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A general approach to medium-sized ring ethers via hydrolytic and oxidative kinetic resolutions: stereoselective syntheses of (−)-*cis*-lauthisan and (+)-isolaurepan

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ABSTRACT

A short and enantioselective approach to medium ring ethers and its application to the syntheses of (−)-*cis*-lauthisan and (+)-isolaurepan are described. The synthetic strategy features Jacobson's Hydrolytic Kinetic Resolution (HKR), oxidative resolution of secondary alcohol, and highly diastereoselective Et_3SiH/TMSOTf-promoted reductive cyclization of a hydroxy ketone to give exclusively the different medium-sized cis-disubstituted cyclic ethers.

1. Introduction

Polyfunctionalized medium-sized cyclic ethers have attracted much attention from synthetic and medicinal chemists due to their presence in a wide range of biologically active natural products, including ladder marine toxins, lauroxanes, antibiotic, etc.[1] These ethers constitute important structural features present in a number of biologically active marine natural products, particularly from *Laurencia* red algae.[2] Many compounds of this class contain a seven or eight-membered cyclic ether ring usually with cis stereochemistry in the alkyl substituents.

In view of the increasing number of biologically active marine natural products containing medium and large sized cyclic ether derivatives, much attention has been focused on efficient approaches toward these systems. However, their synthesis is generally difficult via standard cyclization methodologies.[3] Nevertheless, the challenge in their efficient construction has led to the development of several strategies for their synthesis,[4,5] mainly in racemic form.

(−)-Lauthisan **1**, isolated from a sample of sea alga *Laurencia obtusa* is a fully saturated core of the natural derivative (+)-laurencin **2**, isolated from the extracts of *Laurencia glandulifera* (Fig. 1). Several strategies have been employed for the stereoselective preparation of racemic[6] and enantioriched[7] *cis*-lauthisan, most of them require multistep synthesis or take place with moderate cis selectivities.

(+)-Isolaurepan **3** is a fully saturated analogue of the core of (+)-isolaurepinnacin **4** and other chiral oxepane derivatives.[8] Kotsuki et al. reported the first total synthesis of (+)-isolaurepan via cis-selective reduction mediated by triethylsilane/$TiCl_4$.[9a] A few more groups have described its formal synthesis by different

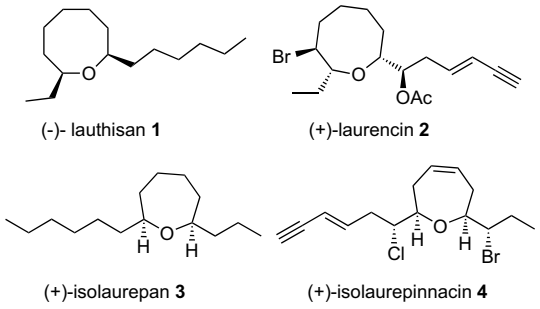

Figure 1.

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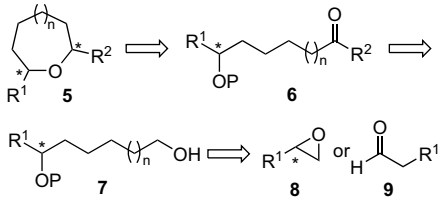
approaches.[10] Although there have been a number of reports on the stereoselective construction of racemic cis-2,7-disubstituted oxepanes, literature describing synthetic strategies for its non-racemic derivatives is rather scarce. Thus development of a general strategy for the enantioselective synthesis of the functionalized medium ring ether skeleton present in many *Laurencia* non-terpenoid metabolites is highly desirable.

As part of our research on the asymmetric synthesis of bioactive molecules,[11] we became interested in developing a general route, which could be useful in the synthesis of a wide variety of functionalized non-racemic cis-disubstituted cyclic ether-based molecules. In our preliminary communication we reported a total synthesis of (+)-isolaurepan **3**.[12] Herein we wish to report a general route to cis-disubstituted cyclic ether-based molecules and its application to the synthesis of (−)-*cis*-lauthisan **1** and (+)-isolaurepan **3** using HKR, oxidative resolution of secondary alcohol, and cis-selective reduction with triethylsilane as the key steps.

2. Results and discussion

Our retrosynthetic approach for the synthesis of cis-disubstituted cyclic ether-based molecule **5** was envisioned via retrosynthetic route as shown in Scheme 1. The hydroxy-keto derivative **6** was visualized as a synthetic intermediate from which (−)-*cis*-lauthisan **1** and (+)-isolaurepan **3** could be synthesized. The hydroxy-keto derivative **6** could be obtained from alcohol **7**, which in turn could be easily synthesized from the enantiomerically pure terminal epoxide **8** or aldehyde **9**.



Scheme 1. Retrosynthetic route to medium-sized ring ethers.

