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Titanium(IV)-Promoted Regioselective Nucleophilic Ring-Opening Reaction of Chiral Epoxyallyl Alcohols with Acids as a Tool for Ready Access to Chiral 1,2,3-Triol Monoesters: Application to Stereoselective Total Synthesis of Macrolides

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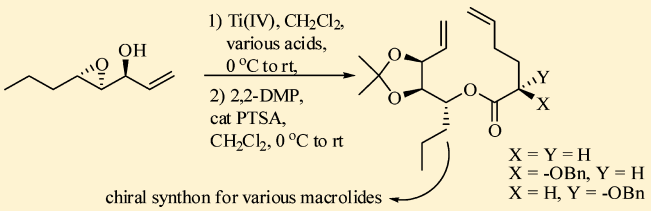
Supporting Information

ABSTRACT: Titanium(IV)-promoted regioselective ring-opening reaction of *chiral epoxy–allyl alcohols* (Sharpless conditions as the key strategic step) is developed as a tool for ready access to chiral 5,6-dihydroxyoct-7-en-4-yl alkoxylates. Later, the synthetic utility of products thereof was demonstrated through the RCM based stereoselective synthesis of various natural products.



The ubiquitous presence of 1,2,3-triol segment in many biologically active natural products has led to the development of multiple synthetic strategies. As a consequence, interest in the structure and biological feature of the polyol containing macrolides[1−6] as appealing synthetic targets increased manifold (Figure 1).

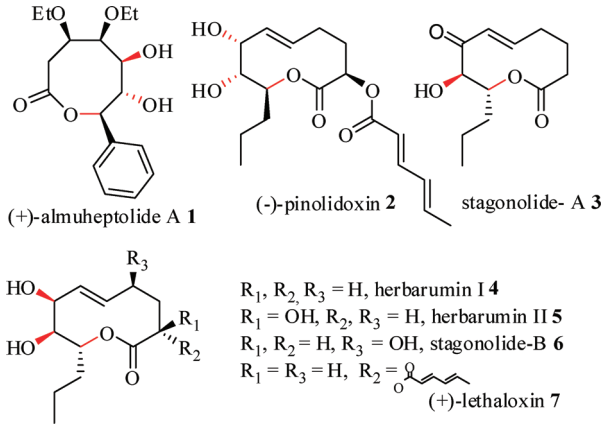


Figure 1. Some representative examples of macrolides.

Conventionally 1,2,3-triol-containing molecules are accessed from carbohydrates via their functional group manipulation,[7] but ever since the discovery of Sharpless asymmetric epoxidation in 1980,[8] ring-opening reaction of enantiopure 2,3 epoxy alcohols with various nucleophiles emerged as an alternate synthetic route to such systems. Interestingly, such a ring-opening reaction has been extensively studied.[9] Of the many metal assisted intermolecular C3-selective substitution reactions of 2,3-epoxy alcohols, Sharpless titanium(IV)-mediated regioselective ring-opening protocol is worth mentioning.[10]

Against this backdrop and mindful of the significance attached to chiral 1,2,3-triol fragments, we devised a Sharpless-based strategy of regioselective ring-opening reaction of internal epoxy alcohols initially with benzoic acid and later with unsaturated acid nucleophiles (Figure 2) as a new method of accessing selectively derivatized polyol esters. Additionally, if these esters (or their precursors) are endowed with appropriately positioned (terminal) olefinic functional groups, then they could undergo ring-closing metathesis (RCM) to furnish a gamut of macrocyles that could be extrapolated to the targets. Thus, the striking difference of the present disclosure is the use of internal chiral epoxy allyl alcohol(s) and aliphatic acid(s) as the nucleophile(s) to afford 1,2,3-triol monoester(s) as valuable synthetic intermediates in a highly regioselective manner (a C5-opening).

Accordingly, two enantiomeric epoxides (epoxy allyl alcohols **9** and *ent*-**9**, Scheme 1) selected for the study were accessed via the Sharpless kinetic resolution of the corresponding racemic divinyl methanol **8**[11] that was in turn obtained from the oxidation–vinylation reaction set of the commercially available (*E*)-2-hexen-1-ol in good yields (for synthesis, see the Supporting Information).

First, we validated the epoxide ring-opening reaction (**9**) using benzoic acid as the nucleophile to afford the corresponding 1,2,3-triol monoester derivative (in this case as benzoate **10**) as the sole product in good yield, favoring an exclusive C5-attack (Scheme 1). To recount, the key transformations are the titanium catalyzed C5-selective ring-opening reaction of epoxy allyl alcohol **9** with benzoic acid,

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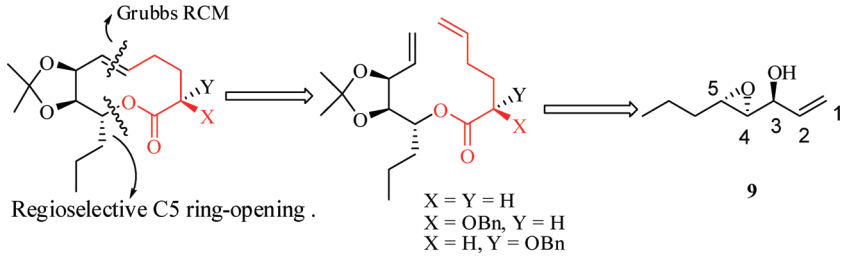
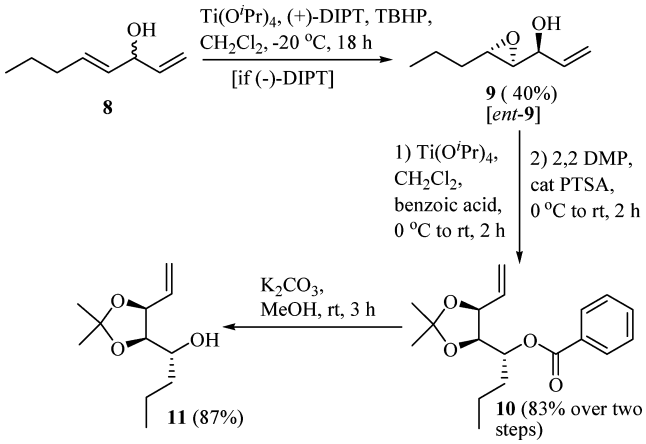


Figure 2. Retrosynthesis of macrolides.

