Synthesis R. Pemha et al. Paper

Synthesis of (2*S*,3*R*,5*R*)-2-Azido-3,5-dihydroxynonadecane Sphingolipid Analogue

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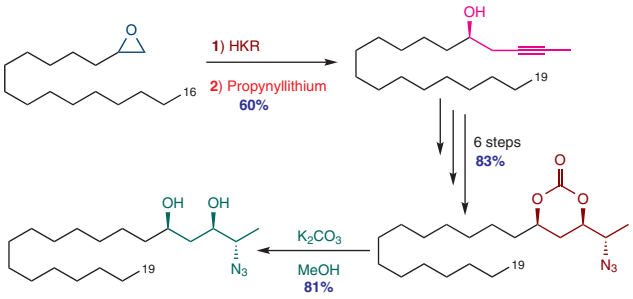

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Abstract A concise and highly efficient synthesis of an enigmol analogue has been achieved. The synthetic strategy features Jacobsen's hydrolytic kinetic resolution (HKR) and epoxide opening by alkynyl boranes as the key steps.

Key words sphingolipid, HKR, epoxide, enigmol, β-hydroxyacetylenes

Sphingolipids (SpLs) are a class of complex lipids containing an amide-linked fatty acid and long chain (sphingoid) base that are important structural components of cell membranes.[1] They exhibit a wide range of biological activities such as cell proliferation, differentiation, adhesion, and signal transduction.[2] SpLs also play an essential role in cell growth, survival, and death.[3] Interest in sphingolipids study have been aroused from the discovery that the D-*erythro* sphingosine **1** (Figure 1) inhibits protein kinace C,[4] as well as activation of caspase pathways for apoptosis.[5,6] It has also appeared that structural modifications in the moieties headgroup of sphingolipid **1** from 2-amino-1,3-diol to 2-amino-3,5-diol may result in compounds that exhibit improved pharmacological profiles (better potency, lower toxicity, more favorable absorption, distribution, metabolism, and excretion properties).

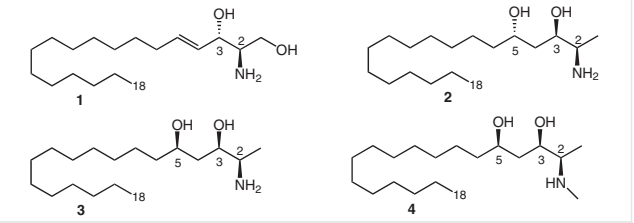

Figure 1 Sphingosine **1** and its analogues **2–4**

Thus, 1-deoxy-5-hydroxysphingoid base analogues **2–4**[7,8] were of particular interest, for the reason that they retain many of the physical characteristics of the natural sphingolipids, but lack a C-1 primary hydroxyl group. For it was hypothesized that by trans-locating the C-1 hydroxyl group to the C-5 position would lead to compounds maintaining similar hydrophobicity and enzymatic recognition, while eliminating the possibility for phosphorylation of the C-1 hydroxyl group by sphingosine kinase (SK). This was desirable due to the fact that the phosphate intermediates formed by SK are subject to catabolic degradation and also possess undesirable pro-mitogenic and anti-apoptotic properties.[9,10] The presence of a hydroxyl group on C-5 allows the 1-deoxy-compounds to firmly mimic the hydrophobicity and log P characteristics of sphingosine, which easily traverses and diffuses between cell membranes.[11] Moreover, sphingolipid analogues can also be used to modulate endogenous sphingolipid levels, thereby amplifying their potential therapeutic effects. Compounds **2** and **3** were reported as anticancer principles[7] while enigmol (**3**) was described as a therapeutic agent for treating prostate cancer[12] and *N*-methylenigmol (**4**) inhibiting the development of malaria parasites.[8]

The moieties headgroup 2-amino-3,5-diols of compounds **2–4** has previously been prepared either from L-alanine via α-aminoaldehyde,[10] or α-aminoketone synthetic intermediate,[13] which are generally subjected to the epimerization of the chiral center.[14] Nokami's enantioselective crotyl transfer methodology also used in the preparations of each diastereomer **2** and **3** generated trace amounts of other diastereomers, arising from the minor enantiomers developed by either the crotyl transfer or Shi-epoxidation step.[7,15]

Although several procedures of the target compounds have already been reported, most of these methods suffer either from large number of steps, low yields or from low

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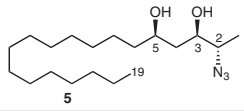
stereo- or regioselectivity. Therefore, a practical concise efficient method with high yield of the target molecules is still on demand.

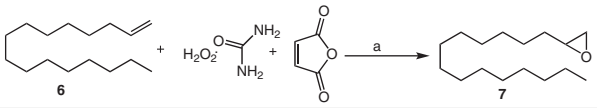
Alkynyl boranes, generated in situ from lithium acetylides and boron trifluoride etherate were found to react with oxiranes under mild reaction conditions to afford β-hydroxyacetylenes in high yields.[16] As a part of our research interest in asymmetric synthesis of bioactive molecules such as fumonisin B[13,17] and amino alcohols,[7,12] we became interested in developing a new and highly concise route to 1-deoxy-5-hydroxysphingoid. Herein, we report a highly efficient synthesis of enigmol analogue **5** (Figure 2) employing Jacobsen's hydrolytic kinetic resolution (HKR) and epoxide opening by alkynyl boranes as the key steps.



