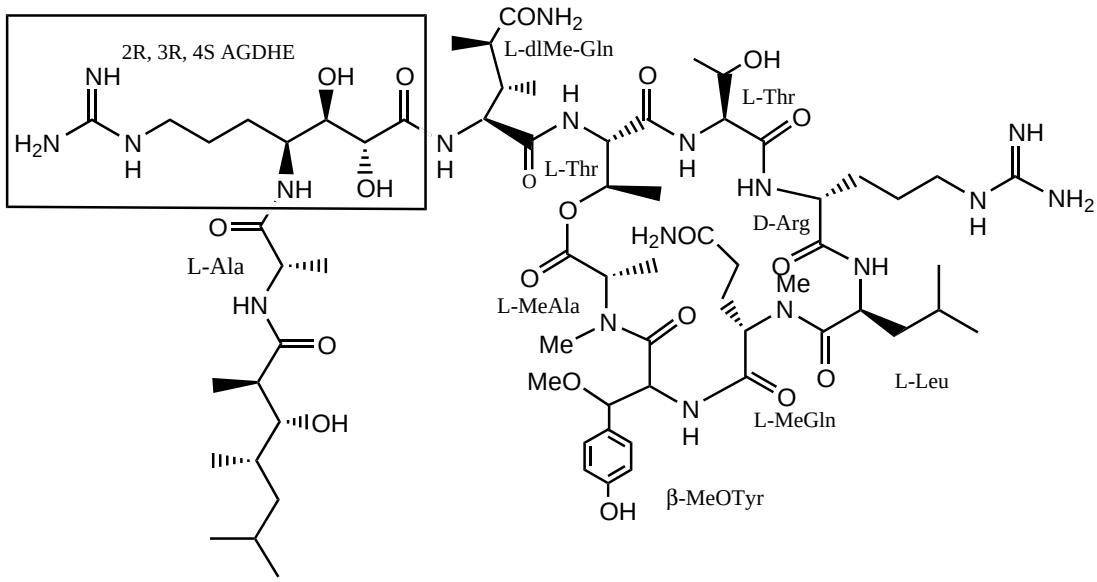
Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 31 July 2001; accepted 11 September 2001

Abstract—Stereoselective synthesis of protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxy heptanoic acid, which is present as a side chain attached to the main macrocyclic depsidecapeptide backbone of callipeltin A (a potent, cytotoxic, anti-HIV and anti-fungal agent) starting from a carbohydrate, is described. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Cyclic depsidecapeptides have emerged as a very important class of bioactive compounds isolated from marine natural products.[1] In 1996, Minale et al. reported the isolation of a cyclic depsidecapeptide, callipeltin A **1**,[2] from a shallow water sponge of the Callipelta species. The compound showed marked activity in cytotoxic assays against KB and P388 cells and in anti-HIV and antifungal tests. The structure of callipeltin A was determined by interpretation of spectral data, chemical degradation, and evaluation of the amino acids obtained by acid hydrolysis.



Callipeltin A 1

* Corresponding author. Fax: +91-40-7170512; e-mail: srivaric@iict.ap.nic.in

† IICT Communication No. 4856.

0957-4166/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0957-4166(01)00400-1

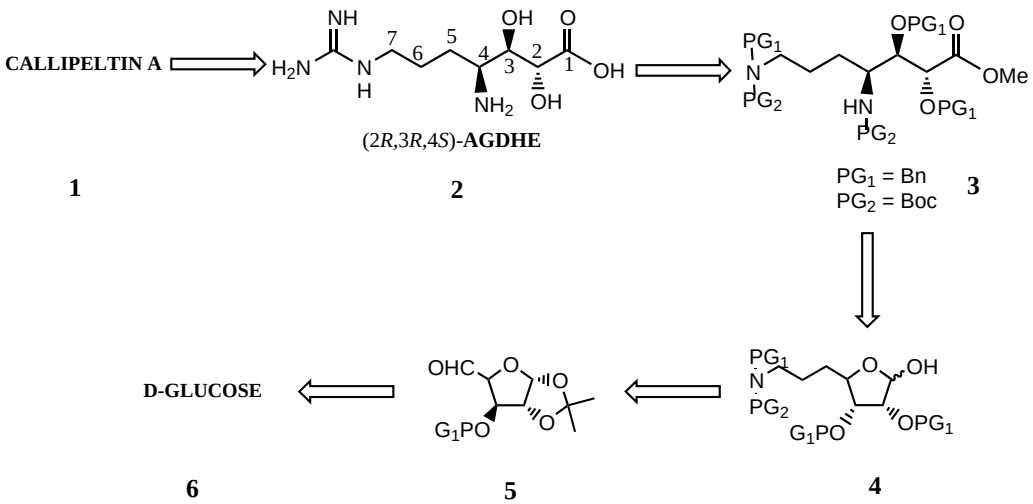
In our efforts to synthesize a series of bioactive molecules, we have chosen callipeltin A as a target molecule due to its interesting anti-HIV properties and its novel amino acid residues: β-methoxy-tyrosine (β-OMeTyr), (2*R*,3*R*,4*S*)-4-amino-7-guanidino-2,3-dihydroxyheptanoic acid (AGDHE) and (3*S*,4*R*)-3,4-dimethyl-L-glutamine. Recently, Joullie et al. reported the synthesis of one of the unusual amino acids, (3*S*,4*R*)-3,4-dimethyl-L-glutamine.[3] As a part of our studies on the total synthesis of callipeltin A, we now describe the first synthesis of fully protected (2*R*,3*R*,4*S*)-4,7-diamino-2,3-dihydroxyheptanoic acid.

