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Asymmetric total synthesis of (−)-mangiferaelactone by using an appropriately substituted thiophene as a masked synthon for *C*-alkyl glycoside

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ABSTRACT

Asymmetric total synthesis of naturally occurring nonenolide (−)-mangiferaelactone was attempted through RCAM (ring closing alkyne metathesis) reaction. As the attempted RCAM reaction failed, the synthesis was finally achieved by successful exploration of a ring closing metathesis (RCM) reaction. 2-Propylthiophene was used as a masked synthon for *n*-heptyl glycoside, which served as main source for one of the RCM precursors and accessed by reductive desulfurization (Mozingo type reduction) of an appropriately substituted thiophene ribofuranoside. The other RCM precursor was accessed by applying an enzymatic kinetic resolution/Mitsunobu inversion sequence to an alkyne alcohol.

1. Introduction

Various polyhydroxylated nonenolides have been isolated from several fungal sources, and have gained significant attraction in natural product research mainly due to their interesting biological profile, which include cholesterol biosynthesis inhibition and microfilament formation.[1] In addition they have also exhibited profound phytotoxicity, and antibacterial activities.[2] Mangiferaelactone **1** is such a polyhydroxylated small ring macrolide recently isolated from small-scale culture of entophytic fungi *Pestalotiopsis mangiferae* by Ortega et al.[3] The parent lactone showed a strong inhibition against bacteria *Listeria monocytogenes* (MIC = 1.6863 mg/mL) and *Bacillus cereus* (0.5529 mg/mL). It also exhibited mild antibacterial activity against *Enterococcus cloacae*, *Enterococcus faecalis*, and *Proteus mirabilis*. The structural elucidation of mangiferaelactone was judiciously done with the help of extensive NMR (^{1}H–^{1}H COSY, HSQC, HMBC, and NOESY) and HRMS analysis, whereas the absolute configuration was assigned as (4*R*,7*R*,8*R*,9*S*) by VCD (vibrational circular dichorism) studies. Mangiferaelactone is the enantiomer of xyolide *ent*-**1** (Fig. 1) a ten membered ring nonenolide isolated recently from an Amazonian endophytes *Xylaria feejeensis* by Handelsman et al.[4] The total synthesis of xyolide was reported by a few groups including ours in recent times.[5] We have been working on the synthesis of medium sized ring macrolides by exploration of chemoenzymatic strategies and recently completed the synthesis of structurally related nonenolides.[6]

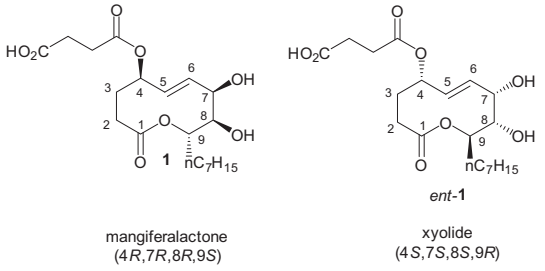

Figure 1. Naturally occurring nonenolide mangiferaelactone and its enantiomer xyolide.

Due to its unique structural features and biological importance mangiferaelactone became an immediate target, and to date, two asymmetric syntheses have been reported.[7] Both of the syntheses feature successful exploration of a late stage '*E*'-selective RCM (ring closing metathesis) reaction. The metathesis precursor was assembled by esterification reaction between properly functionalized carboxylic acid and alcohol fragments, which were accessed from D-ribose in both the cases.

2. Result and discussion

The proposed retrosynthesis for the target molecules is presented in Scheme 1. We visualized that ring closing alkyne

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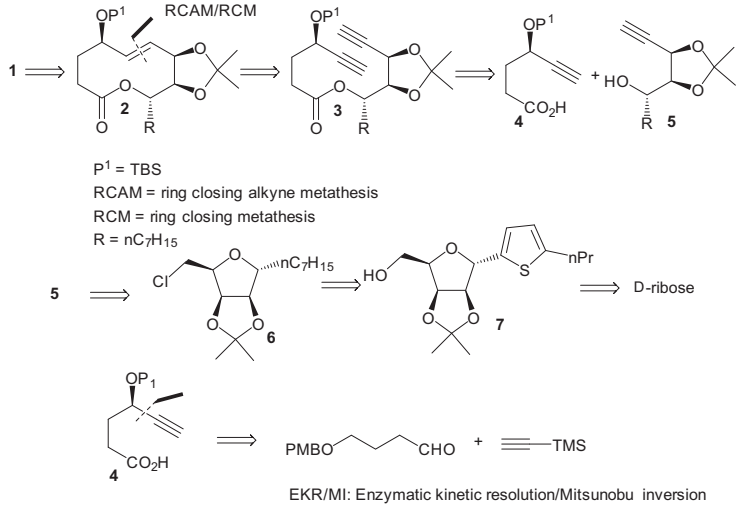


Scheme 1. Retrosynthetic analysis of mangiferaelactone **1** using *C*-alkylglycosides.

metathesis (RCAM) followed by *E*-selective reduction could be an alternative approach to construct the C_5–C_6 unsaturation in mangiferaelactone. RCAM followed by stereoselective reduction of the alkyne functionality serves as an efficient strategy for the construction of macrolide cores with well-defined olefinic unsaturation embedded in it as demonstrated by Furstner et al. at least for $\geqslant$12 membered rings.[8] The RCAM precursor **3** was thought to be assembled by union of two alkyne containing fragments **5** and **6**. The fragment **5** was proposed to be accessed from a *C*-alkyl glycoside **6** by employing an appropriately substituted thiophene as a masked C4-synthon.[9] We visualized that *n*-propylthiophene could serve as a surrogate for the *n*-heptyl appendage present in the target molecule after reductive desulfurization of the thiophene nucleus. The other alkyne fragment **4** was proposed to be accessed by an enzymatic kinetic resolution/Mitsunobu inversion sequence or Trost asymmetric alkynylation protocol[10] as shown in Scheme 1.

2.1. Synthesis of the alcohol fragment 10/11 containing (7*R*,8*R*,9*S*) of the target molecule

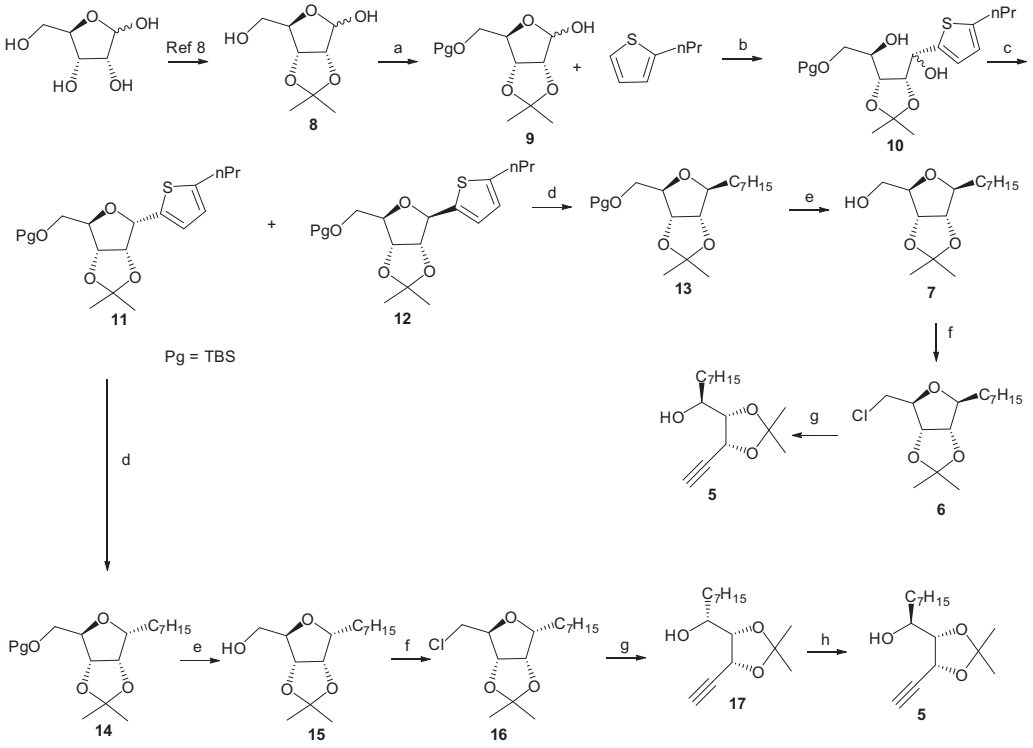
The synthesis was initiated with 2,3-*O*-isoppropylidene-D-ribose **8**.[11] The primary hydroxyl group in compound **8** was protected as the TBS ether using TBSCl and imidazole to furnish compound **9** in 98% yield. Lactol **9** on reaction with 2-propylthiophene (*n*-BuLi, THF, 0 °C to rt) afforded the diol **10** as diastereomeric mixture (1:1) in 75% yield. Mitsunobu cyclization of diol **10** with DIAD (diisopropyl azodicarboxylate) and Ph_3P in THF gave 2-propyl thiophene glycosides **11** (α-isomer 46% yield) and **12** (β-isomer 45% yield). The ribofuranoside **11** and **12** were finally subjected (separately) to Mozingo type reduction (reductive desulfurization) with Raney-Ni in ethanol[12] at reflux to afford the *C*-heptylglycoside **13** and **14** (separately) in 75% yield. The TBS group in compound **13/14** was deprotected by treating them with TBAF (1 M) in THF to afford alcohols **7/15** in 88% yield. For the synthesis of acetylenic alcohols **5** the key chloro derivatives **6** was prepared (in 88% yield) from compound **7** under Appel reaction conditions.[13] Subsequently base induced reductive elimination of compound **7** with $LiNH_2$ in NH_3 (l) afforded the alkyne alcohol **5** in 85% yield.[14] The unwanted *C*-heptylglycoside **14** was also converted to alkynol **5** through a diastereodivergent route involving a Mitsunobu inversion reaction as shown in Scheme 2.