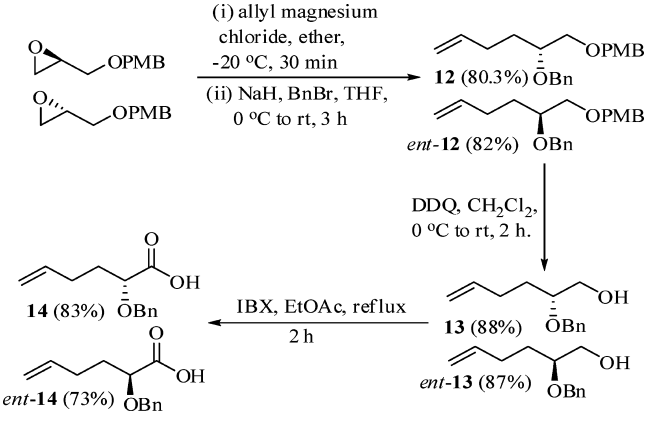
Scheme 1



acetonide protection of the resultant (4*R*,5*S*,6*S*)-5,6-dihydroxyoct-7-en-4-yl benzoate (**10**) followed by its debenzoylation reaction gave alcohol **11** (83% over two steps). Accordingly, the synthesis of alcohol **11**, identified as the crucial intermediate, was accomplished by a three-step strategy. With this promising result in hand the scope of this reaction is investigated.

Having realized that if RCM reaction could be used in conjunction with this methodology an array of macrolides could be synthesized in shorter sequence, next we turned our attention to using aliphatic olefinic acids (hexenoic acid, **14** and

Scheme 2. Preparation of Acid Components



ent-**14**, Scheme 2) as the nucleophiles in the ring-opening reaction.

Accordingly, when epoxide **9** was treated with 5-hexenoic acid under the standardized conditions (route A) gave the corrresponding bis-olefinic ester, which on protection as acetonide furnished the derivatized bis-olefinic ester (**15**). Similarly ring-opening reaction of epoxides **9** and *ent*-**9** with aliphatic olefinic acids **14** and *ent*-**14** gave the respective bis-olefinic esters **15a**–**c** (see Scheme 3). These esters constitute the late-stage intermediates in the synthesis of 10-membered macrolides and some of them (**15**, **15a** and **15b**, Scheme 3) are exemplified herein. Additionally, esters **15**, **15a**, and **15b** were independently synthesized by route B and their data correlated.

Though many syntheses were reported for the macrolides listed in Figure 1, synthesis of select macrolides was undertaken as "proof of concept" (Figure 2). For example, several reported syntheses of herbarumin I (**4**), a biologically active natural product, involved more than 10 steps,[7a,12] but using these sequential reactions **4** was obtained in **5** steps (vide infra, Scheme 3). The use of the some of these esters as advanced intermediates is showcased below.

Total synthesis of Herbarumin I and Formal Synthesis of Stagonolide A. Herbarumin I **4**, one of the bioactive compounds of phytotoxin family was selected as the first target molecule. Although many reported syntheses adopted chiron approach, the one disclosed herein utilizes the present methodology to result in stereoselective synthesis of **4** in five steps (route A) and 7 steps (route B). Thus, the diene system (**15**, Scheme 4) was prepared by two synthetic pathways (route A, Scheme 3), one through the coupling of **9** with 5-hexenoic acid in the presence of titanium(IV) complex, followed by acetonide protection to afford the corresponding diene ester **15**, another (route B, Scheme 3) by the conventional coupling of alcohol (**11**) with 5-hexenoic acid to afford the same diene ester **15** in equally good yields.

The crucial RCM of **15** using Grubbs-I catalyst furnished macrolide **16** as an exclusive *E*-isomer in 76% yield. Macrolide **16** on $TiCl_4$-mediated deprotection of the acetonide group resulted in herbarumin I[12] (**4**, 74%). Herbarumin I **4** itself constitutes a late-stage intermediate in the synthesis of stagonolide A **3**. For instance, selective oxidation of allyl alcohol **4** affords **3**.[13]

Total Synthesis of Herbarumin II.[14] The RCM of **15a** (Scheme 4) using Grubbs II catalyst gave macrolide **17** as the *Z*-isomer in 88% yield. However, the corresponding major *E*-isomer (**16a**) was obtained by Grubbs I catalyst albeit resulting in a inseparable mixture of starting material **15a** and macrolide **16a** (80% combined yield). Hence, global deprotection of the mixture with $TiCl_4$ resulted in the isolation of herbarumin II[14] (**5**, 56%) as a pure product.

