

Stereodivergent Synthesis of all Diastereomers of 4-Aminoheptane-3,5-diol from (L)-Serine

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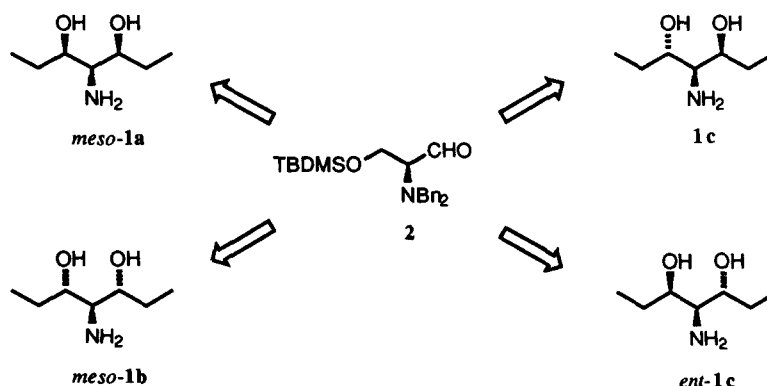
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Abstract: The synthesis of the two diastereomeric *meso* forms of 4-amino-3,5-heptanediol (3*R*,4*r*,5*S*)-**1a** and (3*S*,4*s*,5*R*)-**1b** and the two pseudo *C*₂-symmetric enantiomers (3*S*,5*S*)-**1c** and (3*R*,5*R*)-*ent*-**1c** is described by stereocontrolled ethylmagnesium bromide or diethylzinc addition to diastereomeric α -amino- β -hydroxy pentanal derivatives **9** and **13**. These derivatives were prepared from (2*S*)-*N,N*-dibenzyl-O-TBS-serinal **2**, that in turn were obtained from (L)-serine. © 1998 Elsevier Science Ltd. All rights reserved.

Key words: Asymmetric Synthesis, Amino alcohols, Amino aldehydes, Diastereoselection.

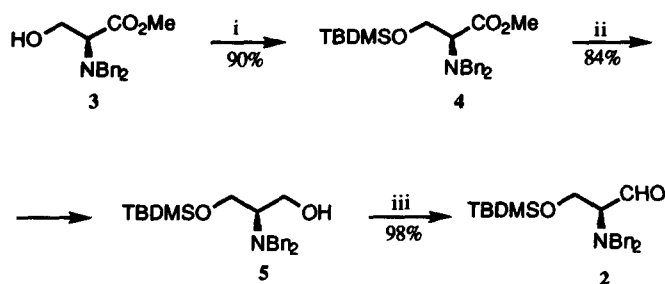
Because the 2-amino-1,3-diol arrangement constitutes part of biologically active compounds such as sphingosines or dihydrosphingosines,¹ and an important building block for the total synthesis of aminosugars,² and α -amino- β -hydroxy acids³ it has attracted a lot of synthetic work. Common starting compounds for the preparation of 2-amino-1,3-diols are amino acids,⁴ olefins,⁵ oxazolidinones,⁶ cyanohydrins⁷ or amino aldehydes.⁸

In this paper we report on the synthesis of the two diastereomeric *meso* forms of the 4-amino-3,5-heptanediol (3*R*, 4*r*, 5*S*)-**1a** and (3*S*, 4*s*, 5*R*)-**1b** and the two pseudo *C*₂-symmetric enantiomers (3*S*, 5*S*)-**1c** and (3*R*, 5*R*)-*ent*-**1c** from a common serinal derivative **2**.



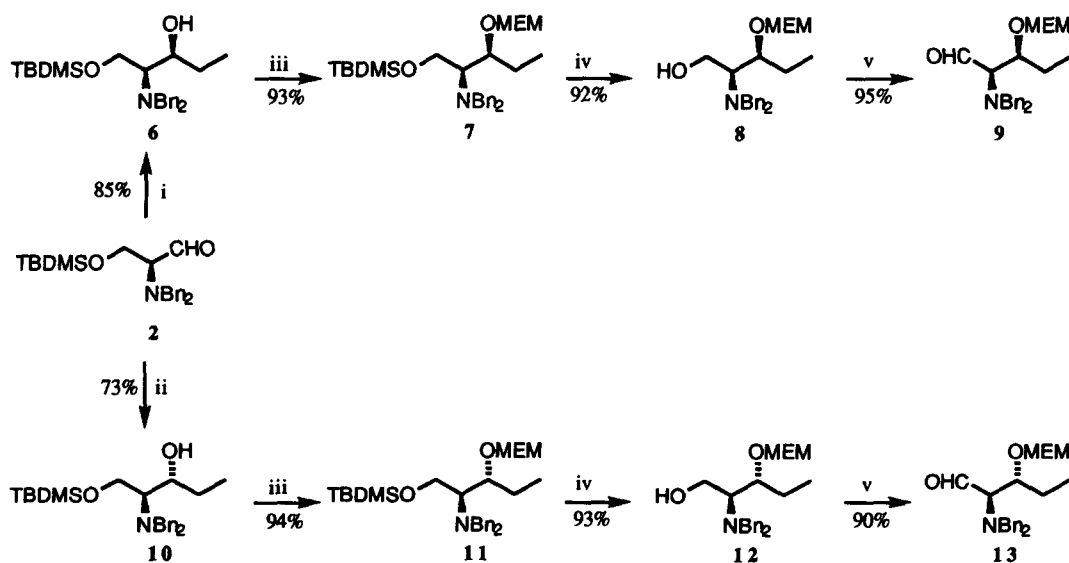
The method develops the concept of protective group tuning and organometallic tuning introduced by Reetz⁹ taking into account that the dibenzylamino substituent in **2** directs the addition on the formyl group to the

*anti*⁸ or *syn*¹⁰ amino alcohols depending on the nature of the organometallics. The different pattern of protection at the hydroxyl groups allowed the selective deprotection and subsequent oxidation of the different compounds.



Scheme 1 Reagents and conditions: (i) TBDMSCl, imidazole, DMF, rt; (ii) NaBH₄, LiCl, THF-EtOH, rt; (iii) (COCl)₂, DMSO, Et₃N, -78°C.

