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A concise enantioselective total synthesis of (+)-*epi*-muricatacin, using asymmetric hydrogenation/intramolecular iodoetherification as key steps

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ABSTRACT

A concise enantioselective total synthesis of (+)-*epi*-muricatacin, a potent cytotoxic agent, is described. A key feature of this protocol is a catalytic asymmetric hydrogenation and a chiral auxiliary mediated intramolecular iodoetherification to ensure a high degree of distereo- and enantiocontrol.

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1. Introduction

The enantioenriched 5-hydroxyalkyl butan-4-olide is a chemically significant moiety and can be found in many natural product molecules that exhibit interesting pharmacologically important properties. This functional group array is mainly originated from the Annonaceae acetogenin family.[1] Among these, the most important structural prototype molecule is muricatacin, which can be isolated as a scalemic mixture from the seeds of *Annona muricata*.[2] Muricatacin and *epi*-muricatacin have received interest due to their anti-proliferative activity against certain cell lines.[3a] A plethora of synthetic strategies have been developed for muricatacin and (+)-*epi*-muricatacin molecules. The genesis of chirality for these synthetic strategies is either from the chiral pool,[3] or initiated through catalytic asymmetric transformations.[4] Herein, we report another alternative synthetic strategy for the synthesis of the (+)-*epi*-muricatacin molecule by means of asymmetric hydrogenation/intramolecular iodoetherification as key steps.

2. Results and discussion

Recently, we have reported a highly enantioselective synthetic route to the synthesis of functionalized scaffolds of medium-sized oxacycles and carbocycles by employing a C_2-symmetric diol tethered with dizoacetate and methoxy *cis*-butene.[5] Along this vein, we envisioned utilizing a C_2-symmetric diol to install the two stereogenic centers with the high degree of diastereo- and enantioselectivity required for (+)-*epi*-muricatacin, **1**. We wanted to generate our critical starting material, that is, the C_2-symmetric (*S*,*S*)-diol tethered with *tert*-butyldimethylsilyloxy *cis*-butene **4**, in a one-pot procedure via a catalytic asymmetric hydrogenation of benzil **2** and subsequent monoprotection of the C_2-symmetric (*S*,*S*)-diol with *tert*-butyldimethylsilyloxy *cis*-butene mesylate **3**, which are readily available, inexpensive starting materials. Our retrosynthetic analysis is outlined in Scheme 1.

Accordingly, benzil **2** was subjected to Noyori's catalytic asymmetric transfer hydrogenation in the presence of 0.1 mol % of catalyst **A** using formic acid–triethylamine.[6] After 24 h at 40 °C, the volatiles were removed under reduced pressure and the resulting crude residue was dissolved in THF and to it sequentially added NaH and *tert*-butyldimethylsilyloxy *cis*-butene mesylate **3**. The expected product **4** was isolated in 70% yield with >97% diastereoselectivity with >99% enantiomeric excess[7] (Scheme 2). Having prepared hydroxylalkene **4**, the enantioselective intramolecular iodoetherification was then evaluated.

Thus, the reaction of **4** with *N*-iodosuccinimide (NIS) in THF at ambient temperature for 6 h gave **5** in a 9:1 ratio of separable diastereomers in a yield of 90%.[8] The stereochemistry of the major diastereomer **5** was determined by an NOE study. The significant NOE correlations are shown in Figure 1. In the major diastereomer **5**, the strong NOE between H_b–H_c and H_c–H_e confirms that they are spatially closer and hence considered to be in a *cis*-relationship.[9]

The exposure of **5** to TBAF in THF at ambient temperature led not only to desilylation, but also to concomitant nucleophilic substitution of the resulting alcohol onto iodine to give highly enantioenriched epoxy intermediate **6** in 85% isolated yield. The relative stereochemistry of **6** was assigned by NOEs between H_b–H_c and H_c–H_e (Fig. 1). The enantiomeric excess was determined by chiral HPLC analysis in comparison with a racemic mixture (>99%ee, Chiralpak OD-H, 254 nm, flow rate = 0.5 mL/min, *n*-hexane/2-propanol [95:5]). The nucleophilic opening of epoxide **6** with undecylmagnesium bromide in the presence of a catalytic amount of CuI led to **7** (89%).[10] Removal of the chiral auxiliary in Li/liq. NH_3 at −78 °C gave **8**. Then, under Mitsunobu conditions[11,3d] (Ph_3P/DIAD, THF), the triol **8** was converted into epoxy alcohol **9** in 90% yield. Finally, substrate **9** was treated with dilithioacetate dianion[12] followed by acidification of the

