Regio- and Stereoselective Monoepoxidation of Dienes using Methyltrioxorhenium: Synthesis of Allylic Epoxides

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Supporting Information

ABSTRACT: Methyltrioxorhenium (MTO) complexed with pyridine was shown to be a highly effective catalyst for the regioselective monoepoxidation of conjugated di- and trienes using 30% H2O2 at or below room temperature. The resultant allylic epoxides, and the triols derived from them, are versatile synthetic intermediates as well as substructures present in many bioactive natural products. The site of epoxidation was dependent upon olefin substitution, olefin geometry (Z vs E), and the presence of electron-withdrawing substituents on adjacent carbons. For 1-acyl(silyl)oxypenta-2,4-dienes, epoxidation of the distal olefin was generally favored in contrast to the adjacent regioselectivity characteristic of Sharpless, peracid, and other directed epoxidations of hydroxylated dienes.

■ INTRODUCTION

An array of protocols is available for the preparation of epoxides as befits their prominence as versatile synthetic intermediates and as substructures in numerous bioactive compounds. The most common and generally economic synthetic approach is the direct, catalytic epoxidation of olefins. The task is more problematic for the monoepoxidation of 1,3-conjugated dienes and higher homologues. Of the few reagents that have been studied, inter alia, Mo(CO)6,6 OTi(tetraphenylporphyrin),7 Mn(tetraphenylporphyrin),8 transition metal salens,9 and dimethyldioxirane,10 most have one or more limitations such as modest yields, variable regioselectivities, low cis-/trans-selectivity, polyoxidation, stereoisomerization, and/or instability of the allylic epoxide product under the reaction conditions. A prominent exception is the Shi fructose-based dioxirane reagents,11 although the strict reaction regimen and catalyst availability can be a deterrence.

The epoxidation of the 2,4-pentadien-1-ol substructure is of particular interest to many laboratories. In addition to being useful synthetic building blocks, the resultant allylic epoxides and their chemically or enzymatically derived allylic triols are well-represented among natural products of current interest. Functional group directed epoxidations, exemplified by peracid, Sharpless,14 and related catalytic reagents, generally offer an excellent level of stereocontrol, but they predominately epoxidize the olefin adjacent to the hydroxyl and not the distal olefin (eq 1). We were, thus, motivated to develop an inexpensive and direct distal-selective, catalytic epoxidation of conjugated buta-1,3-dienes/penta-2,4-dien-1-ols and exploit this methodology as a key transformation in a biogenetically inspired total synthesis of the potent antimitotic marine natural products nigricanoside A/B and their analogues (Scheme 1).

■ RESULTS AND DISCUSSION

A wide variety of catalysts and oxidants were surveyed for distal-selective epoxidation of the penta-2,4-diene-ol moiety. A sampling is compiled in Table 1. Methyl ester 1 was selected as the model substrate because it is readily available in high stereochemical purity via incubation of linoleic acid with soybean lipoxigenase on a multigram scale and also provides a stereochemical vantage point to monitor the influence of an adjacent chiral center on the course of the epoxidation. A prominent exception is the Shi fructose-based dioxirane reagents, although the strict reaction regimen and catalyst availability can be a deterrence.

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It was evident that methyltrioxorhenium (MTO) (entry 1) in CH$_2$Cl$_2$ was the most efficacious for distal epoxidation, although the product was generated as a mixture of diastereomers 2 and 3. Yields were diminished somewhat in CH$_3$CN and CH$_3$NO$_2$, and the dr (2/3) was unchanged. Other common reagents (entries 2−5) were ineffective or gave minor amounts of epoxide. Interestingly, Mn (entry 6) and Fe (entries 7 and 8) complexed with chiral ligands were also distal-selective but still produced mixtures of 2 and 3. To modulate MTO's Lewis acidity, pyridine was added, as recommended by Sharpless; however, increasing the level of pyridine beyond 2.4 equiv with respect to MTO did not improve either the yield or dr. Replacement of the pyridine with other ligands (Table 2) had some effect on yield but, disappointingly, little influence on the dr even when using chiral pyridines and amines (entries 9−14). The latter likely reflects the weak coordination of the chiral bases with the metal center.

In addition to offering the best combined yield of 2/3, there is much to recommend the MTO/H$_2$O$_2$ system versus other catalysts. It is commercially available, inexpensive, air stable, reacts at room temperature or below, uses environmentally friendly H$_2$O$_2$ or H$_2$O$_2$−urea adduct instead of more corrosive oxidants, generates water as the only byproduct, and is operationally simple. Careful optimization of the reaction conditions showed that best results could be obtained with 5 mol % of MTO and 12 mol % of pyridine. Importantly, this methodology was also amenable to the multigram conversion of 1 into a mixture of 2 and 3 in an 84% combined yield.

Early optimization studies of the MTO/H$_2$O$_2$ catalyzed epoxidation of unprotected 4 (PG = H) found that the yields were somewhat compromised by the formation of ketone and other uncharacterized products (Table 3, entry a), so a brief survey of commonly used protecting groups (PGs) was initiated. This revealed bulky (entry b), aryl (entry c), and aliphatic (entry d) esters, ethoxycarbonyl (entry e), and t-butyl diphenylsilylethoxy (entry f) were all well-tolerated and afforded good yields of epoxides 5/6, but they showed little variation in the dr. In concert with acetate, there was a slight preference in favor of the erythro diastereomer 5. All epoxides were identified by comparisons with authentic standards.

