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Synthesis of the γ-Amino-β-hydroxy Acid of Hapalosin via an Asymmetric Dihydroxylation Route

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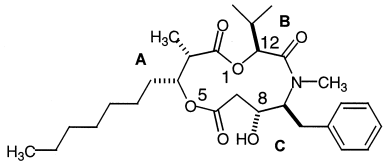
Abstract—Starting from the allylic alcohol **3**, the epoxide **7** was prepared by asymmetric dihydroxylation of the allylic chloride followed by subsequent protection of the secondary hydroxy group. Opening of the oxirane with phenyl cuprate gave the triol **8** with a free hydroxy group. Mitsunobu reaction of **8** with diphenylphosphoryl azide led to the azide **9**. Simple functional group manipulations delivered the acid **2** in further five steps.

Introduction

The cyclic depsipeptide hapalosin (**1**) was found to reverse multidrug resistance[1,2] (MDR) in tumor cells.[3] Common MDR is caused by overexpression of the *MDR1* gene that encodes for a 170 kDa P-glycoprotein. Structurally, hapalosin consists of three subunits, a β-hydroxy acid **A**, an α-hydroxy acid **B**, and a γ-amino-β-hydroxy acid **C**. With the modular structure, this molecule presents itself for analog synthesis in a parallel fashion.[4] Due to the biological activity, syntheses of the natural product[5–10] and of some analogs[10,11] have been reported.



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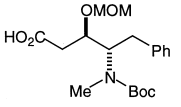
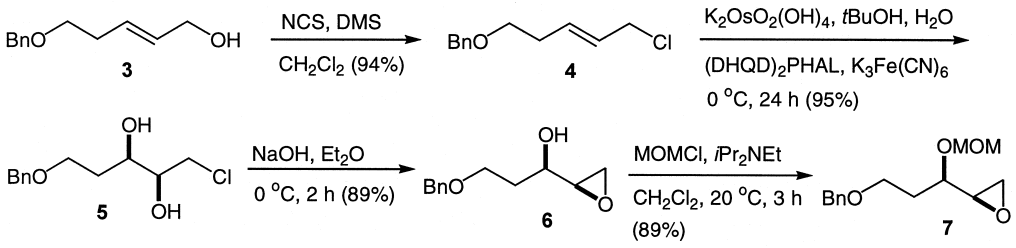


2

While the synthesis and availability of subunits of type **A** and **B** are no problem, the (3*R*,4*S*)-4-*N*-methylamino-3-hydroxy-5-phenylpentanoic acid requires a higher synthetic effort. Typically, amino acid **C** is prepared by elongation of *N*-protected phenylalanine in a sequence of about four to seven steps. Moreover, we recently disclosed the synthesis of acid **2** using the tactical combination of an aldol reaction and a Curtius rearrangement as key steps.[12] However, this and the other known syntheses do not allow for an easy modification or replacement of the aryl group. We therefore devised another route towards **2** that introduces the aryl group through the opening of an epoxide. The stereochemical information was established by a Sharpless asymmetric dihydroxylation reaction (ADH).[13]

Results

The synthesis started from the allylic alcohol **3**, which is available from benzyloxypropanol by an oxidation, Wittig–Horner and reduction sequence.[14–16] Chlorination[17] with *N*-chlorosuccinimide and dimethyl sulfide provided allyl chloride **4** in high yield (Scheme 1). The asymmetric dihydroxylation was performed under standard conditions[18]



Scheme 1.

Keywords: hapalosin; amino acid; epoxides; hydroxylation.

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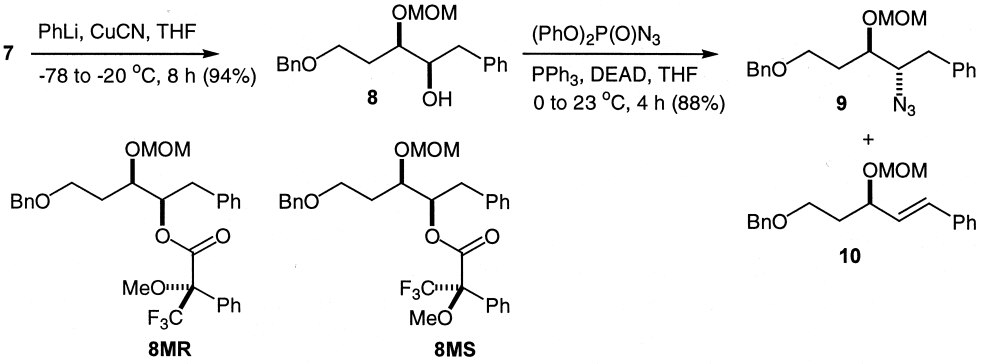


Scheme 2.

using $(DHQD)_2PHAL$ as chiral ligand, which furnished the (2*S*,3*R*)-diol **5**. Treatment of the chlorodiol **5** with pulverized sodium hydroxide led to the epoxy alcohol **6**. Despite the presence of the epoxide, protection of the hydroxyl group as its MOM ether proceeded uneventually to give the key building block **7**.