2.2. Synthesis of the fragment 25 and 26 having the (4*R*) stereocentre of mangiferaelactone

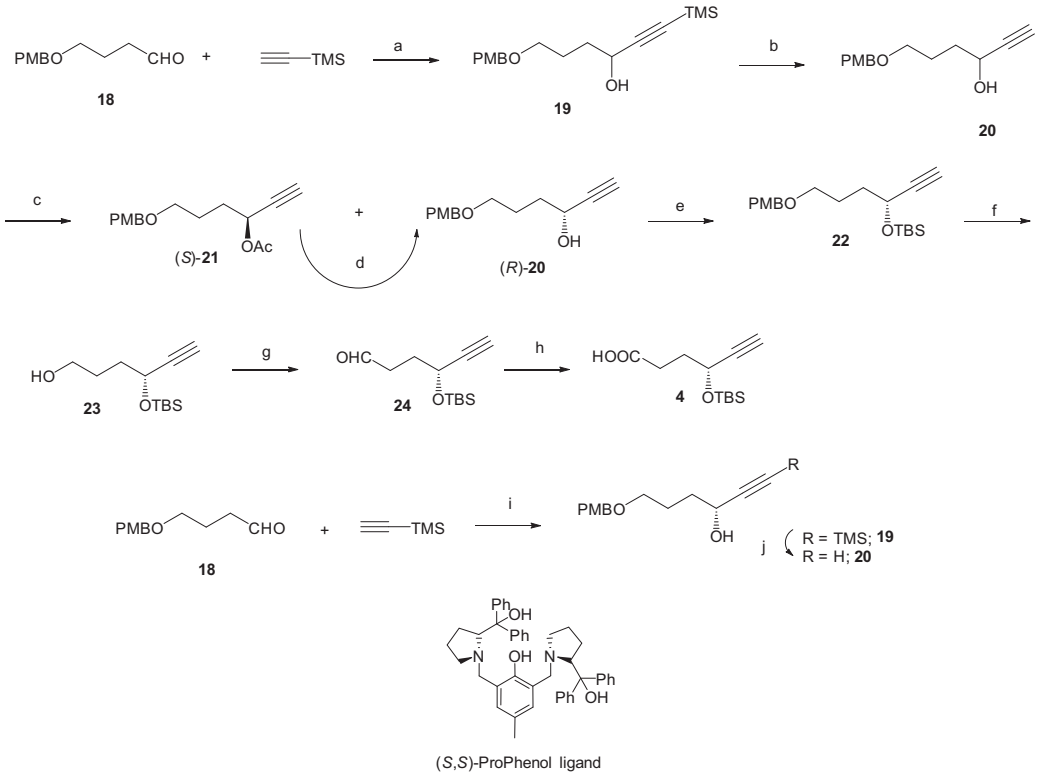
The synthesis was began with known aldehyde **18**, which was treated with TMS acetylene in the presence of *n*-BuLi, to afford the racemic alcohol **19** in 90% yield. The TMS group of alcohol **19** was removed by treating **18** with K_2CO_3 in MeOH to furnish alcohol **20** in 95% yield. Enzymatic kinetic resolution[15] of racemic alcohol **20** was performed using vinyl acetate as the active acyl donor and CAL-B (*Candida antarctica* lipase) as a biocatalyst in DIPE solvent at 34 °C to afford alcohol (*R*)-**20** (yield = 48%, ee = 96%) and acetate (*S*)-**21** (yield = 48%; ee = 96%). The unwanted acetate (*S*)-**21** was then hydrolyzed with 1% NaOH in MeOH and the resulting alcohol was inverted by applying a Mitsunobu inversion to give the desired alcohol (overall yield 83% after three steps). In an alternative approach aldehyde **18** was subjected to asymmetric alkynylation reaction with TMS acetylene in the presence of Trost's (*S*,*S*)-Pro-Phenol ligand to furnish the alcohol **19** in 60% yield (ee = 80%). As the obtained yield and enantioselectivity for compound **19** by this method were not encouraging enough, we subsequently discarded this route. Free hydroxyl group of **20** was protected as its TBS ether by treating it with imidazole and TBS-Cl to afford compound **22** in 95% yield. Deprotection of the PMB group was achieved by treating compound **22** with DDQ[16] to provide primary alcohol **23** in 96% yield. Swern oxidation[17] of the compound **23** afforded aldehyde **24** in 90% yield. Aldehyde **24** on further oxidation by Pinnick condition[18] furnished the carboxylic acid **4** in 80% yield (Scheme 3).

2.3. Fragment coupling by RCAM/RCM

After construction of both the fragments (acid **4** and alcohol **5**), our next job was to couple them by esterification followed by RCAM. The alcohol fragment **5** was coupled with the acid **4** using 2,4,6-trichlorobenzoyl chloride in Et_3N and DMAP (Yamaguchi esterification protocol)[19] to afford the ester **25** in 96% yield (Scheme 4). We attempted cyclization of **25** by the RCAM reaction using tris(triphenylsilyloxy)molybdenum nitride pyridine complex as catalyst,[20] but the reaction did not proceed to yield the desired ring closing product. We thought that the presence of bulky TBS and acetonide group adjacent to the two alkyne termini might be blocking the RCAM catalyst. Hence the TBS and the acetonide group were subsequently deprotected from compound **25** to afford