The starting protected (2*S*)-serinal **2** was prepared in 74% yield from (L)-N,N-dibenzyl methyl serinate as outlined in Scheme 1. Treatment of **3** with tert-butyldimethylsilyl chloride gave the TBDMS ether of the ester **4**, that was selectively reduced to the alcohol **5** with sodium borohydride-lithium chloride in THF-ethanol.¹¹ Swern oxidation of **5** led to the α-amino-β-hydroxy aldehyde **2** without any appreciable racemization. It must be pointed out that the reduction of **4** with lithium aluminum hydride in THF or toluene led to the unprotected 2-dibenzylamino-1,3-propanediol.

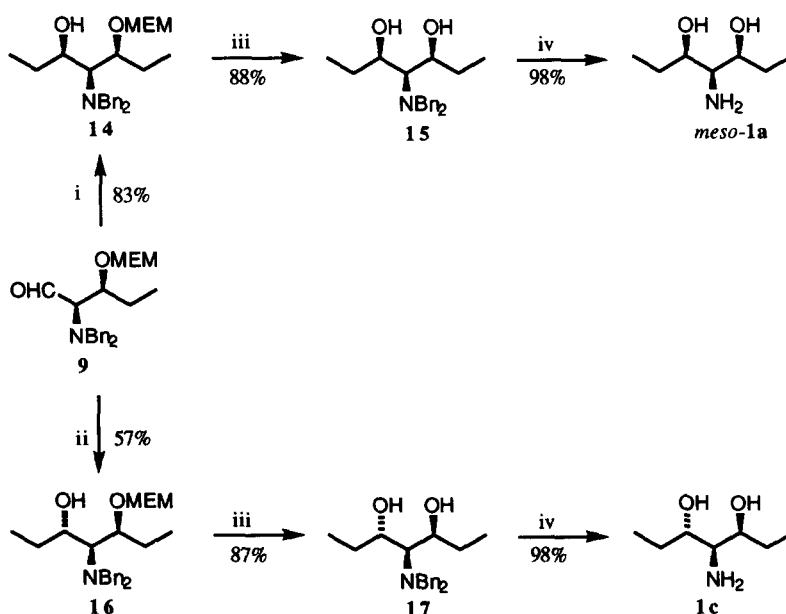


Scheme 2 Reagents and conditions : (i) Et₂Zn, hexane-toluene, 0°C; (ii) EtMgBr, Et₂O, 0°C; (iii) MEMCl, iPr₂NEt, CH₂Cl₂, rt; (iv) TBAF, THF, 0°C; (v) (COCl)₂, DMSO, Et₃N, -78°C.

The (2*S*)-serinal derivative **2** was transformed into the two diastereomeric 3-hydroxynorvalinals **9** and **13** (Scheme 2) in excellent chemical yield by tuning the organometallic in the addition process. Thus **2** was converted into the *syn* aminoalcohol **6** by reaction with diethylzinc at 0°C in hexane-toluene. As expected the addition of the zinc derivative proceeded with chelation control ¹⁰ leading to the (2*S*, 3*S*)-2-amino-1,3-pentanediol derivative **6** as a single enantiomer. The (2*R*, 3*S*)-3-hydroxynorvalinal derivative **9** was obtained from **6** by sequential protection of the OH at C-3 as MEM ether, deprotection of the OH at C-1 with tetrabutylammonium fluoride in THF at 0°C, and Swern oxidation of **8**.

Ethylmagnesium bromide addition to **2** proceeds according to the nonchelation control ⁸ leading to the *anti* aminoalcohol **10** in 73% yield and 90% d.e.. After purification by flash chromatography, the (2*S*, 3*R*)-2-amino-1,3-pentanediol derivative **10** was transformed into (2*R*, 3*R*)-3-hydroxynorvalinal **13** by the same sequence as outlined for **6**.

A similar stereodivergent route allowed the preparation of the *meso* (3*R*, 4*r*, 5*S*)-4-amino-3,5-heptanediol **1a** and the pseudo C₂-symmetric enantiomer (3*S*, 5*S*)-**1c** from **9** (Scheme 3). In fact, treatment of **9** with diethyl zinc led to the (3*R*, 4*S*, 5*S*)-4-amino-3,5-heptanediol derivative **14** as a single enantiomer, whereas the reaction of protected 3-hydroxy norvalinal **9** with ethyl magnesium bromide yielded the (3*S*, 4*S*, 5*S*) stereoisomer **16** but only in 40% d.e. in diethyl ether or 20% d.e. if THF was used as solvent. Flash chromatography of the mixture allowed the isolation of **16** as a pure enantiomer.



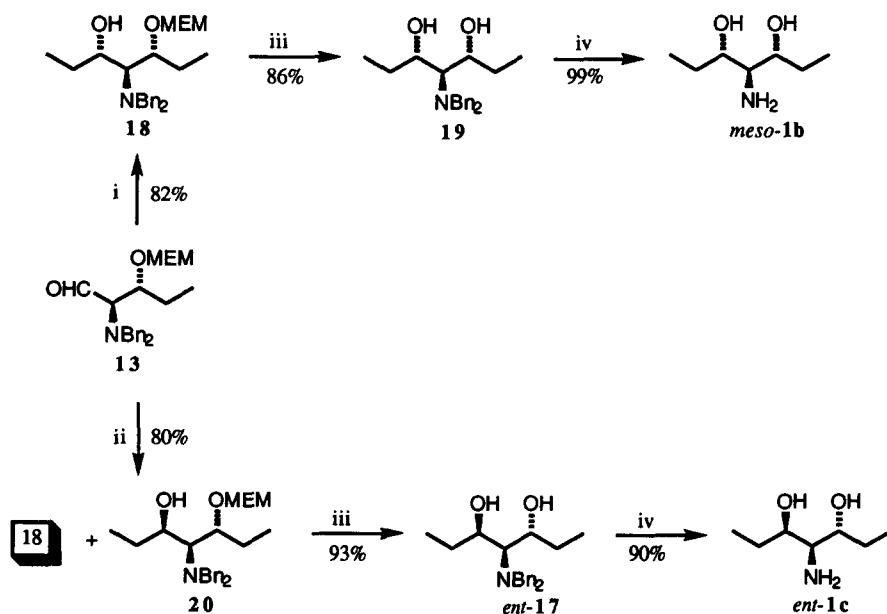
Scheme 3 Reagents and conditions : (i) Et_2Zn , hexane-toluene, 0°C; (ii) EtMgBr , Et_2O , 0°C; (iii) HCl 2*N*, $\text{THF-H}_2\text{O}$, rt; (iv) H_2 , $\text{Pd}(\text{OH})_2$, MeOH , rt.

