(*R*)-2,3-Cyclohexylideneglyceraldehyde, a Chiral Pool Synthon for the Synthesis of 2-Azido-1,3-diols

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A new approach was proposed for the synthesis of 2-azido-1,3-diols from easily available and inexpensive chiral pool synthon (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde, through *Mitsunobu* azidation of 1,2-diols. Both C(2) and C(1) azides in variable ratios were obtained in alkyl substituted diols with C(2) as the major one.

Introduction. – 1,2-Azido alcohols are widely employed in organic synthesis as versatile precursors for the preparation of 1,2-amino alcohols [1], amino acids [2], aziridines [3], triazoles [4], 2-oxazolidinones [5], oxazines [6], and oxazolidines [7]. They are also useful intermediates for the preparation of several target compounds, like carbohydrates/nucleosides [8], peptidomimetics [9], and pseudopeptides [10]. Besides, organic azides are well known substrates in organic synthesis [11], widely applied in click chemistry [12], and used as fluorescent probes [13]. Chiral 2-amino-1,3-diols, which can be easily obtained from 2-azido-1,3-diols are the essential constituents of antibiotics [14], antiviral glycosidase inhibitors [15], sphingolipids [15b][16], and dihydrosphingosines [17].

A number of chemical methods exist in the literature for the synthesis of azido alcohols, the most predominant one is the direct opening of epoxides [18], while other methods involve the synthesis through solid phase approach [19], hydroazidation of aldehydes [20], azidation from 1,2-diols [21], and regioselective azide substitution of diols [22].

Herein, we report the development of an alternate and facile process for the synthesis of 2-azido-1,3-diols as diastereoisomeric mixtures from commercially available and inexpensive starting chiral pool, (*R*)-2,3-cyclohexylideneglyceraldehyde. Recently, we have also successfully utilized cyclohexylideneglyceraldehyde for the synthesis of the antidepressant drug reboxetine [23] and the antihypertensive doxazosin [24].

Results and Discussion. – The synthesis of chiral 2-azido-1,3-diol, involves the utilization of the commercially available and inexpensive sugar D-mannitol (**1**) as a starting material, which possesses the desired chirality. The protection of D-mannitol was accomplished with cyclohexanone in DMSO, with TsOH as a catalyst to form 1,2,5,6-di-*O*-cyclohexylidene-D-mannitol (**2**), which is stable and easy to handle. The intermediate **2** was cleaved into (*R*)-2,3-*O*-cyclohexylidene-D-glyceraldehyde (**3**) by

scissoring with $NaIO_4$ in Et_2O/H_2O in 95% yield [25]. The aldehyde **3**, is an ideal synthon and has multifarious advantages [26][25b], and it can be readily converted into the target molecules.

Thus, *Grignard* reaction of aldehyde (*R*)-**3** with various alkyl halides (such as methyl, ethyl, propyl, butyl, pentyl, hexyl and decyl halides) in dry THF afforded a mixture of *syn*- and *anti*-alkyl glycerol diastereoisomers **4a**–**4g** in 83–90% yield in variable ratios. The diastereoisomeric products were inseparable by CC, therefore, the mixture of diastereoisomers were directly used for further transformations. The OH group of the *Grignard* product was protected by benzylation to form **5a**–**5g**, followed by cyclohexylidene deprotection with TsOH in MeOH affording the diols **6a**–**6g**. The diols **6a**–**6g** were finally converted into the respective azido alcohol regioisomers **7a**–**7g** and **8a**–**8g** *via Mitsunobu* azidation reaction [21b], using Ph_3P, DIAD, and $TMSN_3$ as a source of nucleophile in toluene as a solvent, followed by silyl deprotection under acidic conditions (tetrabutylammonium fluoride, TBAF). It was observed that by *Mitsunobu* azidation, the 2-azidoalcohols **7a**–**7g** were formed as the major products, while the 1-azidoalcohols **8a**–**8g** were obtained as the minor products (*Scheme 1*). Details of the reaction, the products, and the corresponding yields are given in the *Table*.

Scheme 1. *Synthesis of Azido Alcohols* **7** *and* **8**

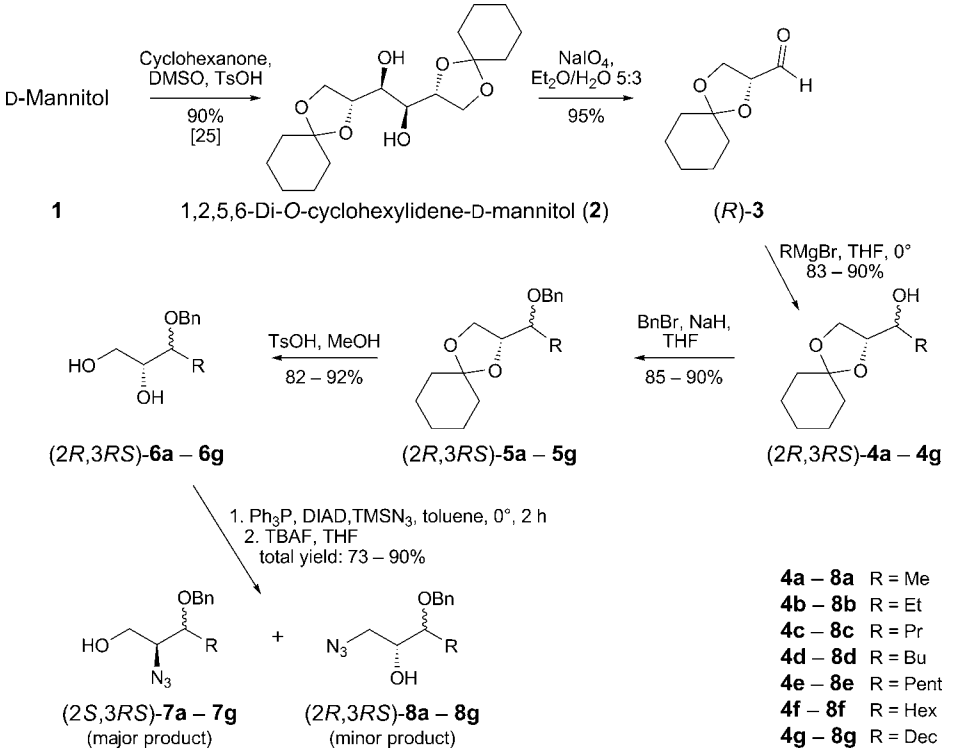
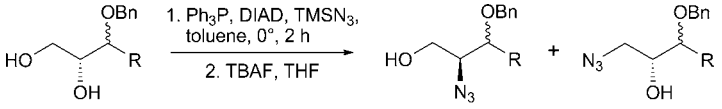