2.1. Synthesis of (−)-lauthisan

The synthesis of (−)-*cis*-lauthisan **1** started from racemic epoxide **10**, which was subjected to Jacobsen's HKR by using (*R*,*R*)-Salen-Co^{III}OAc catalyst (Fig. 2) to give chiral epoxide (*R*)-**10** along with chiral (*S*)-diol **11** as single isomer (Scheme 2).[13] The chiral epoxide (*R*)-**10** was easily isolated from the more polar chiral diol **11** by silica gel column chromatography.

We thought it would be appropriate to convert diol **11** into the required epoxide (*R*)-**10** by means of an internal nucleophilic substitution of a secondary mesylate. Accordingly, the chemoselective pivalation of diol **11** with pivaloyl chloride, followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate product with K_2CO_3 in methanol led to the deprotection of the pivaloyl ester. Concomitant ring closure by intramolecular S_N2 displacement of the mesylate furnished epoxide (*R*)-**10** in 61% overall yield (Scheme 2).

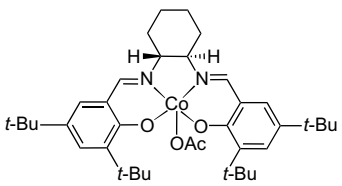
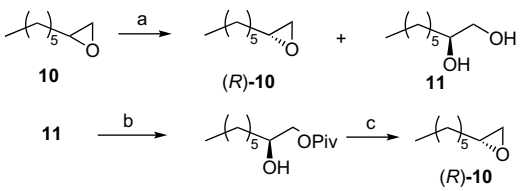
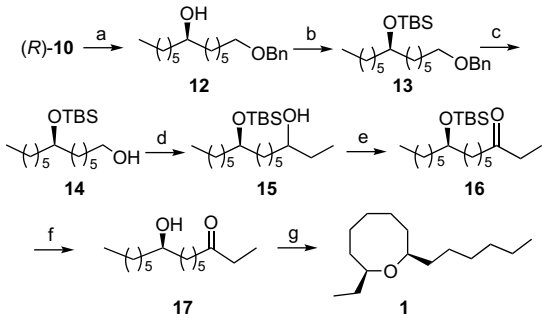


Figure 2. (*R*,*R*)-Salen-Co^{III}OAc complex.



Scheme 2. Reagents and conditions: (a) (*R*,*R*)-Salen-Co-(OAc) (0.5 mol %), dist. H_2O (0.55 equiv), 0 °C, 14 h, 45% for (*R*)-**10**, 43% for **11**; (b) (i) PivCl, Et_3N, cat. DMAP, rt, 2 h; (ii) MsCl, Et_3N, DMAP, 0 °C to rt, 1 h; (c) K_2CO_3, MeOH, rt, overnight (61% for three steps).

With enantiomerically pure epoxide (*R*)-**10** in hand, we subjected it to copper-catalyzed (CuI) regioselective opening with the Grignard reagent, derived from benzyl protected bromopentanol and Mg in THF at −78 °C to obtain alcohol **12** in 72% yield (Scheme 3). Silyl protection of the newly generated secondary alcohol **12** with *tert*-butyldimethylsilyl chloride in the presence of imidazole and catalytic amount of DMAP afforded **13** in 94% yield. Subsequently the terminal benzyl group was deprotected using 20% $Pd(OH)_2/H_2$, which led to compound **14** in excellent yield. Alcohol **14** was subjected to Swern oxidation[14] to give aldehyde which on Grignard reaction with EtMgBr in dry THF at 0 °C furnished compound **15** in 87% yield. Oxidation of free hydroxyl group **15** with IBX (**15**→**16**) and silyl deprotection of **16** by treatment with *p*-TSA in methanol afforded **17** in excellent yield. In order to generate cis-disubstituted cyclic ether, **17** was treated with Et_3SiH and TMSOTf in the next step, which promoted reductive cyclization[9b] to give exclusively the cis-disubstituted cyclic eight-membered ether, (−)-lauthisan **1** as the target compound in 42% yield. The physical and spectroscopic data of **1** were identical with those reported in the literature.[15]

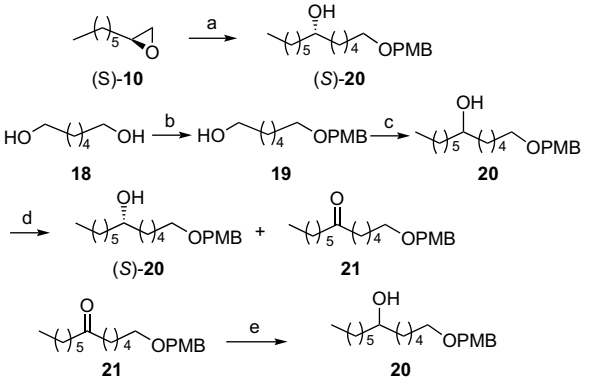


Scheme 3. Reagents and conditions: (a) $C_6H_5CH_2O$-$(CH_2)_5MgBr$, CuI, THF, −78 °C, 2 h, 72%; (b) TBSCl, imidazole, cat. DMAP, dry CH_2Cl_2, 8 h, 0 °C, 94%; (c) 20% $Pd(OH)_2/H_2$, EtOAc, 1 atm, 12 h, 89%; (d) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, −78 °C to −60 °C, 2 h; (ii) *n*-C_2H_5MgBr, THF, 0 °C to rt, 1 h, 87%; (e) IBX, EtOAc, 80 °C, 90%; (f) *p*-TSA, MeOH, rt, 30 min, 96%; (g) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 42%.

