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Stereoselective synthesis of optically active mono and diaminoalcohols

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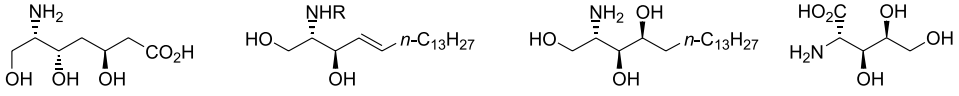
Abstract—Several optically active mono and diaminopolyols have been synthesized starting from the octadienedioate **1**, by regio- and stereo selective azidation of the corresponding alcohol by Mitsunobu/S_N2 substitution.

1. Introduction

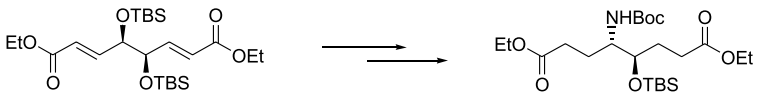
Chiral amino polyols are constituents of several compounds and are of major importance as partial structures of biologically active compounds covering a wide range of biological activities from antibiotic to immunosuppressive properties. For example, (Fig. 1) D-*erythro*-sphingosine and ceramides[1c–e] have been shown to exhibit potent inhibitory activity against protein kinase C. Polyhydroxylated amino acids, like galantinic acid[2] and polyoxamic acid,[3] are components of important biologically active substances such as the complex peptide antibiotic galantin I, which exhibits powerful antibacterial properties and polyoxins (antifungal antibiotics).

Within the scope of our studies on the potential of diversely substituted octadienedioates such as **1** derived from D-mannitol, as building blocks[4a] for the synthesis of polyhydroxylated amino acids and alkaloids,[4b] we have explored a versatile route to functionalised chiral mono and



Galantinic acid | D-*erythro*-sphingosine; R=H ceramide: R=$CO(CH_2)_{14\text{-}22}Me$ | L-Lyxo-sphingosine | Polyoxamic acid

Figure 1.



1 **2**

Scheme 1.

Keywords: Aminoalcohols; Stereoselective; Optically active.
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diamino polyols. Herein, we describe the synthesis of new chiral protected amino alcohols in a highly enantio- and diastereoselective fashion.

We have previously reported[4b] the preparation of the amino diester **2** in five steps starting from the protected diene dioate **1** (Scheme 1). We wished to test the scope of this approach to aminoalcohols and to prepare some diamino-alcohols stereo-and regioselectively.

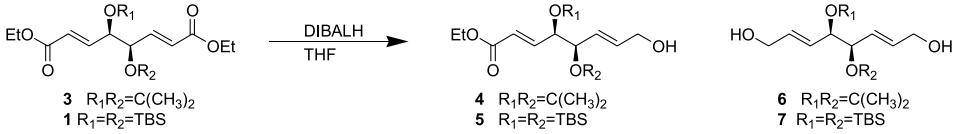
2. Results and discussion

We envisaged the preparation of analogous derivatives where one or both of the ester groups would be reduced to an alcohol. The reduction of the ester groups on the *O*-isopropylidene protected diol dienedioate **3** with DIBALH (*x* equiv) in THF (Scheme 2) afforded the desired allylic mono and diol **4** and **6** in 48 and 32% yield, respectively. The monoreduced compound **4**, obtained as a by-product during the reduction of the 2 ester groups could be prepared up to 50% yield by quenching the reaction after 15 min. However, the lability of the *O*-isopropylidene protecting group prohibited an acidic work-up, making tedious the extraction of the final product. Disilylated analogue **1** (Scheme 2) undergoes the same reactions but the product is more stable to acid and subsequent functionalisations of the double bonds of **5** and **7** were more diastereoselective. By adjusting the experimental conditions (time, temperature and stoechiometry of DIBALH used (see Table 1) it was possible to obtain the monoreduced compound **5** in moderate yield, while the tetrol **7** could be obtained in excellent yield (Table 1).

The selective monoazidation (Scheme 3) of **7** under Mitsunobu conditions using 1.2 equiv of reagents led to the mono azide **8** and the diazide **9** that were readily isolated by chromatography, respectively, in 52 and 19% yield. The two silyl ether groups could be removed by treatment with TBAF in THF. The resulting highly polar triol **10** was benzoylated (**11**, 87%) in order to characterise it. Tosylation with *p*-toluenesulfonic anhydride of all three hydroxyls of **10** was equally achieved in good yield (86%) to give the rather unstable azide **12**.

Finally the *N*-Boc protected amino alcohol **13** was obtained in 56% yield from **8** by the two-step sequence catalytic hydrogenation/N-protection (Scheme 4).

By using 3 equiv of reagent, the diazidation of **7** was achieved in 78% yield (Scheme 5) and following the same sequence as for **8**, the protected bisamine was obtained in good yield. The deprotection of the hydroxyl functions on **14** with TBAF in THF cleanly afforded the diamino diol **15**.

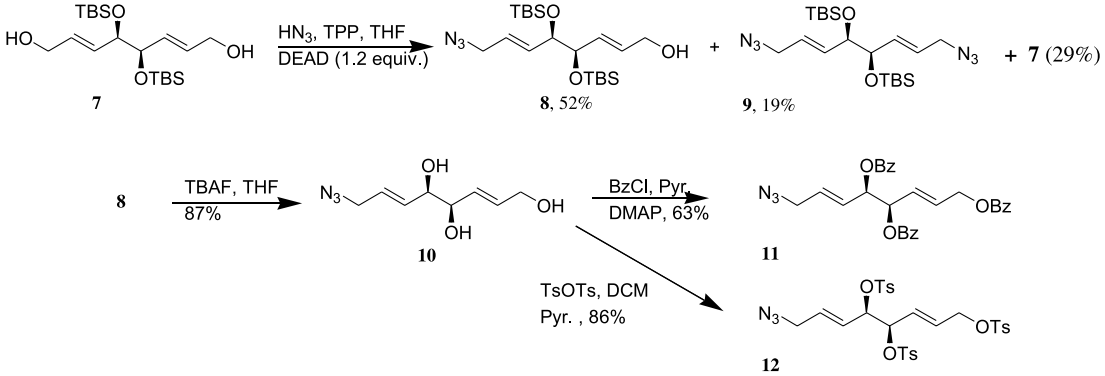


Scheme 2.