To elucidate the scope of MTO-mediated epoxidations of di/trienes, a panel of representative substrates was subjected to the standard epoxidation conditions (Table 4). Acetate 7 (entry 1) and carbonate 9 (entry 2), both derived from the soybean lipoxidase metabolite of linolenic acid, smoothly led to distal epoxides 8 and 10, respectively, in good yields at −5 °C; at room temperature, however, ∼10−15% of the Δ$_{15,16}$-olefin 10 was also epoxidized. Exposure of the structurally related natural fatty acid 11 to the standard reaction conditions revealed a modest 7:3 regioselectivity favoring the Z-olefin 12 (entry 3). This is consistent with inductive and/or steric contributions of the acyloxy group to the observed regioselectivity in the preceding examples (cf., 1, 4, 7, and 9). As a testimony to the mildness of the reaction conditions, the soybean lipoxidase metabolite 35 of linolenic acid, smoothly led to distal epoxides 8 and 10, respectively, in good yields at −5 °C; at room temperature, however, ∼10−15% of the Δ$_{15,16}$-olefin 10 was also epoxidized. Exposure of the structurally related natural fatty acid 11 to the standard reaction conditions revealed a modest 7:3 regioselectivity favoring the Z-olefin 12 (entry 3). This is consistent with inductive and/or steric contributions of the acyloxy group to the observed regioselectivity in the preceding examples (cf., 1, 4, 7, and 9).
to optimize the yields of 21 (entry 7), 23 (entry 8), and 25 (entry 9), respectively, with the latter two produced as diastereomeric mixtures. Notably, an increase in the level of substitution on the allylic olefin induced a change in oxidation regioselectivity and gave rise to a 1:1 mixture of 27 and 28 (entry 10). Increasing the substitution level of the distal olefin, e.g., trialkyl (entries 11 and 12), cyclic trialkyl (entry 13), and cyclic tetraalkyl (entry 14), was well-tolerated and uneventfully afforded 30, 32, 34, and 36, respectively. Unexpectedly, 2,4,6-triene 37 was converted to bis-allylic epoxide 38 as the only mono-oxidation product (entry 15). Both conjugated dienyl esters 39 and 41 underwent epoxidation at the terminal olefin, albeit slowly. Control experiments with both 39 and 41 confirmed that MTO was required for epoxidation.

The mechanism of MTO-mediated epoxidation has been well-studied. Hydrogen bonding between the substrate and peroxyrhenium intermediate in the transition state has been invoked to explain stereospecificity. The faster reaction rate for Z-olefins versus E-olefins is also observed in conjugated dienes (e.g., entry 3). When present, acyloxy groups inductively deactivate the adjacent olefin of the diene, thus directing epoxidation to the distal olefin regardless of olefin configuration (entries 1, 2, and 7); however, this can be overcome, at least partially, by greater olefin substitution (entry 10).

**CONCLUSIONS**

MTO complexed with pyridine was shown to be a highly effective catalyst for the regioselective monoepoxidation of conjugated di- and trienes. The site of epoxidation was dependent upon the olefin substitution, olefin geometry (Z vs E), and the presence of electron-withdrawing substituents on adjacent carbons. For the special case of 1-acyloxypenta-2,4-dienes, the regioselectivity was complementary to that achieved in Sharpless and other directed epoxidations of 1-hydroxypenta-2,4-dienes.

Table 1. Survey of Catalysts for Distal-Selective Epoxidation of Diene 1

| Entry | Catalyst | Additive | Oxidant | Solvent | Yield 2/3 (%)<sup>b</sup> | erythro/threo<sup>c</sup> |
|-------|----------|----------|---------|---------|---------------------------|--------------------------|
| 1     | MnSO<sub>4</sub> (1 mol%) | NaHCO<sub>3</sub> (0.25 equiv) | 30% H<sub>2</sub>O<sub>2</sub> (1.5 equiv) | CH<sub>2</sub>Cl<sub>2</sub> | 92 | 3:2 |
| 2     | Ti(OiPr)<sub>4</sub> (1 equiv) | | 30% H<sub>2</sub>O<sub>2</sub> (1.5 equiv) | t-BuOH | 0<sup>d</sup> | na<sup>e</sup> |
| 3     | MoO<sub>3</sub>(acac)<sub>2</sub> (20 mol%) | | t-BuOOH (1.5 equiv) | PhCH<sub>3</sub> | <5<sup>d</sup> | na<sup>e</sup> |
| 4     | FeCl<sub>3</sub> (10 mol%) | | 30% H<sub>2</sub>O<sub>2</sub> (1.5 equiv) | t-BuOH | <5<sup>d</sup> | na<sup>e</sup> |
| 5     | | | | | |
| 6     | | | | | |
| 7     | | | | | |
| 8     | | | | | |

<sup>a</sup>Epoxidation procedures: entry 1 (ref 20a), entry 2 (ref 21), entry 3 (ref 22), entry 4 (ref 23), entry 5 (ref 24), entry 6 (ref 25), entry 7 (ref 26), and entry 8 (ref 27).<sup>b</sup>Combined, isolated yield. Measured by NMR. <sup>d</sup>90% unreacted 1 recovered. <sup>e</sup>na, not applicable or no analysis.
EXPERIMENTAL SECTION