Table. *Azido Alcohols Obtained during* Mitsunobu *Azidation*



6a – 6g **7a – 7g** **8a – 8g**

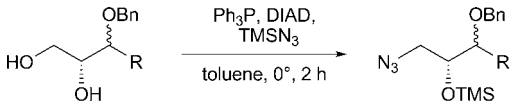
Entry	R	Product ratio **7:8**	Yield of **7** [%]	Total yield **7**+**8** [%]
1	Me	4:1	58	73
2	Et	4:1	68	85
3	Pr	3:1	60	80
4	Bu	3:1	60	80
5	Pent	2:1	59	90
6	Hex	2:1	59	90
7	Dec	2:1	59	90

For the *Mitsunobu* azidation, various solvents, like CH_2Cl_2, THF, and toluene were tested to optimize the formation of (2*S*,3*RS*)-2-azido-3-(benzyloxy)nonan-1-ol, wherein toluene gave the best results.

In case of the aryl-substituted diols **9a** and **9b**, the azidation occurred regioselectively at the primary OH group, probably due to steric hindrance (*Scheme 2*). In our previous work, we have reported a methodology for a *Mitsunobu* chlorination. In that work, we have explained that in sterically hindered diols (aryl-substituted diols) and sugars, the nucleophilic substitution generally occurs regioselectively at the primary OH group [23].

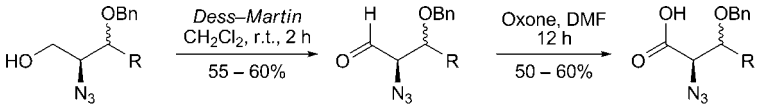
The azido alcohols can be easily transformed into azido acids by oxidation. The 2-azidoalcohols **7f** and **7g** were oxidized to corresponding azido aldehydes (55–60% yields) **11f** and **11g** by *Dess–Martin* periodinane oxidizing reagent and thereafter, converted to the corresponding azido acids **12f** and **12g** by the oxidizing agent oxone ($KHSO_5$, potassium peroxomonosulfate) in DMF in 50–60% yields (*Scheme 3*).

Scheme 2. *Synthesis of Azido Alcohols* **10**



9a R = Ph
9b R = $PhCH_2$
10a R = Ph
10b R = $PhCH_2$

Scheme 3. *Synthesis of Azido Acids* **12**

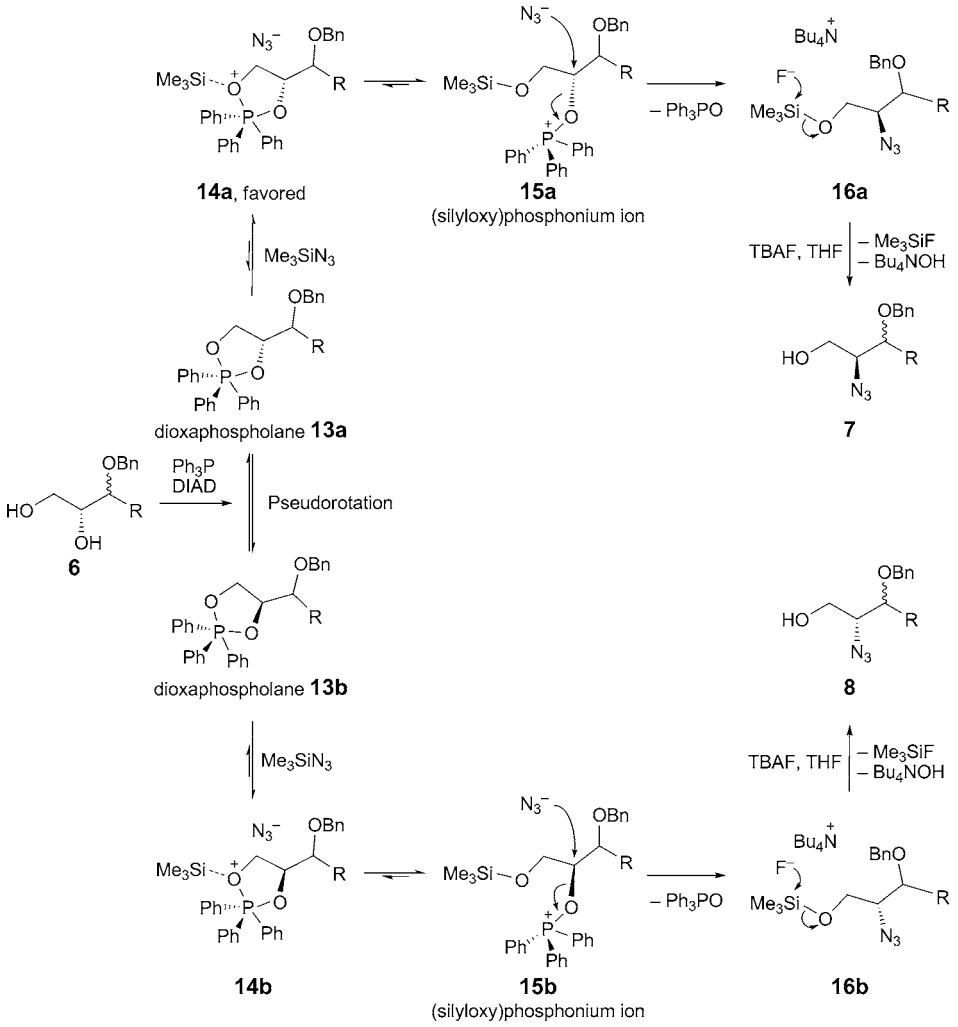


(2*S*,3*RS*)-**7f** R = Hex
(2*S*,3*RS*)-**7g** R = Dec
(2*R*,3*RS*)-**11f** R = Hex
(2*R*,3*RS*)-**11g** R = Dec
(2*R*,3*RS*)-**12f** R = Hex
(2*R*,3*RS*)-**12g** R = Dec

D-Azido acids

The mechanism of the regioselective substitution in diols, as proposed by *Mathieu-Pelta et al.*, occurs through the intermediacy of dioxaphospholanes [21]. The two conformational isomeric dioxaphospholanes **13a** and **13b** formed by the reaction of 1,2-diols with Ph_3P and DIAD, undergo a rapid interconversion through pseudorotation. The silylation at the more basic P–O apical O-atom leads to the formation of (silyloxy)phosphonium ions **15a** and **15b** and subsequent S_N2 displacement of Ph_3PO by an azide ion affords the formation of the C(2) azido regioisomer **16a** as the major product with inversion of configuration and C(1) azido regioisomer **16b** as the minor product (*Scheme 4*). When the R group of the 1,2-diol is changed from Me to $C_{10}H_{21}$, the regioselectivity (**16a**/**16b** ratio) decreases.