The observed less pronounced nonchelation control in this case could be attributed to the competition between 1,2- and 1,3-asymmetric induction leading to contrary configuration at the newly created

stereocenter.¹² Deprotection of **14** and **16** by treatment with a 2N solution of HCl in THF-H₂O led to **15** and **17** respectively, that were efficiently converted into the final *meso*-**1a** and **1c** by low pressure hydrogenolysis over Pd(OH)₂ as described by Yoshida.¹³

Contrary to that described for compound **9**, the (2R, 3R)-3-hydroxy norvalinal derivative **13** reacts with ethyl magnesium bromide, in diethyl ether, in an stereospecific way, leading to **18** as a single diastereomer (Scheme 4). In this case, the 1,2-nonchelated addition and the 1,3-induction have additive effects leading to the *anti* aminoalcohol **18**. This was transformed into *meso*-**1b** (70% yield from **13**) by deprotection of **19** and subsequent debenzylation by hydrogenolysis.

Unexpectedly, the addition of diethylzinc (hexane-toluene, 0°C) to **13** turned out to be nonselective since it produced a mixture of the *anti*-**18** and its epimer *syn*-**20** as minor diastereomer in *ca.* 3:2 ratio. Once again, the 1,2- and 1,3-induction yielded a stereocenter of opposite configuration, but for the addition of diethylzinc to **13**, the latter predominates over the first leading to the "nonchelation" controlled *anti* aminoalcohol as major isomer. Pure (3R, 4S, 5R)-4-amino-3,5-heptanediol **20** was isolated by flash chromatography (silicagel, hexane-Et₂O 4:1) of the crude reaction mixture and transformed into *ent*-**17** by hydrolysis with HCl in THF-H₂O, and the latter converted into the (3R, 5R)-4-amino-3,5-heptanediol *ent*-**1c** by debenzylation over Pearlman's catalyst.



Scheme 4 Reagents and conditions : (i) EtMgBr, Et₂O, 0°C ; (ii) Et₂Zn, hexane-toluene, 0°C ; (iii) HCl 2N, THF-H₂O, rt; (iv) H₂, Pd(OH)₂, MeOH, rt.

In summary, the results summarized here provided a diastereoselective synthesis of the four possible stereoisomers of 4-amino-3,5-heptanediol starting from the (2S)-serinal derivative **2**, in turn prepared from (L)-serine. Stereoselective additions to **2** by tuning the organometallics led to diastereomeric (2R, 3S)- and (2R, 3R)-3-hydroxynorvalinals that were used as starting materials in the preparation of the final products.

Experimental

General. The reactions were carried out in oven-dried glassware, under argon atmosphere, and using anhydrous solvents. Diethylzinc, as 1M solution in hexane or 1.1M solution in toluene, was purchased from Aldrich, and used without further purification. The ^1H -NMR (300 MHz) and ^{13}C -NMR (75 MHz) spectra were registered on a Bruker AC 300 or Bruker AMX 300, using TMS as internal standard. IR spectra were recorded on a Philips PU 9706 Spectrometer, as a film or KBr dispersion. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter in a 1 dm. cell.

(S)-2-(N,N-Dibenzylamino)-3-(tert-butyldimethylsilyloxy)-propanoic methyl ester (4). To a solution of the hydroxy ester **3** (5.98 g, 20 mmol) and imidazole (3.40 g, 50 mmol, 2.5 equiv) in DMF (30 mL) was added tert-butyldimethylsilyl chloride (3.62 g, 24 mmol, 1.2 equiv) and the mixture was stirred at room temperature overnight. The reaction was quenched with aqueous saturated NH_4Cl solution (50 mL) and decanted. The aqueous phase was extracted with ether (3 x 30 mL), the combined organic phases were washed with brine, dried (Na_2SO_4) and the solvent was evaporated. The product was purified by flash chromatography (silica gel, EtOAc/hexane: 1/10) yielding the ester **4** as a colorless oil: 7.42 g (90%). $[\alpha]_{\text{D}}^{23} = -56.7$ ($c = 1$, CHCl_3). IR (film): 1725, 1100, 770, 695 cm^{-1} . ^1H -NMR (CDCl_3): 0.01 (s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.84 (s, 9H, $(\text{CH}_3)_3\text{C}$); 3.54 (m, 1H, CHN); 3.67 (d, 2H, $J = 13.8$ Hz, CHHPh); 3.74 (s, 3H, CH_3O); 3.87 (dd, 1H, $J_1 = 10.1$ Hz, $J_2 = 6.1$ Hz, CHHOTBDMS); 3.94 (d, 2H, $J = 13.8$ Hz, CHHPh); 3.98 (dd, 1H, $J_1 = 10.1$ Hz, $J_2 = 6.7$ Hz, CHHOTBDMS); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): -5.6; 18.1; 25.7; 51.0; 55.4; 62.6; 62.9; 126.9; 128.2; 128.6; 139.8; 172.0.