2.2. Synthesis of (+)-isolaurepan

Our synthetic strategy for the synthesis of (+)-isolaurepan **3** is shown in Scheme 4. The synthesis started from chiral epoxide (*S*)-**10** prepared from Jacobsen's HKR of the racemic epoxide **10** by using (*S*,*S*)-Salen-Co^{III}Ac complex. The copper-catalyzed (CuI) regioselective opening of chiral epoxide (*S*)-**10** with Grignard reagent derived from *p*-methoxybenzyl protected bromobutanol and Mg in THF gave rise to the required alcohol fragment (*S*)-**20**, albeit in low yield (30%). This prompted us to find another suitable route to this fragment with an improved yield. As illustrated in Scheme 4, the synthesis of this fragment commenced with commercially available 1,6-hexanediol **18**. Thus selective monohydroxyl

protection of **18** with *p*-methoxybenzyl bromide in the presence of NaH gave the monoprotected diol **19** in 85% yield. This was then oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with the Grignard reagent derived from 1-bromohexane and Mg in THF at 0 °C to furnish the racemic alcohol **20** in 91% yield.



Scheme 4. Reagents and conditions: (a) *p*-$CH_3OC_6H_4$-$CH_2O(CH_2)_4MgBr$, CuI, THF, −38 °C, 2 h, 30%; (b) *p*-$CH_3OC_6H_4CH_2Br$, NaH, dry DMF, cat. TBAI, 0 °C to rt, 1 h, 85%; (c) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, −78 °C to −60 °C, 2 h; (ii) *n*-$C_6H_{13}MgBr$, THF, 0 °C to rt, 1 h, 91%; (d) (*S*,*S*)-Salen-Mn^{III}(Cl) (0.02 equiv), KBr (0.8 equiv), $PhI(OAc)_2$ (0.7 equiv), H_2O/CH_2Cl_2 2:1, rt, 30 min., 45% for (*S*)-**20** and 43% for **21**; (e) $NaBH_4$, MeOH, 4 h, 89%.

With substantial amounts of racemic alcohol **20** in hand, our next aim was to resolve this alcohol to obtain enantiomerically pure (*S*)**-20**. As illustrated in Scheme 4, the racemic alcohol **20** was subjected to oxidative resolution[16] using (*S*,*S*)-Salen-Mn^{III}Cl as catalyst (Fig. 3) to give the required optically active alcohol (*S*)-**20** in 45% yield and 93% ee along with the oxidized compound **21** in 43% yield, which was easily isolated from the polar alcohol (*S*)-**20** using silica gel chromatography. Ketone **21** was recycled by conversion into the racemic alcohol **20** in 89% yield by reduction with $NaBH_4$ in MeOH.

As shown in Scheme 5, hydroxyl protection of (*S*)-**20** with *tert*-butyldimethylsilyl triflate in the presence of 2,6-lutidine afforded silyl ether **22** in 85% yield. Subsequent *p*-methoxybenzyl deprotection of the primary alcohol was carried out with DDQ in DCM/H_2O (18:1) to give the required alcohol **23** in 94% yield. Alcohol **23** was oxidized to the corresponding aldehyde by Swern oxidation followed by Grignard reaction with 1-bromopropane and Mg in THF at 0 °C to give the desired compound **24** in 62% yield. The newly formed secondary alcohol was oxidized using IBX to give ketone **25**, which on treatment with *p*-TSA in methanol afforded the required deprotected precursor **26**.

In order to generate the cis-disubstituted cyclic ether, ketone **26** was treated with Et_3SiH and TMSOTf, which promoted reductive cyclization to give exclusively, the cis-disubstituted cyclic seven-membered ether, (+)-isolaurepan **3** in 84% yield. The configuration of the newly generated centers in **3** can be deduced by ^1H NMR and NOE experiments.[9a] The physical and spectroscopic data of **3** were identical with those reported in the literature.[9a]