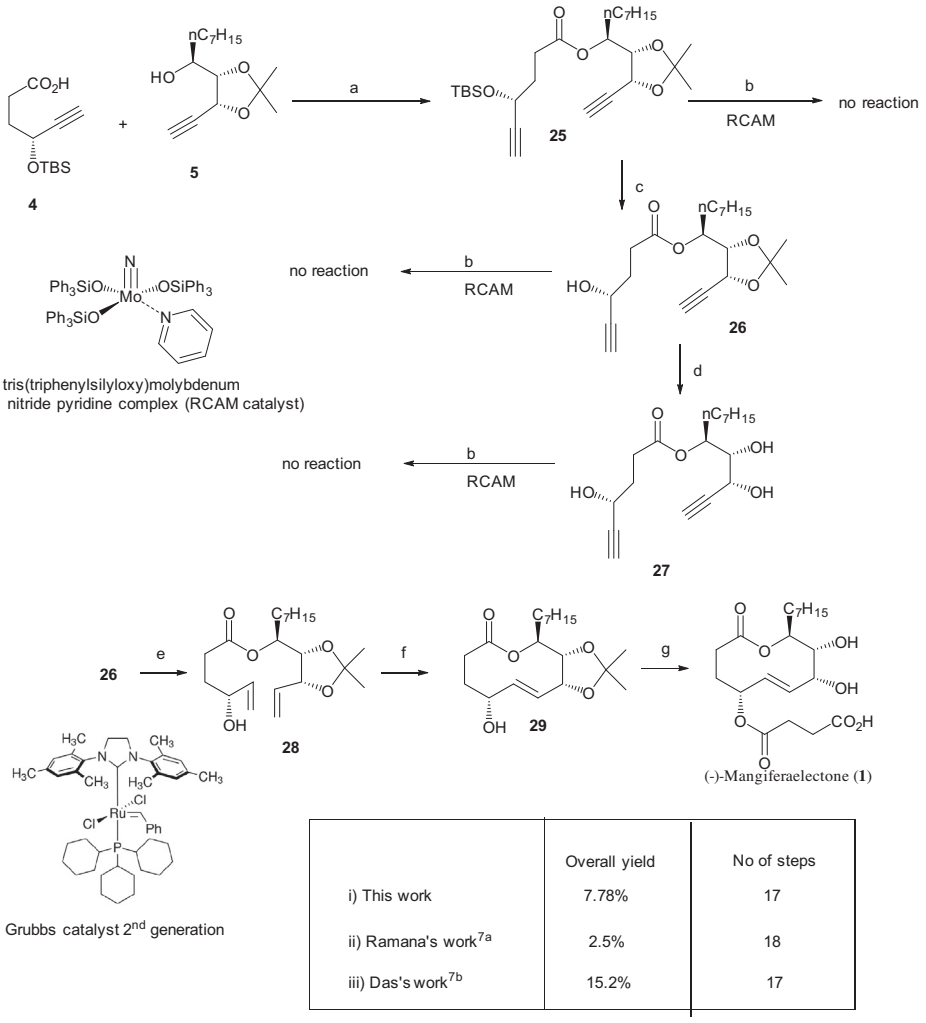


Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, DCM, rt, 98%; (b) *n*-BuLi, THF 0 °C–rt, 2 h, 75%; (c) DIAD, Ph_3P, THF 0 °C–rt, 3 h, 91%; (d) Raney-Ni, EtOH, 80 °C, 4 h, 75%; (e) 1 M TBAF, THF, 88%; (f) Ph_3P, CCl_4, 5 h, reflux 88%; (g) $LiNH_2$, NH_3 (l), −30 °C, THF, 5 h, 85%; (h) DIAD, Ph_3P, $PhCO_2H$, 1% NaOH, 86% (for two steps).



Scheme 3. Reagents and conditions: (a) *n*-BuLi, TMS acetylene, THF, −78 °C–rt, 90%; (b) K_2CO_3, MeOH, 0 °C, 95%; (c) CAL-B, vinyl acetate, $^iPr_2O$, 4 Å-MS, 1 h; (d) (i) K_2CO_3, MeOH; (ii) PPh_3, DIAD, PhCOOH; (iii) 1% NaOH in MeOH; (e) imidazole, TBS-Cl, DCM, rt 95%; (f) DDQ, DCM/H_2O (19:1), rt, 1 h, 96%; (g) $(COCl)_2$, DMSO, Et_3N, DCM, −78 °C, 90%; (h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH/H_2O (1:1), rt, 2 h 80%; (i) (*S*,*S*)-Pro-Phenol, Ph_3PO, Me_2Zn, toluene, 60%; (j) same as b, 95%.

compound **26** and **27** as depicted in Scheme 4. Compound **26** and **27** were separately subjected to the RCAM reaction under similar conditions, however the RCAM reaction did not proceed at all in either case (starting material was recovered). As the attempted RCAM reaction was failed to yield the desired lactone core, we switched over to an RCM strategy to complete the synthesis.



	Overall yield	No of steps
i) This work	7.78%	17
ii) Ramana's work[7a]	2.5%	18
iii) Das's work[7b]	15.2%	17

Scheme 4. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, toluene 0 °C to rt, 6 h, 96%; (b) tris(triphenylsilyloxy)molybdenum nitride pyridine complex, toluene, 80 °C; (c) HF-pyridine, THF, 4 h, 88%; (d) 2 N HCl, THF, rt, 6 h, 90%; (e) Lindlar's catalyst, H_2, Pd–C, EtOAc, 80%; (f) G-II (10 mol %), DCM, 10 h, 85%; (g) succinic anhydride, EDCI·HCl, DMAP, and then same as d.

Compound **26**, upon partial reduction with Lindlar catalyst and H_2 atmosphere afforded the di-olefinic precursor **28** in 80% yield. Ring closing metathesis (RCM) of the resulting diene ester **28** was successfully achieved by using the Grubbs second generation catalyst (G-II) to afford the 10-membered lactone **29** as a single *E*-stereoisomer in good yield (85%).[21] Resulting hydroxylactone **29** was then subjected to esterification with succinic anhydride in the presence of DMAP followed by treatment with 2 N HCl that furnished the target molecule mangiferaelactone **1** in 90% yield (overall yield = 8.6% from compound **9**; Scheme 4). The specific rotation and spectroscopic data (^1H, ^{13}C NMR, ^1H–^1H COSY, HSQC, NOESY, and MS) of the compound were found to be identical to those reported in the literature.[4]

3. Conclusion

In conclusion an efficient stereoselective synthesis of (−)-mangiferaelactone was achieved by using a *C*-alkylribofuranoside as a chiral precursor. The *C*-alkylribofuranoside was accessed from a *C*-thiopheneribofuranoside by reductive desulfurization. Attempts to construct the macrolactone core in the target molecule through exploration of RCAM reaction remain elusive. Finally stereoselective RCM reaction was employed at the penultimate stage to complete the synthesis of the target molecule.

4. Experimental

4.1. General

All oxygen and/or moisture-sensitive reactions were carried out under an N_2 atmosphere in glassware that had been flame-dried under a vacuum (w0.5 mmHg) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. CAL-B (immobilized on acrylic resin) was purchased from Sigma Aldrich Co, USA. THF, diethyl ether, toluene were distilled from sodium benzophenone ketyl. Dichloromethane (DCM) was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 600, 400, and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ, ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Mass spectrometric analysis was performed in the CRF, IIT-

Kharagpur (TOF analyzer). Optical rotations were measured on a JASCO digital polarimeter. HPLC analysis was performed with CHIRALPAK AD-H and OJ-H (Daicel) column by using Shimadzu Prominence LC-20AT system (UV–Vis detector).

4.1.1. (3a*R*,6*R*,6a*R*)-6-((*tert*-Butyldimethylsilyloxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-ol 9

To a stirred solution of **8** (2.25 g, 11.8 mmol) in dry DCM (31 mL) were added imidazole (2.0 g, 29.5 mmol) and *tert*-butyldimethylsilylchloride (2.07 g, 13.75 mmol) at room temperature and the mixture was stirred for 3 h. The solvent was removed in vacuo and the residue partitioned between ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to afford compound **9** (3.52 g) in 98% yield as a colorless oil (9:1, anomeric mixture). R_f = 0.4 (EtOAc/hexane, 1:5). ^{1}H NMR (200 MHz, $CDCl_3$) for major isomer, δ_H: 5.27 (d, 1H, J = 11.2 Hz), 4.78 (d, 1H, J = 11.4 Hz), 4.69 (d, 1H, J = 6.0 Hz), 4.50 (d, 1H, J = 6.0 Hz), 4.34 (br s, 1H), 3.75 (d, 2H, J = 2.2 Hz), 1.47 (s, 3H), 1.31 (s, 3H), 0.92 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 112.1, 103.5, 87.6, 87.0, 81.9, 64.9, 26.5, 25.8, 25.0, 18.3, −5.5. HRMS (ESI) for $C_{14}H_{28}O_5SiNa$ $[M+Na]^+$, calculated: 327.1603; found: 327.1605.