Our synthetic approach to the AGDHE fragment involves a chiron approach via replenishable source of carbohydrates using D-glucose as the starting material. As the first step of retrosynthetic analysis, inversion of the C(3) hydroxyl group of D-glucose was achieved by an oxidation–reduction procedure, followed by the lactol ring opening and inversion of the configuration at C(4) was achieved by tosylation and subsequent azide displacement (Scheme 1).

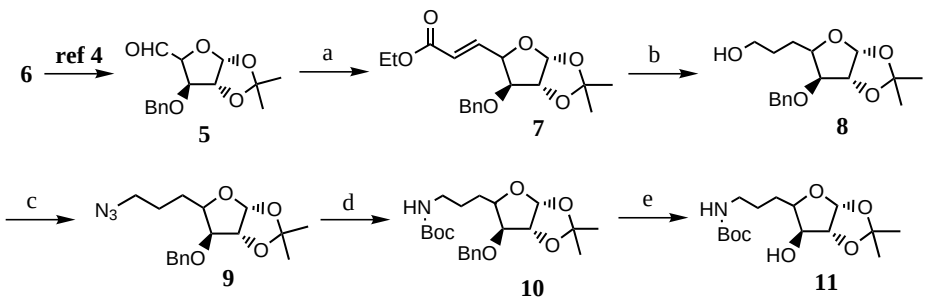
2. Results and discussion

D-Glucose **6** was converted into the dialdo derivative **5** by a sequence of reactions reported earlier.[4] Subsequent olefination with (carboethoxymethylene) triphenylphosphorane[5] yielded the α,β-unsaturated ester **7**. The geometry of the double bond in **7** was of little consequence as it was further reduced in the subsequent step. Reduction with $LiAlH_4$ furnished the saturated alcohol **8**. The alcohol was converted into its azide **9** via the tosylate using TsCl/Py and NaN_3/DMF. Azide **9**, thus obtained, was reduced to the amine using $LiAlH_4$ and protected as its Boc derivative **10** (Scheme 2).

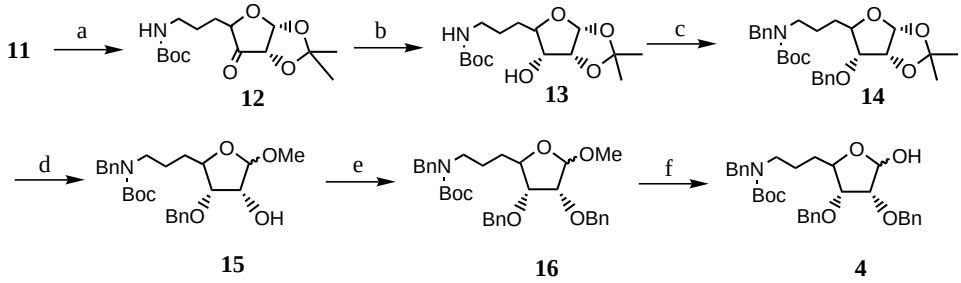
The inversion of configuration at C(3) in **10** was effected in four steps involving an oxidation–reduction[6] protocol to give **14**. Under acidic conditions (MeOH/AcCl), compound **14** underwent isopropylidene cleavage, which was followed by methyl glycosidation and protection of the secondary alcohol as its benzyl ether **16**. Hydrolysis of the *O*-



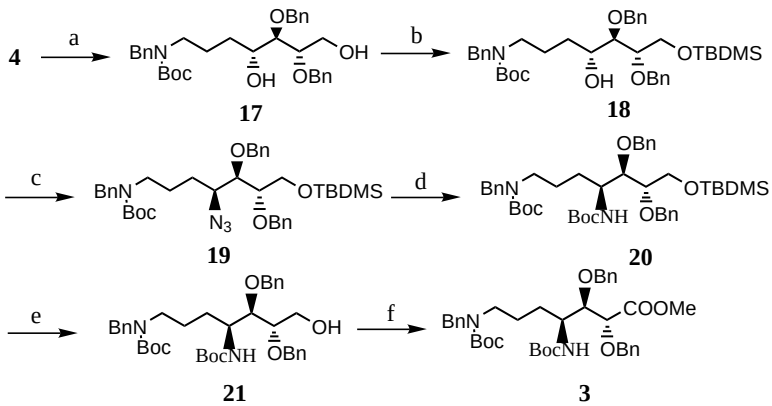
Scheme 1.