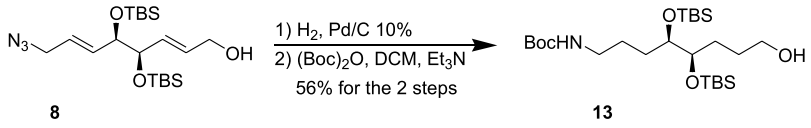
Table 1. DIBAL reduction of diesters **1** and **3**

Experiment[a]	Equiv of DIBALH	Reaction time (min)	% **1** recovered	% **5**	% **5** from unreacted **1**	% **7**
1	2.5	10	72	19	69	2
2	2.5	75	67	13	39	4.6
3	2.5	130	57	25	58	16
4	5.0	45	30	30	47	40
5[b]	5.5	315	0	12	12	66
6[b] (−50 °C)	6.0	60	0	0	0	97

[a] At −78 °C except where indicated.
[b] Acidic work-up.

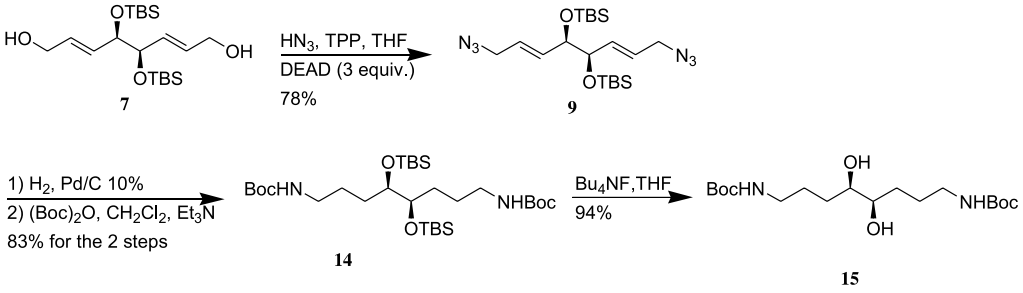


Scheme 3.



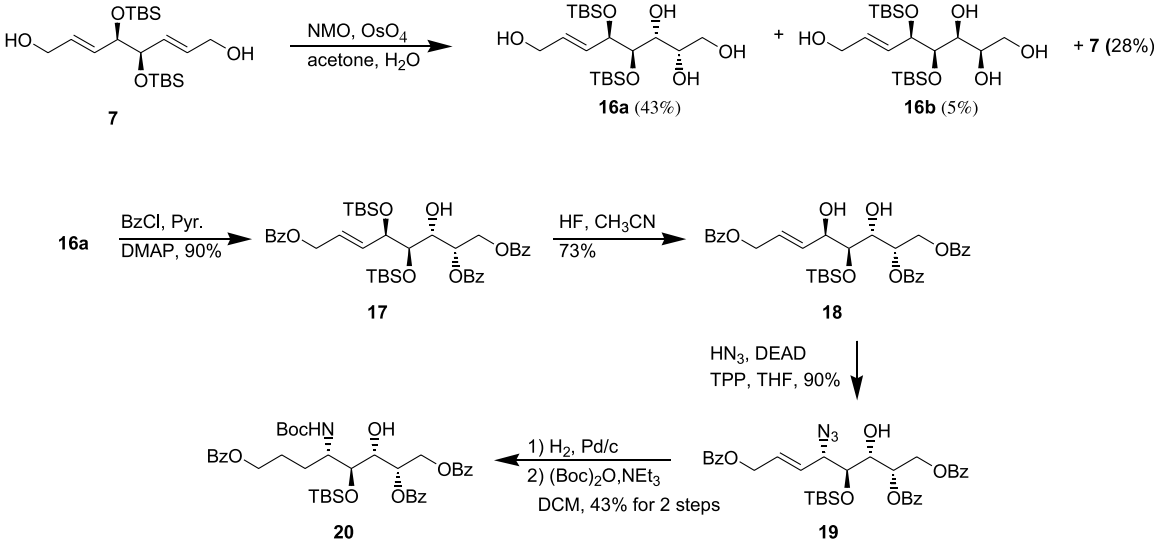
8 13

Scheme 4.



7 9 14 15

Scheme 5.

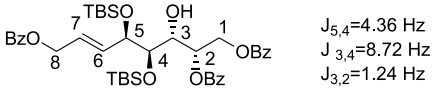


7 16a (43%) 16b (5%) 17 18 20 19

Scheme 6.

We then turned to the preparation of more highly oxygenated compounds (Scheme 6).

The dihydroxylation of one of the two C=C double bond on **7** was performed as described for the dienedioate **1**.[4a] The reaction was stopped before completion as we started to observe dihydroxylation of the second double bond. A slightly lower diastereoselectivity than for **1**[4a] was observed and an easily separable mixture of the diastereoisomers **16a** (majoritary) and **16b** as well as traces of the octitol **16c** was obtained. The stereochemistry of the thus two newly created stereocenters on **16a** was acertained after partial protection of its four free hydroxyl functions: **16a** was selectively benzoylated by treatment with benzoyl chloride in pyridine at rt in the presence of catalytic DMAP, affording tribenzoate **17**.



Scheme 7.

The complete attribution of the signal of the ^{1}H NMR spectrum of **17** was achieved by 2D (Scheme 7 for numbering) was confirmed by the large coupling constant $J_{3,4}=8.72$ Hz while the *syn* relationship between H-5 and H-4 on one hand, H-3 and H-2 on the other hand, was proved by the smaller coupling constants $J_{5,4}=4.36$ Hz, $J_{3,2}=1.24$ Hz, respectively. The silyl protected allylic secondary alcohol on **17** was selectively liberated in good yield by treatment with HF, giving **18**. An azido group was selectively introduced at this allylic position in 90% yield by Mitsunobu reaction. The inversion of configuration on C-5 bearing the azido group was attested by the coupling constants $J_{4,5}=J_{4,3}=5.60$ Hz in the NMR signal of H-4 that appears as a double triplet. The resulting azido compound **19** was lightly contaminated by an unidentified rearrangement product. The two steps sequence hydrogenation/N-protection on **19** led to the expected amino polyol **20** in moderate yield.

