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Asymmetric dihydroxylation and one-pot epoxidation routes to (+)- and (−)-posticlure: a novel *trans*-epoxide as a sex pheromone component of *Orgyia postica* (Walker)

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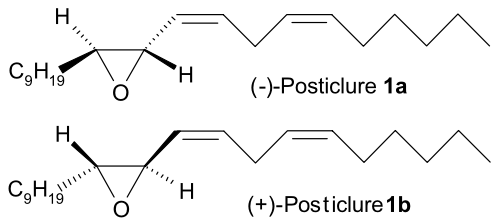
Abstract—A highly enantioselective synthesis of (+)- and (−)-posticlure has been achieved. The synthesis features the Sharpless asymmetric dihydroxylation and one-pot epoxidation as the key steps. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The need for pure enantiomers is particularly apparent in the field of insect pheromone chemistry, since insect chemoreception can be highly stereoselective.[1–3] Optically active epoxides are an important class of natural products commonly encountered as sex attractants of Lepidopteran pests,[4] and self defensive substances against rice blast disease.[5] The advent of Sharpless asymmetric epoxidation (SAE) in 1980[6] dramatically facilitated the synthesis of optically active epoxides.[7] Since then several synthesis of pheromone epoxides such as (+)-disparlure,[8] (3*Z*,6*Z*)-*cis*-9,10-epoxy-3,6-henicosadiene,[8] (6*Z*,9*Z*,3*S*,4*R*)-*cis*-epoxy-6,9-nonadecadiene,[9] (3*Z*,6*Z*)-*cis*-9,10-epoxy-1,3,6-henicosatriene and (3*Z*,6*Z*)-*cis*-9,10-epoxy-1,3,6-icosatriene[10] were reported by employing the SAE reaction. However, there are quite a few methods available for the direct enantioselective epoxidation of olefins bearing no directing functional groups in close proximity to the double bond.[11] In contrast the Sharpless asymmetric dihydroxylation (SAD) of olefins, needless of directing groups has reached a high level of efficiency due to recent advances in reaction conditions and ligands employed.[12] Thus, enantiomeric excesses of greater than 90% can now be achieved with a number of olefins representing four of the six olefin substitution classes. The chiral 1,2-diol provides varied opportunities to achieve different functionalities in asymmetric synthesis.

The diols prepared by the SAD process have recently been used as a precursor for making the *cis*-epoxide in the synthesis of (6*Z*,9*S*,10*R*)-*cis*-9,10-epoxyhenicosa-6-ene,[13] eicosanoid (11*R*,12*S*)-oxidoarachidonic acid,[14] (10*R*,11*S*)-(+)-juvenile hormones I and II.[15] Another recent paper describes the use of asymmetric dihydroxylation route to the synthesis of (3*R*,5*E*)-2,6-dimethyl-2,3-epoxyocta-5,7-diene.[16] Sharpless has reported a simple one-pot sequence for the conversion of vicinal diols into epoxides[17] via halohydrin ester intermediates. This method tolerates a wide range of functionality including acid sensitive functional groups and the transformation proceeds without epimerization even with benzylic substrates in high stereospecificity and yields.



Many mono-epoxy compounds derived from (*Z*)-ene, (*Z*,*Z*)-dienes, (*Z*,*Z*,*Z*)-trienes, and saturated analogues like disparlure, identified as attractant pheromones have a unique and common feature i.e. *cis*-epoxide functionality.[18] No *trans*-epoxide pheromone was known in the literature until Wakamura et al.[19] isolated for the first time, a novel *trans*-epoxide pheromone from the virgin females of the tussock moth, *Orgyia postica* and identified it as (6*Z*,9*Z*,11*S*,12*S*)-*trans*-11,12-epoxyhenicosa-6,9-diene **1a**. This novel *trans*-oxirane pheromone was named 'posticlure' in reference to the species name. The coupling constant of J=2.2 Hz between the epoxide protons confirmed the *trans*-epoxide structure. Wakamura has also reported the synthesis[19] of natural posticlure and its optical antipode by employing the SAE reaction with 59% ee and obtained the pure samples by preparative HPLC. Thus, there is a need for an efficient method to synthesize this pheromone in both large scale and high enantiomeric excess as well.