5

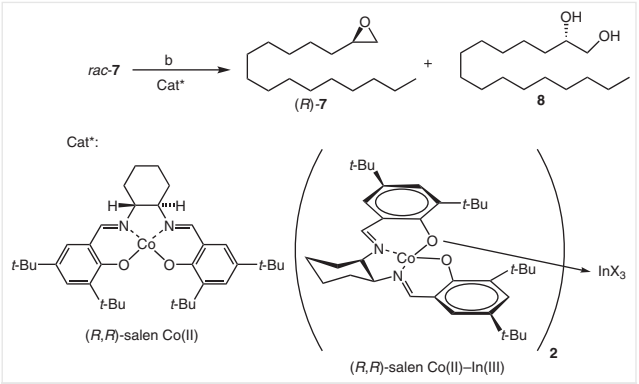
Figure 2 Enigmol analogue **5**

As illustrated in Scheme 1, the synthesis of **5** started from the commercially available hexadec-1-ene (**6**). Racemic epoxide **7** was easily obtained in 93% yield by reaction of hexadec-1-ene (**6**) with urea-hydrogen peroxide complex (UHP) and maleic anhydride in dichloromethane.[18] The reaction was quenched with an aqueous sodium carbonate solution, which allowed removing maleic acid formed during the reaction (Scheme 1).



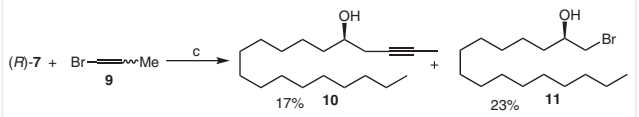
Scheme 1 Synthesis of racemic epoxide **7**. *Reagents and conditions*: (a) DCM, r.t., 93%.

Resolution of racemic epoxide **7** was done by hydrolytic kinetic resolution (HKR). Initially, we have used Jacobsen's method with a (salen)cobalt(III) complex[19] as a catalyst. After that, to expedite the reaction, we used another catalyst, a bimetallic (salen)cobalt(II)-indium(III) complex developed by Geon-Joong Kim et al.[20] (Scheme 2). The latter method presented several advantages: easier handling of the catalyst, faster reaction (overnight vs 3 days), and it was reported to afford a higher enantioselectivity (generally ≥99%) within an enantiomeric ratio 50:50 of relative rates of the two enantiomers.[20] The desired (*R*)-**7** enantiomer from *rac*-**7** was obtained by using the *R*,*R*-enantiomer's catalyst. Compound (*R*)-**7** was easily separated from the diol **8** by column chromatography. HKR using cobalt(III)–salen complex afforded (*R*)-**7** in 46% yield and **8** in 42% yield. HKR using the bimetallic complex afforded (*R*)-**7** in 49% yield and **8** in 47% yield within an enantiomeric ratio 50:50.



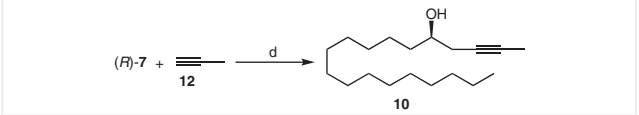
Scheme 2 Resolution of epoxide *rac*-**7** by HKR. *Reagents and conditions*: (b) H_2O (0.55 equiv), THF, r.t., 24 h.

The opening of (*R*)-**7** by propynyllithium generated in situ from (*Z*/*E*)-1-bromopropene (**9**) in anhydrous THF at –78 °C in the presence of boron trifluoride etherate resulted in 17% yield of the expected β-hydroxyacetylene **10**, along with 23% yield of a by-product **11** separable by column chromatography (Scheme 3), arising from a subsequent epoxide opening by LiBr remaining in situ before activation of epoxide by Lewis acid.[16]



Scheme 3 Reaction of epoxide (*R*)-**7** with (*Z*/*E*)-bromopropene. *Reagents and conditions*: (c) *n*-BuLi, THF, $BF_3{\cdot}OEt_2$, 78 °C, 2 h; 17% of **10** and 23% of **11**.

When (*Z*/*E*)-1-bromopropene (**9**) was replaced by propyne (**12**) under the previous conditions, only homopropargylic alcohol **10** was obtained in 72% yield (Scheme 4).



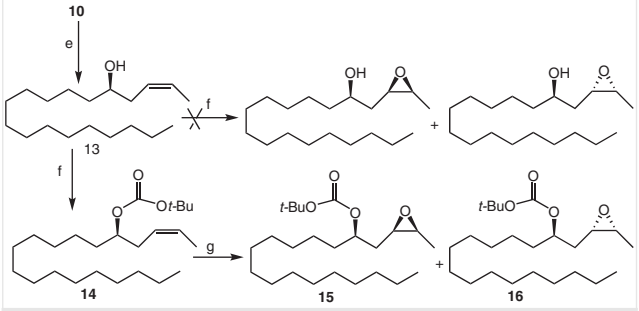
Scheme 4 Epoxide (*R*)-**7** opening by propyne. *Reagents and conditions*: (d) *n*-BuLi, THF, $BF_3{\cdot}OEt_2$, –78 °C, 2 h; 72%.

Treating **10** with nickel P-2 and ethylenediamine in ethanol/THF provided exclusively *Z*-homoallylic alcohol **13** in 95% yield (Scheme 5). As shown in Table 1, reduction of homopropargylic alcohol **10** to homoallylic alcohol **13** was investigated under several conditions to enhance its yield.

Attempts to react **13** with MCPBA in dichloromethane failed. Therefore, **13** was subjected to Boc_2O and *n*-BuLi in THF to provide **14** in 76% yield, which through epoxidation using MCPBA in DCM provided a mixture of epoxides (50:50) *erythro*-**15** and *threo*-**16**.

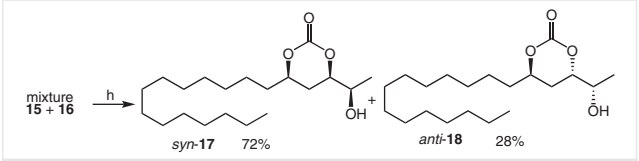
Table 1 Catalytic Hydrogenation of **10** by Nickel P-2

$NaBH_4$(equiv)	$Ni(OAc)_2$ (equiv)	Solvent	Temp	Time (h)	Ethylenediamine (equiv)	Yield (%)
0.4	0.2	EtOH	r.t.	5	1	24
0.4	0.2	*i*-PrOH	r.t.	5	1	38
0.4	0.2	THF	r.t.	5	1	90
0.4	0.2	EtOH/THF	r.t.	5	1	95



Scheme 5 Synthesis of epoxycarbonates **15** and **16**. *Reagents and conditions*: (e) $NaBH_4$/Nickel P-2, ethylenediamine, EtOH/THF, r.t., 5 h; 95%; (f) *n*-BuLi, Boc_2O, THF, 0 °C, 2 h; 76%; (g) MCPBA, DCM, r.t., 2 h, 1:1 mixture of **15** and **16**.

