were identical with those of authentic natural caryophyllene.

Acknowledgment. We are indebted to Prof. Ernest Wenkert (University of California, San Diego) for helpful discussion and Dr. M. Hirama (Santory Institute for Bioorganic Research) for providing a sample of natural caryophyllene and spectral data (^{1}H NMR, mass spectra, and IR) of isocaryophyllene.

Registry No. (±)-1, 61217-74-1; (±)-2, 17627-40-6; (±)-3, 90191-48-3; (±)-4, 90107-84-9; 5 (isomer 1), 90107-85-0; 5 (isomer 2), 90107-86-1; (±)-6, 90191-49-4; 7, 90107-87-2; 8, 54314-85-1; (±)-(*E*)-9, 81491-42-1; (±)-(*Z*)-9, 81521-03-1; 10, 3495-63-4; 11, 37845-64-0; (±)-(*E*)-12, 81521-04-2; (±)-(*Z*)-12, 81491-32-9; (±)-13a, 90191-50-7; (±)-13b, 90191-51-8; (±)-14, 81521-07-5; (±)-15, 81491-43-2; (±)-16, 81570-11-8; (±)-17, 81521-10-0; (±)-18, 81521-12-2; (±)-19, 61217-73-0; 20, 37676-91-8; (±)-21, 90107-88-3; (±)-22, 81491-29-4; (±)-23a, 81491-48-7; (±)-23b, 81491-49-8; (±)-24a, 81491-50-1; (±)-24b, 81491-52-3; (±)-26, 81491-53-4; (±)-27, 81491-55-6; (±)-28, 90107-89-4; (±)-29, 90107-90-7; (±)-30, 81491-28-3; 31a, 90107-91-8; 31b, 90107-92-9; 32a, 81491-46-5; 32b, 81491-47-6; (±)-33, 81491-30-7; 34, 90107-93-0; 34 (TBMS ether), 81491-31-8; (±)-35, 81491-33-0; (±)-36, 90191-52-9; (±)-38, 81521-01-9; (±)-39, 90191-53-0; (±)-40, 90191-54-1; (±)-41, 81491-37-4; (±)-42, 81491-38-5; (±)-43, 81491-39-6; (±)-vi, 81521-11-1; ethyl(phenylsulfonyl)acetate, 7605-30-3; diphenyl disulfide, 882-33-7; nitromethane, 75-52-5.

Supplementary Material Available: Experimental procedures and spectroscopic data for compounds 23–30, 37, and vi, and the process of conversion of 30 into 22 (8 pages). Ordering information is given on any current masthead page.

Synthesis of *Z,Z*-Skipped Diene Macrolide Pheromones for *Cryptolestes* and *Oryzaephilus* Grain Beetles (Coleoptera Cucujidae)

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Three macrolide aggregation pheromones for *Cryptolestes pusillus*, *Cryptolestes turcicus*, and *Oryzaephilus mercator* were synthesized stereoselectively from acyclic precursors. The first, 13-methyl-(5*Z*,8*Z*)-tridecadienolide (I), is an aggregation pheromone for *C. turcicus* and had been tentatively identified previously in *Phoracantha synonyma*. The second, 11-methyl-(3*Z*,6*Z*)-undecadienolide (II), is an aggregation pheromone for *O. mercator*. The third, (3*Z*,6*Z*)-dodecadienolide (III) is an aggregation pheromone for *O. mercator* and is also slightly attractive to *C. pusillus*. The racemic and enantiomeric forms of I were synthesized.

During the past several years, our laboratory has been screening insect-produced volatiles from *Cryptolestes* and *Oryzaephilus* species of grain beetles, in a search for aggregation pheromones for these insects. We now report the syntheses of three macrolides isolated from pentane extracts of Porapak Q captured insect and frass volatiles.

The first, 13-methyl-(5*Z*,8*Z*)-tridecadienolide (I), was tentatively identified by others by analysis of its mass spectrum.[1] We have isolated and fully characterized I from *C. turcicus* (Grouvelle), for which it acts as an aggregation pheromone.[2] Macrolide I was also identified by GLC and mass spectral comparisons in *C. ferrugineus* (Stephens)[3] and in *O. mercator* (Fauvel).[4] It has no apparent biological activity in these latter two insects.