Keywords: asymmetric synthesis; dihydroxylation; one-pot epoxidation; pheromone; posticlure.

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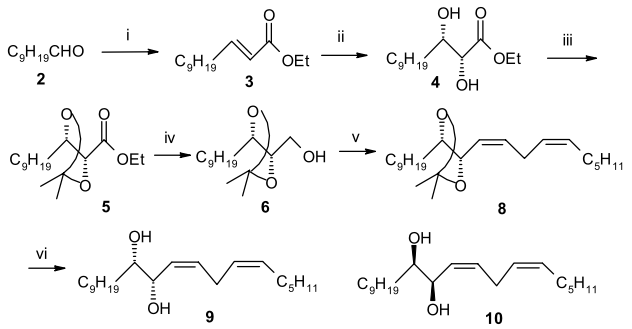


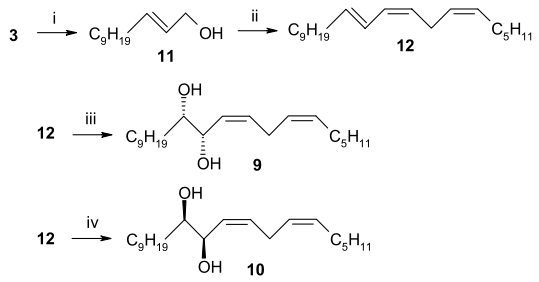
Scheme 1. (i) $Ph_3P{=}CHCO_2Et$, THF, rt, 12 h, 86%; (ii) $(DHQ)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O [1:1], 24 h, 0°C, 94%; (iii) 2,2-DMP, $(CH_3)_2CO$, *p*-TsOH, rt, 8 h, 99%; (vi) $LiAlH_4$, Et_2O, 0°C to rt, overnight, 97%; (v) (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 to −60°C; (b) (*Z*)-$C_5H_{11}CH{=}CHCH_2CH_2P^+Ph_3I^-$ **7**, *n*-BuLi, THF, −80°C, 8 h, 76%; (vi) 3N HCl, MeOH, rt, 12 h, 90%.

As part of our ongoing research aimed at developing enantioselective synthesis of naturally occurring lactones,[20a,b] amino alcohols[20c–e] and diolmycin A2,[20f] we have employed the SAD reaction and the regioselective nucleophilic opening of cyclic sulfites/sulfates as the key steps. Herein we report a highly enantioselective synthesis of the novel first *trans*-epoxide pheromone (+)- and (−)-posticlure by employing the SAD reaction and one-pot epoxidation sequence as the key steps.

2. Results and discussion

The synthesis of target molecule posticlure involves the preparation of enantiomerically pure diols **9** and **10** by employing the SAD reaction and their subsequent one-pot conversion to the *trans*-epoxides via acetoxy bromides. Scheme 1 summarizes our synthesis of the intermediate diol **9**, a precursor for one-pot epoxidation. The commercially available decanal (**2**) was treated with (ethoxycarbonylmethylene)triphenylphosphorane in THF to give the *trans*-Wittig product **3**[21] in 86% yield. The dihydroxylation of olefin **3** with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2$-PHAL ligand under the SAD reaction conditions[12] gave **4** in 94% yield, with $[\alpha]_D^{20}=-10.54$ (*c* 1, $CHCl_3$). The hydroxyl group protection of **4** with 2,2-dimethoxypropane (→**5**) and subsequent ester group reduction with $LiAlH_4$ furnished the primary alcohol **6** in essentially quantitative yield. The enantiomeric purity of greater than 99% ee for **6** was determined by preparing the corresponding Mosher's ester and analyzing the ^{19}F NMR spectrum. Compound **6** was oxidized to the aldehyde under the normal Swern oxidation conditions which on subsequent Wittig reaction with **7** furnished the (*Z*,*Z*)-diene **8** in 76% yield. Deprotection of acetonide **8** was effected with 3N HCl in MeOH to give the desired diol **9** in 90% yield. The enantiomer of **9** i.e **10** was synthesized by employing the $(DHQD)_2$-PHAL ligand in SAD reaction on **3** and following the same reaction sequence as shown in Scheme 1.