The stereochemical assignment of the epoxide has been made by analogy with the precedent literature.[15] Following this, the mixture of epoxycarbonate (**15** + **16**) was subjected to $BF_3{\cdot}OEt_2$ in DCM to provide two cyclic carbonates: *syn*-**17** and *anti*-**18** (72:28) in 56% overall yield, separable by column chromatography (Scheme 6).

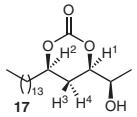
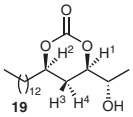
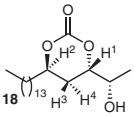
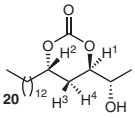


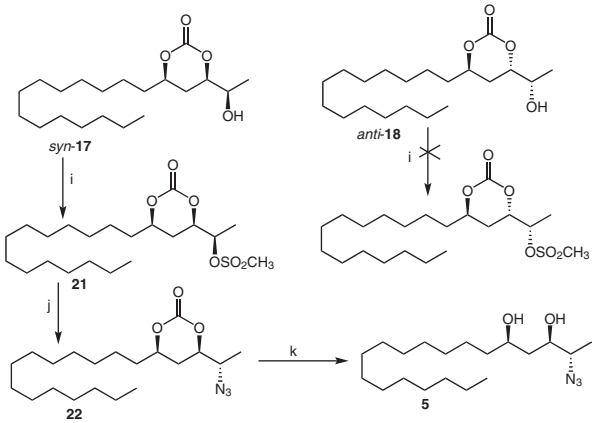
Scheme 6 Synthesis of the key intermediates **17** and **18**. *Reagents and conditions*: (h) $BF_3{\cdot}OEt_2$, DCM, –40 °C, 15 min; 72% of **17** and 28% of **18**.

^{1}H NMR analysis of the coupling constants of **17** is consistent with the presence of the *syn*-1,3-cyclic carbonate in comparison with the diastereomer **18**, which indicates the *anti*-1,3-cyclic carbonate. These relative stereochemical assignments are in full agreement when compared, respectively, with diastereomers **19** and **20** described by Wiseman et al.[7] (Table 2).

When **18** was subjected to mesylation employing mesyl chloride in DCM and Et_3N, only a trace of the desired product was observed along with the starting material. However, using the same conditions, **17** was converted into **21** in 94% yield, which under S_N2 substitution of the intermediate mesylate group using sodium azide in DMSO provided **22** in 94% yield. Treating **22** with potassium carbonate in methanol provided **5** in 81% yield (Scheme 7). Azide group was kept in the alkyl chain to evaluate its effects on the biological activity.

Table 2 Comparison of NMR Data of **17** and **18** with Known Compounds **19** and **20**

Compound	Coupling constant *J* (Hz)				^{13}C NMR, δ (ppm)
	H^1-H^3	H^1-H^4	H^2-H^3	H^2-H^4	Carbonyl group
 **17**	2.9	14.3	3.4	14.1	154.6
 **19**	3.0	14.4	3.6	14.4	149.7
 **18**	6.9		6.9		149.3
 **20**	7.2		6.6		154.8



Scheme 7 Synthesis of enigmol analogue **5**. *Reagents and conditions*: (i) MsCl, Et_3N, DCM, –20 °C, 3 h 30 min; 94%; (j) NaN_3, DMSO, 80 °C, 20 h; 94%; (k) K_2CO_3, MeOH, 14 h, r.t.; 81%.

In summary, we have achieved a concise synthesis of the enigmol analogue **5** using Jacobsen's hydrolytic kinetic resolution as a source of chirality and epoxide opening by alkynyl boranes as the key steps. The generality of the method has shown significant potential of its further extension to the other diastereomers of 1-deoxy-5-hydroxysphingoid and related analogues.

Moisture-sensitive reactions were performed under N_2. Anhyd THF and Et_2O were obtained by percolation through a column of a dry resin. Room temperature (r.t.) means a temperature generally in the range of 18–20 °C. Column chromatography was performed over Kielselgel 60 (40–60 μm). Routine monitoring of reactions was carried out using Merck silica gel 60 F_{254} TLC plates purchased from Fluka and visualized by UV light (254 nm) inspection followed by staining with an acidic ethanolic solution of *p*-anisaldehyde IR spectra were recorded with a Thermo Nicolet Avatar 250 FTIR and are reported using the frequency of absorption (cm^{-1}). ^1H NMR spectra (400.13 MHz) and ^{13}C NMR spectra (100.61 MHz) were recorded on an Avance 400 Bruker spectrometer using TMS as an internal standard. Multiplicity is indicated using standard abbreviations. Specific rotations were measured on a PerkinElmer 341 polarimeter, with a cell of 1 dm long and a Na- or Hg-source (Na at 589 nm; Hg at 578 nm, 546 nm, 436 nm and 365 nm), and concentrations are expressed in g/100 mL. High-resolution mass spectra (HRMS) were recorded using a MicrO-Tof-Q II spectrometer under electrospray using MeOH as solvent. Microanalyses were performed with a CHNS analyzer. Melting points (mp) were determined with a Stuart SMP10 device. Hexadec-1-ene (**6**) (CAS Number: 629-73-2) was purchased from Sigma-Adrich.

rac-2-Tetradecyloxirane (*rac*-7)