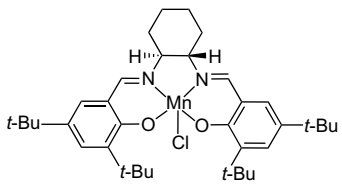
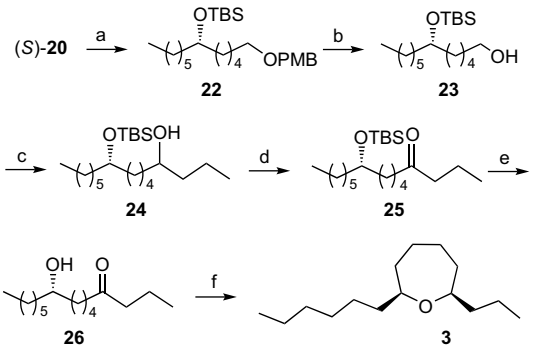
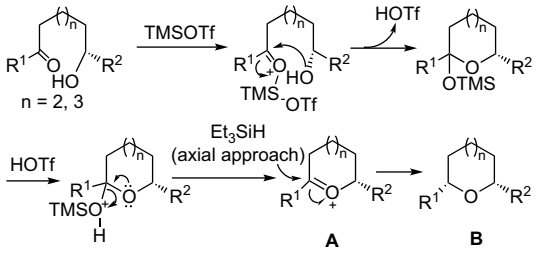


Figure 3. (*S*,*S*)-Salen-Mn^{III} (Cl).



Scheme 5. Reagents and conditions: (a) TBS-OTf, 2,6-lutidine, dry CH_2Cl_2, 30 min, 0 °C, 85%; (b) DDQ, CH_2Cl_2/H_2O (18:1), rt, 1 h, 94%; (c) (i) $(COCl)_2$, DMSO, Et_3N, dry CH_2Cl_2, −78 °C to −60 °C, 2 h, 90%; (ii) *n*-C_3H_7MgBr, THF, 0 °C to rt, 1 h, 62%; (d) IBX, EtOAc, 80 °C; 92% (e) *p*-TSA, MeOH, rt, 30 min; (f) Et_3SiH, TMSOTf, CH_2Cl_2, 0 °C, 1 h, 84%.



Scheme 6. Mechanistic pathway for the reductive cyclization process.

A general possible mechanistic pathway explaining the formation of major cis diastereomer in the cyclization step is shown in Scheme 6. Activation of carbonyl group of the hydroxy ketone by TMSOTf favors the intramolecular nucleophilic addition of the hydroxyl group, which eventually leads to the carboxonium intermediate **A** through an acetal precursor. The axial approach of Et_3SiH[17] to **A**, a seven-membered twist-chair-like transition state (Fig. 4) affording cis diastereomer **B**, is certainly favored because of the higher stability of the resulting chair-like transition state. Similar reasons could explain the major formation of the cis isomer in the case of eight-membered cyclic ether (−)-lauthisan **1**.

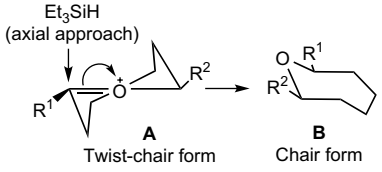


Figure 4. Stereochemical pathway for the reductive cyclization in a seven-membered ring.

3. Conclusions

In conclusion we have developed a new and short approach to cis-disubstituted oxepanes in high enantiomeric excess using Jacobsen Co and Mn and (*R*,*R*)- and (*S*,*S*)-based Salen catalysts. The *R* and *S* configurations of the cis ring can be manipulated simply by changing the catalyst in the resolution step. High yielding reaction steps have been employed. The synthetic strategy described here has significant potential for stereochemical variations and further extension to other stereoisomers and analogues.

4. Experimental

4.1. General methods

Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. Optical rotations were measured using sodium D line on JASCO-181 digital polarimeter. Infrared spectra were recorded on a Perkin–Elmer model 683 grating infrared spectrometer. ^{1}H NMR (200 MHz, 500 MHz) and ^{13}C NMR (50 MHz, 125 MHz) spectra were recorded in $CDCl_3$ solution with residual $CHCl_3$ (=7.27 ppm and =77.00 ppm), respectively, as internal standard. Elemental analyses were carried out on a Carlo Erba CHNS-O analyzer. Petroleum ether of boiling range 60–80 °C was used. Column chromatography was performed on silica gel (60–120 and 100–200 mesh) using a mixture of petroleum ether/ethyl acetate.

4.1.1. 2-Hexyloxirane (R)-**10**

The racemic 2-hexyloxirane **10** was resolved to (*R*)-2-hexyloxirane {(*R*)-**10**} in high enantiomeric excess by the HKR method following a literature procedure.[13] Colorless oil, $[\alpha]_D^{25}$ +13.46 (neat); lit.[13] $[\alpha]_D^{24}$ +14.0 (neat); ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.88 (t, *J*=6.8 Hz, 3H), 1.26–1.51 (m, 10H), 2.44–2.48 (m, 1H), 2.72–2.77 (m, 1H), 2.87–2.93 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9, 22.5, 25.9, 29.1, 31.7, 32.5, 47.1, 52.3.