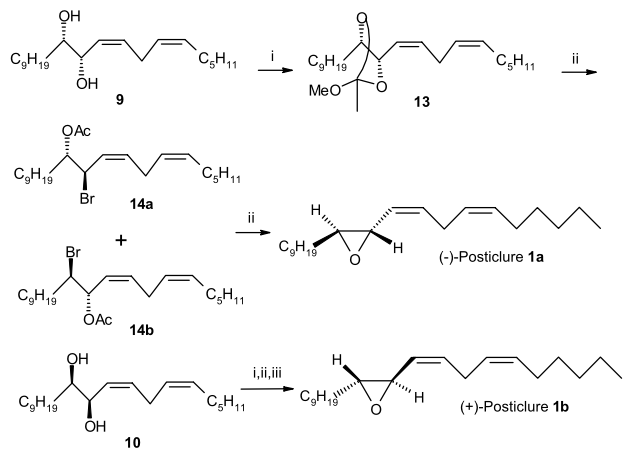
It is known that under the heterogeneous ferricyanide conditions, the SAD reaction may be controlled to selectively produce ene diols from conjugated polyenes.[22] The regioselectivity of mono-dihydroxylation is determined



Scheme 2. (i) DIBAL-H, Et_2O, 0°C, 0.5 h, 90%; (ii) (a) PCC, CH_2Cl_2, rt, 8 h. (b) (*Z*)-$C_5H_{11}CH{=}CHCH_2CH_2P^+Ph_3I^-$ **7**, LiHMDS, THF, −80°C, 8 h, 74%; (iii) $(DHQ)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O [1:1], 10 h, 0°C, 78%; (iv) $(DHQD)_2$-PHAL, OsO_4, $MeSO_2NH_2$, $K_3Fe(CN)_6$, K_2CO_3, *t*-BuOH/H_2O [1:1], 10 h, 0°C, 79%.

both by electronic and steric effects. It has been shown that the rate constants of the dihydroxylation of isolated double bonds are much larger with *trans*-1,2-disubstituted and trisubstituted olefins than with *cis*-1,2-disubstituted and terminal olefins.[23] Taking advantage of *trans*-olefin dihydroxylation to be faster than the *cis*-olefin, we thought of preparing compounds **9** and **10** via an alternative approach by employing selective mono-dihydroxylation of the *trans*-olefin bond of a (*Z*,*Z*,*E*)-triene system like **12**. Toward this end, the synthesis of (*Z*,*Z*,*E*)-triene (**12**) was attempted starting from the *trans*-olefin (**3**) and using the Wittig approach as illustrated in Scheme 2. Thus, the DIBAL-H reduction of the ester **3** afforded the allylic alcohol **11**[13] in 90% yield which on PCC oxidation followed by the Wittig reaction of the corresponding aldehyde with **7** furnished the (6*Z*,9*Z*,11*E*)-triene **12** in 74% yield. The triene **12** was subjected to the dihydroxylation reaction with osmium tetroxide (0.2 mol%) and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2$-PHAL ligand (1 mol%) under the SAD reaction conditions to give the diol **9**[24] in 78% yield. Similarly compound **10**[24] was obtained from **12** by SAD reaction using $(DHQD)_2$-PHAL ligand in 79% yield.

With the enantiomerically pure diols **9** and **10** in hand we then proceeded with the synthetic strategy (Scheme 3) to install the *trans*-epoxide moiety. While a variety of methods have been developed for making the *cis*-epoxide[13–15] from diols, prepared by the SAD process, the literature describing



Scheme 3. (i) $CH_3C(OMe)_3$, *p*-TsOH (cat), CH_2Cl_2, rt, 30 min; (ii) CH_3COBr, CH_2Cl_2, rt, 4 h; (iii) K_2CO_3, MeOH, rt, 4 h, 86–88% overall.

a one-pot method for the *trans*-epoxide[25] is rather scarce. We have employed a one-pot synthetic approach[17] for preparing the *trans*-epoxide from enantiomerically pure diols **9** and **10** via acetoxy bromides as illustrated in Scheme 3. Thus, the treatment of diol **9** with trimethylorthoacetate in the presence of catalytic amount of *p*-TsOH at room temperature followed by subsequent removal of the volatiles gave the cyclic orthoester **13**. The subsequent treatment of compound **13** with 1.3 equiv. of acetyl bromide afforded a mixture of virtually pure acetoxy bromides **14a** and **b**. Base mediated ester saponification with K_2CO_3 in dry MeOH resulted in concomitant cyclization to furnish the *trans*-epoxide, (−)-posticlure **1a**, $[\alpha]_D^{20}=-11.1$ (*c* 1, $CHCl_3$) in 88% yield.

