An Asymmetric Aldol−Ring-Closing Metathesis Strategy for the Enantioselective Construction of Oxygen Heterocycles: An Efficient Approach to the Enantioselective Synthesis of (+)-Laurencin

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Abstract: A strategy is described for the enantioselective construction of medium-ring cyclic ethers by merging the asymmetric aldol addition of glycolates with a ring-closing metathesis reaction. Cyclic ethers of seven-, eight-, and nine-membered rings are readily available through a ring-closing metathesis without cyclic conformational constraints, by exploiting the acyclic conformational bias of the *gauche* effect. A short formal synthesis of the eight-membered ether (+)-laurencin, a red algae metabolite, has been accomplished utilizing the aldol−metathesis combination.

Medium-ring ethers are found in a number of marine natural products, such as brevetoxin A[1] and B,[2] yessotoxin,[3] ciguatoxin,[4] and maitotoxin.[5] In addition, several other marine natural products containing medium-ring ethers, including laurencin,[6] prelaureatin,[7] pannosallene,[8] isolaurallene,[9] and neolaurallene[10] (Figure 1), have been isolated from red algae and species which feed on *Laurencia* sp.[11] Laurencin, a representative member of the red algae oxocenes, has been the subject of significant synthetic effort and has been prepared by several different strategic approaches.[12,13]

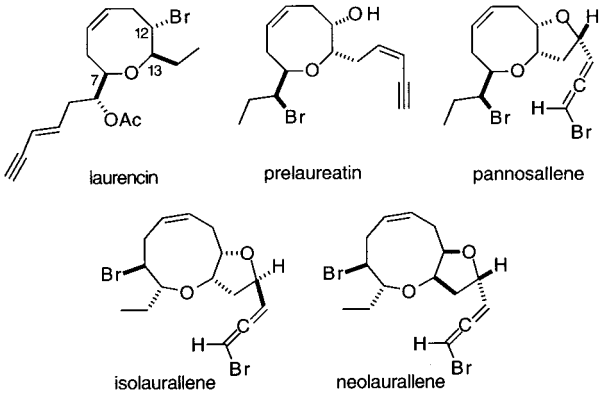

Figure 1.

A General Strategy for the Asymmetric Synthesis of Unsaturated Medium-Ring Ethers. We sought to develop a flexible approach to the synthesis of unsaturated medium-ring ethers[14] which would allow the preparation of a variety of ring sizes and stereochemical substitution patterns. The strategy we pursued was based on the recognition that many of the red algae medium-ring ether natural products were substituted on both carbons flanking the ether linkage. In addition, one or both of the carbons adjacent to the ether linked carbons were substituted,

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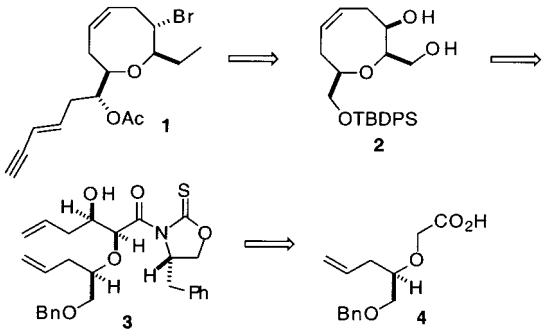
Scheme 1

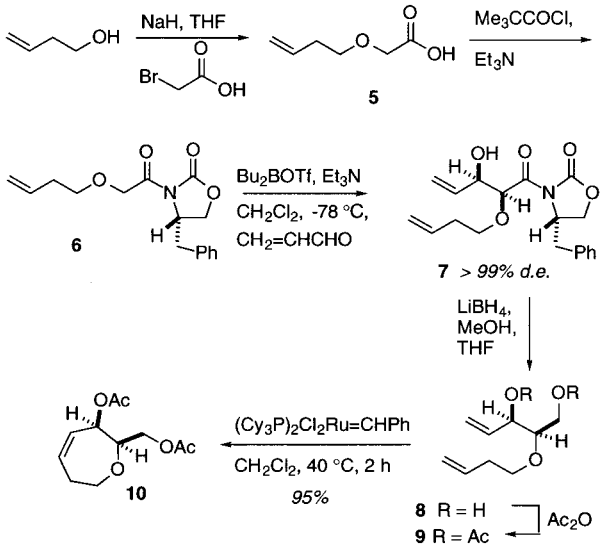


and in particular, substituted with an oxygen group cis or a halide trans on the β-carbon to the ether oxygen. This observation suggested a functional precursor such as diol **2** for laurencin; similar precursors can be imagined for the other aforementioned medium-ring ether natural products. Diol **2**, a key intermediate in Holmes's recently reported synthesis of laurencin,[12] was envisioned to arise from the reduction of an asymmetric aldol product such as **3**, followed by a ring-closing metathesis reaction of the diene to form the Δ-4-oxocene. The aldol product **3** could be prepared from acid **4** by attachment to a chiral auxiliary prior to a boron- or titanium enolate-mediated aldol addition (Scheme 1).

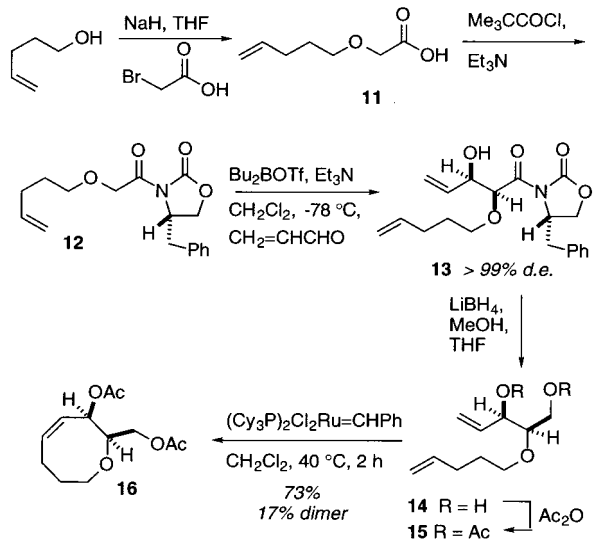
There were two key reactions to the success of the above strategy: the auxiliary-mediated asymmetric aldol addition of a glycolate imide and the ring-closing metathesis reaction to construct the Δ-4-oxocene. While some precedent existed for the aldol addition in reports by Evans,[15] at the time we began this work[16] no examples of construction of eight-membered cyclic ethers by olefin metathesis had been reported. In fact, there was evidence that formation of eight-membered cyclic ethers might not be achievable by ring-closing metathesis without an internal cyclic constraint.[17] Since we began this investigation, reports of the formation of medium-ring ethers both with[18] and without[19] cyclic conformational constraints have appeared. However, at the outset, the uncertainty of the ring-closing metathesis to form the Δ-4-oxocene prompted an investigation of the synthesis of simpler analogues to test the proposed strategy.

An approach to the synthesis of seven-, eight-, and nine-membered cyclic ethers was undertaken using the asymmetric aldol−olefin metathesis sequence. The general strategy for the asymmetric construction of the required dienes is illustrated in Scheme 2 for the preparation of cyclic ether **10**. Treatment of 3-buten-1-ol with sodium hydride and bromoacetic acid in THF gave the alkoxyacetic acid in quantitative yield. Subsequent exposure of the acid to pivaloyl chloride and triethylamine provided the mixed anhydride in situ. Acylation of the lithium salt of (*S*)-2-benzyloxazolidinone with the mixed anhydride provided the acyl oxazolidinone **6** in 82% yield. Formation of the dibutylboron enolate according to the standard Evans[20] protocol and addition of acrolein gave the syn aldol product **7** as single detectable isomer by 300-MHz NMR spectroscopy. Reductive removal of the chiral auxiliary ($LiBH_4$, THF, MeOH) afforded the diol **8** in excellent yield. Acylation of the diol with acetic anhydride produced the required diene **9** in five synthetic steps in good overall yield (>99% ee). Exposure of diene **9** to ring-closing metathesis conditions ($[(C_6H_{11})_3P]_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 0.1 M, 40 °C) resulted in predominant formation of a dimer accompanied by less than 20% of the desired oxepene. Fortunately, when the concentration was lowered (0.003 M CH_2Cl_2, 40 °C, 5 mol % catalyst), the reaction resulted in exclusive formation of the oxepene **10** in 95% yield after 2 h. With the successful ring closure of diene **9** to oxepene **10** with the Grubbs catalyst, the Schrock molybdenum catalyst was not investigated, since is it difficult to handle and also more difficult to prepare because of oxygen sensitivity.