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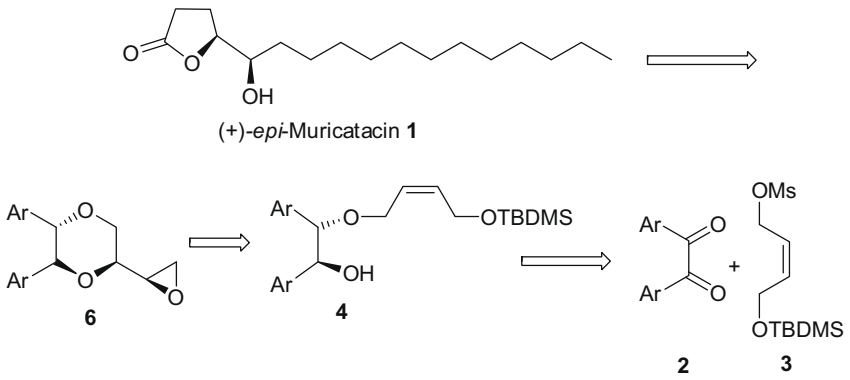
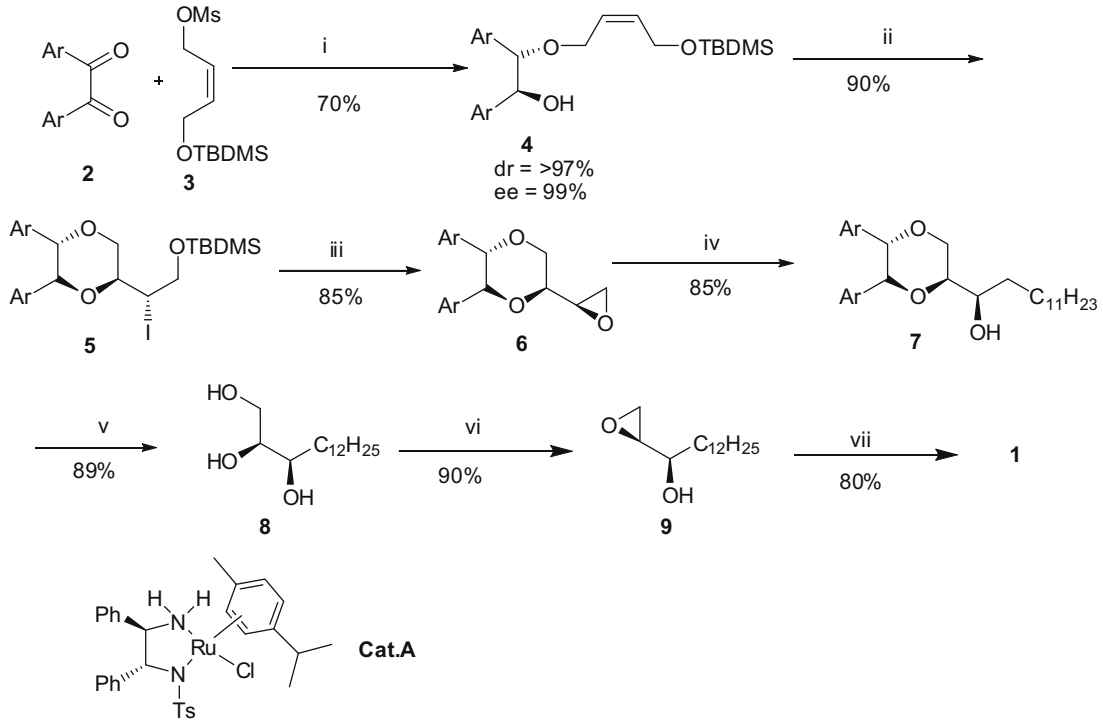


Scheme 1.