General Methods and Materials. Proton and carbon nuclear magnetic resonance spectra (1H and 13C NMR) were recorded at 500 and 126 MHz, respectively, or at 400 and 101 MHz, respectively, in CDCl3 with TMS as internal standard, unless otherwise stated. 1H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, app q = apparent quartet, qn = quintet, app qn = apparent quintet, m = multiplet), and coupling constant (Hz). High-resolution mass spectra (HRMS) were obtained using a TOF mass spectrometer, whereas infrared (IR) spectra were obtained using a Fourier transform infrared spectrometer. Melting points were measured using an automated melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) used EMD Chemicals TLC silica gel 60 F254 plates (0.040–0.063 mm) with visualization by UV light and/or KMnO4 or phosphomolybdic acid (PMA) solution followed by heating. Chromatographic purifications utilized Et3N or t-BuNH2 basified preparative TLC or flash chromatography using prepacked SiO2 columns on an automated medium-pressure chromatograph with eluents containing 0.5–2% t-BuNH2. Determinations of diastereomeric ratios (dr) were conducted by 1H and 13C NMR or chiral phase-HPLC as specified in the experimental. Unless otherwise noted, yields refer to isolated, purified material with spectral data consistent with assigned structures or, if known, were in agreement with published data. All reactions were conducted under an argon atmosphere in oven-dried glassware with magnetic stirring. Reagents were purchased at the highest commercial quality and used without further purification. Dichloromethane (CH2Cl2) and tetrahydrofuran (THF) were dried by passage through a column of activated, neutral alumina under argon and stored under argon until use.

General Epoxidation Procedure. Aqueous 30% H2O2 (1.5–2.0 equiv) was added to a stirring, 0 °C solution of polyene, methyltrioxorhenium (MTO, 5 mol %), and pyridine (12 mol %) in CH2Cl2. The yellow reaction mixture was stirred at the specified temperature for the indicated time and then quenched with 10% tetrasodium EDTA solution. The colorless solution was extracted with CH2Cl2 (3–4 times), and the combined extracts were washed with water and brine and dried over Na2SO4. Evaporation of all volatiles and purification of the residue by flash chromatography using 0.5–2% t-butylamine or 1% Et3N in EtOAc/hexane afforded the allylic epoxide in the indicated yield.

Table 2. MTO Ligand Screening

| Entry | Ligand | Temp (°C) | Yield (%)* | Erythro/threo
|-------|--------|-----------|------------|----------------|
| 1     | NM02   | 23        | 69         | 55:45        |
| 2     | CH3    | 23        | 60         | 60:40        |
| 3     | N      | 23        | 74         | 60:40        |
| 4     | OH     | 23        | 73         | 60:40        |
| 5     | CH3    | 23        | 72         | 55:45        |
| 6     | CH3CH2OH3 | -5       | 50         | 60:40        |
| 7     | N      | 0         | 55         | 55:45        |
| 8     | N      | 23        | 62         | 50:50        |

Table 3. Effect of Alcohol Protecting Group

| Entry | PG      | Time (h) | Yield 5/6 (%) | Erythro/threo |
|-------|---------|----------|---------------|---------------|
| 1     | H       | 6†       | 56            | 60:40         |
| 2     | C(O)Bu  | 3        | 80            | 60:40         |
| 3     | C(O)Ph  | 4        | 78            | 60:40         |
| 4     | C(O)CH2Ph | 3      | 73            | 55:45         |
| 5     | C(O)OEt | 3        | 79            | 55:45         |
| 6     | SiPh2Bu | 5        | 82            | 60:40         |

*12 mol % each MTO and ligand in CH2Cl2. **Combined, isolated yield. †Determined by NMR.
2.28 (t, J = 7.2 Hz, 2H), 2.15 (dt, J = 7.2, 14.4 Hz, 2H), 2.03 (s, 3H), 1.64–1.58 (m, 4H), 1.36–1.26 (m, 14H), 0.86 (t, J = 6.8 Hz, 3H).

Methyl 13(S)-Acetyloxyoctadeca-9(R*),10(S*)-epoxy-11(E)-enoate (2/3). Following the general epoxidation procedure, 1 (2.4 g, 6.81 mmol), MTO (84 mg, 5 mol %), pyridine (66 μL, 12 mol %), and 30% H2O2 (1.30 mL, 10.2 mmol) were stirred in dry CH2Cl2 (70 mL) at −5 °C for 16 h. Chromatographic purification of the crude product afforded the title product as a colorless oil (2.31 g, 92%, ∼3:2 mixture of diastereomers).1H NMR (400 MHz, CDCl3) δ 5.85–5.78 (m, 1H), 5.60–5.52 (m, 1H), 5.27–5.23 (m, 1H), 3.66 (s, 3H), 3.39–3.37 (m, 1H), 3.07–3.04 (m, 1H), 2.29 (t, J = 6.0 Hz, 2H), 2.05 (s, 3H), 1.66–1.27 (m, 20H), 0.87 (t, J = 4.4 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 174.4, 170.41, 170.38, 134.7, 134.6, 127.4, 127.1, 74.1, 73.9, 59.1, 59.0, 56.4, 56.3, 51.6, 34.5, 34.4, 34.2, 31.7, 29.42, 29.39, 29.37, 29.35, 29.2, 27.88, 27.87, 26.5, 26.4, 25.1, 24.93, 24.91, 22.7, 21.5, 21.4, 14.2. HRMS (ESI-TOF) m/z [M + 1]+ calcd for C21H37O5, 369.2642; found, 369.2638.