Scheme 2



Scheme 3



The corresponding eight-membered ring precursor **15** was constructed by a similar route, starting with 4-penten-1-ol, as illustrated in Scheme 3. Exposure of diene **15** to 7 mol % of the Grubbs catalyst in dichloromethane (0.003 M) at 40 °C resulted in the formation of 73% of the oxocene **16**, accompanied by 17% of a dimer. This result was particularly gratifying in light of earlier reports of failed attempts to close

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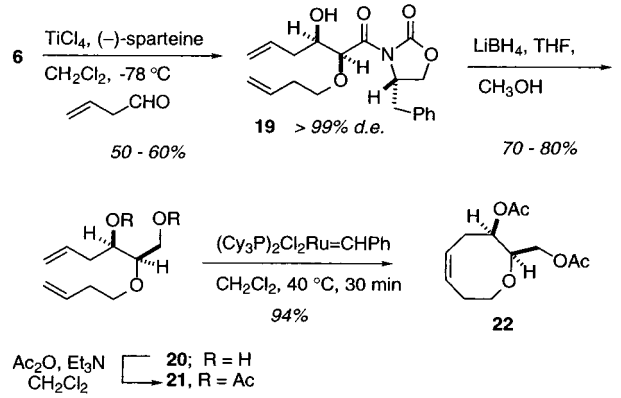
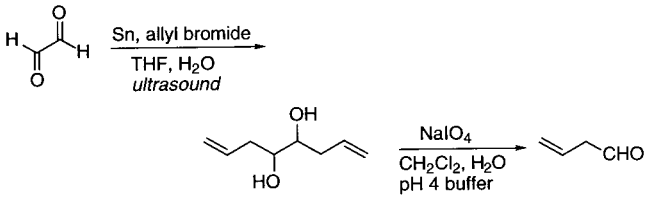
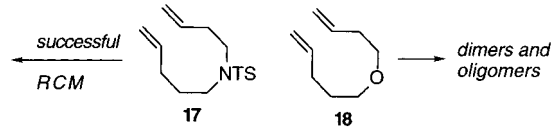
Scheme 4



Scheme 5



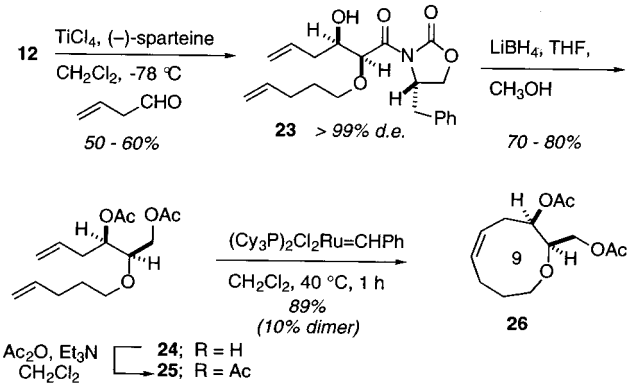
eight-membered rings by olefin metathesis without cyclic constraints. Hoveyda had reported a successful ring-closing metathesis reaction on a sulfonamide linked diene **17** but also reported that the diene ether **18** produced only dimers and oligomers.[21] The successful ring-closing metathesis of diene **15**



in contrast to **18** suggests that the vicinal stereogenic centers in diene **15** provide access to conformations where the olefinic chains are gauche, which are required to facilitate ring closure by virtue of the gearing due to the known *gauche effect* of 1,2-dioxygen substitution. The stabilization which results from the gauche disposition of the two oxygens contributes substantially to the stabilization of one of the conformations with the olefinic chains gauche. The lack of the vicinal oxygen dipolar effect in diene **18** apparently allows dimerization and oligomerization to compete.

The isomeric Δ-4-oxocene **22** and the nine-membered analogue **26** were prepared (Schemes 4 and 6) from the asymmetric aldol reaction of **6** and **12.** The use of 3-butenal or a 3-butenal equivalent as the aldehyde was required to incorporate the correct number of carbons and position the alkene correctly in the Δ-4-oxocene after the olefin metathesis. While 4-*tert*-butyldiphenylsilyloxybutanal had been used as a 3-butenal equivalent in the earlier model studies because of initial problems with generating and purifying 3-butenal, the need to convert the primary silyl ether to a terminal olefin was cumbersome. Thus, a procedure for the simple preparation of 3-butenal was required. A survey of the literature and attempted execution of some known methods[22] for the preparation of 3-butenal met with unsatisfactory results. An alternative, workable synthesis of 3-butenal was needed. Double allylation of glyoxal with allyl bromide and tin metal in aqueous media[23,24] gave 1,7-octadiene-3,4-diol in 85% yield. Cleavage of the diol with sodium periodate in a dichloromethane−pH 4 buffer biphase provided excellent yields of 3-butenal in solution form. The resultant dichloromethane solution of 3-butenal was used directly in the aldol addition.

Scheme 6



A recent modification of the Evans procedure was exploited in the aldol addition. We recently discovered that chlorotitanium enolates of acyloxazolidinethiones undergo rapid, highly selective syn aldol additions when the enolates are formed with titanium tetrachloride using (−)-sparteine as the base.[25] Here we demonstrate that α-alkoxy acyl*oxazolidinones* and α-alkoxy acyl*oxazolidinethiones* also function well in this reaction. Aldol addition of the titanium enolates of **6** and **12** to 3-butenal as described above produced **19** and **23**, respectively, with excellent stereoselectivity. Subsequent removal of the auxiliary and acylation of the resultant diols gave the diene-diacetates **21** and **25**.

The diene **21** was converted to the Δ-4-oxocene **22** in 94% yield in 30 min by exposure to 7 mol % of the Grubbs catalyst. The remarkable ease of the ring closure of diene **21** in contrast to the partial dimerization of the isomeric diene **15** can be rationalized on the basis of the relative energies of the products. The position of the double bond has a dramatic effect on the relative energy of the oxocene. Oxocene **22** was calculated[26] to be on the order of 3−4 kcal lower in energy than oxocene **16**. This difference in energy is presumably reflected in the transition states for formation of the metallocyclobutane intermediates which lead to the ring-closed products.

The nine-membered cyclic ether **26** was also readily formed by ring-closing metathesis of diene **25**. While Clark has shown that nine-membered cyclic ethers can be prepared by ring-closing metathesis with the Schrock molybdenum carbene complex,[18] the closure of diene **25** to ether **26** is the first example of the formation of a nine-membered ring by an olefin metathesis without a cyclic conformational constraint. The remarkable efficiency of this process portends well for its application in the synthesis of marine natural products such as isolaurallene.

Formal Synthesis of (+)-Laurencin. After we demonstrated the feasibility of the basic strategy for the construction of

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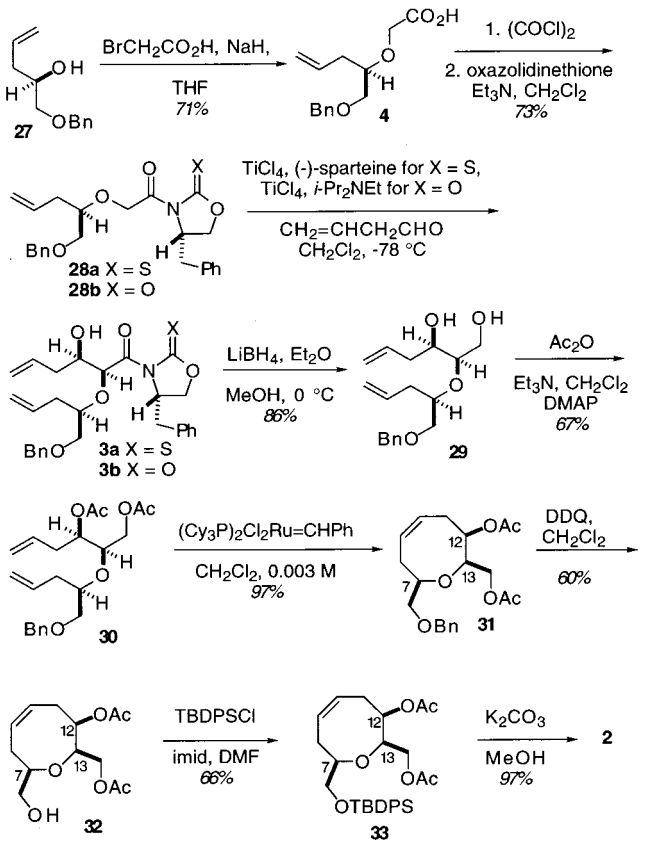
(26) Molecular mechanics calculations were made using the MM2 force field.