Scheme 2. Reagents and conditions: (i) (a) **Cat. A** 0.1 mol %, $HCOOH/Et_3N$, 40 °C, 24 h; (b) NaH, THF, 0 °C to rt, 12 h; (ii) *N*-iodosuccinimide, THF, rt, 6 h; (iii) TBAF, THF, 0 °C, 30 min; (iv) $C_{11}H_{23}MgBr$, CuI (10 mol %), THF, 8 h; (v) Li/liq. NH_3, −78 °C, 30 min; (vi) DIAD, PPh_3, benzene, 0 °C, 30 min and in vacuo 130 °C, 20 min; (vii) (a) $LiCH_2CO_2Li$; (b) H^+.

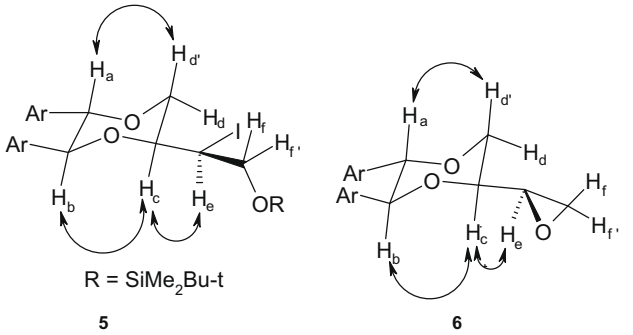


Figure 1. NOE study of **5** and **6**.

resulting lithium carboxylate to furnish the title compound **1** in 80% isolated yield[3a] (Scheme 2). The spectroscopic and specific rotation data of **1** are in full agreement with those reported in the literature[3a] {$[\alpha]_D^{25} = +32.0$ (*c* 0.9, $CHCl_3$), lit.[3a] $[\alpha]_D^{24} = +34.3$ (*c* 2, $CHCl_3$)}.

3. Conclusions

In conclusion, we have accomplished a concise enantioselective total synthesis of (+)-*epi*-muricatacin. A key feature of this protocol is a catalytic asymmetric hydrogenation as the genesis of chirality and a chiral auxiliary mediated intramolecular iodoetherification to ensure a high degree of distereo- and enantiocontrol. The critical starting material **4** was prepared in high efficiency with a substrate/catalyst molar ratio of 1000:1 using asymmetric hydrogenation. Moreover, the flexibility built into the synthesis to generate a library of analogues will be amenable to large-scale synthesis

while the intermediates generated in this protocol will be useful in the total synthesis of biologically active compounds.

4. Experimental

4.1. General information

Starting materials: DCM was distilled from P_2O_5, THF from sodium benzophenone ketyl. All other chemicals used were commercially available. All reactions were conducted under an atmosphere of nitrogen (IOLAR Grade I). Progress of the reactions was monitored by TLC on Merck Silica Gel 60 F-254 precoated. Evaporation of solvents was performed at reduced pressure on a Buchi rotary evaporator. Column chromatography was carried out with silica gel grade 60–120 and 100–200 mesh. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz and ^{13}C NMR 75 and 125 MHz in $CDCl_3$. *J* values were recorded in hertz and abbreviations used were s—singlet, d—doublet, m—multiplet, and br—broad. Chemical shifts (δ) are reported relative to TMS (δ = 0.0) as an internal standard. IR spectra were recorded on Thermo Nicolet FT/IR-5700. Mass spectral data were compiled using MS (ESI), HRMS mass spectrometers. Optical rotations were recorded on HORIBA high sensitive polarimeter with 10 mm cell.

