Stereo- and Regioselective Synthesis of 2-Amino-3,5-diols via Stereospecific Crotyl Transfer and Regioselective Aminohydroxylation

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Abstract: A short synthesis of 2-amino-3,5-diols is described, including the all-*S* isomer enigmol, a synthetic anticancer compound inspired by the structure of fumonisin B_1. The synthetic route features 1) stereospecific crotyl transfer to tetradecanal via pericyclic oxonia-Cope rearrangement; 2) stereoselective epoxidation of the alkene; 3) regioselective epoxide opening with azide; and 4) reduction of azide to amine. This manuscript also corrects a structure assignment error in a previously reported synthesis of one of the diastereomers of enigmol.

Key words: allylation, rearrangement, regioselectivity, sphingolipids, stereoselective synthesis

Fumonisin B_1 (**1**, Figure 1) is a fungal toxin produced by *Fusarium verticillioides*, which has been found as a contaminant in corn and other food grains.[1,2] The toxicity of fumonisin B_1 as well as the potency of activity as a ceramide synthase inhibitor is reduced upon basic hydrolysis of the ester side chains to the aminopentol (**2**).[3,4] Compound **2** and its *N*-palmitoyl derivative **3** exhibit in vitro cytotoxicity to HT29 (colon cancer) cells along with enhanced ceramide synthase inhibition activity.[3] Based on these findings, several laboratories have studied simpler analogues containing only the 2-amino-3,5-diol substructure of fumonisin B_1, especially the all-*S* stereoisomer **4** (dubbed enigmol), which has shown promising in vivo studies on suppression of colon and prostate tumor growth in mouse models.[5]

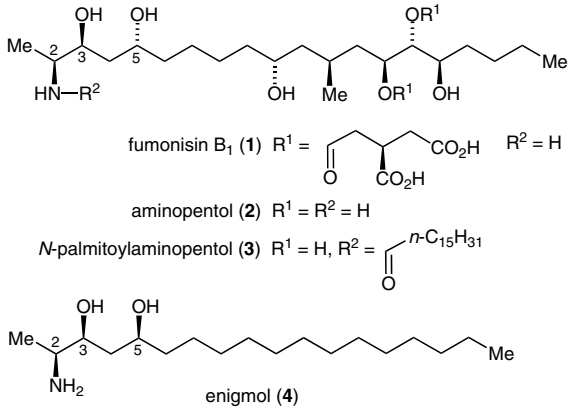
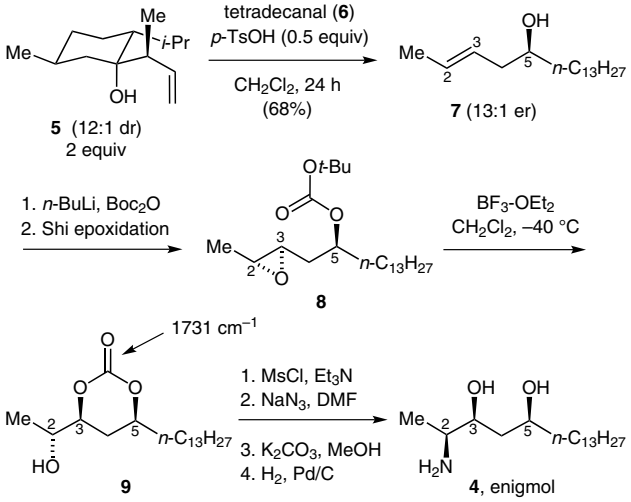


Figure 1 Structures of 1-deoxysphingolipids

Several syntheses of enigmol have been reported featuring a variety of key disconnections ranging from aldol reactions,[6] diastereoselective allylations,[7] and cross-coupling reactions.[8] In each of these syntheses, the C_2-chiral center is potentially prone to epimerization.[6b] In order to avoid this problem with epimerization, we developed a complementary synthesis of enigmol (**4**) involving C_4–C_5 bond formation by stereo- and regioselective crotyl group transfer[9] to provide the homoallylic alcohol **7** (Scheme 1), featuring oxacyclization of the epoxycarbonate **8** with inversion of configuration at C_3.[10] The position of the cyclic carbonate **9** protected the oxygens at C_3 and C_5, allowing for regioselective formation of the C_2 mesylate followed by stereospecific substitution with azide with inversion of configuration at C_2, which upon methanolysis of the cyclic carbonate and hydrogenolysis of the azide afforded a reliable route to provide gram quantities of enigmol (**4**).[10a]



Scheme 1 Our previous (2005) synthesis of enigmol[10]

However, we subsequently observed that the corresponding reaction sequence from the C_5-diastereomer **10** failed due to carbonate migration to afford the five-membered-ring carbonate **12** (Scheme 2).[10b,11] Presumably the *trans*-substitution pattern of an initial six-membered-ring carbonate **11** (never observed) would place the C_2 oxygen in proximity to the carbonyl, so that intramolecular acyl transfer provided isomer **12**. Compound **12** exhibited an infrared stretch of 1792 cm^{-1}, consistent with the increased ring strain of a five-membered ring versus the six-membered ring of compound **9**. Unfortunately, the signif-

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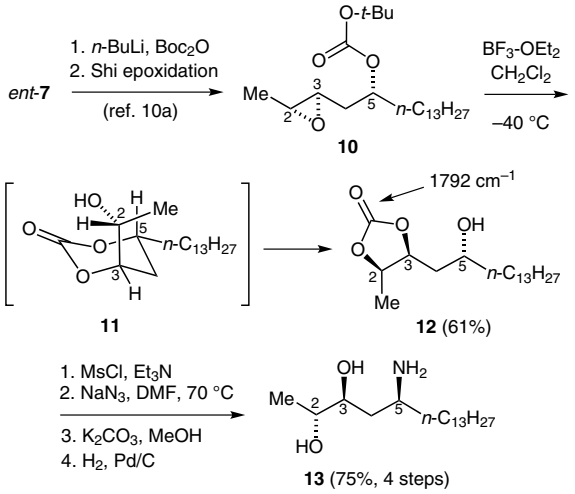
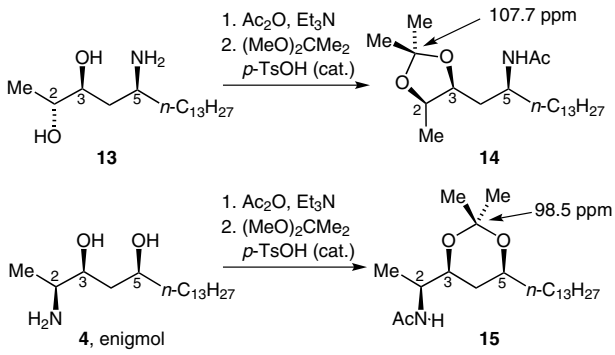
icance of the infrared spectrum was initially overlooked and so compound **12** was subjected to the same sequence of steps as for compound **9**. As the cyclic carbonate of **12** protected the C_2 and C_3 oxygens, the azide substitution reaction now occurred at C_5, resulting in the aminodiol regioisomer **13**.[10b]



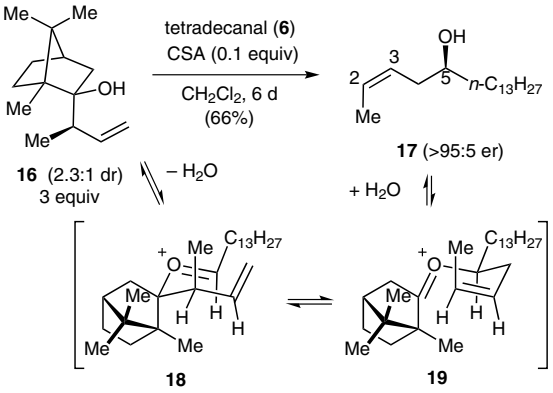
Scheme 2 Divergent behavior of diastereomeric epoxycarbonate **10**