4.1.2. (*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-((4*R*,5*S*)-5-(hydroxy-(5-propylthiophen-2-yl)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl) ethanol 10

To a solution of 2-propyl thiophene (5.3 g, 42.0 mmol) in anhydrous THF (40 mL) was added *n*-BuLi (26.4 mL, 42.18 mmol, 1.6 M in hexane) dropwise over 20 min at 0 °C after which the solution was stirred at room temperature for 0.5 h. To the resultant solution was added dropwise a solution of **9** (3 g, 9.85 mmol) in dry THF (30 mL) over 15 min at 0 °C. The reaction mixture was then stirred at room temperature for 2 h and treated with aq NH_4Cl solution (60 mL). The aqueous layer was separated, extracted with $CHCl_3$ (3 × 150 mL), and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue by silica gel column chromatography (EtOAc/hexane, 1:10) afforded compound **10** as a diastereomeric mixture (3.4 g) in 75% yield as a syrup. R_f = 0.2 (EtOAc/hexane, 1:10).

4.1.3. *tert*-Butyl(((3a*R*,4*R*,6*R*,6a*R*)-2,2-dimethyl-6-(5-propylthiophen-2-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy) dimethylsilane 12 and *tert*-butyl(((3a*R*,4*R*,6*S*,6a*R*)-2,2-dimethyl-6-(5-propylthiophen-2-yl)tetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl) methoxy)dimethylsilane 11

A mixture of **10** (3.4 g, 7.90 mmol) and Ph_3P (5.18 g, 19.75 mmol) in THF (30 mL) was stirred for 15 min and then treated with a solution of DIAD (3.98 g, 19.75 mmol) in THF (32 mL) dropwise at 0 °C. After stirring for 2.5 h at room temperature, the reaction mixture was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (EtOAc/hexane, 1:20) to afford compound **11** and **12** in 91% yield. Compound **11**: R_f = 0.2 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = −38.8 (*c* 3.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 6.85 (d, 1H, J = 3.2 Hz), 6.63 (d, 1H, J = 3.2 Hz), 5.41 (d, 1H, J = 4 Hz), 4.95 (d, 1H, 6 Hz), 4.73 (dd, 1H, J = 4.0, 6.0 Hz), 4.16 (m, 1H), 3.84 (dd, 1H, J = 3.6, 10.8 Hz), 3.77 (dd, 1H, J = 2.8, 10.8 Hz), 2.75 (t, 2H, J = 7.6 Hz), 1.69–1.67 (m, 2H), 1.59 (s, 3H), 1.35 (s, 3H), 0.98–0.96 (m, 3H), 0.94 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ_C: 147.4, 136.1, 126.5, 122.9, 112.8, 84.0, 83.5, 82.8, 81.4, 65.5, 32.5, 26.5, 26.0, 25.0, 24.9, 18.3, 13.9, −5.3, −5.4. HRMS (ESI) for $C_{21}H_{36}O_4SiSNa$ $[M+Na]^+$, calculated: 435.2001; found: 435.2002. Compound **12**: R_f = 0.3 (EtOAc/hexane, 1:20). $[\alpha]_D^{28}$ = −66.9 (*c* 0.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 6.84 (d, 1H, J = 3.4 Hz), 6.61 (d, 1H, J = 3.4 Hz), 5.01 (d, 1H, J = 5 Hz), 4.75 (dd, 1H, J = 3.4, 6.6 Hz), 4.64–4.58 (m, 1H), 4.13–4.11 (m, 1H), 3.78–3.75 (m, 2H), 2.73 (t, 2H, J = 7.5 Hz), 1.71–1.60 (m, 2H), 1.58 (s, 3H), 1.35 (s, 3H), 1.03–0.99 (m, 3H), 0.95 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$), δ_C: 145.7, 140.0, 124.4, 123.5, 114.3, 86.7, 84.6, 82.6, 81.9, 63.3, 32.2, 27.5, 25.9, 25.5, 24.8, 18.3, 13.6, −5.2, −5.4. HRMS (ESI) for $C_{21}H_{36}O_4SiSNa$ $[M+Na]^+$, calculated: 435.2001; found: 435.2002.

4.1.4. *tert*-Butyl(((3a*R*,4*R*,6*S*,6a*S*)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)dimethylsilane 13

Compound **12** (1.46 g, 3.54 mmol) and Raney nickel (12 mL) in ethanol (100 mL) were stirred at reflux for 4 h. After completion of the reaction (TLC analysis) the mixture was filtered over a bed of Celite and washed with ethanol (3 × 100 mL). Evaporation of the solvent and purification of the residue by silica gel column chromatography (EtOAc/hexane, 1:25) furnished compound **13** (1.03 g) in 75% yield as a liquid. R_f = 0.4 ((EtOAc/hexane, 1:25). $[\alpha]_D^{28}$ = −25.7 (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 4.61 (dd, 1H, J = 3.6, 6.6 Hz), 4.29–4.26 (m, 1H), 4.23–4.00 (m, 1H), 3.96 (t, 1H, J = 3.8 Hz), 3.85–3.69 (m, 2H), 1.60–1.53 (m, 2H), 1.52 (s, 3H), 1.34 (s, 3H), 1.32–1.27 (m, 10H), 0.97–0.89 (m, 12H), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 113.7, 85.0, 84.5, 84.2, 81.9, 63.6, 33.8, 31.7, 29.5, 29.1, 27.4, 25.9, 25.5, 22.6, 18.3, 14.0, −5.2, −5.4. HRMS (ESI) for $C_{21}H_{42}O_4SiNa$ $[M+Na]^+$, calculated: 409.2750; found: 409.2752.

4.1.5. (3a*R*,4*R*,6*S*,6a*S*)-6-Heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol 7

To an ice-cooled solution of **13** (1.03 g, 2.66 mmol) in dry THF (10 mL) was added a 1 M solution of TBAF (3.99 mL, 3.99 mmol) and stirred for 2 h at room temperature. After completion of the reaction, water was added to the reaction mixture and THF was removed under vacuum. The aqueous layer was then extracted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was then purified by silica gel column chromatography (EtOAc/hexane, 1:3) to afford compound **7** (0.637 g) in 88% yield as a colorless oil. R_f = 0.4 (EtOAc/hexane, 1:3). $[\alpha]_D^{30}$ = −3.4 (*c* 1.6, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.61 (dd, 1H, J = 4.8, 6.6 Hz), 4.30 (dd, 1H, J = 5.4, 6.6 Hz), 3.98 (dd, 1H, J = 4.2, 7.8 Hz), 3.89– 3.83 (m, 2H), 3.68 (dd, 1H, J = 4.5, 11.7 Hz), 2.19 (br s, 1H), 1.67–1.59 (m, 4H), 1.55 (s, 3H), 1.44–1.33 (m, 2H), 1.32 (s, 3H), 1.31–1.28 (m, 6H), 0.86 (t, 3H, J = 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ_C: 114.7, 85.2, 84.7, 84.1, 81.5, 62.9, 33.8, 31.9, 29.8, 29.3, 27.5, 25.6, 25.6, 22.7, 14.2.

HRMS (ESI) for $C_{15}H_{28}O_4Na$ $[M+Na]^+$, calculated: 295.1885; found: 295.1880.