3. Conclusions

A concise stereo selective route has been developed for the

synthesis of optically active polyhydroxy amino alcohols and diamino alcohols from the readily available D-mannitol. They are promising key intermediates in the synthesis of attractive and potent biological units and for the synthesis of new unnatural amino-acids; that work being in course in our laboratory.

4. Experimental

4.1. General

Melting points were determined on a Büchi 530 apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 7000 FTIR spectrometer. Optical rotations were recorded at 20 °C on an Optical activity AA 1000 polarimeter using a 0.5 dm cell. Concentrations are given in g/100 ml. NMR spectra (^{1}H: 400 MHz; ^{13}C: 100 MHz) were recorded on a Brüker ARX 400 spectrometer in $CDCl_3$ using Me_4Si (^{1}H) and the solvent peak (^{13}C) at δ 77.0 ppm as an internal reference. Chemical shifts are expressed in parts per million downfield. Medium pressure column chromatography were performed on MN Silica gel 60M. Preparative thin-layer chromatography was performed on MN Silica gel G/UV 254 with fluorescent indicator. Elemental analysis were performed by the Micro analytical Laboratory, operated by the Department of Analysis at Instituto Superior Técnico (Lisbon, Portugal).

4.1.1. (4*R*,5*R*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-8-hydroxy-octa-2(*E*),6(*E*)-dienoic acid ethyl ester, 5. Compound **1** (1.550 g, 3.18 mmol) was dissolved under argon in 20 ml of dry THF. DIBALH (8 ml of 1 M sol. in THF, 2.5 equiv) was added at −78 °C and the mixture was stirred for 2 h. A saturated solution of NH_4Cl (25 ml) was then added and the mixture was stirred for 20 min and allowed to reach rt. The crude product was dissolved in AcOEt, filtered and the gel was washed with AcOEt. The organic layer was separated and dried with Na_2SO_4, evaporated and the crude product separated by flash column chromatography (Hex/AcOEt 4:1 then 3:2) to give 0.358 g (25%) of **5**, 0.876 g (57%) of unreacted **1** and 0.207 g (16%) of the di reduced compound **7**. Compound **5**: $[\alpha]_D$ +68.05 (*c* 1.55, $CHCl_3$); IR (neat, cm^{-1}, ν): 3330 (OH); 1722 (C=O); ^{1}H NMR: 7.00 (dd, 1H, J=15.6, 3.6 Hz, H-3); 5.94 (dd, 1H, J=15.6, 1.6 Hz, H-2); 5.78 (dtd, 1H, J=15.6, 4.8, 4.8, 0.8 Hz, H-7); 5.63 (dd, 1H, J=15.6, 4.8 Hz, H-6); 4.29 (m, 1H J=2.0, 3.2, 3.6, 1.6 Hz, H-4); 4.20–4.13 (m, 3H, O*C*H_2CH$_3$, H-5); 4.08 (d, 2H, H-8,8′); 1.81 (sl, 1H, OH); 1.27 (t, 3H, OCH$_2$C*H*$_3$); 0.07, 0.06, 0.04, 0.036 (4s, 12H, SiCH$_3$); ^{13}C NMR: 166.6 (C-1); 147.5 (C-3), 131.2 (C-6); 129.7 (C-7); 121.4 (C-2); 75.0 (C-4); 74.8 (C-5); 63.1 (C-8); 60.3 (O–*C*H$_2$CH$_3$); 25.8 (*t*Bu); 18.2 (*t*Bu quat.); 14.3 (OCH$_2$*C*H$_3$); −4.5, −4.8, −4.8, SiCH$_3$. Anal. Calcd for $C_{22}H_{44}O_5Si_2$: C, 59.41; H, 9.97. Found: C, 59.60; H, 10.29. Compound **7**: mp 58–60 °C. $[\alpha]_D$ +79.44 (*c* 0.79, $CHCl_3$); IR (KBr, cm^{-1}, ν): 3330 (OH); ^{1}H NMR: 6.97 (m, 2H, J= 15.6 Hz, H-3, H-6); 5.97 (d, 2H, J=15.6 Hz, H-2, H-7); 4.37 (m, 2H, H-4, H-5); 4.25–4.12 (m, 4H, O*C*H_2CH$_3$); 1.31–1.26 (m, 6H, OCH$_2$C*H*$_3$); 0.94 (s, 18H, *t*Bu); 0.10 (s, 6H, Si(CH$_3$)$_2$); 0.08 (s 6H, Si(CH$_3$)$_2$)); ^{13}C NMR: 130.9 (C-3, C-6), 130.1 (C-2, C-7); 75.2 (C-4, C-5); 63.1 (C-1, C-8); 25.9 (*t*Bu); 18.2 (*t*Bu quat.); −4.5, −4.7 (SiMe). Anal. Calcd for $C_{20}H_{42}O_4Si_2$: C, 59.65; H, 10.51. Found: C, 59.20; H, 10.38.