Formal Synthesis of (+)-Lethaloxin. Similarly, RCM of **15b** (Scheme 5) using Grubbs I catalyst afforded *E*-isomer **16b**. Later, debenzylation under DDQ reaction conditions resulted in macrolide **18** (54%), which is a known intermediate in the synthesis (+)-lethaloxin (**7**). Thus, synthesis of macrolide **18** constitutes the formal total synthesis of (+)-lethaloxin.[15]

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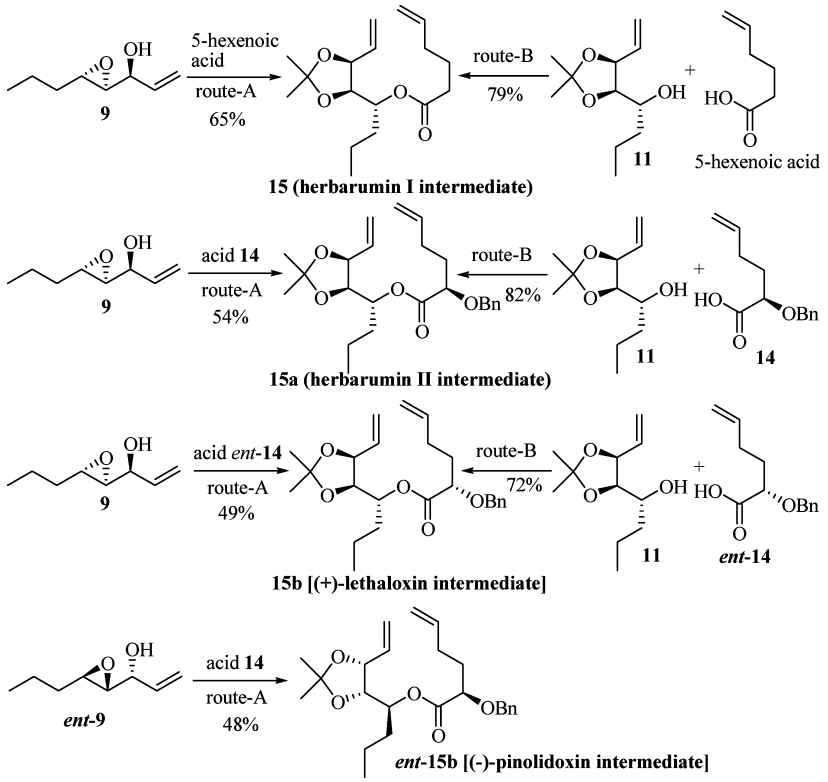
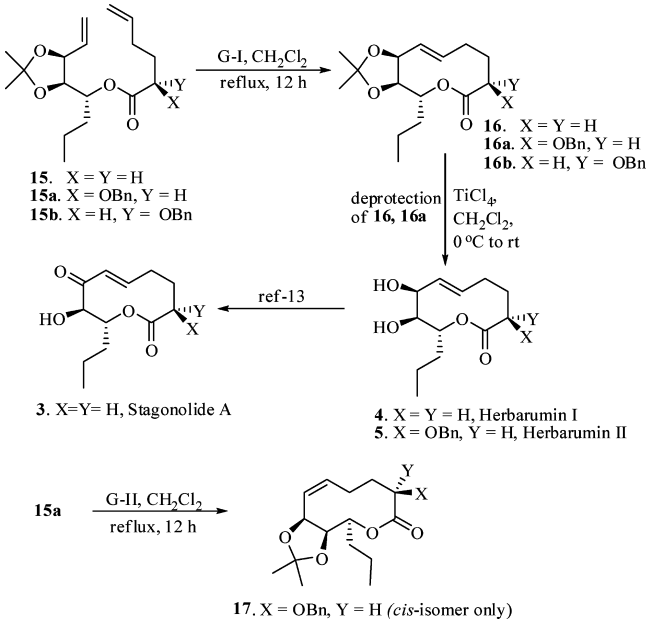
Scheme 3. Preparation of Diene Esters under Different Routes[a]

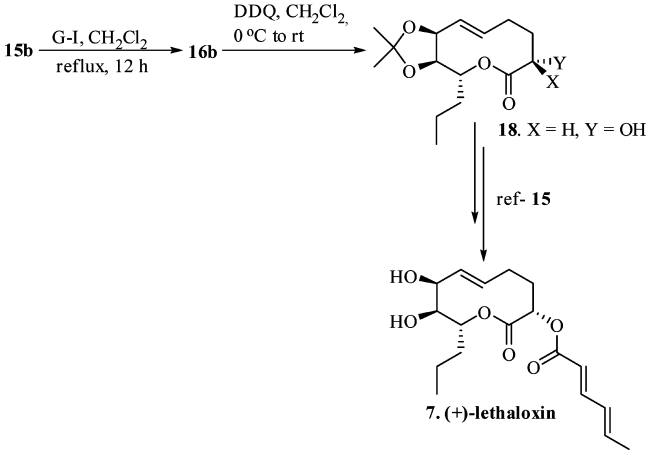


[a]Reaction conditions: (route A) $Ti(O^iPr)_4$, CH_2Cl_2, corresponding acid, 0 °C to rt (Sharpless conditions); (route B) DCC, DMAP, CH_2Cl_2, corresponding acid, 0 °C to rt.

Scheme 4. Synthesis of Macrolides



Scheme 5. Synthesis of (+) -Lethaloxin



CONCLUSION

In summary, we have accomplished a titanium(IV) promoted regioselective oxirane ring-opening reaction of chiral epoxy allyl alcohols as a tool for the ready access to *chiral 1,2,3-triol monoesters*. Further, the synthetic utility of such esters was exemplified by the enantioselective total synthesis of bioactive 10-membered macrolides in shorter sequences. Thus, strategically the transformation described herein opens up new vistas and shorter way of accessing building blocks that are commonly encountered as part structures in many biologically active natural products.

