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Note

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De Novo Asymmetric Synthesis of Avocadyne, Avocadene and Avocadane Stereoisomers

Vitor L. S. Cunha,[†,§] Xiaofan Liu,[⊥,§] Todd L. Lowary,[†,*] and George A. O'Doherty[⊥,*]

In memory of Leo A. Paquette who left us on Jan. 21, 2019.

[†] Department of Chemistry, University of Alberta, Edmonton, Alberta, T6G 2G2 Canada
[⊥] Department of Chemistry and Chemical Biology, Northeastern University, Boston, Massachusetts 02115, US.
tlowary@ualberta.ca
G.ODoherty@neu.edu

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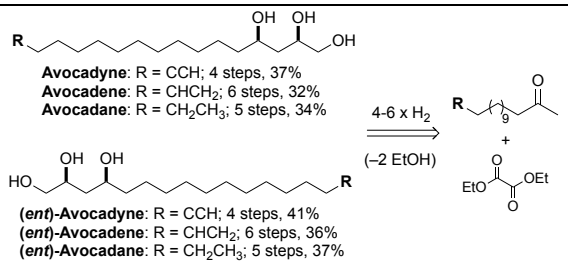


ABSTRACT: The *de novo* asymmetric synthesis of all possible stereoisomers of two polyketide natural products, avocadyne, avocadene, and the saturated variant avocadane is described. The stereodivergent synthesis of the twelve congeners is accomplished in 4–6 steps from an achiral acylpyruvate derivative, which, in turn, is prepared in five steps from commercially available materials. The approach uses, sequentially, a Noyori asymmetric reduction, a diastereoselective chelate- or directed reduction of a β-hydroxyketone, and an ester reduction to a primary alcohol.

The pear-shaped fruit of the avocado tree (*Persea americana*) has garnered a much attention as a superfood for its purported dietary health benefits.[1] In addition to its richness in vitamins (*e.g.*, vitamins B, C, E, K) and minerals (*e.g.*, potassium), avocados are replete with monounsaturated (*e.g.*, oleic acid), saturated (palmitic acid) and poly-unsaturated fats (*e.g.*, linoleic acid).[1] Recently, the health benefits of avocados have been associated with the lipid extract avocatin B, which has been shown to possess potent anticancer activity (1–10 μg/mL against A-549, MCF-7, HT-29, A-498 and PaCa-2 cell lines) and anti-viral activity (HIV-1).[2] Of particular note is the anti-acute myeloid leukemia (AML) activity associated with avocatin B.[2] The cytotoxic effects of the avocatin B extract is believed to occur via inhibition of fatty acid β-oxidation (FAO) which induces mitochondria-mediated cell death.[2,3]

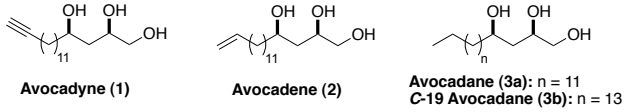
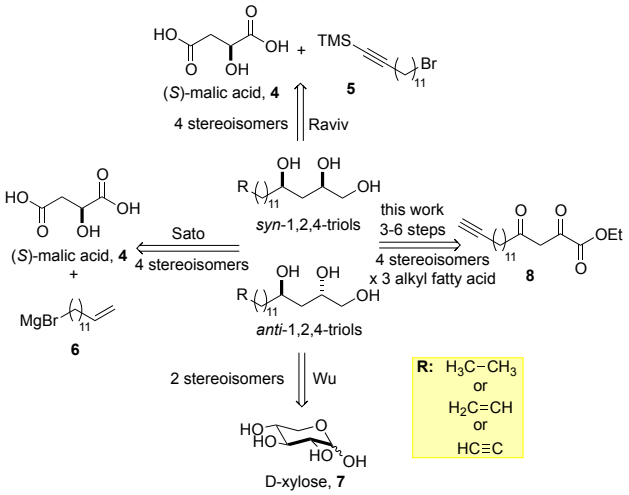


Figure 1: Avocadyne (1), avocadene (2) and avocadane (3a)

The natural extract avocatin B consists of a 1:1 mixture of avocadyne (**1**) and avocadene (**2**), two 17-carbon triols with terminal alkene and alkyne groups (Figure 1).[4] Subsequently, the saturated two carbon extended variant of *C*-19 avocadane (**3b**), was also isolated from avocados.[5] The absolute configuration for all three triols was determined to be (2*R*,4*R*) by a combination of Mosher ester analysis and chemical synthesis.[6]

While the triols (**1**, **2**, and **3b**) with variable degrees of oxidation at the terminal position generally possess similar biological activities, significantly different anticancer activity was observed against the human prostate adenocarcinoma (PC-3: **1**, 0.06 μg/mL ; **2**, 0.5 μg/mL and **3b**, 1.2 μg/mL). A similar trend in activity was seen in a yellow fever mosquito larvae insecticidal assay (YFM LC_{50}: **1**, 0.08 μg/mL ; **2**, 0.2 μg/mL and **3b**, 1.8 μg/mL).[5]

Scheme 1. Approaches to avocadyne (1), -ene (2), and -ane (3a)

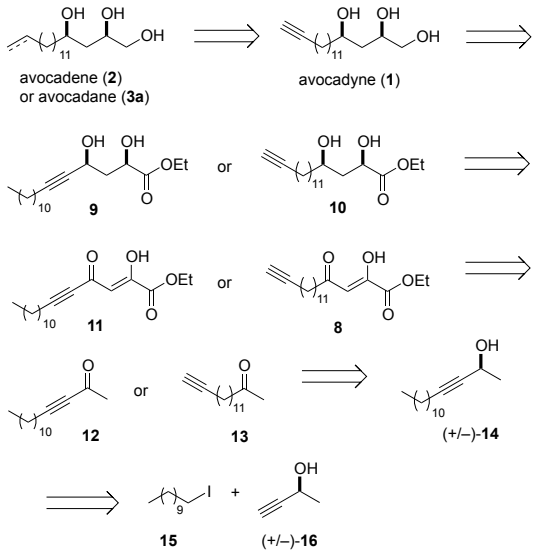


The unique structure and biological activity of these molecules has inspired three successful synthetic efforts by Raviv, Sato and Wu (Scheme 1).[6,7,8] These syntheses, all of which used the chiral pool, were instrumental in establishing the absolute and relative stereochemistry of these compounds and were also important in enabling initial structure–activity relationship studies of this class of natural products. Our interest in compounds **1**–**3** resulted from wonderment at the observation that such disparate biological activity could result from the successive loss of two hydrogen atoms from the terminal position of a long chain lipid (cf, **3** to **2** and **1**). Of particular interest was whether structural changes to the two ends of the lipid chain (*i.e.*, stereoisomers vs oxidation state) would have synergistic or antagonistic effects on the biological activity of this class of lipids. This interest is part of a continuing effort aimed at exploring stereochemical structure–activity relationships (S-SAR) of carbohydrate[9] and polyketide based natural products.[10] Herein we describe our successful efforts to develop a *de novo* asymmetric synthesis of **1**–**3a**, and all of their possible stereoisomers.