4.1.2. 3-[(4*R*,5*R*)-5-(3-Hydroxy-1-(*E*)-propen-1-yl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-2-(*E*)-acrylic acid ethyl ester, 4 and 3-[(4*R*,5*R*)-5-(3-hydroxy-1-(*E*)-propen-1-yl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-prop-2-(*E*)-en-1-ol, 6. To a solution of **3** (0.513 g, 1,7 mmol) in dry THF (5 ml) under argon was added 8.59 ml of 1 M solution of DIBALH in THF at −78 °C. After stirring for 0.5 h, the reaction was quenched with 10 ml of a saturated solution of NH_4Cl and allowed to stir for 20 min. After filtration and extraction of the gel with ethyl acetate, the combined organic phase was dried on Na_2SO_4 and evaporated. Purification by preparative TLC of the crude product offered 0.058 g (11%) of unreacted **3**, 0.186 g (48%) of the monoreduced product **4** and 0.106 g (32%) of the desired **6**. Compound **4**; ^{1}H NMR: 6.75 (ddd, 1H, $J_{5,6}$=15.56 Hz, $J_{3,2}$=15.64 Hz, $J_{3,4}$= 5.20 Hz, H-3); 6.02 (dd, 1H, $J_{2,3}$=15.64 Hz, $J_{2,4}$= 0.84 Hz, H-2); 5.89 (dt, 1H, $J_{7,6}$=15.56 Hz, $J_{7,8}$= 4.64 Hz, H-2″); 5.63 (dd, 1H, $J_{6,7}$=15.56 Hz, $J_{6,5}$= 7.36 Hz, H-1″); 4.20–4.00 (m, 6H, O*C*H_2CH$_3$, H-3″, H-3″, H-4′, H-5′); 2.98 (sl, 1H, OH); 1.35 (s, 3H, Me); 1.34 (s, 3H, Me); 1.20 (t, 3H, O–CH$_2$C*H*$_3$); ^{13}C NMR: 165.9 (C-1); 142.7 (C-3); 135.3 (C-1″); 125.3 (C-2″); 122.6 (C-2); 109.7 (quat., C-2′); 81.4 (C-4′); 79.8 (C-5′); 61.9 (C-3″); 60.5 (O–*C*H$_2$CH$_3$); 26.8, 26.6 (2CH$_3$); 14.07 (OCH$_2$*C*H$_3$). Compound **6**: $[\alpha]_D$ −13.66 (*c* 0.41, $CHCl_3$); IR (neat, cm^{-1}, ν): 3401 (OH); ^{1}H NMR: 5.89 (dt, 2H, $J_{5,6}$= 15.60 Hz, J=15.60 Hz, J=5.00 Hz, H-2, H-2″); 5.62 (m, 2H, J=15.60 Hz, J=3.24 Hz, H-3, H-1″); 4.08 (m, 6H, H-1, H-1, H-3″, H-3″, H-4′, H-5′); 3.31 (s, 2H, OH); 1.40 (s, 6H, 2CH$_3$); ^{13}C NMR: 134.5 (C-3, C-1″); 126.2 (C-2, C-2″); 109.1 (quat., C-2′); 81.4 (C-4′, C-5′); 62.2 (C-1, C-3″); 27.0 (2Me). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.73; H, 8.59.

4.1.3. (4*R*,5*R*)-4,5-Bis(*tert*-butyldimethylsilanyloxy)-octa-2-(*E*),6-(*E*)-diene-1,8-diol, 7. To a solution of **1** (1.206 g, 2.48 mmol) in dry THF (8 ml) at −78 °C was added 14.75 ml (6 equiv) of a 1 M solution of DIBALH in THF. The temperature was allowed to reach −50 °C and the mixture was stirred for 2 h (TLC Hex/EtOAc 1:4). The reaction was quenched with 30 ml of a saturated solution of NH_4Cl and stirred for 20 min. The mixture was diluted with AcOEt and carefully brought to pH=6 by addition of 1 N HCl until dissolution of the gel and clear separation of the 2 phases. The aqueous phase was extracted with AcOEt (5× 50 ml), The combined organic phase were dried on Na_2SO_4. Evaporation of the solvent gave 1.052 g of crude product that was purified by flash chromatography (Hex/EtOAc 1:4) to give 0.997 g (97%) of **7** (see above for characterization).

4.1.4. (4*R*,5*R*)-8-Azido-4,5-bis-(*tert*-butyldimethylsilanyloxy)-octa-2-(*E*),6-(*E*)-dien-1-ol, 8. To 0.281 g (0.70 mmol) of **7** dissolved in 12 ml of dry THF was added triphenylphosphine (TPP) (0.220 g, 1.2 equiv). The mixture was stirred for 20 min then HN_3 (0.655 ml of a 1.28 M solution in benzene, 1.2 equiv) was added, followed by DEAD (0.182 g in 1.5 ml of THF, dropwise). The mixture was stirred at rt for 1 h. The solvent was evaporated; the crude product was taken first in CH_2Cl_2 then AcOEt/ Hexane 1:7, filtered and the filtrate evaporated and purified

by flash chromatography to give successively 0.059 g (19%) of **9**, 0.156 g (52, 74% from reacted **7**) of **8** and 0.085 g (29%) of unreacted **7**. Compound **8**: $[\alpha]_D$ +68.4 (*c* 0.614, $CHCl_3$); IR (neat, cm^{-1}, ν): 3350, 2099; ^1H NMR: 5.85–5.65 (m, 4H, H-2,3,6,7); 4.19–4.12 (m, 4H, H-4, H-5, H-1,1′); 3.73 (AB part of ABX system, $J_{1,1'}=13.60$ Hz); 1.58 (sl, 1H, OH); 0.92 (s, 18H, *t*Bu); 0.84, 0.08, 0.06, 0.06 (s, 3H each, $SiCH_3$); ^{13}C NMR: 135.12 (C-3), 130.64 (C-6), 130.08 (C-7), 123.68 (C-2), 74.91, 74.81 (C-4, C-5), 63.35 (C-1), 52.54 (C-8), 25.90 (*t*Bu), 18.22 (*t*Bu quat.), −4.52, −4.64, −4.76 ($SiCH_3$). Compound **9**; IR (neat, cm^{-1}, ν): 2104 (N_3); ^1H NMR: 5.81 (dd, 2H, $J=15.60$, 1.60 Hz, H-3, H-6); 5.71 (td, 2H, $J=15.60$, 6.40 Hz, H-2, H-7); 4.20 (sl, 2H, H-4, H-5); 3.73 (m, 4H, H-1, H-1′, H-8, H-8′); 0.93 (s, 18H, *t*Bu); 0.10 (s, 6H, $SiCH_3$); 0.07 (s, 6H, $SiCH_3$); ^{13}C NMR: 134.5 (C-3, C-6), 124.2 (C-2, C-7), 74.6 (C-4, C-5), 52.5 (C-1, C-8), 25.9 (*t*Bu), 18.2 (*t*Bu quat.), −4.6, −4.8 ($SiCH_3$).

4.1.5. (4*R*,5*R*)-1,8-Diazido-4,5-bis-(*tert*-butyldimethylsilanyloxy)-octa-2-(*E*),6-(*E*)-diene, 9. To 0.205 g (0.5 mmol) of **7** dissolved in 10 ml of dry THF were added 0.400 g (3 equiv) of TPP. The mixture was stirred for 20 min then 1 ml of a 1.58 M solution of HN_3 in benzene was added, followed by DEAD (0.265 g, 3 equiv in 2 ml of THF, dropwise). Stirring was continued for 1.25 h. The solvent was evaporated and the crude product purified by medium pressure column chromatography (Hex/AcOEt 9:1) to yield 0.179 g (78%) of **9** as a colourless oil that was used immediately for the next step (see upper for characterisation).