Scheme 4. *Mechanism of* Mitsunobu *Azidation in Diols*



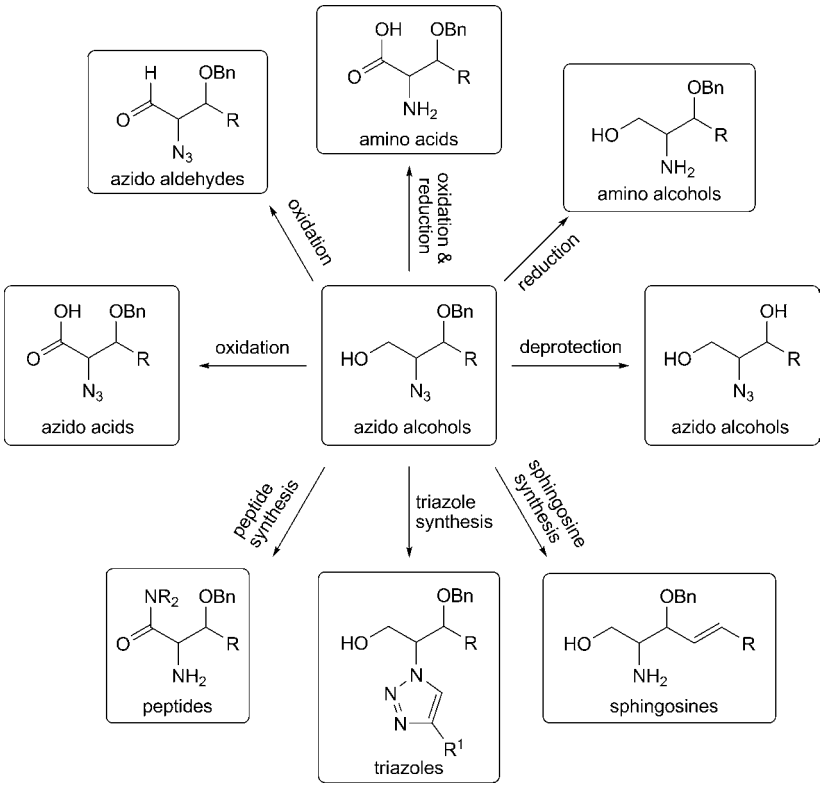


Figure. *Possible applications of azido alcohols*

These azido alcohols can be used as valuable synthetic intermediates for the synthesis of a diversity of bioactive compounds, like amino alcohols, azido acids, azido aldehydes, triazoles, sphingosines, peptides, *etc.*, as summarized in the *Figure*.

Conclusions. – An efficient and new methodology has been developed for the synthesis of 2-azido-1,3-diols as diastereoisomeric mixtures from the synthon (*R*)-cyclohexylideneglyceraldehyde. In this methodology, the *Mitsunobu* reaction was successfully used for the azidation of alkyl substituted diols affording the C(2) and C(1) azides in variable ratios, while in the aryl substituted diols, the C(1) azide was regioselectively formed.

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Experimental Part

General. Reagents and solvents used were mostly Lab grade quality. Chemicals were purchased from *Aldrich Chemicals*, Mumbai. All reactions under anh. conditions were carried out under N_2 atmosphere using freshly dried solvents. The org. extracts were dried over anh. Na_2SO_4. Silica gel-coated aluminum

plates from *Merck* were used for TLC. Silica gel = SiO_2. CC = column chromatography. IR Spectra: *PerkinElmer* FT-IR spectrometer-*Spectrum two*. NMR Spectra: *Bruker* 400 and 500 MHz spectrometers with TMS as the internal standard; chemical shifts are expressed in parts per million (δ ppm). HR-MS: *Q-TOF LC/MS*, *Agilent Technologies 6540*. The diastereoisomeric ratios were calculated on the basis of NMR.

*2,3-*O*-Cyclohexylidene-*D*-glyceraldehyde* (=*(2*R*)-1,4-Dioxaspiro[4.5]decane-2-carbaldehyde*; **3**). Sodium metaperiodate ($NaIO_4$; 7.3 g) and 200 mg of tetrabutylammonium bromide (TBAB) in H_2O (60 ml) were added to a soln. of 10.0 g of 1,2,5,6-di-*O*-cyclohexylidene-D-mannitol (=(1*S*,2*S*)-1,2-di[(2*R*)-1,4-dioxaspiro[4.5]dec-2-yl]ethane-1,2-diol; **2**) in Et_2O (100 ml), and the mixture was stirred for 3 h at r.t. After the completion of the reaction, the org. layer was separated, and the aq. layer was extracted with Et_2O (3 × 35 ml). The combined Et_2O soln. was washed with H_2O (1 × 35 ml) and dried. The solvent was evaporated under vacuum to give the title compound (*R*)-**3** in 95% yield (19.0 g) as a colorless viscous liquid. B.p. 90–94° (2 mm Hg) ([27]: 90–93° (2 mm Hg)). $[\alpha]_D^{25} = +61.2$ (*c* = 3.4, benzene). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.43–1.80 (*m*, 10 H); 3.90–4.22 (*m*, 2 H); 4.40 (*m*, 1 H); 9.7 (*s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.8; 25.0; 34.7; 36.2; 65.7; 98.4; 110.7; 202.2. HR-ESI-MS: 171.1019 ($[M+H]^+$, $C_9H_{15}O_3^+$; calc. 171.1016).

Grignard *Reaction of Aldehyde* **3** *with Alkyl Halides, General Procedure.* The alkyl bromides (29.2 mmol, 4 equiv.) were added dropwise over 15 min at r.t. under N_2 in the presence of a crystal of I_2 to Mg turnings (29.20 mmol, 4 equiv.) placed in a reaction vessel, comprising 60 ml anh. THF, while in the case of alkyl iodides the reaction was carried out without I_2. After the formation of the *Grignard* reagent (indicated by warming of reaction vessel), the soln. was cooled to −10° and cyclohexylideneglyceraldehyde (7.30 mmol, 1 equiv.) in THF (20 ml) was added dropwise to the mixture. The mixture was stirred at r.t. for 18 h and then cooled to 0° before the addition of sat. aq. NH_4Cl (30 ml). The soln. was extracted three times with AcOEt (3 × 40 ml), the org. layers were combined, dried, and the solvent evaporated under reduced pressure. The crude products were purified by CC (SiO_2; 0–15% AcOEt/hexane) to provide a mixture of *syn*- and *anti*-diastereoisomers in 83–90%.