EXPERIMENTAL SECTION

General Experimental Procedures. All the reactions were carried under nitrogen atmosphere (all except those involving water in the reaction medium). The solvents used were purified by distillation over the drying agents indicated and were transferred under nitrogen atmosphere: CH_2Cl_2 (CaH_2), Et_3N (KOH), toluene (Na), THF, and ether were dried by distillation from sodium using sodium benzophenone ketyl as indicator. All organic extracts were dried over anhydrous Na_2SO_4, All crude reaction products were

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purified by column chromatography silica gel (60−120 mesh and 100−200 mesh) by using distilled ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 300, 400, and 500 MHz (using TMS as a reference), and C^{13} were recorded at 75 and 100 MHz (using the $CDCl_3$ triplet centered at δ 77.0 Hz as reference) in $CDCl_3$ as solvent at ambient temperature. Chemical shifts (δ) were recorded in ppm, coupling constant J are in Hz, and signal patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; td, triplet of doublet; t, triplet; m, multiplet; bs, broad singlet. FTIR spectra were recorded as KBr thin films or neat. Optical rotations were measured at 25 °C. For low (MS) and high (HRMS) resolution, m/z ratios are reported as values in atomic mass units.

I). Synthesis of Epoxyallyl Alcohol Components. *(4E)-1,4-Octadien-3-ol (**8**).* DMSO (5.0 mL), in CH_2Cl_2 (60 mL) was added to IBX (2.28 g, 8.1 mmol) at 0 °C followed by the addition of *trans*-2-hexenol (5.0 g, 6.8 mmol) at 0 °C and allowed to stir for 1 h. The crude reaction mixture was filtered through a Celite pad and washed with CH_2Cl_2 (5 × 5.0 mL). The organic layer was washed with water (2 × 10 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was directly used for the next step. The crude aldehyde was taken in THF (100 mL), then vinylmagnesium bromide (56 mL of 1 M solution) was added dropwise at −20 °C, and the reaction mixture was allowed to stir for 15 min. The reaction mixture was quenched with a saturated aq solution of NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to afford pure alcohol **8** (4.5 g, 71%) as a light yellow syrup. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89−5.81 (m, 1H), 5.69−5.60 (m, 1H), 5.49−5.43 (dd, 1H, J = 6.5, 5.4 Hz), 5.2 (dd, 1H, J = 1.09, 17.2 Hz), 5.0 (d, 1H, J = 10.2 Hz), 4.54−4.53 (br. s, 1H), 2.02 (q, 2H, J = 6.5 Hz), 1.40 (q, 2H, J = 7.3 Hz), 0.91 (t, 3H, J = 7.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 132.5, 131.0, 114.5, 73.7, 34.2, 22.1, 13.5. Anal. Calcd for $C_8H_{14}O$ (126.18) C, 76.14; H, 11.18. Found: C, 76.10; H, 11.12.

*(1S)-1-[(2S,3S)-3-Propyloxiran-2-yl]-2-propen-1-ol (**9**).* In a dried two-necked round-bottom flask, 4 Å evacuated molecular sieves powder (3.0 g) was taken, and then CH_2Cl_2 (100 mL) was added. The solution was allowed to cool to −20 °C, and then Ti(O^{i}Pr)$_4$ (11.33 mL, 39.6 mmol) and L-(+)-DIPT (11.15 g, 47.5 mmol) were added sequentially, the mixture was allowed to stir for 10 min, and TBHP (5.92 mL, 48.6 mmol, 3 M in CH_2Cl_2) was added dropwise for 15 min. After the mixture was stirred for 20 min at −20 °C, a solution of allyl alcohol **8** (5.0 g, 39.68 mmol) in CH_2Cl_2 (15 mL) was added to the reaction mixture and allowed it to stir for 18 h at the same temperature (Sharpless kinetic resolution). Reaction mixture was quenched by adding NaOH (2.5 g) in brine solution (25 mL) and stirred at rt. The reaction mixture was filtered through Celite pad, washed with EtOAc (4 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc/*n*-hexane 4:96) to obtain pure epoxy alcohol **9** (2.24 g, 40%) as a colorless liquid. $[\alpha]_D^{25}$ = +17.0 (c 0.008, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 (sept, 1H, J = 5.8, 10.2 Hz), 5.33 (d, 1H, J = 17.5 Hz), 5.23 (d, 1H, J = 10.6 Hz), 4.26 (s, 1H), 2.94 (s, 1H), 2.77 (s, 1H), 1.59−1.42 (m, 4H), 0.97 (t, 3H, J = 6.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.7, 117.2, 70.1, 60.0, 54.9, 33.4, 19.1, 13.0; IR (neat): 3427, 3084, 2962, 2872, 1382, 1079 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2$ (142.20): C, 67.57; H, 9.92. Found: C, 67.55; H, 9.89.

*(1R)-1-[(2R,3R)-3-Propyloxiran-2-yl]-2-propen-1-ol (ent-**9**).* Herein, the same procedure was adopted as described for compound **9**.

Allyl alcohol **8** (1 g, 7.9 mmol), Ti(O^{i}Pr)$_4$ (2.25 mL, 7.9 mmol), D-(−)-DIPT (2.23 g, 9.5 mmol), TBHP (1.0 mL, 3.17 mmol, 3 M in CH_2Cl_2). The residue was purified by column chromatography (EtOAc/*n*-hexane 4:96) to obtain the pure epoxy alcohol *ent*-**9** (0.42 g, 38%) as a colorless liquid. $[\alpha]_D^{25}$ = −22.0 (c 0.007, $CHCl_3$).

