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Enantio- and Diastereocontrolled Total Synthesis of (+)-Strictifolione

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A concise and practical enantioselective synthesis of (+)-strictifolione has been achieved in high diastereomeric excess using Jacobsen's hydrolytic kinetic resolution, proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehyde and cross olefin/ring-closing metathesis as the key steps.

Introduction

Optically active *syn*- and *anti*-1,3-polyols/5,6-dihydropyran-2-ones are ubiquitous structural motifs in various biologically active compounds. The α,β-unsaturated δ-lactone[1] functionality is presumed to be responsible for biological activities as a result of its ability to act as a Michael acceptor, enabling these molecules to bind to a specific target enzyme. The pyrone units are widely distributed in all parts of plants (Lamiaceae, Piperaceae, Lauraceae, and Annonaceae families) including leaves, stems, flowers and fruits. (+)-Strictifolione (1) (Figure 1) has been isolated by Aimi et al. from the stem bark of *Cryptocaria strictifolia* in West Kalimantan, Indonesia.[2]

The main structural features of (+)-strictifolione (**1**) are an *anti*-1,3-diol and a 6-substituted 5,6-dihydro-α-pyrone[3] subunit, which are also present in polyene macrolides[4] and the leptomycin family[5] of natural products, respectively. While the relative stereochemistry of the 1,3-diol function at C4′ and C6′ was elucidated from the ^{13}C NMR spectrum of the acetonide derivative, configurations of their stereogenic centers were deduced by the Mosher method. The absolute configuration at C6 was assumed on the basis of the Cotton effect in the CD spectrum and confirmed by the

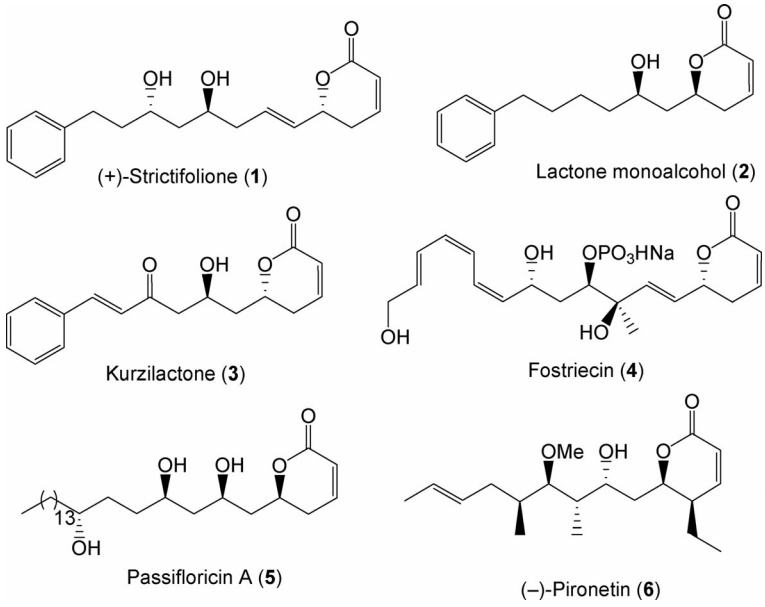

Figure 1. Examples of *anti*- and *syn*-1,3-polyol/5,6-dihydropyran-2-ones natural products.

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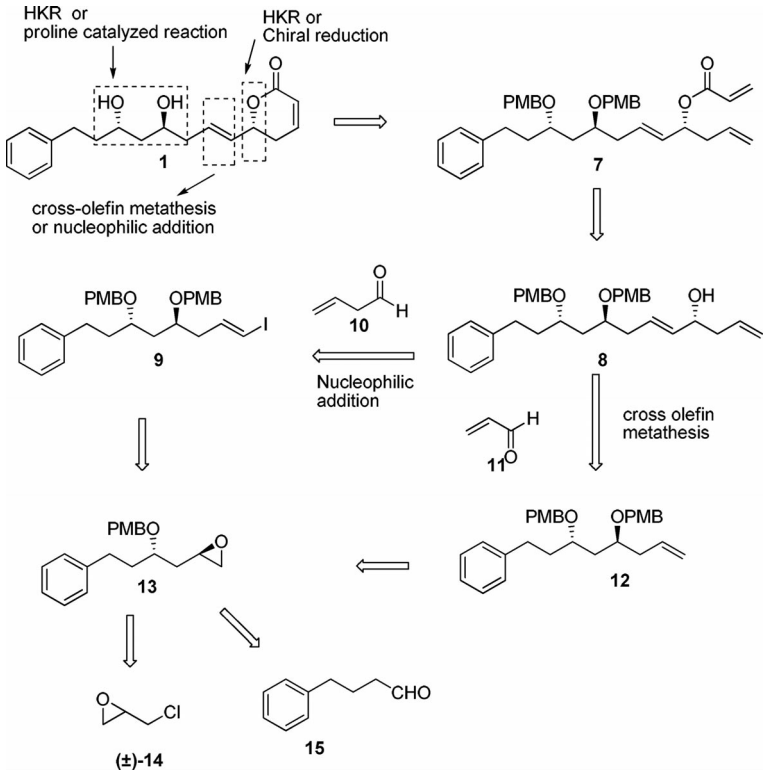
synthesis of the two isomers at C6 with the (*R*)- and (*S*)-configurations. A number of 5,6-dihydro-α-pyrone derivatives having an alkyl side chain at the C6 position with 1,3- or 1,5-diol units have been isolated from plants. Some of these compounds such as lactone monoalcohol (**2**)[6] and passifloricin A (**5**)[7] have been found to exhibit antifungal activity. (–)-Pironetin (**6**)[8], an immunosuppressive agent, is known to inhibit cell-cycle progression in the M-phase. Kurzilactone (**3**)[9] and fostriecin (**4**)[10] are cytotoxic and anticancer agents, respectively.

Various methods for the synthesis of (+)-strictifolione have been reported in the literature.[11] Takayama et al.[11a] reported the first synthesis of **1** from chiral pool starting materials such as malic acid and (*S*)-glycidol and determined its relative and absolute configuration. Later a carbohydrate-based approach was utilised to accomplish the total synthesis of target molecule.[11b] Very recently Yadav et al. have reported its synthesis from chiral pool starting material and using Prins cyclization as the key step.[11c] Asymmetric synthesis reported so far for strictifolione is mainly based on enantioselective allyltitanations,[11d] SAMP-hydrazone α,α′-bisalkylation/deoxygenation protocol,[11e] and Sm-BINOL-Ph_3As=O (1:1:1) complex catalyzed epoxidation.[11f] As a part of our research program aimed at developing enantioselective synthesis of naturally occurring lactones,[12] we became interested in devising a simple and practical route to (+)-strictifolione (**1**). Herein we report our successful endeavors towards the total synthesis of **1** from achiral substrate employing iterative Jacobsen's hydrolytic kinetic resolution,[13] proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehyde[14] and BINAL-H-mediated reduction[15] as the source of chirality.

Results and Discussion

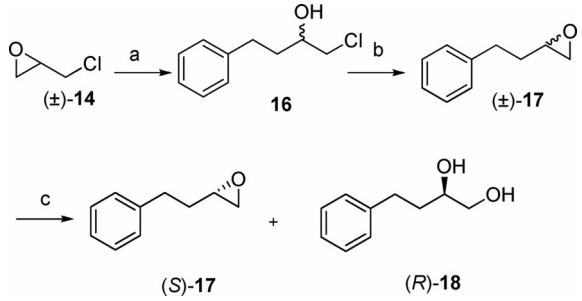
Our synthetic strategy for the synthesis of **1** is outlined in Scheme 1. We envisioned that the lactone ring could be constructed by the ring-closing metathesis of an acrylate ester **7**, which in turn could be obtained from homoallylic alcohol **8**. Homoallylic alcohol could be derived either from **12** via olefin cross-metathesis with acrolein **11**, or from vinylic iodide **9** by chiral reduction. Vinylic iodide **9** and olefin **12** could be derived from terminal acetylene via nucleophilic addition and partial hydrogenation, respectively. Initial two stereogenic centers can easily be established by iterative hydrolytic kinetic resolution from commercially available epichlorohydrin (±)-**14** or by using proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehyde **15**.

In designing a route to **1**, we chose epichlorohydrin as an appropriate starting material. Our synthesis of **1** requires five major reactions that include Jacobsen's hydrolytic kinetic resolution, proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons (HWE) olefination of aldehyde, BINAL-H-mediated chiral reduction, asymmetric allylation using Brown's protocol to install the stereogenic centers, and ring-closing metathesis to construct the δ-lactone moiety.



Scheme 1. Retrosynthetic route to (+)-strictifolione.

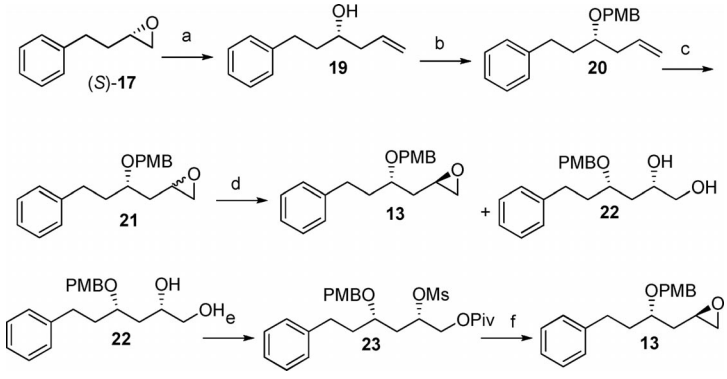
As shown in Scheme 2, commercially available epichlorohydrin (±)-**14** was treated with benzylmagnesium bromide to give the chlorohydrin **16**, which was subsequently treated with pulverized KOH in diethyl ether to furnish the *rac*-epoxide (±)-**17** in essentially quantitative yield. Jacobsen's hydrolytic kinetic resolution of *rac*-epoxide (±)-**17** with (*S*,*S*)-Salen-Co-OAc catalyst gave (*S*)-epoxide (*S*)-**17**[16] as a single isomer in excellent yield, which was easily isolated from the more polar diol (*R*)-**18**[16] by silica gel column chromatography.