4.1.6. (3a*S*,4*S*,6*S*,6a*S*)-4-(Chloromethyl)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole 6

To a stirred solution of compound **7** (0.637 g, 2.33 mmol) in CCl_4 (11 mL) was added TPP (0.916 g, 3.49 mmol) followed by a catalytic amount of imidazole and the resulting reaction mixture was refluxed for 4 h. The reaction mixture was then cooled to 0 °C, diluted with hexane, and filtered through a bed of Celite. After evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:15) to afford compound **6** (0.596 g) in 88% yield as a colorless oil. R_f = 0.5 (EtOAc/hexane, 1:15). $[\alpha]_D^{30}$ = −13.8 (*c* 2.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.60 (dd, 1H, J = 3.9, 6.9 Hz), 4.36 (dd, 1H, J = 4.8, 6.6 Hz), 4.14 (q, 1H, J = 4.6 Hz), 3.91 (dd, 1H, J = 6.6, 11.4 Hz), 3.66 (dd, 1H, J = 4.8, 11.4 Hz), 3.62 (dd, 1H, J = 5.7, 11.7 Hz), 1.64–1.60 (m, 2H), 1.59 (s, 3H), 1.58–1.40 (m, 2H), 1.39 (s, 3H), 1.39–1.28 (m, 8H), 0.89 (t, 3H, J = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 1 14.4, 84.8, 84.7, 82.9, 82.8, 44.5,

33.6, 31.7, 29.4, 29.0, 27.2, 25.3 (2C), 22.5, 14.0. HRMS (ESI) for $C_{15}H_{28}O_3Cl$ $[M+H]^+$, calculated: 291.1727; found: 291.1732.

4.1.7. (*S*)-1-((4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl) octan-1-ol 5

To freshly distilled ammonia (5 mL) in a 100 mL two-necked round-bottomed flask fitted with a cold finger condenser were added freshly cut pieces of lithium metal (0.14 g, 20.44 mmol) at −33 °C and the resulting gray suspension was stirred for 30 min. To this reaction mixture was added chloro compound **6** (0.596 g, 2.04 mmol) in anhydrous THF (4 mL) over a period of 5 min. After being stirred at −33 °C for 5 h, the reaction was quenched by the portion wise addition of solid NH_4Cl after which the ammonia was allowed to evaporate. The reaction mixture was then diluted with water (8 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 1:5) to afford compound **5** (0.44 g) in 85% yield as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{32}$ = +7.8 (*c* 2.2, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.90 (dd, 1H, *J* = 2.1, 5.1 Hz), 3.94–3.93 (m, 2H), 2.64 (d, 1H, *J* = 2.4 Hz), 2.07 (br s, 1H), 1.80–1.78 (m, 1H), 1.58–1.55 (m, 1H), 1.54 (s, 3H), 1.50–1.34 (m, 2H), 1.33 (s, 3H), 1.32–1.30 (m, 8H), 0.90 (t, 3H, *J* = 6.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 110.6, 80.6, 80.3, 76.1, 71.3, 68.0, 33.9, 31.8, 29.5, 29.2, 27.5, 25.8, 25.1, 22.6, 14.0. HRMS (ESI) for $C_{15}H_{26}O_3Na$ $[M+Na]^+$, calculated: 277.1779; found: 277.1780.

4.1.8. *tert*-Butyl(((3a*R*,4*R*,6*R*,6a*S*)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methoxy)dimethylsilane 14

Compound **14** was synthesized by desulfurization of compound **11** (1.49 g, 3.61 mmol) as described earlier. Purification by silica gel column chromatography (EtOAc/hexane, 1:25) gave compound **14** (1.05 g) in 75% yield as a liquid. R_f = 0.3 (EtOAc/hexane, 1:25). $[\alpha]_D^{28}$ = −14.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.81 (dd, 1H, *J* = 0.6, 6.0 Hz), 4.62 (dd, 1H, *J* = 3.6, 6.0 Hz), 4.06–4.03 (m, 2H), 3.70 (dd, 2H, *J* = 2.7, 3.9 Hz), 1.67–1.66 (m, 2H), 1.60–1.51 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.32–1.27 (m, 9H), 0.93 (s, 9H), 0.92–0.84 (m, 3H), 0.07 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 111.9, 83.9, 83.1, 82.5, 82.2, 64.7, 31.8, 29.7, 29.4, 29.2, 26.3, 26.3, 25.8, 25.1, 22.6, 14.1, −5.5, −5.5. HRMS (ESI) for $C_{21}H_{42}O_4SiNa$ $[M+Na]^+$, calculated: 409.2749; found: 409.2749.

4.1.9. (3a*R*,4*R*,6*R*,6a*S*)-6-Heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)methanol 15

Compound **15** was prepared according to the procedure described for compound **7** starting from compound **14** (1.04 g, 2.68 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded compound **15** (0.642 g) in 88% yield as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:3). $[\alpha]_D^{30}$ = −2.3 (*c* 2.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 4.62–4.56 (m, 2H), 4.09 (t, 1H, *J* = 6.2 Hz), 3.84 (td, 1H, *J* = 3.7, 6.6 Hz), 3.56 (d, 2H, *J* = 6.4 Hz), 2.02 (br s, 1H), 1.68 (q, 2H, *J* = 7.33 Hz) 1.48 (s, 3H), 1.43–1.36 (m, 2H), 1.32 (s, 3H), 1.29–1.22 (m, 8H), 0.86 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), δ_C: 112.6, 84.1, 82.5, 81.8, 81.1, 61.7, 31.9, 29.8, 29.3, 29.2, 26.5, 26.4, 25.3, 22.8, 14.2. HRMS (ESI) for $C_{15}H_{28}O_4Na$ $[M+Na]^+$, calculated: 295.1885; found: 295.1880.

4.1.10. (3a*S*,4*S*,6*R*,6a*S*)-4-(Chloromethyl)-6-heptyl-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole 16

Compound **16** was prepared according to the procedure described for compound **6** starting from compound **15** (0.642 g, 2.35 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:10) afforded compound **16** (0.601 g) in 88% yield as a colorless oil. Its analytical data match well with those of reported compounds.[14c]

4.1.11. (*R*)-1-(4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl) octan-1-ol 17

Compound **17** was prepared according to the procedure described for compound **5** starting from compound **16** (0.601 g, 2.06 mmol). Purification by silica gel chromatography (EtOAc/hexane, 1:5) afforded compound **17** (0.45 g) in 85% yield as a colorless oil. R_f = 0.2 (EtOAc/hexane, 1:5). $[\alpha]_D^{30}$ = +46 (*c* 1.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 4.74 (dd, *J* = 5.7, 2.4 Hz, 1H), 4.01–3.85 (m, 2H), 2.56 (d, 1H, *J* = 2.4 Hz,), 2.28 (br s, 1H), 1.57 (s, 3H), 1.55–1.40 (m, 3H), 1.37 (s, 3H), 1.36–1.18 (m, 9H), 0.88 (t, 3H, *J* = 6.6 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 110.4, 81.0, 79.5, 75.9, 71.2, 66.9, 32.7, 31.7, 29.3, 29.1, 27.4, 25.9, 25.2, 22.6, 14.0. HRMS (ESI) for $C_{15}H_{26}O_3Na$ $[M+Na]^+$, calculated: 277.1779; found: 277.1786.

4.1.12. (±)-6-(4-Methoxybenzyloxy)-1-(trimethylsilyl)hex-1-yn-3-ol 19

To a solution of trimethylsilylacetylene (1.95 mL, 14.10 mmol) in anhydrous THF (10 mL) was added dropwise *n*-BuLi (2.0 M in hexane, 6.5 mL, 12.95 mmol) at 0 °C for 30 min. To a stirred solution of aldehyde **18** (2.45 g, 11.75 mmol) in anhydrous THF (10 mL) at −78 °C was added the pre-formed solution of lithium trimethylsilylacetylide via a cannula. After the mixture had been stirred at −78 °C for 40 min, the reaction was gradually warmed to rt. After stirring at rt for 30 min, the reaction was quenched by the addition of a saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by silica gel chromatography (EtOAc/hexane, 1:4) afforded racemic **19** (3.42 g) in 95% yield as a pale yellow oil. R_f = 0.3 (EtOAc/hexane, 1:4). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.2 9 (d, 2H, *J* = 8.6 Hz), 6.90 (d, 2H, *J* = 8.6 Hz), 4.52–4.45 (m, 3H), 3.82 (s, 3H), 3.53 (m, 2H), 2.89 (br s, 1H), 1.90–1.80 (m, 4H), 0.19 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.3, 130.2, 129.5, 113.9, 107.0, 89.2, 72.6, 69.9, 62.5, 55.4, 35.2, 25.5, 0.1. HRMS (ESI) for $C_{17}H_{26}O_3SiNa$ $[M+Na]^+$, calculated: 329.1548; found: 329.1551.