Scheme 7



medium-ring ethers, the application of the asymmetric aldol−olefin metathesis sequence to the synthesis of (+)-laurencin was undertaken. Diol **2** was chosen as the initial target, since its conversion to laurencin had been successfully completed by Holmes et al.[12] A precursor to the C7 (laurencin numbering) side chain would be incorporated at an early stage of the synthesis prior to the asymmetric aldol reaction. The synthesis of the required alkoxy acetic acid **4** is shown in Scheme 7. Ring-opening of commercially available (*R*)-benzyl glycidyl ether with vinylmagnesium bromide in the presence of catalytic copper(I) iodide gave 92% of the secondary alcohol **27**. Exposure of the alcohol **27** and bromoacetic acid to sodium hydride produced the desired alkoxyacetic acid **4** in 71% yield. The acid **4** was treated with oxalyl chloride, and the resultant acid chloride was added to (*S*)-4-benzyloxazolidine-2-thione and triethylamine to provide the acyloxazolidinethione **28a** in 73% overall yield. The corresponding acyl oxazolidinone **28b** was prepared similarly by exposure of the acid chloride to the lithium salt of (*S*)-4-benzyloxazolidine-2-one.

Enolization of acyloxazolidinethione **28a** with $TiCl_4$ and (−)-sparteine[25] at −78 °C, followed by addition of freshly prepared 3-butenal solution, produced the aldol adduct **3a** with excellent diastereoselectivity (>98:2 ds, 90% yield at 30% conversion), thus establishing the C12 and C13 stereogenic centers for (+)-laurencin. Alternatively, the acyloxazolidinone **28b** could be enolized[29] with $TiCl_4$ and Hunig's base followed by aldol reaction with 3-butenal to give 65% yield of the aldol adduct **3b** after purification. The C7 stereogenic center appears to have no influence on the selectivity of the asymmetric aldol addition in either case. The chiral auxiliary was readily removed by reduction of **3a** or **3b** with lithium borohydride in methanol−ether to produce the diol **29** in greater than 80% yield. Acetylation of the diol gave diacetate **30**. The critical ring-closing metathesis reaction proceeded smoothly with 5 mol % $(Cy_3P)_2RuCl_2{=}CHPh$ in dichloromethane (0.003 M) at reflux to give 97% of the eight-membered ether **31**.

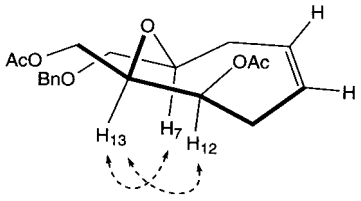


Figure 2.

The stereochemistry of the Δ-4-oxocene **31** which resulted was confirmed by inspection of the NOESY spectrum. A substantial cross-peak was observed between H_7 and H_{13}, indicating a cis relationship on the Δ-4-oxocene (see Figure 2). A significant interaction was also observed for H_{12} and H_{13}, indicating their cis relationship.

The diacetate **31** was converted to the Holmes intermediate **2** by DDQ cleavage of the benzyl ether,[30] protection of the primary alcohol as its *tert*-butyldiphenylsilyl ether, and methanolysis of the two acetates. The diol **2** was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]^{25}_D$) to that reported by Holmes et al.[12] The strategy presented here for the asymmetric construction of medium-ring cyclic ethers by merging the asymmetric aldol addition of glycolates with a ring-closing metathesis reaction should provide efficient entry to a variety of cyclic ethers. Application of this strategy to the synthesis of various marine metabolites is in progress.

Experimental Section

Materials and Methods: General. Infrared (IR) spectra were obtained using a Mattson FT-IR 5000 Galaxy series infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker model AC-200 (^{1}H at 200 MHz; ^{13}C at 50 MHz), Bruker model WM-250 (^{1}H at 250 MHz), and Varian model XL-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz). Optical rotations were determined using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Diethyl ether, tetrahydrofuran (THF), and dichloromethane were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, chlorotrimethylsilane, and acetonitrile were distilled from calcium hydride immediately prior to use.

(*R*)-1-(Benzyloxymethyl)but-3-enyl-1-oxyacetic Acid (4). Sodium hydride (60% dispersion in mineral oil, 2.80 g, 70 mmol) was washed three times with dry hexanes and suspended in 50 mL of THF, and the mixture was cooled to 0 °C. The appropriate alcohol (70 mmol; 3-buten-1-ol for acid **5**; 4-penten-1-ol for acid **11**; and alcohol **27**[27] for acid **4**) was added dropwise over 15 min. The resulting mixture was stirred at 0 °C for 15 min, warmed to 25 °C for 15 min, and then recooled to 0 °C. In a second flask, sodium hydride (60% dispersion in mineral oil, 2.80 g, 70 mmol) was washed three times with dry hexanes and suspended in 25 mL of THF, and the mixture was cooled to 0 °C. Bromoacetic acid (70 mmol) dissolved in 25 mL of THF was cannulated into the second flask, and the mixture was stirred at 0 °C for 5 min. The sodium alkoxide of the alcohol was then cannulated into the flask containing the sodium carboxylate of bromoacetic acid. The resultant mixure was warmed to 25 °C and stirred for 3 h. The reaction was

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(28) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1661−1663.

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(30) Schreiber, S. L.; Ikemoto, N. *J. Am. Chem. Soc.* **1992**, *114*, 2524−2536.

quenched with water, and the THF was removed in vacuo. The aqueous layer was washed with ether, acidified with concentrated H_2SO_4, and then extracted three times with ether. The extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The known[28] alkoxyacetic acid **4** was obtained in 71% yield and was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 5.74 (m, 1H), 5.11 (m, 2H), 4.60 (ABq, J = 12.0 Hz, $\Delta\nu_{AB}$ = 7.2 Hz, 2H), 4.17 (ABq, J = 17.5 Hz, $\Delta\nu_{AB}$ = 56.9 Hz, 2H), 3.59 (m, 1H), 3.47 (m, 2H), 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.7, 67.5, 71.7, 73.1 79.8, 117.8, 127.5, 127.6, 128.2, 133.1, 136.9, 173.4; IR (film) 3600−2700 (br), 1760, 1360, 1120 cm^{-1}; $[\alpha]^{25}_D$ = −31.4 (*c* 0.41, CH_2Cl_2).

3-Butenyl-1-oxyacetic acid (5): 100% yield; ^{1}H NMR ($CDCl_3$) δ 5.80 (m, 1H), 5.10 (m, 2H), 4.12 (s, 2H), 3.62 (t, J = 6.6 Hz, 2H), 2.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 33.6, 67.5, 70.9, 116.7, 134.2, 175.2; IR (film) 3720−2200 (br), 1740, 1430, 1130, 910 cm^{-1}; Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.30; H, 7.86.

4-Pentenyl-1-oxyacetic acid (11): 100% yield; ^{1}H NMR ($CDCl_3$) δ 5.79 (m, 1H), 5.00 (m, 2H), 4.10 (s, 2H), 3.56 (t, J = 6.6 Hz, 2H), 2.13 (dt, J = 7.3, 6.5 Hz, 2H), 1.73 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.5, 30.0, 67.7, 71.3, 115.1, 137.8, 180.2; IR (film) 3700−2500 (br), 1740, 1440, 1140, 910 cm^{-1}. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39. Found: C, 58.05; H, 8.11.

(*S*)-3-[1-Oxo-2-(but-3-enyl-1-oxy)]-4-benzyl-2-oxazolidinone (6). A solution of the alkoxyacetic acid **5** (5.48 g, 42.1 mmol) and triethylamine (6.2 mL, 44.2 mmol) in 350 mL of ether were added to a flask fitted with a mechanical stirrer, and the mixture was cooled to −78 °C. Pivaloyl chloride (5.44 mL, 44.2 mmol) was added slowly over 15 min, and the resultant mixture was stirred for 5 min at −78 °C and then warmed to 0 °C for 1 h. In a separate flask, (*S*)-4-benzyl-2-oxazolidinone (7.46 g, 42.1 mmol) in 50 mL of THF was cooled to −78 °C, and *n*-BuLi (26.0 mL, 42.5 mmol) was added dropwise. After addition was complete, the mixture was stirred at −78 °C for 10 min. The solution of mixed anhydride was recooled to −78 °C, and the lithiated oxazolidinone was then cannulated into the mixed anhydride. After being stirred for 15 min at −78 °C, the mixture was warmed to 0 °C for 30 min. The reaction was quenched with water and warmed to 25 °C. The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 10.0 g (82%) of acyloxazolidinone **6**: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H), 5.85 (m, 1H), 5.10 (m, 2H), 4.66 (m, 3H), 4.24 (m, 2H), 3.64 (t, J = 7.0 Hz, 2H), 3.32 (dd, J = 13.5, 3.2 Hz, 1H), 2.79 (dd, J = 13.5, 9.5 Hz, 1H), 2.43 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.0, 37.7, 54.8, 67.2, 70.7, 71.2, 116.7, 127.4, 129.0, 129.3, 134.7, 134.9, 153.4, 170.2; IR (film) 2920, 1770, 1720, 1390, 1260, 1210, 1130 cm^{-1}; $[\alpha]^{25}_D$ = +79.3° (*c* 0.24, CH_2Cl_2). Anal. Calcd for $C_{16}H_{19}O_4N_1$: C, 66.42; H, 6.62. Found: C, 66.14; H, 6.63.