The stage was now set for the introduction of the phenyl group. Thus, the higher order cyanocuprate,[19] prepared from phenyllithium (2 equiv.) and copper cyanide added smoothly to the terminal carbon of the epoxide **7** affording the di-protected triol **8** in good yield (Scheme 2). The alcohol **8** was used to determine the enantioselectivity of the dihydroxylation reaction. It was converted to the corresponding Mosher esters using both Mosher acids.[20,21] An equimolar mixture of the Mosher esters could be separated on a DAICEL ODH column [250×4.6 mm, 2% *i*PrOH in heptane, flow 0.9 ml min^{-1}, retention times 11.99 and 13.40 min, 254 nm]. Injecting the Mosher ester derived from the (*S*)-acid (**8MS**) gave basically only one peak (13.40 min). The ratio from integration indicated an ee-value of 96%.

In the next step the nitrogen function was introduced through a Mitsunobu reaction[22] with diphenyl-phosphoryl azide[10] in the presence of triphenylphosphine and diethyl azodicarboxylate to furnish the azide **9**. This substitution reaction went in high yield but was accompanied by the elimination product **10**, which could be separated by chromatography.

After reduction of the azide with $LiAlH_4$ the amine **11** was obtained (Scheme 3). The free amine could be converted to the corresponding *N*-Boc derivative **12** (Boc_2O, NEt_3, trace DMAP, THF) and then by methylation (1.3 equiv. NaH, 2.0 equiv. MeI, DMF) to the protected amino alcohol **13**. Reducitve removal of the benzyl group gave the known primary alcohol **14**.[12] The measured optical rotation of **14** $[\alpha]_D^{25}=-16.0$ (c=0.9 in $CHCl_3$) {Ref. 12 $[\alpha]_D^{25}=-17.8$ (c=0.9 in $CHCl_3$)} was proof of the high enantioselectivity in the ADH reaction. To complete the synthesis, the primary alcohol **14** was oxidized to the acid **2** with sodium hypochlorite and TEMPO as described.[12]

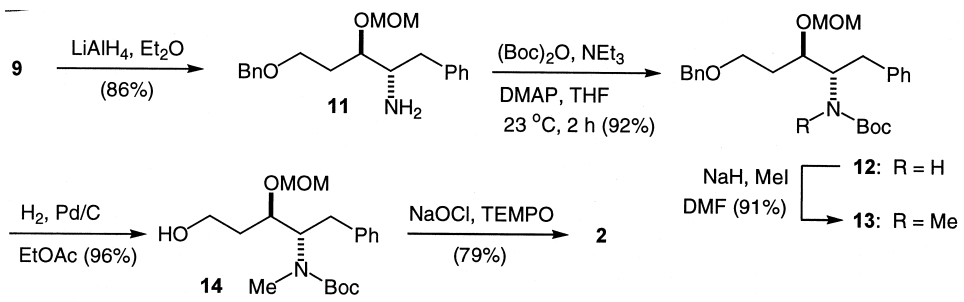
In summary, we prepared the chiral oxirane **7** by an asymmetric dihydroxylation of the allylic chloride **4** and illustrated the use of this polyfunctional C-5 building block by its conversion to the 4-amino-3-hydroxy-5-phenylpentanoic acid **2**.

Experimental

General

^1H and ^{13}C NMR: Bruker AC 250; all spectra were recorded in $CDCl_3$. Optical rotations: JASCO P-1020 polarimeter. IR: JASCO FT/IR-430 spectrometer, EI-MS: AMD Intectra GmbH AMD 402. HPLC: Hewlett Packard HP 1100. Flash chromatography: J. T. Baker silica gel 30–60 μm. Thin-layer chromatography: Merck Si 60 F_{254}. Solvents were distilled prior to use; petroleum ether with a boiling range of 35–65°C was used.