4.1.13. (±)-6-(4-Methoxybenzyloxy)hex-1-yn-3-ol 20

To a solution of racemic compound **19** (3.42 g, 11.15 mmol) in methanol (80 mL) was added K_2CO_3 (1.5 g, 11.15 mmol) and the mixture was stirred at 0 °C for 5 h. The mixture was then poured into 120 mL of saturated aqueous ammonium chloride solution and concentrated in vacuo. The mixture was extracted with ethyl acetate and organic layer was washed with brine and dried over anhydrous $MgSO_4$. The organic layer was concentrated in vacuo to afford the crude residue, which upon purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded racemic compound **20** (2.59 g) in 99% yield as a pale yellow oil. R_f = 0.3 (EtOAc/hexane, 1:3). ^{1}H NMR (400 MHz, $CDCl_3$), δ_H: 7.2 5 (d, 2H, *J* = 8.4 Hz), 6.8 7 (d, 2H, *J* = 8.4 Hz), 4.45 (ABq, 2H, *J* = 11.2 Hz), 4.41–4.39 (m, 1H), 3.80 (s, 3H), 3.53–3.51 (m, 2H), 2.44 (d, 1H, *J* = 2.0 Hz), 2.25 (br s, 1H), 1.90–1.74 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.3, 130.1, 129.5, 113.9, 85.1, 72.8, 69.8, 61.9, 55.4, 33.2, 25.5. HRMS (ESI) for $C_{14}H_{18}O_3Na$ $[M+Na]^+$, calculated: 257.1153; found: 257.1159.

4.1.14. (*S*)-6-(4-Methoxybenzyloxy)hex-1-yn-3-yl acetate 21

In a typical resolution experiment, a solution of racemic alcohol **20** (2.5 g, 11.05 mmol) in anhydrous diisopropyl ether (49 ml) was stirred with vinyl acetate (1 equiv, 1.11 mL) and powdered molecular sieves (16 mg, 4 Å) followed by the addition of CAL-B (0.8 g). The reaction mixture was stirred in an orbit shaker (250 rpm) at

34 °C temperature for 1 h. After 50% conversion (by TLC analysis), the reaction mixture was filtered through a pad of Celite and evaporated to dryness. The alcohol and the acetate were separated by silica gel column chromatography (EtOAc/hexane, 1:10). R_f = 0.5 ((EtOAc/hexane, 1:10). $[\alpha]_D^{28}$ = −37.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$), δ_H: 7.28 (d, 2H, *J* = 8.6 Hz), 6.90 (d, 2H, *J* = 8.6 Hz), 5.39 (dt, 1H, *J* = 2.0, 6.0 Hz), 4.46 (s, 2H), 3.80 (s, 3H), 3.50 (t, 2H, *J* = 5.9 Hz), 2.49 (d, 1H, *J* = 2.0 Hz), 2.10 (s, 3H), 1.97–1.77 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 169.9, 159.1, 130.4, 129.2, 113.8, 81.0, 73.6, 72.5, 69.1, 63.5, 55.2, 31.4, 25.2, 20.9. HRMS (ESI) for $C_{16}H_{20}O_4Na$ $[M+Na]^+$, calculated: 299.1259; found: 299.1263.

4.1.15. (*R*)-6-(4-Methoxybenzyloxy)hex-1-yn-3-ol 20

To a stirred solution of (*S*)-acetate **21** (1.46 g, 5.3 mmol) in 12 mL of MeOH was added K_2CO_3 (219 mg, 1.6 mmol) and stirred for 4 h. Methanol was evaporated in vacuo and 75 mL of diethyl ether was added to it. The organic part was washed with water (12 mL), saturated NH_4Cl solution (12 mL), and then with brine solution (12 mL). The organic part was dried over anhydrous $MgSO_4$ and solvent was removed in vacuo to afford the crude alcohol, which was used for the next step without further purification.

4.2. Mitsunobu inversion

To a stirred solution of the alcohol (1.24 g, 5.3 mmol) in 22 mL of anhydrous THF were added TPP (2 g, 7.8 mmol), DIAD (1.5 mL, 7.8 mmol), and benzoic acid (0.95 g, 7.8 mmol) at 0 °C. The reaction was stirred overnight at room temperature, after which THF was removed in vacuo and the residue was taken in ethyl acetate (50 mL). The organic part was washed with saturated $NaHCO_3$ (2 × 7.5 mL) and brine (12 mL) solution, and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated in vacuo and purification was accomplished by silica gel chromatography (EtOAc/hexane, 1:8) to afford the (*R*)-benzoate (1.5 g) as a colorless liquid in 85% yield.

4.3. Benzoate hydrolysis

To a stirred solution of the benzoate (1.5 g, 4.43 mmol) in 50 mL of MeOH was added NaOH (0.53 g, 13.10 mmol) at room temperature and stirred for 12 h at room temperature. After completion of the reaction MeOH was evaporated in vacuo and the crude residue was diluted with 62 mL of diethyl ether. The organic part was washed with (2 × 15 mL) water, brine solution (15 mL), and then dried over anhydrous $MgSO_4$. The organic solvent was evaporated in vacuo and purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded the (*R*)-alcohol **20** (1.03 g) as a colorless liquid in 100% yield. R_f = 0.3 (EtOAc/hexane, 1:3). $[\alpha]_D^{28}$ = 3.5 (*c* 1.6, EtOH).

4.3.1. (*R*)-*tert*-Butyl(6-(4-methoxybenzyloxy)hex-1-yn-3-yloxy) dimethylsilane 22

To a stirred solution of alcohol (*R*)-**20** (2.28 g, 9.73 mmol) and imidazole (1.32 g, 19.46 mmol) in dry CH_2Cl_2 (30 mL), TBSCl (1.76 g, 11.67 mmol) was added portion wise at 0 °C. The reaction mixture was stirred at the same temperature for 2 h and then quenched with water (15 mL). The dichloromethane (CH_2Cl_2) layer was separated, and the aqueous layer was extracted with additional CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water, saturated Na_2CO_3 solution, and brine solution. The organic layer was then dried over anhydrous $MgSO_4$. The organic solvent was removed in vacuo, and purification was accomplished by silica gel chromatography (EtOAc/hexane, 1:10) to afford the compound (*R*)-**22** (3.22 g) in 95% yield as a colorless liquid. R_f = 0.3 ((EtOAc/hexane, 1:10). $[\alpha]_D^{30}$ = 27.9 (*c* 1.8, EtOH). ^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 7.2 8 (d, 2H, *J* = 8.4 Hz), 6.8 9 (d, 2H, *J* = 8.4 Hz), 4.45 (s, 2H), 4.40–4.38 (m, 1H), 3.82 (s, 3H), 3.49 (m, 2H), 2.39 (d, 1H, *J* = 2.4 Hz), 1.78–1.77 (m, 4H), 0.91 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 159.0, 130.6, 129.1, 113.7, 85.4, 72.4, 72.1, 69.6, 62.5, 55.2, 35.2, 25.7, 25.3, 18.1, −4.6, −5.1. HRMS (ESI) for $C_{20}H_{32}O_3SiNa$ $[M+Na]^+$, calculated: 371.2018; found: 371.2024.

4.3.2. (*R*)-4-(*tert*-Butyldimethylsilyloxy)hex-5-yn-1-ol 23

Compound **22** (3.22 g, 9.23 mmol) was dissolved in 40 mL of DCM/phosphate buffer (19:1; pH = 7) and the solution was cooled to 0 °C. DDQ (2.51 g, 11.07 mmol) was added portion wise to the solution and the mixture was stirred at this temperature for 1 h. Then, the reaction mixture was filtered through a pad of Celite. The residue was then washed with 25 mL of DCM. The combined organic solution was washed successively with 5% $NaHCO_3$ solution, water, and brine solution. The organic layer was then dried over anhydrous $MgSO_4$ and evaporated in vacuo. Purification by silica gel chromatography (EtOAc/hexane, 1:3) afforded compound (*R*)-**23** (2.02 g) in 96% yield as colorless oil. R_f = 0.3 (EtOAc/hexane, 1:3). $[\alpha]_D^{28}$ = 41.6 (*c* 1.0, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.46–4.44 (m, 1H), 3.70–3.67 (m, 2H), 2.42 (d, 1H, *J* = 2.4 Hz), 1.81–1.76 (m, 4H), 0.92 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 84.9, 72.53, 62.5, 34.9, 28.2, 25.7, 18.1, −4.6, −5.1. HRMS (ESI) for $C_{12}H_{24}O_2SiNa$ $[M+Na]^+$, calculated: 251.1443; found: 251.1450.