In a flamed-dried three-necked flask containing maleic anhydride (15.69 g, 160 mmol, 3.2 equiv), were introduced anhyd DCM (80 mL) and refluxed at r.t. under N_2. Grounded UHP (15.05 g, 160 mmol, 3.2 equiv) was added and stirred for 40 min, then a solution of hexadec-1-ene (**6**; 11.22 g, 50 mmol) in DCM (20 mL) was added and the corresponding mixture was stirred overnight 20 h at r.t. TLC monitoring showed completion of the reaction and a solution of Na_2CO_3 (21.2 g, 200 mmol) in distilled H_2O (120 mL) was added dropwise with caution as a white foaming was observed. Extraction was done with DCM and the combined organic layers were dried (Na_2SO_4). The solvent was evaporated and the crude product was filtered over a short plug of silica gel using petroleum ether (PE) to provide *rac*-**7** as a colorless oil; yield: 11.6 g (93%); R_f = 0.76 (PE/acetone 95:5)

IR (KBr): 3431, 3397, 2955, 2918, 2849, 1469, 1349, 1105, 1079, 1027, 849, 721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.71 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.52–3.46 (m, 2 H), 3.39 (dd, *J* = 8.0, 4.0 Hz, 1 H), 3.17–3.13 (m, 1 H), 2.80 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.61 (dd, *J* = 5.0, 4.0 Hz, 1 H), 1.60–1.56 (m, 2 H, CH_2), 1.33–1.25 (m, 20 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (CHO), 47.2 (CH_2O), 32.5 (CH_2), 31.9 (CH_2), 29.8 (2 × CH_2), 29.7 (CH_2), 29.6 (2 × CH_2), 29.5 (2 × CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

(*R*)-2-Tetradecyloxirane [(*R*)-7]

HKR of *rac*-7 Using Jacobsen's Method

In a 10 mL flask, (*R*,*R*)-(–)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (37.8 mg, 0.062 mmol, 0.01 equiv) and toluene (0.37 mL) were introduced followed by AcOH (7.5 μL, 0.13 mmol, 0.02 equiv). The mixture was stirred exposed to air for 1 h, then concentrated under reduced pressure, and put in high vacuum. The remaining brown oil was redissolved in anhyd Et_2O (1.85 mL) and added to *rac*-**7** (1.75 g, 7.28 mmol) followed by distilled H_2O (62 μL, 3.44 mmol, 0.55 eq). The flask was purged with N_2, stoppered, and the contents were left with stirring for 72 h at r.t. L-Ascorbic acid (15 mg, 2 equiv) was added and the stirring was continued for 1 h. Dark brown catalyst was reduced to red salen-cobalt(II) complex. EtOAc was added to the mixture and the organic layer was dried (Na_2SO_4) and concentrated. Chromatography on silica gel provided epoxide (*R*)-**7** (803 mg, 46%, eluted with 0.1% Et_3N in PE) followed by diol **8** (741 mg, 42%, eluted with 5 → 10% acetone in PE).

Bimetallic (Salen)cobalt(II)-Indium(III) Complex

To a dried flask, containing $InCl_3$ (91.6 mg, 0.41 mmol) and anhyd THF (3 mL) with stirring at r.t., was added distilled H_2O (ca. 0.006 mL) to dissolve the $InCl_3$ completely and rapidly. (*R*,*R*)-(–)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) (500 mg, 0.83 mmol) was added in three portions. A fast change of color was observed (from red to dark olive green and then to brown) and a precipitate of bimetallic complex observed. The stirring was pursued for 1 h at r.t. with the flask left open, and the resulting mixture was partionned between H_2O and DCM. The organic layer was filtered over a short plug of silica gel and rinsed with DCM. The solvent was evaporated to afford the bimetallic (salen)cobalt(II)-indium(III) complex as a green powder; yield: 0.54 g (92%).

HKR of Racemic-7 Using Bimetallic (Salen)cobalt(II)-Indium(III) Complex

To a stirred mixture of *rac*-**7** (3.8 g, 16 mmol) and bimetallic (salen)cobalt(II)-indium(III) complex (68.6 mg, 0.05 mmol, 0.003 equiv) in anhyd THF (8 mL) was added distilled H_2O (159 μL, 8.8 mmol, 0.55 equiv). The flask was purged with N_2, stoppered, and the contents were left with stirring for 24 h at 25 °C. L-Ascorbic acid (40 mg) was added to the mixture and the stirring was continued for 1 h. After evaporation, the crude was purified by column chromatography on silica gel to provide a colorless oil of epoxide (*R*)-**7** (1.88 g, 49%) followed by a white solid diol **8** (1.8 g, 47%) in an enantiomeric ratio of 50:50.

(*R*)-2-Tetradecyloxirane [(*R*)-7]

R_f = 0.76 (PE/acetone 95:5); $[\alpha]_D^{21}$ +2.8, $[\alpha]_{578}^{21}$ +2.8, $[\alpha]_{546}^{21}$ +3.0, $[\alpha]_{436}^{21}$ +3.4 (*c* 4.0, $CHCl_3$); $[\alpha]_D^{21}$ +5.9, $[\alpha]_{578}^{21}$ +6.1, $[\alpha]_{546}^{21}$ +6.8, $[\alpha]_{436}^{21}$ +9.6 (*c* 4.3, benzene){Lit.[21] $[\alpha]_D^{25}$ +9.64 (*c* 3.71, *n*-hexane)}.

IR (KBr): 3431, 3397, 2955, 2918, 2849, 1469, 1349, 1105, 1079, 1027, 849, 721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.93–2.88 (m, 1 H), 2.75 (dd, *J* = 8.0, 4.0 Hz, 1 H), 2.46 (dd, *J* = 4.0, 2.7 Hz, 1 H), 1.56–1.41 (m, 5 H), 1.35–1.28 (m, 21 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.4 (CHO), 47.2 (CH_2O), 32.5 (CH_2), 31.9 (CH_2), 29.8 (2 × CH_2), 29.7 (2 × CH_2), 29.5 (CH_2), 29.5 (2 × CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.9 (CH_2), 22.7 (CH_2), 14.1 (CH_3).