Retrosynthetically, we envisioned the reduced forms, avocadene (**2**) and avocadane (**3a**), as coming from a mono- and per-hydrogenation of avocadyne (**1**), respectively (Scheme 2). Alkyne **1**, in turn, could come from an ester reduction of either *syn*-2,4-dihydroxy-esters **9** or **10** and, in the case of **9**, an alkyne zipper reaction.[11] A combination of enantio- and diastereoselective reductions could produce either **9** or **10** from the enol form of the tricarbonyl precursors **8** or **11**. Of particular interest was the potential reduction of the 1,3-diketone form of enol

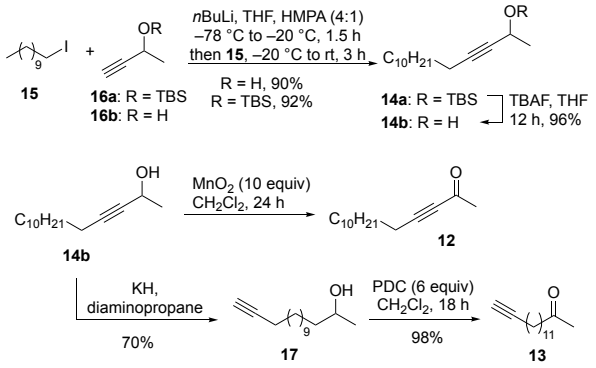
11 using an iterative, reagent-controlled process involving first catalytic Noyori reduction[12] for the enantioselective reduction at *C*-2 and diastereoselective reduction at *C*-4 of the resulting keto-alcohol to give *syn*-diol **9**. A Claisen condensation between **12** or **13** with diethyl oxalate could be used to prepare **8** or **11**. Finally, an oxidation or isomerization/oxidation approach could be used to prepare ketones **12** or **13** from racemic propargylic alcohol **14**. The synthesis of **14** could be achieved by an alkylation reaction involving two commercially available compounds – propargylic alcohol **16** and alkyl iodide **15**.

Scheme 2: Retrosynthetic of Avocadyne, -ene and -ane (1, 2, 3a)



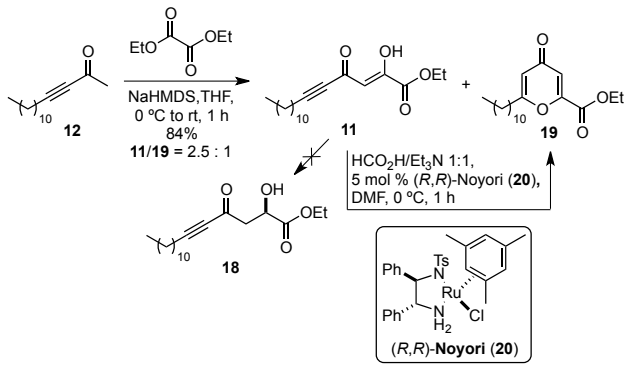
The synthesis of ynone **12** (Scheme 3) began with the alkylation of the lithium acetylide of TBS-protected propargylic alcohol **16a** with *n*-undecyl iodide (**15**) to form the TBS-protected alcohol **14a**, which could be deprotected to form **14b**.[10f] Alternatively, alcohol **16b** could be directly alkylated by double lithiation and treatment with **15** to provide propargylic alcohol **14b**. Both approaches gave **14b** in comparable (88-90%) yield. Finally, a MnO_2 oxidation was used to convert **14b**, in 80% yield, into ynone **12**.[10] Access to ynone **13** from alcohol **14b** was achieved in two steps and 69% overall yield by first isomerization to the terminal alkyne **17** upon exposure to excess KAPA reagent[13] and then oxidation of the secondary alcohol with PDC.

Scheme 3. Synthesis of ynones 12 and 13



Our initial efforts toward avocadyne (**1**) began with the attempted synthesis of ketoenolester **11** (Scheme 4). This was done using an NaHMDS promoted Claisen condensation between ynone **12** and diethyl oxalate. Unfortunately, this reaction gave a mixture of the desired product, **11**, and a cycloisomerized derivative, pyranone **19** (84%, ~2.5:1 **11**/**19**). Purification of the two compounds proved challenging as **11** converted to **19** during column chromatography. Moreover, the use of the typical Noyori hydrogen transfer reaction conditions (5 mol% **20**, HCO_2H/Et_3N 1:1),[12] on the mixture of compounds led to complete cyclization of **11** into **19**. As such, the use of **11** was abandoned and we instead investigated the synthesis of **1** from ynone **13**, which contains a terminal alkyne.

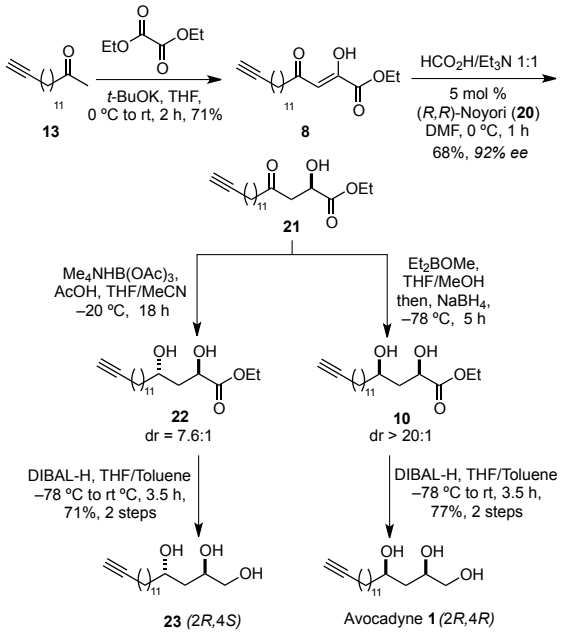
Scheme 4. Synthesis and attempted reduction of precursor 11



Our revised synthesis of avocadyne (**1**) began with the synthesis of ketoenolester **8** (Scheme 5). This commenced with the KO*t*-Bu promoted Claisen condensation between ω-yn-2-one **13** with diethyl oxalate,[14] which occurred in a gratifying 71% yield. Exposure of **8** to our standard Noyori hydrogen transfer reaction (5 mol % **20**, HCO_2H/Et_3N 1:1) proceeded smoothly to give β-hydroxyketone **21** in good yield (68%) and with high chemoselectivity for the more reactive 1,2-dicarbonyl functional group. With the initial asymmetry installed into β-hydroxyketone **21**, we explored the diastereoselective reduction to the *anti*- and *syn*-diol motifs. The *anti*-diol was installed with the use of $Me_4NHB(OAc)_3$-directed reduction[15] of **21** to give the *anti*-2,4-dihydroxyester **22**, which was subsequently reduced with DibalH leading to the *anti*-1,2,4-triol **23** in 71% yield (> 88% dr) for the two steps. Conversely, the *syn*-diol motif was installed by an Et_2BOMe mediated $NaBH_4$ reduction[16] of **21** resulting in the *syn*-2,4-dihydroxyester **10** (77% yield, > 95% dr). Reduction of **10** with DibalH produced the *syn*-1,2,4-triol **1** in 71%

yield over the two steps. Synthetic **1** possessed both physical (mp, optical rotation) and spectral properties (IR, $^{1}H/^{13}C$ NMR, HRMS) that matched that reported by for natural avocadyne.[5,6]