The identities of our synthetic aminodiols were confirmed by selective N-acylation followed by acetonide protection of the diols (Scheme 3). The acetonide **14** exhibited a ^{13}C resonance for the acetal carbon at 107.7 ppm, consistent with a five-membered-ring acetonide,[12] whereas the corresponding acetonide **15** arising from enigmol (**4**) exhibited a ^{13}C resonance at 98.5 ppm as expected for a six-membered-ring acetonide. Moreover, compound **15** was crystalline so that its structure was unambiguously confirmed by X-ray crystallography.[13]



Scheme 3 Structural confirmation of acetonides **14** and **15**

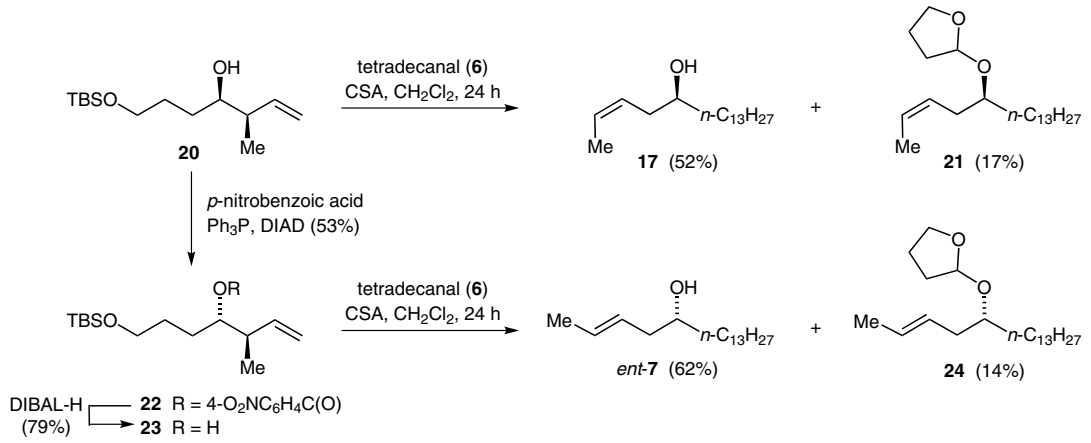
In rethinking the synthetic route for enigmol diastereomers from homoallylic alcohols, we considered that azide nucleophile might be directly added to the C_2–C_3 epoxide. For enigmol itself, this would require preparation of the *cis*-alkene isomer **17**, which was prepared by crotyl transfer to tetradecanal (**6**) using the camphor-derived reagent **16**.[14] However, the reaction was extremely slow, and reaction times of six to seven days were required for complete conversion of aldehyde **6**, even with excess reagent **16**. As the proposed mechanism for crotyl transfer is an oxonia-Cope pericyclic rearrangement of oxonium ion **18** to **19** (Scheme 4), we considered that some of the extraneous features of the camphor skeleton might be responsible for diminishing the reaction rate.[15]



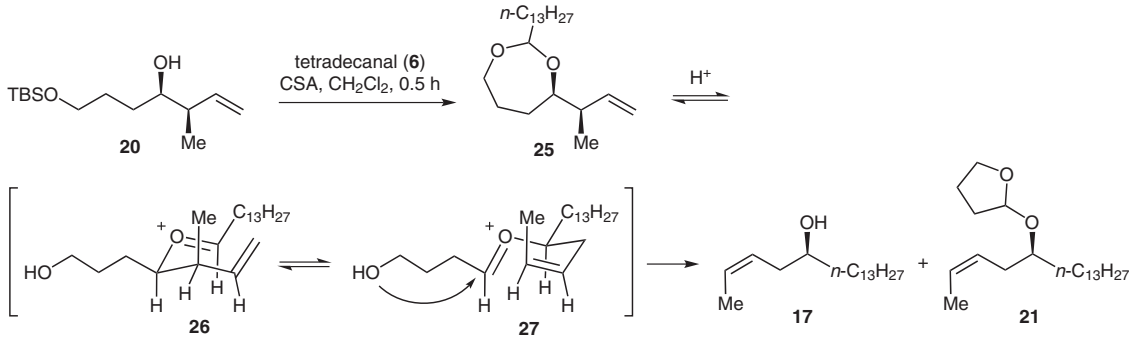
Scheme 4 Oxonia-Cope rearrangement mechanism for crotyl group transfer

To this end, a structurally simpler reagent **20** (arising from enantio- and diastereoselective crotylboration of 4-silyloxybutanal) was designed,[16,17] bearing a tethered nucleophile designed to trap the product oxonium ion.[18] For the reaction of one equivalent of **20** with tetradecanal (**6**), the best results were achieved with stoichiometric camphorsulfonic acid (CSA), providing the alkenyl alcohol **17** with high enantiomeric purity (>95:5 er) as well as complete *cis*-alkene selectivity (Scheme 5). The formation of product **17** was accompanied by small amounts of the *O*-tetrahydrofuranyl derivative **21**. Under the same reaction conditions, the reaction of tetradecanal with the *anti*-diastereomer **23** provided the corresponding *trans*-alkenyl alcohol *ent*-**7** and the corresponding tetrahydrofuranyl derivative **24**.[19,20]

The crotyl transfer reaction of **20** was monitored by ^1H NMR spectroscopy, revealing the rapid formation of a seven-membered-ring acetal intermediate **25**, which could even be isolated as a mixture of diastereomers when the reaction was stopped after 30 minutes (Scheme 6). The stereospecificity of each crotyl transfer process is consistent with acid-catalyzed opening of the seven-membered-ring acetal of **25** to form oxonium ion **26**, which then undergoes oxonia-Cope rearrangement to product oxonium ion **27**. The tetrahydrofuranyl acetal **21** presumably arises from cyclization of the primary hydroxyl onto the product oxonium ion **27**. Notably, we have not found conditions by which the tetrahydrofuranyl derivative **21** is formed as the major product, and thus the mechanistic pathway for the formation of alcohol **17** has not been conclusively established. However, protonation of the acyclic oxygen of acetal **21** and elimination of volatile dihydrofuran may diminish the yield of **21** in favor of the desired alcohol product **17**.



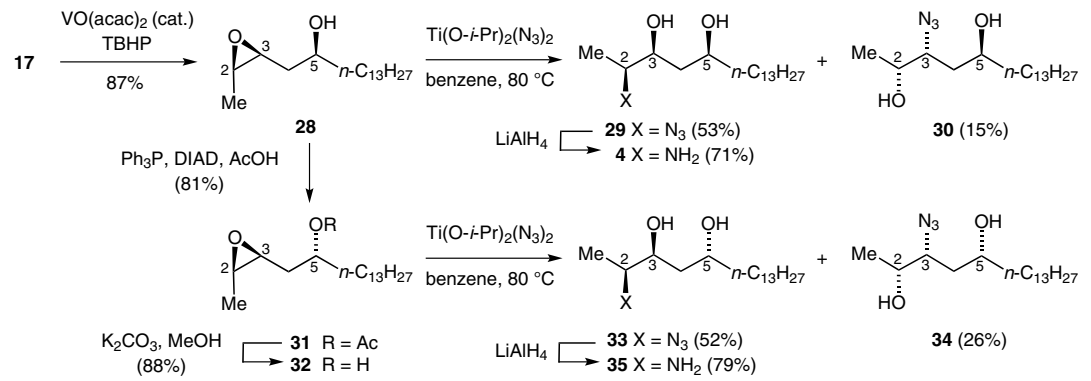
Scheme 5 Crotyl group transfer with reagents **20** and **23**