(*S*)-3-[1-Oxo-2-(pent-4-enyl-1-oxy)]-4-benzyl-2-oxazolidinone (12). By the same procedure described above, 5.45 g of alkoxyacetic acid **11** provided 9.20 g (80%) of acyloxazolidinone **12**: ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 5.82 (m, 1H), 5.00 (m, 2H), 4.67 (m, 3H), 4.24 (m, 2H), 3.58 (t, J = 6.6 Hz, 2H), 3.31 (dd, J = 13.5, 3.1 Hz, 1H), 2.79 (dd, J = 13.5, 9.5 Hz, 1H), 2.16 (m, 2H), 1.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.7, 30.1, 37.7, 54.8, 67.2, 70.6, 71.4, 114.9, 127.4, 129.0, 129.4, 134.9, 138.0, 153.4, 170.3; IR (film) 2920, 1770, 1710, 1390, 1350, 1260, 1210, 1140 cm^{-1}; $[\alpha]^{25}_D$ = +65.4° (*c* 0.19, CH_2Cl_2). Anal. Calcd for $C_{17}H_{21}O_4N_1$: C, 67.31; H, 6.98. Found: C, 67.05; H, 7.01.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-(but-3-enyl-1-oxy)-3-hydroxy-4-pentenyl]-4-benzyl-2-oxazolidinone (7). Acyloxazolidinone **6** (4.5 g, 15.6 mmol) and 30 mL of dichloromethane were cooled to −40 °C in a flask equipped with a low-temperature thermometer. Neat dibutylboron triflate (4.3 mL, 17.1 mmol) was added dropwise, followed by dropwise addition of triethylamine (2.6 mL, 18.7 mmol). The solution was stirred at −40 to −30 °C for 1 h and then cooled to −78 °C. Freshly distilled acrolein (1.3 mL, 18.7 mmol) was added dropwise, and the mixture was stirred at −78 °C for 1.5 h and then warmed to 0 °C for 30 min. The reaction was quenched at 0 °C by the sequential dropwise addition of pH 7 buffer (1.2 mL/mmol of oxazolidinone), methanol (4 mL/mmol of oxazolidinone), and 30% H_2O_2 (1.2 mL/mmol of oxazolidinone). The mixture was stirred for 1 h at 0 °C and then concentrated in vacuo. The aqueous layer was extracted three times with dichloromethane, and the combined extracts were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 2.15 g (40%) of alcohol **7** and 1.80 g (80% brsm) of acyloxazolidinone **6**: ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 5.87 (m, 2H), 5.38−5.02 (m, 4H), 5.13 (d, J = 3.0 Hz, 1H), 4.67 (m, 1H), 4.36 (m, 1H), 4.22 (m, 2H), 3.73 (ddd, J = 9.0, 6.6, 6.6 Hz, 1H), 3.46 (ddd, J = 9.0, 6.9, 6.9 Hz, 1H), 3.33 (dd, J = 13.4, 3.5 Hz, 1H), 2.82 (dd, J = 13.4, 9.6 Hz, 1H), 2.64 (d, J = 7.9 Hz, 1H), 2.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 34.0, 37.7, 55.6, 66.9, 70.4, 73.6, 80.3, 116.9, 117.0, 127.4, 129.0, 129.4, 134.5, 134.9, 136.5, 153.5, 170.3; IR (film) 3720−3000 (br), 1770, 1700, 1390, 1210, 1100 cm^{-1}; $[\alpha]^{25}_D$ = +38.6° (*c* 0.27, CH_2Cl_2). Anal. Calcd for $C_{19}H_{23}O_5N_1$: C, 66.07; H, 6.71. Found: C, 65.79; H, 6.84.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-(pent-4-enyl-1-oxy)-3-hydroxy-4-pentenyl]-4-benzyl-2-oxazolidinone (13). By the same procedure described above, 6.84 g of acyloxazolidinone **12** provided 3.64 g (45%) of **13** and 2.74 g (85% brsm) of acyloxazolidinone **12**: ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 5H), 5.87 (m, 2H), 5.40−5.17 (m, 2H), 5.10 (d, J = 3.0 Hz, 1H), 5.08−4.93 (m, 2H), 4.67 (m, 1H), 4.37 (m, 1H), 4.23 (m, 2H), 3.67 (ddd, J = 9.0, 6.3, 6.3 Hz, 1H), 3.44 (ddd, J = 9.0, 6.6, 6.6 Hz, 1H), 3.34 (dd, J = 13.3, 3.5 Hz, 1H), 2.82 (dd, J = 13.3, 9.6 Hz, 1H), 2.56 (d, J = 7.9 Hz, 1H), 2.15 (m, 2H), 1.72 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.7, 30.0, 37.7, 55.5, 66.9, 70.6, 73.4, 80.3, 115.0, 116.8, 127.4, 128.9, 129.3, 134.9, 136.6, 137.9, 153.4, 170.4; IR (film) 3700−3140 (br), 2920, 1770, 1700, 1390, 1210, 1100 cm^{-1}; $[\alpha]^{25}_D$ = +42.3° (*c* 0.18, CH_2Cl_2). Anal. Calcd for $C_{20}H_{25}O_5N_1$: C, 66.83; H, 7.01. Found: C, 66.58; H, 7.09.

(2*R*,3*R*)-2-(But-3-enyl-1-oxy)-4-pentene-1,3-diol (8). Alcohol **7** (0.16 g. 0.5 mmol), 5 mL of THF, and anhydrous methanol (0.04 mL) were cooled to 0 °C. Lithium borohydride (2.0 M in THF, 0.51 mL, 1.0 mmol) was added dropwise, and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with 15% NaOH and then concentrated in vacuo. The aqueous layer was extracted with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography gave 0.052 g (66%) of diol **8**: ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 2H), 5.40−5.04 (m, 4H), 4.18 (m, 1H), 3.68 (m, 4H), 3.27 (ddd, J = 6.2, 4.4, 4.4 Hz, 1H), 2.58 (d, J = 4.0 Hz, H), 2.34 (m, 2H), 2.01 (t, J = 6.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.4, 61.3, 70.3, 72.8, 82.6, 117.2, 117.3, 135.1, 136.9; IR (film) 3700−3040 (br), 2880, 1640, 1430, 1100, 920 cm^{-1}; $[\alpha]^{25}_D$ = +2.3° (*c* 0.17, CH_2Cl_2). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.99; H, 9.30.

(2*R*,3*R*)-2-(Pent-4-enyl-1-oxy)-4-pentene-1,3-diol (14). By the same procedure described above, 0.323 g of alcohol **13** provided 0.149 g (89%) of diol **14**: ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 2H), 5.41−4.94 (m, 4H), 4.20 (m, 1H), 3.78 (m, 1H), 3.70−3.50 (m, 3H), 3.26 (ddd, J = 5.8, 4.4, 4.4 Hz, 1H), 2.50 (d, J = 4.0 Hz, 1H), 2.13 (m, 2H), 1.90 (t, J = 6.0 Hz, 1H), 1.70 (m, 2H).; ^{13}C NMR ($CDCl_3$) δ 29.0, 30.2, 61.1, 70.4, 72.6, 82.1, 114.9, 116.9, 137.0, 138.0; IR (film) 3700−3120 (br), 2940, 1640, 1420, 1100, 910 cm^{-1}; $[\alpha]^{25}_D$ = +4.2° (*c* 0.22, CH_2Cl_2). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.61; H, 9.77.