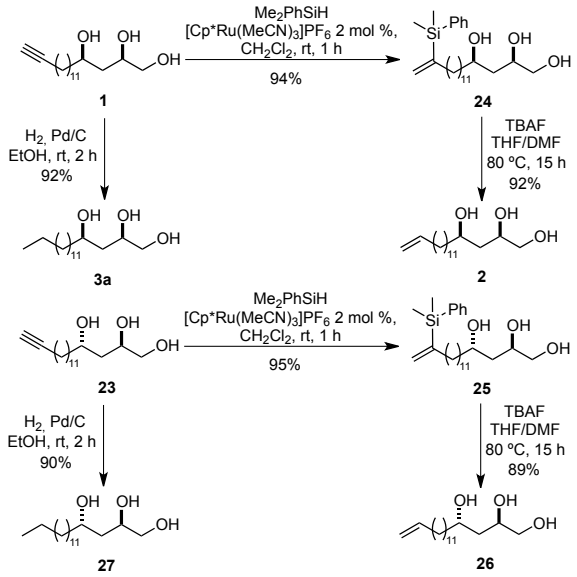
Scheme 5. Synthesis and iterative reduction of achiral 8



With synthetic access to avocadyne (**1**) and *C*-4 epimer **23** we turned our attention to the selective reduction of **1** into avocadene (**2**) and avocadane (**3a**) (Scheme 6). Our initial attempts to reduce the alkyne group in **1** chemoselectively under the typical Lindlar's conditions proved problematic; i.e., over-reduction and difficulties separating the alkene and alkane products. Therefore, we turned to a stepwise procedure involving Trost Cp*Ru(II)-catalyzed hydrosilylation[17] of **1** to give vinylsilane **24**. The compound was obtained in excellent yield (94%) and regioselectivity (> 20:1). Exposure of **24** to the protodesilylation conditions of TBAF cleanly gave avocadene (**2**) in excellent yield (92%). Finally, the alkyne in **1** can be reduced under typical hydrogenation conditions (H_2, Pd/C, EtOH) to give avocadane (**3a**) in excellent yield (92%). The synthetic sample of **2** possessed physical and spectral properties consistent with that reported for natural avocadene (**2**),[5,6] and the saturated variant avocadane (**3a**) has been fully characterized for the first time.[18]

Application of the same two-step hydrosilylation–protodesilylation protocol to the *anti*-diastereomer **23** cleanly converted it into the *anti*-diastereomer of avocadene (**26**, via vinylsilane **25**). Alkyne **23** was also fully reduced to form the *anti*-diastereomer of avocadane, **27**.

Scheme 6. Synthesis of avocadene (2), avocadane (3a) and *anti*-diastereomer

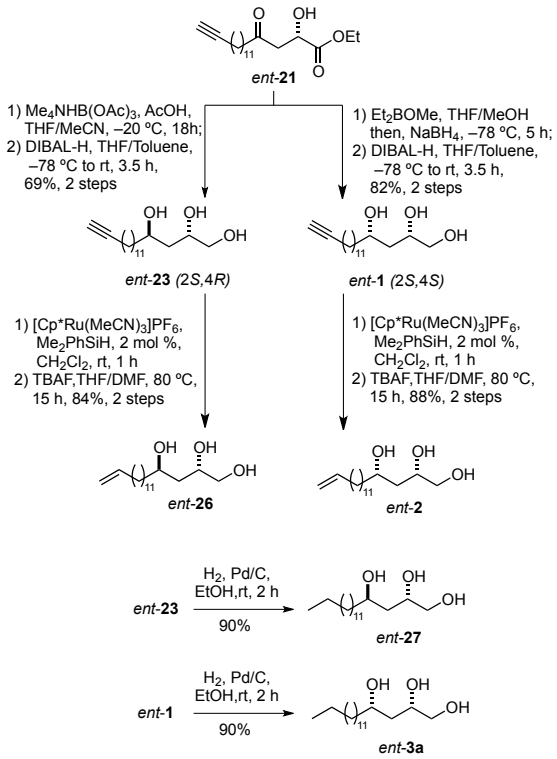


The power of this *de novo* asymmetric synthetic approach is evident in its ability to prepare all of the possible stereoisomers of **1**–**3** efficiently. This includes the *anti*-diastereomers **23**, **26** and **27** of the natural products (Schemes 5 and 6), as well as the six enantiomers: (*ent*)-**1**, (*ent*)-**2**, (*ent*)-**3a**, (*ent*)-**23**, (*ent*)-**2**, and (*ent*)-**27** (Scheme 7). By simply switching to the (*S*,*S*)-Noyori catalyst, achiral **8** can be readily reduced to (*ent*)-**21**. Similarly, (*ent*)-**21** can, in a stereodivergent fashion, be diastereoselectively converted into either (*ent*)-**1** or (*ent*)-**23**. Stepwise reduction of (*ent*)-**1** or (*ent*)-**23** leads to first the terminal alkenes (*ent*)-**2** and (*ent*)-**26** and then the saturated variants (*ent*)-**3a** and (*ent*)-**27**.

Conclusions:

In conclusion, a highly efficient four-step enantio- and diastereoselective synthesis of avocadyne (**1**) was accomplished from achiral methyl ketone **13**, which itself can be prepared in three steps from commercial materials. The approach can be readily adapted to prepare the related natural product avocadene (**2**) and the saturated variant avocadane (**3a**) in six and five steps, respectively. Compared to previous syntheses of compounds (**1**-**2**), the approach described compares very favorably in terms of number of steps and overall yield.[3,7,8] Moreover, the stereodivergent nature of the approach is demonstrated by the preparation of all nine possible stereoisomers of these three natural products in a similar 4–6 step manner. The use of these compounds in structure–activity relationship studies of this class of natural products will be disclosed in due course.

Scheme 7. Enantiomeric synthesis of (*ent*)-1/2/3a and *anti*-diastereomers



Experimental Section:

General Methods

All reagents were purchased from commercial sources and used without further purification. Dichloromethane, DMF and THF used in reactions were taken from a solvent purification system in which the solvents are purified by successive passage through columns of alumina and copper under argon. Methanol used in reactions was dried in a sealed bottle over activated 3 Å molecular sieves. 1,3-diaminopropane was dried in a sealed bottle over 4 Å molecular sieves. Unless stated otherwise, all reactions were monitored by thin layer chromatography on silica gel 60 F254 (0.25 mm, Merck) glass plates. Spots were detected by charring with a solution of ceric ammonium nitrate (0.5 g) and ammonium molybdate (12 g) in water (235 mL) and sulfuric acid (15 mL). In the reaction work-up involving extractions, solutions of organic solvents were washed with equal amounts of aqueous solutions, unless otherwise noted. All column chromatography was performed on silica gel 60 (40–60 μm). Melting points were measured on a Gallenkamp apparatus and are not corrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter at the sodium D line (589 nm) at 21 ± 2 ºC and are in units of (deg·mL)/(dm·g). FTIR spectra were run on Thermo Nicolet (Madison Wisconsin, USA) 8700 main bench with a Continuum FTIR microscope attached, and samples cast from a chloroform solution onto an IR-transparent silicone wafer. ^{1}H NMR spectra were recorded at 500 and 700 MHz and the chemical shifts were referenced to $CHCl_3$ (7.26 ppm, $CDCl_3$) or CD_2HOD (3.30 ppm, CD_3OD). ^{13}C NMR spectra were recorded at 126, 151 or 176 MHz and are proton decoupled; and the chemical shifts were referenced to $CDCl_3$ (77.06 ppm, $CDCl_3$) or CD_3OD (49.00, CD_3OD). High resolution electrospray mass spectra were recorded on an Agilent Technologies 6220 Accurate-Mass TOF spectrometer with samples dissolved in a suitable solvent.