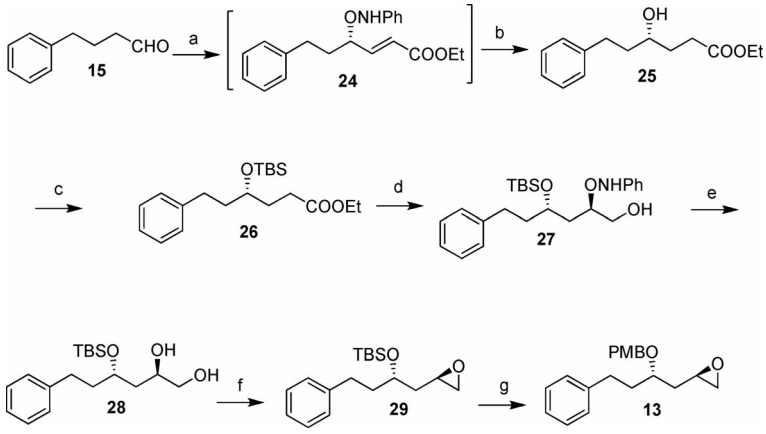
Scheme 2. *Reagents and conditions:* (a) benzylmagnesium bromide, diethyl ether, 0 °C to room temp., 5 h, 89%; (b) KOH, diethyl ether, 0 °C to room temp., 4 h, 96%; (c) *S*,*S*-salen-Co-(OAc) (0.5 mol-%), dist. H_2O (0.6 equiv.), 0 °C, 10 h, [48% for (*S*)-**17**, 46% for (*R*)-**18**].

With enantiomerically pure epoxide (*S*)-**17** in hand, our next aim was to construct the *anti*-1,3-diol. As depicted in Scheme 3, the epoxide (*S*)-**17** was treated with vinylmagnesium bromide in the presence of CuI to give the homoallylic alcohol **19** in excellent yield. To establish the second stereogenic center with required stereochemistry, we protected the hydroxy group of homoallylic alcohol **19** as PMB ether, followed by epoxidation with *m*-CPBA. The epoxide **21** obtained was found to be a mixture of two diastereomers (*anti:syn*, 2.1:1) as determined from ^1H and ^{13}C NMR spectral analysis. The two diastereomers could not be differentiated on TLC. In order to improve the diastereoselectivity, we next attempted the Jacobsen's hydrolytic kinetic resolution (HKR). Towards this end the epoxide **21** was treated with (*R*,*R*)-salen-Co-OAc complex (0.5 mol-%) and water in THF to afford the epoxide **13**[16a] as a single diastereomer (determined from the ^1H and ^{13}C NMR spectral analysis) in 90% yield and the diol **22**[16a] in 92% yield (according to the ratio of starting material). Epoxide **13** could easily be separated from the more polar diol **22** through silica gel column chromatography. In order to achieve the synthesis of target molecule **1**, we required epoxide **13** in substantial amount. As the HKR method provided the desired epoxide **13** along with unwanted diol **22**, we thought it would be appropriate to convert the diol into the required epoxide via internal nucleophilic substitution of a secondary mesylate.[17] The diol **22** was easily converted into the required epoxide **13** via internal nucleophilic substitution in a secondary mesylate (Scheme 3).

Although by using the HKR approach, in principle one can prepare all the stereoisomers from easily available epoxides, however, the sequence of reactions either suffers from disadvantage due to the loss of 50% of starting compound as diol in each resolution step, or more steps are required to convert the diol into the required epoxide. Therefore, we thought it might be worthwhile to synthesize the epoxide **13** via our recently developed methodology for enantiopure *syn*/*anti*-1,3-polyols via proline-catalyzed sequential α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehydes.[14] Towards this end, the aldehyde **15** was subjected to sequential α-aminoxylation using D-proline as a catalyst followed by HWE-olefination reaction to furnish *O*-amino-substituted allylic alcohol which was directly subjected to hydrogenation conditions using catalytic amounts of Pd/C to furnish the γ-hydroxy ester **25** in good yield and in >98% *ee*.[18] The free hydroxy group of γ-hydroxy ester **25** was protected as TBS ether to furnish compound **26**. The Dibal-H reduction of ester furnished aldehyde which was subjected to α-aminoxylation catalyzed by L-proline, followed by in situ reduction using $NaBH_4$ to furnish the *O*-amino-substituted diol **27** in 71% yield and >95% de (determined from the ^1H and ^{13}C NMR spectral analysis). Compound **27** was subjected to reductive hydrogenation conditions to afford the diol **28**, which on selective monotosylation and base treatment furnished epoxide **29** in



Scheme 3. *Reagents and conditions:* (a) vinylmagnesium bromide, THF, CuI, –20 °C, 16 h, 88%; (b) NaH, PMBBr, THF, TBAI, 0 °C to room temp., overnight, 97%; (c) *m*-CPBA, CH_2Cl_2, 0 °C to room temp., 10 h, 96%; (d) *R*,*R*-Salen-Co-(OAc) (0.5 mol-%), dist. H_2O (0.55 equiv.), THF, 0 °C, 24 h, (90% for **13**, 92% for **22** according to the ratio of starting material); (e) (i) PivCl, Et_3N, cat. DMAP, room temp.; (ii) MsCl, Et_3N, DMAP, 0 °C to room temp.; (f) K_2CO_3, MeOH, room temp. (61% for three steps).



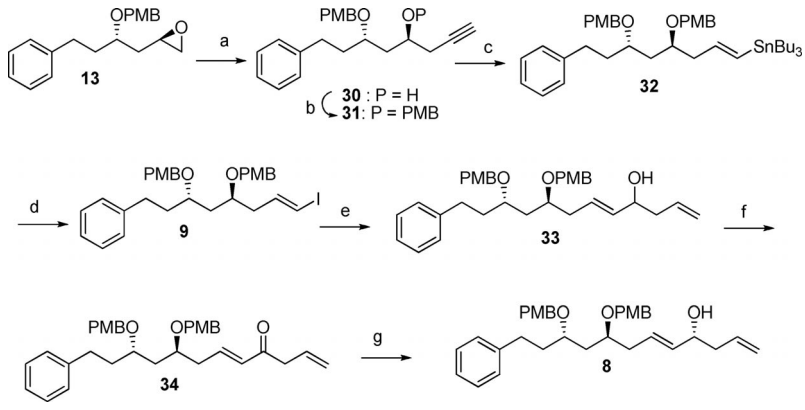
Scheme 4. *Reagents and conditions:* (a) nitrosobenzene, D-proline, DMSO, HWE salt, DBU, LiCl, CH_3CN; (b) H_2/Pd-C, EtOAc, 71% (over two steps); (c) TBSCl, imidazole, DMF, overnight, 91%; (d) (i) DIBAL, DCM, –78 °C; (ii) L-proline, nitrosobenzene, DMSO; (iii) $NaBH_4$, MeOH; (e) H_2/Pd-C, EtOAc, 85%; (f) (i) TsCl, Bu_2SnO, Et_3N; (ii) K_2CO_3, MeOH, room temp., 79%; (g) (i) TBAF, THF; (ii) NaH, PMBBr, THF, TBAI, 0 °C to room temp., 76%.

79% yield. The TBS group of epoxide was deprotected and free hydroxy group was protected as PMB ether to get the required epoxide **13** (Scheme 4). It should be noted that by this method the epoxide **13** was synthesized in 6 steps and 43% overall yield, while the HKR method required 8 steps furnishing only 15% overall yield.

With substantial amount of **13** in hand, we required to generate the *trans*-olefin and carry out the subsequent reactions to complete the synthesis of (+)-strictifolione. We then further proceeded for the synthesis of **1** by ring opening of the epoxide **13** with an excess of lithium acetylide to furnish the acetylene **30** in 86% yield. The free hydroxy group of **30** was protected as its PMB ether to give **31** in excellent yield. Acetylene **31** was treated with tri-*n*-butyltin hydride and AIBN in refluxing benzene[19] to give the (*E*)-vinylstannane **32** in 96% yield. Tributyltin was then replaced with iodide by using I_2[20] in CH_2Cl_2 to afford the corresponding iodo compound **9** in excellent yield. Vinylic iodide **9** was treated with *n*BuLi in THF at –78 °C for 1 h and further treated with CuCN followed by addition of but-3-enal **10** to form the coupling product **33** in 68% yield in 2:1 diastereomeric ratio. The secondary hydroxy group was further oxidized with IBX to give the keto product **34** in good yield.

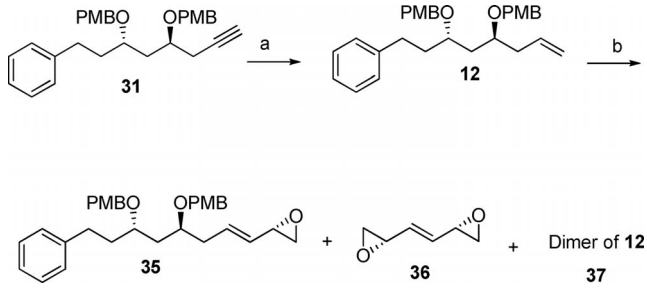
With the desired allylic ketone **34** in hand, we turned our attention to the installation of the pyranone portion of the natural product (+)-strictifolione. Thus, asymmetric reduction of **34** using (*R*)-BINAL-H[15] in THF proceeded in a stereoselective fashion to give the allylic alcohol **8** in substantially high enantiomeric excess (91% *de*, determined from the ^1H and ^{13}C NMR spectral analysis) (Scheme 5).