(2*R*,3*R*)-2-(But-3-enyl-1-oxy)-5-hexene-1,3-diol (20). By the same procedure described above, 0.300 g of alcohol **19** provided 0.106 g (68%) of diol **20**: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H), 5.09 (m, 4H), 3.85−3.50 (m, 5H), 3.24 (dd, J = 9.3, 4.5 Hz, 1H), 2.55 (d, J = 4.7 Hz, 1H), 2.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 34.5, 37.8, 61.5, 70.1, 71.1, 81.3, 117.1, 117.7, 134.4, 135.1; IR (film) 3720−3100 (br), 2900, 1640, 1430, 1080, 910 cm^{-1}; $[\alpha]^{25}_D$ = −6.5° (*c* 0.28, CH_2Cl_2). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.35; H, 9.52.

(2*R*,3*R*)-2-(Pent-4-enyl-1-oxy)-5-hexene-1,3-diol (24). By the same procedure described above, 0.253 g of alcohol **23** provided 0.116 g (85%) of diol **24**: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H), 5.05 (m, 4H), 3.80 (m, 2H), 3.66 (m, 2H), 3.50 (ddd, J = 9.2, 6.5, 6.5 Hz, 1H), 3.24 (dd, J = 9.0, 4.6 Hz, 1H), 2.43−2.04 (m, 6H), 1.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.1, 30.3, 38.0, 61.6, 70.2, 71.2, 81.0, 115.1, 117.8, 134.5, 138.1; IR (film) 3700−3100 (br), 2940, 1640, 1440, 1090, 910 cm^{-1}; $[\alpha]^{25}_D$ = −6.5° (*c* 0.20, CH_2Cl_2). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.10; H, 9.98.

(2*R*,3*R*)-2-[(*R*)-1-(Benzyloxymethyl)but-3-enyl-1-oxy]-5-hexene-1,3-diol (29). The same procedure described above was used except

that the alcohol **3b** (770 mg) was diluted with 17 mL of ether instead of with THF. An 80% yield of diol **29** (400 mg) was realized.

(2*R*,3*R*)-2-(But-3-enyl-1-oxy)-4-pentene-1,3-diol Bis(acetate) (9). Diol **8** (0.172 g, 1.0 mmol) and 5 mL of dichloromethane were cooled to 0 °C. Triethylamine (0.35 mL, 2.5 mmol) was added dropwise, and the mixture was stirred for 10 min. Acetic anhydride (0.28 mL, 3.0 mmol) was added dropwise, and then a catalytic amount of 4-(dimethylamino)pyridine (0.012 g, 0.10 mmol) was added. The reaction was warmed to 25 °C and stirred for 2−4 h. After the reaction was quenched with 5% HCl, the layers were quickly separated. The organic layer was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 0.180 g (70%) of diacetate **9**: ^{1}H NMR ($CDCl_3$) δ 5.81 (m, 2H), 5.44−4.98 (m, 5H), 4.10 (AB portion of ABX, J_{AB} = 11.8 Hz, J_{AX} = 6.9 Hz, J_{BX} = 4.1 Hz, $\Delta\nu_{AB}$ = 44.8 Hz, 2H), 3.63 (m, 3H), 2.30 (m, 2H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.1, 34.3, 63.3, 71.0, 73.3, 78.3, 116.6, 118.5, 132.2, 134.9, 169.9, 170.8; IR (film) 1750, 1370, 1230, 1050 cm^{-1}; $[\alpha]^{25}_D$ = +25.2° (*c* 0.63, CH_2Cl_2).

(2*R*,3*R*)-2-(Pent-4-enyl-1-oxy)-4-pentene-1,3-diol Bis(acetate) (15). By the same procedure described above, 0.05 g of diol **14** provided 0.066 g (91%) of diacetate **15**: ^{1}H NMR ($CDCl_3$) δ 5.81 (m, 2H), 5.33 (m, 3H), 4.99 (m, 2H), 4.10 (AB portion of ABX, J_{AB} = 11.8 Hz, J_{AX} = 6.8 Hz, J_{BX} = 4.1 Hz, $\Delta\nu_{AB}$ = 37.0 Hz, 2H), 3.56 (m, 3H), 2.09 (s, 3H), 2.09 (m, 2H), 2.05 (s, 3H), 1.64 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 29.1, 30.0, 63.3, 70.8, 73.4, 78.3, 114.8, 118.4, 132.3, 138.0, 169.9, 170.7; IR (film) 1750, 1370, 1230, 1100, 1050 cm^{-1}; $[\alpha]^{25}_D$ = +24.5° (*c* 0.96, CH_2Cl_2).

(2*R*,3*R*)-2-(But-3-enyl-1-oxy)-5-hexene-1,3-diol Bis(acetate) (21). By the same procedure described above, 0.861 g of diol **20** provided 0.465 g (88%) of diacetate **21**: ^{1}H NMR ($CDCl_3$) δ 5.77 (m, 2H), 5.08 (m, 5H), 4.12 (AB portion of ABX, J_{AB} = 11.5 Hz, J_{AX} = 6.5 Hz, J_{BX} = 4.9 Hz, $\Delta\nu_{AB}$ = 15.3 Hz, 2H), 3.62 (m, 3H), 2.39 (m, 4H), 2.05 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 34.3, 34.4, 63.1, 70.9, 71.9, 77.2, 116.6, 118.0, 133.4, 134.8, 170.4, 170.7; IR (film) 2950, 1750, 1370, 1225, 1050 cm^{-1}; $[\alpha]^{25}_D$ = +4.8° (*c* 0.11, CH_2Cl_2).

(2*R*,3*R*)-2-(Pent-4-enyl-1-oxy)-5-hexene-1,3-diol Bis(acetate) (25). By the same procedure described above, 0.170 g of diol **24** provided 0.095 g (89%) of diacetate **25**.: ^{1}H NMR ($CDCl_3$) δ 5.74 (m, 2H), 5.02 (m, 5H), 4.10 (AB portion of ABX, J_{AB} = 11.3 Hz, J_{AX} = 10.8 Hz, J_{BX} = 1.3 Hz, $\Delta\nu_{AB}$ = 15.8 Hz, 2H), 3.55 (m, 3H), 2.37 (m, 2H), 2.04 (m, 2H), 2.03 (s, 6H), 1.65 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 29.1, 30.1, 34.4, 63.1, 70.8, 71.9, 77.2, 114.9, 118.0, 133.4, 138.0, 170.4, 170.8; IR (film) 1750, 1380, 1230 cm^{-1}; $[\alpha]^{25}_D$ = +4.9° (*c* 0.18, CH_2Cl_2).

(2*R*,3*R*)-2-[(*R*)-1-(Benzyloxymethyl)but-3-enyl-1-oxy]-5-hexene-1,3-diol Bis(acetate) (30). By the same procedure described above, 0.043 g of diol **29** provided 0.036 g (67%) of diacetate **30**: ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 5.76 (m, 2H), 5.05 (m, 5H), 4.51 (s, 2H), 4.13 (AB portion of ABX, J_{AB} = 11.5 Hz, J_{AX} = 4.5 Hz, J_{BX} = 3.5 Hz, $\Delta\nu_{AB}$ = 22.1 Hz, 2H), 3.73 (m, 2H), 3.45 (app d, *J* = 5.5 Hz, 2H), 2.48 (m, 1H), 2.41−2.18 (band, 3H), 2.03 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 34.0, 36.8, 63.4, 72.1, 72.4, 73.3, 76.5, 79.0, 117.5, 117.8, 127.5, 128.3, 133.6, 134.3, 138.2, 170.4, 170.7; IR (film) 1740, 1370, 1230, 1100 cm^{-1}; $[\alpha]^{25}_D$ = −0.2 (*c* 0.56, CH_2Cl_2).

(2*R*,3*R*)-3-Acetoxy-2-(acetoxymethyl)-2,3,6,7-tetrahydrooxepin (10). A solution of diene **9** (0.061 g, 0.24 mmol) in 80 mL of dichloromethane (0.003 M) was heated to reflux, and then 0.014 g of $(Cy_3P)_2Cl_2Ru$=CHPh (7 mol %) was added in one portion. The mixture was heated at reflux for 2 h and then cooled to 25 °C. After dilution with dichloromethane, air was bubbled through the mixture for several hours. Purification by flash chromatography gave 0.052 g (95%) of oxepin **10**: ^{1}H NMR ($CDCl_3$) δ 5.93 (m, 2H), 5.24 (dd, *J* = 6.5, 1.5 Hz, 1H), 4.10 (m, 3H), 3.88 (ddd, *J* = 7.4, 6.1, 1.6 Hz, 1H), 3.62 (ddd, *J* = 12.4, 10.2, 2.6 Hz, 1H), 2.58 (m, 1H), 2.26 (m, 1H), 2.07 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.8, 20.9, 31.4, 63.6, 70.0, 71.1, 78.1, 127.3, 134.9, 170.4, 170.7; IR (film) 1740, 1380, 1230, 1050 cm^{-1}; $[\alpha]^{25}_D$ = −181.5° (*c* 0.81, CH_2Cl_2); MS *m*/*z*168 (M^+ − CH_3CO_2H). Anal. Calcd for $C_{11}H_{16}O_5$: C, 57.89; H, 7.07. Found: C, 57.68; H, 7.15.