4.1.6. (4*R*,5*R*)-8-Azido-octa-2-(*E*),6-(*E*)-diene-1,4,5-triol, 10. The azide **8** (0.088 g, 0.21 mmol) in 4 ml of anhydrous THF was stirred at rt for 45 min with 0.412 ml (2 equiv) of a 1 M solution of Bu_4NF in THF. Evaporation of the solvent followed by flash chromatography (AcOEt) gave **10** (0.034 g, 82%) as a viscous syrup. The product has been characterized as its tribenzoate.

4.1.7. (4*R*,5*R*)-8-Azido-1,4,5-tribenzoyloxy-octa-2-(*E*),6-(*E*)-diene, 11. Compound **10** (0.042 g, 0.21 mmol) was dissolved in 1.5 ml of pyridine. BzCl (0.141 g, 4.5 equiv) and a catalytic amount of DMAP were added The mixture was stirred for 0.5 h at rt and the reaction was quenched with 8 ml of a saturated sol. of $NaHCO_3$. The product was extracted with DCM (3×15 ml) and the organic phase was dried on Na_2SO_4. The crude was purified by preparative TLC (Hex/AcOEt 7:1) to give 0.068 g of **11** as an oil. $[\alpha]_D$ +29.3 (*c* 1.37, $CHCl_3$); IR (neat, cm^{-1}, ν): 2102 (N_3), 1723 (C═O); ^1H NMR: 8.15–7.98 (m, 6H, arom.); 7.62–7.34 (m, 9H, arom.); 6.18 (dt, 1H, $J=5.60$, 5.60, 14.96 Hz, H-2); 6.06–5.87 (m, 5H, H-3, H-4, H-5, H-6, H-7); 4.85 (d, 2H, $J=5.60$ Hz, H-1, H-1′); 3.78 (d, 2H, $J=5.60$ Hz, H-8, H-8′); ^{13}C NMR: 166.1, 165.7 (C═O), 133.7, 133.3, 133.1, 130.2, 129.9, 129.7, 129.7, 129.7, 129.0, 128.5, 128.4, 128.3, 127.4 (C-2, C-3, C-6, C-7, arom.); 73.9 (C-4, C-5); 64.0 (C-1); 51.8 (C-8).

4.1.8. (4*R*,5*R*)-8-Azido-1,4,5-tri-*O*-tosyl-octa-2-(*E*),6-(*E*)-diene, 12. 0.055 g (0.28 mmol) of **10** were dissolved in 3 ml of dry DCM. TsOTs (0.543 g, 6 equiv) and pyridine (0.135 ml, 6 equiv) were added at 0 °C. The mixture was stirred for 30 min at rt then HCl 1 N (2 ml) was added. The organic phase was decanted and the aqueous phase extracted with CH_2Cl_2. The combined organic phase were washed with saturated $NaHCO_3$, dried on Na_2SO_4. The crude product (0.254 g) was purified by preparative TLC (Hex/AcOEt 6:4) to yield 0.158 g (86%) of **12**. $[\alpha]_D$ +3.3 (*c* 0.484, $CHCl_3$); IR (neat, cm^{-1}, ν): 2104 (N_3); 1364, 1176 (OTs); ^1H NMR: 7.76–7.67 (m, 6H, arom. tosyl); 7.38–7.29 (m, 6H, arom. tosyl); 5.69–5.60 (m, 2H, H-2, H-7); 5.57–5.46 (m, 2H, $J=15.40$, 6.28 Hz, H-3, H-6); 4.94 (m, 2H, H-4, H-5); 4.34 (d, 2H, $J=5.12$ Hz, H-1, H-1′); 3.64 (d, 2H, $J=5.40$ Hz, H-8, H-8′); 2.46 (s, 9H, Me); ^{13}C NMR: 145.5, 145.5, 145.2 (quat. tosyl); 133.3, 133.24 (quat. tosyl); 131.1, 129.5, 126.3, 125.3 (C-2, C-3, C-6, C-7); 130.0, 128.1, 128.0 (arom. tosyl); 79.6, 79.3 (C-4, C-5); 68.5 (C-1); 51.5 (C-8); 21.8 (Me Tosyl).

4.1.9. (4*R*,5*R*)[4,5-Bis-(*tert*-butyl-dimethylsilanyloxy)-8-hydroxy-octyl]-carbamic acid *tert*-butyl ester, 13. 0.131 g (0.30 mmol) of **8** were dissolved in 6 ml of absolute ethanol and submitted to a pressure of 15 psi of hydrogen in the presence of 32 mg of Pd/C 10% for 45 min, then 50 psi for more 2.25 h. The catalyst was filtered off and washed with EtOH then AcOEt; the solvent was evaporated in vacuo to yield 0.132 g of crude product that was dissolved in 5 ml of dry DCM. $(Boc)_2O$ (0.080 g, 2.2 equiv) was added at rt and the mixture was stirred for 1 h. The reaction was quenched with HCl 1 N (12 ml); the organic phase was decanted, washed successively with saturated $NaHCO_3$ then water, dried on Na_2SO_4 and the solvent was evaporated in vacuo. Purification by medium pressure column chromatography (Hex/AcOEt 5:1) yielded 0.087 g (56%) of **13** as a viscous oil. $[\alpha]_D$ +34.54 (*c* 1.60, $CHCl_3$); IR (neat, cm^{-1}, ν): 3356 (OH); 1694 (C═O); ^1H NMR: 4.54 (br s, 1H, NH); 3.60 (m, 2H, H-4, H-5); 3.52 (m, 2H, H-8, H-8′); 3.07 (m, 2H, H-1, H-1′); 2.01–1.20 (m, 26H, H-3,3′; H-6,6′; H-2,2′; H-7,7′, OH, 2Boc); 0.85 0.84 (2s, 18H, Si*t*Bu); 0.01 (s, 12H, $SiCH_3$); ^{13}C NMR: 156.2 (C═O), 75.3, 75.2 (C-4, C-5); 63.2 (C-8); 40.7 (C-1); 30.1 (C3, C-6); 28.3 (Boc); 27.3, 26.3 (C-2, C-7); 25.8 (Si*t*Bu); 17.9 (*t*Bu quat.); −4.2, −4.3, −4.7 ($SiCH_3$). Anal. Calcd for $C_{22}H_{55}NO_5Si_2$: C, 59.36; H, 10.96; N, 2.77. Found: C, 59.48; H, 11.04; N, 2.66.