Scheme 2. *Reagents and conditions*: (a) Ph_3P=CHCOOEt, benzene, rt 4 h, 90%; (b) LAH, THF, 0°C, 6 h, 85%; (c) (i) TsCl, Py, 6 h; (ii) NaN_3, DMF, 80°C, 12 h, 68% (two steps); (d) (i) LAH, THF, 0°C, 12 h; (ii) NaOH, $(Boc)_2O$, 3 h, 43% (two steps); (e) Na/liq. NH_3, THF, −78°C, 2 h, 80%.



Scheme 3. *Reagents and conditions*: (a) PDC, DCM, 0°C, 4 h; (b) $NaBH_4$, MeOH, 0°C, 2 h, 38%; (c) NaH, BnBr, DMF, 0°C, 1 h, 74%; (d) (i) MeOH, CH_3COCl (cat.), reflux, 6 h; (ii) Et_3N, $(Boc)_2O$, 3 h, 40% (two steps); (e) NaH, BnBr, DMF, 0°C, 1 h, 75%; (f) (i) 60% AcOH, conc. HCl (cat.), 4 h; (ii) Et_3N, $(Boc)_2O$, 3 h, 40% (two steps).



Scheme 4. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0°C, 1 h, 80%; (b) imidazole, TBDMSCl, DCM, 0°C, 6 h, 85%; (c) (i) MsCl, Et_3N, DCM, 0°C, 5 h; (ii) NaN_3, DMF, 80°C, 12 h, 29% (two steps); (d) (i) PPh_3, H_2O, benzene, 11 h; (ii) Et_3N, $(Boc)_2O$, 12 h, 63% (two steps); (e) TBAF, THF, 0°C, 3 h, 70%; (f) (i) Jones oxidation; (ii) CH_2N_2, dry ether, 41% (two steps).

glycosidic bond of **16** using 60% acetic acid and catalytic conc. HCl at 50°C afforded the corresponding lactols **4** (Scheme 3).

Reduction of hemiketal **4** ($NaBH_4$, MeOH) then afforded the open chain diol **17**. The primary alcohol was then protected selectively using TBDMSCl/imidazole and the free secondary alcohol in **18** was converted to its azide **19** via the mesylate ester (MsCl/Py; NaN_3/DMF).

Azide **19** was reduced with triphenylphosphine/benzene/H_2O and the resulting free amine was protected as its Boc derivative **20**. After obtaining the diamine functionality, the TBDMS ether was deprotected using TBAF. Finally, the free alcohol **21** was subjected to oxidation with Jones' reagent to yield the acid, which was protected as its methyl ester **3** using ethereal diazomethane (Scheme 4).

3. Conclusion

In conclusion, we have developed an efficient protocol for the synthesis of the fully protected AGDHE fragment, utilizing D-glucose as the chiral raw material. This synthetic approach is flexible and other analogues can be synthesized by changing the starting sugar or by varying the length of the Wittig reagent.

4. Experimental

Crude products were purified by column chromatography on silica gel of 60–120 mesh. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini-200 MHz spectrometer, and chemical shifts are reported in ppm unless otherwise stated. Mass spectra were recorded on VG micromass-7070H (70 eV). The optical rotations were recorded on Jasco Dip 360 digital polarimeter. Infrared spectra were obtained neat and only the most significant absorptions in cm^{-1} are indicated. All solvents used were purified by a known procedure. All reactions were carried out under an atmosphere of nitrogen using dry glassware.

4.1. Ethyl 5,6-dideoxy-1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-hept-5-enofuranuronoate 7

Aldehyde **5** (10 g, 0.036 mol) was dissolved in benzene (100 mL) at 0°C and (carboethoxymethylene)triphenylphosphorane (12.53 g, 0.0359 mol) was added portion wise under a nitrogen atmosphere. The reaction mixture was allowed to stir at rt for 4 h and benzene was evaporated under reduced pressure and purification by column chromatography yielded conjugated ester **7** (11.24 g, 90%). IR (neat): 1760 and 960 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.24–1.38 (m, 6H, OCH_2CH_3, CH_3), 1.48 (s, 3H, CH_3), 3.92 (d, $J=2.38$ Hz, 1H) 4.20

(q, $J=4.76$ Hz, 2H, OCH_2CH_3), 4.42–4.65 (m, 3H), 4.70–4.78 (m, 1H), 5.95 (d, $J=4.76$ Hz, 1H, C1-H), 6.12 (d, $J=14.3$ Hz, 1H, olefinic), 6.90 (dd, $J=4.8$, 14.3 Hz, 1H, olefinic), 7.20–7.38 (m, 5H, aromatic); EI MS: m/z 348 (M^+); $[\alpha]_D$ −27.2 (c 1, $CHCl_3$).