Scheme 6 Proposed oxonia-Cope mechanism for crotyl transfer with reagent **20**

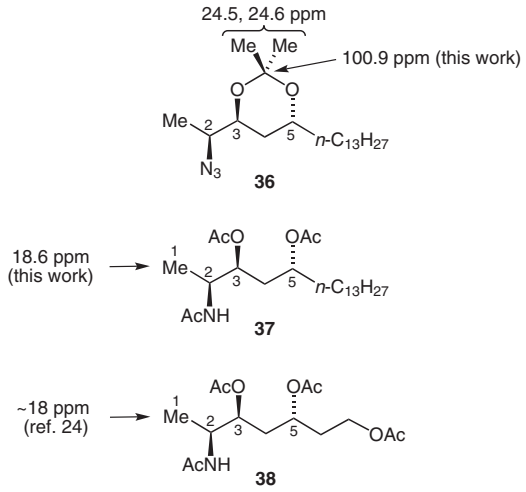
Returning to the synthesis of enigmol, we utilized hydroxyl-directed vanadium-catalyzed epoxidation of the *cis*-homoallylic alcohol **17**, providing the epoxy alcohol **28** with high diastereoselectivity.[21] Ti(O*i*-Pr)$_2$(N$_3$)$_2$-promoted addition of azide to epoxy alcohol **28** exhibited modest regioselectivity in favor of the azidodiol **29**,[22] and lithium aluminum hydride reduction of the azide afforded enigmol (**4**), which matched the physical and spectroscopic characteristics of enigmol prepared by our previous synthesis (Scheme 7). Diastereomer **32** was synthesized by Mitsunobu inversion from **28** followed by methanolysis of the acetate ester intermediate **31**. Ti(O*i*-Pr)$_2$(N$_3$)$_2$-promoted azide addition provided predominantly **33** as the penultimate precursor to the aminodiol diastereomer **35**.

In light of the previous erroneous claim of compound **35** from our laboratory,[10] we now carefully established the relative stereochemistry of the diol moiety of **35** generated in this work by forming the acetonide **36** from the azidodiol **33** (Scheme 8). The ^{13}C NMR acetal resonance at 100.9 ppm and methyl resonances at 24.6 ppm and 24.5 ppm were consistent with a six-membered-ring acetonide with *anti*-stereochemistry of the oxygens at C$_3$ and C$_5$.[23] Moreover, compound **35** was converted into the triacetyl derivative **37**, for which the ^{13}C NMR resonance for C$_1$ at 18.6 ppm was consistent with the 18 ppm resonance re-



Scheme 7 Preparation of enigmol (**4**) and diastereomer **35**

ported for the reference compound **38** bearing *syn*-relationship between the C_2 nitrogen and C_3 oxygen.[24,25]



Scheme 8 Confirmation of relative stereochemistry for derivatives **36** and **37**

For the *trans*-epoxide diastereomers **39** and **43** (arising from Shi epoxidation of **7** and *ent*-**7**, respectively),[26] the azide addition proceeded with nearly exclusive formation of the C_2-azide regioisomers **40** and **44**, respectively (see Scheme 9), with formation of less than 5% of the C_3-azide regioisomer in either case. Although the choice of reagent $Ti(O\textit{i}\text{-}Pr)_2(N_3)_2$ was originally viewed as an extended application of the method described earlier by Sharpless in the analogous reactions of 2,3-epoxy-1-alcohols,[27] the differences in regioselectivity may arise from differing steric factors upon nucleophilic additions to C_2 versus C_3 in *trans*- versus *cis*-disubstituted epoxides.[28] Lithium aluminum hydride reduction of azides **40** and **44** afforded the corresponding 2-amino-3,5-diol diastereomers **41** and **45**. The relative stereochemistry was confirmed by ^{13}C NMR analysis of the corresponding acetonides **42** and **46**.[23]

In conclusion, we have developed a synthetic route providing all diastereomers of 2-amino-3,5-dihydroxyoctadecane, including enigmol (**4**). In the course of this work, we have undertaken preliminary work towards new reagents for stereoselective crotyl group transfer with generality for both *cis*- and *trans*-disubstituted homoallylic alcohols, as well as uncovering the regioselectivities of azide-openings with epoxy alcohols arising from homoallylic alcohols.[27]

^1H NMR and ^{13}C NMR spectra were recorded in deuterated solvents on Varian INOVA 600, Unity 600, and INOVA 400 spectrometers. Chemical shift values were recorded in parts per million relative to residual ^1H and ^{13}C in $CDCl_3$ (7.27 ppm for ^1H, 77.23 for ^{13}C), CD_3OD (3.31 ppm for ^1H, 49.3 ppm for ^{13}C), or C_6D_6 (7.16 ppm for ^1H, 128.23 ppm for ^{13}C), and coupling constants in hertz. IR spectra were recorded on a Mattson Genesis II FT-IR spectrometer as neat films on NaCl discs. Mass spectral data (high resolution EI, ESI and APCI) were recorded on a Finnigan LTQ FT-mass spectrometer. Optical rotations were measured on a PerkinElmer 341 polarimeter (concentration in g/100 mL). Flash column chromatography was conducted with silica gel 60 (230–400 mesh ASTM) from EM Science. All reactions were conducted with anhydrous solvents in oven-dried or flame-dried and argon-charged glassware. Anhyd solvents were dried with 4 Å molecular sieves and tested for trace H_2O content with Coulometric KF titrator from Denver Instruments.

(4*S*,5*R*)-4-[(*R*)-2-Hydroxypentadecyl]-5-methyl-1,3-dioxolan-2-one (12)

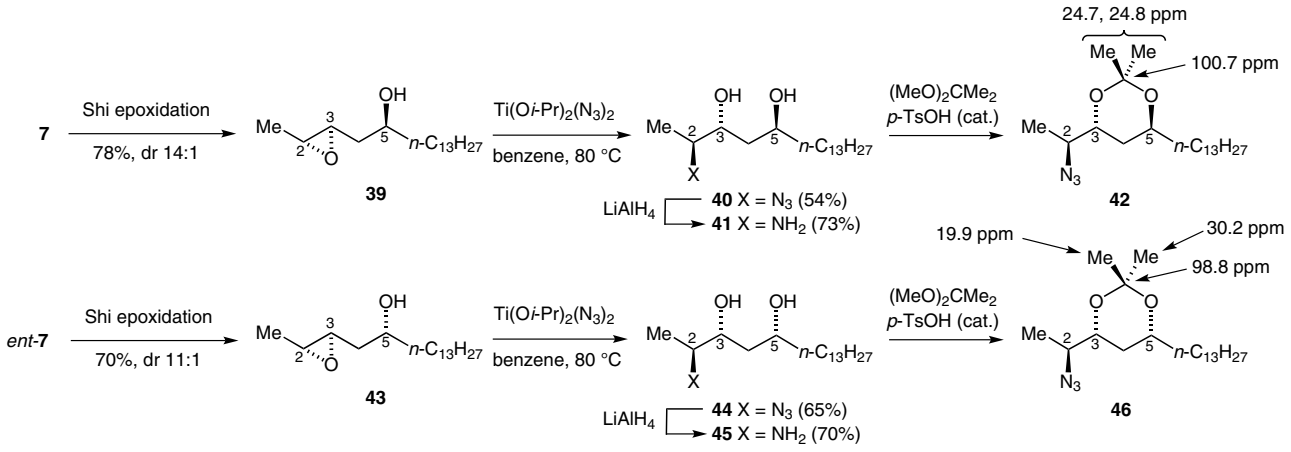
Epoxycarbonate **10** (0.513 g, 1.34 mmol) was dissolved in anhyd CH_2Cl_2 (27 mL) under argon atmosphere. The solution was cooled to –40 °C, and a 0.195 M $Et_2O{\cdot}BF_3$ solution in CH_2Cl_2 (7.0 mL, 1.36 mmol) was added in one portion. The solution was stirred vigorously at –40 °C for 5 min, and then quenched with sat. aq $NaHCO_3$ (7 mL). The organic layer was separated, and aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and washed with H_2O (20 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. Chromatography on silica gel with hexanes–EtOAc (1: 1) gave **12** (0.27 g, 61%) as a white solid; mp 63–63.5 °C; $[\alpha]_D^{25}$ –33.6 (*c* 1.0 CH_2Cl_2).