(*S*)-Hexadecane-1,2-diol (8)

Mp 60 °C; R_f = 0.3 (PE/acetone 95:5); $[\alpha]_D^{23}$ –2.4 (*c* 2.0, $CHCl_3$){Lit.[22] $[\alpha]_D^{31}$ –2.49 (*c* 2.0, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.69–3.65 (m, 1 H), 3.54 (dd, *J* = 11.0, 7.7 Hz, 1 H), 2.14 (br s, 1 H), 2.05 (br s, 1 H), 1.49–1.36 (m, 3 H), 1.34–1.12 (m, 24 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.2 (CH), 66.8 (CH_2), 33.2 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (2 × CH_2), 27.2 (CH_2), 27.1 (CH_2), 25.5 (CH_2), 22.6 (CH_2), 14.1 (CH_3).

(*R*)-Nonadec-2-yn-5-ol [(*R*)-10]

To a cooled solution of THF (8 mL) at –78 °C under N_2 was added propyne (**12**; 360 mL, 12 mmol) under stirring, followed by the addition of *n*-BuLi (7.5 mL, 12 mmol, 1.5 equiv). After 10 min, a solution of BF_3·OEt_2 (1.5 mL, 12 mmol, 1.5 equiv) was added. A solution of (*R*)-**7** (1.9 g, 8 mmol) in THF (3.2 mL) was added and the transfer of (*R*)-**7** was completed by rinsing the flask with THF (2 × 0.5 mL), then the stirring was continued for 1 h at –78 °C. TLC monitoring showed completion of the reaction and an aqueous solution of NH_4Cl (2 mL) was added to the mixture and the extraction was done with EtOAc/PE (80:20). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude purified by column chromatography on silica gel (0 → 5% acetone in PE). After recrystallization from PE, (*R*)-**10** was obtained as white crystals; yield: 1.6 g (72%); mp 59 °C; R_f = 0.54 (PE/acetone 90:10); $[\alpha]_D^{21}$ –3.2, $[\alpha]_{578}^{21}$ –3.5, $[\alpha]_{546}^{21}$ –4.0, $[\alpha]_{436}^{21}$ –6.8, $[\alpha]_{365}^{21}$ –10.6 (c 1.5, $CHCl_3$); $[\alpha]_D^{21}$ +16.0, $[\alpha]_{578}^{21}$ +16.2, $[\alpha]_{546}^{21}$ +18.4, $[\alpha]_{436}^{21}$ +31.1, $[\alpha]_{365}^{21}$ +48.1 (*c* 1.5, THF); $[\alpha]_D^{21}$ –3.2, $[\alpha]_{578}^{21}$ –3.6, $[\alpha]_{546}^{21}$ –4.1, $[\alpha]_{436}^{21}$ –7.3, $[\alpha]_{365}^{21}$ –11.2 (*c* 0.9, CH_2Cl_2).

IR (KBr): 3352, 3285, 3013, 2917, 2848, 1473, 1463, 1347, 1262, 1098, 1028, 861, 802, 729, 719, 695 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.72–3.65 (m, 1 H), 2.38 (ddt, *J* = 16.5, 5.1, 2.5 Hz, 1 H), 2.24 (dddd, *J* = 16.5, 7.0, 5.1, 2.5 Hz, 1 H), 1.92 (d, *J* = 4.8 Hz, 1 H), 1.81 (t, *J* = 2.5 Hz, 3 H), 1.61 (s, 1 H), 1.53–1.41 (m, 3 H), 1.34–1.26 (m, 22 H), 0.89 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 78.4 (C), 75.4 (C), 70.2 (CH), 36.3 (CH_2), 31.9 (CH_2), 29.8 (2 × CH_2), 29.7 (CH_2), 29.6 (2 × CH_2), 29.6 (CH_2), 29.5 (2 × CH_2), 29.3 (CH_2), 27.7 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 3.5 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{36}ONa$ [M + Na]$^+$: 303.2687; found: 303.2683.

Anal. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.12; H, 12.78

(5*R*,2*Z*)-Nonadec-2-en-5-ol (13)

To a solution of $Ni(OAc)_2$·$4H_2O$ (113.1 mg, 0.45 mmol, 0.2 equiv) in EtOH (6.8 mL 95% of purity) under N_2 was added a solution of $NaBH_4$ (36.4 mg, 0.93 mmol, 0.41 equiv) in EtOH/THF (1:1, 2.26 mL). After the addition, the flask was purged under H_2, stoppered, and left with stirring for 15 min. A solution of ethylenediamine (155 µL, 2.293 mmol, 1 equiv) was added followed by the addition of a solution of compound (*R*)-**10** (638.5 mg, 2.27 mmol) in THF (2.21 mL). The transfer of (*R*)-**10** was completed by rinsing the flask with THF (2 × 0.12 mL) and the stirring was continued for 5 h. TLC monitoring showed completion of the reaction and the mixture was filtered over a short plug of Celite, rinsed with PE, and evaporated under reduced pressure. Compound **13** was obtained as white crystals; yield: 612 mg (95%); mp 46 °C; R_f = 0.39 (PE/acetone 90:10); $[\alpha]_D^{20}$ +1.3, $[\alpha]_{578}^{20}$ +1.2, $[\alpha]_{546}^{20}$ +1.3, $[\alpha]_{436}^{20}$ +1.1, $[\alpha]_{365}^{20}$ –0.8 (*c* 2.5, $CHCl_3$); $[\alpha]_D^{20}$ +4.0, $[\alpha]_{578}^{20}$ +3.9, $[\alpha]_{546}^{20}$ +4.5, $[\alpha]_{436}^{20}$ +6.9, $[\alpha]_{365}^{20}$ +9.2 (*c* 2,5, THF).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.65 (dqt, *J* = 10.9, 6.8, 1.5 Hz, 1 H), 5.44 (dtq, *J* = 10.9, 7.4, 1.8 Hz, 1 H), 3.63 (ddt, *J* = 6.3, 6.1, 5.7 Hz, 1 H), 2.24–2.21 (m, 2 H), 1.65 (ddt, *J* = 6.8, 1.8, 0.85 Hz, 3 H), 1.59–1.45 (m, 5 H), 1.37–1.26 (m, 22 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.3 (CH), 126.2 (CH), 71.5 (CH), 36.9 (CH_2), 34.9 (CH_2), 31.9 (CH_2), 29.8 (2 × CH_2), 29.7 (2 × CH_2), 29.6 (2 × CH_2), 29.5 (2 × CH_2), 29.3 (CH_2), 25.7 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 13.0 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{38}ONa$ [M + Na]$^+$: 305.4885; found: 305.4881.