This stereospecific one-pot epoxidation sequence involved the first inversion at the bromide-receiving center followed by a second inversion at the bromide-leaving center to give the *trans*-epoxide. Thus, this transformation resulted in overall retention of configuration and therefore the regioselectivity of the acetyl bromide formation is immaterial. The unnatural antipode was synthesized following the above one-pot epoxidation sequence on **10** to give (+)-posticlure **1b**, $[\alpha]_D^{20}=+11.33$ (*c* 1, $CHCl_3$) in 86% yield.

3. Conclusion

In summary we have employed an alternative sequence of reaction to SAE involving a two-step process, SAD and stereospecific one-pot epoxidation. Although two steps, it is much compatible in terms of both yields and enantioselectivity. Thus, a highly enantioselective synthesis of a novel first *trans*-epoxide pheromone posticlure has been achieved. This alternative route will provide an easy excess to the large-scale synthesis of posticlure, both (+)- and (−)-isomers for biological studies and pest control.

4. Experimental

4.1. General information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80°C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO P-1020 microprocessor based polarimeter. Infrared spectra were recorded on ATI MATTSON RS-1 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer or otherwise indicated. Mass spectra were obtained with a TSQ 70, Finningen MAT mass spectrometer. Elemental analyses were carried on a Carlo Erba CHNS-O analyzer.

4.1.1. (2*E*)-Ethyl dodec-2-enoate (3). To a solution of (ethoxycarbonylmethylene) triphenylphosphorane (12.2 g, 35 mmol) in dry THF (100 mL) was added decanal **2** (5 g, 32 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 12 h and then concentrated. To the residue was added ether and the precipitated solids of triphenylphosphine oxide were filtered off and washed with ether. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) to give **3** (6.23 g, 86%) as a colorless oil. Spectroscopic data are in consistence with the literature data.[21]

4.1.2. (2*R*,3*S*)-Ethyl-2,3-dihydroxydodecanoate (4). To a mixture of $K_3Fe(CN)_6$ (13.06 g, 39.76 mmol), K_2CO_3 (5.49 g, 39.76 mmol) and $(DHQ)_2$-PHAL (104 mg, 0.133 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 140 mL) cooled at 0°C was added osmium tetroxide (536 μL, 0.1 M solution in toluene, 0.4 mol%) followed by methanesulfonamide (1.26 g, 13.25 mmol). After stirring for 5 min at 0°C, the olefin **3** (3 g, 13.25 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 24 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5×30 mL). The combined organic phases were washed with 10% aq KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave **4** (3.24 g, 94%) as a white solid; mp 52–53°C; $[\alpha]_D^{20}=-10.54$ (*c* 1, $CHCl_3$); IR ($CHCl_3$): ν_{max} 3377, 1736, 1460 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, *J*=7 Hz, 3H), 1.2–1.3 (m, 14H), 1.31 (t, *J*=8 Hz, 3H), 1.52–1.59 (m, 2H), 3.06 (br s, 2H), 3.84 (br t, *J*=6 Hz, 1H), 4.0–4.1 (m, 1H), 4.24 (q, *J*=8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.81, 13.82, 22.38, 25.54, 29.07, 29.33 (overlapping 3C), 31.64, 33.29, 61.41, 72.44, 73.25, 173.45; EIMS *m*/*z* (%): 187 [M^+-CO_2Et] (3.3), 157 (1.4), 133 (2.4), 104 (100), 95 (4.7), 76 (88.4), 55 (23.1). Anal. Calcd for $C_{14}H_{28}O_4$ (260.37): C, 64.58; H, 10.84. Found: C, 64.66; H, 10.71.