4.3.3. (*R*)-4-(*tert*-Butyldimethylsilyloxy)hex-5-ynoic acid 4

Aldehyde **24** (1.8 g, 7.95 mmol) was dissolved in *t*BuOH (40 mL) and a 2.0 M solution of 2-methyl-2-butene (23.87 mL, 47.74 mmol) in THF was added to it. To this mixture was added a solution of $NaClO_2$ (4.32 g, 47.74 mmol) and NaH_2PO_4 (2.86 g, 23.85 mmol) in H_2O (40 mL). After one hour, the yellow biphasic reaction mixture was poured onto H_2O (50 mL) and EtOAc (60 mL). The organic layer was separated and the aqueous part was washed with EtOAc (2 × 50 mL). The combined organic part was washed with brine solution (140 mL) and dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to afford the crude acid. The crude material was purified by silica gel chromatography (EtOAc/hexane, 1:1) to afford acid **25** (1.54 g) in 80% yield as a colorless oil. R_f = 0.3 (EtOAc/hexane, 1:1) $[\alpha]_D^{28}$ = 28.9 (*c* 1.0, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$), δ_H: 4.5 0 (dt, 1H, *J* = 1.8, 6.0 Hz), 2.5 8 (dd, 2H, *J* = 8.1, 15.3 Hz), 2.42 (d, 1H, *J* = 2.4 Hz), 2.05–2.00 (m, 2H), 0.92 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 179.9, 84.4, 72.8, 61.4, 33.3, 29.4, 25.8, 18.1, −4.7, −5.5. HRMS (ESI) for $C_{12}H_{23}O_3Si$ $[M+H]^+$, calculated: 243.1418; found: 243.1416.

4.3.4. (*R*)-4-(*tert*-Butyldimethylsilyloxy)hex-5-ynal 24

Oxalyl chloride (1.16 ml, 13.26 mmol) was taken in DCM (32 mL) and the reaction vessel was kept at −78 °C. Dimethyl sulfoxide (DMSO, 1.88 ml, 26.52 mmol) was then added and the reaction mixture was kept at the same temperature for 25 min. Alcohol **23** (2.02 g, 8.84 mmol) in DCM was then added to it and the mixture was kept for a further 45 min at the same temperature, after which triethyl amine (7.37 ml, 53 mmol) was added and the reaction mixture was gradually warmed to the room temperature over 1 h. The reaction was quenched by adding water and extracted with DCM. The organic layer was washed successively with water, $NaHCO_3$ solution, and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification through silica gel chromatography (EtOAc/hexane, 1:10) afforded aldehyde **24** (1.8 g) in 90% yield. R_f = 0.4 (EtOAc/hexane, 1:10).

4.3.5. Asymmetric catalytic alkynylation of aldehyde 18

A microwave vial equipped with a stirrer bar was charged with trimethylsilylacetylene (2 mmol, 196 mg), (*S,S*)-Pro-Phenol ligand

(0.4 mmol, 251 mg), and $P(O)Ph_3$ (0.8 mmol, 219 mg). Dry toluene (30 mL) was then added and the mixture was cooled to 0 °C under N_2. A solution of Me_2Zn (5 mL; 1.2 M in toluene) was then slowly added over 25 min and the mixture was stirred at 0 °C for 30 min. The mixture was then placed at −20 °C, after which aldehyde **18** (8 mmol, 1.66 g) was slowly added to the solution over 30 min. The resulting mixture was then stirred at the same temperature for 2 h before being quenched by the slow addition of 30 mL of aqueous NH_4Cl. After stirring for 15 min, this solution was extracted four times each with 30 mL of diethyl ether. The organic extracts were dried over $MgSO_4$, filtered, and the solvent was evaporated in vacuum. Purification of the crude residue by silica gel chromatography (EtOAc/hexane, 1:4) afforded alcohol **25** (1.46 g) in 60% yield with ee = 80% as a pale yellow oil. R_f = 0.3 (EtOAc/hexane, 1:4).

4.3.6. (*R*)-((*S*)-1-((4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)octyl)4-(*tert*-butyldimethylsilyloxy)hex-5-ynoate 25

Distilled Et_3N (1.3 mL, 9.54 mmol) was added to a solution of acid **4** (1.16 g, 4.77 mmol) in anhydrous toluene (172 mL) at room temperature. Distilled 2,4,6-trichlorobenzoyl chloride (0.97 mL, 6.36 mmol) was added dropwise and the resulting clear, colorless solution was stirred at room temperature. After 1 h, TLC showed the complete consumption of the acid. Alcohol **5** (0.81 g, 3.18 mmol) in anhydrous toluene (180 mL) was then added, followed by DMAP (1.4 g, 11.13 mmol) to give a white suspension. After completion of the reaction (5 h), as indicated by TLC analysis, toluene was evaporated under reduced pressure to afford a crude product. The crude residue was directly loaded on a silica gel column and purified by column chromatography (EtOAc/hexane, 1:15) to afford the compound **25** (1.46 g) in 96% as a liquid. R_f = 0.3 (EtOAc/hexane 1:15). $[\alpha]_D^{28}$ = 25.4 (*c* 1.0, $CHCl_3$). HRMS (ESI) for $C_{27}H_{46}O_5Si$ $[M+H]^+$, calculated: 479.3193; found: 479.3183. ^1H NMR (600 MHz, $CDCl_3$), δ_H: 5.1 8 (dt, 1H, *J* = 3.9, 11.4 Hz), 4.84 (dd, 1H, *J* = 2.1, 6.3 Hz), 4.46 (td, 1H, *J* = 2.0, 6.0 Hz), 4.19 (dd, 1H, *J* = 6.3, 7.5 Hz), 2.52 (d, 1H, *J* = 2.4 Hz), 2.50–2.46 (m, 2H), 2.41 (d, 1H, *J* = 2.4 Hz), 2.00–1.99 (m, 2H), 1.87–1.85 (m, 1H), 1.70–1.67 (m, 1H), 1.57 (s, 3H), 1.55 (s, 3H), 1.37–1.28 (m, 10H), 0.92 (s, 9H), 0.90 (t, 3H, *J* = 3.3 Hz), 0.16 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 172.3, 110.9, 84.7, 79.5, 78.5, 77.9, 73.6, 72.9, 68.2, 61.7, 33.6, 31.9, 31.6, 29.9, 29.8, 29.4, 27.4, 25.9, 24.8, 22.8, 18.3, 14.3, −4.4, −4.9.

4.3.7. (*R*)-((*S*)-1-((4*S*,5*R*)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)octyl)4-hydroxyhex-5-ynoate 26

Compound **25** (1.46 g, 3.04 mmol) was dissolved in 12 ml of anhydrous THF in a polyethylene vessel and 3 ml of HF-Py was added to it at 0 °C. The mixture was then stirred for 7 h at room temperature followed by the addition of 75 mL of EtOAc and 25 mL of brine solution. The organic layer was then separated and the aqueous layer was washed with (2 × 75 mL) EtOAc. The combined organic part was washed with brine (30 mL) and the solution was dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The crude material was then purified by silica gel column chromatography (EtOAc/hexane, 1:5) to afford compound **26** (0.97 g) in 88% yield as a liquid. R_f = 0.3 (EtOAc/hexane, 1:5). $[\alpha]_D^{28}$ = +21.3 (*c* 1.0, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$), δ_H: 5.1 6 (q, 1H, *J* = 3.8 Hz), 4.83 (dd, 1H, *J* = 2.4, 6.0 Hz), 4.49– 4.47 (m, 1H), 4.18 (dd, 1H, *J* = 6.0, 7.8 Hz), 2.60–2.48 (m, 4H), 2.05–2.01 (m, 2H), 1.85 (m, 1H), 1.67–1.66 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.34–1.24 (m, 10H), 0.89–0.87 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 172.5, 110.8, 84.0, 79.2, 78.2, 76.2, 73.7, 73.4, 67.9, 61.1, 32.2, 31.7, 31.4, 30.0, 29.5, 29.1, 27.2, 25.7, 24.5, 22.6, 14.0. HRMS (ESI) for $C_{21}H_{32}O_5Na$ $[M+Na]^+$, calculated: 387.2148; found: 387.2149.