***tert*-Butyl (2*Z*)-Nonadec-2-en-5-yl Carbonate (14)**

To a solution of compound **13** (634.1 mg, 2.24 mmol) in THF (10.22 mL) cooled at 0 °C was slowly added *n*-BuLi (1.88 mL, 3.006 mmol, 1.34 equiv, 1.6 M in hexane) dropwise with stirring at the same temperature under N_2. After 15 min, a solution of Boc_2O (1.31 g, 6.12 mmol, 2 equiv) in THF (2 mL) was added, then the stirring was continued for 2 h at r.t. A change of color was observed from yellow at the beginning to colorless at the end. TLC monitoring showed completion of the reaction and the reaction was quenched with aq NH_4Cl (2.83 mL). Extraction was done with DCM and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude was purified by column chromatography on basic alumina (0 → 5% PE/acetone) to provide **14** as a yellow oil; yield: 652.8 mg (76%); R_f = 0.72 (PE/acetone 98:2); $[\alpha]_D^{20.5}$ +13.6, $[\alpha]_{578}^{20.5}$ +14.2, $[\alpha]_{546}^{20.5}$ +16.1, $[\alpha]_{436}^{20.5}$ +27.9, $[\alpha]_{365}^{20.5}$ +44.8 (*c* 3.0, $CHCl_3$); $[\alpha]_D^{20.5}$ +15.1, $[\alpha]_{578}^{20.5}$ +15.3, $[\alpha]_{546}^{20.5}$ +17.6, $[\alpha]_{436}^{20.5}$ +30.7, $[\alpha]_{365}^{20.5}$ +48.9 (*c* 3.0, acetone)

IR (KBr): 3458, 2925, 2854, 1813, 1803, 1739, 1458, 1369, 1280, 1256, 1170, 1120, 846, 794 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.57 (dqt, *J* = 10.9, 6.8, 1.6 Hz, 1 H), 5.39 (dtq, *J* = 10.9, 7.3, 1.7 Hz, 1 H), 4.65 (ddt, *J* = 7.3, 6.3, 5.4 Hz, 1 H), 2.36–2.32 (m, 2 H), 1.62 (ddt, *J* = 6.8, 1.7, 0.8 Hz, 3 H), 1.56 (s, 1 H), 1.48 (s, 9 H), 1.37–1.25 (m, 25 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (C=O), 126.7 (CH), 125.0 (CH), 81.5 (C), 77.2 (CH), 33.6 (CH_2), 31.9 (CH_2), 31.7 (CH_2), 29.8 (CH_2), 29.7 (2 × CH_2), 29.6 (2 × CH_2), 29.5 (2 × CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.8 (3 × CH_3), 25.4 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 12.9 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{46}O_3Na$ [M + Na]$^+$: 405.3283; found: 405.3283.

***tert*-Butyl {(*R*)-1-[(2*R*,3*S*)-3-Methyloxiran-2-yl]hexadecan-2-yl} Carbonate (15) + *tert*-Butyl {(*R*)-1-[(2*S*,3*R*)-3-Methyloxiran-2-yl]hexadecan-2-yl} Carbonate (16)**

To a stirred solution of compound **14** (356 mg, 0.93 mmol) in DCM (4.2 mL), was added MCPBA (402.1 mg, 1.874 mmol, 2 equiv, 80% of purity), then stirring was continued for 2 h at r.t. TLC monitoring showed completion of the reaction and a solution of triethyl phosphate (2 drops, 20 mg) was added followed by a solution of NaOH (0.20 mL) to solubilize the metachlorobenzoic acid salt formed during the reaction. Distilled H_2O (0.18 mL) was added again and the mixture was extracted with EtOAc/PE (80:20). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude was purified by column chromatography on silica gel (0 → 3% acetone in PE) to provide a mixture of two inseparable compounds **15** and **16** in an enantiomeric ratio of 50:50 as a colorless oil; yield: 255.1 mg (68%); R_f = 0.30 (PE/acetone 98:2); $[\alpha]_D^{21}$ +4.9, $[\alpha]_{578}^{21}$ +5.1, $[\alpha]_{546}^{21}$ +5.7, $[\alpha]_{436}^{21}$ +9.5, $[\alpha]_{365}^{21}$ +14.5 (*c* 3.0, $CHCl_3$).

IR (KBr): 3463, 2929, 2921, 2852, 1740, 1470, 1368, 1279, 1257, 1165, 1097, 795 cm^{-1}.

15

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (dddd, *J* =7.4, 6.8, 5.5, 5.4 Hz, 1 H), 3.07–2.98 (m, 2 H), 1.88–1.78 (m, 2 H), 1.71–1.60 (m, 4 H), 1.49 (s, 9 H), 1.32–1.25 (m, 25 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4 (C=O), 81.9 (C), 75.5 (CH), 54.0 (CH), 52.5 (CH), 34.6 (CH_2), 34.0 (CH_2), 32.9 (2 × CH_2), 32.3 (CH_2), 31.9 (2 × CH_2), 29.7 (2 × CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.8 (3 × CH_3), 25.4 (CH_2), 22.2 (CH_2), 14.1 (CH_3), 13.3 (CH_3).