4.1.1. (*Z*)-4-(*tert*-Butyldimethylsilyloxy)but-2-en-1-ol

To a mixture of (*Z*)-but-2-ene-1,4-diol (43.0 mL, 0.52 mol) and triethylamine (87.5 mL, 0.63 mol) in dry dichloromethane (250 mL), a solution of TBDMSCl (75.30 g, 0.50 mol, DCM,150 mL) was slowly added over a period of 3 h at room temperature. The resulting contents were stirred further for 3 h at the same temperature. Then, water (250 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with brine solution (250 mL) and dried (anhydrous Na_2SO_4). Removal of the solvent resulted in an oil which was distilled at 85–90 °C at 1 mmHg to give pure product as a colorless oil (93.48 g, 0.46 mmol, 89% Yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.60–5.50 (m, 2H), 4.16 (d, *J* = 5.2 Hz, 2H), 4.14 (d, *J* = 4.2 Hz, 2H), 0.82 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.0, 128.9, 63.2, 63.1, 25.9, 14.4, −5.3; IR (Neat): 3623, 3015, 2931, 2858, 2300, 1650, 1251, 838 cm^{-1}; (ESIMS) *m*/*z*: 203 (M+H)$^+$ 225 (M+Na)$^+$.

4.1.2. (1*S*,2*S*,*Z*)-2-(4-(*tert*-Butylmethoxysilyloxy)but-2-enyloxy)-1,2-diphenylethanol 4

Step 1: To a dry dichloromethane (100 mL) solution of (*Z*)-4-(*tert*-butyldimethylsilyloxy)but-2-en-1-ol (11.62 g, 57.53 mmol) was added Et_3N (9.19 mL, 66.12 mmol). To this reaction mixture, methanesulfonyl chloride (4.66 mL, 60.33 mmol) was added slowly at 0 °C. Then, the mixture was allowed to stir for only a period of 2 min at 0 °C. The reaction was quenched with water (100 mL). The organic layer was separated, washed with brine solution (2 × 100 mL), and dried over anhydrous Na_2SO_4. The contents were filtered and concentrated under reduced pressure. The crude mesylate **3** was used in the next step without purification.

Step 2: A 100 mL two-necked round-bottomed flask equipped with a reflux condenser bearing a guard tube and a dropping funnel was charged with triethylamine (18.92 mL, 136.00 mmol). The triethylamine was cooled to 4 °C in an ice bath and formic acid (8.67 mL, 230 mmol) was slowly added. To the mixture of formic acid and triethylamine at ambient temperature were added benzil (11.19 g, 52.30 mmol) and RuCl[(1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethanediamine](η^6-*p*-cymene) (33.3 mg, 0.0523 mmol) at ambient temperature. The combined reaction mixture was stirred at 40 °C for 24 h, after which time the volatiles were removed under vacuum. The crude residue was dissolved in dry THF (150 mL) and NaH (60% dispersion in mineral oil) (2.30 g, 57.53 mmol) was added portionwise at 0 °C. After 30 min, mesylate **3** in THF (15 mL) was added over a period of 10 min. The resulting mixture was warmed to rt and stirred overnight. The reaction was quenched with water (~25 mL) until the mixture became clear. The reaction mixture was then extracted with ethyl acetate (4 × 50 mL). The combined organic layers were washed with brine solution (2 × 50 mL) and dried over anhydrous Na_2SO_4. The contents were filtered and concentrated under reduced pressure to yield a crude residue. The residue was subjected to silica gel (100–200 mesh) column chromatography eluting with hexane/EtOAc (97:3) and furnished the pure product **4** as a light yellow oil (14.57 g, 36.61 mmol, yield 70%); $[\alpha]_D^{24} = -43.5$ (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.10 (m, 6H), 6.98–6.95 (m, 4H), 5.72–5.57 (m, 2H), 4.62 (d, *J* = 8.3 Hz, 1H), 4.21 (d, *J* = 8.3 Hz, 1H), 4.07 (d, *J* = 5.3 Hz, 2H), 3.94–3.88 (m, 2H), 3.49 (br s, 1H), 0.86 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 133.5, 128.3, 128.2, 127.8, 127.2, 126.7, 86.8, 85.3, 78.4, 29.6, 27.1, −5.3**;** IR (Neat): 3695, 3605, 3580, 2952, 2877, 2856, 1731, 1456, 1080, 838 cm^{-1}; MS (ESIMS) *m*/*z*: 399 (M+H)$^+$, 418 (M+NH$_4$)$^+$, 421 (M+Na)$^+$.