(R)-2-(N,N-Dibenzylamino)-3-(tert-butyldimethylsilyloxy)-1-propanol (5). The α -aminoacid methyl ester **4** (7.42 g, 18 mmol) obtained as above was dissolved in tetrahydrofuran (50 mL) under argon, and anhydrous lithium chloride (3.05 g, 72 mmol, 4 equiv) and the sodium borohydride (2.27 g, 72 mmol, 4 equiv) were added. After addition of ethanol (100 mL), the mixture was stirred at room temperature overnight. The mixture was cooled in an ice-water bath, hydrolyzed with saturated NH_4Cl (125 mL), and concentrated in vacuo. The residue was extracted with methylene chloride (3 x 50 mL) and dried over anhydrous Na_2SO_4 . Removal of the solvent gave **5** as colorless oil, which was purified by flash chromatography (silica gel, EtOAc/hexane: 1/10): 5.83 g (84%). $[\alpha]_{\text{D}}^{23} = +52.0$ ($c = 0.9$, CHCl_3). IR (film): 3410 cm^{-1} . ^1H -NMR (CDCl_3): 0.07 and 0.08 (2s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.92 (s, 9H, $(\text{CH}_3)_3\text{C}$); 2.91 (broad s, 1H, OH); 3.00 (m, 1H, CHN); 3.55 (m, 2H, CH_2OH); 3.65 (d, 2H, $J = 13.4$ Hz, CHHPh); 3.72 (dd, 1H, $J_1 = 10.6$ Hz, $J_2 = 5.8$ Hz, CHHOTBDMS); 3.85 (dd, 1H, $J_1 = 10.6$ Hz, $J_2 = 4.4$ Hz, CHHOTBDMS); 3.89 (d, 2H, $J = 13.4$ Hz, CHHPh); 7.30–7.35 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): -5.6; 18.1; 25.8; 54.0; 59.5; 59.6; 60.8; 127.1; 128.4; 128.9; 139.6.

(S)-2-(N,N-Dibenzylamino)-3-(tert-butyldimethylsilyloxy)-propanal (2). To a stirred solution of oxalyl chloride (0.65 mL, 7.45 mmol) in 15 mL of dichloromethane cooled to -78°C under argon was added dropwise 1.1 mL (15.5 mmol) of DMSO. After 15 min, a solution of 2.12 g (5.5 mmol) of aminoalcohol **5** in 15 mL of dichloromethane was added, and the mixture was stirred for 30 min at -78°C before addition of triethylamine (2.2 mL, 15.8 mmol). Then, the reaction was allowed to reach the room temperature under stirring for 45 min and the mixture quenched with water (15 mL). The aqueous phase was extracted with CH_2Cl_2 (15 mL), and the combined organic layers were washed with saturated aqueous NaHCO_3 and brine. The organic phase was dried (MgSO_4) and then concentrated to yield an oil that was used immediately in the next reaction: 2.07 g (98%). $[\alpha]_{\text{D}}^{23} = -16.0$ ($c = 1.7$, CHCl_3). IR (film): 1715 cm^{-1} . ^1H -NMR (CDCl_3): 0.08 and 0.09 (2s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.91 (s, 9H, $(\text{CH}_3)_3\text{C}$); 3.39 (t, 1H, $J = 5.8$ Hz, CHN); 3.86 (d, 2H, $J = 14.1$

Hz, CHHPh); 3.91 (d, 2H, $J = 14.1$ Hz, CHHPh); 4.05 (d, 2H, $J = 5.8$ Hz, CH_2OTBDMS); 7.20–7.45 (m, 10H, H_{arom}); 9.73 (s, 1H, CHO). $^{13}\text{C-NMR}$ (CDCl_3): -5.6; 18.1; 25.8; 55.7; 59.9; 67.7; 127.2, 128.3, 128.7; 139.5; 203.3.

(2S, 3S)-2-(N,N-Dibenzylamino)-1-(tert-butyldimethylsilyloxy)-3-pentanol (6). A 50 mL oven-dried flask equipped with a septum and a magnetic stirrer and purged with argon, was charged with the aminoaldehyde **2** (1.92 g, 5 mmol) and 25 mL of anhydrous toluene. The solution was cooled to 0°C (ice bath), and 10 mL of 1M solution of diethyl zinc in hexane (10 mmol., 2 equiv) were injected through the septum. The mixture was stirred at that temperature until the reaction was finished (TLC), and then quenched with 80 mL of a saturated solution of ammonium chloride. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3x 20 mL). The combined organic layers were washed with brine, and dried over anhydrous Na_2SO_4 . The solvents were eliminated on Rotavapor and the residue purified by flash chromatography (silica gel, hexane/ethyl acetate: 15/1): 1.76 g (85%). Colorless oil. $[\alpha]_{\text{D}}^{23} = +53.7$ ($c = 1$, CHCl_3). IR (film): 3390 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.11 and 0.12 (2s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.91 (t, 3H, $J = 7.3$ Hz, CH_3CH_2); 0.95 (s, 9H, $(\text{CH}_3)_3\text{C}$); 1.17 (m, 1H, CHHCH_3); 1.55 (m, 1H, CHHCH_3); 2.60 (m, 1H, CHN); 3.59 (m, 1H, CHOH); 3.62 (d, 2H, $J = 13.4$ Hz, CHHPh); 3.83 (dd, 1H, $J_1 = 11.2$ Hz, $J_2 = 6.3$ Hz, CHHOTBDMS); 3.89 (dd, 1H, $J_1 = 11.2$ Hz, $J_2 = 3.4$ Hz, CHHOTBDMS); 3.99 (d, 2H, $J = 13.4$ Hz, CHHPh); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): -5.7; -5.6; 10.0; 18.1; 25.8; 26.7; 54.4; 59.4; 62.9; 67.9; 127.1, 128.4, 129.1; 139.3.

(2S,3S)-2-(N,N-Dibenzylamino)-1-(tert-butyldimethylsilyloxy)-3-[(2-methoxyethoxy)methoxy]-pentane (7). To a solution of **6** (1.65 g, 4 mmol) and diisopropylethylamine (2.1 mL, 12 mmol) in CH_2Cl_2 (15 mL) at 0°C was added dropwise MEM chloride (1.37 mL, 12 mmol). After 48 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (silica gel, CH_2Cl_2) to give **7** as a colorless oil: 1.87 g (93%). $[\alpha]_{\text{D}}^{23} = +25.1$ ($c = 1$, CHCl_3). IR (film): 1110, 1040, 740, 695 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.11 (s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.46 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 0.95 (s, 9H, $(\text{CH}_3)_3\text{C}$); 1.60 (m, 1H, CHHCH_3); 1.77 (m, 1H, CHHCH_3); 2.77 (td, 1H, $J_1 = 6.5$ Hz, $J_2 = 3.5$ Hz, CHN); 3.39 (s, 3H, CH_3O); 3.53 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.57 (m, 1H, CHOMEM); 3.65 (d, 2H, $J = 13.3$ Hz, CHHPh); 3.68 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.87 (dd, 1H, $J_1 = 10.1$ Hz, $J_2 = 6.5$ Hz, CHHOTBDMS); 4.07 (dd, 1H, $J_1 = 10.1$ Hz, $J_2 = 6.6$ Hz, CHHOTBDMS); 4.09 (d, 2H, $J = 13.3$ Hz, CHHPh); 4.69 (d, 1H, $J = 6.9$ Hz, OCHHO); 4.74 (d, 1H, $J = 6.9$ Hz, OCHHO); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): -5.4; 9.9; 18.1; 24.1; 25.9; 55.8; 58.9; 59.3; 60.2; 67.1; 71.7; 81.4; 95.7; 126.5, 127.9, 129.1; 140.9.