4.2. 5,6-Dideoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-heptofuranose 8

To a suspension of lithium aluminium hydride (1.08 g, 0.028 mol) in dry THF (100 mL) at 0°C under a nitrogen atmosphere was added a solution of the conjugated ester **7** (5 g, 0.014 mol) in THF (25 mL) and stirred at rt for 6 h. The reaction mixture was quenched with a saturated solution of Na_2SO_4 at 0°C and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried (anhydrous, Na_2SO_4), concentrated and on purification by column chromatography afforded saturated alcohol **8** (3.74 g, 85%). IR (neat): 3400, 3030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.48 (s, 3H, CH_3) 1.54–1.94 (m, 4H, 2×CH_2), 3.63 (t, $J=3.25$ Hz, 2H, CH_2OH), 3.75 (d, $J=2.3$ Hz, 1H, C3-H), 4.10–4.20 (m, 1H, C4-H), 4.60 (d, $J=2.8$ Hz, 1H, C2-H), 4.40–4.70 (AB quartet, 2H, benzylic CH_2), 5.85 (d, $J=2.8$ Hz, 1H, C1-H), 7.20–7.40 (m, 5H, aromatic); EI MS: m/z 308 (M^+); $[\alpha]_D$ −15.2 (c 1, $CHCl_3$).

4.3. 7-Azido-3-*O*-benzyl-1,2-*O*-isopropylidene-5,6,7-trideoxy-α-D-*xylo*-heptofuranose 9

To a stirred solution of alcohol **8** (2.5 g, 0.008 mol) was added a solution of pyridine (1.3 g, 0.016 mol) in dry CH_2Cl_2 (50 mL) at 0°C under a nitrogen atmosphere. Tosyl chloride (2.3 g, 0.012 mol) was added slowly and the reaction mixture was allowed to stir at rt for 6 h. The reaction mixture was extracted with CH_2Cl_2, washed with a $CuSO_4$ solution, water, brine, dried over anhydrous Na_2SO_4, concentrated and on purification by column chromatography afforded tosylate as a viscous liquid.

The above tosylate (2.5 g, 0.005 mol) was dissolved in dry DMF (40 mL) and heated at 90°C with NaN_3 (1.05 g, 0.015 mol) for 12 h. The reaction mixture was brought to rt and diluted with water and extracted with ether. The combined ethereal layers were washed with water, brine, dried (anhydrous Na_2SO_4), concentrated and on purification by column chromatography yielded azide **9** (1.2 g, 68%). IR (neat): 2097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.50–1.58 (m, 1H), 1.60–1.75 (m, 2H), 1.76–1.85 (m, 1H), 3.20–3.36 (m, 2H, CH_2N_3), 3.75 (d, 1H, C3-H), 4.10 (m, 1H, C4-H), 4.45–4.70 (AB quartet, 2H, benzylic CH_2), 4.56 (d, 1H, C2-H), 5.86 (d, 1H, C1-H), 7.13–7.19 (m, 5H, aromatic); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3, 25.7, 26.1, 26.7, 51.4, 71.7, 79.7, 82.1, 82.2, 104.7, 111.3, 127.7, 127.9, 128.4, 137.5; EI MS: m/z 333 (M^+); $[\alpha]_D$−49.1 (c 1, $CHCl_3$).

4.4. 3-*O*-Benzyl-7-*tert*-butoxycarbonylamino-1,2-*O*-isopropylidene-5,6,7-trideoxy-α-D-*xylo*-heptofuranose 10

To a cooled suspension of lithium aluminium hydride (0.54 g, 0.014 mol) in dry THF (25 mL) at 0°C under a nitrogen atmosphere, was added azide **9** (4 g, 0.012 mol). The reaction mixture was allowed to warm to rt and stirred for 12 h, then cooled to 0°C and quenched with 1N NaOH solution and extracted with ethyl acetate. The combined organic extracts were concentrated to give amine (2.0 g) as syrup.

The above obtained crude amine (2 g, 0.006 mol) was dissolved in dry CH_2Cl_2 (50 mL) cooled to 0°C, triethylamine (1.25 g, 0.012 mol) followed by Boc_2O (1.62 g, 0.078 mol) was added under a nitrogen atmosphere and allowed to stir at rt for 3 h. The reaction mixture was then extracted with DCM. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and on purification by column chromatography yielded protected amine **10** (2.10 g, 43% overall) as a viscous liquid. IR (neat): 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.3 (s, 3H, CH_3), 1.43 (s, 9H, 3×CH_3), 1.46 (s, 3H, CH_3), 1.52–1.70 (m, 3H), 1.72–1.85 (m, 1H), 3.14 (m, 2H, CH_2-NH-Boc), 3.72 (d, 1H, C3-H), 4.08 (m, 1H, C4-H), 4.40–4.65 (AB quartet, 2H, benzylic CH_2), 4.58 (d, 1H, C2-H), 5.85 (d, $J=4$ Hz, 1H, C1-H), 7.14–7.19 (m, 5H, aromatic); ^{13}C NMR (50 MHz, $CDCl_3$): δ 25.3, 26.2, 26.7, 28.4, 40.5, 71.7, 79.0, 80.0, 82.1, 82.2, 104.6, 111.2, 127.7, 127.9, 128.4, 137.5, 155.9; FAB MS: m/z 408 $(M+1)^+$; $[\alpha]_D$−32.2 (c 1.25, $CHCl_3$).