*(1R)-1-[(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl Benzoate (**10**).* To a stirred solution of epoxy allyl alcohol **9** (2.1 g, 14.7 mmol) in dry CH_2Cl_2 (30 mL) was added Ti(O^{i}Pr)$_4$ (6.33 mL, 22.1 mmol) under argon (Sharpless conditions). The mixture was stirred for 15 min, benzoic acid (2.7 g, 22.1 mmol) was added, and the mixture was allowed to warm to room temperature and allowed to stir for 2 h. The CH_2Cl_2 was evaporated under reduced pressure, the mixture was diluted with diethyl ether (30 mL), and 3% H_2SO_4 (10 mL) was added, and the mixture was allowed to stir until two clear layers were obtaine(1 h). The two layers were separated. The organic layer was washed with a saturated aq solution of brine (20 mL) and $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated in vacuo. In order to overcome the difficulty of separation of diol from the reaction mixture and to check if the regioselective ring-opening of epoxy alcohol favored the formation of 1,2-diols or 1,3-diols, the crude diol was taken to the next step and protected as its acetonide derivative.

To a stirred solution of crude diol (3.9 g, 14.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added PTSA (cat.) and the solution stirred for 20 min, and then 2,2-DMP (3.6 mL, 29.5 mmol) was added and the solution stirred for ∼2 h. The reaction mixture was quenched with Et_3N (2.0 mL) and concentrated in vacuo. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to obtain the pure compound **10** (3.6 g, 83%) as a colorless liquid. $[\alpha]_D^{25}$ = +20.6 (c 0.005, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, 2H, J = 6.7 Hz), 7.52 (t, 1H, J = 7.5 Hz), 7.40 (t, 2H, J = 7.9 Hz), 5.78 (td, 1H, J = 7.1, 10.5, 17.3 Hz), 5.24 (d, 1H, J = 16.9 Hz), 5.13−5.05 (m, 2H), 4.62 (dd, 1H, J = 6.4, 13.5 Hz), 4.29 (dd, 1H, J = 6.4, 7.9 Hz), 1.85−1.67 (m, 2H), 1.45−1.34 (m, 2H), 0.93 (t, 3H, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.8, 132.9, 132.8, 129.5, 128.3, 118.6, 108.8, 78.9, 78.4, 72.4, 33.5, 27.6, 25.2, 17.9, 14.0. IR (neat): 3448, 2962, 1720, 1069 cm^{-1}. HRMS: m/z calcd for $C_{18}H_{24}O_4Na$ $[M + Na]^+$ 327.1572, found 327.1576.

*(1R)-1-[(4R,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butan-1-ol (**11**).* To a stirred solution of benzoate **10** (1.7 g, 5.5 mmol) in MeOH was added K_2CO_3 (1.54 g, 11.5 mmol) and the solution stirred for 2 h. Then MeOH was removed in vacuo, and the mixture was filtered through Celite pad, washed with EtOAc (4 × 10 mL), concentrated in vacuo, and then purified by column chromatography (EtOAc/*n*-hexane 12:88) to obtain the pure compound **11** (1.0 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = +9.0 (c 0.05, $CHCl_3$). The spectral data was matched with reported values.[16]

II). Synthesis of Acid Components. *(i). (5R)-5-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]-1-hexene (**12**).*[17] A stirred suspension of Mg (0.74 g, 30.8 mmol) in dry ether was treated with allyl chloride (1.67 mL, 20.5 mmol) at room temperature, the mixture was stirred for 30 min and allowed to cool to −20 °C, (2*S*)-2-[(benzyloxy)methyl]-oxirane (2.0 g, 10.3 mmol) in ether (15 mL) was added dropwise at −20 °C, the reaction mixture was allowed to stir for 30 min, and then the reaction mixture was quenched with a saturated aq solution of NH_4Cl (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo. Crude alcohol was directly used for the next step.

To a cooled (0 °C) suspension of NaH (0.81 g, 20.4 mmol, 60% w/w dispersion in paraffin oil) in THF (15 mL) was added dropwise a solution of alcohol (2.5 g, 10.3 mmol) in THF (10 mL). After 15 min, benzyl bromide (1.63 mL, 13.3 mmol) was added dropwise at 0 °C and the mixture allowed to stir for 6 h at room temperature. The reaction mixture was quenched with a satd aq solution of NH_4Cl (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/*n*-hexane 3:97) to afford compound **12** (2.7 g, 80.3% in overall yield for two steps) as a light yellow syrup. $[\alpha]_D^{25}$ = +5.2 (c 0.15, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.18 (m, 7H), 6.82 (d, 2H, J = 8.3 Hz), 5.81−5.67 (m, 1H), 4.97−4.89 (m, 2H), 4.67 (d, 1H, J = 11.7 Hz), 4.48 (d, 1H, J = 11.8 Hz), 4.43 (s, 2H), 3.79 (s, 3H), 3.56−3.40 (m, 3H), 2.21−2.02 (m, 2H), 1.62 (q, 2H, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 143.4, 143.0, 135.0, 133.8, 132.8, 132.3, 132.0, 119.2, 118.3, 82.0, 81.6, 81.2, 59.8, 35.8, 34.2. HRMS: m/z calcd for $C_{21}H_{26}O_3Na$ $[M + Na]^+$ 349.1779, found 349.1774.