Benzyl (3*E*)-5-chloro-3-pentenyl ether (4). To a solution of NCS (15.4 g, 115 mmol) in dry CH_2Cl_2 (300 ml) was added DMS (8.5 ml, 115 mmol) at 0°C. After stirring for 1 h at 0°C the mixture was cooled to −20°C and a solution



Scheme 3.

of the allylic alcohol **3** (11.1 g, 57.7 mmol) in CH_2Cl_2 (100 ml) was added dropwise over a period of 30 min. After stirring for 30 min at 0°C the mixture was allowed to warm slowly to room temperature and stirred at this temperature for 1 h. Water (150 ml) was added, the two layers were separated, and the CH_2Cl_2 layer was washed with brine (2×150 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate 96:4 and 90:10) gave **4** (11.5 g, 94%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 95:5): R_f=0.48; IR (neat): 1495, 1453, 1363, 1252, 1204, 1102, 1028, 967, 738, 698 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$):δ=2.39 (dt, J=6.5, 6.5 Hz, 2H), 3.50 (t, J=6.6 Hz, 2H, CH_2OBn), 4.04 (d, J=6.7 Hz, 2H, CH_2Cl), 4.50 (s, 2H, CH_2Ph), 5.60–5.90 (m, 2H, olefinic), 7.26–7.35 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$):δ=32.6, 45.2, 69.3, 73.0, 127.7, 128.4, 132.3, 138.0; HRMS (EI) calcd for $C_{12}H_{15}ClO$ 210.08113, found 210.07991.

5-*O*-Benzyl-1-chloro-1,4-dideoxy-D-threo-pentitol (5). A solution of $(DHQD)_2PHAL$ (370 mg, 1 mol%), $K_2OsO_2(OH)_4$ (87 mg, 0.5 mol%), $K_3[Fe(CN)_6]$ (47.0 g, 142 mmol), K_2CO_3 (20.0 g, 142 mmol), $NaHCO_3$ (12 g, 142 mmol) and $CH_3SO_2NH_2$ (4.50 g, 47.5 mmol) in *t*-BuOH/H_2O (1:1, 500 ml) was cooled to 0°C and treated with the allylic halide **4** (10.0 g, 47.5 mmol). The mixture was stirred vigorously for 24 h at 0°C. $Na_2S_2O_5$ (45 g, 237 mmol) was added carefully, and stirring was continued for 1 h at room temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate (150 ml). The combined organic layers were washed with a 1N KOH (150 ml), 5% aqueous HCl (150 ml) and brine (150 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 1:1 and 2:3) to give **5** (11.1 g, 95%) as a colorless solid. $[\alpha]_D^{29}$=−13.0 (c 2.0, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 6:4): R_f=0.44; IR (neat): 1453, 1366, 1252, 1094, 849, 742, 6999, 612 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.73–1.82, 1.91–2,08 (2 m, 2H), 2.9 (br s, 1H, OH), 3.30 (br s, 1H, OH), 3.56–3.77 (m, 5H, CH_2Cl, CH_2OBn, CH) 3.97–4.02 (m, 1H, CH), 4.53 (s, 2H, CH_2Ph), 7.26–7.40 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=33.2, 45.9, 68.5, 70.6, 73.5, 74.0, 127.8, 128.6, 137.6.

4,5-Anhydro-1-*O*-benzyl-2-deoxy-D-threo-pentitol (6). To a cooled (0°C) solution of chlorodiol **5** (5.0 g, 20.5 mmol) in THF (30 ml) was added pulverized NaOH (1.64 g, 41.0 mmol). After stirring for 2 h at 0°C the mixture was diluted with diethyl ether (100 ml). Water (40 ml) was added, the layers were separated, and the organic layer was washed with saturated aqueous NH_4Cl (50 ml), brine (50 ml), dried ($MgSO_4$), filtered and concentrated in vacuo to give **6** (3.8 g, 89%) as a colorless oil. $[\alpha]_D^{28}$=−2.8 (c 1.0, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 6:4): R_f=0.44; ^1H NMR (250 MHz, $CDCl_3$):δ=1.82–1.93 (m, 2H), 2.59–2.61 (m, 1H, OH), 2.70–2.73, 2.75–2.79 (2m, 2H, CH_2O), 2.98–3.02 (m, 1H, CH), 3.63–3.79 (m, 3H, CH, CH_2OBn), 4.51 (d, J=1.5 Hz, 2H, CH_2Ph), 7.26–7.37 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$):δ=33.9, 44.6, 55.1, 67.6, 69.9, 73.3, 127.7, 128.5, 138.0; HRMS (EI) calcd for $C_{12}H_{16}O_3$ 208.10993, found 208. 10051.