4.5. 7-*tert*-Butoxycarbonylamino-1,2-*O*-isopropylidene-5,6,7-trideoxy-α-D-*xylo*-heptofuranose 11

To liquid NH_3 (100 mL) at −78°C, was added the protected amine **10** (2 g, 0.0051 mol) in THF (10 mL), followed by metallic sodium (0.46 g, 0.0204 mol). After 2 h, ammonia was allowed to completely evaporate by warming the reaction mixture to rt. Then saturated NH_4Cl was added and extracted with CH_2Cl_2. The organic layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and purified by column chromatography to afford the debenzylated alcohol **11** (1.25 g, 80%) as a syrupy liquid. IR (neat): 3410, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.3 (s, 3H, CH_3), 1.45 (s, 9H, 3×CH_3), 1.5 (s, 3H, CH_3), 1.55–1.80 (m, 4H, 2×CH_2), 3.10–3.23 (m, 2H, CH_2-NH-Boc), 4.0–4.10 (m, 2H, C3-H, C4-H), 4.48 (d, $J=2.4$ Hz, 1H, C2-H), 4.70 (bs, 1H, *NH*), 5.82 (d, $J=2.4$ Hz, 1H, C1-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.8, 26.1, 26.6, 26.7, 28.3, 40.5, 75.1, 79.3, 80.3, 85.3, 104.2, 111.2, 156.3; EI MS: m/z 201 $(M-116)^+$; $[\alpha]_D$ −9.29 (c 1, $CHCl_3$).

4.6. 7-*tert*-Butoxycarbonylamino-1,2-*O*-isopropylidene-5,6,7-trideoxy-α-D-*ribo*-heptofuranose 13

To compound **11** (3 g, 0.01 mol) was added pyridinium dichromate (7.11 g, 0.02 mol) in dry CH_2Cl_2 (70 mL) at

0°C and the mixture was stirred for 4 h. The mixture was concentrated in vacuo and the residue was dissolved in ether and filtered through a small pad of silica gel. The combined ether layers were washed with 1N NaOH, dil. HCl and a satd. $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated to give compound **12** (1.5 g) as a liquid, which was used without any further purification.

The above ketone **12** (1.5 g, 0.005 mol) was dissolved in methanol (50 mL), cooled to 0°C and $NaBH_4$ (0.32 g, 0.01 mol) was added in small portions under a nitrogen atmosphere. After complete addition, the reaction mixture was brought to rt and allowed to stir for 2 h, methanol was removed under reduced pressure, and the residue was dissolved in water and extracted with chloroform. The combined organic layers were washed with aqueous sodium bicarbonate, water, brine, dried over anhydrous Na_2SO_4 and concentrated to afford inverted alcohol **13** as a white solid (1.14 g, 38% overall yield). IR (neat): 3500, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.45 (s, 9H, 3×CH_3), 1.55 (s, 3H, CH_3), 1.60–1.80 (m, 4H, 2×CH_2), 2.30 (bs, 1H, *OH*), 3.10–3.24 (m, 2H, CH_2-NH-Boc), 3.50–3.60 (m, 1H, C3-H), 3.61–3.75 (m, 1H, C4-H), 4.50 (t, $J=2.4$ Hz, 1H, C2-H), 4.65 (bs, 1H, NH), 5.75 (d, $J=2.4$ Hz, 1H, C1-H); EI MS: m/z 201 $(M-116)^+$; $[\alpha]_D$ +10.0 (*c* 1.1, $CHCl_3$).

4.7. *N*-Benzyl-3-*O*-benzyl-7-*tert*-butoxycarbonylamino-1,2-*O*-isopropylidene-5,6,7-trideoxy-α-D-*ribo*-heptofuranose 14

To an ice cold solution of compound **13** (1 g, 0.003 mol) in dry DMF (20 mL) was added NaH (0.3 g, 60% dispersion in oil, 0.012 mol) and the mixture stirred at rt for 1 h. Benzyl bromide (1.19 g, 0.007 mol) was then added at 0°C and the reaction mixture was stirred over night. Excess NaH was quenched with saturated NH_4Cl and extracted with ethyl acetate, washed with water, brine, dried (anhydrous Na_2SO_4), concentrated and on purification by column chromatography afforded benzyl derivative **14** (1.16 g, 74%). IR (neat): 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H, CH_3), 1.45 (s, 9H, 3×CH_3), 1.55 (s, 3H, CH_3), 1.60–1.75 (m, 4H, 2×CH_2), 3.05–3.25 (m, 2H, CH_2-NBn), 3.26–3.38 (m, 1H, C3-H), 3.88–4.0 (m, 1H, C4-H), 4.34–4.44 (m, 2H, -N-CH_2-Ph), 4.45–4.80 (AB quartet, 2H, benzylic CH_2), 4.53 (m, 1H, C2-H), 5.65 (d, $J=2.8$ Hz, 1H, C1-H), 7.15–7.40 (m, 10H, aromatic); FAB MS: m/z 497 (M^+); $[\alpha]_D$ +48.5 (*c* 1, $CHCl_3$).