16

^1H NMR (400 MHz, $CDCl_3$): δ = 4.83 (dddd, *J* = 7.4, 6.8, 5.5, 5.4 Hz, 1 H), 3.07–2.98 (m, 2 H), 1.88–1.78 (m, 2 H), 1.71–1.60 (m, 4 H), 1.49 (s, 9 H), 1.32–1.25 (m, 25 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3 (C=O), 81.8 (C), 75.3 (CH), 53.4 (CH), 52.0 (CH), 34.6 (CH_2), 34.0 (CH_2), 32.8 (2 × CH_2), 32.2 (CH_2), 31.9 (2 × CH_2), 29.7 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.8 (3 × CH_3), 25.4 (CH_2), 22.2 (CH_2), 14.1 (CH_3), 13.3 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{46}O_4Na$ $[M + Na]^+$: 421.3283; found: 421.3288; *m*/*z* calcd for $C_{20}H_{38}O_4Na$ $[M - C_4H_8 + Na]^+$: 365.2662; found: 365.2659.

Anal. Calcd for $C_{24}H_{46}O_4$: C, 72.31; H, 11.63: Found: C, 70.16; H, 11.64.

(4*R*,6*R*)-4-[(*R*)-1-Hydroxyethyl]-6-tetradecyl-1,3-dioxan-2-one (17) and (4*S*,6*R*)-4-[(*S*)-1-Hydroxyethyl]-6-tetradecyl-1,3-dioxan-2-one (18)

To a cooled solution (–40 °C) of a mixture of epoxycarbonate **15**/**16** (780.6 mg, 1.95 mmol) in DCM (39 mL) was slowly added a solution of $BF_3{\cdot}OEt_2$ (279 mg, 1.966 mmol, 1.01 equiv) in CH_2Cl_2 (10 mL) under N_2 and the stirring was continued for 15 min at the same temperature. TLC monitoring showed completion of the reaction and sat. aq $NaHCO_3$ (15.1 mL) was added to the mixture. Extraction was done with EtOAc/PE (80:20). The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the crude purified by column chromatography on silica gel (0 → 2% MeOH in DCM) to provide successively compounds **17** (270.86 mg, 72%) and **18** (105.34 mg, 28%) in an enantiomeric ratio 72:28 as white crystals in 56% overall yield, along with a small amount of the starting material.

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White crystals (major amount); mp 70 °C; R_f = 0.35 (PE/acetone 80:20); $[\alpha]_D^{21}$ –31.9, $[\alpha]_{578}^{21}$ –33.3, $[\alpha]_{546}^{21}$ –37.6, $[\alpha]_{436}^{21}$ –62.2, $[\alpha]_{365}^{21}$ –93,7 (*c* 1,5, CH_2Cl_2); $[\alpha]_D^{21}$ –33.9, $[\alpha]_{578}^{21}$ –35,6, $[\alpha]_{546}^{21}$ –40.3, $[\alpha]_{436}^{21}$ –66.2, $[\alpha]_{365}^{21}$ –98.8 (*c* 1.5, THF).

IR (KBr): 3447, 2920, 2851, 1712, 1473, 1406, 1376, 1268, 1257, 1242, 1223, 1170, 1104, 1082, 774, 719, 684, 485 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.42 (dddd, *J* = 11.6, 7.2, 5.4, 2.9 Hz, 1 H), 4.26 (ddd, *J* = 11.9, 7.2, 5.4, 2.9 Hz, 1 H), 3.92–3.82 (m, 1 H), 1.90 (ddd, *J* = 14.3, 3.5, 2.9 Hz, 1 H), 1.71 (ddd, *J* = 14.1, 3.4, 2.9 Hz, 1 H), 1.68–1.60 (m, 2 H), 1.47 (d, *J* = 6.5 Hz, 3 H), 1.45–1.37 (m, 1 H), 1.32–1.27 (m, 24 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6 (C=O), 81.0 (CH), 79.0 (CH), 68.0 (CH), 40.7 (CH_2), 38.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (3 × CH_2), 29.5 (2 × CH_2), 29.4 (2 × CH_2), 29.3 (CH_2), 25.2 (CH_2), 22.7 (CH_2), 18.8 (CH_3), 14.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{38}O_4Na$ $[M + Na]^+$: 365.2783; found: 365.2779.

Anal. Calcd for $C_{20}H_{38}O_4$: C, 70.13; H, 11.18. Found: C, 70.20; H, 11.09.

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White crystals (minor amount); mp 97–98 °C; R_f = 0.28 (PE/acetone 80:20) $[\alpha]_D^{21}$ +3.0; $[\alpha]_{578}^{21}$ +2.8; $[\alpha]_{546}^{21}$ +3.0; $[\alpha]_{436}^{21}$ +5.4; $[\alpha]_{365}^{21}$ +8.9 (c 2.7, CH_2Cl_2) $[\alpha]_D^{21}$ +6.4; $[\alpha]_{578}^{21}$ +6.1; $[\alpha]_{546}^{21}$ +6.7; $[\alpha]_{436}^{21}$ +11.5; $[\alpha]_{365}^{21}$ +17.8 (c 1.4, THF).

IR (KBr): 3523, 2918, 2851, 1757, 1471, 1380, 1221, 1059, 782, 718 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.42 (ddd, *J* = 8.9, 6.9, 3.8 Hz, 1 H), 4.26 (dq, *J* = 6.9, 6.1 Hz, 1 H), 3.82–2.78 (m, 1 H), 2.49 (s, 1 H), 1.98 (ddd, *J* = 14.4, 4.1, 3.8 Hz, 1 H), 1.83–1.70 (m, 3 H), 1.62 (ddd, *J* = 14.4, 4.1, 3.8 Hz, 1 H), 1.50–1.34 (m, 3 H), 1.32–1.25 (m, 23 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.3 (C=O), 82.5 (CH), 78.5 (CH), 69.1 (CH), 52.5 (CH_2), 35.2 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.67 (CH_2), 29.6 (2 × CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 24.4 (CH_2), 22.8 (CH_2), 18.2 (CH_3), 14.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{38}O_4Na$ $[M + Na]^+$: 365.2783; found: 365.2774.