*(ii). (2R)-2-(Benzyloxy)-5-hexen-1-ol (**13**).* To a stirred solution of compound **12** (2.60 g, 7.9 mmol) in CH_2Cl_2/H_2O (19:1) (25 mL) was added DDQ (2.17 g, 9.5 mmol) at 0 °C, and the reaction mixture

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was allowed to stir at room temperature for 1 h. Then satd aq $NaHCO_3$ (10 mL) was added and the mixture extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with water (30 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo, and the crude residue was purified by column chromatography (EtOAc/*n*-hexane 10:90) to afford alcohol **13** (1.45 g, 88%) as a light yellow syrup. $[\alpha]_D^{25}$ = −16.2 (*c* 0.16, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.25 (m, 5H), 5.82−5.70 (m, 1H), 4.96 (dd, 2H, *J* = 9.8, 18.2 Hz), 4.58 (d, 1H, *J* = 11.9 Hz), 4.54 (d, 1H, *J* = 11.9 Hz), 3.69−3.66 (m, 1H), 3.50−3.48 (m, 2H), 2.11 (dd, 2H, *J* = 6.7, 14.0 Hz), 1.76−1.69 (m, 2H), 1.62−1.55 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 138.1, 128.4, 127.7, 114.9, 79.0, 71.5, 64.0, 30.0, 29.5. HRMS: *m*/*z* calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$ 229.1204, found 229.1201.

*(iii). (2R)-2-(Benzyloxy)-5-hexenoic Acid (**14**).* DMSO (2.0 mL) in EtOAc (20 mL) was added to IBX (2.28 g, 8.1 mmol) at 0 °C, followed by the addition of alcohol **13** (1.4 g, 6.8 mmol) at 0 °C, and allowed to reflux for 1 h.[5] The crude reaction mixture was filtered and washed with EtOAc (2 × 10 mL). The organic layer was washed with water (2 × 10 mL) and brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 18:82) to afford acid **15** (1.25 g, 83%) as a colorless liquid. $[\alpha]_D^{25}$ = +23.3 (*c* 0.45, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.26 (m, 5H), 5.80−5.68 (m, 1H), 4.97 (dd, 2H, *J* = 10.7, 17.0 Hz), 4.71 (d, 1H, *J* = 11.7 Hz), 4.41 (d, 1H, *J* = 11.7 Hz), 3.96 (dd, 1H, *J* = 6.3, 5.8 Hz), 2.27−2.14 (m, 2H), 1.90 (q, 2H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 137.1, 130.0, 128.4, 128.1, 128.0, 115.6, 76.6, 72.5, 31.7, 29.1. IR (neat): 3071, 2925, 1109, 1024, 914 cm^{-1}. HRMS: *m*/*z* calcd for $C_{13}H_{16}O_3Na$ $[M + Na]^+$ 243.0997, found 243.0992.

*(iv). (5S)-5-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]-1-hexene (ent-**12**).* NaH (0.56 g, 23.3 mmol, 60% w/w dispersion in paraffin oil) was added to the alcohol (1.7 g, 7.2 mmol) followed by benzyl bromide (1.14 mL, 9.3 mmol). After completion of the reaction, the crude product was purified by column chromatography (EtOAc/*n*-hexane 3:97) to afford compound *ent*-**12** (1.3 g, 82% overall yield for two steps) as a light yellow syrup. $[\alpha]_D^{25}$ = −2.9 (*c* 0.12, $CHCl_3$).

*(v). (2S)-2-(Benzyloxy)-5-hexen-1-ol (ent-**13**).* To compound *ent*-**12** (1.3 g, 3.9 mmol), DDQ (1.08 g, 4.7 mmol) was added and the crude product was purified by column chromatography (EtOAc:*n*-hexane 10:90) to afford compound *ent*-**13** (0.720 g, 87%) as a light yellow syrup. $[\alpha]_D^{25}$ = +25.4 (c 0.1, $CHCl_3$).

*(vi). (2S)-2-(Benzyloxy)-5-hexenoic Acid (ent-**14**).* The same procedure was adopted as described for compound **14**. IBX (0.7 g, 3.39 mmol), alcohol *ent*-**13** (1.14 g, 4.0 mmol). The crude product was purified by column chromatography (EtOAc:*n*-hexane 15:85) to afford compound *ent*-**14** (0.55 g, 73%) as a light yellow syrup. $[\alpha]_D^{25}$ = −22.2 (*c* 0.9, $CHCl_3$).

III). Examples of Regioselective Ring-Opening Reaction of Chiral Epoxyallyl Alcohols. *(1R)-1-[(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl 5-Hexenoate (**15**).* Route A. The same procedure was adopted as described for compound **10**.

Epoxy allyl alcohol **9** (0.100 g, 0.70 mmol), $Ti(O^iPr)_4$ (0.3 mL, 1 mmol), and commercially available 5-hexenoic acid (0.096 g, 0.84 mmol), followed by the acetonide protection. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to obtain pure compound **15** (0.135 g, 65%) as a colorless liquid.

Route B. To a stirred solution of alcohol **11** (0.05 g, 0.35 mmol) in CH_2Cl_2 (2.0 mL) was added DCC (0.056 g, 0.27 mmol) and DMAP (0.033 g, 0.27 mmol) at 0 °C, followed by 5-hexenoic acid (0.034 g, 0.29 mmol) was added at same temperature and allowed to stirr for 3 h, and the crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to obtain pure compound **15** (0.058 g, 79%) as a colorless liquid. $[\alpha]_D^{25}$ = +18.9 (*c* 0.08, $CHCl_3$). The spectral data was matched with reported values.[18]

*(1R)-1-[(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl (2R)-2-(Benzyloxy)-5-hexenoate (**15a**).* Route A. The same procedure was adopted as described for compound **10**.