(2S,3S)-2-(N,N-Dibenzylamino)-3-[(2-methoxyethoxy)methoxy]-1-pentanol (8). To a solution of **7** (1.51 g, 3 mmol) in THF (25 mL) at 0°C was slowly added a solution of tetrabutylammonium fluoride (1.42 g, 4.5 mmol) in THF (5 mL). The mixture was stirred during 8 h at 0°C, and the reaction was quenched by addition of water (25 mL). The aqueous phase was extracted with ether (2 x 25 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (silica gel, AcOEt /hexane: 1/2) to yield **8** as a colorless oil: 1.07 g (92%). $[\alpha]_{\text{D}}^{23} = +22.1$ ($c = 1$, CHCl_3). IR (film): 3460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.69 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 1.54 (m, 1H, CHHCH_3); 1.81 (m, 1H, CHHCH_3); 2.90 (td, 1H, $J_1 = 7.4$ Hz, $J_2 = 5.5$ Hz, CHN); 3.43 (s, 3H, CH_3O); 3.60 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.70 (m, 3H, OCHHCH_2O and CH_2OH); 3.72 (d, 2H, $J = 13.2$ Hz, CHHPh); 3.84 (m, 1H, CHOMEM); 3.90 (m, 1H, OCHHCH_2O); 3.99 (d, 2H, $J = 13.2$ Hz, CHHPh); 4.77 (d, 1H, $J = 7.0$ Hz, OCHHO); 4.80 (d, 1H,

$J = 7.0$ Hz, OCH_2HO); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): 8.9; 23.7; 54.8; 57.0; 59.0; 67.5; 71.6; 79.5; 94.9; 126.9, 128.2, 129.1; 140.1.

(2R,3S)-2-(N,N-Dibenzylamino)-3-[(2-methoxyethoxy)methoxy]-1-pentanal (9).

The aminoaldehyde **9** was obtained from the aminoalcohol **8** (581 mg, 1.5 mmol) by Swern oxidation as described for compound **2**: 549 mg (95%). $[\alpha]_{\text{D}}^{23} = +16.4$ ($c = 1$, CHCl_3). IR (film): 1715 cm^{-1} . ^1H -NMR (CDCl_3): 0.60 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 1.80 (m, 2H, CH_2CH_3); 3.36 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 4.0$ Hz, CHN); 3.39 (s, 3H, CH_3O); 3.54 (t, 2H, $J = 4.5$ Hz, $\text{OCH}_2\text{CH}_2\text{O}$); 3.65 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 4.00 (d, 2H, $J = 13.8$ Hz, CHHPh); 4.12 (m, 1H, CHOMEM); 4.20 (d, 2H, $J = 13.8$, CHHPh); 4.68 (d, 1H, $J = 7.2$ Hz, OCH_2HO); 4.78 (d, 1H, $J = 7.2$ Hz, OCH_2HO); 7.20–7.40 (m, 10H, H_{arom}); 9.89 (s, 1H, CHO). ^{13}C -NMR (CDCl_3): 9.7; 24.0; 55.9; 59.0; 67.3; 67.8; 71.6; 79.5; 95.0; 127.0, 128.2, 128.9; 139.9; 204.1.

(2S, 3R)-2-(N,N-Dibenzylamino)-1-(tert-butyltrimethylsilyloxy)-3-pentanol (10). To a solution of EtMgBr (2.4 mmol, 1.2 equiv.) in ether (5 mL) at 0°C was added dropwise a solution of aminoaldehyde **2** (767 mg, 2 mmol) in ether (3 mL). After stirring at this temperature for 1h, saturated NH_4Cl (10 mL) was added and the mixture was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. After flash chromatography (silica gel: hexane/ EtOAc : 15/1), the compound **10** was obtained as a colorless oil: 604 mg (73%). $[\alpha]_{\text{D}}^{23} = +52.8$ ($c = 1$, CHCl_3). IR (film): 3440 cm^{-1} . ^1H -NMR (CDCl_3): 0.12 and 0.13 (2s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.88 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 0.93 (s, 9H, $(\text{CH}_3)_3\text{C}$); 1.38 (m 1H, CHHCH_3); 1.83 (m, 1H, CHHCH_3); 2.68 (m, 1H, CHN); 3.03 (broad s, 1H, OH); 3.63 (d, 2H, $J = 13.7$ Hz, CHHPh); 3.82 (m, 1H, CHOH); 3.89 (d, 2H, $J = 13.7$ Hz, CHHPh); 4.03 (m, 2H, CH_2OTBDMS); 7.20–7.35 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): -5.7; -5.6; 10.0; 18.0; 25.8; 27.7; 55.2; 61.0; 61.2; 73.6; 126.9, 128.2, 128.7; 140.0.

(2S,3R)-2-(N,N-Dibenzylamino)-1-(tert-butyltrimethylsilyloxy)-3-[(2-methoxyethoxy)methoxy]-pentane (11).