*(2*R*,3*RS*)-1,2-Cyclohexylidenebutane-1,2,3-triol* (=*1-[(2*R*)-1,4-dioxaspiro[4.5]dec-2-yl]ethanol*; **4a**): *syn*/*anti* 1:1. Yield 83%. Colorless oil. IR ($CHCl_3$): 950, 1060, 1120, 1180, 1290, 1340, 1380, 1460, 2948, 3450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.94 (*d*, *J* = 6.8, 3 H); 1.32–1.80 (*m*, 10 H); 3.72–3.76 (*m*, 1 H); 3.77–4.23 (*m*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 19.5; 22.6; 23.4; 37.5; 68.8; 69.4; 83.4; 109.9. HR-ESI-MS: 209.1144 ($[M+Na]^+$, $C_{10}H_{18}NaO_3^+$; calc. 209.1154).

*(2*R*,3*RS*)-1,2-Cyclohexylidenepentane-1,2,3-triol* (=*4,5-*O*-Cyclohexane-1,1-diyl-1,2-dideoxy-*D*-glycero-pentitol*; **4b**). *syn*/*anti* 1:1. Yield 84%. Transparent liquid. IR ($CHCl_3$): 946, 1062, 1136, 1180, 1290, 1340, 1380, 1472, 2940, 3457. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.00 (*t*, *J* = 7.5, 3 H); 1.32–1.47 (*m*, 3 H); 1.48–1.72 (*m*, 9 H); 3.64–3.73 (*m*, 1 H); 3.80–3.91 (*m*, 1 H); 3.97 (*dd*, *J* = 6.4, 7.8, 1 H); 4.04 (*ddd*, *J* = 5.1, 8.4, 11.2, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 8.8; 22.8; 23.6; 23.8; 24.5; 33.5; 34.8; 63.2; 71.0; 76.8; 108.1. HR-ESI-MS: 223.1300 ($[M+Na]^+$, $C_{11}H_{20}NaO_3^+$; calc. 223.1310).

(2R,3RS)-1,2-Cyclohexylidenehexane-1,2,3-triol (=*1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]butan-1-ol*; **4c**). *syn*/*anti* 27:73. Yield 85%. Transparent liquid. IR ($CHCl_3$): 955, 1056, 1130, 1180, 1280, 1336, 1380, 1460, 2950, 3453. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*dt*, *J* = 8.3 (for *syn*-isomer), 19.9 (for *anti*-isomer), 3 H); 1.26 (*t*, *J* = 7.1, 1 H); 1.30–1.48 (*m*, 3 H); 1.49–1.72 (*m*, 10 H); 2.06 (*s*, OH); 3.75–3.84 (*m*, 1 H); 3.89 (*t*, *J* = 7.6, 1 H); 3.95 (*t*, *J* = 7.1, 1 H); 3.99–4.05 (*m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.3; 20.6; 21.8; 22.1; 32.2; 36.7; 65.1; 65.9; 79.7; 109.9. HR-ESI-MS: 237.1456 ($[M+Na]^+$, $C_{12}H_{22}NaO_3^+$; calc. 237.1467).

*(2*R*,3*RS*)-1,2-Cyclohexylideneheptane-1,2,3-triol* (=*1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]pentan-1-ol*; **4d**). *syn*/*anti* 9:11. Yield 85%. Transparent liquid. IR ($CHCl_3$): 950, 1060, 1130, 1180, 1285, 1340, 1380, 1460, 2950, 3450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91 (*t*, *J* = 6.5, 3 H); 1.24–1.75 (*m*, 16 H); 3.70–3.75 (*m*, 1 H); 3.84–3.87 (*m*, 1 H); 3.93–4.15 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 10.8; 22.2; 23.8; 25.4; 27.9; 31.1; 36.3; 37.2; 67.5; 69.2; 80.1; 109.4. HR-ESI-MS: 251.1616 ($[M+Na]^+$, $C_{12}H_{24}NaO_3^+$; calc. 251.1623).

*(2*R*,3*RS*)-1,2-Cyclohexylideneoctane-1,2,3-triol* (=*1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]hexan-1-ol*; **4e**). *syn*/*anti* 9:11. Yield 88%. Transparent liquid. IR ($CHCl_3$): 950, 1060, 1130, 1180, 1285, 1340, 1380, 1460, 2940, 3450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.85 (*t*, *J* = 6.5, 3 H); 1.23–1.73 (*m*, 18 H); 2.04 (*s*, OH);

3.75–4.22 (*m*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 10.1; 24.3; 24.9; 25.8; 26.9; 31.5; 32.4; 35.8; 37.1; 67.9; 69.4; 80.2; 111.3. HR-ESI-MS: 265.1773 ($[M+Na]^+$, $C_{14}H_{26}NaO_3^+$; calc. 265.1780).

*(2*R*,3*RS*)-1,2-Cyclohexylidenenonane-1,2,3-triol* (*=1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]heptan-1-ol*; **4f**). *syn*/*anti* 36:64. Yield 90%. Transparent liquid. IR ($CHCl_3$): 950, 1060, 1130, 1180, 1285, 1340, 1380, 1460, 2950, 3450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82 (*t*, *J* = 6.7, 6 H); 1.25–1.72 (*m*, 40 H); 2.25 (*s*, OH); 3.58–3.61 (*m*, 1 H, *anti*-isomer); 3.70–3.75 (*m*, 1 H, *syn*-isomer); 3.82–3.85 (*m*, 1 H, *anti*-isomer); 3.95–3.98 (*m*, 2 H, *syn*-isomer); 3.99–4.01 (*m*, 1 H, *anti*-isomer); 4.03–4.12 (*m*, 1 H, *anti*-isomer); 4.14–4.17 (*m*, 1 H, *syn*-isomer). ^{13}C-NMR (125 MHz, $CDCl_3$): 14.4; 22.5; 24.1; 24.7; 25.1; 26.9; 26.9; 29.1; 29.4; 32.2; 33.4; 34.6; 35.6; 62.0; 62.6; 71.2; 79.9; 110.2; 110.4. HR-ESI-MS: 279.1925 ($[M+Na]^+$, $C_{15}H_{28}NaO_3^+$; calc. 279.1936).