(7*R*,8*R*)-7-Acetoxy-8-(acetoxymethyl)-2,3,7,8-tetrahydro-(4*H*)-oxocin (16). By the same procedure desribed above, 0.046 g of diene **15** provided 0.030 g (73%) of oxocin **16** and 17% of a dimer: ^{1}H NMR ($CDCl_3$) δ 5.90 (m, 1H), 5.68 (m, 1H), 5.53 (ddd, *J* = 11.0, 7.0, 1.0 Hz, 1H), 4.26 (dd, *J* = 11.2, 3.2 Hz, 1H), 4.10 (ddd, *J* = 12.4, 3.9, 3.9 Hz, 1H), 3.93 (m, 2H), 3.52 (ddd, *J* = 12.4, 10.7, 3.1 Hz, 1H), 2.43 (m, 1H), 2.14 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 1.94−1.53 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 25.7, 30.5, 63.5, 69.6, 77.2, 78.1, 126.3, 133.8, 170.1, 170.9; IR (film) 2940, 1740, 1370, 1230, 1100, 1040 cm^{-1}; $[\alpha]^{25}_D$ = +22.6° (*c* 0.80, CH_2Cl_2); MS *m*/*z* 182 (M^+ − CH_3CO_2H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.21; H, 7.33.

(2*R*,3*R*)-3-Acetoxy-2-(acetoxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin (22). By the same procedure desribed above, 0.039 g of diene **21** provided 0.033 g (94%) of oxocin **22** in 30 min with no detectable dimerization: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 2H), 4.98 (ddd, *J* = 11.2, 5.6, 2.4 Hz, 1H), 4.13 (ddd, *J* = 12.2, 3.7, 3.7 Hz, 1H), 3.95 (m, 3H), 3.39 (m, 1H), 2.64 (m, 2H), 2.33 (m, 1H), 2.07 (s, 3H), 2.06 (m, 1H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.0, 28.9, 29.8, 64.1, 72.9, 74.6, 78.2, 127.7, 131.6, 170.4, 170.7; IR (film) 2940, 1740, 1370, 1230 cm^{-1}; $[\alpha]^{25}_D$ = −41.0° (*c* 1.27, CH_2Cl_2); MS *m*/*z* 182 (M^+ − CH_3CO_2H). Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.66; H, 7.80.

(2*R*,3*R*)-3-Acetoxy-2-(acetoxymethyl)-Δ5,6-oxonene (26). By the same procedure described above, 0.020 g of diene **25** provided 0.016 g (89%) of oxocene **26** in 1 h and 10% of a dimer: ^{1}H NMR ($CDCl_3$) δ 5.66 (ddd, *J* = 11.0, 11.0, 6.0 Hz, 1H), 5.46 (ddd, *J* = 11.0, 11.0, 6.0 Hz, 1H), 5.01 (ddd, *J* = 10.0, 6.0, 3.0 Hz, 1H), 4.08 (m, 3H), 3.55 (ddd, *J* = 7.3, 5.7, 2.9 Hz, 1H), 3.26 (ddd, *J* = 10.4, 10.4, 5.1 Hz, 1H), 2.85 (dd, *J* = 22.9, 11.2 Hz, 1H), 2.69 (m, 1H), 2.29 (m, 1H), 2.06 (s, 3H), 2.02 (s, 3H), 2.00 (m, 2H), 1.58 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.8, 27.4, 28.1, 64.1, 72.4, 72.7, 79.3, 124.7, 132.9, 170.4, 170.7; IR (film) 2960, 1740, 1370, 1230, 1040 cm^{-1}; $[\alpha]^{25}_D$ = −31.7° (*c* 0.60, CH_2Cl_2); MS *m*/*z* 136 (M^+ − $2CH_3CO_2H$). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.09; H, 7.56.

(2*R*,3*R*,8*R*)-8-(Benzyloxymethyl)-3-acetoxy-2-(acetoxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin (31). A solution of diene **30** (24 mg, 0.062 mmol) in dichloromethane (0.003 M) was heated to reflux, and then 4 mg of $(Cy_3P)_2Cl_2Ru$=CHPh (7 mol %) was added in one portion. The mixture was heated at reflux for 2 h and then cooled to 25 °C. After the mixture was diluted with dichloromethane, air was bubbled through the mixture for several hours. Purification by flash chromatography gave 22 mg (97%) of oxocin **31** with no detectable dimerization: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.80 (m, 2H), 4.98 (ddd, *J* = 11.0, 5.3, 2.8 Hz, 1H), 4.53 (s, 2H), 4.12 (dd, *J* = 12.2, 10.0 Hz, 1H), 3.95 (dd, *J* = 12.2, 5.1 Hz, 1H), 3.95 (m, 1H), 3.53 (m, 2H), 3.40 (m, 1H), 2.70 (dt, *J* = 11.0, 11.0 Hz, 1H), 2.32 (m, 3H), 2.06 (s, 3H), 1.92 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.7, 21.1, 28.8, 31.6, 64.1, 73.2, 73.3, 74.6, 78.0, 82.3, 127.6, 127.9, 128.3, 130.7, 138.1, 170.5, 170.7; IR (film) 3020, 2980, 1740, 1450, 1370, 1230, 1090, 1040, 730, 690 cm^{-1}; $[\alpha]^{25}_D$ = −7.3 (*c* 0.26, CH_2Cl_2). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.35; H, 7.29.

(4*S*)-3-[1-Oxo-2-[(*R*)-1-(benzyloxymethyl)but-3-enyl-1-oxy]-4-benzyl-1,3-oxazolidinone-2-thione (28a). A solution of the alkoxyacetic acid **4** (0.25 g, 1 mmol), 5 mL of dichloromethane, catalytic dimethylformamide (0.1 mmol), and 2.0 M oxalyl chloride in dichloromethane (0.6 mL, 1.2 mmol) was stirred for 2 h at 25 °C. The mixture was concentrated in vacuo, and the resultant acid chloride (0.27 g, 1 mmol) was diluted with 2 mL of dichloromethane and cooled to 0 °C. In a separate flask, triethylamine (0.33 mL, 2.4 mmol) was added dropwise to (*S*)-4-benzyloxazolidine-2-thione (0.155 g, 0.8 mmol) in 3 mL of dichloromethane. The mixture was stirred for 5 min at 25 °C and then slowly cannulated into the solution of acid chloride. The resultant mixture was stirred at 0 °C for 1 h, warmed to 25 °C, and stirred for 12 h. The reaction was quenched with water, the aqueous layer was extracted with dichloromethane, and the combined extracts were washed with 10% H_2SO_4, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 0.250 g (73%) of acyloxazolidinethione **28a**: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 10H), 5.88 (m, 1H), 5.25 (ABq, *J* = 18.0 Hz, $\Delta\nu_{AB}$ = 18.8 Hz, 2H), 5.10 (m, 2H), 4.86 (m, 1H), 4.53 (s, 2H), 4.26 (m, 2H), 3.77 (m, 1H), 3.62 (m,