4.1.10. (4*R*,5*R*) [8-*tert*-Butoxycarbonylamino-4,5-bis-(*tert*-butyldimethylsilanyloxy)-octyl]-carbamic acid *tert*-butyl ester, 14. 0.179 g (0.40 mmol) of **9** dissolved in 12 ml of absolute ethanol were hydrogenated for 30 min at 15 psi in the presence of 43 mg of Pd/C 10%, then for 3 h at 50 psi. The mixture was filtered on celite and concentrated in vacuo. The crude product (0.191 g) was dissolved in 6 ml of dry DCM. Et_3N (0.25 ml, 4.4 equiv) followed by $(Boc)_2O$ (0.196 g, 2.2 equiv) was added. The mixture was stirred for 1.5 h at rt and quenched with 12 ml of HCl (1 N). The organic phase was decanted and the aqueous phase extracted with CH_2Cl_2 (2×20 ml). The combined extracts were washed with saturated $NaHCO_3$ then water, dried on Na_2SO_4 and concentrated in vacuo. Medium pressure column chromatography (2×35 cm, eluent Hex/AcOEt 8:1) of the crude product (0.267 g) afforded **14** (0.179 g, 83%) as a white solid. Mp 99–101 °C. $[\alpha]_D$ +34.0 (*c* 0.31, $CHCl_3$); IR (KBr, cm^{-1}, ν): 3357 (NH), 1694 (C═O); ^1H NMR: 4.52 (br s, 2H, NH); 3.50 (bd, 2H, $J=8.24$ Hz, H-4, H-5); 3.08 (br s, 4H, H-1, H-1′, H-8, H-8′); 1.67–1.18 (m,

26H, H-3,3′; H-6,6′; H-2,2′; H-7,7′, 2Boc); 0.85 (s, 18H, Si*t*Bu); 0.03 (s, 12H, $SiCH_3$); ^{13}C NMR: 156.1 (C=O), 75.2 (C-4, C-5); 40.7 (C-1, C-8); 28.4 (Boc); 27.2 (C-2, C-3, C-6, C-7); 25.8 (Si*t*Bu); 17.9 (*t*Bu quat.); −4.3, −5.0 ($SiCH_3$). Anal. Calcd for $C_{30}H_{64}N_2O_6Si_2$: C, 59.56; H, 10.66; N, 4.63. Found: C, 59.91; H, 10.75; N, 4.50.

4.1.11. (4*R*,5*R*) (8-*tert* Butoxycarbonylamino-4,5-dihydroxy-octyl)-carbamic acid *tert*-butyl ester, 15. Compound **14** (0.133 g, 0.22 mmol) was dissolved in 5 ml of dry THF. Then TBAF (0.115 g, 2 equiv) was added at rt. The mixture was stirred for 5 h. Evaporation of the solvent gave 0.275 g of a crude product that was purified by medium pressure column chromatography (Hex/AcOEt 6:1 then AcOEt) to yield 0.078 g (94%) of **15** as a colourless viscous syrup that crystallized on standing in fridge. Mp 81–82 °C. $[\alpha]_D$ +14.61 (*c* 0.96, $CHCl_3$); IR (KBr, cm^{-1}, *ν*): 3386, 3365 (OH, NH), 1687.80 (C=O); ^1H NMR: 4.92 (br s, 2H, NH); 3.51 (br s, 2H, OH); 3.37 (br s, 2H, H-4, H-5); 3.10 (m, 4H, H-1, H-1′, H-8, H-8′); 1.72–1.35 (m, 26H, H-3,3′; H-6,6′; H-2,2′; H-7,7′, OH, 2Boc); ^{13}C NMR: 156.6 (C=O), 79.2 (Boc, quat.); 74.1 (C-4, C-5); 40.3 (C-1, C-8); 30.3 (C3, C-6); 28.3 (Boc); 26.3 (C-2, C-7). Anal. Calcd for $C_{18}H_{36}N_2O_6$: C, 57.42; H, 9.64; N, 7.44. Found: C, 57.49; H, 9.71; N, 7.43.

4.1.12. (2*S*,3*S*,4*R*,5*R*)-4,5-Bis-(*tert*-butyldimethylsilanyloxy)-oct-6-(*E*)-ene-1,2,3,8-tetraol, 16a. To 0.807 g (2.0 mmol) of **7** dissolved in 10 ml of acetone and cooled by an ice bath were added 0.406 g (1.5 equiv) of NMO in 0.8 ml of H_2O and 5 drops of a solution of OsO_4 in acetonitrile. After 0.5 h, the stirring was continued at rt for 3 h then solid $K_2S_2O_3$ was added an the mixture was stirred for more 0.5 h, extracted with AcOEt, dried on Na_2SO_4 and concentrated in vacuo. Purification of the crude by flash chromatography gave 0.330 g (40%) of unreacted **7**, 0.336 g (39%) of **16a** and 0.043 g (5%) of **16b**. Compound **16a**: $[\alpha]_D$ +57.68 (*c* 0.99, $CHCl_3$); IR (neat, cm^{-1}, *ν*): 3326 (OH); ^1H NMR: 5.94 (m, 2H, H-6, H-7); 4.40 (m, 1H); 4.21 (m, 2H); 3.83 (dd, 1H, *J*=4.36, 8.76 Hz, H-4);3.78–3.63 (m, 4H); 2.81 (br s, 4H, OH); 0.93 (s, 9H, Si*t*Bu); 0.90 (s, 9H, Si*t*Bu); 0.16, 0.14, 0.13, 0.11 (s, 3H each, $SiCH_3$); ^{13}C NMR: 131.19 (C-6); 128.15 (C-7); 75.72, 74.22, 71.12, 69.05, 65.53, 63.08 (C-8, C-5, C-4, C-3, C-2, C-1); 25.84, 25.80 (Si*t*Bu); 18.12, 18.02 (Si*t*Bu quat.); −4.34, −4.78, −4.92, −5.06 ($SiCH_3$). Anal. Calcd for $C_{20}H_{44}O_6Si_2$: C, 55.00; H, 10.16. Found: C; H; %. Compound **16b**: $[\alpha]_D$ +41.56 (*c* 0.90, $CHCl_3$); ^1H NMR: 5.84 (m, 2H, H-6, H-7); 4.20 (m, 1H); 4.10 (m, 2H); 3.75 (dd, 1H, *J*=3.12, 5.00 Hz, H-4); 3.71–3.54 (m, 4H); 3.15 (br s, 4H, OH); 0.92 (s, 9H, Si*t*Bu); 0.91 (s, 9H, Si*t*Bu); 0.15, 0.14, 0.08, 0.06 (s, 3H each, $SiCH_3$); ^{13}C NMR: 130.6 (C-6); 129.4 (C-7); 74.3, 73.7, 72.6, 69.6, 64.0, 62.8 (C-8, C-5, C-4, C-3, C-2, C-1); 25.9 (Si*t*Bu); 18.2, 18.1 (Si*t*Bu quat.); −4.2, −4.6, −4.7, −4.8 ($SiCH_3$).