IR (thin film, CH_2Cl_2): 3402, 2918, 2849, 1792, 1763, 1063 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.01 (ddd, *J* = 10.2, 7.2, 3.0 Hz, 1 H), 4.88 (m, *J* = 6.6 Hz, 1 H), 3.87 (m, *J* = 4.2, 2.4, 1.8 Hz, 1 H), 1.82 (ddd, *J* = 13.8, 3.6, 1.8 Hz, 1 H), 1.63 (br s, 1 H), 1.57 (ddd, *J* = 13.8, 10.8, 3.0 Hz, 1 H), 1.50 (q, *J* = 7.2 Hz, 2 H), 1.42 (br m, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H), 1.27 (br s, 21 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 154.8, 76.3, 68.1, 38.5, 36.2, 32.1, 29.83, 29.73, 29.66, 29.54, 25.6, 22.9, 15.1, 14.3.

HRMS (EI): *m*/*z* calcd for $C_{19}H_{36}O_4$: 335.2774; found: 335.2771.



Scheme 9 Preparation of enigmol diastereomers **41** and **45**

Anal. Calcd for $C_{19}H_{36}O_4$: C, 69.47; H, 11.05. Found: C, 69.47; H, 11.16.

(2*R*,3*S*,5*S*)-5-Aminooctadecane-2,3-diol (13)

Compound **18** (0.27 g, 0.82 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) and cooled to 0 °C under argon atmosphere. Et_3N (120 μL, 0.9 mmol) was added followed by dropwise addition of MsCl (100 μL, 0.8 mmol) over 10 min. The reaction mixture gradually warmed to r.t. and was stirred for 6 h. The mixture was then partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL), the organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. The crude mesylate was dissolved in DMF (15 mL), and NaN_3 (0.37 g, 5.7 mmol) was added. The reaction mixture was stirred at 68 °C for 24 h, then cooled to r.t. and diluted with CH_2Cl_2 (30 mL) and H_2O (30 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), the organic layers were combined, dried (Na_2SO_4), and concentrated by rotary evaporation. Chromatography on silica gel with eluent of hexanes–EtOAc (1: 1) afforded the azidocarbonate (0.252 g, 87%, 2 steps) as a clear colorless oil. A portion of this azidocarbonate (0.118 g, 0.33 mmol) was dissolved in anhyd MeOH (7 mL), K_2CO_3 (0.32 g, 2.34 mmol) was added, and the reaction mixture was stirred at r.t. for 12 h. The mixture was then diluted with CH_2Cl_2 (15 mL) and H_2O (15 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), and concentrated by rotary evaporation to provide the crude azidodiol (99 mg). Without further purification, the crude azidodiol was mixed with 10% Pd/C (24 mg, 20% by mass), and the reaction vessel was evacuated under high vacuum for 5 min, and then filled with H_2 atmosphere. This cycle of evacuation and H_2 filling was repeated three more times. Then, 95% EtOH (7 mL) was added, and the reaction mixture was degassed by three cycles of partial evacuation and filling with H_2 atmosphere. The mixture was stirred at r.t. for 6 h under a positive pressure of H_2 gas delivered by a balloon. The mixture was then filtered through a 1 cm plug of packed Celite, washing with CH_2Cl_2 (20 mL). The filtrate was dried (Na_2SO_4) and concentrated by rotary evaporation to afford aminodiol **13** (93 mg, 86%, 2 steps) as a white solid; mp 65–66 °C; $[\alpha]_D^{25}$ +3.1 (*c* 1.0, CH_2Cl_2).

IR (thin film, CH_2Cl_2): 3331, 2918, 2850, 1467 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.77 (m, *J* = 3.6, 2.4 Hz, 1 H), 3.73 (d, *J* = 10.2 Hz, 1 H), 3.2 (br s, 4 H), 2.81 (m, *J* = 5.4 Hz, 1 H), 1.57 (d, *J* = 14.4 Hz, 1 H), 1.43 (m, 3 H), 1.24 (br s, 22 H), 1.11 (d, *J* = 6.0 Hz, 3 H), 0.86 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 76.4, 70.1, 52.4, 41.2, 35.4, 32.1, 29.80, 29.75, 29.67, 29.51, 25.8, 22.8, 17.4, 14.3.

HRMS (EI): *m*/*z* calcd for $C_{18}H_{40}NO_2$: 302.30543; found: 302.30536.

Anal. Calcd for $C_{18}H_{39}NO_2$: C, 71.70; H, 13.04; N. 4.65. Found: C, 71.47; H, 12.93; N, 4.49.

***N*-{(*S*)-1-[(4*S*,5*R*)-2,2,5-Trimethyl-1,3-dioxolan-4-yl]pentadecan-2-yl}acetamide (14)**

A solution of aminodiol **13** (50 mg, 0.17 mmol) in anhyd CH_2Cl_2 (2.2 mL) under argon atmosphere was cooled to 0 °C. Et_3N (46 μL, 0.33 mmol) was added with stirring, and after 5 min,Ac_2O (15 μL, 0.16 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1 h, after which time aq 1 N HCl (1 mL) was added to quench the reaction. The organic layer was separated and subsequently washed with aq 1 N NaOH (2 mL), H_2O (2 mL), and brine (2 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to provide the crude *N*-acetyldiol (16 mg) as a white solid. Without further purification, a portion of this *N*-acetyldiol (6 mg) was dissolved in 2,2-dimethoxypropane (0.19 mL) and cooled to 0 °C under argon atmosphere. *p*-TsOH (0.9 mg) was added and the reaction mixture was stirred at 0 °C for 15 min, after which Et_3N (0.5 mL) and a few drops of sat. aq $NaHCO_3$ was added to quench the reaction. The mixture was extracted with Et_2O (2 × 2 mL), the combined Et_2O layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to obtain a colorless oil. This material was purified by silica gel chromatography using 0.5% MeOH in CH_2Cl_2 as the eluent, to provide compound **14** (3 mg, 44%) as a colorless oil, which solidified upon standing.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.43 (d, *J* = 8.4 Hz, 1 H), 4.26 (dq, *J* = 6.3 Hz, 1 H), 4.09 (ddd, *J* = 4.8, 8.4 Hz, 1 H), 4.02–3.96 (m, 1 H), 1.97 (s, 3 H), 1.69 (ddd, *J* = 4.8, 14.4 Hz, 1 H), 1.57–1.50 (m, 3 H), 1.45 (s, 3 H), 1.31 (s, 3 H), 1.25 (br s, 27 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.0, 107.7, 75.9, 74.1, 48.1, 35.7, 35.1, 32.1, 30.2, 29.8, 29.7, 29.5, 28.7, 26.0, 25.9, 23.8, 22.9, 15.9, 14.3.

***N*-{(*S*)-1-[(4*S*,6*S*)-2,2-Dimethyl-6-tridecyl-1,3-dioxan-4-yl]ethyl}acetamide (15)**

Following the procedure described above for compound **14**, a sample of enigmol (**4**; 25 mg, 80 mmol) prepared as previously reported[10a] was converted into compound **15** (18 mg, 28%, 2 steps, unoptimized) as a colorless oil, which solidified upon standing. The compound was dissolved in a small quantity of CH_2Cl_2 (2 mL) and refrigerated (ca. 4 °C) for approximately one week, after which crystals were harvested for structural confirmation by X-ray crystallography;[13] mp 61–62 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 (d, *J* = 8.8 Hz, 1 H), 3.97 (dq, *J* = 2.0, 7.2 Hz, 1 H), 3.83–3.77 (m, 2 H), 2.00 (s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.40–1.36 (m, 2 H), 1.25 (br s, 23 H), 1.16 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 98.5, 71.5, 68.9, 48.1, 36.6, 33.8, 32.1, 30.2, 29.8 (2 C), 29.7, 29.6, 29.5, 25.1, 23.7, 22.9, 19.9, 18.4, 14.3.