Methyl 13(S)-Hydroxyoctadeca-9(R*),10(S*)-epoxy-11(E)-enoate (5a/6a). Following the general epoxidation procedure, 4a (100 mg, 0.32 mmol), MTO (4 mg, 5 mol %), pyridine (4 μL, 12 mol %), and 30% H2O2 (72 μL, 0.64 mmol) were stirred in dry CH2Cl2 (3 mL) at −10 °C for 6 h. Chromatographic purification of the crude product by silica gel column using a gradient of 50–70% EtOAc/hexanes + 2% t-BuNH2 as eluent afforded the known diastereomeric epoxides 5/6 as a colorless oil (58 mg, 56%, ∼3:2 mixture). TLC: Rf 0.5 (3:2 mixture).

Table 4. MTO Epoxidation of Representative Conjugated Dienes/Trienesa

| Entry | Polyene | Epoxide | Temp (°C) | Time (h) | Yield (%) | erythro:threo |
|-------|---------|---------|-----------|----------|-----------|---------------|
| 1     | 9       | 10      | -5        | 22       | 81        | 60:4          |
| 2     | 9       | 12      | -5        | 28       | 78        | 60:4          |
| 3     | 11      | 12      | -10       | 22       | 71        | na            |
| 4     | 14      | 15      | -5        | 24       | 74        | na            |
| 5     | 16      | 17      | -5        | 14       | 59        | na            |
| 6     |         |         | -5        | 14       | 59        | na            |
| 7     | 18      | 20      | -10       | 14       | 79        | 50:50         |
| 8     | 19      | 21      | -10       | 12       | 84        | 50:50         |
| 9     |         |         | -5        | 20       | 66        | na            |
| 10    | 30      | 31      | -10       | 14       | 73        | na            |
| 11    | 32      | 33      | -10       | 14       | 78        | na            |
| 12    | 32      | 33      | -10       | 14       | 78        | na            |
| 13    | 33      | 34      | -5        | 24       | 82        | 50:50         |
| 14    | 33      | 34      | -5        | 24       | 65        | na            |
| 15    | 33      | 34      | -5        | 24       | 65        | na            |
| 16    | 39      | 40      | -10       | 60       | 64        | na            |
| 17    | 39      | 40      | -10       | 24       | 94        | na            |

a 5 mol % MTO, 12 mol % pyridine, and 2 equiv H2O2 in CH2Cl2. b Isolated yield. c Determined by 1H/13C NMR or chiral-phase HPLC. d 10–15% bis-epoxide also formed. e Combined, isolated yield. f na, not applicable.
Methyl 13-((E)-3-(tert-Butyldiphenylsilyloxy)octadeca-9,11-(E)-enoate (5b/6b).
Following the general epoxidation procedure, 4b (50 mg, 0.13 mmol), MTO (2 mg, 5 mol %), pyridine (1.5 μL, 12 mol %), and 30% H2O2 (23 μL 0.19 mmol) were stirred in dry CH2Cl2 (3 mL) at rt for 4 h. Chromatographic purification of the crude product afforded the title product as a colorless oil (41 mg, 78%, ~3:2 mixture of diastereomers). 1H NMR (500 MHz, CDCl3) δ 8.05 (d, J = 7.5 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.47–7.43 (m, 2H), 7.59–7.52 (m, 1H), 5.54 (dt, J = 6.5, 13.5 Hz, 1H), 3.67 (s, 3H), 3.43–3.40 (m, 1H), 3.05–3.03 (m, 1H), 2.39 (t, J = 7.5 Hz, 2H), 1.83–1.69 (m, 2H), 1.61–1.24 (m, 18H), 0.89 (t, J = 7.5 Hz, 3H). 13C NMR (125 MHz, CDCl3) δ 174.47, 174.46, 165.9, 134.6, 134.5, 133.14, 133.12, 127.3, 127.2, 126.4, 124.7, 123.6, 121.3, 112.7, 72.7, 69.3, 59.1, 59.0, 56.4, 56.3, 51.7, 49.1, 49.0, 43.4, 34.2, 34.1, 31.0, 29.1, 28.7, 27.8, 25.1, 22.8, 14.2. HRMS (ESI-TOF) m/z [M + Na]+ calc’d for C34H51O3SiNa, 518.3379; found, 518.3378.

Methyl 13-((E)-3-(2-Phenylacetoxy)octadeca-9,11-(E)-enoate (4d).
Following the acylation procedure above, 1a (100 mg, 0.32 mmol) was treated with phenylacetyl chloride (70 μL, 0.48 mmol) and pyridine (52 μL, 0.64 mmol) in CH2Cl2 (5 mL) at rt for 12 h. Chromatographic purification of the crude product afforded the title compound using 10–20% EtOAc/hexanes as eluent afforded the title compound 4d (130 mg, 91%) as a clear oil. TLC: Rf ≈ 0.6 (10% EtOAc/hexanes).