Pentadec-3-yn-2-ol (14b). A solution of *n*BuLi (36 mL, 90 mmol) in hexanes was slowly added to a solution of freshly distilled propargylic alcohol **16** (3.2 g, 45 mmol) in 4:1 THF–HMPA (100 mL) at –78 °C by syringe and needle. The reaction mixture was then warmed to –20 °C and the alkyl iodide **15** (10 g, 35 mmol) was added dropwise. After complete addition, the cooling bath was removed, and the reaction mixture allowed to warm to rt and stirred overnight (16 h). Saturated aqueous NH_4Cl solution was added and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (1%–20%, EtOAc–hexane) to give pentadec-3-yn-2-ol **14b** (7.0 g, 90%) as a colorless oil: $R_f = 0.30$ (10% EtOAc–hexane); IR (neat): 3405, 2923, 2853, 1743, 1728, 1238, 1154, 1076 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.47 (q, J = 7.3 Hz, 1H), 2.40–2.20 (m, 1H), 2.15 (td, J = 7.2, 2.0 Hz, 2H), 1.49–1.40 (m, 2H), 1.39 (d, J = 6.7 Hz, 3H), 1.32 (dd, J = 7.2, 7.4 Hz, 2H), 1.28–1.18 (m, 14H), 0.85 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 84.9, 82.3, 58.4, 31.9, 29.60, 29.59, 29.5, 29.3, 29.1, 28.8, 28.6, 24.66, 22.65, 18.59, 14.1; HRMS (MALDI–TOF, CCA) *m/z* calcd for $C_{15}H_{28}ONa$ $[M + Na]^+$ 247.2038, found 247.2039.

Pentadec-14-yn-2-ol (17). A 30% suspension of KH in mineral oil (5.62 g, 140 mmol) was washed three times under argon with ether, the organic layer was transferred to isopropanol for quenching KH residues and then remained ether on KH solid was removed under vacuum. Dry 1,3-diaminopropane (28 mL) was added at 0 °C. The reaction warmed slowly to room temperature with stirring over an hour. Then the mixture was cooled to 0 °C, and the alkynol **14b** (3.15 g, 28.1 mmol) was added dropwise over 20 min. The resulting slurry was warmed to room temperature and stirred at the same temperature for 10 h. The mixture was stirred at 0 °C, and ice chips were added slowly to quench the reaction till the bubbling stop forming. Resulting mixture was extracted with ether (3 □ 300 mL). The combined extracts were washed with 1 N HCl, saturated aqueous sodium bicarbonate and brine, and then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (20–30% Et_2O–hexane) to give **17** (2.23 g, 19.9 mmol, 70%) as a white solid:: R_f = 0.40 (20% EtOAc–hexane); mp: 34–35 ºC IR (neat): 2924, 2853, 1593, 1458, 1329, 1129, 1081, 623 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.79–3.70 (m, 1H), 2.18–2.10 (td, J = 7.1, 2.6 Hz, 2H), 1.94 (t, J = 2.5 Hz, 1H), 1.55–1.49 (m, 4H), 1.51–1.27 (m, 16H), 1.19 (d, J = 6.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 84.9, 68.2, 68.1, 39.4, 29.7, 29.65, 29.62 (2C), 29.5, 29.2, 28.8, 28.5, 25.8, 23.6, 18.4. HRMS (MALDI–TOF, CCA) *m/z* calcd for $C_{15}H_{28}ONa$ $[M + Na]^+$ 247.2038, found 247.2011.

Pentadec-14-yn-2-one (13). To a solution of **17** (2.0 g, 8.9 mmol) in CH_2Cl_2 (60 mL) at room temperature was added pyridinium dichromate (19.7 g, 53 mmol). The reaction mixture was stirred for 18 h then filtered through celite, washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure to give ketone **13** (1.9 g, 35 mmol, 90%) as yellow oil: $R_f = 0.40$ (10% EtOAc–hexane); IR (neat) 2923, 1713, 1461, 1351, 1165, 965, 822, 624 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (m, 2H), 2.18 (td, J = 7.1, 2.6 Hz, 2H), 2.13 (s, 3H), 1.94 (t, J = 2.6 Hz, 1H), 1.6–1.38 (m, 4H), 1.31–1.19 (m, 14H); $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$) δ 209.4, 84.8, 68.1, 43.9, 29.9, 29.6, 29.49, 29.46, 29.42, 29.2, 29.1, 28.8, 28.5, 23.9, 18.4; HRMS (MALDI–TOF, CCA) *m/z* calcd for $C_{15}H_{26}ONa$ $[M + Na]^+$ 245.1881, found 245.1872.

Pentadec-3-yn-2-one (12). To a solution of **14** (4.00 g, 35.7 mmol) in THF (100 mL) at room temperature was added activated MnO_2 (31.3 g, 0.36 mol). The reaction mixture was stirred for 24 h then filtered through celite and concentrated under pressure to give ketone **12** (3.53 g, 90%) as yellow oil: $R_f = 0.40$ (10% EtOAc–hexane); IR (neat): 2960, 2871, 2210, 1675, 1358, 1226 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ

2.35 (t, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.57 (m, J = 7.5 Hz, 2H), 1.39 (m, 2H), 1.24–1.28 (m, 14H), 0.88 (t, J = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 184.9, 94.2, 81.4, 32.7, 31.9, 29.6 (2C), 29.4, 29.3, 29.0, 28.8, 27.7, 22.7, 18.9, 14.1; HRMS (MALDI–TOF, CCA) *m/z* calcd for $C_{15}H_{26}ONa^+$ $[M + Na]^+$ 245.1881, found 245.1852.