4.1.3. (2*R*,3*S*)-Ethyl-2,3-*O*-isopropylidenedodecanoate-2,3-diol (5). To a solution of the diol **4** (5 g, 19.2 mmol), *p*-TsOH (cat) in acetone (100 mL) was added 2,2-dimethoxypropane (4 g, 38.4 mmol) and stirred at room temperature for 8 h. Solid $NaHCO_3$ (1 g) was added and stirred for 30 min. The reaction mixture was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the residue using petroleum ether/EtOAc (24:1) gave **5** (5.71 g, 99%) as a colorless liquid; $[\alpha]_D^{20}=-15$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1758, 1460, 1376, 1097 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.85 (t, *J*=7 Hz, 3H), 1.2–1.26 (m, 14H), 1.30 (t, *J*=7.5 Hz, 3H), 1.41 (s, 3H), 1.43 (s, 3H), 1.60–1.70 (m, 2H), 4.06–4.10 (m, 2H), 4.23 (q, *J*=7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 13.5, 13.52, 22.08, 25.02 (overlapping 2C), 26.57, 28.74, 28.96 (overlapping 3C), 31.35, 33.04, 60.31, 78.69, 78.7, 109.97, 170.18; EIMS *m*/*z* (%): 285 [M^+-15] (100), 271 (4.8), 227 (29.3), 197 (2.7), 144 (17), 109 (15), 95 (38.1), 69 (22.4), 59 (59.2), 55 (40.8). Anal. Calcd for $C_{17}H_{32}O_4$ (300.43): C, 67.96; H, 10.73. Found: C, 67.88; H, 10.93.

4.1.4. (2*S*,3*S*)-2,3-*O*-Isopropylidenedodecane-1,2,3-triol (6). To a stirred suspension of $LiAlH_4$ (0.615 g, 16.2 mmol) in dry Et_2O (100 mL) at 0°C was added the solution of **5** (3.25 g, 10.81 mmol) in Et_2O (10 mL) dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight. Excess $LiAlH_4$ was destroyed by slow addition of 10% aq NaOH (2 mL) and EtOAc (20 mL). The white precipitate was filtered through

a pad of neutral alumina and washed with MeOH (3×100 mL). The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1) as eluent to give **6** (2.71 g, 97%) as a colorless oil; $[\alpha]_D^{20}=-21.16$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3460, 1462, 1378, 1246 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, *J*=7.5 Hz, 3H), 1.2–1.35 (m, 14H), 1.38 (s, 6H), 1.49–1.54 (m, 2H), 2.58 (s, 1H), 3.54–3.60 (m, 1H), 3.69–3.73 (m, 2H), 3.78–3.84 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 13.52, 22.16, 25.5, 26.53, 26.86, 28.85, 29.07, 29.25 (overlapping 2C), 31.42, 32.82, 61.89, 77.00, 81.45, 107.95; EIMS *m/z* (%): 243 [M^+-15] (97.4), 227 (21.7), 155 (1.6), 109 (17.8), 95 (28.3), 81 (19), 69 (19), 59 (100), 55 (44). Anal. Calcd for $C_{15}H_{30}O_3$ (258.4): C, 69.72; H, 11.70. Found: C, 69.63; H, 11.82.

4.1.5. (3*Z*)-Non-3-ene-triphenylphosphoniumiodide (7). To a solution of triphenylphosphine (13.72 g, 52.3 mmol) in dry CH_2Cl_2 (50 mL) was added iodine (13.27 g, 52.3 mmol). The orange precipitate was stirred for 30 min and a solution of *cis*-3-nonen-1-ol (6.2 g, 43.58 mmol) and imidazole (3.56 g, 52.3 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1.5 h and then CH_2Cl_2 was evaporated. The residue was diluted with water and the solution was extracted with EtOAc (3×50 mL). The combined organic extracts were washed with 20% aq $Na_2S_2O_3$, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/ether (9.8:0.2) to give *cis*-3-nonen-1-iodide (10.77 g, 98%) as a colorless oil; IR (neat): ν_{max} 1648, 1457 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88 (t, *J*=7 Hz, 3H), 1.25–1.35 (m, 6H), 1.97–2.04 (m, 2H), 2.65 (dd, *J*=8, 6 Hz, 2H), 3.14 (t, *J*=7 Hz, 2H), 5.34 (dt, *J*=11, 6 Hz, 1H), 5.55 (dt, *J*=11, 6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 5.18, 13.96, 22.41, 27.30, 29.07, 31.35 (overlapping 2C), 127.62, 132.47; EIMS *m/z* (%): 252 [M^+] (1.6), 155 (2.6), 127 (5.9), 83 (29.4), 69 (71.2), 55 (100).