1H NMR (500 MHz, CDCl3) δ 7.70–7.62 (m, 6H), 7.50–7.47 (m, 6H), 5.98–5.71 (m, 1H), 5.40 (dd, J = 15.6, 7.8 Hz, 0.4 Hz), 5.28 (dd, J = 15.5, 7.5 Hz, 0.6 Hz), 4.22–4.19 (m, 2H), 3.85–3.84 (m, 1H), 3.45–3.43 (m, 1H), 3.05–3.03 (m, 1H), 2.29 (t, J = 7.5 Hz, 2H), 2.14–1.09 (m, 8H), 1.08 (s, J = 6.5 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 174.3, 174.2, 170.8, 133.6, 133.0, 129.2, 128.5, 127.8, 127.5, 126.9, 51.4, 41.7, 34.5, 34.1, 31.5, 29.4, 29.10, 29.08, 29.05, 29.03, 29.01, 27.7, 24.9, 24.7, 22.5, 14.0. HRMS (ESI-TOF) m/z [M + Na]+ calc’d for C34H51O3Na, 545.3379; found, 545.3379.

Methyl 13-((Z)-3-(2-Phenylacetoxy)octadeca-9,11-(Z)-enoate (4f).
Following the general acylation procedure above, 1a (100 mg, 0.32 mmol) was treated with phenylacetyl chloride (70 μL, 0.48 mmol) and pyridine (52 μL, 0.64 mmol) in CH2Cl2 (5 mL) at rt for 12 h. Chromatographic purification of the crude product afforded the title compound using 10–20% EtOAc/hexanes as eluent afforded the title compound 4f (130 mg, 91%) as a clear oil. TLC: Rf ≈ 0.6 (10% EtOAc/hexanes).

1H NMR (500 MHz, CDCl3) δ 7.70–7.62 (m, 6H), 7.50–7.47 (m, 6H), 5.98–5.71 (m, 1H), 5.40 (dd, J = 15.6, 7.8 Hz, 0.4 Hz), 5.28 (dd, J = 15.5, 7.5 Hz, 0.6 Hz), 4.22–4.19 (m, 2H), 3.85–3.84 (m, 1H), 3.45–3.43 (m, 1H), 3.05–3.03 (m, 1H), 2.29 (t, J = 7.5 Hz, 2H), 2.14–1.09 (m, 8H), 1.08 (s, J = 6.5 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 174.3, 174.2, 170.8, 133.6, 133.0, 129.2, 128.5, 127.8, 127.5, 126.9, 51.4, 41.7, 34.5, 34.1, 31.5, 29.4, 29.10, 29.08, 29.05, 29.03, 29.01, 27.7, 24.9, 24.7, 22.5, 14.0. HRMS (ESI-TOF) m/z [M + Na]+ calc’d for C34H51O3Na, 545.3379; found, 545.3379.
Methyl 13-(S)-Acetoxyoctadeca-9(Z),11(E),15(Z)-triene-10(S)-epoxy-11(E),15(Z)-dienoate (7). Following the acylation procedure above, methyl 13(S)-hydroxyoctadeca-9(Z),11(E),15(Z)-triene-10(S)-epoxy-11(E),15(Z)-dienoate (7) (210 mg, 0.43 mmol) was treated with acetic anhydride (80 µL, 0.78 mmol) and pyridine (68 µL, 0.84 mmol) in CH₂Cl₂ (10 mL) at rt for 6 h. Chromatographic purification of the crude product using 10-20% ETOAc/hexanes as eluent afforded the title compound (7) (210 mg, 93%) as a clear oil. TLC: Rf = 0.6 (20% ETOAc/hexanes); [α]D 247.1669°. 1H NMR (500 MHz, CDCl₃) δ 6.54 (dd, J = 11.2, 15.5 Hz), 5.93 (t, J = 11.2 Hz), 5.59 (dd, J = 7.6, 15.2 Hz), 5.35-5.42 (m, JH = 3.3), 5.33-5.25 (m, JH = 3.3), 5.11 (dt, JH = 7.2, 14.4 Hz), 4.16 (q, JH = 7.2 Hz), 3.65 (s, JH = 2.5-3.2), 2.28 (t, JH = 7.6 Hz), 2.30 (dt, JH = 6.8, 14.0 Hz), 2.07-1.98 (m, JH = 6.0), 1.70 (t, JH = 7.2 Hz), 1.37-1.25 (m, JH = 10.0), 0.94 (t, JH = 7.6 Hz). 13C NMR (100 MHz, CDCl₃) δ 174.3, 154.7, 135.0, 134.3, 129.9, 128.8, 127.6, 127.8, 78.4, 63.8, 51.5, 34.2, 32.6, 29.6, 29.3, 29.2, 29.1, 27.9, 25.1, 20.8, 14.4. 14.2. HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₂₉H₄₃O₄Na, 465.3339; found, 465.3345.