The second, 11-methyl-(3*Z*,6*Z*)-undecadienolide (II), was isolated from *C. ferrugineus*[3] and frass volatiles and had no discernable biological activity for these insects. Macrolide II was also found in *O. mercator*,[4] for which it is an aggregation pheromone.

The third compound, (3*Z*,6*Z*)-dodecadienolide (III), was isolated from frass volatiles of *O. mercator*,[4] and *C. pusillus*.[5] Macrolide III is an aggregation pheromone for *O. mercator*,[4] and is also attractive to *C. pusillus*[5] at high concentrations.

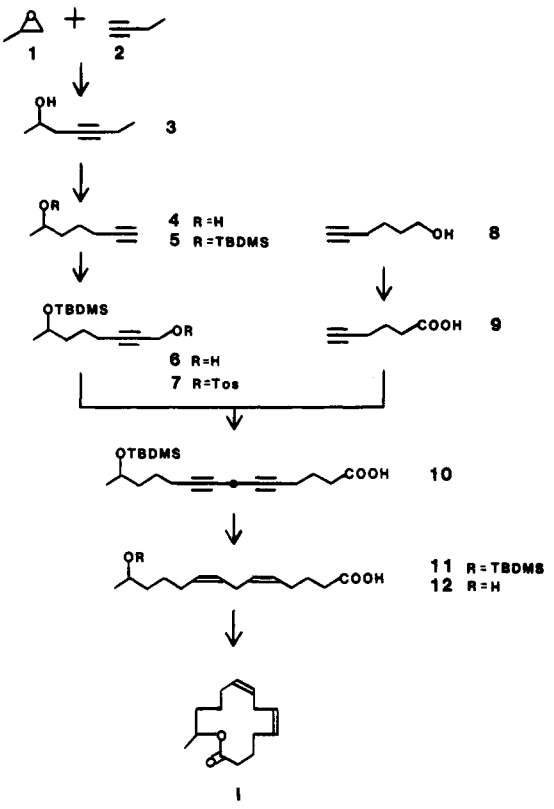
Of the various methods available to obtain macrolides, cyclization of appropriate acyclic hydroxy acid precursors offers the advantages of flexibility in terms of substrates and lactonization under mild conditions. One key feature common to I–III is the sensitive skipped diene system, which, in the case of II and III, was also β,γ to a carbonyl, leading to a propensity to isomerize and/or decompose. Several approaches, e.g., Wittig reactions, have been used in syntheses of skipped dienes.[6,7] However, the stereochemical control is not usually absolute. Vinylic organocuprates[8] and organoboranes[9] have been coupled with allylic halides, but these reactions have limitations with respect to compatability with various functional groups. Dibutyl-1,5-stannacyclohexadiene as the synthetic equivalent of (*Z,Z*)-LiCH=CHCH$_2$CH=CHLi has similar drawbacks.[10]

A straightforward method of making *Z,Z*-skipped dienes involves the selective reduction of an appropriate diyne precursor. The required diynes are easily made by coupling a propargyl halide or propargyl tosylate[11,12] with the Grignard derivative of a terminal alkyne, with cuprous salt