Alternatively, it was thought worthwhile to convert the acetylene into the olefin and examine the olefin cross-metathesis to construct the *trans*-olefin with chiral epoxide. Thus, acetylene **31** was converted into olefin **12** by partial hydrogenation using Lindlar's catalyst in excellent yield. Olefin **12** was subjected to the olefin cross-metathesis with 3 equiv. of (*S*)-butadiene mono-epoxide using Grubbs' 1st generation catalyst, in refluxing CH_2Cl_2 or in benzene; however, formation of the desired product **35** could not be



Scheme 5. *Reagents and conditions:* (a) LiC≡C·EDA, DMSO, 0 °C to room temp., 5 h, 86%; (b) NaH, PMBBr, THF, TBAI, 0 °C to room temp., overnight, 97%; (c) $(n\text{Bu})_3SnH$, AIBN, C_6H_6, reflux, 4 h, 96%; (d) I_2, CH_2Cl_2, 30 min, 94%; (e) *n*BuLi, THF, –78 to 0 °C for 1.5 h, then CuCN, –78 to –50 °C, 1.5 h, then but-3-enal **10**, 68%; (f) IBX, EtOAc, reflux, 6 h; (g) (*R*)-BINAL-H, THF, –100 °C for 1 h, –78 °C, 3 h, 75%.

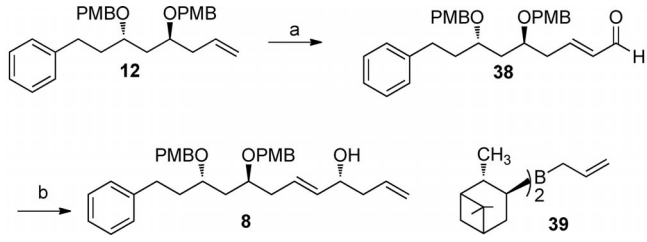
observed. Use of Grubbs' 2nd generation catalyst in refluxing CH_2Cl_2 furnished compound **35** in only 16% yield as a 6:1 mixture of *E*/*Z* isomers along with homodimer of **12**, homodimer of (*S*)-butadiene mono-epoxide and unreacted compound **12** (Scheme 6).



Scheme 6. *Reagents and conditions:* (a) H_2, $Pd/BaSO_4$, quinoline, EtOAc, 1 h, 95%; (b) $RuCl_2(=CHPh)(PCy_3)(IEMS)$, (*S*)-2-vinyloxirane CH_2Cl_2, reflux, 18 h, 16% of **35**.

In another attempt to improve the selectivity and yield, we examined the olefin cross-metathesis[21] of olefin **12** by treatment with 3 equiv. of acrolein using 10 mol-% Grubbs' 2nd generation catalyst in refluxing CH_2Cl_2 to afford the α,β-unsaturated aldehyde **38** in 76% yield with an *E*/*Z* ratio of >30:1.

Next we attempted the asymmetric allylation of α,β-unsaturated aldehyde **38** using Brown's protocol.[22] Thus, an allylating reagent (allylBIpc$_2$) **39**, prepared from allylmagnesium bromide and (+)-DIP-Cl (diisopinocampheylboron chloride), was treated with **38** at –100 °C to afford the homoallylic alcohol **8** in 74% yield with diasteromeric ratio 96:4 (determined from the ^1H and ^{13}C NMR spectral analysis) (Scheme 7).



Scheme 7. *Reagents and conditions:* (a) acrolein (**11**), $RuCl_2(=CHPh)(PCy_3)(IEMS)$, 10 mol-%, CH_2Cl_2, room temp., 76%; (b) (+)-DIP-Cl, allylmagnesium bromide, Et_2O/pentane, –100 °C, 74%.

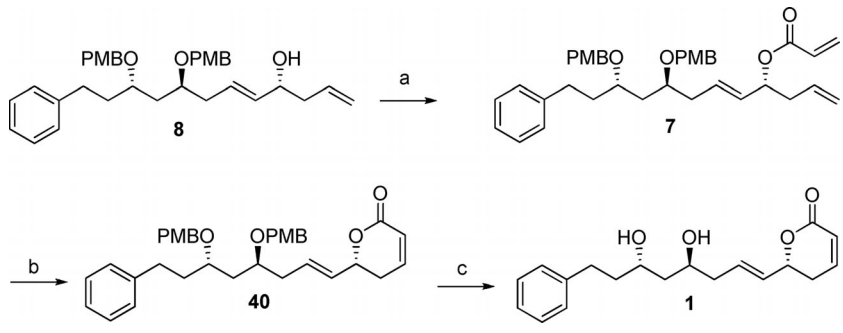
With the desired allylic alcohol **8** in hand, our next aim was to construct the pyranone by ring-closing metathesis. Thus, alcohol **8** was esterified with acryloyl chloride in the presence of Et_3N and catalytic amount of DMAP to afford the acryloyl ester **7** in 82% yield (Scheme 8). Subsequent ring-closing metathesis[23] of the ester **7** with commercially available Grubbs' 1st generation catalyst in presence of Ti(*i*PrO)$_4$ in refluxing CH_2Cl_2 for 6 h afforded the α,β-unsaturated δ-lactone **40** in 87% yield. In the absence of Ti(*i*PrO)$_4$, the reaction was found to be sluggish. In contrast to this, the reaction proceeded well in almost comparable yield with the use of 5 mol-% Grubbs' 2nd generation catalyst without addition of any Ti(*i*PrO)$_4$. Now all that remained to complete the synthesis was to remove the PMB groups. Thus, debenzylation of **40** in the presence of DDQ gave (+)-strictifolione (**1**) in 89% yield (Scheme 8). $[\alpha]_D^{25}$ = +72 (*c* = 0.6, $CHCl_3$); ref.[2] $[\alpha]_D^{25}$ = +81.5 (*c* = 0.52, $CHCl_3$); ref.[11c] $[\alpha]_D^{25}$ = +54.1 (*c* = 0.33, $CHCl_3$). The physical and spectroscopic data of **1** were in full agreement with the literature data.[11]

Conclusions

We have accomplished the total synthesis of (+)-strictifolione by using a practical and efficient strategy amenable to both *syn*- and *anti*-1,3-diols with a high degree of enantio- and diastereoselectivities. The desired stereocenters can simply be achieved by changing the catalyst. The lactone moiety was constructed by ring-closing metathesis. Further application of this methodology to the syntheses of biologically active compounds containing 1,3-polyols and lactone moiety is currently underway in our laboratory.

Experimental Section

General Methods: All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which was cooled under argon. Solvents used for chromatography were distilled at respective boiling points using known procedures. All commercial reagents were obtained from Sigma–Aldrich Chemical Co. and Lancaster Chemical Co. (UK). The progress of the reactions was monitored by TLC using precoated aluminium plates (silica gel 60 F254, Merck). Column chromatography was performed on silica gel 60–120/100–200/230–



Scheme 8. *Reagents and conditions:* (a) acryloyl chloride, Et_3N, CH_2Cl_2, 0 °C to room temp., 5 h, 82%; (b) $(PCy_3)_2Ru(Cl)_2$ = CH-Ph (20 mol-%), CH_2Cl_2, Ti(*i*PrO)$_4$ (0.03 equiv.), reflux, 6 h, 87%; (c) DDQ, CH_2Cl_2/H_2O (9:1), 91%.

400 mesh obtained from S. D. Fine Chemical Co. India or Spectrochem India. Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. IR spectra were recorded on a Perkin–Elmer infrared spectrometer model 599-B and model 1620 FTIR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX-500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br. broad, s singlet, d doublet, t triplet, m multiplet). ^{13}C NMR spectra were recorded on Bruker AC-200, Bruker AV- 400 and Bruker DRX-500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). Microanalytical data were obtained using a Carlo–Erba CHNS-0 EA 1108 elemental analyzer. All the melting points were recorded on a Büchi B-540 electrothermal melting point apparatus. Yields refer to chromatographically and spectroscopically pure compounds.

1-Chloro-4-phenylbutan-2-ol (16): A round-bottomed flask was charged with Mg (9.19 g, 378.38 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry diethyl ether (100 mL) was added. To this was slowly added benzyl bromide (55.77 g, 302.70 mmol) in diethyl ether (50 mL) at room temperature, the mixture was stirred vigorously. After 50% addition of benzyl bromide the reaction mixture was cooled to 0 °C followed by addition of epichlorohydrin (14.0 g, 151.35 mmol) in diethyl ether (25 mL) slowly with simultaneous addition of remaining amount of benzyl bromide. After the completion of addition of both the reagents, the reaction mixture was stirred at the room temperature for 5 h. The reaction was quenched by pouring into a saturated aqueous solution of NH_4Cl at 0 °C, then the aqueous layer was extracted with diethyl ether (3 × 50 mL). The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave the chlorohydrin **16** (24.87 g, 89%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.85–1.96 (m, 2 H, PhCH$_2$CH_2), 2.52 (dd, *J* = 5.2, 2.2 Hz, 2 H, PhCH_2), 3.55 (d, *J* = 8.1 Hz, 2 H, CH_2Cl), 3.83–3.91 (m, 1 H, C*H*OH), 7.25–7.41 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.9, 33.8, 48.8, 70.4, 125.7, 128.0, 140.9 ppm.

(±)-2-Phenethyloxirane [(±)-17]: To a solution of chlorohydrin **16** (15.0 g, 81.49 mmol) in diethyl ether (100 mL) was added pulverized KOH (9.14 g, 162.98 mmol) at 0 °C and reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by addition of water (50 mL), then the mixture was extracted with diethyl ether (3 × 50 mL). The combined extracts were dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the epoxide (±)-**17** (11.56 g, 96%) as a colorless liquid. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2993, 2295, 1496, 1454, 904, 829, 756 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.86–1.95 (m, 2H PhCH$_2$CH_2), 2.52 (dd, *J* = 5.2, 2.2 Hz, 1 H, CH_AO), 2.75–2.88 (m, 3 H, PhCH_2, C*H*O), 2.96–3.30 (m, 1 H, CH_BO), 7.25–7.41 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8, 33.9,46.7, 51.4, 125.6,128.0, 140.9 ppm.