4.3.8. (*R*)-((*S*)-1-((4*S*,5*R*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)octyl)4-hydroxyhex-5-enoate 28

Compound **26** (0.2 g, 0.54 mmol) was taken in anhydrous EtOAc (5 ml) in a round bottom flask. Lindlar catalyst (30 mg) and catalytic amount of quinoline were added and the reaction mixture was stirred for 4 h at room temperature under H_2 (500 psi) atmosphere. After the completion of reaction it was filtered with a Celite pad and the organic solvent was dried over anhydrous $MgSO_4$ and then concentrated in vacuo. The crude material was then purified by silica gel column chromatography (EtOAc/hexane, 1:10) to afford compound **28** (0.16 g) in 80% yield as a colorless oil. R_f = 0.2 (EtOAc/hexane, 1:10). $[\alpha]_D^{30}$ = +3.4 (*c* 1.4, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$), δ_H: 5.94–5.72 (m, 2H), 5.38–5.11 (m, 4H), 4.96–4.87 (m, 1H), 4.61 (t, 1H, *J* = 6.9 Hz), 4.22–4.11 (m, 2H), 2.47–2.39 (m, 4H), 1.89–1.74 (m, 2H), 1.58 (s, 3H), 1.48 (s, 3H), 1.37–1.26 (m, 10H), 0.88 (t, 3H, *J* = 6.2 Hz). ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 173.1, 140.5, 133.3, 118.6, 115.2, 108.9, 78.9, 78.4, 72.2, 72.1, 31.9, 31.6, 31.2, 30.4, 29.6, 29.2, 27.6, 25.3, 24.7, 22.7, 14.2. HRMS (ESI) for $C_{21}H_{36}O_5Na$ $[M+Na]^+$, calculated: 391.2461; found: 391.2465.

4.3.9. (3a*S*,4*S*,9*R*,11a*R*,*E*)-4-Heptyl-9-hydroxy-2,2-dimethyl-7,8,9,11a-tetrahydro-3a*H*-[1,3]dioxolo[4,5-*c*]oxecin-6(4*H*)-one 29

The starting compound **28** (80 mg, 0.21 mmol) was taken in anhydrous degassed DCM (30 mL). Grubbs second generation metathesis catalyst (G-II, 7 mg, 0.008 mmol) was then added and the solution was stirred at room temperature for 12 h. The solution was then evaporated and the contents of the flask were directly loaded onto a silica gel column. The crude material was then purified by silica gel column chromatography (EtOAc/hexane, 1:4) to afford the product **29** (52 mg) in 85% yield as a liquid. R_f = 0.3 (EtOAc/hexane, 1:4). $[\alpha]_D^{30}$ = −73.4 (*c* 1.4, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$), δ_H: 5.7 8 (dd, 1H, *J* = 3.0, 15.8 Hz), 5.62 (dd, 1H, *J* = 8.6, 15.8 Hz), 4.89 (td, 1H, *J* = 2.4, 10.8 Hz), 4.66 (br s, 1H), 4.14–4.09 (m, 1H), 3.94 (dd, 1H, *J* = 4.8, 10 Hz), 2.32–2.31 (m, 2H), 2.03–2.01 (m, 3H), 1.80–1.74 (m, 1H), 1.52 (s, 3H), 1.35 (s, 3H), 1.26–1.23 (m, 10H), 0.84 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$), δ_C: 175.2, 128.4, 126.6, 109.5, 78.7, 75.8, 75.8, 71.2, 33.8, 32.1, 31.9, 31.4, 29.5, 29.3, 28.6, 26.3, 24.6, 22.8, 14.2. HRMS (ESI) for $C_{19}H_{32}O_5Na$ $[M+Na]^+$, calculated: 363.2148.; found: 363.2150.

4.3.10. 4-((5*R*,8*R*,9*R*,10*S*,*E*)-10-Heptyl-8,9-dihydroxy-2-oxo-3,4,5,8,9,10-hexahydro-2*H*-oxecin-5-yloxy)-4-oxobutanoic acid 1

Succinic anhydride (22 mg, 0.22 mmol) was taken in dry DCM (2 ml). Next, DCC (61 mg, 0.3 mmol), DMAP (5 mg), and alcohol **19** (50 mg, 0.15 mmol) were sequentially added to the reaction mixture. The reaction mixture was kept at room temperature for 24 h, after which DCM was evaporated and the crude ester was used for the next step.

To a solution of the obtained crude ester (59.47 mg, 0.13 mmol) in THF (10 ml), HCl (2 ml, 2 M) was added at room temperature and stirred for 6 h. Water was then added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine. It was then dried over $MgSO_4$, concentrated in a rotary evaporator, and purified by silica gel column chromatography (EtOAc/hexane, 1:1) to afford the target molecule mangiferaelactone **1** (47.95 mg) in 80% overall yield for two steps. R_f = 0.3 (EtOAc/hexane 2:1). $[\alpha]_D^{30}$ = −2.3 (*c* 1.0, MeOH). ^1H NMR (600 MHz, $CDCl_3$), δ_H: 5.87 (dd, 1H, *J* = 1.8, 15.6 Hz), 5.52 (ddd, 1H, *J* = 1.4, 9.6, 15.4 Hz), 5.16 (d, 1H, *J* = 4.8 Hz), 5.03–5.00 (m, 1H), 4.52–4.49 (m, 1H), 3.59 (dd, 1H, *J* = 2.7, 9.9 Hz), 2.66 (t, 2H, *J* = 4.8 Hz), 2.61 (t, 2H, *J* = 5.4 Hz), 2.39–2.36 (m, 1H), 2.19–2.08 (m, 2H), 2.08–2.00 (m, 1H), 1.99–1.88 (m, 1H), 1.56–1.54 (m, 1H), 1.37–1.26 (m, 10H), 0.88 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (150 MHz, $CDCl_3$), δ_C: 176.1, 174.6, 171.7, 132.9, 123.4, 73.4, 72.4,

70.9, 31.8, 31.55, 31.2, 29.6, 29.5, 29.4, 29.2, 28.9, 24.6, 22.6, 14.1. ^{1}H NMR (600 MHz, CD_3OD), δ_H: 5.91 (dd, 1H, J = 2.1, 15.6 Hz), 5.49 (ddd, 1H, J = 2.2, 9.5, 15.5 Hz), 5.18 (dt, 1H, J = 4.7, 10.2 Hz), 5.13 (dt, 1H, J = 2.6, 9.4 Hz), 4.40 (br d, 1H, J = 2.2 Hz), 3.52 (dd, 1H, J = 2.4, 9.7 Hz), 2.56 (s, 4H), 2.34 (ddd, 1H, J = 2.2, 6.1, 13.9 Hz), 2.10 (dt, 1H, J = 1.9, 13.9 Hz), 2.00–1.95 (m, 1H), 1.91 (dt, 1H, J = 2.2, 13.2 Hz), 1.87–1.82 (m, 1H), 1.49–1.47 (m, 1H), 1.36–1.25 (m, 10H), 0.88 (t, 3H, J = 6.8 Hz). ^{13}C NMR (150 MHz, CD_3OD), δ_C: 175.9 (2C), 173.5, 136.0, 123.8, 78.2, 74.5, 73.5, 72.2, 33.1, 32.8, 32.3, 30.9, 30.8 (2C), 30.5, 25.7, 23.8, 14.6. HRMS (ESI) for $C_{20}H_{32}O_8Na$ $[M+Na]^+$, calculated: 423.1995.; found: 423.2016.

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