(3*R*,4*R*)-7-[(*tert*-Butyldimethylsilyl)oxy)-3-methylhept-1-en-4-ol (20)

By Ipc$_2$B-Mediated Crotylboration: *cis*-But-2-ene (3.7 g, 65.9 mmol) was added to a cooled solution of *t*-BuOK (1.8 g, 16.0 mmol) in THF (34 mL) at –78 °C. *n*-BuLi (1.02 g, 16.0 mmol, 2.5 M in hexanes) was then added, and the yellow reaction mixture was warmed to –45 °C and stirred for 10 min. After cooling back to –78 °C, $[(+)Ipc]_2BOMe$ (5.0 g, 16.0 mmol) in THF (27 mL) was then added and the mixture was stirred for 30 min. $Et_2O{\cdot}BF_3$ (2.27 g, 16.0 mmol) was then added, followed by 4-[(*tert*-butyldimethylsilyl)oxy]butanal (2.7 g, 13.3 mmol),[29] and the mixture was stirred for 5 h. The mixture was quenched by addition of aq 3 M NaOH (13.5 mL), followed by 30% H_2O_2 (10.0 mL), and stirring at r.t. for 18 h. The aqueous layer was then extracted with EtOAc (3 × 50 mL), dried ($MgSO_4$), filtered, and concentrated to obtain an oil. The crude product was purified by flash chromatography using 8% EtOAc in hexanes to obtain compound **20** (1.7 g, 50%) as a colorless oil.

By VIVOL-Catalyzed Crotylboration: A mixture of preactivated 4Å molecular sieves (0.11 g), (*S*,*S*)-VIVOL catalyst (0.028 g, 0.064 mmol),[17] and anhyd Na_2CO_3 (0.01 g, 0.049 mmol) was suspended in toluene (2.0 mL). After stirring for 5 min at r.t., $SnCl_4$ (0.012 g, 0.049 mmol) was added, and the reaction mixture was cooled to –75 °C, and stirred for 15 min. (*Z*)-2-(But-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.10 g, 0.54 mmol) was then added and the mixture was stirred for 30 min at –75 °C, followed by addition of 4-[(*tert*-butyldimethylsilyl)oxy]butanal (0.10 g, 0.49 mmol).[29] The mixture was stirred at –67 °C for 19 h before quenching with DIBAL (0.9 mL, 1.0 M in toluene). After stirring for 15 min, the cold bath was removed, aq 1.0 M HCl (1.8 mL) was added, and the mixture was stirred at r.t. for 1 h. The aqueous layer was extracted with hexanes (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (6% EtOAc in hex-

anes) to provide compound **20** as a colorless oil (70 mg, 55%); $[\alpha]_D^{25}$ –17.4 (*c* 1.14, $CHCl_3$).

IR (film): 3367, 2954, 2857, 1471, 1253, 1095, 995, 832, 773 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.80 (ddd, *J* = 7.2, 10.5, 17.4 Hz, 1 H), 5.08–5.04 (m, 2 H), 3.66 (t, *J* = 5.7 Hz, 2 H), 3.50–3.46 (m, 1 H), 2.45 (d, *J* = 4.2 Hz, 1 H), 2.29–2.26 (m, 1 H), 1.68–1.61 (m, 3 H), 1.42–1.37 (m, 1 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 141.4, 115.0, 74.7, 63.6, 43.8, 31.4, 29.5, 26.1, 18.5, 14.9, –5.1.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{31}O_2Si$ ($M + H^+$): 259.2088; found: 259.2087.

(3*R*,4*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-methylhept-1-en-4-ol *p*-Nitrobenzoate Ester (22)

Compound **20** (0.80 g, 3.0 mmol), Ph_3P (1.6 g, 6.19 mmol), and *p*-nitrobenzoic acid (1.0 g, 6.19 mmol) were dissolved in benzene (40 mL) at r.t. DIAD (1.25 g, 6.19 mmol) was added, and the reaction mixture was stirred for 24 h. The solvents were then removed by rotary evaporation to obtain the crude product as a semisolid, which was purified by flash chromatography using 1% Et_2O in hexanes to afford the nitrobenzoate ester **22** (0.67 g, 53%) as an oil; $[\alpha]_D^{25}$ +9.7 (*c* 0.875, $CHCl_3$).

IR (film): 2954, 2856, 1721, 1528, 1318, 1270, 1098, 872, 831, 717 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 8.4 Hz, 2 H), 8.20 (d, *J* = 9.6 Hz, 2 H), 5.80 (ddd, *J* = 7.8, 10.2, 17.7 Hz, 1 H), 5.15 (ddd, *J* = 4.8, 9.0 Hz, 1 H), 5.08 (dd, *J* = 16.8, 18.3 Hz, 2 H), 3.65–3.59 (m, 2 H), 2.59–2.53 (m, 1 H), 1.81–1.70 (m, 2 H), 1.60–1.51 (m, 2 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 0.08 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.5, 150.6, 139.2, 136.2, 130.8, 123.7, 116.2, 78.8, 62.7, 42.0, 28.9, 28.0, 26.1, 18.5, 16.3, –5.1.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{34}NO_5Si$ ($M + H^+$): 408.2200; found: 408.2202.

(3*R*,4*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-3-methylhept-1-en-4-ol (23)

A solution of compound **22** (0.67 g, 1.64 mmol) in CH_2Cl_2 (21 mL) was cooled to –78 °C, and DIBAL (4.9 mL, 4.9 mmol, 1.0 M in hexanes) was added. The reaction mixture was stirred for 30 min at –78 °C, after which the reaction was quenched with EtOH (0.5 mL) at –78 °C and saturated Rochelle salt (25 mL). After stirring the mixture at r.t. for 1 h, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to obtain the crude product as an oil, which was purified by silica gel chromatography using a gradient of 2–5% EtOAc in hexanes to provide compound **23** (0.27 g, 79%) as a colorless oil; $[\alpha]_D^{25}$ +0.8 (*c* 0.625, $CHCl_3$).

IR (film): 3399, 2954, 2856, 1471, 1253, 1094, 832, 773 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.79 (ddd, *J* = 9.0, 19.2 Hz, 1 H), 5.10–5.07 (m, 2 H), 3.69–3.63 (m, 2 H), 3.45–3.43 (m, 1 H), 2.38 (d, *J* = 3.6 Hz, 1 H), 2.26–2.20 (m, 1 H), 1.68–1.62 (m, 3 H), 1.44–1.38 (m, 1 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.06 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 140.8, 115.9, 74.7, 63.6, 44.2, 31.2, 29.3, 26.1, 18.5, 16.2, –5.1.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{31}O_2Si$ ($M + H^+$): 259.2088; found: 259.2086.

(*S*,*Z*)-Octadec-2-en-5-ol (17)

*From Camphor-Derived **16***: Tetradecanal (**6**; 4.00 g, 18.8 mmol) and compound **16** (11.7 g, 56.1 mmol)[14] were dissolved in CH_2Cl_2 (3 mL). CSA (0.44 g, 1.9 mmol) was then added and the reaction mixture was stirred at r.t. for 6 days. The mixture was then diluted with CH_2Cl_2 (15 mL), dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to obtain a colorless oil. This was purified by flash chromatography using 6% EtOAc in hexanes as eluent to obtain compound **17** as a white solid (3.3 g, 66%); mp 28–29 °C; $[\alpha]_D^{25}$ –2.7 (*c* 1.03, $CHCl_3$).

IR (film, CH_2Cl_2): 3345, 3021, 2915, 2848, 1469 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.66 (dqt, *J* = 10.8, 6.6, 1.8 Hz, 1 H), 5.44 (dtq, *J* = 10.8, 7.8, 1.8 Hz, 1 H), 3.63 (br pent, *J* = 4.8 Hz, 1 H), 2.22 (app t, *J* = 6.6 Hz, 2 H), 1.64 (dd, *J* = 1.2, 6.6 Hz, 3 H), 1.58 (s, 1 H), 1.49–1.44 (m, 3 H), 1.31–1.26 (m, 21 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 127.4, 126.4, 71.7, 37.0, 35.1, 32.1, 29.9, 29.8, 29.5, 25.9, 22.9, 14.3, 13.2.