4.1.2. (R)-1-(Benzyloxy)tridecan-7-ol (**12**)

To a stirred solution of (*R*)-**10** (4.8 g, 37.38 mmol) and CuI (0.306 g, 3.73 mmol) in dry THF (30 mL) was added Grignard reagent prepared from benzyl protected bromopentanol (19.23 g, 74.76 mmol) and Mg-turning (2.72 g, 112.14 mmol) in dry THF, dropwise at −78 °C. The mixture was warmed to −78 °C over 2 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **12** as colorless oil (8.26 g, 72%). $[\alpha]_D^{25}$ +1.85 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) ν=3426, 3011, 2857, 2930, 1712, 1454, 1364, 1277, 1216, 1099, 755 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.90 (t, *J*=6.9 Hz, 3H), 1.29–1.43 (m, 16H), 1.61–1.63 (m, 4H), 3.47 (t, *J*=6.9 Hz, 2H), 3.60–3.63 (m, 1H), 4.51 (s, 2H), 7.27–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 22.5, 25.5, 26.1, 29.3, 29.4, 29.6, 31.7, 70.4, 71.8, 72.8, 127.4, 127.5, 128.3, 138.5. Anal. Calcd for $C_{20}H_{34}O_2$ (306.48): C, 78.38; H, 11.18%. Found: C, 78.52; H, 11.35%.

4.1.3. (R)-(1-(Benzyloxy)tridecan-7-yloxy)(tert-butyl)-dimethylsilane (**13**)

Imidazole (1.59 g, 23.49 mmol) and catalytic amount of DMAP were added to a stirred solution of alcohol **12** (3.2 g, 10.44 mmol) in CH_2Cl_2 (25 mL). *tert*-Butyl dimethylchlorosilane (2.04 g, 13.57 mmol) was then added to this solution at 0 °C, and the reaction mixture was stirred at room temperature for 8 h. After this time, the reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3×30 mL). The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product (petroleum ether/EtOAc 19:1) provided **13** (4.13 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$ +1.35 (*c* 0.92, $CHCl_3$); IR ($CHCl_3$) ν=3018, 2932, 1463, 1361, 1255, 1215, 1092, 1028 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.88–0.92 (m, 12H), 1.27–1.49 (m, 20H), 3.60–3.63 (m, 1H), 3.65 (t, *J*=6.5 Hz, 2H), 4.51 (s, 2H), 7.31–7.37 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−4.4, 14.1, 18.1, 22.6, 25.3, 25.9, 26.2, 26.9, 29.5, 29.7, 31.9, 37.1, 70.5, 72.3, 72.8, 127.4, 127.6, 128.2, 138.6. Anal. Calcd for $C_{26}H_{48}O_2Si$ (420.74): C, 74.22; H, 11.50%. Found: C, 74.35; H, 11.39%.

4.1.4. (R)-7-(tert-Butyldimethylsilyloxy)tridecan-1-ol (**14**)

Compound **13** (4 g) was dissolved in dry EtOAc (10 mL) and 20% $Pd(OH)_2$ (70 mg) was added carefully. The reaction mixture was stirred under an atmosphere of H_2 filled in a balloon for 12 h at room temperature. The mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc/pet ether (18:2) as eluent to give **14** (2.8 g) in 89% yield. $[\alpha]_D^{25}$ +2.92 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) ν=3440, 3018, 2931, 1471, 1361, 1255, 1215, 1049 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.85–0.92 (m, 12H), 1.27–1.49 (m, 20H), 3.65 (t, *J*=6.5 Hz, 2H), 3.60 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−5.4, −4.5, 14.0, 18.1, 22.6, 25.3, 25.6, 25.8, 25.9, 29.4, 31.8, 32.7, 37.1, 62.8, 72.3. Anal. Calcd for $C_{19}H_{42}O_2Si$ (330.62): C, 69.02; H, 12.80%. Found: C, 69.21; H, 12.69%.

4.1.5. (9R)-9-(tert-Butyldimethylsilyloxy)pentadecan-3-ol (**15**)

To a solution of oxalyl chloride (1.13 mL, 12.7 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added dropwise dry DMSO (5.4 mL, 76.22 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **14** (2.8 g, 8.46 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (5.31 mL, 38.11 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was diluted with water (50 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4), and passed through short pad of Celite. The filtrate was concentrated to give the crude aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a stirred solution of the above crude aldehyde was added a solution of Grignard reagent dropwise at 0 °C, prepared from ethyl bromide (1.18 mL, 15.82 mmol) and Mg-turning (0.72 g, 23.73 mmol) in dry THF. The mixture was warmed to rt over 1 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3×30 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **15** as colorless oil (2.64 g, 87%). $[\alpha]_D^{25}$ +3.16 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) ν=3616, 3443, 3019, 2932, 2400, 1463, 1377, 1215, 1049 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.87–0.92 (m, 15H), 1.27–1.52 (m, 22H), 3.50–3.66 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−4.5, 9.8, 14.1, 18.1, 22.6, 25.3, 25.7, 26.0, 29.5, 29.5, 29.9, 30.1, 31.9, 36.9, 37.1, 37.2. Anal. Calcd for $C_{21}H_{46}O_2Si$ (358.67): C, 70.32; H, 12.93%. Found: C, 70.19; H, 12.78%.