*(2*R*,3*RS*)-1,2-Cyclohexylidenetridecane-1,2,3-triol* (*=1-[(2*R*)-1,4-Dioxaspiro[4.5]dec-2-yl]undecan-1-ol*; **4g**). *syn*/*anti* 1:4. Yield 90%. Transparent liquid. IR ($CHCl_3$): 955, 1060, 1115, 1179, 1295, 1345, 1380, 1460, 2934, 3450. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*t*, *J* = 6.2, 3 H); 1.20–1.80 (*m*, 28 H); 2.09 (*s*, OH); 3.70–4.23 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.6; 20.7; 21.5; 21.9; 25.3; 30.4;, 30.9; 31.3; 35.7; 67.2; 67.8; 67.9; 85.1; 109.3; 109.5. HR-ESI-MS: 335.2557 ($[M+Na]^+$, $C_{19}H_{36}NaO_3^+$; calc. 335.2562).

Benzyl Protection. NaH (1.2 equiv.) was added to the soln. of alcohol (**4a**–**4g**) in anh. THF at 0°. After 20 min, benzyl bromide (1.2 equiv.) was added, and the mixture stirred for 3–5 h, until the protection was completed as indicated by TLC. The mixture was extracted with AcOEt (3 × 20 ml) and washed with H_2O (2 × 15 ml). The AcOEt layer was washed with brine (1 × 15 ml), dried over anh. Na_2SO_4 and purified by CC (SiO_2; 0–10% AcOEt/hexane) to obtain the benzyl protected pure compound in 85–90%.

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxybutane* (*=(2*R*)-2-[1-(Benzyloxy)ethyl]-1,4-dioxaspiro[4.5]decane*; **5a**). *syn*/*anti* 1:1. Yield 85%. Transparent liquid. IR ($CHCl_3$): 959, 1102, 1209, 1457, 1645, 2855, 3088. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*d*, *J* = 7.0, 3 H); 1.37–1.68 (*m*, 10 H); 3.92–3.96 (*m*, 2 H); 4.00–4.12 (*m*, 1 H); 4.18–4.26 (*m*, 1 H); 4.58 (*s*, 2 H); 7.20–7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.7; 22.3; 22.6; 23.4; 24.0; 36.5; 66.3; 73.1; 74.8; 82.5; 109.6; 127.4; 128.6; 128.5; 139.1; 139.9. HR-ESI-MS: 299.1616 ($[M+Na]^+$, $C_{17}H_{24}NaO_3^+$; calc. 299.1623).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxypentane* (*=3*-O-*Benzyl-4,5*-O-*cyclohexane-1,1-diyl-1,2-dideoxy*-D-glycero-*pentitol*; **5b**). *syn*/*anti* 1:1. Yield 85%. Colorless oil. IR ($CHCl_3$): 959, 1102, 1209, 1457, 1645, 3088. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 6.8, 3 H); 1.24–1.28 (*m*, 1 H); 1.34–1.37 (*m*, 2 H); 1.50–1.74 (*m*, 9 H); 3.87–3.94 (*m*, 1 H); 4.00–4.06 (*m*, 2 H); 4.12–4.17 (*m*, 1 H); 4.50–4.56 (*m*, 2 H); 7.24–7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 10.2; 22.3; 22.7; 23.4; 23.8; 25.4; 36.3; 36.4; 68.4; 74.7; 77.6; 83.5; 108.8; 127.7; 128.3; 138.7; 139.3. HR-ESI-MS: 313.1773 ($[M+Na]^+$, $C_{18}H_{26}NaO_3^+$; calc. 313.1780).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxyhexane* (*=(2*R*)-2-[1-(Benzyloxy)butyl]-1,4-dioxaspiro[4.5]decane*; **5c**). *syn*/*anti* 27:73. Yield 86%. Transparent liquid. IR ($CHCl_3$): 955, 1112, 1239, 1454, 1646, 2978. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, *J* = 6.6, 3 H); 1.28–1.74 (*m*, 14 H); 3.87–3.94 (*m*, 1 H); 4.05–4.24 (*m*, 3 H); 4.56 (*m*, 2 H); 7.24–7.45 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 8.6; 19.3; 21.6; 22.6; 24.1; 31.5; 36.2; 62.2; 62.9; 68.6; 77.5; 81.4; 109.3; 128.1; 129.2; 130.3; 139.2; 139.5. HR-ESI-MS: 327.1932 ($[M+Na]^+$, $C_{19}H_{28}NaO_3^+$; calc. 327.1936).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxyheptane* (*=(2*R*)-2-[1-(Benzyloxy)pentyl]-1,4-dioxaspiro[4.5]decane*; **5d**). *syn*/*anti* 9:11. Yield 88%. Transparent liquid. IR ($CHCl_3$): 950, 1142, 1209, 1444, 1646, 2856, 2978. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.87 (*t*, *J* = 6.8, 3 H); 1.24–1.68 (*m*, 16 H); 3.80–3.83 (*m*, 1 H); 3.91–3.95 (*m*, 1 H); 4.00–4.07 (*m*, 1 H); 4.11–4.16 (*m*, 1 H); 4.51–4.56 (*m*, 2 H); 7.33–7.38 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 11.1; 23.4; 24.3; 25.1; 27.8; 35.5; 36.3; 64.5; 75.0; 77.3; 78.3; 80.1; 81.1; 109.3; 128.3; 129.1; 129.5; 138.5. HR-ESI-MS: 341.2083 ($[M+Na]^+$, $C_{20}H_{30}NaO_3^+$; calc. 341.2093).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxyoctane* (*=(2*R*)-2-[1-(Benzyloxy)hexyl]-1,4-dioxaspiro[4.5]decane*; **5e**). *syn*/*anti* 9:11. Yield 88%. Transparent liquid. IR ($CHCl_3$): 950, 1102, 1201, 1404, 1656, 2858, 2948. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.92 (*t*, *J* = 6.8, 3 H); 1.25–1.72 (*m*, 18 H); 3.21–3.27 (*m*, 1 H); 3.26–4.25 (*m*, 3 H); 4.56 (*s*, 2 H); 7.64–7.68 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 8.6; 24.8; 24.9; 25.6; 26.9; 29.6; 30.3; 37.7; 38.6; 67.7; 74.4; 80.5; 83.2; 110.4; 130.2; 130.5; 140.6. HR-ESI-MS: 355.2243 ($[M+Na]^+$, $C_{21}H_{32}NaO_3^+$; calc. 355.2249).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxynonane* (= *(2*R*)-2-[1-(Benzyloxy)heptyl]-1,4-dioxaspiro[4.5]decane*; **5f**). *syn*/*anti* 36:64. Yield 90%. Transparent liquid. IR ($CHCl_3$): 970, 1110, 1241, 1424, 1656, 2853, 2928. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.82–0.87 (*m*, 3 H); 1.16–1.40 (*m*, 10 H); 1.41–1.75 (*m*, 10 H); 3.61–3.64 (*m*, 1 H); 3.90–3.94 (*m*, 1 H); 4.00–4.21 (*m*, 2 H); 4.56 (*s*, 2 H); 7.40–7.85 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 10.1; 20.1; 20.8; 21.7; 21.8; 22.4; 23.1; 24.4; 25.8; 36.5; 37.4; 63.8; 75.9; 79.2; 110.0; 128.3; 128.8; 129.5; 139.5. HR-ESI-MS: 369.2401 ($[M+Na]^+$, $C_{22}H_{34}NaO_3^+$; calc. 369.2406).