Methyl 13-(S)-Acetoxyoctadeca-9(Z),11(E),15(Z)-triene-10(S)-epoxy-11(E),15(Z)-dienoate (9). Following the acylation procedure above, methyl 13(S)-hydroxyoctadeca-9(Z),11(E),15(Z)-triene-10(S)-epoxy-11(E),15(Z)-dienoate (9) (330 mg, 0.78 mmol) was treated with acetic anhydride (80 µL, 0.78 mmol) and pyridine (68 µL, 0.84 mmol) in CH₂Cl₂ (10 mL) at rt for 6 h. Chromatographic purification of the crude product using 10-20% ETOAc/hexanes as eluent afforded the title compound (9) (330 mg, 0.78 mmol) as a clear oil. TLC: Rf = 0.6 (20% ETOAc/hexanes). 1H NMR (400 MHz, CDCl₃) δ 6.54 (dd, J = 11.2, 15.5 Hz), 5.93 (t, J = 11.2 Hz), 5.59 (dd, J = 7.6, 15.2 Hz), 5.35-5.42 (m, JH = 3.3), 5.33-5.25 (m, JH = 3.3), 5.11 (dt, JH = 7.2, 14.4 Hz), 4.16 (q, JH = 7.2 Hz), 3.65 (s, JH = 2.5-3.2), 2.28 (t, JH = 7.6 Hz), 2.30 (dt, JH = 6.8, 14.0 Hz), 2.07-1.98 (m, JH = 6.0), 1.70 (t, JH = 7.2 Hz), 1.37-1.25 (m, JH = 10.0), 0.94 (t, JH = 7.6 Hz). 13C NMR (100 MHz, CDCl₃) δ 174.3, 154.7, 135.0, 134.3, 129.9, 128.8, 127.6, 127.8, 78.4, 63.8, 51.5, 34.2, 32.6, 29.6, 29.3, 29.2, 29.1, 27.9, 25.1, 20.8, 14.4. 14.2. HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₂₉H₄₃O₄Na, 465.3345; found, 465.3345.

Dodeca-2(7),4(E)-dien-1-yl Acetate (10). Following the acylation procedure above, dodeca-2(7),4(E)-dien-1-yl acetate (10) (2.2 g, 12 mmol) was treated with acetic anhydride (1.4 mL, 14.5 mmol) and pyridine (1.45 mL, 18 mmol) in CH₂Cl₂ (30 mL) at rt for 3 h. Chromatographic purification of the crude product using 10-20% ETOAc/hexanes as eluent afforded 20 (2.5 g, 93%) as a clear oil. TLC: Rf = 0.6 (10% ethyl acetate/hexanes). 1H NMR (400 MHz, CDCl₃) δ 6.25 (dd, J = 10.4, 15.2 Hz, 1H), 6.02 (dd, J = 10.4, 15.2 Hz, 1H), 5.74 (dt, J = 6.8, 14.4 Hz, 1H), 5.63 (dt, J = 6.8, 14.4 Hz, 1H), 4.59 (d, J = 6.8 Hz, 2H), 2.10-2.03 (m, 2H), 2.06 (3H, J = 14.0-1.25 (m, 10 H), 0.87 (t, J = 6.8 Hz, 3H). 13C NMR (101 MHz, CDCl₃) δ 170.7, 136.9, 135.1, 129.2, 123.9, 65.0, 32.7, 31.9, 29.3, 29.2, 22.7, 21.0, 14.2. HRMS (ESI-TOF) m/z [M + Na]⁺ calcd for C₂₉H₄₃O₄Na, 476.1767; found, 476.1769.

E(3)-3-Heptyloxiran-2-yljallyl Acetate (21). Following the general epoxidation procedure, MTO (100 mg, 0.45 mmol), MTO (6 mg, 5 mol %), pyridine (5 µL, 12 mol %), and 30% H₂O₂ (16 µL, 0.14 mmol) were stirred in dry CH₂Cl₂ (2 mL) at −10 °C for 6 h. Chromatographic purification of the crude product afforded the title product as a colorless oil (30 mg, 71%, 7:3 mixture of regioisomers) whose spectral data were in accord with literature values. 3

2-Phenyl-3-(2-phenyloxiran-2-yl)oxirane (15). Following the general epoxidation procedure, commercial 4-phenyl-1(E),3(E)-butadiene (benzene) (14) (200 mg, 1.00 mmol), MTO (12 mmol, 5 mol %), pyridine (10 µL, 12 mol %), and 30% H₂O₂ (226 µL, 2.0 mol) were stirred in dry CH₂Cl₂ (10 mL) at −10 °C for 24 h. Chromatographic purification of the crude product afforded the title product 15 as a colorless oil (169 mg, 74%). TLC: Rf = 0.5 (20% ETOAc/hexanes).
1H), 5.52 (dd, J = 7.5, 15.5 Hz, 4H), 4.58 (d, J = 6.5 Hz, 2H), 3.10 (dd, J = 2.0, 7.5 Hz, 1H), 2.84–2.80 (m, 1H), 2.08 (s, 3H), 1.95–1.49 (m, 2H), 1.47–1.38 (m, 2H), 1.31–1.25 (m, 8H, 0.89 (t, J = 6.0 Hz, 3H). 13C NMR (500 MHz, CDCl3) δ 170.9, 132.2, 128.7, 64.1, 60.9, 57.8, 32.2, 32.0, 29.6, 29.4, 26.1, 22.9, 21.1, 14.3. HRMS (ESI-TOF) m/z [M + Na]+ calcd for C19H32O5Na, 363.1924; found, 363.1914.