Epoxide [(*S*)-17]: Racemic epoxide **(±)-17** (8.0 g, 54.02 mmol) and THF (583 μL) were added to (*S*,*S*)-Salen-Co-OAc catalyst (179 mg, 0.27 mmol, 0.5 mol-%) and the solution was cooled to 0 °C. Every 5 min, H_2O (117 μL) was added until 583 μL (0.6 equiv., 32.41 mmol) had been added; after another 5 min the ice bath was removed and the reaction was stirred at room temperature for 10 h. The reaction mixture was concentrated and purified through silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish the epoxide (*S*)-**17** as a single stereoisomer as a yellow colored liquid. Continued chromatography with petroleum ether/EtOAc (4:6) provided the diol (*R*)-**18** as a brown colored liquid as a single diastereomer. All spectroscopic data for (*S*)-**17** (^{1}H NMR, ^{13}C NMR and IR) were identical to the epoxide (±)-**17**, except optical rotation; yield 3.84 g (48%). $[a]_D^{25}$ = –21.8 (*c* = 0.9, $CHCl_3$) [ref.[16] $[a]_D^{20}$ = –22.5 (*c* = 1.0, $CHCl_3$)]. $C_{10}H_{12}O$: calcd. C 81.04, H 8.16; found C 81.21, H 8.23.

[(*R*)-4-Phenylbutane-1,2-diol] [(*R*)-18]: $[a]_D^{25}$ = +13.1 (*c* = 0.7, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3359, 2931, 1498, 1454, 1391, 701 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83 (t, *J* = 14.0 Hz, 2 H, PhCH$_2$CH_2), 2.64–2.93 (m, 2 H, PhCH_2), 3.57–3.69 (m, 1 H, C*H*OH), 3.82–3.89 (m, 1 H, CH_AOH), 3.91–4.12 (m, 1 H, CH_BOH), 7.17–7.41 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8, 32.3, 66.1, 71.1, 125.8, 128.3, 141.7 ppm. $C_{10}H_{14}O_2$: calcd. C 72.26, H 8.49; found C 72.41, H 8.32.

(*S*)-1-Phenylhex-5-en-3-ol (19): A round-bottomed flask was charged with copper(I) iodide (39 mg, 0.20 mmol), gently heated under vacuum and slowly cooled with a flow of argon and THF (20 mL) was added. The suspension was cooled to –20 °C, stirred and vinylmagnesium bromide (1 M in THF, 40.5 mL, 40.51 mmol) was added to it. A solution of epoxide (*S*)-**17** (3.0 g, 20.25 mmol) in THF (15 mL) was added to the above-mentioned reagent and the mixture was stirred at –20 °C for 16 h. After consumption of the starting material, the reaction was quenched with a saturated aqueous solution of NH_4Cl. The water layer was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent afforded **19** (3.14 g, 88%) as a colorless liquid. $[a]_D^{25}$ = –29.98 (*c* = 2.06, $CHCl_3$), [ref.[24] $[a]_D^{25}$ = –25.66 (*c* = 0.24, $CHCl_3$)]. IR (neat): $\tilde{\nu}_{max}$ = 3386, 1640, 1603, 1493, 1453 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78–1.82 (m, 2 H, PhCH$_2$CH_2), 2.22–2.35 (m, 2 H, PhCH_2), 2.72–2.87 (m, 2 H, CH_2CH=CH$_2$), 3.66–3.78 (m, 1 H, C*H*OH), 5.14–5.24 (m, 2 H, =CH_2), 5.80–5.97 (m, 1 H, C*H*=CH$_2$), 7.23–7.37 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.9, 134.5, 128.2, 125.6, 117.8, 69.8, 41.8, 38.2, 31.8 ppm. $C_{12}H_{16}O$ (176.26): calcd. C 72.26, H 8.49; found C 72.41, H 8.32.

1-[(*S*)-3-(4-Methoxybenzyloxy)hex-5-enyl]benzene (20): To a solution of **19** (4.0 g, 22.69 mmol) in dry DMF (100 mL) was added sodium hydride (50%, 1.53 g, 31.77 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (5.02 g, 24.96 mmol) and tetra *n*-butylammonium iodide (838 mg, 2.26 mmol) with further stirring for overnight at the same temperature. The reaction was quenched by addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water (3 × 50 mL), brine, dried (Na_2SO_4) and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to furnish the PMB-protected homoallylic alcohol **20** (6.52 g, 97%) as colorless oil. $[a]_D^{25}$ = –27.41(*c* = 1.66, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1641, 1606, 1491, 1462 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.78–1.86 (m, 2 H, PhCH$_2$CH_2), 2.37 (t, *J* = 5.7 Hz, 2 H, PhCH_2), 2.55–2.86 (m, 2 H, CH_2CH=CH$_2$), 3.39–3.54 (m, 1 H, C*H*OPMB), 3.81 (s, 3 H, OCH_3), 4.45 (dd, *J* = 24.8, 11.2 Hz, 2 H, OCH_2Ar), 5.05–5.18 (m, 2 H, =CH_2), 5.71–5.96 (m, 1 H, C*H*=CH$_2$), 6.91 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 7.08–7.31 (m, 7 H, Ar*H*, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.7, 35.7, 38.2, 55.3, 70.6, 113.8, 117.0, 125.7, 128.4, 129.3, 129.7, 130.9,

134.8, 142.4, 159.1 ppm. $C_{20}H_{24}O_2$ (296.41): calcd. C 81.04, H 8.16; found C 81.29, H 8.31.

Epoxide 21: To a solution of PMB ether **20** (4.6 g, 15.51 mmol) in CH_2Cl_2 (150 mL), *m*-chloroperbenzoic acid (6.43 g, 18.62 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 10 h, then diluted with saturated aqueous Na_2SO_3 at 0 °C, stirred for 30 min, neutralized with saturated $NaHCO_3$ and extracted with CH_2Cl_2. Combined organic fractions were dried (Na_2SO_4), filtered, concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent provided **21** (4.65 g, 96%; approximately 2.1:1 mixture of diastereomers) as a colorless liquid. $[\alpha]_D^{25} = -38.6$ (c = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2960, 2860, 1470, 1410, 1340, 1250, 1095, 1035, 840, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64–1.77 (m, 2 H, CH_2CHO), 1.83–2.10 (m, 2 H, PhCH$_2$CH_2), 2.47–2.54 (m, 1 H, CH_AO), 2.62–2.84 (m, 3 H, PhCH_2, CHO), 3.04–3.10 (m, 1 H, CH_BO), 3.66–3.76 (m, 1 H, CHOCH$_2$Ar), 3.80 (s, 3 H, OCH$_3$), 4.53 (s, 2 H, OCH_2Ph), 6.89 (d, J = 8.7 Hz, 2 H, ArH), 7.17–7.35 (m, 7 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): [mixture of diastereomers, *dr* (*anti*:*syn*) = 2.2:1]: δ = 31.1, 31.3, 35.9, 37.2, 46.4, 47.2, 49.5, 54.9, 70.1, 70.7, 75.4, 75.6, 113.5, 125.5, 128.1, 129.1, 130.3, 141.8, 158.9 ppm.

Hydrolytic Kinetic Resolution of 21 with Jacobsen Cobalt Catalyst: A solution of epoxide **21** (2.4 g, 7.68 mmol) and (*R*,*R*)-Salen-Co^{III}-OAc (26 mg, 0.038 mmol) in THF (83 μL) was stirred at 0 °C for 5 min, and then distilled water (83 μL, 4.6 mmol) was added. After stirring for 24 h, it was concentrated and purified by silica gel column chromatography using petroleum ether/EtOAc (8:2) to afford **13** (2.8 g, 90%) as a yellow colored liquid. Continued chromatography with petroleum ether/EtOAc (6:4) provided the diol **22** (1.44 g, 92%) as a brown colored liquid as a single diastereomer.

(*R*)-2-[(*S*)-2-(4-Methoxybenzyloxy)-4-phenylbutyl]oxirane (13): $[\alpha]_D^{25}$ = –49.4 (c = 0.9, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2960, 2860, 1470, 1410, 1340, 1250, 1095, 1035, 840, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.60–1.72 (m, 1 H, CH_ACHO), 1.82–2.0 (m, 3 H, PhCH$_2$CH_2, CH_BCHO), 2.52 (dd, J = 5.1, 2.8 Hz, 1 H, CH_AO), 2.63–2.77 (m, 2 H, PhCH_2), 2.82 (dd, J = 4.9, 4.0 Hz, 1 H, CHO), 3.03–3.13 (m, 1 H, CH_BO), 3.61–3.76 (m, 1 H, CHOCH$_2$Ar), 3.82 (s, 3 H, OCH_3), 4.46–4.49 (m, 1 H, OCH_BAr), 4.53 (s, 1 H, OCH_AAr), 6.92 (d, J = 8.7 Hz, 2 H, ArH), 7.17–7.32 (m, 7 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.3, 36.1, 37.4, 47.2, 49.5, 54.9, 70.9, 75.8, 113.7, 125.6, 128.2, 129.2, 130.6, 141.7, 159.1 ppm. $C_{20}H_{24}O_3$ (312.41): calcd. C 81.04, H 8.16; found C 81.29, H 8.31.

(2*S*,4*S*)-4-(4-Methoxybenzyloxy)-6-phenylhexane-1,2-diol (22): $[\alpha]_D^{25}$ = –50.9 (c = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3354, 2961, 2896, 2861, 1478, 1411, 1251, 1105, 1022, 978, 847, 780 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.26–1.52 (m, 2 H, OCHCH_2), 1.81–2.16 (m, 4 H, CH_2CHO, PhCH$_2$CH_2), 2.74 (m, 2 H, PhCH_2), 3.51–3.61 (m, 1 H, CHOCH$_2$Ph), 3.85 (br. s, 6 H, OCH_3, CH_2OH, CHOH), 4.42–4.63 (m, 2 H, OCH_2Ar), 6.96 (d, J = 7.7 Hz, 2 H, ArH), 7.33 (m, 7 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.3, 36.1, 37.4, 54.9, 66.3, 70.9, 71.4, 75.6, 113.8, 125.6, 128.1, 129.2, 130.5, 141.8, 159.2 ppm. $C_{20}H_{26}O_4$ (330.42): calcd. C 81.04, H 8.16; found C 81.29, H 8.31.