*(2*R*,3*RS*)-3-Benzyloxy-1,2-cyclohexylidenedioxytridecane* (= *(2*R*)-2-[1-(Benzyloxy)undecyl]-1,4-dioxaspiro[4.5]decane*; **5g**). *syn*/*anti* 1:4. Yield 90%. Colorless liquid. IR ($CHCl_3$): 950, 1102, 1201, 1404, 1656, 2858, 2948. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*t*, *J* = 6.6, 3 H); 1.22–1.46 (*m*, 18 H); 1.46–1.78 (*m*, 10 H); 3.60–3.64 (*m*, 1 H); 3.68–3.72 (*m*, 1 H); 3.78–3.83 (*m*, 1 H); 3.81–3.85 (*m*, 1 H); 4.50–4.54 (*m*, 2 H); 7.50–7.53 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 13.2; 14.1; 22.6; 23.3; 23.4; 24.1; 24.2; 25.2; 25.5; 30.8; 30.8; 31.3; 31.9; 34.9; 36.4; 36.6; 65.6; 65.7; 72.0; 72.9; 78.4; 80.6; 109.8; 110.0; 127.4; 127.7; 127.9; 128.2; 138.7; 138.9. HR-ESI-MS: 425.3026 ($[M+Na]^+$, $C_{26}H_{42}NaO_3^+$; calc. 425.3032).

Deprotection of Cyclohexylidene Group. A mixture of the benzyl protected compound (**5a**–**5g**; 12.76 mmol) and TsOH (20 mol-%) in MeOH (30 ml) was stirred at 50° until the starting material disappeared (as monitored by TLC, 8 h). The mixture was concentrated *in vacuo*, treated with H_2O (1 × 25 ml) and extracted with AcOEt (3 × 25 ml). A $NaHCO_3$ soln. (20%, 20 ml) was added to remove the excess TsOH, and the org. layer was dried and concentrated *in vacuo*. The residue was subjected to CC (SiO_2; 0–50% AcOEt/hexane) to obtain the pure product.

*(2*R*,3*RS*)-3-*O*-Benzylbutane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)butane-1,2-diol*; **6a**). *syn*/*anti* 1:1. Yield 82%. Transparent liquid. IR ($CHCl_3$): 950, 1102, 1201, 1404, 1656, 2858, 2948, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.03 (*d*, *J* = 6.2, 3 H); 3.53 (*d*, *J* = 7.0, 1 H); 3.71–3.81 (*m*, 3 H); 4.55 (*s*, 2 H); 7.19–7.39 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 11.2; 63.5; 71.5; 71.9; 75.5; 128.0; 129.5; 129.8; 139.4. HR-ESI-MS: 219.0987 ($[M+Na]^+$, $C_{11}H_{16}NaO_3^+$; calc. 219.0997).

*(2*R*,3*RS*)-3-*O*-Benzylpentane-1,2,3-triol* (= *3*-O-*Benzyl-1,2-dideoxy*-D-glycero-*pentitol*; **6b**). *syn*/*anti* 1:1. Yield 82%. Colorless oil. IR ($CHCl_3$): 950, 1067, 1201, 1404, 1656, 2858, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*t*, *J* = 6.8, 2 H); 1.52–1.72 (*m*, 4 H); 3.52–3.85 (*m*, 3 H); 3.90–3.93 (*m*, 1 H); 4.58 (*s*, 2 H); 7.30–7.38 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 17.8; 26.7; 26.9; 65.7; 66.0; 77.6; 78.4; 86.3; 86.9; 131.2; 131.8; 132.1; 142.3; 142.7. HR-ESI-MS: 233.1149 ($[M+Na]^+$, $C_{12}H_{18}NaO_3^+$; calc. 33.1154).

*(2*R*,3*RS*)-3-*O*-Benzylhexane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)hexane-1,2-diol*; **6c**). *syn*/*anti* 27:73. Yield 85%. Transparent liquid. IR ($CHCl_3$): 950, 1067, 1201, 1404, 1656, 2888, 3380. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80–0.89 (*m*, 3 H); 1.26–1.52 (*m*, 3 H); 1.61–1.66 (*m*, 1 H); 3.25 (*s*, OH); 3.61–3.65 (*m*, 1 H); 3.71–3.75 (*m*, 3 H); 4.58 (*s*, 2 H); 7.41–7.46 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 9.2; 19.6; 33.2; 33.9; 64.3; 64.7; 73.6; 74.9; 80.6; 81.3; 129.2; 129.7; 130.1; 139.1; 139.6. HR-ESI-MS: 247.1322 ($[M+Na]^+$, $C_{13}H_{20}NaO_3^+$; calc. 247.1310).

*(2*R*,3*RS*)-3-*O*-Benzylheptane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)heptane-1,2-diol*; **6d**). *syn*/*anti* 9:11. Yield 86%. Transparent liquid. IR ($CHCl_3$): 950, 1201, 1496, 1656, 2858, 3108, 3405. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 6.2, 3 H); 1.37–1.46 (*m*, 6 H); 1.65 (*s*, OH); 3.42–3.49 (*m*, 1 H); 3.60–3.72 (*m*, 3 H); 4.41–4.49 (*m*, 2 H); 7.31–7.36 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.5; 19.6; 23.5; 28.4; 29.1; 65.3; 75.9; 80.0; 129.3; 129.6; 129.9; 139.4; 139.8. HR-ESI-MS: 261.1460 ($[M+Na]^+$, $C_{14}H_{22}NaO_3^+$; calc. 261.1467).