4.1.6. (R)-9-(tert-Butyldimethylsilyloxy)pentadecan-3-one (**16**)

To a solution of **15** (2.0 g, 5.57 mmol) in EtOAc (5 mL) in 25 mL R.B. flask was added IBX (4.68 g, 16.72 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give the crude aldehyde **16** (1.78 g) in 90% yield, which was used without any further purification. $[\alpha]_D^{25}$ −2.39 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) ν=2932, 1710, 1462, 1255, 1215, 1051 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.03 (s, 6H), 0.88–0.92 (m, 12H), 1.05 (t, *J*=7.3 Hz, 3H), 1.27–1.38 (m, 18H), 2.40–2.44 (m, 4H) 3.52–3.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−4.5, 7.9, 14.1, 18.1, 22.6, 23.9, 25.1, 25.3, 25.9, 29.5, 31.9, 35.8, 36.8, 37.1, 42.34, 72.2, 211.9. Anal. Calcd for $C_{21}H_{44}O_2Si$ (356.66): C, 70.72; H, 12.43%. Found: C, 70.58; H, 12.61%.

4.1.7. (R)-9-Hydroxypentadecan-3-one (**17**)

To a stirred solution of compound **16** (1.0 g) in MeOH was added a catalytic amount of *p*-TSA at room temperature and the reaction mixture stirred for 30 min at the same temperature. The mixture was filtered through a Celite pad, washed with MeOH, and

concentrated to give **17** (651.8 mg) in 96% yield. $[\alpha]_D^{25}$ −4.92 (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) ν=3421, 3019, 2932, 2858, 2400, 1709, 1461, 1215, 1047 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.05 (t, *J*=7.4 Hz, 3H), 1.28–1.42 (m, 12H), 1.55–1.63 (m, 6H), 2.37–2.48 (m, 4H) 3.56–3.58 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=7.8, 14.0, 22.5, 23.7, 25.3, 25.5, 29.3, 31.7, 35.8, 37.1, 37.4, 42.2, 71.7, 211.9. Anal. Calcd for $C_{15}H_{30}O_2$ (242.40): C, 74.32; H, 12.47%. Found: C, 74.51; H, 12.37%.

4.1.8. (2S,8R)-2-Ethyl-8-hexyloxocane: (+)-cis-lauthisan (**1**)

To a solution of hydroxy ketone **17** (400 mg, 1.65 mmol) in dry CH_2Cl_2 (4 mL), TMSOTf (0.328 mL, 1.81 mmol), followed by Et_3SiH (0.58 mL, 3.63 mmol), was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and quenched with a saturated aqueous solution of NH_4Cl. After workup and flash chromatography (eluent EtOAc/hexane 1:40), pure (−)-*cis*-lauthisan **1** (157 mg) was obtained as a colorless oil, in 42% yield (EtOAc/petroleum ether 1:19). $[\alpha]_D^{24}$ −3.92 (*c* 0.15, $CHCl_3$); lit.[15] $[\alpha]^{20}{}_D$ −4.0 (*c* 0.15, $CHCl_3$); IR ($CHCl_3$) ν=2910, 2860, 1460, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.88 (t, *J*=7.5 Hz, 3H), 0.93 (t, *J*=7.5 Hz, 3H), 1.8–1.2 (m, 22H), 3.35–3.57 (m, 1H), 3.43–3.45 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=10.9, 14.2, 22.7, 24.2, 26.4, 27.2, 29.6, 30.0, 32.0, 33.5, 33.7, 37.1, 79.6, 81.1.

4.1.9. 6-(4-Methoxybenzyloxy) hexan-1-ol (**19**)

To a solution of 1,5-hexanediol **18** (8.0 g, 67.79 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.44 g, 45.76 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (9.55 g, 61.01 mmol) and *tetra-N*-butylammonium iodide (cat.) with further stirring for 1 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) as eluent to furnish the mono-PMB protected alcohol **19** (13.54 g, 85%) as a colorless oil. IR ($CHCl_3$) ν=3402, 3009, 2938, 1718, 1496, 1454, 1216, 1096 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=1.32–1.60 (m, 6H), 3.43 (t, *J*=6.5 Hz, 2H), 3.62 (t, *J*=6.4 Hz, 2H), 3.79 (d, 3H), 4.05–4.13 (m, 1H), 4.42 (s, 1H), 4.61 (s, 1H), 6.84–6.90 (m, 2H), 7.23–7.31 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.4, 20.2, 24.8, 25.2, 28.9, 31.8, 54.5, 113.1, 127.86, 129.9, 132.5, 158.4. Anal. Calcd for $C_{13}H_{20}O_3$ (224.30): C, 69.61; H, 8.99%. Found: C, 69.48; H, 9.12%.