The compound **11** was obtained from the aminoalcohol **10** (580 mg, 1.4 mmol) by the method described for **7**, and purified by flash chromatography (silicagel, $\text{CH}_2\text{Cl}_2/\text{hexane}$: 3/1): 660 mg (94%). $[\alpha]_{\text{D}}^{23} = +32.4$ ($c = 1.1$, CHCl_3). IR (film): 1100, 1040, 740, 700 cm^{-1} . ^1H -NMR (CDCl_3): 0.13 and 0.15 (2s, 6H, $(\text{CH}_3)_2\text{Si}$); 0.55 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 0.98 (s, 9H, $(\text{CH}_3)_3\text{C}$); 1.72 (m, 2H, CH_2CH_3); 2.80 (m, 1H, CHN); 3.38 (s, 3H, CH_3O); 3.52 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.62 (m, 1H, $\text{OCH}_2\text{CH}_2\text{HO}$); 3.70 (m, 1H, $\text{OCH}_2\text{CH}_2\text{HO}$); 3.73 (d, 2H, $J = 13.6$ Hz, CHHPh); 3.78 (m, 1H, CHOMEM); 3.89 (d, 2H, $J = 13.6$, CHHPh); 3.90 (m, 1H, CHHOTBDMS); 4.07 (dd, 1H, $J_1 = 10.7$ Hz, $J_2 = 3.0$ Hz, CHHOTBDMS); 4.69 (d, 1H, $J = 6.9$ Hz, OCH_2HO); 4.73 (d, 1H, $J = 6.9$ Hz, OCH_2HO); 7.20–7.40 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): -5.6; -5.5; 7.9; 18.1; 23.8; 26.0; 55.3; 58.8; 59.0; 59.9; 67.2; 71.7; 78.5; 95.7; 126.6; 128.0; 129.0; 140.4.

(2S,3R)-2-(N,N-Dibenzylamino)-3-[(2-methoxyethoxy)methoxy]-1-pentanol (12).

The aminoalcohol **12** was obtained from **11** (577 mg, 1.15 mmol) by the method described for **8** and purified by flash chromatography (silicagel, hexane/ EtOAc : 2/1): 414 mg (93%). $[\alpha]_{\text{D}}^{23} = -38.8$ ($c = 1.1$, CHCl_3). IR (film): 3420 cm^{-1} . ^1H -NMR (CDCl_3): 0.66 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 1.73 (m, 2H, CH_2CH_3); 2.76 (m, 1H, CHN); 3.12 (broad s, 1H, OH); 3.39 (s, 3H, CH_3O); 3.56 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.67 (m, 1H, $\text{OCH}_2\text{CH}_2\text{HO}$); 3.75 (s, 4H, CH_2Ph); 3.79 (m, 1H, $\text{OCH}_2\text{CH}_2\text{HO}$); 3.90 (m, 2H, CH_2OH); 4.01 (m, 1H, CHOMEM); 4.74 (d, 1H, $J = 6.9$ Hz, OCH_2HO); 4.82 (d, 1H, $J = 6.9$ Hz, OCH_2HO); 7.20–7.35 (m, 10H, H_{arom}). ^{13}C -NMR (CDCl_3): 8.2; 23.8; 54.4; 57.9; 58.9; 59.5; 67.6; 71.6; 77.4; 94.8; 126.9, 128.2, 128.9; 139.6.

(2R,3R)-2-(N,N-Dibenzylamino)-3-[(2-methoxyethoxy)methoxy]-1-pentanal (13).

The aminoaldehyde **13** was obtained from the aminoalcohol **12** (407 mg, 1.05 mmol) by Swern oxidation as described for compound **2**: 364 mg (90%). $[\alpha]_D^{23} = -18.8$ ($c = 1$, CHCl_3). IR (film): 1715 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.62 (t, 3H, $J = 7.4\text{ Hz}$, CH_3CH_2); 1.80 (m, 2H, CH_2CH_3); 3.21 (dd, 1H, $J_1 = 8.3\text{ Hz}$, $J_2 = 2.7\text{ Hz}$, CHN); 3.37 (s, 3H, CH_3O); 3.51 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.64 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.77 (d, 2H, $J = 13.6\text{ Hz}$, CHHPh); 3.96 (d, 2H, $J = 13.6\text{ Hz}$, CHHPh); 4.22 (m, 1H, CHOMEM); 4.67 (d, 1H, $J = 7.2\text{ Hz}$, OCHHO); 4.77 (d, 1H, $J = 7.2\text{ Hz}$, OCHHO); 7.20–7.40 (m, 10H, H_{arom}); 9.97 (d, 1H, $J = 2.7\text{ Hz}$, CHO). $^{13}\text{C-NMR}$ (CDCl_3): 7.4; 23.1; 54.9; 58.9; 65.9; 67.4; 71.5; 76.1; 94.5; 127.1; 128.2; 128.8; 138.9; 204.8.

(**3R**, **4S**, **5S**)-4-(*N,N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-3-heptanol (**14**). This aminoalcohol was obtained from the aminoaldehyde **9** (540 mg, 1.4 mmol) by the method described for compound **6**. The product **14** was purified by flash chromatography (silica gel, EtOAc/hexane: 1/5): 483 mg (83%). $[\alpha]_D^{23} = -45.1$ ($c = 1$, CHCl_3). IR (film): 3420 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.91 (t, 3H, $J = 7.3\text{ Hz}$, CH_3CH_2); 0.98 (t, 3H, $J = 7.3\text{ Hz}$, CH_3CH_2); 1.21 (m, 1H, CHHCH_3); 1.77 (m, 3H, CH_2CH_3 and CHHCH_3); 2.65 (dd, 1H, $J_1 = 9.2\text{ Hz}$, $J_2 = 2.4\text{ Hz}$, CHN); 3.41 (s, 3H, CH_3O); 3.56 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.68 (d, 2H, $J = 13.3\text{ Hz}$, CHHPh); 3.70 (m, 1H, CHOH); 3.80 (m, 3H, $\text{OCH}_2\text{CH}_2\text{O}$ and CHOMEM); 4.05 (d, 2H, $J = 13.3\text{ Hz}$, CHHPh); 4.72 (d, 1H, $J = 7.3\text{ Hz}$, OCHHO); 4.75 (d, 1H, $J = 7.3\text{ Hz}$, OCHHO); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 9.9; 10.8; 25.4; 27.0; 54.7; 58.9; 62.9; 67.5; 68.4; 71.6; 78.5; 94.7; 127.0; 128.3; 129.0; 139.4.