Epoxy allyl alcohol **9** (0.100 g, 0.70 mmol), $Ti(O^iPr)_4$ (0.3 mL, 1 mmol) acid **14** (0.185 g, 0.84 mmol), followed by acetonide protection. The crude residue was purified by column chromatography (EtOAc/:*n*-hexane 1.5:98.5) to obtain pure compound **15a** (0.159 g, 54%) as a colorless liquid.

Route B. Alcohol **11** (0.05 g, 0.25 mmol), DCC (0.056 g, 0.27 mmol) and DMAP (0.033 g, 0.27 mmol), acid *ent*-**14** (0.06 g, 0.27 mmol). The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1.5:98.5) to obtain pure compound **15a** (0.086 g, 82%) as a colorless liquid. $[\alpha]_D^{25}$ = +4.3 (*c* 0.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33−7.21 (m, 5H), 5.84−5.68 (m, 2H), 5.33 (d, 1H, *J* = 17.1 Hz), 5.21 (d, 1H, *J* = 10.3 Hz), 5.0−4.93 (m, 3H), 4.66 (d, 1H, *J* = 11.3 Hz), 4.53 (t, 1H, *J* = 6.7 Hz), 4.31 (d, 1H, *J* = 11.5 Hz), 4.15 (t, 1H, *J* = 6.9 Hz), 3.8 (dd, 1H, *J* = 5.1, 7.5 Hz), 2.25−2.07 (m, 2H), 1.85−1.58 (m, 2H), 0.94 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 137.0, 132.6, 128.3, 128.2, 128, 127.9, 109.9, 78.6, 77.6, 74.5, 73.4, 71.4, 43.3, 35.7, 32.4, 28.0, 22.8, 18.0, 14.1. IR (neat): 3021, 2925, 1725 cm^{-1}. HRMS: *m*/*z* calcd for $C_{24}H_{34}O_5Na$ $[M + Na]^+$ 425.2303, found 425.2301.

*(1R)-1-[(4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl (2S)-2-(Benzyloxy)-5-hexenoate (**15b**).* Route A. The same procedure was adopted as described for compound **10**.

Epoxy allyl alcohol **9** (0.1 g, 0.70 mmol), $Ti(O^iPr)_4$ (0.3 mL, 1 mmol) acid *ent*-**14** (0.185 g, 0.84 mmol), followed by acetonide protection. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1.5:98.5) to obtain pure compound **15b** (0.144 g, 49%) as a colorless liquid.

Route B. Alcohol **11** (0.05 g, 0.25 mmol), DCC (0.056 g, 0.27 mmol) and DMAP (0.033 g, 0.27 mmol), acid *ent*-**14** (0.06 g, 0.27 mmol). The crude residue was purified by column chromatography (EtOAc:n-hexane 1.5:98.5) to obtain pure compound **15b** (0.075 g, 72%) as a colorless liquid. $[\alpha]_D^{25}$ = +65.4 (c 0.006, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37−7.17 (m, 5H), 5.83−5.67 (m, 2H), 5.32 (d, 1H, *J* = 16.7 Hz), 5.17 (d, 1H, *J* = 10.3 Hz), 5.0−4.94 (m, 3H), 4.66 (d, 1H, *J* = 11.5 Hz), 4.56 (t, 1H, *J* = 6.7 Hz), 4.29 (d, 1H, *J* = 11.5 Hz), 4.15 (t, 1H, *J* = 7.1 Hz), 3.82 (dd, 1H, *J* = 5.9, 6.3 Hz), 2.17 (q, 2H, *J* = 7.1 Hz), 1.80 (q, 2H, *J* = 7.1 Hz), 1.72−1.59 (m, 2H), 1.46 (br. s, 2H), 1.35 (br. s, 6H), 0.92 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 137.3, 133.1, 128.4, 127.9, 118.6, 115.5, 108.8, 96.1, 78.7, 78.0, 77.1, 72.3, 33.3, 32.1, 29.5, 27.6, 25.3, 17.8, 14.1. IR (neat): 3012, 2923, 1728, 1025 cm^{-1}. HRMS: *m*/*z* calcd for $C_{24}H_{34}O_5Na$ $[M + Na]^+$ 425.2303, found 425.2295.

*(1S)-1-[(4R,5R)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl]butyl (2R)-2-(Benzyloxy)-5-hexenoate (**15c**).* Route A. The same procedure was adopted as described for compound **10**.

Epoxy allyl alcohol **9** (0.100 g, 0.70 mmol), $Ti(O^iPr)_4$ (0.3 mL, 1 mmol) acid **14** (0.185 g, 0.84 mmol), followed by acetonide protection. The crude residue was purified by column chromatography (EtOAc/*n*-hexane 1.5:98.5) to obtain pure compound **15c** (0.159 g, 54%) as a colorless liquid. $[\alpha]_D^{25}$ = −83.3 (*c* 0.003, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 5.86−5.66 (m, 2H), 5.32 (d, 1H, *J* = 17.3 Hz), 5.16 (d, 1H, *J* = 10.5 Hz), 4.99−4.93 (m, 3H), 4.68 (d, 1H, *J* = 11.3 Hz), 4.56 (t, 1H, *J* = 6.7 Hz), 4.28 (d, 1H, *J* = 11.3 Hz), 4.14 (dd, 1H, *J* = 6.4, 7.5 Hz), 3.82 (t, 1H, *J* = 6.4 Hz), 2.20−2.14 (m, 2H), 1.78 (q, 2H, *J* = 7.5 Hz), 1.71−1.58 (m, 2H), 1.46 (br. s, 2H), 1.35 (d, 6H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 137.3, 137.2, 133.0, 128.3, 127.9, 127.8, 118.7, 115.4, 109.0, 78.7, 77.9, 77.1, 72.2, 72.2, 33.2, 32.1, 29.4, 27.5, 25.2, 17.8, 14.0. IR (neat): 3125, 2921, 1724, 1063 cm^{-1}. HRMS: *m*/*z* calcd for $C_{24}H_{34}O_5Na$ $[M + Na]^+$ 425.2303, found 425.2299.