Synthesis and Attempted Reduction of Precursor 11. Pentadec-3-yn-2-one (**12**, 229 mg, 1.03 mmol) was dissolved in THF (5 mL) and diethyl oxalate (0.37 mL, 2.74 mmol) was added. The solution was cooled to 0 ºC and NaHMDS (1 M in THF, 1.1 mL, 1.1 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 1 h. Distilled water was added, followed by 1 M HCl until the pH of the solution was 7. The mixture was extracted with EtOAc (3 □ 30 mL) and the combined organic fractions were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness to afford a brown oil (270 mg, 84%, ratio **11/19** 2.5:1, crude NMR spectrum in page S27). HRMS (ESI) *m/z* calcd for $C_{19}H_{30}NaO_4$ $[M + Na]^+$ 345.2036, found 345.2039. To a flask containing triethylamine (0.39 mL, 2.82 mmol), formic acid (0.11 mL, 2.82 mmol) was added dropwise at 0 ºC. The mixture was stirred at room temperature for 30 min and then transferred via cannula to a flask containing the previous crude oil (101 mg), RuCl(mesitylene)[(*R,R*)-TsDPEN] (10 mg, 0.02 mmol) and DMF (0.2 mL) at 0 ºC. The reaction mixture was stirred at 0 ºC for 1 h and then distilled water (10 mL) was added and the mixture was extracted with EtOAc (3 □ 10 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. NMR analysis (page S28) of the crude material showed that no reduction occurred, and that compound **11** was converted fully to **19** under the reaction conditions. Data for **19**: ^1H NMR (700 MHz, $CDCl_3$) δ 7.02 (d, J = 2.3 Hz, 1H), 6.24 (d, J = 2.3 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 2.59 (t, J = 7.7 Hz, 2H), 1.68 (quint, J = 7.7 Hz, 2H), 1.40–1.26 (m, 18H), 0.88 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 179.9, 170.4, 160.0, 152.9, 118.7, 115.1, 62.9, 33.6, 31.9, 29.6, 29.47, 29.35, 29.2, 28.9, 26.74, 22.72, 14.2, 14.1.

Ethyl 2-hydroxy-4-oxoheptadec-2-en-16-ynoate (8). Pentadec-14-yn-2-one (**13**, 2.08 g, 9.35 mmol) was dissolved in THF (8 mL) under argon and diethyl oxalate (1.5 mL, 11 mmol) was added. The solution was cooled to 0 ºC and *t*-BuOK (1 M in THF, 9.9 mL, 9.9 mmol) was added dropwise. The reaction mixture was warmed to room temperature and was stirred for 2 h. Distilled water was added, followed by 1 M HCl until the pH of the solution was 7. The mixture was extracted with EtOAc (3 □ 30 mL) and the combined organic fractions were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude solid was purified by silica gel flash chromatography (90:9:1 hexane–EtOAc–HOAc) to afford **8** (2.12 g, 71%) as an orange solid: R_f = 0.33 (85:14:1 hexane–EtOAc–HOAc); mp 44–45 ºC; IR (cast film): 3423, 3278, 3109, 2924, 2850, 2113, 1720, 1644, 1604, 1284, 1139 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 14.50 (br s, 1H), 6.36 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.47 (t, J = 7.5 Hz, 2H), 2.18 (td, J = 7.2, 2.6 Hz, 2H), 1.93 (t, J = 2.7 Hz, 1H), 1.64 (quint, J = 7.2 Hz, 2H), 1.52 (quint, J = 7.2 Hz, 2H), 1.44–1.24 (m, 17H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 203.3, 166.8, 162.2, 101.6, 84.8, 68.1, 62.5, 41.0, 29.54, 29.49, 29.4, 29.3, 29.2, 29.1, 28.8, 28.5, 25.0, 18.5, 14.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{30}NaO_4$ $[M + Na]^+$ 345.2036, found 345.2034.

(*R*)-Ethyl 2-hydroxy-4-oxoheptadec-16-ynoate (21). To a flask containing triethylamine (1.8 mL, 13 mmol), formic acid (0.50 mL, 13 mmol) was added dropwise at 0 ºC. The mixture was stirred at room temperature for 30 min and then cooled to 0 ºC. Compound **8** (450 mg, 1.40 mmol), RuCl(mesitylene)[(*R,R*)-TsDPEN] (45 mg, 0.07 mmol) and DMF (0.9 mL) were then added and the reaction mixture was stirred

at 0 ºC for 1 h. Distilled water (10 mL) was added and the mixture was extracted with EtOAc (3 □ 10 mL). The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude solid was purified by silica gel flash chromatography (3:1 hexane–EtOAc) to afford **21** (306 mg, 68%) as an off-white solid: R_f = 0.21 (3:1 hexane–EtOAc); mp 39–40 ºC; $[\alpha]_D$ +3.8 (*c* 1.5, $CHCl_3$); IR (cast film): 3421, 3280, 2930, 2914, 2850, 1724, 1707, 1471, 1262, 1114 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 4.48–4.44 (m, 1H), 4.28–4.21 (m, 2H), 3.19 (br s, 1H), 2.92 (dd, *J* = 17.2, 3.9 Hz, 1H), 2.86 (dd, *J* = 17.2, 6.3 Hz, 1H), 2.43 (t, *J* = 7.5 Hz, 2H), 2.16 (td, *J* = 7.2, 2.6 Hz, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.59–1.54 (m, 2H), 1.51 (quint, *J* = 7.2 Hz, 2H), 1.40–1.35 (m, 2H), 1.30–1.24 (m, 15H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 208.6, 173.7, 84.8, 68.1, 67.1, 61.8, 45.9, 43.5, 29.5, 29.44, 29.40, 29.35, 29.09, 29.08, 28.7, 28.5, 23.5, 18.4, 14.1; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}NaO_4$ $[M + Na]^+$ 347.2193, found 347.2193. The determination of enantiomeric excess for compound **21** is reported at the end of the experimental section.

(*S*)-Ethyl 2-hydroxy-4-oxoheptadec-16-ynoate (*ent*-21). Compound ***ent*-21** was obtained from **8** (468 mg, 1.45 mmol) using RuCl(*p*-cymene)[(*S,S*)-TsDPEN] (47 mg, 0.07 mmol) as the catalyst under the same conditions as those used for the synthesis of **21**. Compound ***ent*-21** (330 mg, 70%) was isolated as an off-white solid: mp 38–39 ºC; $[\alpha]_D$ –3.5 (*c* 1.5, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{19}H_{32}NaO_4$ $[M + Na]^+$ 347.2193, found 347.2191. The IR and NMR data for ***ent*-21** was the same as that for **21**. The determination of enantiomeric excess for compound ***ent*-21** is reported at the end of the experimental section.