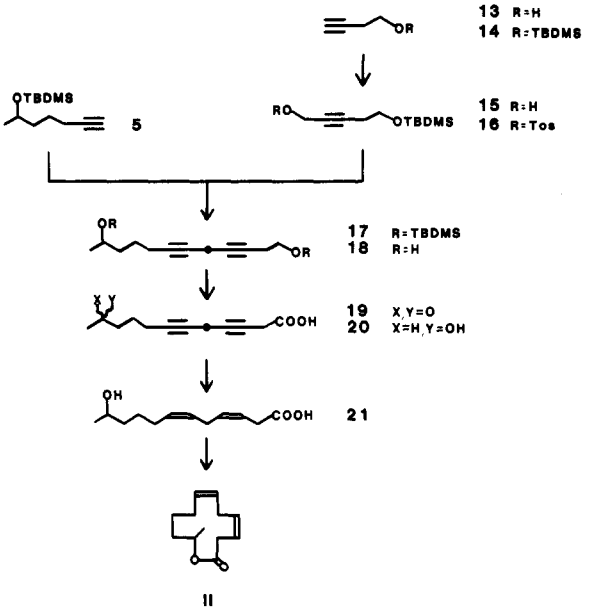
(1) Moore, B. P.; Brown, W. V. *Aust. J. Chem.* **1976**, *29*, 1365.
(2) Millar, J. G.; Pierce, H. D., Jr.; Pierce, A. M.; Oehlschlager, A. C.; Borden, J. H. *J. Chem. Ecol.*, in press.
(3) Wong, J. W.; Verigin, V.; Oehlschlager, A. C.; Borden, J. H.; Pierce, H. D., Jr.; Pierce, A. M.; Chong, L. *J. Chem. Ecol.* **1983**, *9*, 451.
(4) Pierce, A. M.; Borden, J. H.; Oehlschlager, A. C. *Environ. Entomol.* **1983**, *12*, 1367.
(5) Millar, J. G.; Pierce, A. M.; Pierce, H. D., Jr.; Oehlschlager, A. C.; Borden, J. H. *J. Chem. Ecol.*, in press.
(6) Bestmann, H. J.; Vostrowsky, O. *Chem. Phys. Lipids* **1974**, *24*, 335.
(7) Bestmann, H. J.; Vostrowsky, O. *Top. Curr. Chem.* **1983**, *109*, 85.
(8) Alexakis, A.; Cahiez, G.; Normant, J. F. *Synthesis* **1979**, 826.
(9) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.
(10) Kang, J.; Corey, E. J. *Tetrahedron Lett.* **1982**, *23*, 1651.
(11) Verkruijsse, H. D.; Hasselaar, M. *Synthesis* **1979**, 292.
(12) Mori, K.; Ebata, T. *Tetrahedron Lett.* **1981**, *22*, 4281.

0022-3263/84/1949-2332$01.50/0

Scheme I



Scheme II



catalysis. In addition, it is possible to couple the bis(Grignard derivative) of an ω-acetylenic acid of five carbons or more with a propargyl halide or tosylate.[13,14] Thus, in the case of I, the required unsaturation and the free carboxyl group could be introduced in one step. This method did not work for 3-butynoic acid, since the methylene protons between the carboxyl and the triple bond are more acidic than the terminal alkyne proton. Consequently, a more circuitous route was employed in the syntheses of II and III.

Both I and II have chiral centers, which are easily introduced via stereo- and regioselective ring opening of (*R*)-(+)- and (*S*)-(−)-methyloxirane. The syntheses of the racemic and enantiomeric forms of I are reported here; the enantiomers of II are available from the same precursors, (*R*)- and (*S*)-**3**.

The syntheses of *R*, *S*, and racemic I are outlined in Scheme I. The appropriate methyloxirane (**1**) was opened stereo- and regioselectively by the lithium salt of 1-butyne (**2**) in THF at −20 to 20 °C, giving the propargyl alcohol **3**. Isomerization of the alkyne to the terminal position with potassium 3-aminopropylamide[15] gave alkyne **4**, the hydroxyl of which was protected as the *tert*-butyldimethylsilyl ether **5**.[16] The order of the steps was important. If alcohol **3** was first protected, followed by the acetylene zipper reaction, a mixture of alkynol products resulted. The lithium salt of **5** in THF was homologated with paraformaldehyde,[17] giving the propargyl alcohol **6**. Tosylation of **6** with *p*-tosyl chloride and powdered KOH in ether at −10 to 0 °C[17] completed the synthesis of a portion of the carbon skeleton of I.

The enantiomers of **4** were determined to be >98% enantiomerically pure by ^{1}H NMR of their (+)-α-methoxy-α-(trifluoromethyl)phenylacetates,[18] the methyl doublets of which are cleanly separated. Only one isomer was seen in each case.

Racemic **4** was also prepared by oxidation of 5-hexyn-1-ol[8] to 5-hexyn-1-al with pyridinium dichromate in CH_2Cl_2,[19] followed by treatment of an ether solution of the aldehyde with methylmagnesium bromide.