HRMS (APCI): *m*/*z* calcd for $C_{18}H_{35}O$ (M^+): 267.2682; found: 267.2683.

The absolute stereochemistry and enantioselectivity was determined by Mosher (MTPA) ester analysis.[30] Each Mosher ester was diastereomerically pure, that is, uncontaminated by any evidence of the other diastereomer. Resonances were clearly assignable for H_1–H_5 (Table 1).

Table 1 Diagnostic Resonances for Mosher Esters of **17**

	R-Ester, from (*S*)-MTPACl	*S*-Ester, from (*R*)-MTPACl	Δδ (*R*–*S*)
H_1	1.49 ppm	1.56 ppm	–0.07 ppm
H_2	5.47 ppm	5.54 ppm	–0.07 ppm
H_3	5.22 ppm	5.34 ppm	–0.12 ppm
H_4	2.35 ppm	2.42 ppm	–0.07 ppm
$H_{4'}$	2.26 ppm	2.32 ppm	–0.06 ppm
H_5	5.08 ppm	5.09 ppm	not applicable

*From **20***: Tetradecanal (**6**; 0.25 g, 1.17 mmol) and compound **20** (0.34 g, 1.29 mmol) were dissolved in CH_2Cl_2 (8 mL) at r.t., and CSA (0.33 g, 1.4 mmol) was added. The reaction mixture was stirred for 24 h. The mixture was then quenched with MeOH (0.1 mL) and stirred for 1 h, before evaporating solvents by rotary evaporation. The crude product was purified by flash chromatography using a gradient of 2–3% EtOAc in hexanes to obtain compound **17** as a white solid (160 mg, 52%).

(*R*,*E*)-Octadec-2-en-5-ol (*ent*-7)

Following the procedures described above for reactions with **20**, the reaction of compound **23** (0.24 g, 0.93 mmol), tetradecanal (**6**; 0.18 g, 0.84 mmol), and CSA (0.24 g, 1.01 mmol) in CH_2Cl_2 (5.5 mL) for 24 h provided the *trans*-homoallylic alcohol *ent*-**7** as a white solid (0.14 g, 62%). The physical and spectroscopic properties matched those reported earlier.[10a]

(*S*)-1-[(2*S*,3*R*)-3-Methyloxiran-2-yl]pentadecan-2-ol (28)

The homoallylic alcohol **17** (3.25 g, 12.1 mmol) and $VO(acac)_2$ (0.16 g, 0.60 mmol) were dissolved in CH_2Cl_2 (120 mL), and the resulting solution was cooled to 0 °C. *tert*-Butyl hydroperoxide (TBHP, 5.5 M in decane, 3.3 mL, 18.1 mmol) was then added dropwise, and the reaction mixture was stirred at 0 °C for 3 h before warming to r.t. and stirring for 24 h at r.t. The mixture was then diluted with aq 10% $Na_2S_2O_3$ (25 mL). The organic layer was separated, washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to obtain the crude product as a brown oil, which was purified by flash chromatography using 20% EtOAc in hexanes as eluent to obtain epoxy alcohol **28** (3.0 g, 87%) as a colorless oil, which solidified upon standing; mp 32–33 °C; $[\alpha]_D^{25}$ –3.2 (*c* 1.05, $CHCl_3$).

IR (film, CH_2Cl_2): 3415, 2994, 2923, 2854, 1463 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.93–3.87 (m, 1 H), 3.12–3.09 (m, 1 H), 3.07–3.04 (m, 1 H), 2.29 (s, 1 H), 1.56–1.40 (m, 4 H), 1.30–1.25 (m, 25 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 71.0, 55.5, 52.1, 37.6, 34.6, 32.1, 29.85, 29.8, 29.5, 25.7, 22.8, 14.3, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{37}O_2$ (M + H^+): 285.2788; found: 285.2785.

(2*S*,3*S*,5*S*)-2-Azidooctadecane-3,5-diol (29)

Me_3SiN_3 (0.4 g, 3.47 mmol) was added to a solution of Ti(O*i*-Pr) (0.49 g, 1.72 mmol) in benzene (12.5 mL) and the solution was heated to 80 °C for 5 h. A solution of epoxy alcohol **28** (0.50 g, 1.75 mmol) in benzene (5 mL) was then added and the reaction mixture was stirred for 15 min before cooling to r.t. Benzene was removed under vacuum and the crude product was diluted with Et_2O (20 mL). Aq 5% H_2SO_4 (10 mL) was then added and the resulting solution was stirred for 1 h at r.t. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to obtain a brown oil. The crude product was purified by flash chromatography using 25% EtOAc in hexanes as eluent to obtain the azidodiol **29** (0.30 g, 53%) as a colorless oil which solidified on standing; mp 42–44 °C; $[\alpha]_D^{25}$ +31.0 (*c* 1.07, $CHCl_3$). The C_3-azide regioisomer **30** was also formed (0.085 g, 15%).

IR (thin film, CH_2Cl_2): 3390, 2923, 2854, 2109, 1463, 1261, 1066 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.88–3.84 (m, 1 H), 3.75–3.72 (m, 1 H), 3.58 (br s, 1 H), 3.43–3.39 (m, 1 H), 2.89 (br s, 1 H), 1.60–1.55 (m, 2 H), 1.54–1.44 (m, 2 H), 1.43–1.38 (m, 1 H), 1.31–1.25 (m, 24 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 75.6, 72.7, 62.1, 39.2, 38.4, 32.1, 29.85, 29.8, 29.5, 25.5, 22.8, 15.3, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{38}N_3O_2$ (M + H^+): 328.2958; found: 328.2952.

(2*S*,3*S*,5*S*)-2-Aminooctadecane-3,5-diol (Enigmol, 4)

$LiAlH_4$ (2.0 M in THF, 0.23 g, 3 mL, 6.0 mmol) was added to THF (3.2 mL) at r.t. A solution of azidodiol **29** (0.1 g, 0.3 mmol) in THF (0.75 mL) was then added dropwise and the reaction mixture stirred at r.t. for 15 min. The reaction was quenched by dropwise addition of aq Rochelle salt (5 mL). The biphasic solution was stirred for 30 min at r.t., before separating the organic layer. The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to obtain the aminodiol enigmol (**4**) as a white solid (65 mg, 71%); mp 71–72 °C; $[\alpha]_D^{25}$ –12.1 (*c* 1.05, MeOH).

IR (thin film, CH_2Cl_2): 3402, 3328, 3277, 2917, 2846, 1598, 1463, 984 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.87 (m, 1 H), 3.45 (t, *J* = 7.2 Hz, 1 H), 2.76–2.74 (br m, 1 H), 1.64 (d, *J* = 13.8 Hz, 1 H), 1.53–1.48 (m, 1 H), 1.44–1.39 (m, 3 H), 1.25 (br s, 22 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 76.6, 72.1, 51.7, 40.5, 38.2, 32.1, 29.8, 29.5, 25.7, 22.9, 21.1, 14.3.

(*R*)-1-[(2*S*,3*R*)-3-Methyloxiran-2-yl]pentadecan-2-ol Acetate Ester (31)

To a solution of epoxy alcohol **28** (3.0 g, 10.5 mmol) in anhyd Et_2O (190 mL) were added Ph_3P (5.5 g, 21.0 mmol) and AcOH (1.26 g, 21.0 mmol) and the mixture was cooled to 0 °C. Diisopropyl azodicarboxylate (4.26 g, 21.0 mmol) was then added, and the reaction mixture was stirred at 0 °C for 2 h. The mixture was diluted with H_2O (75 mL), the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to obtain the crude acetate intermediate as a yellow oil. Purification by flash chromatography using 10% EtOAc in hexanes as eluent afforded the epoxy acetate intermediate **31** (2.8 g, 81%) as a colorless oil; $[\alpha]_D^{25}$ +7.2 (*c* 1.04, $CHCl_3$).