(**3R**, **4r**, **5S**)-4-(*N,N*-Dibenzylamino)-3,5-heptanediol (**15**). A mixture of the aminoalcohol **14** (457 mg, 1.1 mmol) and 2N HCl solution in THF- H_2O (15 mL) was stirred for 8 h at room temperature. The mixture was basified with saturated NaHCO_3 and extracted with ether (2 x 20 mL). The combined organic layers were washed with saturated NaCl, dried (Na_2SO_4), concentrated and chromatographed (EtOAc/hexane: 1/5) to yield **15** as a colorless solid: 317 mg (88%). M.p. $90\text{--}91^\circ\text{C}$ (from hexane-ethyl acetate). IR (film): 3320 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.98 (t, 6H, $J = 7.3\text{ Hz}$, CH_3); 1.45 (m, 2H, CHHCH_3); 1.69 (m, 2H, CHHCH_3); 2.54 (t, 1H, $J = 6.4\text{ Hz}$, CHN); 2.99 (broad s, 2H, OH); 3.81 (m, 2H, CHOH); 3.98 (s, 4H, CH_2Ph); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 10.4; 28.1; 55.3; 64.9; 71.8; 127.1; 128.4; 129.2; 139.5. Anal. Calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.15; H, 8.76; N, 4.02.

meso-(**3R**, **4r**, **5S**)-4-Amino-3,5-heptanediol (*meso*-**1a**). To a solution of *N,N*-dibenzylaminoalcohol **15** (164 mg, 0.5 mmol) in 5 mL of anhydrous methanol was added 40 mg of 20% $\text{Pd}(\text{OH})_2\text{-C}$ in one portion. The mixture was stirred under 1 hydrogen atmosphere and the reaction was monitored by TLC. After 2 h the reaction was completed, the catalyst was removed by filtration through celite and washed with 20 mL of methanol. The solvent was concentrated under reduced pressure to afford the compound **1a** as pure colorless oil: 72 mg (98%). IR (film): 3400 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.95 (t, 6H, $J = 7.4\text{ Hz}$, CH_3); 1.53 (m, 4H, CH_2); 2.60 (t, 1H, CHN); 3.41 (broad s, 4H, NH_2 and OH); 3.58 (m, 2H, CHOH). $^{13}\text{C-NMR}$ (CDCl_3): 10.0; 27.0; 56.5; 74.1.

(**3S**, **4S**, **5S**)-4-(*N,N*-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-3-heptanol (**16**). To a solution of EtMgBr (1.32 mmol, 1.2 equiv) in ether (2 mL) at 0°C was added dropwise a solution of aminoaldehyde **9** (423 mg, 1.1 mmol) in ether (2 mL). After stirring at this temperature for 2 h, saturated NH_4Cl (5 mL) was added and the mixture was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent evaporated under vacuum. The mixture of diastereomers **16:14** (7:3 by $^1\text{H-NMR}$) was purified by flash chromatography (silicagel, hexane/ Et_2O : 3/2), to give **16** as a colorless oil: 260 mg (57%). $[\alpha]_D^{23} = +13.2$ ($c = 1$, CHCl_3). IR (film): 3460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.55 (t, 3H, $J = 7.4\text{ Hz}$, CH_3CH_2); 1.00 (t, 3H, $J = 7.3\text{ Hz}$, CH_3CH_2); 1.48 (m, 1H, CHHCH_3);

1.63 (m, 1H, CHHCH_3); 1.75 (m, 2H, CH_2CH_3); 2.61 (dd, 1H, $J_1 = 7.0$ Hz, $J_2 = 3.4$ Hz, CHN); 3.39 (s, 3H, CH_3O); 3.55 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.63 (m, 1H, OCH_2CHHO); 3.75 (d, 2H, $J = 13.4$ Hz, CHHPh); 3.81 (m, 1H, OCH_2CHHO); 3.88 (m, 1H, CHOH); 3.96 (m, 1H, CHOMEM); 4.03 (d, 2H, $J = 13.4$ Hz, CHHPh); 4.71 (d, 1H, $J = 7.0$ Hz, OCHHO); 4.75 (d, 1H, $J = 7.0$ Hz, OCHHO); 7.20–7.35 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 9.8; 10.8; 24.2; 28.3; 56.1; 58.9; 60.9; 67.6; 70.8; 71.5; 81.5; 95.2; 126.7; 128.0; 129.3; 140.5.

(3S, 5S)-4-(N,N-Dibenzylamino)-3,5-heptanediol (17). The compound **17** was obtained from the aminoalcohol **16** (208 mg, 0.5 mmol) by the method described for compound **15** and purified by flash chromatography (silica gel, EtOAc/hexane: 1/5): 142 mg (87%). $[\alpha]_{\text{D}}^{23} = +27.2$ ($c = 1.1$, CHCl_3). IR (film): 3400 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.87 (t, 3H, $J = 7.4$ Hz, CH_3); 0.96 (t, 3H, $J = 7.3$ Hz, CH_3); 1.35–1.75 (m, 4H, CH_2); 2.25 (broad s, 2H, OH); 2.48 (dd, 1H, $J_1 = 6.8$ Hz, $J_2 = 2.2$ Hz, CHN); 3.54 (d, 2H, $J = 13.5$ Hz, CHHPh); 3.95 (m, 1H, CHOH); 4.02 (m, 1H, CHOH); 4.09 (d, 2H, $J = 13.5$ Hz, CHHPh); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 10.1; 10.8; 27.3; 30.0; 55.2; 63.0; 70.7; 70.9; 127.0; 128.3; 129.0; 139.5.

(3S, 5S)-4-Amino-3,5-heptanediol (1c). The aminoalcohol **1c** (130 mg, 0.40 mmol) was obtained by debenzilation of **17** as described for **1a**: 58 mg (98%). $[\alpha]_{\text{D}}^{23} = -13.2$ ($c = 0.9$, CHCl_3). IR (film): 3280 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.97 (t, 3H, $J = 7.4$ Hz, CH_3); 1.0 (t, 3H, $J = 7.4$ Hz, CH_3); 1.55 (t, 4H, CH_2); 2.87 (m, 1H, CHN); 3.80 (m, 2H, CHOH); 4.42 (broad s, 4H, NH_2 and OH). $^{13}\text{C-NMR}$ (CDCl_3): 10.1; 10.5; 26.1; 26.9; 56.8; 71.0; 74.7.