(2*R*,4*R*)-Heptadec-16-yne-1,2,4-triol, Avocadyne (1). Compound **21** (493 mg, 1.52 mmol) was dissolved in THF (3.0 mL) and CH_3OH (0.8 mL). The solution was cooled to –78 ºC and diethylmethoxyborane (0.23 mL, 1.8 mmol) was added dropwise. The mixture was stirred at –78 ºC for 15 min, and sodium borohydride (68 mg, 1.8 mmol) was then added. After 5 h of stirring at –78 ºC, acetic acid (2 mL) was added, followed by distilled water (20 mL). The mixture was extracted with EtOAc (3 □ 20 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution (3 □ 20 mL) and brine (20 mL), dried over sodium sulfate, filtered and concentrated to dryness. Methanol was then added to the residue and removed under reduced pressure three times. The crude solid was then dried under high vacuum overnight and used in the next step without further purification. ^1H NMR analysis of the crude indicates that the *syn/anti* diastereomeric ratio was >20:1. The solid was dissolved in dry THF (10 mL) and the solution was cooled to –78 ºC before DIBAL-H (1 M in toluene, 8.8 mL, 8.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3.5 h. After cooling to 0 ºC, a saturated solution of potassium sodium tartrate was added as well as EtOAc. The mixture was stirred for 2 h and the layers separated. The aqueous layer was vigorously extracted with EtOAc an additional four times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude product was purified by silica gel flash chromatography (95:5 EtOAc–CH_3OH) to afford **1** (332 mg, 77%) as a white solid: R_f = 0.42 (95:5 EtOAc–CH_3OH); mp 72–73 ºC (lit.[4] 76 ºC); $[\alpha]_D$ –5.0 (*c* 0.6, $CHCl_3$) [lit.[4] –4.9 (*c* 1.0, $CHCl_3$)]; IR (cast film): 3434, 3344, 3279, 2918, 2850, 2111, 1468, 1435, 1133, 1064, 1043 cm^{-1}; ^1H NMR (700 MHz, CD_3OD) δ 3.82–3.72 (m, 2H), 3.49 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.45 (dd, *J* = 11.2, 6.0 Hz, 1H), 2.17–2.12 (m, 3H), 1.65 (app dt, *J* = 14.1, 4.5 Hz, 1H), 1.54–1.23 (m, 21H); $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ 85.1, 72.2, 71.2, 69.3, 67.3, 41.2, 38.7, 30.83, 30.75, 30.70, 30.65, 30.2, 29.8, 29.7, 26.6, 19.0; HRMS (ESI) *m/z* calcd for $C_{17}H_{32}NaO_3$ $[M + Na]^+$ 307.2244, found 307.2242.

(2*S*,4*S*)-Heptadec-16-yne-1,2,4-triol (*ent*-1). Compound ***ent*-21** (136 mg, 0.42 mmol) was treated as described for the conversion of **21** into **1** to afford **(*ent*)-1** (97 mg, 82%) as a white solid: mp 71–72 ºC; $[\alpha]_D$ +5.0 (*c* 0.6, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{32}NaO_3$ $[M + Na]^+$ 307.2244, found 307.2245. The IR and NMR data for ***ent*-1** was the same as that for **1**.

(2*R*,4*S*)-Heptadec-16-yne-1,2,4-triol (23). Tetramethylammonium triacetoxyborohydride (1.60 g, 6.08 mmol) was stirred in a mixture of CH_3CN–HOAc (1:1, 10 mL) for 30 min at room temperature. This solution was then transferred to a mixture of **21** (423 mg, 1.30 mmol) in THF–CH_3CN (1:1, 13 mL) at –30 ºC. The reaction flask was kept in a freezer at –20 ºC for 18 h and then a saturated potassium sodium tartrate solution and EtOAc was added. The aqueous layer was extracted three additional times with EtOAc and the combined organic fractions were washed with saturated sodium bicarbonate solution and brine, dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude solid was then dried under high vacuum overnight and used in the next step without further purification. ^{1}H NMR analysis of the crude indicates that the *anti*/*syn* diastereomeric ratio was 7.6:1. The solid was dissolved in THF (10 mL) and the solution was cooled to –78 ºC before DIBAL-H (1 M in toluene, 7.8 mL, 7.8 mmol) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 3.5 h. After cooling to 0 ºC, a saturated solution of potassium sodium tartrate was added as well as EtOAc. The mixture was stirred for 2 h and the layers separated. The aqueous layer was vigorously extracted with EtOAc an additional four times. The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated to dryness. The crude product was purified by silica gel flash chromatography (95:5 EtOAc–CH_3OH) to afford **23** (262 mg, 71%) as a white solid: R_f = 0.33 (95:5 EtOAc–CH_3OH); mp 81–82 ºC; $[\alpha]_D$ +3.1 (*c* 0.5, $CHCl_3$); IR (cast film): 3394, 3287, 2916, 2849, 2113, 1471, 1464, 1125, 1079, 1016 cm^{-1}; ^{1}H NMR (700 MHz, CD_3OD) δ 3.86–3.82 (m, 1H), 3.81–3.77 (m, 1H), 3.47 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.43 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.17–2.11 (m, 3H), 1.53–1.25 (m, 22H); ^{13}C{^{1}H} NMR (176 MHz, CD_3OD) δ 85.1, 70.3, 69.3, 69.1, 67.9, 41.9, 39.3, 30.81, 30.76, 30.71, 30.65, 30.2, 29.8, 29.7, 26.8, 19.0; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{32}NaO_3$ $[M + Na]^+$ 307.2244, found 307.2244.

(2*S*,4*R*)-Heptadec-16-yne-1,2,4-triol (*ent*-23). Compound ***ent*-21** (138 mg, 0.43 mmol) was treated as described for the conversion of **21** into **23** to afford ***ent*-23** (83 mg, 69%) as a white solid: 81–82 ºC; $[\alpha]_D$ –2.6 (*c* 0.5, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{32}NaO_3$ $[M + Na]^+$ 307.2244, found 307.2245. The IR and NMR data for ***ent*-23** was the same as that for **23**.

(2*R*,4*R*)-16-(Dimethyl(phenyl)silyl)heptadec-16-ene-1,2,4-triol (24). To a solution of **1** (59 mg, 0.21 mmol) in dry CH_2Cl_2 (1.3 mL), dimethylphenylsilane (38 μL, 0.25 mmol) and pentamethylcyclopentadienyltris(acetonitrile)ruthenium(II) hexafluorophosphate (2 mg, 0.004 mmol) were added. The reaction mixture was stirred at room temperature for 1 h and the mixture was directly loaded onto a silica gel column. Flash chromatography (95:5 EtOAc–CH_3OH), provided **24** (84 mg, 94%) as a colourless oil: R_f = 0.43 (95:5 EtOAc–CH_3OH); $[\alpha]_D$ –3.4 (*c* 0.3, $CHCl_3$); IR (cast film): 3019, 3340, 3069, 3050, 2925, 2853, 1465, 1428, 1248, 1111, 1067 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.53–7.48 (m, 2H), 7.38–7.31 (m, 3H), 5.67 (dt, *J* = 3.1, 1.5 Hz, 1H), 5.39 (dt, *J* = 3.1, 1.0 Hz, 1H), 4.00–3.94 (m, 1H), 3.93–3.88 (m, 1H), 3.67–3.62 (m, 1H), 3.52–3.47 (m, 1H), 3.45 (br s, 1H), 2.49 (br s, 1H), 2.12–2.04 (m, 3H), 1.63–1.16 (m, 22H), 0.36 (s, 6H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 150.6, 138.6, 134.0, 128.9, 127.7, 125.7, 72.64, 72.60, 66.9, 39.1, 38.4, 36.1, 29.7, 29.63, 29.62, 29.61, 29.53, 29.47, 28.9, 25.4, –2.8; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{44}NaO_3Si$ $[M + Na]^+$ 443.2952, found 443.2949.