(*S*)-Ethyl 4-Hydroxy-6-phenylhexanoate (25): To a solution of phenyl butanal **15** (2.0 g, 13.5 mmol) and nitroso benzene (1.44 g, 13.5 mmol) in anhydrous DMSO (29 mL) was added D-proline (0.62 g, 5.4 mmol) at 20 °C. The mixture was vigorously stirred for 25 min under argon (the color of the reaction changed from green to yellow during this time), then cooled to 0 °C. Thereafter, a premixed and cooled (0 °C) solution of triethylphosphonoacetate (8.1 mL, 40.5 mmol), DBU (6.1 mL, 40.5 mmol) and LiCl (1.7 g, 40.5 mmol) in CH_3CN (29 mL) was added quickly (1–2 min) at 0 °C. The resulting mixture was warmed to room temperature over 1 h, the reaction was quenched by addition of ice pieces. The acetonitrile was evaporated under vacuum. The reaction mixture was then poured into water (100 mL) and extracted with Et_2O (5 × 100 mL). The combined organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated in vacuo to give the crude product which was directly subjected to the next step without purification. To the crude allylic alcohol in ethyl acetate was added Pd-C (10%) under hydrogenation conditions and the reaction mixture was allowed to stir overnight. After completion of the reaction (until ^1H NMR analysis of the crude mixture indicated complete conversion), the mixture was filtered through a pad of Celite and concentrated in vacuo to give the γ-alcohol. The crude product was then purified by using flash column chromatography using petroleum ether/EtOAc (85:15) as eluent to give **25** (2.26 g, 71%) as a colorless liquid. $[\alpha]_D^{25}$ = +12.38 (c = 1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3486, 1730, 1602, 1491, 1023, 931 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.2 Hz, 3 H, CH_3), 1.86–1.71 (m, 2 H, PhCH$_2$CH_2), 1.87–2.00 (m, 2 H, CHOHCH_2), 2.52 (t, J = 7.08 Hz, 2H CH_2COOEt), 2.67–2.95 (m, 2 H, PhCH_2), 3.66–3.76 (m, 1 H, CHOH), 4.18 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 7.40–7.23 (m, 5 H, PhH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 27.9, 30.8, 32.2, 39.1, 60.5, 70.6, 125.8, 128.4, 128.5,141.9, 174.2 ppm. $C_{14}H_{20}O_3$ (236.31): calcd. C 71.16, H 8.53; found C 71.26, H 8.42.

(*S*)-Ethyl 4-(*tert*-Butyldimethylsilyloxy)-6-phenylhexanoate (26): To an ice-cold stirred solution of **25** (1.4 g, 5.92 mmol) in CH_2Cl_2 (10 mL) were added imidazole (0.81 g, 11.85 mmol) and TBSCl (1.33 g, 8.89 mmol) at 0 °C. The resulting mixture was stirred overnight at room temp. before H_2O (20 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/ethyl acetate (99:1) gave TBS ether **26** (1.89 g, 91%) as a colorless liquid. $[\alpha]_D^{25}$ = +19.31 (c = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2955, 1736, 1684, 1454 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 3 H, SiCH_3), 0.06 (s, 3 H, SiCH_3), 0.91 [s, 9 H, SiC(CH_3)$_3$], 1.26 (t, J = 7.2 Hz, 3 H, CH_3), 1.65–1.75 (m, 2 H, PhCH$_2$CH_2), 1.79–1.86 (m, 2 H, CHOCH_2), 2.38 (t, J = 7.3 Hz, 2 H, CH_2COOEt), 2.60–2.69 (m, 2 H, PhCH_2), 3.71–3.83 (m, 1 H, CHOTBS), 4.11 (q, J = 7.2 Hz, 2 H, OCH_2CH$_3$), 7.20–7.31 (m, 5 H, PhH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.6, –4.4, 14.2, 18.1, 25.7, 25.9, 30.0, 31.7, 38.9, 60.3, 70.7, 125.7, 128.3, 128.4, 142.4, 173.9 ppm. $C_{20}H_{34}O_3Si$ (350.57): calcd. C 68.52, H 9.78; found C 68.41, H 9.71.

(2*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)-6-phenylhexane-1,2-diol (28): To a solution of ester **26** (0.34 g, 0.98 mmol) in dry DCM (300 mL) at 0 °C was added dropwise DIBAL-H (1.96 mL, 196 mmol, 1 M in toluene) through a syringe. The reaction mixture was warmed to room temperature over 1 h, then recooled to 0 °C and treated with satd. aqueous solution of sodium potassium tartrate (50 mL). The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give the crude aldehyde, which was used for the next step without purification. To a stirred solution of aldehyde (0.30 g, 0.98 mmol) and nitrosobenzene (0.105 g, 0.98 mmol) in DMSO (9 mL) was added L-proline (0.04 g, 0.34 mmol, 20 mol-%) in one portion at 25 °C. After 1 h, the temperature was lowered to 0 °C, followed by dilution with anhyd. MeOH (10 mL) and careful addition of excess $NaBH_4$ (0.13 g, 3.4 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic

solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic phase was dried with anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/petroleum ether (40:60) as eluent to give pure aminoxy alcohol **27**. The aminoxy alcohol **27** (0.33 g, 0.86 mmol) was dissolved in EtOAc (10 mL) and to the solution was added 10% Pd/C (0.050 g) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using petroleum ether/ethyl acetate (3:2) as eluent to give pure diol **28** (0.27 g, 85%) as a colorless liquid. $[\alpha]_D^{25}$ = + 6.36, (*c* = 0.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3412, 3018, 2938, 1612, 1513, 1248, 1215 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, SiC*H*$_3$), 0.09 (s, 3 H, SiC*H*$_3$), 0.9 [s, 9 H, SiC(C*H*$_3$)$_3$], 1.21–1.31 (m, 2 H, PhCH$_2$C*H*$_2$), 1.51–1.62 (m, 1 H, C*H*$_A$CHOH), 1.73 (dd, *J* = 6.7, 3.4 Hz, 1 H, C*H*$_B$CHOH), 1.86–1.97 (m, 2 H, OH), 2.57–2.63 (m, 2 H, PhC*H*$_2$), 3.45 (dd, *J* = 4.9, 6.2 Hz, 1 H, C*H*OTBS), 3.60 (dd, *J* = 3.4, 7.7 Hz, 1 H, C*H*OH), 4.01–4.31 (m, 2 H, C*H*$_2$OH), 7.19–7.32 (m, 5 H, Ar*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.7, –4.6, 17.9, 25.8, 32.0, 37.3, 38.1, 67.1, 68.9, 70.8, 122.8, 125.9, 128.2, 128.4, 141.8 ppm. $C_{18}H_{32}O_3Si$ (324.54): calcd. C 66.62, H 9.94; found C 66.58, H 9.84.

***tert*-Butyldimethyl{(*S*)-1-[(*R*)-oxiran-2-yl]-4-phenylbutan-2-yloxy}-silane (29):** To a mixture of diol **28** (0.142 g, 0.44 mmol), in dry DCM (5 mL) was added dibutyltin oxide (2.2 mg, 0.009 mol) followed by the addition of *p*-toluenesulfonyl chloride (0.08 g, 0.44 mmol) and triethylamine (0.06 mL, 0.43 mmol) and reaction was stirred at room temperature under nitrogen. The reaction was monitored by TLC, after completion of reaction the mixture was quenched by adding water. The solution was extracted with DCM (3 × 10 mL) and then combined organic phase was washed with water, dried (Na_2SO_4) and concentrated. To this crude mixture in MeOH at 0 °C was added K_2CO_3 (91 mg, 0.66 mmol) and the resultant mixture was allowed to stir for 1 h at same temp. After completion of reaction as indicated by TLC the reaction was quenched by addition of ice pieces and methanol was evaporated. The concentrated reaction mixture was then extracted with ethyl acetate (3 × 20 mL), the combined organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The column chromatography of crude product using petroleum ether: ethyl acetate (9:1) gave the epoxide **29** (yield 0.15 mg, 79%) as a colorless liquid. $[\alpha]_D^{25}$ = + 4.78 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2934, 2858, 1612, 1586, 1513, 1463, 1248 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = –0.08 (s, 6 H, SiC*H*$_3$), 0.91 [s, 9 H, SiC(C*H*$_3$)$_3$], 1.64–1.76 (m, 2 H, C*H*$_2$CHO), 1.79–1.90 (m, 2 H, PhCH$_2$C*H*$_2$), 2.49 (dd, *J* = 2.8, 2.3 Hz, 1 H, PhC*H*$_A$CH$_2$), 2.57–2.63 (m, 1 H, PhC*H*$_B$CH$_2$), 2.65–2.68 (m, 1 H, C*H*O), 2.80 (t, *J* = 4.71 Hz, 1 H, C*H*$_A$O), 2.98–3.07 (m, 1 H, C*H*$_B$O), 3.91–4.02 [m, 1 H, C*H*OSiC(CH$_3$)$_3$], 7.15–7.31 (m, 5 H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.4, 18.1, 25.9, 30.4, 39.7, 40.2, 47.8, 49.9, 69.8, 125.8, 18.3.1, 128.4 ppm. $C_{18}H_{30}O_2Si$ (306.52): calcd. C 70.53, H 9.87; found C 70.59, H 9.96.

(*R*)-2-[(*S*)-2-(4-Methoxybenzyloxy)-4-phenylbutyl]oxirane (13): To a solution of epoxide **29** (0.15 g, 0.30 mmol) in THF (10 mL) was added TBAF (0.45 mL, 0.45 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol which was used for the next step without purification. To a solution of alcohol (0.094 g, 0.49 mmol) in dry THF (50 mL) was added sodium hydride (50%, 0.035 g, 0.73 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (0.12 g, 0.59 mmol) with further stirring for 2 h at room temperature. The reaction 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 (3 × 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product with petroleum ether/EtOAc (8:2) as eluent furnished epoxide **13** (0.116 g, 76%). All data (IR, ^1H NMR, and ^{13}C NMR) were identical to the compound **13** derived by hydrolytic kinetic resolution.