*(2*R*,3*RS*)-3-*O*-Benzyloctane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)octane-1,2-diol*; **6e**). *syn*/*anti* 9:11. Yield 90%. Transparent liquid. IR ($CHCl_3$): 957, 1107, 1224, 1454, 1656, 2908, 3406. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.91–0.95 (*m*, 3 H); 1.27–1.50 (*m*, 4 H); 1.52–1.73 (*m*, 4 H); 3.27–3.40 (*qq*, *J* = 4.6, 5.6, 11.3, 12.7, 2 H); 3.50–3.53 (*m*, 1 H); 3.72 (*q*, *J* = 4.6, 11.3, 1 H); 4.50–4.57 (*m*, 2 H); 7.22–7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 9.2; 23.6; 24.5; 26.2; 30.3; 64.4; 71.2; 72.9; 74.3; 129.2; 129.8; 139.2. HR-ESI-MS: 275.1619 ($[M+Na]^+$, $C_{15}H_{24}NaO_3^+$; calc. 275.1623).

*(2*R*,3*RS*)-3-*O*-Benzylnonane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)nonane-1,2-diol*; **6f**). *syn*/*anti* 36:64. Yield 92%. Transparent liquid. IR ($CHCl_3$): 950, 1067, 1201, 1404, 1656, 2858, 2952, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, *J* = 6.8, 3 H); 1.50–1.72 (*m*, 10 H); 2.75 (*s*, OH); 3.51–3.88 (*m*, 4 H); 4.54 (*s*, 2 H); 7.41–7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.6; 23.5; 26.2; 30.5; 32.4; 64.2; 73.1; 82.3; 128.8; 129.4; 139.2. HR-ESI-MS: 289.1774 ($[M+Na]^+$, $C_{16}H_{26}NaO_3^+$; calc. 289.1780).

*(2*R*,3*RS*)-3*-O-*Benzyltridecane-1,2,3-triol* (= *(2*R*)-3-(Benzyloxy)tridecane-1,2-diol*; **6g**). *syn*/*anti* 1:4. Yield 92%. Colorless thick oil. IR ($CHCl_3$): 950, 1067, 1201, 1404, 1656, 2858, 2903, 3390. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*t*, *J* = 6.6, 3 H); 1.22–1.49 (*m*, 18 H); 2.09 (*s*, OH); 3.64 (*q*, *J* = 2.3, 4.6, 1 H); 3.75 (*q*, *J* = 6.4, 12.8, 1 H); 3.76–3.82 (*m*, 1 H); 4.00–4.14 (*m*, 1 H); 4.50–4.54 (*m*, 2 H); 7.23–7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1; 22.7; 25.3; 29.4; 29.8; 30.1; 30.3; 31.9; 64.1; 72.5; 73.2; 79.9; 127.8; 127.9; 128.5; 138.3. HR-ESI-MS: 345.2395 ($[M+Na]^+$, $C_{20}H_{34}NaO_3^+$; calc. 345.2406).

General Procedure for the Azidation of 1,2-Diols. To a soln. of a diol (1.0 mmol) and Ph_3P (342 mg, 1.3 mmol) in 18 ml of dry toluene was injected DIAD (1.5 mmol) at 0°. Stirring the yellow mixture at this temp. for 20 min under N_2 was followed by injection of Me_3SiN_3 (1.3 mmol). (Note: Me_3SiN_3 is sensitive to H_2O, releasing toxic hydrazoic acid on hydrolysis. Therefore, Me_3SiN_3 should be used only in a well-ventilated hood, and skin contact should be avoided). The mixture (either a clear soln. or sometimes a suspension) was stirred at the same temp. for 2 h and then allowed to warm to r.t. After the removal of the solvent, the residue was dissolved in 3 ml THF and treated with 2.5 ml of a 1M tetrabutylammonium fluoride (TBAF) soln. in THF containing 5 wt-% of H_2O. The brown mixture was stirred at r.t. until all of the silyloxy azides **16a**-OTMS and **16b**-OTMS were consumed completely (TLC). Concentration of the solvent gave a slurry, which was dissolved in CH_2Cl_2 (3 × 30 ml) and washed with brine (1 × 30 ml) and dried, concentrated *in vacuo* to give the regiomeric mixture **7a**–**7g** and **8a**–**8g** in 73–90%. The mixtures were separated by CC over SiO_2 using 0–12% AcOEt/hexane to obtain **7a**–**7g**.

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)butan-1-ol* (**7a**). *syn*/*anti* 1:1. Yield 58%. Transparent liquid. IR ($CHCl_3$): 1018, 1098, 1272, 1454, 1667, 2101, 2856, 2930, 3064, 3435. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*d*, *J* = 6.1, 3 H); 3.40–3.72 (*m*, 4 H); 4.51–4.56 (*m*, 2 H); 7.41–7.46 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 17.3; 54.4; 59.3; 72.5; 73.6; 128.6; 128.9; 129.4; 138.7. HR-ESI-MS: 244.1057 ($[M+Na]^+$, $C_{11}H_{15}N_3NaO_2^+$; calc. 244.1062).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)pentan-1-ol* (**7b**). *syn*/*anti* 1:1. Yield 68%. Transparent liquid. IR ($CHCl_3$): 1028, 1099, 1273, 1453, 1496, 2100, 2852, 2922, 3392. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*m*, 3 H); 1.41–1.46 (*m*, 2 H); 3.54–3.77 (*m*, 4 H); 4.56 (*s*, 2 H); 7.51–7.54 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.3; 23.2; 23.4; 60.6; 69.6; 73.6; 77.0; 127.7; 127.9; 128.2; 129.1; 137.3; 137.8. HR-ESI-MS: 258.1211 ($[M+Na]^+$, $C_{12}H_{17}N_3NaO_2^+$; calc. 258.1218).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)hexan-1-ol* (**7c**). *syn*/*anti* 27:73. Yield 60%. Transparent liquid. IR ($CHCl_3$): 1027, 1208, 1454, 1496, 1604, 1723, 2101, 2871, 2930, 2958, 3434. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*t*, *J* = 6.3, 3 H); 1.35–1.55 (*m*, 4 H); 3.38–3.42 (*m*, 1 H); 3.72–4.23 (*m*, 3 H); 4.58 (*s*, 2 H); 7.51–7.56 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 12.0; 16.3; 30.1; 63.8; 64.0; 72.8; 78.5; 127.7; 128.1; 128.5; 137.5. HR-ESI-MS: 272.1371 ($[M+Na]^+$, $C_{13}H_{19}N_3NaO_2^+$; calc. 272.1375).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)heptan-1-ol* (**7d**). *syn*/*anti* 9:11. Yield 60%. Transparent liquid. IR ($CHCl_3$): 1027, 1208, 1454, 1496, 1604, 1723, 2101, 2871, 2930, 2958, 3434. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.98 (*t*, *J* = 6.2, 3 H); 1.35–1.65 (*m*, 6 H); 3.38–3.43 (*m*, 1 H); 3.67–4.23 (*m*, 3 H); 4.55 (*s*, 2 H); 7.52–7.57 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.6; 19.3; 29.9; 30.1; 64.7; 66.0; 72.8; 79.5; 128.7; 129.1; 129.5; 137.6. HR-ESI-MS: 286.1527 ($[M+Na]^+$, $C_{14}H_{21}N_3NaO_2^+$; calc. 286.1531).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)octan-1-ol* (**7e**). *syn*/*anti* 9:11. Yield 59%. Transparent liquid. IR ($CHCl_3$): 1028, 1100, 1273, 1495, 1587, 2101, 2850, 2921, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.92–0.95 (*m*, 3 H); 1.11–1.41 (*m*, 8 H); 3.39 (*dd*, *J* = 6.8, 12.7, 1 H); 3.47 (*dd*, *J* = 4.7, 12.7, 1 H); 3.60 (*d*, *J* = 5.2, 1 H); 3.67–3.77 (*m*, 1 H); 4.57 (*s*, 2 H); 7.31–7.41 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.2; 20.1; 25.1; 29.1; 29.5; 58.5; 65.4; 72.2; 79.5; 128.3; 129.0; 129.4; 139.4. HR-ESI-MS: 300.1681 ($[M+Na]^+$, $C_{15}H_{23}N_3NaO_2^+$; calc. 300.1688).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)nonan-1-ol* (**7f**). *syn*/*anti* 36:64. Yield 59%. Transparent liquid. IR ($CHCl_3$): 1028, 1098, 1272, 1454, 1667, 2101, 2856, 2930, 3064, 3435. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 6.0, 3 H); 1.22–1.62 (*m*, 10 H); 3.52–4.32 (*m*, 4 H); 4.55 (*s*, 2 H); 7.40–7.46 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.3; 22.3; 25.3; 29.7; 30.7; 31.9; 59.3; 65.0; 72.1; 81.2; 128.4; 128.7; 129.0; 139.2. HR-ESI-MS: 314.1840 ($[M+Na]^+$, $C_{16}H_{25}N_3NaO_2^+$; calc. 314.1844).