2H), 3.25 (dd, J = 13.2, 3.3 Hz, 1H), 2.64 (dd, J = 13.2, 10.1 Hz, 1H), 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 36.3, 37.2, 59.6, 71.1, 71.6, 72.9, 73.2, 78.7, 117.3, 127.2, 127.3, 127.4, 128.2, 128.8, 129.2, 134.1, 135.0, 138.0, 171.3, 184.6; IR (film) 2900, 1710, 1360, 1320, 1200, 1120, 960, 740, 690 cm^{-1}; $[\alpha]^{25}_D$ = +75.1 (c 0.49, CH_2Cl_2). Anal. Calcd for $C_{24}H_{27}O_4N_1S_1$: C, 67.74; H, 6.39. Found: C, 67.68; H, 6.43.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-[(*R*)-1-(benzyloxymethyl)but-3-enyl-1-oxy]-3-hydroxy-5-hexenyl]-4-benzyl-1,3-oxazolidine-2-thione (3a). The acyloxazolidinethione **28a** (0.627 g, 1.47 mmol) and 7 mL of dichloromethane were cooled to −78 °C. Titanium tetrachloride (0.16 mL, 1.47 mmol) was added dropwise, and the mixture was stirred for 10 min at −78 °C. (−)-Sparteine (0.85 mL, 3.68 mmol) was added dropwise, and the mixture was stirred at −78 °C for 1 h. A solution of 3-butenal (7.35 mmol) in dichloromethane was added dropwise, and the reaction was stirred for 1 h at −78 °C. The reaction was quenched at −78 °C with half-saturated NH_4Cl and warmed to 25 °C. The solution was filtered through Celite, and the salts were washed with dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 0.194 g of alcohol **3a** (27%) and 0.396 g (90% brsm) of acyloxazolidinethione **28a**: ^{1}H NMR ($CDCl_3$) δ 7.21 (m, 10H), 6.34 (d, J = 2.0 Hz, 1H), 5.87 (m, 2H), 5.12 (m, 4H), 4.74 (m, 1H), 4.48 (ABq, J = 12.0 Hz, $\Delta\nu_{AB}$ = 10.6 Hz, 2H), 4.16 (m, 2H), 4.07 (dt, J = 7.0, 2.0 Hz, 1H), 3.83 (m, 1H), 3.67 (dd, J = 10.3, 7.3 Hz, 1H), 3.50 (dd, J = 10.3, 2.9 Hz, 1H), 3.20 (dd, J = 13.2, 3.3 Hz, 1H), 2.50−2.27 (band, 5H), 2.05 (dd, J = 13.2, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 36.5, 36.8, 38.8, 61.0, 70.7, 72.3, 73.1, 73.5, 79.9, 79.9, 117.6, 118.0, 127.0, 127.2, 127.5, 128.4, 128.4, 128.8, 128.9, 129.3, 134.2, 134.4, 135.5, 138.0, 172.1, 185.1; IR (film) 3700−3040 (br), 2900, 1710, 1360, 1320, 1190, 910, 730, 690 cm^{-1}; $[\alpha]^{25}_D$ = +15.3 (c 0.30, CH_2Cl_2). Anal. Calcd for $C_{28}H_{33}O_5N_1S_1$: C, 67.85; H, 6.71; N, 2.83. Found: C, 67.41; H, 6.78; N, 2.66.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-(but-3-enyl-1-oxy)-3-hydroxy-5-hexenyl]-4-benzyl-2-oxazolidinone (19). By the same procedure described above, 1.45 g of acyloxazolidinone **6** provided 0.845 g (47%) of alcohol **19** and 0.608 g (89% brsm) of acyloxazolidinone **6**: ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H), 5.85 (m, 2H), 5.18−5.04 (m, 4H), 5.03 (d, J = 2.0 Hz, 1H), 4.68 (ddd, J = 12.5, 6.0, 3.2 Hz, 1H), 4.22 (m, 2H), 3.95 (m, 1H), 3.76 (ddd, J = 8.8, 6.5, 6.5 Hz, 1H), 3.42 (ddd, J = 8.8, 7.0, 7.0 Hz, 1H), 3.35 (dd, J = 13.2, 3.1 Hz, 1H), 2.81 (dd, J = 13.2, 9.5 Hz, 1H), 2.41 (m, 4H), 2.25 (d, J = 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 34.0, 37.6, 38.7, 55.6, 67.0, 70.1, 71.6, 79.6, 116.8, 117.6, 127.3, 128.9, 129.3, 134.1, 134.6, 134.9, 153.4, 170.7; IR (film) 3720−3120 (br), 2920, 1770, 1700, 1640, 1390, 1210, 1110, 910, 730, 690 cm^{-1}; $[\alpha]^{25}_D$ = +33.3° (c 0.24, CH_2Cl_2). Anal. Calcd for $C_{20}H_{25}O_5N_1$: C, 66.83; H, 7.01. Found: C, 66.59; H, 6.98.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-(pent-4-enyl-1-oxy)-3-hydroxy-5-hexenyl]-4-benzyl-2-oxazolidinone (23). By the same procedure described above, 0.556 g of acyloxazolidinone **12** provided 0.325 g (48%) of alcohol **23** and 0.238 g (90% brsm) of acyloxazolidinone **12**: ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 5H), 5.84 (m, 2H), 5.16−4.94 (m, 4H), 5.01 (d, J = 3.0 Hz, 1H), 4.68 (ddd, J = 13.0, 7.0, 3.3 Hz, 1H), 4.22 (m, 2H), 3.95 (m, 1H), 3.68 (ddd, J = 9.0, 6.3, 6.3 Hz, 1H), 3.40 (ddd, J = 9.0, 6.7, 6.7 Hz, 1H), 3.34 (dd, J = 13.5, 3.3 Hz, 1H), 2.81 (dd, J = 13.5, 9.5 Hz, 1H), 2.43 (dt, J = 7.0, 1.1 Hz, 2H), 2.23 (d, J = 9.5 Hz, 1H), 2.17 (m, 2H), 1.75 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.8, 30.1, 37.7, 38.8, 55.7, 67.0, 70.4, 71.6, 79.6, 115.0, 117.7, 127.4, 129.0, 129.4, 134.1, 135.0, 138.0, 153.4, 170.9; IR (film) 3720−3140 (br), 2920, 1780, 1700, 1640, 1390, 1210, 1100, 910, 690 cm^{-1}; $[\alpha]^{25}_D$ = +37.4° (c 0.17, CH_2Cl_2). Anal. Calcd for $C_{21}H_{27}O_5N_1$: C, 67.54; H, 7.29. Found: C, 66.87; H, 7.41.

(4*S*)-3-[1-Oxo-2-[(*R*)-1-(benzyloxymethyl)but-3-enyl-1-oxy]-4-benzyl-1,3-oxazolidinone (28b). The alkoxyacetic acid **4** (1.43 g, 5.7 mmol), 25 mL of dichloromethane, catalytic dimethylformamide (0.6 mmol), and 2.0 M oxalyl chloride in dichloromethane (3.4 mL, 6.8 mmol) were stirred for 2 h at 25 °C. The mixture was concentrated in vacuo to afford a quantitative yield of the acid chloride. In a separate flask, (*S*)-4-benzyl-2-oxazolidinone (1.11 g, 6.3 mmol) was dissolved in 25 mL of THF and then cooled to −78 °C. After the mixture was stirred for 15 min at −78 °C, the acid chloride in 50 mL of THF was cannulated into the deprotonated oxazolidinone. The reaction mixture was stirred for 30 min at −78 °C and then warmed to 25 °C and stirred for 15 min. The reaction was quenched with saturated NH_4Cl and then concentrated in vacuo. The aqueous layer was extracted with ether, and the combined extracts were washed with saturated NH_4Cl and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 2.09 g (89%) of acyloxazolidinone **28b**: ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 10H), 5.88 (m, 1H), 5.09 (m, 2H), 4.87 (s, 2H), 4.60 (m, 1H), 4.52 (s, 2H), 4.15 (m, 2H), 3.75 (m, 1H), 3.60 (m, 2H), 3.28 (dd, J = 13.5, 3.3 Hz, 1H), 2.61 (dd, J = 13.5, 9.7 Hz, 1H), 2.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.6, 153.4, 138.2, 135.1, 134.2, 129.4, 129.0, 128.4, 127.54, 127.47, 127.35, 117.4, 79.0, 73.3, 72.8, 70.0, 67.1, 54.8, 37.6, 36.3; IR (film) 3010−2800 (br), 1780, 1720, 1390, 1260, 1210, 1130 cm^{-1}; $[\alpha]^{25}_D$ = +67.5 (c 0.24, CH_2Cl_2). Anal. Calcd for $C_{24}H_{27}O_5N_1$: C, 70.40; H, 6.65. Found: C, 70.38; H, 6.67.