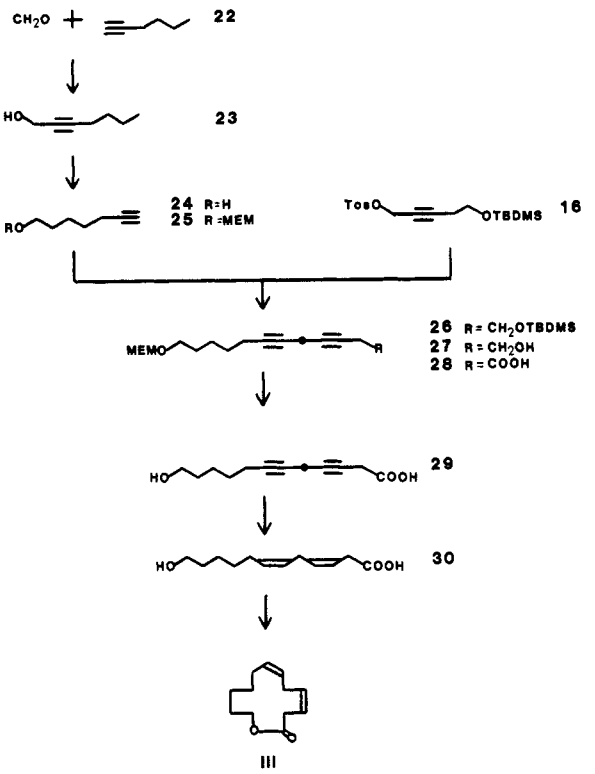
The remaining fragment of the carbon skeleton of I, 5-hexynoic acid (**9**), was prepared by oxidation of 5-hexyn-1-ol (**8**) with Jones reagent. The two fragments **7** and **9** were coupled by cuprous bromide catalyzed reaction of the bis(Grignard derivative) of acetylenic acid **9** with tosylate **7**, giving a good yield of crude diynoic acid **10**.[13,14] Crude **10** was stereoselectively reduced with P-2 nickel[20] to the *Z*,*Z* dienoic acid **11**. The hydroxyl of this acid was deprotected using AcOH:H_2O:THF (3:1:1), to yield **12**. Hydroxy acid **12** was cyclized with 2-chloro-1-methylpyridinium iodide[21] in an overall 8% yield of *R*, *S*, and racemic I from methyloxirane.

Acids **10**, **11**, and **12** were unstable. Thus, **10** and **11** were carried through subsequent steps without purification. Attempts to purify analytical samples of **10** and **11** were not successful, as the acidic conditions required to prevent ionization of the carbonyls during TLC caused some hydrolysis of the acid-labile hydroxyl protecting group.

Macrolide II was prepared by a similar route (Scheme II), utilizing **5**. The complimentary fragment was assembled from 3-butyn-1-ol (**13**). Thus, **13** was protected as the *tert*-butyldimethylsilyl ether **14** followed by homologation of the lithium salt of **14** with dry paraformaldehyde.[17] The resulting alcohol **15** was then tosylated, giving **16**.[17] Cuprous bromide catalyzed coupling of the Grignard of **5** and tosylate **16** gave diyne **17**. The silyl ether protecting groups of **17** were hydrolyzed with *p*-toluenesulfonic acid

(13) Osbond, J. M.; Philpott, P. G.; Wickens, J. C. *J. Chem. Soc.* **1961**, 2779.
(14) Beerthius, R. K.; Nugteren, D. H.; Pabon, H. J.; Steenhoek, A.; Van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas.* **1971**, *90*, 943.
(15) Midland, M. M.; Halterman, R. L.; Brown, C. A.; Yamaichi, A. *Tetrahedron Lett.* **1981**, *22*, 4171.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(17) Brandsma, L. "Preparative Acetylenic Chemistry", 1st ed.; Elsevier: New York, 1971.
(18) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(19) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(20) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.
(21) Mukaiyama, T.; Vsui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

Scheme III



in dry MeOH, yielding diol **18**. Oxidation of the diol by inverse addition to cold Jones reagent[22] gave a moderate yield of keto acid **19**. The ketone was selectively reduced with $NaBH_4$ in an ethanolic solution at −10 to 0 °C, giving hydroxy acid **20**. Stereoselective reduction of **20** with P-2 nickel[20] produced the *Z,Z* dienoic hydroxy acid **21**, with a small amount of product resulting from overreduction of the double bond β,γ to the carboxyl. Cyclization of **21** with 2-chloro-1-methylpyridinium iodide[21] gave a very low yield of macrolide II (7–10%). Several attempts revealed that the molecule is intrinsically difficult to cyclize. This would perhaps be expected, considering the conformational constraints caused by the double bonds, and possible steric hindrance by the methyl group.