Dodeca-4(E)-6(E)-dien-3-yl Acetate (22). Ethyl magnesium bromide (2.6 mL, 7.9 mmol, 3 M in THF) was added over 10 min to a 0 °C solution of E,E-2,4-decadienyl (1.0 g, 6.6 mmol) in dry THF (60 mL). After 3 h, the reaction was worked up with 10% aq. NH4Cl (20 mL), the THF was removed under reduced pressure, and the reaction mixture was extracted with EtOAc (2 × 80 mL). The combined organic extracts were washed with water (2 × 40 mL) and brine (30 mL) and dried, and the residue purified by flash chromatography to provide dodeca-4(E)-6(E)-dien-3-ol (1.0 g, 84%). As a colorless liquid. TLC: Rf ≈ 0.5 (20% EtOAc/hexanes). 1H NMR (500 MHz, CDCl3) δ 6.19 (dd, J = 10.5, 15.5 Hz, 1H), 6.05 (dd, J = 10.5, 15.5 Hz, 1H), 5.71 (dt, J = 7.0, 14.5 Hz, 1H), 5.57 (dd, J = 7.5, 15.0 Hz, 1H), 4.05 (dt, J = 6.5, 13.5 Hz, 1H), 2.08 (q, J = 7.0 Hz, 2H), 1.63–1.49 (m, 3H), 1.42–1.36 (m, 2H), 1.39–1.25 (m, 4H), 0.90–0.87 (m, 6H). 13C NMR (125 MHz, CDCl3) δ 135.7, 133.4, 131.4, 129.6, 77.4, 32.8, 31.6, 30.3, 29.1, 22.7, 14.3, 9.9. HRMS (ESI-TOF) m/z [M + Na]+ calcd for C19H34ONa, 295.2077; found, 295.2076.

Following the acylation procedure above, dodeca-4(E)-6(E)-dien-3-ol (500 mg, 2.7 mmol) was treated with acetic anhydride (0.3 mL, 3.2 mmol), and pyridine (0.30 mL, 3.5 mmol) in CH2Cl2 (15 mL) at rt for 3 h. Chromatographic purificiation of the crude product using 5–10% EtOAc/hexanes as eluent afforded the title compound 22 (580 mg, 94%) as a colorless oil. TLC: Rf ≈ 0.5 (10% EtOAc/hexanes). 1H NMR (500 MHz, CDCl3) δ 6.21 (dd, J = 10.5, 15.0 Hz, 1H), 6.00 (dd, J = 10.4, 15.0 Hz, 1H), 5.72 (dt, J = 7.5, 14.5 Hz, 1H), 5.47 (dt, J = 7.5, 15.5 Hz, 1H), 5.17 (dt, J = 7.5, 14.0 Hz, 1H), 2.07 (app q, J = 7.0 Hz, 2H), 2.05 (s, 3H), 1.70–1.58 (m, 3H), 1.41–1.34 (m, 2H), 1.33–1.24 (m, 3H), 0.90–0.87 (m, 6H). 13C NMR (125 MHz, CDCl3) δ 170.6, 136.6, 133.4, 129.3, 128.5, 76.1, 32.8, 31.6, 31.9, 27.7, 22.7, 21.5, 11.4, 9.7. HRMS (ESI-TOF) m/z [M + Na]+ calcd for C19H34O3Na, 247.1676; found, 247.1674.

(E)-1-(3-Pentylidene-2-yl)-pent-1-en-3-yl Acetate (23). Following the general epoxidation procedure, 22 (50 mg, 0.22 mmol), TMO (5 mg, 5 mol %), pyridine (2.0 µL, 0.02 mmol), and diphenylsilane (26). To a solution of 26 (143 mg, 0.52 mmol) after stirring at 0 °C for 30 min, the reaction was continued at rt for 16 h. The mixture was washed with saturated NaHCO3 solution and water (2 mL) and dried over anhydrous Na2SO4 and all volatiles were evaporated in vacuo. Purification of the residue via silica gel column chromatography using 0–20% ethyl acetate/hexane as eluent gave 26 (140 mg, 80%) as a clear oil. TLC: Rf ≈ 0.3 (hexanes). 1H NMR (400 MHz, CDCl3) δ 7.70–7.64 (m, 4H), 7.44–7.33 (m, 6H), 6.26 (d, J = 15.0, 10.9 Hz, 1H), 6.08 (d, J = 10.8 Hz, 1H), 5.65 (dt, J = 14.6, 7.0 Hz, 1H), 4.08 (s, 2H), 2.10 (q, J = 7.2 Hz, 2H), 1.69 (s, 3H), 1.46–1.34 (m, 2H), 1.34–1.20 (m, 8H), 1.05 (s, 9H), 0.87 (t, J = 6.7 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 135.8(4), 134.3, 134.2, 133.7, 129.5(2), 127.6(5), 127.3, 126.1, 68.6, 33.0, 29.7, 29.1, 22.9, 26(3), 22.7, 19.3, 14.1, 13.9. Molecular ion could not be found by HRMS.