(4*S*,6*S*)-6-(4-Methoxybenzyloxy)-8-phenyloct-1-yn-4-ol (30): To a solution of **13** (1.8 g, 5.76 mmol) in DMSO (5 mL) at 0 °C was added lithium acetylide-EDA complex (0.778 g, 8.64 mmol) in one portion. The reaction mixture was stirred at 0 °C for 30 min and 5 h at room temperature. The excess of reagent was quenched with 0.3 N H_2SO_4 and extracted with ethyl ether, washed with water, brine, dried (Na_2SO_4) and concentrated. The residue was purified by silica gel chromatography by eluting with light petroleum/EtOAc (8:2) to afford the alkyne **30** (1.677 g, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = +21.24 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3454, 2957, 2898, 2861, 2214, 1466, 1390, 1360, 1257, 1100, 1005, 980, 835, 777 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.83–1.92 (m, 2 H, PhCH$_2$C*H*$_2$), 2.08 (t, *J* = 2.6 Hz, 2 H, CH$_2$C*H*OH), 2.40 (dd, *J* = 2.5, 1.3 Hz, 1 H, CHOHC*H*$_A$), 2.43 (dd, *J* = 2.7, 1.1 Hz, 1 H, CHOHC*H*$_B$), 2.72 (t, *J* = 8.0 Hz, 2 H, PhC*H*$_2$), 3.09 (s, 1 H, C*H*), 3.73–3.81 (m, 1 H, C*H*OCH$_2$Ar), 3.85 (s, 3 H, OC*H*$_3$), 4.07–4.20 (m, 1 H, C*H*OH), 4.53 (d, *J* = 2.5 Hz, 2 H, OC*H*$_2$Ar), 6.94 (d, *J* = 7.0 Hz, 2 H, Ar*H*), 7.20–7.38 (m, 7 H, Ar*H*,Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.2, 31.46, 35.2, 38.7, 55.1, 66.9, 70.5, 70.8, 75.6, 80.9, 113.8, 125.8, 128.3, 129.5, 130.1, 141.8, 159.2 ppm. $C_{22}H_{26}O_3$ (338.45): calcd. C 78.07, H 7.74; found C 78.22, H 7.61.

1-{[(3*S*,5*S*)-5-(4-Methoxybenzyloxy)-1-phenyloct-7-yn-3-yloxy]-methyl}-4-methoxybenzene (31): Compound **31** was prepared following the procedure as described for compound **20** in 97% yield as a colorless liquid. $[\alpha]_D^{25}$ = +19.4 (*c* = 1.1, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.66–1.79 (m, 2 H, CHOC*H*$_2$CHO), 1.83–1.91 (m, 2 H, PhCH$_2$C*H*$_2$), 2.04 (d, *J* = 2.2 Hz, 1 H, CH), 2.47 (dd, *J* = 5.3, 2.7 Hz, 2 H, CHOC*H*$_2$), 2.69–2.88 (m, 2 H, PhC*H*$_2$), 3.49–3.75 (m, 2 H, 2XC*H*OCH$_2$Ar), 3.79 (s, 3 H, OC*H*$_3$), 3.82 (s, 3 H, OC*H*$_3$), 4.20–4.63 (m, 4 H, 2XOC*H*$_2$Ar), 6.88 (d, *J* = 8.6 Hz, 4 H, Ar*H*), 7.11–7.32 (m, 9 H, Ar*H*, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.2, 31.4, 38.6, 39.2, 55.1, 70.1, 70.5, 71.1, 71.3, 75.6, 80.1, 103.9, 113.7, 114.2, 125.7, 128.3, 129.3, 130.8, 131.8, 142.4, 158.6, 159.1 ppm. $C_{30}H_{34}O_4$ (458.60): calcd. C 78.57, H 7.47; found C 78.63, H 7.28.

[(*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl]tributyl-stannane (32): To a stirred solution of **31** (1.10 g, 2.40 mmol) in benzene (40 mL) were added *n*Bu$_3$SnH (0.768 g, 0.71 mL, 2.64 mmol) and AIBN (79 mg, 0.48 mmol) at room temperature under N_2. The reaction mixture was gently refluxed with stirring for 4 h. The solvent was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **32** (1.73 g, 96%) as a yellowish oil. $[\alpha]_D^{25}$ = +8.8 (*c* = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2958, 2929, 2853, 1612, 1513, 1464, 1378, 1249, 1171, 1035 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.94 [dt, *J* = 7.2, 2.3 Hz, 9 H, Sn(CH$_2$CH$_2$CH$_2$-C*H*$_3$)$_3$], 1.27–1.43 [m, 10 H, Sn(C*H*$_2$C*H*$_2$C*H*$_2$CH$_3$)$_3$, 1.59–1.74 (m, 10 H, SnC*H*$_2$C*H*$_2$C*H*$_2$CH$_3$)$_3$], CHOC*H*$_2$CHO, 1.82–2.02 (m, 2 H,

CHOCH_2), 2.23 (t, J = 7.0 Hz, 2 H, PhCH$_2$CH_2), 2.69 (ddd, J = 6.6, 2.3, 2.3 Hz, 2 H, PhCH_2), 3.69–3.77 (m, 1 H, CHOCH$_2$Ar), 3.79 (s, 3 H, OCH$_3$), 3.81 (s, 3 H, OCH_3), 3.97–4.04 (m, 1 H, CHO-CH$_2$Ar), 4.36–4.63 (m, 4 H, OCH_2Ar), 5.15 (d, J = 15.5 Hz, 1 H, -CHSn), 5.85 (ddd, J = 16.7, 7.1, 7.1 Hz, 1 H, CH=CHSn), 6.91 (d, J = 8.6 Hz, 4 H, ArH), 7.17–7.31 (m, 9 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 13.4, 16.2, 17.3, 26.6, 26.8, 27.6, 30.7, 31.5, 35.0, 35.3, 39.3, 42.0, 54.9, 70.0, 70.3, 75.4, 75.7, 113.7, 114.2, 117.3, 125.6, 128.2, 129.4, 130.2, 131.6, 134.8, 141.8, 158.6, 159.1 ppm. $C_{42}H_{62}O_4Sn$ (749.64): calcd. C 67.29, H 8.34; found C 67.34, H 8.25.

1-{[(*E*,3*S*,5*S*)-5-(4-Methoxybenzyloxy)-8-iodo-1-phenyloct-7-en-3-yloxy]methyl}-4-methoxybenzene (9): To a cooled (0 °C) and stirred solution of **32** (1.3 g, 1.73 mmol) in CH$_2$Cl$_2$ (40 mL) was added iodine (484 mg, 1.91 mmol). After 30 min at 0 °C, the reaction mixture was diluted with CH$_2$Cl$_2$, washed with saturated Na$_2$S$_2$O$_3$ and 10% KF solutions, and brine. The organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9.5:0.5) as eluent gave **9** (0.96 g, 94% yield) as a yellowish oil. $[\alpha]_D^{25}$ = +6.6 (c = 0.7, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2986, 2937, 2858, 1614, 1511, 1467, 1379, 1171, 1092, 948 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.29–1.39 (m, 2 H, CHOCH_2CHO), 1.71 (t, J = 6.2 Hz, 1 H PhCH$_2$CH_A), 1.81–1.93 (m, 1 H, PhCH$_2$CH_B), 2.36 (dd, J = 6.8, 5.8 Hz, 2 H, CH_2C=CHI), 2.65 (t, J = 8.5 Hz, 2 H, PhCH_2), 3.69–3.77 (m, 1 H CHOCH$_2$Ar), 3.79 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.97–4.04 (m, 1 H, CHOCH$_2$Ar), 4.36–4.63 (m, 4 H, OCH_2Ar), 6.19 (m, 2 H, CH=CHI), 6.89 (d, J = 8.8 Hz, 4 H, ArH), 7.17–7.31 (m, 9 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 31.3, 35.8, 38.4, 39.7, 55.1, 70.1, 70.4, 75.3, 75.8, 113.7, 114.5, 117.2, 125.8, 128.2, 129.5, 130.2, 131.6, 134.8, 141.8, 158.6, 159.1 ppm. $C_{30}H_{35}IO_4$ (586.51): calcd. C 61.44, H 6.01; found C 61.68, H 6.22.

(*E*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol (33): To a solution of vinylic iodide **9** (540 mg, 0.927 mmol) in THF (15 mL) was added *n*BuLi (0.58 mL, 1.0 mmol, 1.6 M solution in hexane) at –78 °C. The yellow mixture was warmed to 0 °C for 30 min before recooling to –78 °C. Then, the reaction mixture was treated with CuCN (96 mg, 1.38 mmol), followed by addition of but-3-enal **10** (78 mg, 0.39 mmol) at –78 °C. Stirring was continued at –50 °C for 1.5 h. The reaction was quenched by addition of aqueous NH$_4$Cl, then the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na$_2$SO$_4$), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **33** (0.49 g, 68%) as a yellow syrupy liquid. $[\alpha]_D^{25}$ = –31.8 (c = 1.1, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 3443, 3064, 3028, 2938, 2864, 1949, 1870, 1710, 1641, 1603, 1496, 1454, 1350, 1067 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): (as a diastereomeric mixture, dr = 2:1): δ = 1.62–1.76 (m, 2 H, CHOCH_2CHO), 1.78–1.94 (m, 2 H, PhCH$_2$CH_2), 2.05 (br. s, 1 H, OH), 2.23–2.41 (m, 4 H, CH_2CH=CH, CH_2CH=CH$_2$), 2.59–2.79 (m, 2 H, PhCH_2), 3.41–3.58 (m, 1 H, CHOH), 3.65–3.74 (m, 2 H, 2XCHOCH$_2$Ar), 3.78 (s, 3 H), 3.79 (s, 3 H, OCH$_3$), 3.82 (m, 3 H, OCH$_3$), 4.16 (d, J = 6.1 Hz, 1 H, OCH_AAr), 4.19 (d, J = 11.1 Hz, 1 H, OCH$_B$Ar), 4.43 (d, J = 8.3 Hz, 1 H, OCH$_A$Ar), 4.48 (d, J = 8.0 Hz, 1 H, OCH$_B$Ar), 5.10–5.18 (m, 2 H, CH=CH_2), 5.51–5.92 (m, 3 H, CH=CH, CH=CH$_2$), 6.83 (d, J = 8.7 Hz, 4 H, ArH), 7.17–7.34 (m, 9 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): (as a diastereomeric mixture, dr = 2:1): δ = 29.9, 31.2, 31.3, 31.5, 35.8, 36.83, 36.89, 39.9, 41.9, 55.2, 70.3, 70.6, 71.6, 71.69, 74.64, 74.88, 74.96, 113.7, 117.98, 118.0, 125.7, 127.4, 127.5, 128.32, 128.37, 129.33, 129.36, 129.42, 129.48, 130.76, 130.79, 130.86, 134.39, 134.86, 134.90, 134.94, 142.31, 159.02, 159.11 ppm.