4,5-Anhydro-1-*O*-benzyl-2-deoxy-3-*O*-(methoxymethyl)-D-threo-pentitol (7). To a cooled (0°C) solution of epoxy alcohol **6** (4.60 g, 22.3 mmol) and diisopropylethylamine (11.4 ml, 66.8 mmol) in dry CH_2Cl_2 (6 ml) was added dropwise chloromethyl methylether (3.9 ml, 44.6 mmol). The reaction mixture was stirred at 0°C for 1 h and then at room temperature for 2 h. Water (60 ml) and CH_2Cl_2 (100 ml) were added, the two layers separated, and the aqueous layer was extracted with CH_2Cl_2 (2×60 ml). The combined CH_2Cl_2 layers were washed with 1 N HCl (40 ml), water (80 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (petroleum ether/ethyl acetate, 80:20 and 75:25) gave **7** (5.0 g, 89%) as a colorless oil. $[\alpha]_D^{28}$=+40.9 (c 1.0, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.38; IR (neat); 1496, 1454, 1404, 1364, 1242, 1208, 1155, 1102, 1032, 919, 851, 813, 740, 699, 610 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$):δ=1.86–1.94 (m, 2H), 2.51–2.55, 2.75–2.77 (2m, 2H, CH_2O), 2.99–3.04 (m, 1H, CH), 3.37 (s, 3H, CH_3), 3.44–3.52 (m, 1H, CH) 3.60 (t, J=6.2 Hz, 2H, CH_2OBn), 4.49 (s, 2H, CH_2Ph), 4.66, 4.84 (2 d, J=6.25 Hz, 1H each, CH_2OMe), 7.27–7.37 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=32.6, 43.9, 54.6, 55.7, 66.2, 73.1, 75.5, 95.8, 127.7, 128.4, 138.3; HRMS (EI) calcd for $C_{12}H_{15}O_3$ ($M-CH_2OCH_3$) 207.10211, found 207.10007.

5-*O*-Benzyl-1,4-dideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (8). To a cooled (−78°C) suspension of copper cyanide (2.44 g, 27.2 mmol) in dry THF (60 ml) was added dropwise phenyllithium [30.2 ml, 1.8 M solution in diethylether/(30%) cyclohexane, 54.4 mmol]. The mixture was allowed to warm to −20°C for complete dissolution and was then recooled to −78°C. Now the epoxide **7** (4.90 g, 19.4 mmol) was added neat slowly via syringe. After warming to −20°C stirring was continued at this temperature for 8 h. The reaction was quenched with a mixture of 10% concentrated aqueous NH_3 in saturated aqueous NH_4Cl (60 ml) and allowed to warm to room temperature. Ether (60 ml) was added, the layers were separated followed by extracting the aqueous layer with ether (2×100 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and filtered. The solvent was removed in vacuo and the residue purified by flash chromatography (petroleum ether/ethyl acetate, gradient: 8:2, 7:3 and 6:4) to give **8** (6.04 g, 94%) as a light yellow oil. $[\alpha]_D^{25}$=+15.3 (c 0.51, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.17; IR (neat): 1603, 1495, 1454, 1364, 1208, 1100, 1030, 918, 743, 699, 606 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ=1.82–1.92, 1.97–2.04 (2m, 2H), 2.70–2.91 (m, 3H, CH_2Ph, OH), 2.85–2.92 (m, 2H, CH_2Ph), 3.40 (s, 3H, CH_3), 3.58–3.70 (m, 3H, CH_2OBn, CH), 3.76–3.83 (m, 1H, CH), 4.48 (d, J=1.9 Hz, 2H,CH_2Ph), 4.68–4.69 (m, 2H, CH_2OMe), 7.18–7.27, 7.28–7.38 (2m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=31.6 39.6, 56.0, 56.0, 66.4, 73.1, 74.1, 76.6, 97.3, 126.3, 127.7, 128.5, 138.2, 139.0; HRMS (EI) calcd for $C_{19}H_{23}O_3$ ($M-OCH_3$) 299.16471, found 299. 15907.