Several variations of Scheme II were explored. For instance, the tetrahydropyranyl ether analogues of **5** to **16** were prepared and transformed to diol **18**, using conditions previously described for the diyne coupling reaction followed by deprotection of the diol. Yields were approximately as before. It was concluded that the silyl derivatives are preferred because their lower boiling points allowed facile purification and because they are not mixtures of diastereomers.

The (β-methoxyethoxy)methyl ether analogue of **5** was also synthesized and coupled with tosylate **16**. The primary hydroxyl of the resulting diyne was selectively deprotected with PTSA in dry MeOH, which was then oxidized as previously described. The secondary alcohol of the resulting acid was then deprotected with THF:H_2O:HCl (8:2:1), yielding the diynoic hydroxy acid **20**.

It was essential to reduce the diyne after oxidation of the alcohol to a carboxyl, as all attempts to oxidize the dienol or dienediol obtained from reduction of **18** resulted in mixtures. This may be due to facile intramolecular cyclization of the 3,6-dienal[23] intermediates or to electrophilic additions to the triple bonds.[24]

As with the intermediates in the synthesis of I, all the diyne intermediates were unstable, contributing to low overall yields.

Fragment **16** was also used in the synthesis of III (Scheme III). Synthesis of the remaining portion of the carbon skeleton commenced with 1-hexyne (**22**). Reaction of the lithium salt of 1-hexyne with paraformaldehyde in THF gave alcohol **23**.[17] The triple bond was then isomerized to the terminal position with potassium 3-aminopropylamide.[15] The hydroxyl function was protected as the acid-insensitive (β-methoxyethoxy)methyl ether, **25**.[25] III was then synthesized from **16** and **25** by using the same sequence of reactions as in the synthesis of II. Yields were approximately the same with the exception of the cyclization step, which proceeded more favorably, reflecting the increased flexibility of the 13-membered ring of III vs. the constrained, sterically hindered 12-membered ring of II. In addition, as was found in the production of **21**, there was a small amount of overreduction of the corresponding diene **30**, with the double bond β,γ to the carboxyl being reduced.

As with the skipped dienic hydroxy acid precursors macrolides I, II, and III were found to be unstable even when stored at −20 °C. Purification (to eliminate β,γ-saturated analogues) was best performed by preparative GLPC as previously described.[3]

Experimental Section

General Procedures. Routine GLC analyses were run on a Hewlett-Packard 5880A gas chromatograph, with WCOT capillary columns coated with OV-101, SP-2100, or Durabond 1.

Column chromatography was performed by the flash chromatography method on silica gel (Kieselgel 60, 40–63 μm, E. Merck, Darmstadt). Chromatographic solvents were distilled before use.

IR spectra were determined on a Perkin-Elmer 599B spectrophotometer. Samples were run as a neat film on NaCl plates or as solutions in a cell with NaCl windows.

^1H NMR were recorded on a Brüker 400 WM NMR spectrometer.

Low-resolution mass spectra were obtained via direct insertion or GLC inlet on a Hewlett-Packard 5985B coupled gas chromatograph–mass spectrometer. All samples were run by using electron-impact ionization (70 eV) unless otherwise specified. Samples run with chemical ionization (denoted by CI) were run with isobutane as the ionizing gas, unless otherwise stated. High-resolution mass spectra were obtained on a Kratos DS-50 instrument at the University of British Columbia. Elemental analyses were performed by M. Yang (Department of Biological Sciences, S.F.U.) on a Perkin-Elmer Model 240 elemental analyzer.

Optical rotations were measured with a Rudolph Model 70 polarimeter, using a 1 dm × 2 mm ID sample cell, or with a Perkin-Elmer P_{22} spectropolarimeter, using a 0.5 dm × 5 mm i.d. sample cell. Concentrations are reported in g/100 mL of solvent.