Synthesis of Compound 8 by Chiral Reduction

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol (8): To a solution of **33** (0.35 g, 0.66 mmol) in EtOAc (5 mL) in a round-bottomed flask was added IBX (557 mg, 1.99 mmol) in one portion and the reaction mixture was refluxed for 6 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude enone product **34**, which was pure enough and used in the next step without further purification. To a solution of above crude product **34** (349.0 mg, 0.570 mmol) in THF (10 mL) was added (*R*)-BINAL-H (0.5 M solution in THF, 7.52 mL, 3.76 mmol) at –78 °C. The reaction mixture was stirred at –78 °C for 3 h. The resultant mixture was treated with 1.0 N HCl (10 mL) and extracted with CHCl$_3$ (3 × 20 mL). The organic layer was washed with 1.0 N NaOH (20 mL), brine (20 mL), dried (Na$_2$SO$_4$), filtered, and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent gave **8** (210 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = +7.9 (c = 1.1, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 3522, 2935, 2857, 1454, 1342, 1104, 1026, 914, 752, 698 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.69 (t, J = 5.8 Hz, 2 H, CHOCH_2CHO), 1.81–1.94 (m, 2 H, PhCH$_2$CH_2), 2.05 (br. s, 1 H, OH), 2.23–2.41 (m, 4 H, CH_2CH=CH, CH_2CH=CH$_2$), 2.67 (t, J = 7.9 Hz, 2 H, PhCH_2), 3.43–3.58 (m, 1 H, CHOH), 3.65–3.70 (m, 2 H, 2XCHOCH$_2$Ar), 3.78 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 4.25 (d, J = 11.1 Hz, 2 H, OCH_2Ar), 4.47 (d, J = 8.4 Hz, 2 H, OCH_2Ar), 5.10–5.18 (m, 2 H, CH=CH_2), 5.51–5.71 (m, 2 H, CH=CH), 5.75–5.92 (m, 1 H, CH$_2$CH=CH$_2$), 6.88 (d, J = 8.7 Hz, 4 H, ArH), 7.17–7.34 (m, 9 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 31.2, 35.8, 36.8, 39.9, 41.9, 55.2, 70.5, 70.7, 71.7, 74.6, 74.9, 113.8, 118.0, 125.7, 127.4, 128.3, 129.4, 130.8, 134.3, 134.9, 142.3, 159.3, 159.1 ppm. $C_{34}H_{42}O_5$ (530.70): calcd. C 76.95, H 7.98; found C 77.16, H 7.83.

1-[(3*S*,5*S*)-3,5-Bis(4-methoxybenzyloxy)oct-7-enyl]benzene (12): To a solution of **31** (1.60 g, 3.49 mmol) in ethyl acetate (40 mL) was added Lindlar's catalyst (20 mg). The reaction mixture was stirred for 1 h under a balloon of H$_2$ at room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to give **12** (590 mg, 95%) as a pale yellow oil. $[\alpha]_D^{25}$ = +16.1 (c = 0.9, CHCl$_3$). IR (neat): $\tilde{\nu}_{max}$ = 2938, 2864, 1949, 1870, 1710, 1641, 1603, 1496, 1454, 1350, 1067 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ = 1.22–1.29 (m, 1 H, CHOCH-$_A$CHO), 1.34–1.39 (m, 1 H, CHOCH_BCHO), 1.71 (t, J = 6.2 Hz, 1 H, PhCH$_2$CH_A), 1.81–1.93 (m, 1 H, PhCH$_2$CH_B), 2.36 (dd, J = 6.8, 5.8 Hz, 2 H, CH_2CH=CH$_2$), 2.67 (t, J = 8.5 Hz, 2 H, PhCH_2), 3.61–3.74 (m, 2 H, 2 × CHOCH$_2$Ar), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.25 (dd, J = 10.9, 4.3 Hz, 1 H, OCH_AAr), 4.47 (s, 3 H, OCH_BAr, OCH_2Ar), 5.03–5.15 (m, 2 H, CH=CH_2), 5.76–5.93 (m, 1 H, CH=CH$_2$), 6.87 (t, J = 8.8 Hz, 4 H, ArH), 7.17–7.31 (m, 9 H, ArH, PhH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 31.1, 35.7, 38.4, 39.8, 55.0, 70.3, 70.5, 74.5, 74.7, 113.6, 114.2, 117.1, 125.6, 128.3, 129.3, 130.3, 130.7, 131.8, 142.2, 158.9, 159.0 ppm. $C_{30}H_{36}O_4$ (460.61): calcd. C 78.23, H 7.88; found C 78.31, H 7.67.

(*S*)-2-[(*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl]-oxirane (35): Olefin **12** (0.218 g, 0.47 mmol) was diluted with CH$_2$Cl$_2$ (10 mL) and degassed for 15 min. Vinyl epoxide (0.099 g, 1.42 mmol) was then added to the reaction flask followed by the catalyst (40 mg, 0.047 mmol). The reaction was allowed to reflux for eighteen hours under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated and purified by flash

column chromatography to give the product (0.038 g, 16%). $[\alpha]_D^{25}$ = +11.6 (*c* = 0.6, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 1.58 (dd, *J* = 7.6, 7.8 Hz, 2 H, CHOCH_2CHO), 1.73–1.84 (m, 2 H, PhCH_2CH_2), 2.24 (m, 2 H, CH_2CH=CH), 2.61–2.81 (m, 3 H, PhCH_2, C*H*OCH_2Ar), 2.88 (dd, *J* = 5.9, 4.0 Hz, 1 H, C*H*OCH_2Ar), 3.07–3.13 (m, 1 H, CH_AO oxirane), 3.61–3.74 (m, 2 H, C*H*O, CH_BO oxirane), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.25–4.47 (m, 4 H, OCH_2Ph), 5.58 (dd, *J* = 15.6, 6.4 Hz, 1 H, CH=C*H*), 5.74 (ddd, *J* = 15.5, 7.3, 7.3 Hz, 1 H, CH$_2$C*H*=CH), 6.88 (t, *J* = 8.8 Hz, 4 H, Ar*H*), 7.17–7.31 (m, 9 H, Ar*H*, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.6, 31.2, 36.9, 38.9, 48.1, 51.6, 55.2, 70.7, 71.9, 74.6, 74.8, 113.8, 118.0, 125.7, 127.4, 128.3, 129.6, 130.8, 131.5, 134.4, 134.8, 141.9, 159.0, 159.1 ppm. $C_{32}H_{38}O_5$ (502.65): calcd. C 76.46, H 7.62; found C 76.59, H 7.41.

(*E*,5*S*,7*S*)-5,7-Bis(4-methoxybenzyloxy)-9-phenylnon-2-enal (38): Olefin **12** (0.810 g, 1.75 mmol) was diluted with CH_2Cl_2 (10 mL) and degassed for 15 min. Acrolein (394 mg, 7.03 mmol) was then added to the reaction flask followed by the catalyst (149 mg, 0.175 mmol, 10 mol-%). The reaction was allowed to stir for 4 d under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated and purified by flash column chromatography to give the product **38** (653 mg, 76%) as brown colored liquid. $[\alpha]_D^{25}$ = +26.1 (*c* = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2920, 2939, 2862, 1690, 1513, 1248, 1130, 1032 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.29 (m, 1 H, OCHCH_AOCH), 1.34–1.39 (m, 1 H OCHCH_BOCH), 1.71 (m, 1 H, PhCH$_2$CH_A), 1.81–1.93 (m, 1 H, PhCH$_2$CH_B), 2.36 (dd, *J* = 6.8, 5.8 Hz, CH_2CH=CH), 2.67 (t, *J* = 8.5 Hz, 2 H, PhCH_2), 3.61–3.74 (m, 2 H, 2XC*H*OCH$_2$Ar), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.37 (s, 2 H, OCH_2Ar), 4.47 (s, 2 H, OCH_2Ar), 5.76–5.93 (m, 1 H, CH=C*H*CHO), 6.52–6.61 (m, 1 H, C*H*=CHCHO), 6.87 (m, 4 H, Ar*H*), 7.17–7.31 (m, 9 H, Ar*H*, Ph*H*), 9.52 (s, 1 H, C*H*O) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.1, 35.7, 38.4, 39.8, 70.3, 70.5, 74.5, 74.7, 113.6, 114.2, 117.1, 125.6, 128.3, 129.3, 130.3, 130.7, 131.8, 142.2, 158.9, 159.0, 185.2 ppm.

Synthesis of Compound 8 by Chiral Allylation

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-ol (8): Allylmagnesium bromide (0.78 mL, 1.0 M, 0.78 mmol) was added dropwise to a well-stirred solution of (+)-DIP chloride (251 mg, 0.78 mmol) in Et_2O (5 mL) at –78 °C. The mixture was then stirred for 0.5 h at –78 °C, warmed to room temperature, and stirred for 4 h. The solvent was removed under vacuum, and the residue was extracted with pentane (3 × 10 mL) filtered and concentrated to afford $^{\prime}Ipc_2BAll$ (**39**) in essentially quantitative yield. The reagent was dissolved in pentane to make a 1 M solution. A 0.57 mmol (0.57 mL) amount of the above $^{\prime}Ipc_2BAll$ was dissolved in Et_2O (0.6 mL) and cooled to –100 °C. A solution of aldehyde **38** (255 mg, 0.52 mmol) in anhydrous Et_2O (0.5 mL) was added dropwise, and the reaction mixture was stirred at –100 °C for 2 h. Addition of methanol (0.5 mL) to this intermediate, followed by the usual workup with NaOH and H_2O_2, afforded the crude product which was extracted with Et_2O, washed with brine, and dried (Na_2SO_4). Purification of the crude product by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent afforded **8** (207 mg, 74%) as a yellowish syrupy liquid. All data (IR, ^1H NMR, and ^{13}C NMR) were identical to the compound **8** derived by chiral reduction.