4.8. Methyl 7-*N*-benzyl-3-*O*-benzyl-7-*tert*-butoxycarbonylamino-5,6,7-trideoxy-α/β-D-*ribo*-heptofuranoside 15

Compound **14** (1 g, 0.002 mol) was dissolved in dry methanol (50 mL) and cooled to 0°C, to which a catalytic amount of acetyl chloride (2–4 drops) was added. It was allowed to warm to rt and then stirred under reflux for over a period of 6 h. The reaction mixture was cooled, filtered and washed with methanol. The filtrate was evaporated and the residue was used without any further purification. The proton NMR spectra of the residue indicated the absence of Boc peak and therefore the crude free amine was protected as its Boc derivative using Boc_2O (0.525 g, 0.0024 mol) and Et_3N (0.4 g, 0.004 mol) in dry CH_2Cl_2 at 0°C under an inert atmosphere. The reaction mixture was stirred at rt for 3 h, extracted with CH_2Cl_2, washed with water, brine, dried and concentrated. The residue was purified by column chromatography to furnish compound **15** (0.38 g, 40%) as an α,β-mixture. IR (neat): 3400, 1167, 1023 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.70 (m, 13H), 2.5 (s, 1H, OH), 3.10–3.28 (m, 2H, CH_2-NBn), 3.31 (s, 3H, O-CH_3), 3.80 (m, 3H, C2-H, C3-H, C4-H), 4.40 (m, 2H, N-CH_2-Ph), 4.55 (m, 2H, O-CH_2-Ph), 4.78 (m, 1H, C1-H), 7.05–7.40 (m, 10H, aromatic); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.6, 28.5, 32.8, 46.4, 54.8, 72.9, 73.3, 79.5, 80.8, 82.8, 96.2, 108.4, 127.1, 127.3, 127.4, 128.0, 128.3, 128.4, 128.6, 137.1, 138.6; FAB MS: m/z 471 (M^+); $[\alpha]_D$ +10.2 (*c* 1, $CHCl_3$).

4.9. Methyl 7-*N*-benzylamino-7-*tert*-butoxycarbonylamino-2,3-di-*O*-benzyl-5,6,7-trideoxy-α/β-D-*ribo*-heptofuranoside 16

To an ice cooled solution of compound **15** (2 g, 0.0042 mol) in dry DMF (40 mL), NaH (0.2 g, 60% dispersion in oil, 0.0084 mol) was added and the mixture stirred at rt for 1 h under a nitrogen atmosphere. Benzyl bromide (0.87 g, 0.0051 mol) was added and the reaction mixture was stirred overnight. Excess NaH was quenched with a saturated ammonium chloride solution and extracted with ether. The organic layer was washed with brine, dried, concentrated and on purification by column chromatography afforded the benzyl derivative **16** (1.78 g, 75%). IR (neat): 1696, 1120, 1067 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40–1.70 (m, 13H), 3.10–3.20 (m, 2H, CH_2-NBn), 3.30 (s, 3H, OCH_3), 3.65–3.80 (m, 2H, C3-H, C4-H), 4.0–4.10 (m, 1H, C2-H), 4.40 (m, 2H, -N-CH_2-Ph), 4.50–4.70 (AB quartet, 4H, 2×O-CH_2-Ph), 4.80 (s, 1H, C1-H), 7.10–7.40 (m, 15H, aromatic); FAB MS: m/z 561 (M^+); $[\alpha]_D$ +12.3 (*c* 1, $CHCl_3$).

4.10. *N*-Benzyl-7-*tert*-butoxycarbonylamino-2,3-di-*O*-benzyl-5,6,7-trideoxy-α/β-D-*ribo*-heptofuranose 4

Compound **16** (1.5 g, 0.0027 mol) was hydrolysed using 60% acetic acid (15 mL) and catalytic conc. HCl (2–4 drops) and heating the mixture at 80°C for 4 h. The reaction mixture was cooled to rt, neutralized with solid sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate layers were washed with brine and dried over Na_2SO_4. The volatiles were evaporated and the residue was used without further purification. The proton NMR spectra of the residue indicated the absence of Boc peak and therefore the crude free amine was protected as its Boc derivative using Boc_2O (0.7 g, 0.0032 mol) and Et_3N (0.54 g, 0.0054 mol) in dry CH_2Cl_2 at 0°C under an inert atmosphere. The reaction mixture was stirred at rt for 3 h, extracted with CH_2Cl_2, washed with water, brine, dried and concentrated. The residue was purified by column chromatography to

furnish compound **4** (0.58 g, 40%) as an α,β-mixture of lactol. IR (neat): 3450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40–1.70 (m, 13H), 3.10–3.20 (m, 2H, CH_2-NBn), 3.50–3.60 (bs, 1H, OH), 3.65–3.75 (m, 2H, C3-H, C4-H), 4.10 (m, 1H, C2-H), 4.40 (m, 2H, -N-CH_2-Ph), 4.50–4.75 (m, 4H, 2×O-CH_2-Ph), 5.2 (d, 1H, anomeric), 7.10–7.35 (m, 15H, aromatic); FAB MS: m/z 548 (M+1); $[\alpha]_D$ +25.1 (c 1, $CHCl_3$).