Preparation of the Mosher esters from the alcohol 8. To a solution of (*S*)-MTPA (24 mg, 0.10 mmol) and DMF (7 mg, 0.1 mmol) in hexane (4 ml) was added dropwise $(COCl)_2$ (54.6 mg, 0.43 mmol) at room temperature. A white

precipitate formed immediately. After stirring for 1 h the precipitate had disappeared and some oily drops resulted. The hexane solution was separated and concentrated under reduced pressure. A solution of the di-protected triol **8** (25 mg, 0.076 mmol), DMAP (5 mg, 0.04 mmol) and NEt_3 (23 mg, 0.23 mmol) in $CHCl_3$ (1 ml) was added to the residue at room temperature. After 2 h CH_2Cl_2 (5 ml) was added and the solution washed with 1 M $KHSO_4$ (5 ml) and brine (5 ml), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 8:2) to give the Mosher ester (33 mg, 80%) as a colorless oil. TLC (petroleum ether/ethyl acetate, 8:2); R_f=0.61.

Mosher ester derived from the (*S*)-acid: ^{1}H NMR (250 MHz, $CDCl_3$):δ=1.64–1.75 (m, 2H, CH_2), 2.75 (dd, *J*=14.4, 10.3 Hz, 1H, CH_2Ph), 3.11 (dd, *J*=14.4, 3.3 Hz, 1H, CH_2Ph), 3.19 (d, *J*=1.2 Hz, 3H, OCH_3), 3.34 (s, 3H, CH_3 (MOM)), 3.38–3.53 (m, 2H, CH_2OBn), 3.81–3.88 (m, 1H, CHOMOM), 4.39 (d, *J*=1.5 Hz, 2H, CH_2Ph), 4.57–4.63 (m, 2H, CH_2OMe), 5.49–5.54 (m, 1H, CH), 7.02–7.61 (m, 15H); ^{13}C NMR (62.9 MHz. $CDCl_3$):δ=30.2, 34.6, 55.3, 56.1, 66.4, 73.0, 75.5, 78.1, 97.6, 125.6, 126.7, 127.7, 128.3, 128.6, 129.4, 132.3, 137.3, 138.4, 166.2.

Mosher ester derived from the (*R*)-acid: ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.73–1.82, 1.83–1.91 (2m, 2H, CH_2), 2.73 (dd, *J*=14.4, 9.9 Hz, 1H, CH_2Ph), 3.04 (dd, *J*=14.4, 3.4 Hz, 1H, CH_2Ph), 3.23 (d, *J*=1.1 Hz, 3H, OCH_3), 3.34 (s, 3H, CH_3 (MOM)), 3.45–3.56 (m, 2H, CH_2OBn), 3.82–3.89 (m, 1H, CHOMOM), 4.41 (d, *J*=1.3 Hz, 2H, CH_2Ph), 4.60–4.64 (m, 2H, CH_2OMe), 5.46–5.53 (m, 1H, CH), 7.00–7.03, 7.07–7.12, 7.15–7.43 (3m, 15H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=30.8, 35.1 55.4, 56.0, 66.2, 73.1, 75.7, 77.8, 97.5, 125.6, 126.6. 127.5, 127.7, 128.3, 128.5, 129.3, 132.0, 137.1, 138.4, 166.1.

2-Azido-5-*O*-benzyl-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (9). To a solution of the di-protected triol **7** (6.90 g, 20.9 mmol) and triphenylphosphine 6.0 g, 23 mmol) in dry THF (60 ml) at 0°C was added dropwise diethyl azodicarboxylate (DEAD, 4.0 g, 23 mmol) and subsequently diphenylphosphoryl azide (DPPA, 6.0 g, 21.8 mmol). After stirring for 20 min at 0°C the solution was allowed to stir at room temperature for 3 h. The reaction solution was partitioned between diethyl ether (100 ml) and water (80 ml), the two layers were separated, and the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2 as eluent) to give **9** (6.54 g, 88%) as a colorless oil and the by-product **10** (0.55 g, 8%). $[\alpha]_D^{29}$=+18.5 (*c* 0.504, CH_2Cl_2); TLC (CH_2Cl_2): R_f=0.53; IR (neat): 2170, 2120, 1603, 1590, 1495, 1454, 1365, 1271, 1206, 1184, 1154, 1101, 1030, 965, 918, 739, 700, 618 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$):δ=1.89–1.96 (m, 2H), 2.64–2.85 (m, 2H, CH_2Ph), 3.39 (s, 3H CH_3), 3.59–3.66 (m, 2H, CH_2OBn), 3.81–3.91 (m, 2H, 2CH), 4.56–4.63 (m, 2H, CH_2Ph), 4.66 (q, 2H, CH_2OMe), 7.20–7.27, 7.28–7.39 (2m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$); δ=30.5, 36.8, 56.0, 66.4, 67.2, 73.1, 97.0, 126.8, 127.7, 128.5, 129.2, 130.1, 138.0, 138.3.