4.1.10. (S)-1-(4-Methoxybenzyloxy)dodecan-6-ols: (S)-**20** and **21**

To a solution of oxalyl chloride (5.60 g, 29.4 mmol) in dry CH_2Cl_2 (100 mL) at −78 °C was added dropwise dry DMSO (6.88 g, 6.2 mL, 88.21 mmol) in CH_2Cl_2 (20 mL). After 30 min, alcohol **19** (7.0 g, 29.40 mmol) in CH_2Cl_2 (20 mL) was added over 10 min giving a copious white precipitate. After stirring for 1 h at −78 °C the reaction mixture was brought to −60 °C and Et_3N (5.72 g, 7.88 mL, 132.32 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was diluted with water (150 mL) and CH_2Cl_2. The organic layer was separated and washed with water and brine, dried (Na_2SO_4), and passed through short pad of Celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

To a stirred solution of the above crude aldehyde in dry THF (50 mL) was added Grignard reagent prepared from a solution of 1-bromohexane (6.08 g, 36.84 mmol) and Mg-turning (0.78 g, 31.93 mmol), dropwise at 0 °C. The mixture was warmed to rt over 1 h and poured into a saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined EtOAc extracts were dried over Na_2SO_4. The extracts were concentrated to near dryness and purified on silica gel column chromatography (EtOAc/petroleum ether, 1:9) to give **20** as colorless oil (7.2 g, 91%).

A mixture of substrate **20** (7.0 g, 21.70 mmol), catalyst (*S,S*)-Salen-Mn^{III} (Cl) (276 mg, 0.43 mmol), additive, KBr (207 mg, 1.73 mmol), CH_2Cl_2 (5 mL), and water (10 mL) was stirred in a 5 mL tube for a few minutes at room temperature. The oxidant $PhI(OAc)_2$ (4.89 g, 15.19 mmol) was added and the mixture was stirred for 30 min until the completion of reaction. The products were extracted by using diethyl ether giving yields as 45% for (*S*)-**20** (3.15 g) and 43% for **21** (3 g). The conversion and ee values were determined by chiral HPLC. The ee was measured by HPLC using a Chiralcel OD column (isopropyl alcohol/petroleum ether=1:99); flow, 1.0 mL/min. Compound (*S*)-**20**: $[\alpha]_D^{25}$ +2.35 (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) ν=3426, 3011, 2857, 2930, 1712, 1454, 1364, 1277, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.89 (t, *J*=6.7 Hz, 3H), 1.22–1.61 (m, 18H), 3.44 (t, *J*=6.4 Hz, 2H), 3.57 (m, 1H), 3.80 (s, 3H), 4.43 (s, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 7.29 (d, *J*=8.7 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 22.5, 25.4, 25.6, 26.2, 29.3, 29.6, 31.8, 37.4, 55.2, 55.2, 69.9, 71.8, 72.4, 113.6, 127.1, 129.2, 130.6, 158.9. Anal. Calcd for $C_{20}H_{34}O_3$ (322.48): C, 74.49; H, 10.63%. Found: C, 74.26; H, 10.85%.

4.1.11. Conversion of compound **21** to **20**

To a solution of **21** (3 g, 10.79 mmol) in EtOH (10 mL) was added $NaBH_4$ (1.22 g, 32.37 mmol). After stirring for 4 h at room temperature, the reaction mixture was quenched with 10% AcOH aqueous solution. After the removal of solvents under reduced pressure, the mixture was added to water (20 mL) and extracted with ether (250 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give a residue, which was purified by silica gel column chromatography to give **20** (2.68 g) in 89% yield.

4.1.12. (S)-tert-Butyl(1-(4-methoxybenzyloxy)dodecan-6-yloxy)dimethylsilane (**22**)

To a stirred solution of alcohol (*S*)-**20** (4.83 g, 3.10 mmol) in CH_2Cl_2 (50 mL) and 2,6-lutidine (0.58 g, 1.08 mL, 5.43 mmol) was added TBS-OTf (1.22 g, 4.65 mmol) at 0 °C and the mixture was stirred at the same temperature for 30 min. The reaction mixture was quenched with water and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave compound **22** as a yellow syrup, 85% yield. $[\alpha]_D^{25}$ +2.85 (*c* 1.4, $CHCl_3$); IR ($CHCl_3$) ν=3018, 2857, 2932, 1463, 1361, 1255, 1215, 1092, 1028, 836, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.87–0.92 (m, 12H), 1.27–1.37 (m, 12H), 1.55–1.60 (m, 6H), 3.44 (t, *J*=6.7 Hz, 2H), 3.59–3.64 (m, 1H), 3.81 (s, 3H), 4.44 (s, 2H), 6.91 (d, *J*=8.8 Hz, 2H), 7.29 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−4.4, 14.1, 18.1, 22.6, 25.2, 25.3, 25.9, 26.4, 29.5, 29.8, 31.9, 37.1, 55.2, 70.1, 72.3, 72.5, 113.7, 129.2, 130.7, 159.1. Anal. Calcd for $C_{26}H_{48}O_3Si$ (436.74): C, 71.50; H, 11.08%. Found: C, 71.68; H, 11.10%.