*(2*S*,3*RS*)-2-Azido-3-(benzyloxy)tridecan-1-ol* (**7g**). *syn*/*anti* 1:4. Yield 59%. Transparent liquid. IR ($CHCl_3$): 1103, 1269, 1374, 1454, 1657, 1746, 2102, 2854, 2925, 3400. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 7.3, 3 H); 1.23–1.52 (*m*, 6 H); 1.53–1.78 (*m*, 12 H); 3.52–4.35 (*m*, 4 H); 4.60–4.65 (*m*, 2 H); 7.41–

7.45 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 15.4; 22.4; 25.4; 27.1; 29.3; 31.2; 60.0; 71.2; 73.2; 80.5; 128.2; 128.5; 129.3; 138.3. HR-ESI-MS: 370.2466 ($[M+Na]^+$, $C_{20}H_{33}N_3NaO_2^+$; calc. 370.2470).

Oxidation of Azido-Alcohols – General Procedure. The azido alcohols (**7f** and **7g**; 1 equiv.) were dissolved in anh. CH_2Cl_2, and *Dess–Martin* periodinane (1.3 equiv.) was slowly added at 0°. The mixture stirred for 3–4 h and after completion of the reaction as indicated by TLC, the reaction was quenched with H_2O (1 × 20 ml). The extraction was carried out with CH_2Cl_2 (3 × 20 ml), and the org. solvent washed with $NaHCO_3$ (10%, 20 ml), $Na_2S_2O_3$ (10%, 15 ml), and brine (10 ml), resp. The org. solvent was dried (anh. Na_2SO_4) and removed under reduced pressure to obtain the aldehyde.

The aldehyde (1 equiv.) obtained as described above was dissolved in DMF (0.1M). Potassium peroxomonosulfate ($KHSO_5$; Oxone; 1 equiv.) was added in one portion and the mixture was stirred at r.t. for 8–10 h until the consumption of starting material was indicated by TLC. 1N HCl was used to dissolve the salts, and AcOEt (3 × 15 ml) was added to extract the products. The org. extract was washed with 1N HCl and brine (1 × 10 ml), dried, then the solvent was removed under reduced pressure to obtain the crude product, which was purified by CC to give the azido acids (SiO_2; 0–20% MeOH/$CHCl_3$).

*(2*R*,3*RS*)-2-Azido-3-(benzyloxy)nonanoic Acid* (**12f**). *syn*/*anti* 36:64. Yield 50%. Semi-solid. IR ($CHCl_3$): 1113, 1260, 1334, 1430, 1615, 1667, 2103, 2850, 2924, 2505–3380. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*t*, *J* = 6.9, 3 H); 1.27–1.32 (*m*, 3 H); 1.51–1.57 (*m*, 7 H); 2.82–2.87 (*m*, 1 H); 3.31–3.37 (*m*, 1 H); 4.51–4.56 (*m*, 2 H); 7.58–5.63 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 11.1; 21.8; 25.0; 29.7; 29.9; 31.2; 73.1; 73.7; 75.7; 75.7; 128.3; 129.4; 129.6; 138.2; 177.6. HR-ESI-MS: 328.1630 ($[M+Na]^+$, $C_{16}H_{23}N_3NaO_3^+$; calc. 328.1637).

*(2*R*,3*RS*)-2-Azido-3-(benzyloxy)tridecanoic Acid* (**12g**). *syn*/*anti* 1:4. Yield 60%. Semi-solid. IR ($CHCl_3$): 1103, 1209, 1354, 1452, 1634, 1696, 2102, 2830, 2922, 2500–3381. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.96 (*t*, *J* = 6.9, 3 H); 1.41–1.75 (*m*, 18 H); 2.51–2.56 (*m*, 1 H); 3.67–3.69 (*m*, 1 H); 4.52–4.58 (*m*, 2 H); 7.24–7.44 (*m*, 5 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 13.3; 21.3; 23.4; 25.4; 26.2; 28.6; 30.1; 30.3; 31.2; 74.9; 75.6; 75.7; 77.5; 128.3; 130.4; 130.5; 139.2; 139.3; 178.2. HR-ESI-MS: 384.2257 ($[M+Na]^+$, $C_{20}H_{31}N_3NaO_3^+$; calc. 384.2263).

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