2-Amino-5-*O*-benzyl-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (11). To a suspension of $LiAlH_4$ (1.1 g, 28.8 mmol) in dry diethyl ether (80 ml) was added dropwise a solution of the azide **9** (5.1 g, 14.4 mmol) in dry diethyl ether (10 ml) at room temperature. The reaction mixture was stirred for 3 h at room temperature. After cooling to 0°C wet diethyl ether (80 ml) was added followed by the dropwise addition of water (60 ml). The aqueous layer was removed and then extracted with ether (300 ml). The combined ether layers were washed with brine (2×100 ml), dried ($MgSO_4$), filtered and evaporated in vacuo. The residue was purified by flash chromatography on silica gel (50% petroleum ether in ethyl acetate and 20% methyl alcohol in ethyl acetate as eluents) to give **11** (4.1 g, 86%) as a colorless oil. $[\alpha]_D^{25}$=+9.7 (*c* 0.45, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 1:1): R_f=0.1; IR (neat): 3377 (w), 1603, 1495, 1454, 1364, 1207, 1151, 1098, 10.35, 917, 839, 740, 700, 607, 536 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.43 (br s, 2H, NH_2), 1.90–1.97 (m, 2H), 2.40–2.49, 2.83–2.89 (2m, 2H, CH_2Ph), 3.10–3.24 (m, 1H, CH), 3.37 (s, 3H, CH_3), 3.59–3.70 (m, 2H, CH_2OBn), 3.71–3.76 (m, 1H, CHOMOM), 4.51 (s, 2H, CH_2Ph), 4.63–4.70 (m, 2H, CH_2OMe), 7.17–7.26, 7.27–7.37 (2m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$):δ=30.2, 39.7 55.6, 55.8, 66.9, 73.1, 79.6, 96.8, 126.3, 127.6, 128.4, 129.2, 138.5, 139.6; HRMS (EI) calcd for $C_{20}H_{27}NO_3$ 329.19908, found 329.20495.

5-*O*-Benzyl-2-[(*tert*-butoxycarbonyl)amino]-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (12). To a cooled (0°C) solution of the amine **11** (4.2 g, 12.4 mmol) in dry tetrahydrofuran (40 ml) were added $(Boc)_2O$ (3.5 g, 16 mmol), triethylamine (1.5 g, 14.8 mmol) and dimethylaminopyridine (DMAP, 0.3 g, 2.5 mmol). The solution was stirred for 2 h at room temperature, then diluted with ether (120 ml), washed successively with a 1 M aqueous $KHSO_4$ solution (40 ml), water (40 ml), a saturated aqueous $NaHCO_3$ solution (40 ml), water (40 ml) and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (20% and 30% ethyl acetate in petroleum ether as eluents) gave **12** (4.9 g, 92%). $[\alpha]_D^{26}$=−18.0 (*c* 0.5, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 8:2): R_f=0.43; IR (neat): 3364 (s), 1711 1604, 1498, 1454, 1365, 1245, 1171, 1100, 1034, 918, 851, 739, 699, 607, 463 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$):δ=1.31 (s, 9H), 1.83–1.91 (m, 2H), 2.61–2.70 (m, 1H, CH_2Ph), 2.91 (dd, *J*=13.9, 4.8 Hz, 1H, CH_2Ph), 3.40 (s, 3H, CH_3), 3.51–3.65 (m, 2H, CH_2OBn), 3.76–3.82 (m, 1H, CH), 3.91–4.00 (m, 1H, CH), 4.50 (m, 2H, CH_2Ph), 4.53–4.61 (m, 2H, CH_2OMe), 5.08 (br d, *J*=8.5, 1H, NH), 7.14–7.26, 7.27–7.41 (2m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.3, 32.2, 36.2, 54.3, 55.9. 66.7, 73.1, 79.0, 97.3, 126.2, 127.8, 128.4, 129.3, 138.3, 138.6, 155.4.