4.1.13. (2*S*,3*S*,4*R*,5*R*)-1,2,8-Tri-benzoyloxy-4,5-bis(*tert*-butyldimethylsilanyloxy)-oct-6-(*E*)-ene-3-ol, 17. To 0.321 g (0.74 mmol) of **16a** dissolved in 5 ml of dry pyridine at 0 °C were added 0.52 ml (4.4 mmol, 6 equiv) of BzCl and a catalytic amount of DMAP. The mixture was stirred at rt for 1.5 h (TLC Hex/AcOEt 4:1). The reaction was quenched with a saturated solution of $NaHCO_3$. The product was extracted with DCM (4×20 ml), the organic phase dried on Na_2SO_4. Evaporation of the solvent and purification of the crude product by flash chromatography afforded **17** (0.495 g, 90%). $[\alpha]_D$ +32.15 (*c* 2.42, $CHCl_3$); IR (neat, cm^{-1}, *ν*): 3483 (OH), 1724 (C=O); ^1H NMR: 8.11 (d, 2H, *J*=7.36 Hz, arom. *ortho*); 8.06 (d, 2H, *J*=7.48 Hz, arom. *ortho*); 8.0 (d, 2H, *J*=7.40 Hz, arom. *ortho*); 7.60–7.34 (m, 9H, arom. *meta*, *para*); 6.20 (ddt, 1H, *J*=15.60, 4.36, 1.84 Hz, H-6); 6.06 (ddt, 1H, *J*=15.60, 4.56, 1.24 Hz, H-7); 5.57 (dt, 1H, *J*=6.24, 6.24, 1.24 Hz, H-2); 4.92 (AB part of ABX system, *J*=13.64 Hz H-8, H-8′); 4.66 (, 2H, *J*=6.36 Hz, H-1, H-1′); 4.52 (m, 1H, *J*=4.36, 1.88 Hz, H-5); 4.19 (br s, 1H, OH); 4.03 (dd, 1H, *J*=8.72, 1.24 Hz, H-3); 3.88 (dd, 1H, *J*=4.36, 8.72 Hz, H-4); 0.98 (s, 9H, *t*Bu); 0.88 (s, 9H, *t*Bu); 0.15 (s, 3H, $SiCH_3$); 0.14 (s 3H, $SiCH_3$); 0.03 (s, 3H, $SiCH_3$); −0.04 (s, 3H, $SiCH_3$); ^{13}C NMR: 166.20, 165.85 (C=O); 133.10, 133.03, 132.89 (arom. *para*); 130.4 (C-7); 130.3, 130.2, 130.1 (arom. quat.); 129.8, 129.8, 129.7 (arom. *ortho*); 128.4, 128.3 (arom. *meta*); 126.3 (C-6); 75.5 (C-2); 72.5 (C-3); 71.0 (C-5, C-4); 64.6 (C-8); 63.4 (C-1); 25.8, 25.8 (*t*Bu); 18.2, 18.0 (*t*Bu quat.); −3.8, −4.7, −5.2 ($SiCH_3$). Anal. Calcd for $C_{41}H_{56}O_9Si_2$: C, 65.47; H, 7.54. Found: C, 65.73; H, 7.53.

4.1.14. (2*S*,3*S*,4*R*,5*R*)-1,2,8-Tri-benzoyloxy-4-*tert*-butyldimethylsilanyloxy-oct-6-(*E*)-ene-3,5-diol, 18. Compound **17** (0.263 g, 0.35 mmol) was dissolved in 7 ml of acetonitrile. HF (40% in water, 0.216 ml) was added and the mixture was stirred at rt for 30 min (A longer reaction time resulted in lower yield in expected product) until apparition of a more polar compound (checked by TLC Hex/AcOEt 4:1). The reaction was quenched with saturated $NaHCO_3$, extracted with DCM, and the organic phase dried on Na_2SO_4. Evaporation of solvent and purification of the crude product by preparative TLC gave 0.053 g (22%) of **17** and 0.174 g (73%) of **18**. $[\alpha]_D$ +12.31 (*c* 0.93, $CHCl_3$); IR (neat, cm^{-1}, *ν*): 3456 (OH); 1723 (C=O); ^1H NMR: 8.08 (dd, 2H, *J*=8.76, 1.28 Hz, arom. *ortho*); 8.02 (dd, 2H, *J*=8.12, 1.28 Hz, arom. *ortho*); 7.97 (dd, 2H, *J*=8.08, 1.24 Hz, arom. *ortho*); 7.60–7.50 (m, 3H, arom *para*); 7.47–7.35 (m, 6H, arom. *meta*); 6.05 (AB part of ABMX system, J_{AB}=15.60 Hz, H-6, H-7); 5.49 (dt, 1H, *J*=6.24, 1.88 Hz, H-2); 4.83 (AB part of ABX system, *J*=12.76 Hz, H-8, H-8′); 4.76 (dd, 1H, *J*=11.24, 6.24 Hz, H-1); 4.60 (dd, 1H, *J*=11.24, 6.24 Hz, H-1′); 4.43 (m, 1H, H-5); 3.96 (AB part of ABMX system, H-3, H-4, J_{AB}=7.48 Hz); 3.20 (br s, 2H, OH; 0.85 (s, 9H, Si*t*Bu); 0.03 (s, 3H, $SiCH_3$); −0.01 (s 3H, $SiCH_3$); ^{13}C NMR: 166.6, 166.3, 166.0 (C=O); 133.4, 133.3, 133.0 (arom. *para*); 132.6 (C-6); 130.2 (arom. quat.); 130.0, 129.8, 129.7 (arom. *ortho*); 129.5 (arom. quat.); 128.6; 128.5, 128.4 (arom. *meta*); 125.9 (C-7); 73.4 (C-2); 72.8 (C-3); 72.4 (C-5); 71.3 (C-4); 64.8 (C-8); 62.7 (C-1); 25.9 (*t*Bu); 18.0 (*t*Bu quat.); −4.0, −4.9 ($SiCH_3$). Anal. Calcd for $C_{35}H_{42}O_9Si$: C, 66.22; H, 6.67. Found: C, 66.50; H, 6.50.