All reactions requiring anhydrous and/or oxygen-free conditions were run under a positive pressure of nitrogen or argon, in flame-dried glassware. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride. Dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride under reduced pressure. 1,3-Diaminopropane was distilled from barium oxide. Dry methanol was distilled from Mg turnings.

Boiling points are uncorrected.

Synthesis of I. Preparation of (*R*,*S*)-4-Heptyn-2-ol (3). Dry THF (40 mL) in a 250-mL three-necked flask was cooled to −40 °C under argon. Condensed 1-butyne (6.6 mL, 83 mmol) was added in one portion, followed by dropwise addition of *n*-BuLi in hexane (2.1 M, 21 mL, 44 mmol). The reaction mixture was

(22) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*, 203.
(23) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647.
(24) March, J. "Advanced Organic Chemistry: Reactions, Mechanisms and Structure"; McGraw-Hill: New York, 1968; pp 573–576.
(25) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

warmed to 0 °C over 30 min and then cooled to −20 °C. Dry HMPA (15 mL) was added, followed by dropwise addition, over 15 min, of racemic methyloxirane (2.61 g, 45 mmol) in HMPA (15 mL). The reaction was stirred at −20 °C for 30 min, warmed to 20 °C over 4 h, and stirred an additional 12 h. The mixture was then poured into ice water (100 mL) and extracted with ether (4 × 50 mL). The combined organic extracts were backwashed with brine, dried ($MgSO_4$), and concentrated at reduced pressure with no heating. Distillation of the residue gave (*R,S*)-**3** (4.93 g, 100%): bp 41 °C (2.0 mmHg); IR (film) 3360 cm^{-1}; mass spectrum, *m/e* (relative intensity) 112 (0.5), 97 (9), 68 (81), 67 (100), 53 (36), 45 (81); ^1H NMR ($CDCl_3$) δ 1.07 (t, 3 H, CH_2CH_3, *J* = 7.5 Hz), 1.18 (d, 3 H, C_1, *J* = 6.1 Hz), 2.13 (quartet of triplets, 2 H, $C{\equiv}CH_2CH_3$, *J* = 7.5, 2.3 Hz), 2.20–2.36 (m, 2 H, C_3), 2.74 (broad d, 1 H, OH), 3.65–3.94 (m, 1 H, C_2). Anal. Calcd for $C_7H_{12}O$: C, 74.96; H, 10.78. Found: C, 74.91; H, 11.00.

Preparation of (*S*)-(+)-4-Heptyn-2-ol ((*S*)-(+)-3) and (*R*)-(−)-3. The lithium salt of 1-butyne (6.7 g, 120 mmol) was reacted with (*S*)-(−)-methyloxirane (6.0 g, 103 mmol, $[\alpha]^{23}_D$ −14.06°) neat, prepared by the method of Seuring and Seebach,[26] to give 10.05 g (87%) of (*S*)-(+)-**3**: $[\alpha]^{32}_D$ +17.7° (*c* 1.60, $CHCl_3$).

(*R*)-(−)-**3** was prepared from the lithium salt of 1-butyne (10.8 g, 200 mmol) and (*R*)-(+)-methyloxirane (7.0 g, 120 mmol, $[\alpha]^{21}_D$ +12.1°) neat, prepared by the method of Hillis and Ronald,[27] yielding (*R*)-(−)-**3** (10.8 g, 81%): $[\alpha]^{32}_D$ −17.5° (*c* 2.13, $CHCl_3$).