5-*O*-Benzyl-2-[(*tert*-butoxycarbonyl)(methyl)amino]-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (13). To a cooled (0°C) solution of **12** (4.6 g, 10.8 mmol) and MeI (3.1 g, 21.5 mmol) in dry DMF (40 ml) was added NaH (0.56 g, 14 mmol, 60% in mineral oil). After complete addition, the suspension was allowed to warm to room temperature and stirred at this temperature for

18 h. The reaction was quenched at 0°C with saturated aqueous NH_4Cl (25 ml). The mixture was partitioned between ethyl acetate (80 ml) and water (20 ml). The aqueous layer was extracted with ethyl acetate (2×80 ml). Then the combined organic layers were washed with water (3×40 ml), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (30% ethyl acetate in petroleum ether) to give **13** (4.38 g, 91%) as a colorless oil. $[\alpha]_D^{25}=-26.2$ (*c* 0.578, CH_2Cl_2); TLC (petroleum ether/ethyl acetate, 8:2); R_f=0.43; IR (neat): 1738, 1693, 1604, 1585, 1496, 1479, 1454, 1391, 1365, 1321, 1244, 1169, 1151, 1034, 959, 919, 874, 824, 772, 738, 699, 607, 544, 520, 464 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$):δ (two rotamers)=1.19 (br, s, 9H, minor), 1.29 (s, 9H, major), 1.69–1.82, 1.93–2.05 (2m, 2H), 2.53 (s, 3H, minor, NCH_3), 2.68 (br s, 3H, major, NCH_3), 2.70–2.85 (m, 1H, CH_2Ph), 3.11–3.21 (m, 1H, CH), 4.18–4.22 (m, 1H, CH), 4.49 (s, 2H, CH_2Ph), 4.65–4.78 (m, 2H, CH_2OMe), 7.12–7.26, 7.27–7.33 (2m, 10H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ=28.3, 32.2, 32.4, 34.5, 56.4, 66.4, 66.8, 73.2, 79.3, 97.2, 126.1, 126.3, 127.7, 128.3, 129.2, 138.5, 139.2, 155.7; HRMS (EI) calcd for $C_{26}H_{37}NO_5$ 443.26715, found 443.27049.

2-[(*tert*-Butoxycarbonyl)(methyl)amino]-1,2,4-trideoxy-3-*O*-(methoxymethyl)-1-phenyl-D-threo-pentitol (14). A solution of the protected amine **13** (4.3 g, 9.7 mmol) in ethyl acetate (100 ml) was hydrogenated over 10% Pd/C (1.4 g) at room temperature and ordinary pressure for 5 h. After removal of the catalyst, the solution was concentrated in vacuo to leave an oil, which was purified by flash chromatography on silica gel (30% ethyl acetate in petroleum ether) to give **14** (3.3 g, 96%). $[\alpha]_D^{25}=-16.0$ (*c* 0.9, $CHCl_3$); TLC (petroleum ether/ethyl acetate, 3:7): R_f=0.42; IR (neat): 1738, 1686, 1604, 1496, 1480, 1454, 1392, 1366, 1324, 1249, 1217, 1153, 1034, 958, 920, 871, 824, 772, 751, 701, 545, 521, 464 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (two rotamers)=1.16, 1.24 (2 s, 3H, CH_3), 1.52–1.66, 1.82–1.98 (2m, 2H), 2.25 (br s, 1H, OH), 2.49 (s, 3H, minor NCH_3), 2.62 (s, 3H, major, NCH_3), 2.70–2.90 (complex, 1H, CH_2Ph), 3.01–3.14 (m, 1H, CH_2Ph), 3.38 (s, 3H, minor, CH_3), 3.41 (s, 3H, major, CH_3), 3.62–3.84 (m, 3H, CH_2(OH), CH), 4.20 (br s, 1H, CH), 4.64–4.76 (m, 2H, CH_2OMe), 7.07–7.23 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ (two rotamers)=28.1 28.3, 34.1, 34.3, 34.6, 56.2, 56.4, 58.8, 78.3, 79.6, 79.8, 97.4, 97.7, 126.1, 126.3, 128.9, 129.0, 138.8, 155.5, 156.0; HRMS (EI) calcd for $C_{19}H_{32}NO_5$ (M+1) 354.22802, found 354.23059. HRMS (EI) calcd for $C_{19}H_{32}NO_5$ (M+1) 354.22802, found 354.23059.

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