4.1.15. (2*S*,3*S*,4*R*,5*R*)-5-Azido-1,2,8-tri-benzoyloxy-4-*tert*-butyldimethylsilanyloxy-oct-6-(*E*)-ene-3-ol, 19. To 0.296 g (0.47 mmol) of **18** dissolved in 9 ml of dry THF was added TPP (0.186 g, 1.5 equiv), followed by 0.400 ml (1.5 equiv) of a 1.7 M solution of hydrazoic acid in benzene. The mixture was stirred at rt for 20 min then DEAD (0.124 g in 1.7 ml of dry THF) was added dropwise. After 30 min of stirring, the solvent was evaporated and the crude product

was purified by preparative TLC (Hex/EtOAc 4:1) to give 0.277 g (90%) of **19** as a colourless syrup. $[\alpha]_D$ −13.36 (*c* 1.05, $CHCl_3$); IR (neat, cm^{-1}, ν): 3475 (OH), 2106 (N_3), 1724 (C=O); ^1H NMR: 8.08–8.03 (m, 4H, arom. *ortho*); 8.00–7.97 (m, 2H, arom. *ortho*); 7.59–7.50 (m, 3H, arom. *para*); 7.47–7.37 (m, 6H, arom. *meta*); 6.06 (ddd, 1H *J*= 15.60, 6.24, 1.24 Hz, H-6); 5.81 (ddd, 1H, *J*=15.60, 6.24, 1.24 Hz, H-7); 5.69 (ddd, 1H, *J*=6.24, 5.00, 2.48 Hz, H-2); 4.63 (m, 2H, AB part of ABX system, J_{AB}=11.84 Hz, H-8, H-8′); 4.45 (dd, 1H, *J*=10.60, 3.12 Hz, H-1); 4.39 (dt, 1H, *J*=5.62, 1.24 Hz, H-4); 4.36–4.27 (m, 2H, H-1′ and H-3 or H-5); 3.87 (m, 1H, *J*=5.60, 3.12 Hz, H-5 or H-3); 2.30 (br s, 1H, OH); 0.82 (s, 9H, *t*Bu); 0.01, −0.01, −0.04 (3s, 3H each, $SiCH_3$); ^{13}C NMR: 166.3, 166.2, 165.6 (C=O); 135.4 (C-6), 133.3, 133.3, 133.2 (arom. *para*); 129.9; 129.9; 129.8 (arom. *meta*); 129.5 (arom. quat.); 128.5, 128.5 (arom. *ortho*); 126.7 (C-7); 73.83, 73.22, 70.51, 66.12; 63.61 (C-8); 61.74 (C-1); 25.77 (*t*Bu); 18.06 (Si*t*Bu quat.); −4.13, −5.00 ($SiCH_3$).

4.1.16. (2*S*,3*S*,4*R*,5*R*)-5-*tert*-Butoxycarbonylamino-1,2,8-tri-benzoyloxy-4-*tert*-butyldimethylsilanyloxy-oct-6-(*E*)-ene-3-ol, 20. 0.167 g (0.25 mmol) of **19** in 10 ml of EtOH were submitted to a pressure of 15 psi of hydrogen in the presence of 30 mg of 10% Pd/C for 0.5 h then to 55 psi for 3 h. The catalyst was filtered off and the solvent evaporated in vacuo. The crude product was taken in DCM (5 ml) then Et_3N (0.1 ml, 2.2 equiv) was added at 0 °C followed by $(Boc)_2O$ (63 mg, 1.1 equiv) then the mixture was stirred at rt for 2 h. The reaction was quenched with HCl 1 N, the product was extracted with DCM, washed with $NaHCO_3$ sat. and dried on Na_2SO_4. The solvent was evaporated in vacuo and the crude product was purified by preparative TLC (Hex/AcOEt 3:1) to give 0.080 g (43%) of **20** as a colourless viscous oil. $[\alpha]_D$ +9.7 (*c* 1.53, $CHCl_3$); IR (neat, cm^{-1}, ν): 3444, 3379 (OH, NH), 1722, 1713 (C=O); ^1H NMR: 8.07–7.95 (m, 6H, arom. *ortho*); 7.56–7.48 (m, 3H, arom. *para*); 7.42–7.32 (m, 6H, arom. *meta*); 4.89–4.20 (m, 7H); 1.38 (s, 9H, *t*Bu Boc); 0.88 (s, 9H, Si*t*Bu); 0.06 (s, 3H, $SiCH_3$); 0.03 (s 3H, $SiCH_3$); ^{13}C NMR: 166.54, 166.51, 166.08 (C=O Bz); 155.58 (C=O Boc); 133.49, 133.30, (arom. *para*); 129.94; 129.86; 129.75 (arom. *meta*); 128.54, 128.42 (arom. *ortho*); 79.6 (quat. Boc); 73.30; 73.12 (C-1, C-8); 68.27, 66.72, 65.78 (C-2, C-4, C-3); 49.56 (C-5); 30.22 (C-6); 28.11 (*t*Bu, Boc); 27.32 (C-7); 25.55 (Si*t*Bu); 17.69 (Si*t*Bu quat.); −4.76, −5.11 ($SiCH_3$). Anal. Calcd for $C_{40}H_{53}NO_{10}Si$: C, 65.28; H, 7.26; N, 1.90. Found: C, 64.99; H, 7.29; N, 1.85.

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