(2*R*)-1-[(4*R*,6*R*)-2-Oxo-6-tetradecyl-1,3-dioxan-4-yl]ethyl Methanesulfonate (21)

To a cooled solution (–20 °C) of **17** (153 mg, 0.45 mmol) in DCM (2.7 mL) was added Et_3N (129 µL, 0.92 mmol, 2.05 equiv) and a solution of MsCl (56 µL, 0.72 mmol, 1.6 equiv) in DCM (0.5 mL). The resulting white suspension was left with stirring for 3 h 30 min at –20 °C. TLC monitoring showed completion of the reaction and distilled H_2O (120 mL) was added when the temperature had reached –5 °C. Extraction was done with DCM and the combined organic layers were dried (Na_2SO_4). DCM was evaporated under reduced pressure to provide **21** as a colorless oil and was used without further purification; yield: 175.7 mg (94%); R_f = 0.69 (PE/acetone 80:20).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.86 (dq, *J* = 6.9, 6.1 Hz, 1 H), 4.45–4.37 (m, 2 H), 3.06 (s, 3 H), 2.04–2.01 (m, 2 H), 1.83–1.73 (m, 2 H), 1.49 (d, *J* = 6.1 Hz), 3 H), 1.44–1.26 (m, 24 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

(4*R*,6*R*)-4-[(*S*)-1-Azidoethyl]-6-tetradecyl-1,3-dioxan-2-one (22)

In a dried flask were introduced compound **21** (175.7 mg, 0.42 mmol), NaN_3 (136 mg, 2.1 mmol, 5 equiv), and DMSO (2.1 mL). The flask was purged under N_2 and the contents were refluxed at 80 °C. The color changed from cream at the beginning to orange after stirring for 20 h at 80 °C. TLC monitoring showed completion of the reaction and extraction was done with EtOAc/PE (80:20). The combined organic layers were washed with brine, filtered over a short plug of silica gel, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to provide **22** as a yellow oil; yield: 140.7 mg (94%); R_f = 0.47 (PE/acetone 90:10); $[\alpha]_D^{21}$ –4.3, $[\alpha]_{578}^{21}$ –4.7, $[\alpha]_{546}^{21}$ –5.1, $[\alpha]_{436}^{21}$ –7.2 (*c* 1.5, CH_2Cl_2); $[\alpha]_D^{21}$ –8.5, $[\alpha]_{578}^{21}$ –9.4, $[\alpha]_{546}^{21}$ –10.4, $[\alpha]_{436}^{21}$ –15.8 (*c* 1.47, THF).

IR (KBr): 2925, 2854, 2103 (N_3), 1805, 1466, 1459, 1376, 1187, 1074, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.46 (dq, *J* = 7.0, 6.2 Hz, 1 H), 4.34 (ddd, *J* = 7.2, 7.0, 5.5 Hz, 1 H), 3.48 (dddd, *J* = 7.2, 6.6, 6.5, 5.6 Hz, 1 H), 2.02 (ddd, *J* = 14.6, 7.3, 7.2 Hz, 1 H), 1.84 (ddd, *J* = 14.6, 5.5, 5.4 Hz, 1 H), 1.65–1.60 (m, 4 H), 1.49 (d, *J* = 4.8 Hz, 3 H), 1.44–1.33 (m, 2 H), 1.31–1.26 (m, 20 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1 (C=O), 82.3 (CH), 78.2 (CH), 58.5 (CH), 37.3 (CH_2), 33.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (3 × CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (2 × CH_2), 25.9 (CH_2), 22.7 (CH_2), 19.0 (CH_3), 14.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{37}N_3O_3Na$ [M + Na]$^+$: 390.2779; found: 390.2780.

(2*S*,3*R*,5*R*)-2-Azidononadecane-3,5-diol (5)

In a flammed-dried flash were introduced compound **22** (132 mg, 0.36 mmol), K_2CO_3 (351.21 mg, 2.54 mmol, 2.5 equiv), and MeOH (3.64 mL), and the mixture was stirred for 14 h at r.t. TLC monitoring showed completion of the reaction and distilled H_2O was added to the mixture and extraction was done with DCM. The combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. The crude was purified by column chromatography on silica gel (0 → 2% MeOH in DCM) to provide **5** as white crystals; yield: 99 mg (81%); mp 41–41.5 °C; R_f = 0.47 (PE/acetone 80:20); $[\alpha]_D^{20.5}$ +8.5, $[\alpha]_{578}^{20.5}$ +8.4, $[\alpha]_{546}^{20.5}$ +9.8, $[\alpha]_{436}^{20.5}$ +17.5, $[\alpha]_{365}^{20.5}$ +31.1 (*c* 1.26, CH_2Cl_2); $[\alpha]_D^{20.5}$ –17.6, $[\alpha]_{578}^{20.5}$ –19.1, $[\alpha]_{546}^{20.5}$ –21.4, $[\alpha]_{436}^{20.5}$ –34.7, $[\alpha]_{365}^{20.5}$ –51.3 (*c* 1.29, THF).

IR (KBr): 3337, 2915, 2849, 2103, 1470, 1378, 1261, 1151, 1051, 1046, 1037, 1006, 997, 850, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.64 (dq, *J* = 6.3, 5.5 Hz, 1 H), 3.59–3.43 (m, 2 H), 2.71 (s, 1 H), 2.17 (s, 1 H), 1.68–1.57 (m, 4 H), 1.45–1.26 (m, 24 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 0.88 (pseudo t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.2 (CH), 70.6 (CH), 60.9 (CH), 37.6 (CH_2), 34.3 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (3 × CH_2), 29.5 (2 × CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.8 (CH_2), 22.7 (CH_2), 19.5 (CH_3), 14.1 (CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{39}N_3O_2Na$ [M + Na]$^+$: 364.2979; found: 364.2975.

Anal. Calcd for $C_{19}H_{39}N_3O_2$: C, 66.82; H, 11.51; N, 12.30. Found: C, 66.89; H, 11.66; N, 12.29.

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Supporting Information

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