(2*S*,4*S*)-16-(Dimethyl(phenyl)silyl)heptadec-16-ene-1,2,4-triol (*ent*-24). Compound ***ent*-1** (61 mg, 0.21 mmol) was treated as described for conversion of **1** into **24** to afford ***ent*-24** (87 mg, 97%) as a colourless oil: $[\alpha]_D$ +3.9 (*c* 0.3, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{44}NaO_3Si$ $[M + Na]^+$ 443.2952, found 443.2949. The IR and NMR data for ***ent*-24** was the same as that for **24**.

(2*R*,4*S*)-16-(Dimethyl(phenyl)silyl)heptadec-16-ene-1,2,4-triol (25). Compound **23** (64 mg, 0.23 mmol) was treated as described for the conversion of **1** into **24** to afford **25** (91 mg, 95%) as a colourless oil: R_f = 0.38 (95:5 EtOAc–CH_3OH); $[\alpha]_D$ +2.6 (*c* 0.3, $CHCl_3$); IR (cast film): 3326, 3069, 3050, 3027, 2925, 2853, 1466, 1428, 1248, 1111, 1077 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ 7.53–7.49 (m, 2H), 7.36–7.32 (m, 3H), 5.67 (dt, *J* = 3.2, 1.6 Hz, 1H), 5.39 (app d, *J* = 3.0 Hz, 1H), 4.03 (app tt, *J* = 7.2, 3.4 Hz, 1H), 3.96–3.89 (m, 1H), 3.66 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.54 (dd, *J* = 11.0, 7.2 Hz, 1H), 2.92 (br s, 1H), 2.21–2.06 (m, 4H), 1.69 (ddd, *J* = 14.5, 8.6, 2.8 Hz, 1H), 1.58–1.15 (m, 21H), 0.36 (s, 6H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ 150.6, 138.6, 134.0, 128.9, 127.7, 125.7, 69.7, 69.5, 67.0, 38.9, 37.7, 36.1, 29.7, 29.64, 29.63, 29.62, 29.53, 29.47, 28.9, 25.8, –2.8; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{44}NaO_3Si$ $[M + Na]^+$ 443.2952, found 443.2952.

(2*S*,4*R*)-16-(Dimethyl(phenyl)silyl)heptadec-16-ene-1,2,4-triol (*ent*-25). Compound ***ent*-23** (55 mg, 0.19 mmol) was treated as described for the conversion of **1** into **24** to afford ***ent*-25** (75 mg, 92%) as a colourless oil.: $[\alpha]_D$ –3.0 (*c* 0.3, $CHCl_3$); HRMS (ESI) *m*/*z* calcd for $C_{25}H_{44}NaO_3Si$ $[M + Na]^+$ 443.2952, found 443.2951. The IR and NMR data for ***ent*-25** was the same as that for **25**.

(2*R*,4*R*)-Heptadec-16-ene-1,2,4-triol (2). Vinylsilane **24** (76 mg, 0.18 mmol) was dissolved in DMF (1.8 mL) and TBAF (1.0 M in THF, 0.90 mL, 0.90 mmol) was added. The mixture was heated to 80 ºC for 15 h, cooled to room temperature and then the solvent was removed under reduced pressure. The crude mixture was purified by silica gel flash chromatography (95:5 EtOAc–CH_3OH) to afford **2** (48 mg, 92%) as a white solid: R_f = 0.42 (95:5 EtOAc–CH_3OH); mp 63–64 ºC (lit.[8] 66.5–67 ºC); $[\alpha]_D$ –5.4 (*c* 0.5, $CHCl_3$) [lit.[8] –6.4 (*c* 1.1, $CHCl_3$)]; IR (cast film): 3301, 3082, 2923, 2851, 1641, 1471, 1216, 1134, 1068, 909, 758 cm^{-1}; ^1H NMR (700 MHz, CD_3OD) δ 5.80 (ddt, *J* = 17.0, 10.2, 6.8 Hz, 1H), 4.99–4.95 (m, 1H), 4.90 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 3.83–3.72 (m, 2H), 3.49 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.45 (dd, *J* = 11.2, 6.0 Hz, 1H), 2.07–2.00 (m, 2H), 1.65 (app dt, *J* = 14.1, 4.5 Hz, 1H), 1.56–1.20 (m, 21H); $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ 140.2, 114.7, 72.2, 71.2, 67.3, 41.2, 38.7, 34.9, 30.84, 30.76, 30.75, 30.7, 30.6, 30.2, 30.1, 26.6; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{34}NaO_3$ $[M + Na]^+$ 309.2400, found 309.2401.

(2*S*,4*S*)-Heptadec-16-ene-1,2,4-triol (*ent*)-2. Compound ***ent*-24** (72 mg, 0.17 mmol) was treated as described for the conversion of **24** into **2** to afford ***ent*-2** (44 mg, 91%) as a white solid: mp 63–64 ºC (lit.[8] 65.5–66 ºC); $[\alpha]_D$ +5.0 (*c* 0.5, $CHCl_3$) [lit.[8] +6.0 (*c* 1.0, $CHCl_3$)]; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{34}NaO_3$ $[M + Na]^+$ 309.2400, found 309.2399. The IR and NMR data for ***ent*-2** was the same as that for **2**.

(2*R*,4*S*)-Heptadec-16-ene-1,2,4-triol (26). Compound **25** (90 mg, 0.21 mmol) was treated as described for the conversion of **24** into **2** to afford **26** (54 mg, 89%) as a white solid: R_f = 0.33 (95:5 EtOAc–CH_3OH); mp 79–81 ºC (lit.[8] 82–82.5 ºC); $[\alpha]_D$ +3.7 (*c* 0.5, $CHCl_3$) [lit.[8] +7.23 (*c* 0.83, $CHCl_3$)]; IR (cast film): 3256, 2916, 2848, 1643, 1469, 1076, 1031, 989, 913 cm^{-1}; ^1H NMR (700 MHz, CD_3OD) δ 5.80 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.00–4.94 (m, 1H), 4.92–4.88 (m, 1H), 3.87–3.83 (m, 1H), 3.81–3.76 (m, 1H), 3.47 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.43 (dd, *J* = 11.1, 6.4 Hz, 1H), 2.06–2.00 (m, 2H), 1.52–1.23 (m, 22H); $^{13}C\{^1H\}$ NMR (176 MHz, CD_3OD) δ 140.2, 114.7, 70.4, 69.1, 67.9,

41.9, 39.3, 34.9, 30.82, 30.77, 30.75, 30.7, 30.6, 30.2, 30.1, 26.8; HRMS (ESI) *m/z* calcd for $C_{17}H_{34}NaO_3$ [M + Na]$^+$ 309.2400, found 309.2398.

(2*S*,4*R*)-Heptadec-16-ene-1,2,4-triol (*ent*-26). Compound ***ent*-25** (69 mg, 0.16 mmol) was treated as described for the conversion of **24** into **2** to afford ***ent*-26** (43 mg, 91%) as a white solid: mp 79–80 ºC (lit.[8] 82–82.5 ºC); $[\alpha]_D$ –3.9 (*c* 0.5, $CHCl_3$) [lit.[8] –7.3 (*c* 0.8, $CHCl_3$)]; HRMS (ESI) *m/z* calcd for $C_{17}H_{34}NaO_3$ [M + Na]$^+$ 309.2400, found 309.2400. The IR and NMR data for ***ent*-26** was the same as that for **26**.