4.1.13. (S)-6-(tert-Butyldimethylsilyloxy)dodecan-1-ol (**23**)

To a stirring solution of PMB ether **22** (4.8 g, 2.77 mmol) in CH_2Cl_2/H_2O (18:1) was added DDQ (756 mg, 3.33 mmol). The resulting mixture was stirred for 1 h at rt. The mixture was poured into saturated aqueous $NaHCO_3$ and further diluted with CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was then filtered through a pad of Celite and washed with 50% EtOAc/hexane (20 mL). The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column

chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent afforded **23** (3.27 g) as colorless oil in 94% yield. $[\alpha]_D^{25}$ +5.24 (*c* 1.62, $CHCl_3$); IR ($CHCl_3$) ν=3626, 3018, 2857, 2931, 1471, 1361, 1255, 1215, 1049 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.87–0.92 (m, 12H), 1.27–1.37 (m, 12), 1.55–1.60 (m, 6H), 3.44 (t, *J*=6.7 Hz, 2H), 3.59–3.64 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=−4.4, 14.1, 22.7, 25.4, 25.9, 29.6, 30.92, 31.8, 32.2, 37.1, 37.2, 62.8, 72.4. Anal. Calcd for $C_{18}H_{40}O_2Si$ (316.59): C, 68.29; H, 12.73%. Found: C, 68.38; H, 12.61%.

*4.1.14. (9S)-9-(tert-Butyldimethylsilyloxy)pentadecan-4-ol (**24**)*

Compound **24** was prepared following the procedure described for compound **15** in 62% yield as a yellow syrup. $[\alpha]_D^{25}$ +2.08 (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) ν=3616, 3443, 3019, 2932, 2400, 1463, 1377, 1215, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.04 (s, 6H), 0.89 (s, 9H), 0.88 (t, *J*=6.8 Hz, 3H), 0.94 (t, *J*=6.6 Hz, 3H), 1.27–1.32 (m, 14H), 1.39–1.44 (m, 8H), 3.61 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=0.5, 18.6, 18.9, 22.2, 23.0, 27.5, 28.9, 29.9, 30.1, 30.8, 34.4, 36.8, 41.7, 41.9, 47.7, 49.6, 81.6, 81.8, 82.1. Anal. Calcd for $C_{21}H_{46}O_2Si$ (358.67): C, 70.32; H, 12.93%. Found: C, 70.48; H, 12.81%.

*4.1.15. (S)-9-(tert-Butyldimethylsilyloxy)pentadecan-4-one (**25**)*

Compound **25** was prepared following the procedure described for compound **16** in 92% yield as a yellow syrup. $[\alpha]_D^{25}$ +4.0 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) ν=2932, 2400, 1710, 1215, 1051, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.03 (s, 3H), 0.04 (s, 3H), 0.88 (s, 9H), 0.92 (t, *J*=7.4 Hz, 6H), 1.27–1.30 (m, 10H), 1.39–1.41 (m, 4H), 1.59–1.61 (m, 4H), 2.36–2.39 (m, 4H), 3.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=0.5, 18.6, 18.9, 22.2, 23.0, 27.5, 28.9, 29.9, 30.1, 30.8, 34.4, 36.8, 41.7, 41.9, 47.7, 49.6, 81.6, 81.8, 82.1, 216.3. Anal. Calcd for $C_{21}H_{44}O_2Si$ (356.66): C, 70.72; H, 12.43%. Found: C, 70.58; H, 12.61%.

*4.1.16. (2S,7R)-2-Pentyl-7-propyloxepane: (+)-isolaurepan (**3**)*

Compound **3** was prepared following the procedure described for compound **1** in 84% yield as a yellow syrup. $[\alpha]_D^{25}$ +1.5 (*c* 0.97, $CHCl_3$); lit.[7] $[\alpha]_D^{24}$ +1.5 (*c* 0.97, $CHCl_3$); IR ($CHCl_3$) ν=2950, 2920, 2850, 1465, 1455, 1375, 1340,1140, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=0.88 (t, *J*=6.8 Hz, 3H), 0.90 (t, *J*=7.0 Hz, 3H), 1.26–1.44 (m, 10H), 1.47–1.55 (m, 8H), 1.65–1.73 (m, 4H), 3.37–3.39 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=14.0, 19.4, 22.6, 25.3, 26.2, 29.3, 31.8, 36.8, 36.9, 37.4, 39.6, 80.0, 80.3.

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