(3S, 4S, 5R)-4-(N,N-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-3-heptanol (18). The compound **18** was obtained from the aminoaldehyde **13** (289 mg, 0.75 mmol) by reaction with EtMgBr as described for compound **10**. The product was purified by flash chromatography (silicagel, hexane/ether: 4/1): 255 mg (82%). Colorless oil. $[\alpha]_{\text{D}}^{23} = -32.6$ ($c = 1.3$, CHCl_3). IR (film): 3460 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.66 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 0.97 (t, 3H, $J = 7.4$ Hz, CH_3CH_2); 1.57 (m, 1H, CHHCH_3); 1.78 (m, 3H, CH_2CH_3 and CHHCH_3); 2.61 (m, 1H, CHN); 3.38 (s, 3H, CH_3O); 3.55 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.69 (m, 4H, CH_2Ph); 3.74 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.95 (m, 1H, CHOH); 4.05 (m, 1H, CHOMEM); 4.81 (d, 1H, $J = 6.7$ Hz, OCHHO); 4.85 (d, 1H, $J = 6.7$ Hz, OCHHO); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 8.7; 10.6; 25.3; 29.2; 54.8; 59.0; 61.4; 68.0; 71.6; 71.7; 78.5; 95.3; 126.8; 128.1; 128.9; 139.8.

(3S, 4s, 5R)-4-(N,N-Dibenzylamino)-3,5-heptanediol (19). The compound **19** was obtained from **18** (166 mg, 0.4 mmol) by the method described for compound **15** and purified by flash chromatography (silicagel, hexane/ EtOAc: 5/1): 113 mg (86%). M.p. $76\text{--}77^\circ\text{C}$ (from hexane). IR (film): 3440 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.92 (t, 6H, $J = 7.4$ Hz, CH_3CH_2); 1.49 (m, 2H, CHHCH_3); 1.80 (m, 2H, CHHCH_3); 2.40 (broad s, 2H, OH); 2.49 (t, 1H, $J = 5.3$ Hz, CHN); 3.71 (s, 4H, CH_2Ph); 3.98 (m, 2H, CHOH); 7.20–7.40 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 10.1; 29.6; 54.9; 63.5; 72.2; 126.8; 128.1; 128.9; 139.8. Anal. Calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 77.16; H, 8.75; N, 4.42.

meso-(3S, 4s, 5R)-4-Amino-3,5-heptanediol (meso-1b). The aminoalcohol **19** (91 mg, 0.28 mmol) was debenzylated by hydrogenolysis as described for compound **15** to afford **1b**: 41 mg (99%). IR (film): 3300 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.99 (t, 6H, $J = 7.4$ Hz, CH_3CH_2); 1.44 (m, 2H, CHHCH_3); 1.69 (m, 2H, CHHCH_3); 2.80 (t, 1H, $J = 5.9$ Hz, CHN); 3.06 (broad s, 4H, OH and NH_2); 3.60 (ddd, 2H, $J_1 = 9.1$ Hz, $J_2 = 5.9$ Hz, $J_3 = 2.8$ Hz, CHOH). $^{13}\text{C-NMR}$ (CDCl_3): 10.2; 25.9; 58.8; 74.3.

(3R, 4S, 5R)-4-(N,N-Dibenzylamino)-5-[(2-methoxyethoxy)methoxy]-3-heptanol (20). The compound **20** was obtained as the minor diastereomer in the reaction of aminoaldehyde **13** (359 mg, 0.93 mmol) with Et_2Zn 1M in hexane (1.86 mL, 1.86 mmol, 2 equiv.) at 0°C and purified by flash chromatography

(silicagel, hexane/ether: 4/1): 131 mg (34%). $[\alpha]_D^{23} = -40.5$ ($c = 1$, CHCl_3). IR (film): 3480 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 0.86 (t, 3H, $J = 7.4\text{ Hz}$, CH_3CH_2); 0.93 (t, 3H, $J = 7.4\text{ Hz}$, CH_3CH_2); 1.41 (m, 1H, CHHCH_3); 1.60 (m, 1H, CHHCH_3); 1.72 (m, 1H, CHHCH_3); 1.82 (m, 1H, CHHCH_3); 2.53 (dd, 1H, $J_1 = 7.0\text{ Hz}$, $J_2 = 2.3\text{ Hz}$, CHN); 3.39 (s, 3H, CH_3O); 3.50 (d, 2H, $J = 13.5\text{ Hz}$, CHHPh); 3.55 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.75 (m, 2H, $\text{OCH}_2\text{CH}_2\text{O}$); 3.97 (m, 2H, CHOH and CHOMEM); 4.08 (d, 2H, $J = 13.5\text{ Hz}$, CHHPh); 4.83 (d, 1H, $J = 7.1\text{ Hz}$, OCHHO); 4.89 (d, 1H, $J = 7.1\text{ Hz}$, OCHHO); 7.20–7.35 (m, 10H, H_{arom}). $^{13}\text{C-NMR}$ (CDCl_3): 10.4; 10.6; 26.7; 27.1; 54.5; 59.0; 62.4; 67.8; 69.8; 71.6; 76.6; 95.3; 127.0; 128.3; 129.0; 139.3.

(3R, 5R)-4-(N,N-Dibenzylamino)-3,5-heptanediol (ent-17). The aminoalcohol *ent-17* was obtained from compound **20** (125 mg, 0.3 mmol) by the method described for **15** and purified by flash chromatography (silicagel, hexane/ EtOAc: 5/1): 91 mg (93%). $[\alpha]_D^{23} = -28.4$ ($c = 1.1$, CHCl_3).

(3R, 5R)-4-Amino-3,5-heptanediol (ent-1c). This compound (75 mg, 0.23 mmol) was obtained by debenzilation of *ent-17* as described for **1a**: 30 mg (90%). $[\alpha]_D^{23} = +13.9$ ($c = 0.5$, CHCl_3).

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