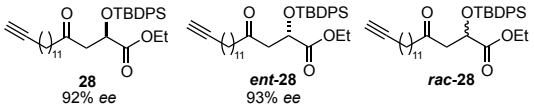
(2*R*,4*R*)-Heptadecane-1,2,4-triol (3). Avocadyne **1** (24 mg, 0.08 mmol) was dissolved in ethanol and the reaction flask was flushed with argon. Then, Pd/C (10% wt, 2.4 mg) was added and the mixture was stirred under hydrogen for 2 h at room temperature. The reaction mixture was filtered through Celite and the filtrate was concentrated to dryness. The crude product was purified through a silica gel plug (95:5 EtOAc–CH_3OH) to afford **3** (22 mg, 92%) as a white solid: R_f = 0.42 (95:5 EtOAc–CH_3OH); mp 70–71 ºC (lit.[18b] 75.5–76.6 ºC); $[\alpha]_D$ –6.8 (*c* 0.5, $CHCl_3$); IR (cast film): 3303, 2920, 2850, 1471, 1136, 1066 cm^{-1}; ^{1}H NMR (700 MHz, CD_3OD) δ 3.81–3.73 (m, 2H), 3.49 (dd, *J* = 11.2, 4.6 Hz, 1H), 3.45 (dd, *J* = 11.2, 6.0 Hz, 1H), 1.65 (app dt, *J* = 14.1, 4.5 Hz, 1H) 1.54–1.39 (m, 4H), 1.38–1.23 (m, 21H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (176 MHz, CD_3OD) δ 72.2, 71.2, 67.3, 41.2, 38.7, 33.1, 30.9, 30.79, 30.78, 30.77, 30.76, 30.75, 30.5, 26.6, 23.7, 14.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{36}NaO_3$ [M + Na]$^+$ 311.2557, found 311.2557.

(2*S*,4*S*)-Heptadecane-1,2,4-triol (*ent*-3). Compound ***ent*-1** (20 mg, 0.07 mmol) was treated as described for the conversion of **1** into **3** to afford ***ent*-3** (18 mg, 90%) as a white solid: mp 69–70 ºC; $[\alpha]_D$ +1.7 (*c* 0.5, $CHCl_3$); HRMS (ESI) *m/z* calcd for $C_{17}H_{36}NaO_3$ [M + Na]$^+$ 311.2557, found 311.2557. The IR and NMR data for ***ent*-3** was the same as that for **3**.

(2*R*,4*S*)-Heptadecane-1,2,4-triol (27). Compound **23** (21 mg, 0.07 mmol) was treated as described for the conversion of **1** into **3** to afford **27** (19 mg, 90%) as a white solid: R_f = 0.33 (95:5 EtOAc–CH_3OH); mp 87–88 ºC; $[\alpha]_D$ +6.1 (*c* 0.5, THF); IR (cast film): 3260, 2914, 2848, 1470, 1083, 1031 cm^{-1}; ^{1}H NMR (700 MHz, CD_3OD) δ 3.87–3.81 (m, 1H), 3.81–3.76 (m, 1H), 3.47 (dd, *J* = 11.1, 4.7 Hz, 1H), 3.43 (dd, *J* = 11.1, 6.4 Hz, 1H), 1.52–1.39 (m, 5H), 1.29 (m, 21H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (176 MHz, CD_3OD) δ 70.3, 69.1, 67.9, 41.8, 39.3, 33.1, 30.82, 30.80, 30.78, 30.76, 30.75, 30.5, 26.8, 23.7, 14.4; HRMS (ESI) *m/z* calcd for $C_{17}H_{36}NaO_3$ [M + Na]$^+$ 311.2557, found 311.2557.

(2*S*,4*R*)-Heptadecane-1,2,4-triol (*ent*-27). Compound ***ent*-23** (20 mg, 0.07 mmol) was treated as described for the conversion of **1** into **3** to afford ***ent*-27** (18 mg, 90%) as a white solid: mp 87–88 ºC (lit.[19] 88–89 ºC); $[\alpha]_D$ –13.0 (*c* 0.5, THF) [lit.[19] –7.76 (*c* 0.55, THF); HRMS (ESI) *m/z* calcd for $C_{17}H_{36}NaO_3$ [M + Na]$^+$ 311.2557, found 311.2557. The IR and NMR data for ***ent*-27** was the same as that for **27**.

Determination of enantiomeric excess for compounds 21 and *ent*-21. The determination of enantiomeric excess for compounds **21** and ***ent*-21** was initially attempted on the free alcohols, but good HPLC separation and consistent measurements were difficult to obtain. The compounds were then converted to the 2-OTBDPS derivatives (**28** and ***ent*-28**), using TBDPSCl (1.2 equiv), imidazole (2.0 equiv) and DMAP (0.2 equiv) in CH_2Cl_2 for 3 h at rt.



Compound **28** was isolated via silica gel flash chromatography (9:1 hexane–EtOAc) for characterization. Compounds ***rac*-28** and ***ent*-28** were partially purified via silica gel flash chromatography and were obtained in a mixture with residual silanol. The mixtures were directly subjected to HPLC analysis. Separation conditions: Chiracel IC column, 95:5 hexanes–*i*-PrOH), 0.5 mL/min, 20 ºC. UV detection at 220 nm. Data for **28**: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.71–7.67 (m, 2H), 7.66–7.63 (m, 2H), 7.45–7.40 (m, 2H), 7.39–7.34 (m, 4H), 4.61 (dd, *J* = 6.1, 5.8 Hz, 1H), 3.99–3.89 (m, 2H), 2.81 (dd, *J* = 16.2, 5.8 Hz, 1H), 2.77 (dd, *J* = 16.2, 6.1 Hz, 1H), 2.40–2.32 (m, 2H), 2.18 (td, *J* = 7.2, 2.7 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.55–1.48 (m, 4H), 1.41–1.35 (m, 2H), 1.32–1.19 (m, 12H), 1.05 (m, 12H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ 207.5, 172.2, 136.0, 135.9, 133.09, 133.07, 129.9, 129.8, 127.7, 127.5, 84.8, 69.4, 68.1, 60.9, 47.2, 43.8, 29.6, 29.51, 29.46, 29.4, 29.2, 29.1, 28.8, 28.5, 26.9, 23.5, 19.4, 18.4, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{35}H_{50}NaO_4Si$ $[M + Na]^+$ 585.3371, found 585.3374.

AUTHOR INFORMATION

Corresponding Author:

* T.L.L.: email, tlowary@ualberta.ca

* G.A.O.: email, G.ODoherty@neu.edu

Author Contributions:

§ Co-first authors, the order is alphabetical

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Supporting Information

This material is available free of charge via the internet at http://pubs.acs.org

NMR spectra and chiral HPLC data (PDF)

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