4.1.3. *tert*-Butyl((*S*)-2-((2*S*,5*S*,6*S*)-5,6-diphenyl-1,4-dioxan-2-yl)-2 iodoethoxy)dimethylsilane 5

A solution of *N*-iodosuccinimide (11.25 g, 50.00 mmol) in dry THF (40 mL) was added to a predissolved solution (40 mL, dry THF) of **4** (9.95 g, 25.00 mmol) at rt and the resulting reaction mixture was left for 6 h. The reaction was quenched with an aqueous solution of hypo (120 mL of 0.63 M). The reaction mixture was extracted with ethyl acetate (4 × 100 mL). The combined organic layers were washed with brine solution (2 × 50 mL) and dried over anhydrous Na_2SO_4. The contents were filtered, and concentrated under reduced pressure to yield a crude residue. The crude residue was subjected to silica gel (100–200 mesh) column chromatography eluting with hexane/EtOAc (97:2) and furnished the pure product **6** as an oil (11.79 g, 22.5 mmol, yield 90% and diastereomeric ratio is 9:1); $[\alpha]_D^{24} = -39.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.12 (m, 6H), 6.99–6.93 (m, 4H), 4.55 (d, *J* = 9.1 Hz, 1H), 4.33 (d, *J* = 9.1 Hz, 1H), 4.10 (ddd, *J* = 2.9, 5.5, 9.2 Hz, 1H), 4.07 (dd, *J* = 2.9, 11.6 Hz, 1H), 3.97 (dd, *J* = 10.4, 11.6 Hz, 1H), 3.95 (dd, *J* = 9.2, 10.3 Hz, 1H), 3.89 (dd, *J* = 5.5, 10.3 Hz, 1H), 3.69–3.66 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.7, 137.6, 128.3, 128.2, 127.8, 127.7, 127.5, 127.0, 126.6 84.1, 83.8, 72.1, 65.3, 33.1, 25.7, −5.5; IR (Neat): 3458, 3427, 2951, 2856, 1254, 1090, 839 cm^{-1}; MS (ESIMS) *m*/*z*: 525 (M+H)$^+$, 542 (M+NH$_4$)$^+$, 547 (M+Na)$^+$; HRMS (ESIMS): calcd for $C_{24}H_{33}O_3NaSi$ (M+Na)$^+$ 547.1141, found 547.1126.

4.1.4. (2*S*,3*S*,5*S*)-5-((*R*)-Oxiran-2-yl)-2,3-diphenyl-1,4-dioxane 6

A 1 M solution of tetrabutyl ammonium fluoride (8.00 mL, 8.00 mmol) in THF was added to a predissolved solution of **5** (4.19 g, 8.00 mmol, THF, 32 mL) under a nitrogen atmosphere at 0 °C. The reaction was allowed to stir for 30 min at the same temperature after which, the contents were concentrated under reduced pressure to give a crude residue. The crude residue was subjected to silica gel (60–120 mesh) column chromatography eluting with hexane/EtOAc (95:5) to give the pure product **6** as a white solid (1.92 g, 6.80 mmol, Yield 85%); Chiral HPLC analysis (>99%ee, Chiralpak OD-H, 254 nm, flow rate = 0.5 mL/min, *n*-hexane/2-propanol [95:5]) the major isomer was eluted after 27.3 min and the minor isomer was eluted after 24.2 min; Mp: 89–91 °C; $[\alpha]_D^{24} = +39.5$ (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16–7.09 (m, 6H), 6.99–6.90 (m, 4H), 4.46 (d, *J* = 9.0 Hz, 1H), 4.36 (d, *J* = 9.0 Hz, 1H), 4.17 (dd, *J* = 1.9, 10.9 Hz, 1H), 3.83 (dd, *J* = 10.3, 10.9 Hz, 1H), 3.79 (ddd, *J* = 1.9, 4.9, 10.3 Hz, 1H), 3.05 (ddd, *J* = 2.4, 3.7, 4.9 Hz, 1H), 2.83 (dd, *J* = 3.7, 4.9 Hz, 1H), 2.77

(dd, J = 2.4, 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.2, 128.1, 128.0, 127.8, 127.4, 127.3, 127.2, 126.6 83.9, 83.7, 75.4, 68.4, 50.6, 45.2; IR (Neat): 2866, 1254, 1101, 925, 698 cm^{-1}; MS (ESIMS) m/z: 283 $(M+H)^+$, 300 $(M+NH_4)^+$, 305 $(M+Na)^+$; HRMS (ESIMS): calcd for $C_{18}H_{18}O_3Na$ $(M+Na)^+$ 305.1153, found 305.1139.