To a solution of triphenylphosphine (10.4 g, 39.65 mmol) in dry benzene (50 mL) was added the above iodide (10 g, 39.65 mmol) and the solution refluxed for 24 h. The reaction mixture was cooled to room temperature and benzene removed under reduced pressure. The sticky solid was triturated with dry Et_2O to remove unreacted starting materials. The residue was dried under high vacuum to a white sticky solid of (3*Z*)-non-3-ene-triphenylphosphonium-iodide **7**[19] (19.4 g, 95%) and was used as such immediately.

4.1.6. (6*Z*,9*Z*,11*S*,12*S*)-11,12-*O*-Isopropylidenehenicosa-6,9-diene (8). To a solution of oxalyl chloride (5.89 g, 4.05 mL, 46.42 mmol) in dry CH_2Cl_2 (250 mL) cooled at −78°C was added dropwise DMSO (6.6 mL, 92.84 mmol) in CH_2Cl_2 (15 mL) over 20 min. The reaction mixture was stirred for 30 min at −78°C and the solution of alcohol **6** (8 g, 30.95 mmol) in CH_2Cl_2 (15 mL) was added dropwise at −60°C over 20 min. The reaction mixture was stirred for 30 min when a copious white precipitate was obtained. Et_3N (16 mL) was added dropwise and stirred for 1 h allowing the temperature to rise to room temperature. The reaction mixture was quenched with 2% aq HCl (200 mL) and the new phase extracted with EtOAc. The combined organic phases were washed (brine), dried (Na_2SO_4) and concentrated to give the crude aldehyde, which was used in the next step without further purification.

To a stirred suspension of the Wittig salt **7** (19.4 g, 37.7 mmol) in dry THF (100 mL) was added *n*-BuLi (20 mL, 40 mmol, 2 M in hexane) dropwise at 0°C. The reaction mixture was stirred till all solids dissolved (30 min). To the dark red solution was added the above aldehyde in dry THF (20 mL) dropwise at −80°C. The reaction mixture was stirred for 8 h at −80°C and then allowed to warm to room temperature. It was quenched with sat. aq NH_4Cl and extracted with EtOAc (3×50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/-EtOAc (9:1) as eluent to give **8** (8.58 g, 76%) as a colorless oil; $[\alpha]_D^{20}=-8.37$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 1723, 1464, 1378, 1221, 1052 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85–0.92 (m, 6H), 1.2–1.35 (m, 20H), 1.42 (s, 3H), 1.43 (s, 3H), 1.51–1.53 (m, 2H), 2.00–2.07 (m, 2H), 2.83–2.92 (m, 2H), 3.64–3.70 (m, 1H), 4.4 (t, *J*=8 Hz, 1H), 5.3–5.5 (m, 3H), 5.7 (dt, *J*=8, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.8, 13.81, 22.3, 22.45, 25.83, 25.98, 26.83, 27.01 (overlapping 2C), 29.1, 29.33 (overlapping 3C), 29.55, 31.27, 31.68 (overlapping 2C), 76.38, 80.68, 107.91, 126.45, 126.51, 130.63, 133.57; EIMS *m/z* (%): 364 [M^+] (1.3), 349 [M^+-15] (11), 289 (2.6), 208 (11.3), 155 (9.7), 97 (92.3), 80 (51.6), 69 (40.3), 55 (100). Anal. Calcd for $C_{24}H_{44}O_2$ (364.61): C, 79.06; H, 12.16. Found: C, 79.32; H, 11.88.