IR (film): 2994, 2925, 2854, 1739 1465, 1373, 1240, 1022, 829 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 5.06–5.02 (m, 1 H), 3.06–3.02 (m, 1 H), 2.97–2.94 (m, 1 H), 2.05 (s, 3 H), 1.78–1.76 (m, 2 H), 1.64–1.59 (m, 2 H), 1.29–1.25 (m, 26 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.8, 72.4, 54.1, 52.5, 34.5, 32.7, 32.1, 29.8 (2 C), 29.7 (2 C), 29.6 29.5, 25.4, 22.8, 21.4, 14.3, 13.5.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{39}O_3$ (M + H^+): 327.2893; found: 327.2886.

(*R*)-1-[(2*S*,3*R*)-3-Methyloxiran-2-yl]pentadecan-2-ol (32)

The epoxy acetate **31** (0.30 g, 0.91 mmol) was dissolved in MeOH (3 mL). K_2CO_3 (63 mg, 0.45 mmol) was then added and the reaction mixture was stirred at r.t. for 4 h. MeOH was removed by rotary evaporation and the crude product mixture was dissolved in H_2O (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated to obtain the crude product as a white solid. Purification by flash chromatography using 20% EtOAc in hexanes as eluent gave the epoxy alcohol **32** (0.23 g, 88%) as a white solid; mp 48–49 °C; $[\alpha]_D^{25}$ –13.2 (*c* 1.0, $CHCl_3$).

IR (thin film, CH_2Cl_2): 3334, 3257, 2915, 2848, 1467, 721 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.88–3.83 (m, 1 H), 3.15–3.09 (m, 1 H), 3.07–3.04 (m, 1 H), 1.74–1.70 (m, 2 H), 1.62–1.58 (ddd, *J* = 3.6, 7.8, 14.4 Hz, 1 H), 1.55–1.51 (m, 2 H), 1.48–1.44 (m, 1 H), 1.29 (d, *J* = 6.6 Hz, 3 H), 1.25 (br s, 22 H), 0.87 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 70.3, 54.6, 52.9, 37.9, 35.0, 32.1, 29.8 (2 C), 29.5, 25.8, 22.9, 14.3, 13.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{37}O_2$ (M + H^+): 285.2788; found: 285.2785.

(2*S*,3*S*,5*R*)-2-Azidooctadecane-3,5-diol (33)

Following the procedure described above for compound **29**, epoxy alcohol **32** (0.2 g, 0.7 mmol) was converted into azidodiol **33** (0.12 g, 52%); mp 56–58 °C; $[\alpha]_D^{25}$ +17.2 (*c* 0.52, $CHCl_3$). The C_3-azide regioisomer **34** was also formed (0.06 g, 26%).

IR (thin film, CH_2Cl_2): 3305, 2954, 2913, 2848, 2123, 1469, 1022, 981 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.97–3.91 (m, 1 H), 3.81–3.76 (m, 1 H), 3.49–3.45 (m, 1 H), 2.63 (d, *J* = 4.2 Hz, 1 H), 2.08 (s, 1 H), 1.70 (ddd, *J* = 3.0, 9.6, 14.2 Hz, 1 H), 1.60–1.51 (m, 2 H), 1.49–1.40 (m, 2 H), 1.32–1.26 (m, 24 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 72.2, 69.2, 62.6, 39.5, 37.6, 32.1, 29.8 (2 C), 29.5, 25.9, 22.9, 15.8, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{38}N_3O_2$ (M + H^+): 328.2958; found: 328.2952.

(2*S*,3*S*,5*R*)-2-Aminooctadecane-3,5-diol (35)

Following the procedure described for compound **4**, azidodiol **33** (0.05 g, 0.15 mmol) was converted into aminodiol **35** (36 mg, 79%); mp 64–66 °C; $[\alpha]_D^{25}$ –2.7 (*c* 0.87, $CHCl_3$).

IR (thin film, CH_2Cl_2): 3359, 3307, 2917, 2850, 1592, 1467, 1064 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.92–3.87 (m, 1 H), 3.52–3.49 (m, 1 H), 2.85–2.81 (m, 1 H), 2.78–2.20 (br s, 3 H), 1.66–1.50 (m, 3 H), 1.47–1.39 (m, 2 H), 1.36–1.25 (br s, 22 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 73.7, 69.2, 51.2, 39.6, 37.8, 32.1, 29.8, 29.5, 26.0, 22.9, 20.8, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{40}NO_2$ (M + H^+): 302.3053; found: 302.3047.

(4*S*,6*R*)-4-[(1*S*)-1-Azidoethyl]-2,2-dimethyl-6-(tridecyl)-1,3-dioxane (36)

The *anti*-diol stereochemistry of **33** was confirmed by converting a portion of azidodiol **33** (10 mg) into the 3,5-acetonide **36** (8 mg) using dimethoxypropane and catalytic *p*-TsOH, as described for the preparation of compound **15**. The ^{13}C NMR acetal resonance at 100.9 ppm and methyl resonances at 24.6 ppm and 24.5 ppm were consistent with a six-membered-ring acetonide with *anti*-stereochemistry of the oxygens at C_3 and C_5.[23]

^1H NMR (600 MHz, $CDCl_3$): δ = 3.80–3.74 (m, 2 H), 3.39–3.34 (m, 1 H), 1.73 (ddd, *J* = 6.0, 9.9, 12.6 Hz, 1 H), 1.54–1.49 (m, 2 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.30–1.26 (m, 23 H), 1.18 (d, *J* = 7.2 Hz, 3 H), 0.89 (t, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 100.9, 70.8, 66.9, 60.2, 36.06, 36.04, 32.1, 29.87, 29.81, 29.7, 29.5, 25.5, 24.6, 24.5, 22.9, 15.3, 14.3.

(2*S*,3*S*,5*R*)-2-Acetamidooctadecane-3,5-diol 3,5-Bisacetoxy Diester (37)

The *syn*-stereochemistry of the C_2 and C_3 amino alcohol was confirmed from a portion of aminodiol **35** (6 mg), which was dissolved in anhyd CH_2Cl_2 (0.7 mL) under argon, to which Et_3N (13 μL) was added. This mixture was cooled to 0 °C after which Ac_2O (4 μL) was added. After stirring for 30 min, TLC showed that the reaction was complete. The reaction mixture was quenched with aq 1 N HCl (0.5 mL), the organic layer was separated, and washed with brine (2 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to give compound **37** as a white solid (6 mg, 80%).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.57 (d, *J* = 9.2 Hz, 1 H), 4.99–4.95 (m, 1 H), 4.91–4.85 (m, 1 H), 4.20–4.11 (m, 1 H), 2.07 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.79–1.76 (m, 2 H), 1.51 (br s, 2 H), 1.24 (br s, 25 H), 1.10 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.7, 169.6, 72.2, 70.0, 48.4, 45.0, 36.2, 35.0, 32.1, 29.8, 29.7, 29.5, 25.3, 23.6, 22.9, 21.3, 21.1, 18.6, 14.3.