(E)-tart-Butyl(2(E)-4(E)-2-methyl-2-methyleneocta-2,4-dien-1-ol)(oxy) diphenylsilane (27) (E)-tart-Butyl(2(E)-methyl-3(4-on-1-en-1-yl)-oxirane-2-yl)methoxy)diphenylsilane (28). Following the general epoxidation procedure, 26 (66 mg, 0.17 mmol), TMO (2 mg, 5 mol %), pyridine (2 µL, 0.02 mmol), and 30% H2O2 (39 µL, 0.34 mmol) were stirred in dry CH2Cl2 (2.5 mL) at −5 °C for 20 h. Chromatographic purification of the crude product afforded the title products as a colorless oil (46 mg, 66%, 1:1 mixture of regioisomers). TLC: Rf ≈ 0.75 and 0.72 for 27 and 28, respectively (4% EtOAc/ hexanes). 1H NMR of 27 (2400 MHz, CDCl3) δ 7.72–7.62 (m, 4H), 7.48–7.34 (m, 6H), 7.24–7.18 (m, 4H), 6.87 (d, J = 8.8, 1.6 Hz, 1H), 4.05 (d, J = 15.5 Hz, 2H), 3.34 (d, J = 8.9, 2.3 Hz, 1H), 2.84 (dd, J = 5.6, 2.3 Hz, 1H), 1.74 (d, J = 1.3 Hz, 3H), 1.64–1.54 (m, 1H), 1.54–1.40 (m, 1H), 1.40–1.22 (m, 8H), 1.06 (s, 9H), 0.89 (t, J = 6.7 Hz, 3H). 13C NMR (100 MHz, CDCl3) δ 121.1, 120.9(2), 125.2, 133.5, 133.2, 129.6(2), 127.6(5), 121.2, 67.9, 60.4, 55.1, 32.2, 31.8, 29.4, 29.2, 26.8(3), 26.0, 22.6, 19.3, 14.1. HRMS (ESI-TOF) m/z [M + Na]+ calcd for C27H42O2Si, 473.2846; found, 473.2859.
To a 0 °C solution of ethyl 4-methylhepta-2(E),4(E)-dien-1-yl acetate (29) (200 mg, 1.16 mmol) in CH₂Cl₂ (10 mL) at rt for 3 h. Chromatographic purification of the crude product using 5−10% EtOAc/hexanes as eluent afforded 29 (254 mg, 91%) as a clear oil. TLC: Rf ≈ 0.5 (70% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 6.29 (d, J = 15.6 Hz, 1H), 3.62 (dt, J = 6.8, 14.4 Hz, 1H), 5.52 (t, J = 7.2 Hz, 1H), 4.90 (d, J = 6.8 Hz, 2H), 2.06 (3H), 1.73 (3H), 0.98 (t, J = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 139.9, 133.6, 123.1, 119.9, 65.7, 21.2, 21.1, 14.1, 12.3. HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C₁₀H₁₆O₂Na: 191.1050; found, 191.1044.

(E)-3-(3-Ethyl-2-methoxyxiran-2-yl)allyl Acetate (30). Following the general epoxidation procedure, 29 (50 mg, 0.29 mmol), MTO (4 mg, 5 mol%), pyridine (4 μL, 0.12 mol%), and 30% H₂O₂ (3 μL, 0.04 mmol) were stirred in dry CH₂Cl₂ (5 mL) at 0 °C for 10 h. Chromatographic purification of the crude product using 20−20% EtOAc/hexanes as eluent afforded 30 (210 mg, 85%) as a clear oil. TLC: Rf ≈ 0.6 (10% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 6.49 (dd, J = 10.8, 14.8 Hz, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.60 (dt, J = 7.6, 15.2 Hz, 1H), 4.58 (d, J = 6.8 Hz, 2H), 2.04 (3H), 1.77 (s, 3H), 1.75 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 137.6, 131.5, 123.9, 123.3, 65.6, 26.0, 21.0, 18.3.

(E)-3-(3-Dimethoxymethoxiran-2-yl)allyl Acetate (31). Following the general epoxidation procedure, 29 (50 mg, 0.32 mmol), MTO (4 mg, 5 mol%), pyridine (3.1 μL, 12 mol%), and 30% H₂O₂ (55 μL, 0.48 mmol) were stirred in dry CH₂Cl₂ (4 mL) at −10 °C for 14 h. Chromatographic purification of the crude product using 10−20% EtOAc/hexanes as eluent afforded 31 (210 mg, 85%) as a clear oil. TLC: Rf ≈ 0.6 (10% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 6.49 (dd, J = 10.8, 14.8 Hz, 1H), 5.82 (d, J = 10.8 Hz, 1H), 5.60 (dt, J = 7.6, 15.2 Hz, 1H), 4.58 (d, J = 6.8 Hz, 2H), 2.04 (3H), 1.77 (s, 3H), 1.75 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.9, 137.6, 131.5, 123.9, 123.3, 65.6, 26.0, 21.0, 18.3. HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C₁₀H₁₆O₃Na: 187.1012; found, 187.1018.

(E)-3-(Cyclohex-1-en-1-yl)allyl Acetate (33). Following the general epoxidation procedure, 29 (800 mg, 1.66 mmol) was treated with acetic anhydride (0.78 mL, 8.30 mmol) and pyridine (1.3 mL, 8.83 mmol) in CH₂Cl₂ (10 mL) at rt for 12 h. Chromatographic purification of the crude product using 10−20% EtOAc/hexanes as eluent afforded the title compound 33 (1.1 g, 91%) as a clear oil. TLC: Rf ≈ 0.6 (10% ethyl acetate/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 6.27 (d, J = 15.6 Hz, 1H), 5.70 (t, J = 6.8 Hz, 1H), 5.61 (d, J = 6.4, 14.4 Hz, 1H), 4.91 (d, J = 6.8 Hz, 2H), 2.16−1.99 (m, 4H), 2.06 (s, 3H), 1.69−1.56 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 170.9, 138.5, 130.5, 131.0, 119.0, 65.7, 26.0, 24.5, 22.6, 22.5, 21.1. HRMS (ESI-TOF) m/z [M + Na]⁺ calc for C₁₀H₁₆O₂Na: 203.1050; found, 203.1044.
graphic comparisons. This material is available for free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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