4.11. (4*R*,5*R*,6*S*)-1-*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-5,6-di-benzyloxy-4,7-dihydroxy-heptylamine 17

To a solution of the mixture **4** (1 g, 0.0018 mol) in methanol (30 mL) was added sodium borohydride (0.075 g, 0.0022 mol) at rt. After 1 h, the reaction mixture was neutralised with saturated ammonium chloride and the resulting solution was extracted with dichloromethane and washed with brine. The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under vacuo and purification by column chromatography yielded the open chain diol **17** (0.8 g, 80%). IR (neat): 3500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.4–1.75 (m, 13H), 2.80 (bs, 2H, 2×OH) 3.10–3.30 (m, 2H, CH_2-NBn), 3.45 (m, 1H), 3.64–3.92 (m, 4H), 4.30–4.40 (m, 2H, N-CH_2-Ph), 4.50–4.75 (m, 4H, 2×O-CH_2-Ph), 7.15–7.38 (m, 15H, aromatic); FAB MS: m/z 550 $(M+1)^+$; $[\alpha]_D$ +16.3 (c 1.5, $CHCl_3$).

4.12. (4*R*,5*R*,6*S*)-1-*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-5,6-di-benzyloxy-4-hydroy-7-(*tert*-butyldimethylsilyloxy)-heptylamine 18

To a solution of **17** (1.5 g, 0.0027 mol) in dry CH_2Cl_2 (30 mL) was added imidazole (0.28 g, 0.0041 mol) and *tert*-butyldimethylsilyl chloride (0.45 g, 0.003 mol) and the temperature was maintained at 0°C. The reaction mixture was stirred for 6 h at rt after which it was diluted with CH_2Cl_2. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The volatiles were removed under reduced pressure. The crude product was purified by column chromatography to afford the silyl ether **18** as a viscous liquid (1.54 g, 85%). IR (neat): 3500 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.20 (s, 6H, Si-2×CH_3), 0.90 (s, 9H, 3×CH_3), 1.40 (s, 9H), 1.43–1.65 (m, 4H), 3.05–3.20 (m, 2H, CH_2-NBn), 3.45 (m, 1H), 3.60–3.78 (m, 3H), 3.82–4.0 (m, 1H), 4.38–4.42 (m, 2H, N-CH_2-Ph), 4.50–4.78 (m, 4H, 2×O-CH_2-Ph), 7.10–7.38 (m, 15H, aromatic); FAB MS: m/z 506 $(M-158+1)^+$; $[\alpha]_D$ +10.2 (c 0.5 $CHCl_3$).

4.13. (4*S*,5*R*,6*S*)-1-*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-4-azido-5,6-di-benzyloxy-7-(*tert*-butyldimethylsilyloxy)-heptylamine 19

A stirred solution of alcohol **18** (1 g, 0.0015 mol) in dry CH_2Cl_2 at 0°C under a nitrogen atmosphere was treated with triethylamine (0.46 g, 0.0045 mol) and a catalytic amount of DMAP. Methanesulphonyl chloride (0.2 g, 0.0018 mol) was added to the mixture very slowly. The reaction mixture was allowed to stir at rt for 5 h. The reaction mixture was poured into crushed ice and extracted with CH_2Cl_2. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to yield the mesylate (0.5 g) as a pale reddish solution. The product was used without any further purification.

A solution of mesylate (0.5 g, 0.007 mol) in dry DMF (10 mL) was heated at 90°C with NaN_3 (0.175 g, 0.0028 mol) for 12 h. The reaction mixture was allowed to cool to rt and diluted with water and extracted with ether. The combined ethereal layers were washed with water, brine, dried over anhydrous Na_2SO_4, concentrated and the residue purified by column chromatography to afford azide **19** (0.30 g, 29%). IR (neat): 2095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H, Si-2×CH_3), 0.90 (s, 9H, 3×CH_3), 1.50 (bs, 11H), 1.60–1.80 (m, 2H), 3.05–3.20 (m, 2H, CH_2-NBn), 3.40–3.45 (m, 1H, CH-N_3), 3.56 (m, 2H), 3.80–3.90 (dd, 2H), 4.35–4.42 (m, 2H, N-CH_2-Ph), 4.50–4.64 (AB quartet, 2H, O-CH_2-Ph), 4.70–4.78 (m, 2H, O-CH_2-Ph), 7.10–7.38 (m, 15H, aromatic); FAB MS: m/z 327 $[(M+23)-384]^+$; $[\alpha]_D$−6.2 (c 0.5, $CHCl_3$).

4.14. (4*S*,5*R*,6*S*)-1*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-5,6-di-benzyloxy-7-(*tert*-butyldimethylsilyloxy)-4-(*tert*-butoxycarbonylamino)-heptylamine 20

To a stirred solution of compound **19** (0.3 g, 0.43 mmol) in benzene (10 mL) at 45°C was added triphenylphosphine (0.23 g, 0.87 mmol). After 30 min, water (0.8 mL, 43 mmol) was added and stirring was continued at 45°C for 11 h. The mixture was cooled to rt and extracted with ethyl acetate, washed with a saturated ammonium chloride solution, dried over anhydrous Na_2SO_4, filtered and concentrated to give the amine product (0.28 g), which was contaminated with triphenylphosphine oxide. This impurity was removed after the next step.