Synthesis of Herbarumin I. *Macrolide (**16**).* To a solution of bis-olefin **15** (0.130 g, 0.43 mmol) in CH_2Cl_2 (120 mL) was added Grubbs' first-generation catalyst (0.03 g, 10 mol %) and the mixture allowed to stir at reflux for 18 h. The solvent was removed in vacuo, and the crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to afford macrolide **16** (0.090 g, 76%) as a light yellow liquid. $[\alpha]_D^{25}$ = +90.0 (*c* 0.05, $CHCl_3$): The spectral data was matched with reported values.[18]

*Herbarumin I (**4**).* To a cooled solution of lactone **16** (0.070 g, 0.37 mmol) in CH_2Cl_2 was added $TiCl_4$ (10 mol % in CH_2Cl_2), and allowed to stir for 30 min. The reaction mixture was neutralized with a saturated aq solution of $NaHCO_3$ (3 mL) and extracted with EtOAc

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(4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/*n*-hexane 20:80) to afford the title compound **4** (0.039 g, 74%) as a colorless syrup. $[\alpha]_D^{25}$ = +33.0 (*c* 0.02, $CHCl_3$). The spectral data was matched with reported values.[18]

Synthesis of Herbarumin II. *Macrolide 16a.* To a solution of bis-olefin **15a** (0.100 g, 0.37 mmol) in toluene (100 mL) was added Grubbs' first-generation catalyst (0.03 g, 10 mol %) and the mixture allowed to stir for 36 h at reflux. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (EtOAc/hexane 1:99) to afford macrolide **16a** (mixed with some unreacted starting material). We were not able to isolate the pure *trans*-isomer due to little R_f difference between starting material **15a** (unreacted) and the product **16a**. In order to overcome this difficulty, we proceeded to the next step (global deprotection of acetonide and benzyl ether groups) to afford the pure *trans*-isomer.

Macrolide (17). To a solution of bis-olefin **15a** (0.100 g, 0.37 mmol) in dry toluene (100 mL) was added Grubbs' second-generation catalyst (0.03 g, 10 mol %) and the mixture allowed to stir at reflux temperature for 2 h. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (EtOAc/*n*-hexane 2:98) to afford macrolide **17** (0.082 g, 88%) as a colorless liquid. $[\alpha]_D^{25}$ = +16.6 (*c* 0.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32−7.24 (m, 5H), 5.38−5.32 (m, 2H, *J* = 9.8 Hz), 4.83 (dd, 1H, *J* = 6.7, 7.2 Hz), 4.55 (d, 1H, *J* = 11.4 Hz), 4.26 (d, 1H, *J* = 11.4 Hz), 4.13 (dd, 1H, *J* = 6.2, 9.8 Hz), 3.74 (q, 1H, *J* = 10.4 Hz), 2.21−2.14 (m, 2H), 1.85−1.74 (m, 2H), 1.65−1.58 (m, 1H), 1.45−1.39 (m, 3H), 1.33 (d, 6H, *J* = 14.5 Hz), 0.98 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 132.8, 128.3, 128.2, 128.0, 127.9, 109.9, 78.6, 77.6, 74.5, 73.4, 71.4, 43.3, 35.7, 32.4, 28.0, 25.5, 18.0, 14.1. IR (neat): 2940, 1724 cm^{-1}. ESI-MS: 397 $[M + Na]^+$, 392 $[M + NH_4]^+$. Anal. Calcd for $C_{22}H_{30}O_5$ (374.47): C, 70.56; H, 8.07. Found: C, 70.92; H, 8.28.

Herbarumin II (5). To a cooled solution of macrolide **16a** (0.080 g, 0.37 mmol) in CH_2Cl_2 was added $TiCl_4$ (15 mol % in CH_2Cl_2) and the mixture allowed to stir for 2 h. The reaction mixture was neutralized with a saturated aq solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (4 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by column chromatography (EtOAc:*n*-hexane 35:65) to afford the title compound **5** (0.028 g, 56%) as light yellow crystals. $[\alpha]_D^{25}$ = +42.0 (*c* 0.06, $CHCl_3$). The spectral data was matched with reported values.[19]

Formal Synthesis of (+)-Lethaloxin. *Macrolide (18).* To a stirred solution of bis-olefin **15b** (0.110 g, 0.37 mmol) in toluene (100 mL) was added Grubbs' first-generation catalyst (0.03 g, 10 mol %) and the mixtrue allowed to stir at reflux temperature for 36 h, solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (EtOAc/*n*-hexane 1:99) to afford macrolide **16b** (mixed with some unreacted starting material). The same problem was encountered in the isolation of ring-closed product, as observed in the case of herbarumin **II**. Since the scenario is similar to the previous case, we proceeded to the next step, i.e., deprotection of benzyl ether group under standard conditions, to afford the *trans*-isomer **18** (0.042 g, 54%). $[\alpha]_D^{25}$ = +72.8 (*c* 0.05, $CHCl_3$). The spectral data was matched with reported values.[15]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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