4.1.5. (*R*)-1-((2*S*,5*S*,6*S*)-5-6-Diphenyl-1,4-dioxan-2-yl)tridecan-1-ol 7

To magnesium turnings (536.16 mg, 22.34 mmol) dried at 125 °C overnight, and a crystal of iodine to start the reaction, a solution of 1-bromoundecane (3.58 mL, 16.00 mmol) in dry THF (20 mL) was added dropwise at room temperature. The mixture was kept at 60 °C for 2 h and then cooled to −25 °C. Copper iodide (301 mg, 1.6 mmol) was then added together with toluene (~5 mL) to make the stirring more effective. After 40 min at −25 °C, **6** (3.00 g, 10.64 mmol) was added over 10 min, after which time the cooling bath was removed and allowed to stir for 2 h at room temperature and then mixture was refluxed for 8 h. The reaction was quenched with saturated solution of NH_4Cl. The reaction mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed with brine (2 × 30 mL) and dried over anhydrous Na_2SO_4. The contents were filtered, and concentrated under reduced pressure to yield crude residue. The crude product was subjected to silica gel (100–200 mesh) column chromatography eluting with hexane/EtOAc (94:6) to give **7** as a white solid (4.14 g, 9.46 mmol, yield 89%); Mp: 84–85 °C; $[\alpha]_D^{24} = -20.0$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.10 (m, 6H), 6.95–6.92 (m, 4H), 4.43 (d, J = 9.4 Hz, 1H), 4.28 (d, J = 8.3 Hz, 1H), 4.10 (d, J = 9.3 Hz, 1H), 3.88–3.86 (m, 1H), 3.84–3.78 (m, 2H), 1.53–1.47 (m, 2H), 1.26–1.20 (m, 20H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 137.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.4, 127.3, 84.2, 83.8, 77.9, 71.8, 66.9, 32.2, 31.9, 29.6, 29.5, 29.4, 29.3, 25.8, 22.7, 14.1; IR(Neat): 3444, 2917, 2850, 1099, 760 cm^{-1}; MS (ESIMS) m/z: 439 $(M+H)^+$, 456 $(M+NH_4)^+$, 461 $(M+Na)^+$; HRMS (ESIMS): calcd for $C_{29}H_{42}O_3Na$ $(M+Na)^+$ 461.3031, found 461.3046.

4.1.6. (2*S*,3*R*)-Pentadecane-1,2,3-triol 8

A 50 mL two-necked RB was equipped with a dry-ice condenser with a guard tube and a stopper. Ammonia (15–20 mL) was condensed at −78 °C. Then, Li granules (140 mg, 20.00 mmol) were slowly added. A blue color then appeared. Then the stopper was replaced by a septum. To this blue solution, above (*R*)-1-((2*S*,5*S*,6*S*)-5-6-diphenyl-1,4-dioxan-2-yl)tridecan-1-ol, **7** (876 mg, 2 mmol) in THF (10 mL) was added while maintaining the same temperature. After 30 min, the reaction was quenched by addition of solid NH_4Cl (~2 g). Then ammonia condenser was removed so as to allow evaporation of the excess liquid ammonia. To this reaction mixture water was added carefully and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The contents were filtered, and concentrated under reduced pressure to yield a crude residue. The crude residue was subjected to silica gel (60–120 mesh) column chromatography eluting with hexane/EtOAc (10:90) and furnished the pure product **8** as a white solid (442 mg, 1.7 mmol, yield 85%); Mp: 95–96 °C; $[\alpha]_D^{24} = +6$ (c 1, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO): δ = 3.71–3.54 (m, 5H), 3.44–3.40 (m, 2H), 1.51–1.47 (m, 2H), 1.40–1.20 (m, 20H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (60 MHz, $CDCl_3$ + DMSO): δ = 73.2, 71.2, 62.3, 31.7, 30.4, 28.3, 27.8, 27.7, 24.4, 21.1, 12.8; IR (Neat): 3728, 3194, 2915, 2849, 1467, 1076 cm^{-1}; MS (ESIMS) m/z 261 $(M+H)^+$, 278 $(M+NH_4)^+$, 283 $(M+Na)^+$; HRMS (ESIMS): calcd for $C_{15}H_{32}O_3Na$ $(M+Na)^+$ 283.2249, found 283.2255.