4.1.7. (6*Z*,9*Z*,11*S*,12*S*)-11,12-Dihydroxyhenicosa-6,9-diene (9). To a solution of **8** (2.6 g, 7.13 mmol) in MeOH (50 mL) was added 3N HCl (6 mL) and stirred at room temperature for 12 h. Excess HCl was quenched by adding solid $NaHCO_3$ and the reaction mixture diluted with water (50 mL). The solution was extracted with EtOAc (4×50 mL), washed (brine), dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the residue with petroleum ether/EtOAc (3:2) as eluent gave **9** (2.09 g, 90%) as a colorless syrup; $[\alpha]_D^{20}=-5.93$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 3384, 1723, 1714, 1465, 1067 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85–0.90 (m, 6H), 1.2–1.35 (m, 22H), 2.00–2.07 (m, 2H), 2.34 (br s, 2H), 2.84–2.91 (m, 2H), 3.4–3.5 (m, 1H), 4.23 (t, *J*=8 Hz, 1H), 5.34–5.46 (m, 3H), 5.61 (dt, *J*=8, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.81, 13.82, 22.49 overlaping 2C), 25.69, 26.16, 27.05, 29.10 (overlapping 2C), 29.51 (overlapping 3C), 31.31, 31.75, 32.67, 70.9, 74.79, 126.66, 129.12, 130.63, 131.84; EIMS *m/z* (%): 324 [M^+] (1.7), 306 (8.7), 290 (3.3), 213 (11.4), 157 (17.4), 97 (27.5), 83 (65.7), 69 (53.7), 57 (100). Anal. Calcd for $C_{21}H_{40}O_2$ (324.54): C, 77.72; H, 12.42. Found: C, 77.98; H, 12.26.

4.1.8. (2*E*)-Dodec-2-ene-1-ol (11). To a solution of **3** (2 g, 8.83 mmol) in dry Et_2O (70 mL) at 0°C was added dropwise DIBAL-H (19.5 mL, 19.5 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 0.5 h, then recooled to 0°C and treated with 1N HCl (50 mL). The resulting gel was dissolved by dropwise addition of 6N HCl. The ethereal phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with sat. aq $NaHCO_3$, dried (Na_2SO_4), filtered and

concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **11** (1.47 g, 90%) as a colorless oil. Spectroscopic data are in consistence with the literature data.[13]

4.1.9. (6*Z*,9*Z*,11*E*)-Henicosatriene (12). To a stirred suspension of PCC (11.76 g, 54.55 mmol) and powdered molecular sieves (3 Å, 4 g) in dry CH_2Cl_2 (200 mL) was added **11** (6.7 g, 36.35 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 8 h and then concentrated. The residue was triturated with ether and filtered through a pad of celite and washed with ether (3×50 mL). The filtrate was concentrated to give virtually pure aldehyde (5.62 g, 85%) as colorless oil. This was used as such in subsequent reaction.

To a suspension of the Wittig salt **7** (19.4 g, 37.7 mmol) in dry THF (100 mL) was added LiHMDS (45 mL, 45 mmol, 1 M solution in THF) dropwise at 0°C. The reaction mixture was stirred till all solids dissolved (30 min). To the dark red solution was added the above aldehyde in dry THF (20 mL) dropwise at −80°C. The reaction mixture was stirred for 8 h at −80°C and then allowed to warm to room temperature. It was quenched with sat. aq NH_4Cl and extracted with EtOAc (3×50 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/ether (99:1) as eluent to give **12** (7.81 g, 74%) as a colorless oil; IR (neat): ν_{max} 1680, 1642, 1465 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84–0.93 (m, 6H), 1.25–1.3 (m, 20H), 2.01–2.22 (m, 6H), 5.38–5.63 (m, 4H), 5.94–6.10 (m, 1H), 6.24 (dd, J=15, 4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.96, 14.07, 22.27, 22.78, 29.36, 29.47, 29.66 (overlapping 3C), 31.53, 32.01, 32.34, 32.71, 33.00, 34.8, 125.81, 128.98, 129.49, 130.48, 130.81, 134.53; EIMS *m*/*z* (%): 290 [M^+] (3.3), 247 (1.3), 193 (2.6), 109 (14.4), 95 (34.6), 81 (56.2), 67 (100), 55 (78.4). Anal. Calcd for $C_{21}H_{38}$ (290.53): C, 86.81; H, 13.18. Found: C, 87.01; H, 12.98.