Preparation of (*R,S*)-6-Heptyn-2-ol ((*R,S*)-4). KH in mineral oil (25% suspension, 2.4 g, 15 mmol) was introduced into a dry flask under argon. The oil was removed by washing the KH with dry THF (2 × 5 mL) and the last traces of THF were removed by pumping under vacuum. The flask was then refilled with argon, and 1,3-diaminopropane (15 mL, dried by distillation from BaO) was added to the residue. The resulting orange suspension was stirred for 1 h, following which 4-heptyn-1-ol (**3**) (0.56 g, 5 mmol) was added in one aliquot. The reaction was stirred at 20 °C for 1 h and then quenched by the cautious addition of crushed ice (5 g) in portions. The resulting mixture was poured into ice water (50 mL) and extracted with ether (4 × 30 mL). The combined ether extracts were backwashed with brine, dried ($MgSO_4$), and concentrated under reduced pressure without heating. The residue was distilled in a Kugelrohr tube to yield (*R,S*)-**4**: bp ≈70–80 °C (15 mmHg); IR (film) 3360, 3310, 2120, 1378 cm^{-1}; mass spectrum, *m/e* (relative intensity) 112 (0.5), 97 (9), 79 (18), 67 (33), 45 (100); ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, C_1, *J* = 6.5 Hz), 1.57–1.73 (m, 4 H, C_3–C_4), 1.57 (s, 1 H, OH), 1.96 (t, 1 H, C_7, *J* = 2.5 Hz), 2.23 (td, 2 H, C_5, *J* = 6.75, 2.5 Hz), 3.84 (m, 1 H, C_2). Anal. Calcd for $C_7H_{12}O$: C, 74.96; H, 10.78. Found: C, 74.86; H, 10.84.

Preparation of (*S*)-(+)-6-Heptyn-2-ol ((*S*)-(+)-4) and (*R*)-(−)-4. (*S*)-(+)-**3** (9.5 g, 85 mmol) was subjected to the "acetylene zipper" reaction, as described for the preparation of (*R,S*)-**4**, yielding (*S*)-(+)-**4** (5.82 g, 62%): $[\alpha]^{30}_D$ +13.4° (*c* 1.57, $CHCl_3$). (*R*)-(−)-**3** (9.5 g, 85 mmol) was treated identically, yielding (*R*)-(−)-**4** (7.6 g), contaminated with starting material. An analytical sample was further purified by flash chromatography on silica gel (2 cm ID × 15 cm) eluting with hexane:EtOAc (4:1): $[\alpha]^{30}_D$ −13.6° (*c* 0.404, $CHCl_3$).

Preparation of (*R,S*)-6-(*tert*-Butyldimethylsiloxy)-1-heptyne ((*R,S*)-5). The *tert*-butyldimethylsilyl ether of (*R,S*)-**4** was prepared by the standard procedure,[16] yielding (*R,S*)-**5** (6.14 g, 88%): bp 105 °C (15 mmHg) as a colorless oil; IR (film) 3322, 2865, 2124, 1259 cm^{-1}; mass spectrum, CI, *m/e* 227 (M + 1); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, CH_3Si), 0.88 (s, 9 H, $C(CH_3)_3$), 1.13 (d, 3 H, CH_3, *J* = 6.1 Hz), 1.48–1.67 (m, 4 H, C_4 and C_5), 1.94 (t, 1 H, C≡CH, *J* = 2.5 Hz), 2.20 (td, 2 H, $CH_2C{\equiv}C$, *J* = 6.5, 2.5 Hz), 3.84 (sextet, 1 H, C_6, *J* ≃ 6 Hz). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 69.16; H, 11.76.

Preparation of (*S*)-(+)-6-(*tert*-Butyldimethylsiloxy)-1-heptyne ((*S*)-(+)-5) and (*R*)-(−)-5. (*S*)-(+)-**4** (5.6 g, 55 mmol) yielded (*S*)-(+)-**5** (10.85 g, 99%). This material was >98% pure by GLC and was used without further purification: $[\alpha]^{31}_D$ +13.8° (*c* 2.696, $CHCl_3$).

(*R*)-(−)-**5** was prepared in similar yield: $[\alpha]^{33}_D$ −14.1° (*c* 3.096, $CHCl_3$).

(26) Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1175.
(27) Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1981**, *46*, 3348.

Preparation of (*R,S*)-7-(*tert*-Butyldimethylsiloxy)-2-octyn-1-ol ((*R,S*)-6). Racemic **5** (5.65 g, 25 mmol) was dissolved in dry THF (75 mL) under argon and the solution was cooled to −10 °C in an ice salt bath. *n*-BuLi in hexane (1.3 M, 20 mL, 26 mmol) was added dropwise, maintaining the temperature below 0 °C and the resulting solution was stirred at 0 °C for 30 min. The solution was then cooled to −10 °C and dry paraformaldehyde (1.13 g, 37.5 mmol) was added in one portion. The mixture was warmed to 20 °C over several hours and stirred at 20 °C for 12 h. The reaction was worked up by pouring into ice water (100 mL) and extracting with ether (3 × 100 mL).