To a solution of the above crude amine (0.28 g, 0.42 mmol) in dry THF (10 mL) were added Et_3N (0.128 g, 1.26 mmol) and $(Boc)_2O$ (0.11 g, 0.05 mmol) at 0°C. The mixture was stirred at rt for 12 h. The solvent was evaporated in vacuo and the residue was purified by column chromatography to give compound **20** (0.21 g, 63% overall). IR (neat): 3300, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.10 (s, 6H, Si-2×CH_3), 0.90 (s, 9H, 3×CH_3), 1.50 (bs, 20H), 1.58–1.70 (m, 2H), 3.10–3.14 (m, 2H, CH_2-NBn), 3.48 (m, 1H), 3.58 (d, 1H), 3.78–3.98 (dd, 2H), 4.0–4.08 (m, 1H), 4.36–4.44 (m, 2H), 4.50–4.60 (m, 2H), 4.64–4.72 (m, 2H), 4.96 (d, J=3.55 Hz, 1H, NH), 7.20–7.44 (m, 15H, aromatic); FAB MS: m/z 762 (M^+); $[\alpha]_D$ −3.0 (c 0.5, $CHCl_3$).

4.15. (4*S*,5*R*,6*S*)-1*N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-5,6-di-benzyloxy-7-hydroxy-4-(*tert*-butoxycarbony-lamino)-heptylamine 21

To a stirred solution of compound **20** (0.2 g, 0.26 mmol) in THF (10 mL) at 0°C was added TBAF (0.14 g, 1 M solution in THF, 0.52 mmol). The reaction mixture was allowed to warm to rt and stirred for a further 3 h. The reaction mixture was quenched with a

saturated NH_4Cl solution, extracted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and the volatiles were removed under reduced pressure. The crude product thus obtained was purified by column chromatography to afford compound **21** as a colorless viscous oil (0.13 g, 70%). IR (neat): 3500, 3300, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (bs, 20H), 1.52–1.70 (m, 2H), 2.10 (bs, 1H, O*H*), 3.08–3.12 (m, 2H, CH_2-NBn), 3.40–3.60 (m, 2H), 3.65–3.90 (m, 2H), 3.92–4.08 (m, 1H), 4.40 (m, 2H), 4.5–4.76 (m, 4H, 2×O-CH_2-Ph), 4.86 (bd, 1H, N*H*-Boc), 7.20–7.44 (m, 15H, aromatic); FAB MS: m/z 648 (M^+); $[\alpha]_D$ −14.8 (*c* 0.7, $CHCl_3$).

4.16. Methyl (2*R*,3*R*,4*S*)-7-*N*-benzyl-*N*-(*tert*-butoxycarbonyl)-2,3-di(benzyloxy)-4-(*tert*-butoxycarbonylamino)-heptanoate 3

The alcohol **21** (0.1 g, 0.15 mmol) was dissolved in dry acetone (10 mL) at 0°C and treated with Jones reagent, then stirred for 15 min at the same temperature. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated to furnish the acid (0.066 g).

The above acid (0.066 g, 0.099 mmol) was immediately dissolved in dry ether at 0°C and treated with ethereal diazomethane. After 0.5 h, ether was removed and the residue on purification by column chromatography afforded amino acid ester **3** (0.043 g, 41%) as a syrup. IR (neat): 3500, 1745, 1695 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.30 (s, 9H), 1.40 (s, 9H), 1.43–1.65 (m, 4H), 3.10–3.33 (m, 3H, C*H*-NH-Boc, CH_2-NBn), 3.80 (s, 3H, OCH_3), 3.95 (m, 2H), 4.30–4.45 (m, 2H, N-CH_2-Ph), 4.50–4.70 (m, 4H, 2×O-CH_2-Ph), 5.0 (d, 1H, N*H*-Boc), 7.16–7.40 (m, 15H, aromatic); FAB MS: m/z 545 $(M+1-131)^+$; $[\alpha]_D$ −17.2 (*c* 0.5, $CHCl_3$).

Acknowledgements

T.R. thanks CSIR, New Delhi for financial support.

References

1. Ireland, C. M.; Molinski, T. F.; Roll, D. M.; Zabriskie, T. M.; McKee, T. C.; Swersey, J. C.; Foster, M. P. In *Natural Product Peptides from Marine Organisms*; Scheuer, P. J., Ed. Bioorganic Marine Chemistry; Springer-Verlag: Berlin, Heidelberg, 1989; pp. 1–46.
2. (a) Zampella, A.; Valeria D'Auria, M.; Gomez Paloma, L.; Casapullo, A.; Minale, L.; Debitus, C.; Henin, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6202; (b) Valeria D'Auria, M.; Zampella, A.; Gomez Paloma, L.; Minale, L. *Tetrahedron* **1996**, *52*, 9589.
3. Bo, L.; Carroll, P. J.; Joullie, M. M. *Org. Lett.* **2000**, *2*, 4157.
4. Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 1800.
5. Sueda, N.; Ohrui, H.; Kuzuhara, H. *Tetrahedron Lett.* **1979**, *22*, 2039.
6. (a) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *14*, 1699; (b) Baker, D. C.; Horton, D.; Tindall, Jr., C. G. *Carbohydr. Res.* **1972**, *24*, 192.