(2*S*,3*R*,5*S*)-2-Azidooctadecane-3,5-diol (40)

The homoallylic alcohol **7** (0.30 g, 1.1 mmol) was dissolved in dimethoxymethane (16.8 mL) and MeCN (8.4 mL). A solution of $Na_2B_4O_7{\cdot}10\ H_2O$ (16.2 mL, 0.05 M in 4×10^{-4} M Na_2EDTA solution) was added, followed by Bu_4NHSO_4 (15 mg, 44 mmol) and D-epoxone (86 mg, 0.33 mmol).[26] The reaction mixture was cooled to 0 °C. Solutions of Oxone (1.09 g, 1.78 mmol) in 4×10^{-4} M Na_2EDTA (5 mL) and K_2CO_3 (1.04 g, 7.53 mmol) in H_2O (5 mL) were simultaneously added dropwise over a period of 1.5 h, as the reaction mixture was stirred at 0 °C. The mixture was stirred at 0 °C for 30 min more after the additions were completed. The mixture was then diluted with hexanes (25 mL), the organic layer was separated, and the aqueous layer was extracted with hexanes (2 × 25 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation, and the crude product was purified by silica gel chromatography using a gradient of 5–10% EtOAc in hexanes as eluent. The resulting epoxy alcohol **39** (0.20 g, 63%) was added to an 80 °C benzene solution of $Ti(O\textit{i}\text{-}Pr_2)(N_3)_2$ [prepared from Me_3SiN_3 (0.4 g, 3.47 mmol) and $Ti(O\textit{i}\text{-}Pr)_3$ (0.49 g, 1.72 mmol) which had been refluxed in benzene (12.5 mL) for 5 h], and the reaction mixture was stirred for 15 min before cooling to r.t. Benzene was removed under vacuum and the crude product was diluted with Et_2O (25 mL). Aq 5% H_2SO_4 (10 mL) was then added and the resulting solution was stirred for 1 h at r.t. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to obtain a brown oil. The crude product was purified by flash chromatography using 25% EtOAc in hexanes as eluent to obtain the azidodiol **40** (0.125 g, 54%); mp 57–59 °C; $[\alpha]_D^{25}$ +29.8 (*c* 1.04, $CHCl_3$). Traces of the C_3-azide regioisomer (0.01 g, 2%) were also observed.

IR (thin film, CH_2Cl_2): 3297, 2954, 2913, 2848, 2129, 1469, 1259, 1022 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.98–3.94 (m, 1 H), 3.90–3.87 (m, 1 H), 3.59–3.55 (m, 1 H), 2.85 (br s, 1 H), 1.69 (ddd, *J* = 3.0, 9.6, 14.1 Hz, 1 H), 1.58–1.46 (m, 3 H), 1.44–1.39 (m, 1 H), 1.29 (d, *J* = 6.6 Hz, 3 H), 1.26 (br s, 21 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 71.5, 69.6, 61.9 38.1, 37.6, 32.1, 29.8, 29.7, 29.5, 25.9, 22.9, 14.5, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{38}N_3O_2$ (M + H^+): 328.2958; found: 328.2953.

(2*S*,3*S*,5*R*)-2-Aminooctadecane-3,5-diol (41)

Following the procedure described for compound **4**, azidodiol **40** (75 mg, 0.22 mmol) was converted into aminodiol **41** as a white solid (50 mg, 73%); mp 71–73 °C; $[\alpha]_D^{25}$ +13.9 (*c* 0.55, $CHCl_3$).

IR (thin film, CH_2Cl_2): 3307, 2915, 2848, 1469, 1051 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.94–3.88 (m, 1 H), 3.78–3.74 (m, 1 H), 2.96–2.92 (m, 1 H), 1.65–1.60 (m, 1 H), 1.55–1.41 (m, 4 H), 1.32–1.25 (br s, 22 H), 1.06 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 71.8, 69.2, 51.1, 39.0, 37.8, 32.1, 29.9, 29.8, 29.5, 26.1, 22.9, 18.3, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{40}NO_2$ (M + H^+): 302.3053; found: 302.3051.

(4*R*,6*S*)-4-[(1*S*)-1-Azidoethyl]-2,2-dimethyl-6-(tridecyl)-1,3-dioxane (42)

The *anti*-diol stereochemistry of **40** was confirmed by converting a portion of azidodiol **40** (15 mg) into the 3,5-acetonide **42** (12 mg) using dimethoxypropane and catalytic *p*-TsOH, as described for the preparation of compound **15**. The ^{13}C NMR acetal resonance at 100.7 ppm and methyl resonances at 24.8 ppm and 24.7 ppm were consistent with a six-membered-ring acetonide with *anti*-stereochemistry of the oxygens at C_3 and C_5.[23]

^1H NMR (600 MHz, $CDCl_3$): δ = 3.79–3.75 (m, 2 H), 3.56–3.51 (m, 1 H), 1.81 (ddd, *J* = 5.4, 12.6 Hz, 1 H), 1.57–1.50 (m, 2 H), 1.46–1.39 (m, 2 H), 1.35 (s, 6 H), 1.30–1.26 (m, 21 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 100.7, 69.9, 66.9, 60.4, 36.0, 34.2, 32.1, 29.87, 29.81, 29.7, 29.5, 25.5, 24.8, 24.7, 22.9, 15.3, 14.3.

(2*S*,3*R*,5*R*)-2-Azidooctadecane-3,5-diol (44)

Using the same procedure as described for **39**, compound *ent*-**7** (0.50 g, 1.86 mmol) was converted into epoxy alcohol **43** (0.345 g, 65%), and a portion of this epoxy alcohol (0.20 g) was further converted into azidodiol **44** (0.15 g, 65%); mp 31–33 °C; $[\alpha]_D^{25}$ +10.8 (*c* 0.86, $CHCl_3$). Traces of the C_3-azide regioisomer (0.01 g, 4%) were also observed.

IR (thin film, CH_2Cl_2): 3369, 2923, 2854, 2115, 2098, 1461, 1261, 1051 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.89–3.85 (m, 1 H), 3.83–3.80 (m, 1 H), 3.52–3.48 (m, 1 H), 2.57 (br s, 1 H), 1.68–1.66 (m, 1 H), 1.53–1.47 (m, 3 H), 1.41–1.37 (m, 1 H), 1.30–1.26 (m, 21 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 75.5, 73.3, 61.9 38.5, 38.3, 32.1, 29.8, 29.7, 29.5, 25.9, 22.8, 14.3 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{38}N_3O_2$ (M + H^+): 328.2958; found: 328.2959.

(2*S*,3*R*,5*R*)-2-Aminooctadecane-3,5-diol (45)

Following the procedure described for compound **4**, azidodiol **44** (75 mg, 0.22 mmol) was converted into aminodiol **45** (50 mg, 70%); mp 82–83 °C; $[\alpha]_D^{25}$ +3.1 (*c* 0.98, $CHCl_3$).

IR (thin film, CH_2Cl_2): 3340, 2917, 2848, 1461, 1076 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 3.99–3.83 (m, 1 H), 3.74–3.70 (m, 1 H), 3.03–2.99 (m, 1 H), 2.90–2.00 (br s, 3 H), 1.58–1.40 (m, 5 H), 1.30–1.26 (br s, 21 H), 1.57 (d, *J* = 6.6 Hz, 3 H), 0.88 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 75.7, 72.0, 50.7, 38.3, 38.0, 32.1, 29.8, 29.5, 25.7, 22.9, 18.0, 14.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{40}NO_2$ ($M + H^+$): 302.3053; found: 302.3050.

(4*R*,6*R*)-4-[(1*S*)-1-Azidoethyl]-2,2-dimethyl-6-(tridecyl)-1,3-dioxane (46)

The *syn*-diol stereochemistry of **44** was confirmed by converting a portion of azidodiol **44** (15 mg) into the 3,5-acetonide **46** (10 mg) using dimethoxypropane and catalytic *p*-TsOH, as described for the preparation of compound **15**. The ^{13}C NMR acetal resonance at 98.8 ppm and methyl resonances at 30.2 ppm and 19.9 ppm were consistent with a six-membered-ring acetonide with *syn*-stereochemistry of the oxygens at C_3 and C_5.[23]

^1H NMR (600 MHz, $CDCl_3$): δ = 3.80–3.75 (m, 2 H), 3.45–3.41 (m, 1 H), 1.57–1.53 (m, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.31–1.26 (m, 22 H), 1.22 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 98.8, 72.4, 68.9, 60.8, 36.6, 32.4, 32.1, 30.2, 29.8, 29.7, 29.5, 25.5, 22.9, 19.9, 15.1, 14.3.

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