(*E*,4*R*,8*S*,10*S*)-8,10-Bis(4-methoxybenzyloxy)-12-phenyldodeca-1,5-dien-4-yl Acrylate (7): Acryloyl chloride (0.029 g, 0.025 mL, 0.317 mmol) was added dropwise under argon to a solution of **8** (112 mg, 0.211 mmol) and triethylamine (0.053 g, 0.074 mL, 0.528 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred for 5 h at room temperature. The resulting mixture was filtered through a pad of Celite and poured into water and organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and combined organic layer was washed with brine, dried (Na_2SO_4), and concentrated. Purification of the crude product by silica gel column chromatography using petroleum ether/EtOAc (19:1) as eluent afforded **7** (101 mg, 82%) as a yellowish syrupy liquid. $[\alpha]_D^{25}$ = +29.1 (*c* = 1.1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3068, 3025, 2985, 2934, 2857, 1721, 1639, 1494, 1454, 1404, 1296, 1224, 1194, 1117, 1041, 971, 917, 810, 750, 699, 500 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.60 (t, *J* = 7.6 Hz, 2 H, OCHCH_2CHO), 1.68–1.92 (m, 2 H, PhCH$_2$CH_2), 2.26 (m, 2 H, PhCH_2), 2.44 (m, 2 H, CH_2CH=CH$_2$), 2.56–2.64 (m, 1 H, CH_ACH=CH), 2.71–2.79 (m, 1 H CH_BCH=CH), 3.62–3.75 (m, 2 H, 2XC*H*OCH$_2$Ar), 3.78 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 4.25–4.47 (m, 4 H, OCH_2Ar), 5.02–5.11 (m, 2 H, OCH$_2$CH=CH_2), 5.37 (q, *J* = 6.7 Hz, 1 H, C*H*OCOCH=CH$_2$), 5.55 (ddt, *J* = 15.4, 7.1, 1.1 Hz, 1 H, OCOC*H*=CH$_2$), 5.68–5.79 (m, 2 H, C*H*=C*H*), 5.82 (dd, *J* = 10.2, 1.5 Hz, 1 H OCOCH=CH_A), 6.14 (dd, *J* = 17.3, 10.3 Hz, 1 H, CH$_2$C*H*=CH$_2$), 6.43 (dd, *J* = 17.3, 1.8 Hz, 1 H, OCOCH=CH_B), 6.89 (t, *J* = 8.7 Hz, 4 H, Ar*H*), 7.18–7.31 (m, 9 H, Ar*H*, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.7, 37.5, 38.1, 38.5, 39.0, 55.0, 70.1, 70.6, 73.9, 74.5, 74.7, 117.9, 125.8, 128.3, 128.5, 128.8, 130.1, 130.5, 133.3, 142.0, 158.9, 159.0, 165.4 ppm. $C_{37}H_{44}O_6$ (584.75): calcd. C 76.00, H 7.58; found C 76.22, H 7.41.

(*R*)-6-[(*E*,4*S*,6*S*)-4,6-Bis(4-methoxybenzyloxy)-8-phenyloct-1-enyl]-5,6-dihydropyran-2-one (40): Grubb's catalyst (13 mg, 0.016 mmol) dissolved in CH_2Cl_2 (10 mL) was added dropwise to a refluxing solution of acrylate **7** (94 mg, 0.161 mmol), Ti(*i*PrO)$_4$ (1.4 mg, 0.005 mmol) in dry CH_2Cl_2 (60 mL). Refluxing was continued for 6 h by which time all the starting material was consumed. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford **40** (78 mg, 87%) as a yellowish syrupy liquid. $[\alpha]_D^{25}$ = –49.2 (*c* = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2929, 2857, 1730, 1245, 1119, 1026, 699 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.61 (dd, *J* = 7.6, 7.9 Hz, 2 H, CHOCH_2CHO), 1.73–1.91 (m, 2 H, PhCH$_2$CH_2), 2.24–2.29 (m, 2 H, CHOCH_2CH=CH), 2.41–2.46 (m, 2 H, PhCH_2), 2.60–2.2.67 (m, 1 H, CH_ACH=CH-COO), 2.74–2.85 (m, 1 H, CH_BCH=CHCOO), 3.61–3.75 (m, 2 H, 2XC*H*OCH$_2$Ar), 3.79 (s, 3 H, OCH$_3$), 3.82 (s, 3 H, OCH$_3$), 4.25–4.47 (m, 4 H, 2× OCH_2Ar), 4.86–5.01 (m, 1 H, C*H*OCO), 5.64 (ddd, *J* = 10.3, 2.4, 1.8 Hz, 1 H CH$_2$CH=C*H*), 5.81 (ddd, *J* = 15.5, 7.2, 7.2 Hz, 1 H, CH$_2$C*H*=CH), 6.04 (ddd, *J* = 10.3, 2.4, 1.8 Hz, 1 H, COC*H*=CH), 6.87 (ddd, *J* = 9.7, 4.1, 4.1 Hz, 1 H, COCH=C*H*), 6.87 (t, *J* = 8.8 Hz, 4 H, Ar*H*), 7.17–7.31 (m, 9 H, Ar*H*, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7, 31.6, 37.4, 38.1, 38.4, 55.0, 70.3, 70.5, 74.5, 74.7, 77.9, 113.6, 121.6, 125.6, 125.7, 128.3, 128.4, 129.1, 130.3, 131.0, 134.8, 141.9, 144.6, 158.9, 159.0 ppm. 163.9. $C_{35}H_{40}O_6$ (556.70): calcd. C 75.51, H 7.24; found C 75.37, H 7.11.

(+)-Strictifolione (1): To a stirring solution of PMB ether **40** (35 mg, 0.062 mmol) in CH_2Cl_2/H_2O (18:1) was added DDQ (43 mg, 0.19 mmol). The resulting mixture was stirred for 45 min at room temp. 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 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as a yellow oil. Silica gel column chromatography of the crude product using MeOH/EtOAc (1:9) as eluent gave **1** (18 mg, 91%) as a colorless

solid; m.p. 111–114 °C; ref.[2] 119–121 °C. $[\alpha]_D^{25}$ = +72 (*c* = 0.6, $CHCl_3$); ref.[2] $[\alpha]_D^{25}$ = +81.5 (*c* = 0.52, $CHCl_3$), ref.[11e] $[\alpha]_D^{25}$ = +54.1 (*c* = 0.33, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1048, 1238, 1380, 1437, 1724, 2934 and 3328 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.64 (t, *J* = 5.6 Hz, 2 H, CHOHCH_2CHOH), 1.73–1.91 (m, 2 H, PhCH_2CH_2), 2.29 (t, *J* = 6.6 Hz, 2 H, CH_2CH=CH), 2.41–2.46 (m, 2 H, CHOCH_2CH=CH), 2.55 (d, *J* = 4.5 Hz, 2 H, 2XOH), 2.64–2.86 (m, 3 H, C*H*OH, PhCH_2), 3.98–4.03 (m, 1 H, C*H*OH), 4.90 (m, 1 H, C*H*OCO), 5.69 (dd, *J* = 15.5, 6.6 Hz, 1 H, CH_2C*H*=CH), 5.88 (ddt, *J* = 15.6, 7.3, 1.1 Hz, 1 H, CH_2CH=C*H*), 6.05 (dt, *J* = 9.8, 1.8 Hz, 1 H, OCOC*H*=CH), 6.90 (ddd, *J* = 9.7, 4.8, 3.6 Hz, 1 H, OCOCH=C*H*), 7.21–731 (m, 5 H, Ph*H*) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.7, 32.1, 38.9, 40.3, 42.1, 68.29, 68.78, 77.73, 121.4, 125.57, 128.36, 128.37, 129.46, 131.0, 141.8, 144.6, 163.8 ppm.

Natural (+)-Strictifolione:[2] Fine colorless solid; m.p. 119–121 °C. $[\alpha]_D^{25}$ = +81.58 (*c* = 0.52, $CHCl_3$), FABMS(NBA) *m*/*z*: 317 [M + H]$^+$. IR (neat): $\tilde{\nu}_{max}$ = 1048, 1239, 1380, 1437, 1723 2932, and 3325 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.65 (dd, *J* = 5.2, 6.1 Hz, 2 H, CHOHCH_2CHOH), 1.78 (m, 1 H, PhCH_2CH_A), 1.87 (m, 1 H, PhCH_2CH_B), 2.28 (dd, *J* = 6.7 and 7.0 Hz, 2 H, CH_2CH=CH), 2.36 (d, *J* = 4.6 Hz, 1 H, OH), 2.43 (m, 2 H, CHOCH_2CH=CH), 2.52 (d, *J* = 3.9 Hz, 1 H, OH), 2.68 (m, 1 H, PhCH_A), 2.79 (m, 1 H, PhCH_B), 3.99 (m, 1 H, C*H*OH), 4.03 (m, 1 H, C*H*OH), 4.89 (ddd, *J* = 6.0, 6.0, 9.4 Hz, 1 H, C*H*OCO), 5.68 (ddd, *J* = 1.2, 6.4, 15.6 Hz, 1 H, CH_2C*H*=CH), 5.86 (dddd, *J* = 1.2, 7.5, 7.5, 15.4 Hz, 1 H, CH_2CH=C*H*), 6.05 (ddd, *J* = 1.7, 2.1, 9.6 Hz, 1 H OCOC*H*=CH), 6.88 (ddd, *J* = 3.6, 4.9, 9.7 Hz, 1 H, OCOCH=C*H*), 7.17–7.21 (m, 3 H, Ph*H*), 7.27–7.29 (m, 2 H, Ph*H*) ppm. ^{13}C NMR (125 MHz, CDCl3): δ = 29.74, 32.17, 38.97, 40.34, 42.09, 68.29, 68.82, 77.73, 121.56, 125.92, 128.38, 128.46, 130.0, 131.07, 141.80, 144.64, 163.96 ppm.

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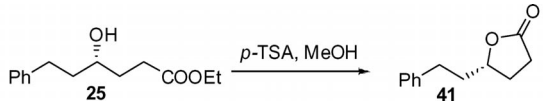

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