4.1.10. Monodihydroxylation of triene 12 to 9. To a mixture of $K_3Fe(CN)_6$ (3.4 g, 10.33 mmol), K_2CO_3 (1.43 g, 10.33 mmol) and $(DHQ)_2$-PHAL (27 mg, 0.0344 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 40 mL) cooled at 0°C was added osmium tetroxide (68 μL, 0.1 M solution in toluene, 0.2 mol%) followed by methanesulfonamide (0.327 g, 3.44 mmol). After stirring for 5 min at 0°C, the triene **12** (1 g, 3.44 mmol) was added in one portion. The reaction mixture was stirred at 0°C for 10 h and then quenched with solid sodium sulfite (5 g). The stirring was continued for an additional 45 min and then the solution was extracted with EtOAc (5×30 mL). The combined organic phases were washed with 10% aq KOH, brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave **9** (0.87 g, 78%) as colorless syrup; $[\alpha]_D^{20}=-5.69$ (*c* 1, $CHCl_3$).

4.1.11. (−)-Posticlure (1a). To a solution of diol **9** (0.8 g, 2.46 mmol), and *p*-TsOH (8 mg) in dry CH_2Cl_2 (5 mL) was added trimethylorthoacetate (0.385 g, 3.2 mmol) and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residual methanol was removed under high vacuum. The residue was taken in CH_2Cl_2 (5 mL) and acetyl bromide (0.237 mL, 3.2 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 4 h and concentrated to give a mixture of virtually pure acetoxy bromides **14a** and **b**: ^1H NMR ($CDCl_3$): δ 0.85–0.91 (m, 6H), 1.2–1.35 (m, 20H), 1.62–1.7 (m, 2H), 2.03–2.85 (m, 2H), 2.09 (s, 3H), 2.87 (br t, J=7 Hz, 2H), 4.91–4.98 (m, 1H), 5.06–5.2 (m, 1H), 5.4–5.75 (m, 4H); EIMS *m*/*z* (%): 429 [M^+] (0.3), 369 (0.7), 349 (0.5), 307 (6.6), 289 (11.9), 195 (4.6), 155 (15.5), 109 (13.2), 95 (29.8), 81 (47.7), 67 (56.3), 55 (100).

To a solution of the mixture of **14a** and **b** in dry MeOH (4 mL) was added powdered K_2CO_3 (0.443 g, 3.2 mmol) and the mixture was stirred for 4 h at room temperature. The reaction mixture was filtered through a pad of neutral alumina and the pad washed with Et_2O (3×50 mL). The filtrate was concentrated and the residue purified by silica gel column chromatography using petroleum ether/ether (9:1) as eluent to give **1a** (0.665 g, 88%) as a colorless oil; $[\alpha]_D^{20}=-11.1$ (*c* 1, $CHCl_3$); IR (neat): ν_{max} 2956, 1725, 1708, 1465, 1389 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.85–0.90 (m, 6H), 1.2–1.45 (m, 20H), 1.56–1.62 (m, 2H), 2.04–2.09 (m, 2H), 2.80–2.84 (dt, J=2.1 Hz, 1H), 2.97 (dd, J=7.1, 7.5 Hz, 2H), 3.36 (dd, J=2.1, 8.7 Hz, 1H), 5.08 (ddd, J=8.7, 10.8 Hz, 1H), 5.37 (dtt, J=7.1, 10.7 Hz, 1H), 5.44 (dtt, J=7.5, 10.7 Hz, 1H), 5.67 (dt, J=7.5, 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.74, 13.75, 22.3, 22.41, 25.76, 26.94, 29.07 (overlapping 2C), 29.21, 29.33 (overlapping 3C), 31.24, 31.64, 31.82, 53.77, 59.5, 126.59, 127.28, 130.59, 133.53; EIMS *m*/*z* (%): 306 [M^+] (15), 290 (3.4), 235 (1.4), 209 (2), 195 (17), 179 (4.1), 155 (16.3), 136 (8.1), 109 (12.2), 95 (32), 79 (76.8), 71 (47.6), 67 (58.5), 55 (100). Anal. Calcd for $C_{21}H_{38}O$ (306.53): C, 82.28; H, 12.49. Found: C, 82.32; H, 12.43.

4.1.12. (+)-Posticlure (1b). Prepared by following the same procedure as described for compound **1a**. Yield 86%; colorless oil; $[\alpha]_D^{20}=+11.33$ (*c* 2, $CHCl_3$).

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