4.1.7. (*R*)-1-((*S*)-Oxiran-2-yl)tridecan-1-ol 9

At 0 °C, diisopropyl azodicarboxylate (DIAD, 0.25 mL, 1.30 mmol) was added dropwise to a stirred solution of (2*S*,3*R*)-pentadecane-1,2,3-triol, **8** (260 mg, 1.00 mmol) and triphenylphosphine (340 mg, 1.3 mmol) in dry benzene (2 mL). After stirring for 2 h at 0 °C, the benzene was removed in vacuo and the residue was heated to 130 °C (4 mmHg) for 6 h. The crude product was subjected to silica gel (100–200 mesh) column chromatography eluting with hexane/EtOAc (90:10) to furnish the pure product (217 mg, 0.9 mmol, yield 90%). $[\alpha]_D^{24} = -11.0$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.85 (m, 1H), 3.02 (dd, J = 3.2, 7.3 Hz, 1H), 2.82 (dd, J = 2.6, 5.0 Hz, 1H), 2.72 (dd, J = 4.1, 4.8 Hz, 1H), 1.72–1.20 (m, 22H), 0.86 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 68.3, 54.5, 43.4, 33.4, 31.8, 29.6, 29.5, 29.4, 25.2, 22.6, 14.1; MS (ESIMS) m/z 243 $(M+H)^+$, 265 $(M+Na)^+$; HRMS (ESIMS): calcd for $C_{15}H_{30}O_2Na$ $(M+Na)^+$ 265.2143, found 265.2149.

4.1.8. (+)-(4*S*,5*R*)-5-Hydroxyheptadeca-4-nolide 1

To an ice-cooled solution of LDA (1.6 M, 2 mmol) in THF (4 mL), dry acetic acid (57.2 μL, 1 mmol) was added while stirring. After 30 min, the epoxy alcohol **9** (48.4 mg, 0.2 mmol) was added and the resulting mixture was stirred overnight at reflux. It was then cooled, acidified with saturated aqueous sodium hydrogen sulfate and extracted with ether (2 × 5 mL). The combined extracts were concentrated and treated with a benzene solution of *p*-toluene sulfonic acid (0.05 equiv in benzene, 5 mL) and refluxed for 1 h. The reaction mixture was cooled to rt and then washed with an aqueous solution of sodium hydrogen carbonate. The organic layer was dried (Na_2SO_4 anhydrous) and concentrated. The crude residue was subjected to silica gel (100–200 mesh) column chromatography eluting with hexane/EtOAc (50:50) to give the pure product **1** as a white solid (45 mg, 0.16 mmol, yield 80%); Mp: 66–67 °C, $[\alpha]_D^{24} = +32.0$ (c 0.9, $CHCl_3$), lit. $[\alpha]_D^{24} = +34.5$ (c 2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.45–4.25 (m, 1H), 3.96–3.80 (m, 1H), 2.57–2.40 (m, 2H), 2.3–2.0 (m, 2H), 1.82–1.20 (m, 22H), 0.88 (t, J = 6.7 Hz, 3H): ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1, 82.5, 71.9, 31.9, 29.5, 29.2, 28.5, 25.9, 23.1, 21.8, 13.9; IR (Neat): 3400, 2918, 2849, 1780 cm^{-1}; MS (ESIMS): m/z 285 $(M+H)^+$; HRMS (ESIMS): calcd for $C_{17}H_{32}O_3Na$ $(M+Na)^+$ 307.2249, found 307.2262.

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8. The enantioselective intramolecular iodoetherification was performed in various solvent systems such as toluene, CH_2Cl_2, *t*-BuOMe, and THF. Only THF gave better yields. When reaction was conducted at sub-zero temperature and at 0 °C, ti gave **5** in lower yields.
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