(4*S*)-3-[(2*S*,3*R*)-1-Oxo-2-[(*R*)-1-(benzyloxymethyl)but-3-enyl-1-oxy]-3-hydroxy-5-hexenyl]-4-benzyl-1,3-oxazolidinone (3b). The acyloxazolidinone **28b** (0.38 g, 0.93 mmol) and 6 mL of dichloromethane were cooled to −78 °C. Titanium tetrachloride (0.11 mL, 1.02 mmol) was added dropwise, and the mixture was stirred for 10 min at −78 °C. Diisopropylethylamine (0.40 mL, 2.32 mmol) was diluted with 0.4 mL of dichloromethane and then added very slowly dropwise. After complete addition, the mixture was stirred at −78 °C for 2.5 h. A solution of 3-butenal (4.64 mmol) in dichloromethane was added dropwise, and the reaction was stirred for 1.5 h at −78 °C. The reaction was quenched at −78 °C with half-saturated NH_4Cl and warmed to 25 °C. The aqueous layer was extracted with dichloromethane, and the combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography afforded 0.288 g of alcohol **3b** (65%): ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 10H), 5.88 (m, 2H), 5.38 (d, J = 2.0 Hz, 1H), 5.14 (m, 4H), 4.47 (m, 1H), 4.46 (ABq, J = 12.0 Hz, $\Delta\nu_{AB}$ = 18.4 Hz, 2H), 4.05 (m, 1H), 3.86 (m, 3H), 3.68 (dd, J = 10.3, 7.7 Hz, 1H), 3.49 (dd, J = 10.3, 3.0 Hz, 1H), 3.22 (dd, J = 13.3, 3.1 Hz, 1H), 2.39 (m, 4H), 1.74 (dd, J = 13.3, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 171.2, 153.5, 138.2, 135.7, 134.4, 134.3, 129.3, 128.9, 128.4, 127.5, 127.1, 127.0, 118.1, 117.5, 80.10, 80.11, 74.1, 73.0, 72.3, 66.8, 55.8, 38.9, 36.9, 36.5; IR (film) 3700−3020 (br), 3010−2800 (br), 1775, 1710, 1390, 1350, 1300−1180 (br), 1180−950 (br), 910 cm^{-1}; $[\alpha]^{25}_D$ = +0.4 (c 0.25, CH_2Cl_2). Anal. Calcd for $C_{28}H_{33}O_6N$: C, 70.13; H, 6.94. Found: C, 70.11; H, 6.90.

(2*R*,3*R*)-2-[(*R*)-1-(Benzyloxymethyl)but-3-enyl-1-oxy]-5-hexene-1,3-diol (29). Alcohol **3** (0.097 g, 0.196 mmol), 1 mL of ether, and 16 mL of anhydrous methanol (0.392 mmol) were cooled to 0 °C. A 2.0 M solution of lithium borohydride in THF (0.20 mL, 0.392 mmol) was added dropwise, and the reaction was stirred for 2 h at 0 °C. After 15% NaOH was added, the mixture was warmed to 25 °C for 15 min to deprotonate the free (*S*)-4-benzyloxazolidine-2-thione. The aqueous layer was separated, and the organic layer was washed six times with 15% NaOH. The organic layer was then washed with brine, dried over Na_2SO_4, and concentrated in vacuo to afford 51.4 mg of diol **29** (86%), which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.81 (m, 2H), 5.10 (m, 4H), 4.55 (s, 2H), 3.88−3.42 (band, 7H), 3.37 (dt, J = 5.7, 2.7 Hz, 1H), 2.74 (d, J = 2.9 Hz, 1H), 2.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 36.9, 37.7, 62.4, 71.3, 72.7, 73.6, 77.9, 81.8, 117.4, 118.3, 127.8, 128.0, 128.5, 133.7, 134.5, 137.1; IR (film) 3720−3100 (br), 2920, 1090, 910, 730, 690 cm^{-1}; $[\alpha]^{25}_D$ = −20.8 (c 0.65, CH_2Cl_2). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.89; H, 8.69.

(2*R*,3*R*,8*R*)-8-(Hydroxymethyl)-3-acetoxy-2-(acetoxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin (32). Oxocin **31** (0.030 g, 0.083 mmol) was dissolved in 3 mL of dichloromethane and 0.3 mL of pH 7 buffer (10:1 dichloromethane/buffer). Recrystallized DDQ (0.075 g, 0.332 mmol) was added in one portion, and the reaction was stirred for 12 h at 25 °C. An additional 4 equiv of DDQ (0.075 g) and 0.15 mL of pH 7 buffer were then added, and the reaction was stirred for another 12 h. The reaction was quenched by the dropwise addition of saturated $NaHCO_3$ and diluted with dichloromethane. The organic layer was washed with saturated $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 13.3 mg (60%) of oxocin **32**: ^{1}H NMR ($CDCl_3$) δ 5.87 (m, 1H), 5.73 (m, 1H), 5.01 (ddd, J = 11.1, 5.3, 2.8 Hz, 1H), 4.11 (m, 2H), 3.97 (m, 1H), 3.51 (m,

3H), 2.68 (dt, $J = 11.0, 11.0$ Hz, 1H), 2.35 (m, 3H), 2.08 (s, 3H), 2.05 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 20.8, 21.1, 28.9, 30.7, 64.8, 66.1, 74.7, 78.3, 84.9, 127.8, 130.3, 170.3, 171.0; IR (film) 3800−3060 (br), 2940, 1730, 1650, 1380, 1260, 1050, 800, 730 cm^{-1}; $[\alpha]^{25}_D = -18.1$ (*c* 0.41, CH_2Cl_2). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.07; H, 7.44.

(2*R*,3*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-acetoxy-2-(acetoxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin (33). The oxocin **32** (6.4 mg, 0.024 mmol), 0.12 mL of dimethylformamide, imidazole (3.6 mg, 0.053 mmol), and *tert*-butylchlorodiphenylsilane (7 μL, 0.026 mmol) were stirred for 1 h at 25 °C. The reaction was quenched with water, and the aqueous layer was extracted three times with ethyl acetate. The combined extracts were washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography afforded 8.1 mg (66%) of oxocin **33**: ^{1}H NMR ($CDCl_3$) δ 7.66 (m, 4H), 7.38 (m, 6H), 5.91 (m, 1H), 5.73 (m, 1H), 4.97 (ddd, $J = 11.0, 5.5, 2.3$ Hz, 1H), 3.97 (m, 3H), 3.75 (dd, $J = 9.7, 5.1$ Hz, 1H), 3.53 (dd, $J = 9.7, 7.3$ Hz, 1H), 3.44 (m, 1H), 2.68 (dt, $J = 11.0, 11.0$ Hz, 1H), 2.37 (m, 3H), 2.05 (s, 3H), 1.88 (s, 3H), 1.04 (s, 9H).; ^{13}C NMR ($CDCl_3$) δ 19.2, 20.7, 21.1, 26.8, 28.8, 31.3, 63.9, 66.6, 74.5, 77.7, 83.6, 127.6, 127.9, 129.7, 131.0, 133.4, 133.6, 135.5, 135.6, 170.5, 170.6; IR (film) 2940, 2860, 1750, 1430, 1370, 1240, 1110, 700 cm^{-1}; $[\alpha]^{25}_D = +2.1$ (*c* 0.40, CH_2Cl_2).

(2*R*,3*R*,8*R*)-8-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-3-hydroxy-2-(hydroxymethyl)-3,4,7,8-tetrahydro-(2*H*)-oxocin (2). The oxocin **33** (8.1 mg, 0.016 mmol), methanol (1.3 uL, 0.033 mmol), water (0.2 μL, 8:1 MeOH/H_2O), and potassium carbonate (4.6 mg, 0.033 mmol) were stirred for 2 h at 25 °C. The mixture was diluted with water and concentrated in vacuo. The aqueous layer was extracted with dichloromethane, and the combined extracts were dried over Na_2SO_4. Purification by flash chromatography afforded 6.6 mg (97%) of **2**, identical in all respects to that reported by Holmes et al.:[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.41 (m, 6H), 5.73 (m, 2H), 3.86 (m, 1H), 3.80 (m, 1H), 3.71 (ddd, $J = 9.1, 3.3, 2.2$ Hz, 1H), 3.66 (m, 2H), 3.60 (m, 1H), 3.48 (dd, $J = 15.3, 8.4$ Hz, 1H), 3.03 (d, $J = 10.1$ Hz, 1H), 2.55 (dt, $J = 12.1, 9.6$ Hz, 1H), 2.32 (m, 1H), 2.21 (m, 1H), 1.96 (ddd, $J = 14.0, 8.2, 1.2$ Hz, 1H), 1.65 (d, $J = 8.7$ Hz, 1H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.7, 30.4, 33.6, 64.1, 67.7, 73.1, 82.1, 83.4, 127.7, 127.8, 128.7, 129.3, 129.8, 132.9, 135.6, 135.6; IR (film) 3700−3120 (br), 2920, 2860, 1430, 1110, 1070, 820, 800, 740, 700 cm^{-1}; $[\alpha]^{25}_D = -14.7$ (*c* 0.33, CH_2Cl_2).

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Supporting Information Available: Experimental details for the 1,7-octadiene-4,5-diol, 3-butenal, and the dimers from olefin metathesis of dienes **9** and **15** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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