The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Distillation of the residue gave racemic **6** (4.76 g, 74%): bp 104–107 °C (0.2 mmHg); IR (film) 3360, 2862, 2226, 1259 cm^{-1}; mass spectrum, CI, *m/e* 257 (M + 1); ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H, CH_3Si), 0.88 (s, 9 H, $C(CH_3)_3$), 1.13 (d, 3 H, CH_3, *J* = 6.1 Hz), 1.48–1.67 (m, 4 H, C_5 and C_6), 1.47 (t, 1 H, OH, *J* = 6.0 Hz), 2.22–2.27 (m, 2 H, C_4), 3.82 (sextet, 1 H, C_7, *J* ≃ 6.1 Hz), 4.26 (dt, 2 H, CH_2OH, *J* = 6.4, 2.1 Hz). Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.01. Found: C, 65.72; H, 11.26.

Preparation of (*S*)-(+)-7-(*tert*-Butyldimethylsiloxy)-2-octyn-1-ol ((*S*)-(+)-6) and (*R*)-(−)-6. (*S*)-(+)-**6** was produced in 77% yield: $[\alpha]^{32}_D$ +12.3° (*c* 3.98, $CHCl_3$).

(*R*)-(−)-**6** was produced in 67% yield: $[\alpha]^{31}_D$ −11.0° (*c* 6.62, $CHCl_3$).

Preparation of (*R,S*)-7-(*tert*-Butyldimethylsiloxy)-2-octyn-1-yl *p*-Toluenesulfonate ((*R,S*)-7). Racemic **6** (40 g, 15.6 mmol) and *p*-toluenesulfonyl chloride (3.6 g, 18.7 mmol) were dissolved in anhydrous ether (30 mL) and cooled to −5 °C in an ice salt bath. Finely powdered KOH (8.74 g, 156 mmol) was added in five equal portions at 5-min intervals, maintaining the temperature below 0 °C. The mixture was then stirred at 0 °C for 30 min and poured into ice water (100 mL). The organic layer was removed and the aqueous residue was extracted twice more with ether (2 × 50 mL). The combined organic extracts were backwashed with brine, dried (Na_2SO_4), and concentrated in vacuo without heating. Final traces of solvent were removed under vacuum (0.1 mmHg) for 4 h, yielding the tosylate **7** as an oil (6.2 g, 96%). Tosylate **7** gave one spot on TLC (hexane:EtOAc, 3:1) and was used without further purification: IR (film) 2862, 2244, 1601, 1375, 1259 cm^{-1}; mass spectrum, CI, *m/e* 411 (M + 1); ^1H NMR ($CDCl_3$) δ 0.03 (s, 6 H, CH_3Si), 0.86 (s, 9 H, $C(CH_3)_3$), 1.09 (d, 3 H, CH_3, *J* = 6.1 Hz), 1.48–1.68 (m, 4 H, C_5 and C_6), 2.03–2.10 (m, 2 H, C_4), 2.43 (s, 3 H, $ArCH_3$), 3.75 (sextet, 1 H, C_7, *J* ≈ 6.0 Hz), 4.67 (t, 2 H, CH_2OSO_2, *J* = 2.2 Hz), 7.33 (d, 2 H, tosyl, *J* = 8.0 Hz), 7.79 (d, 2 H, tosyl, *J* = 8.0 Hz).

Preparation of (*S*)-(+)-7-(*tert*-Butyldimethylsiloxy)-2-octyn-1-yl *p*-Toluenesulfonate ((*S*)-(+)-7) and (*R*)-(−)-7. (*S*)- and (*R*)-**7** were prepared exactly as described for racemic **7** and used without further purification. The optical rotations of the enantiomers were too small to measure accurately (<1°).

Preparation of 5-Hexynoic Acid (9). Acid **9** was prepared by oxidation of 5-hexyn-1-ol (**8**) with cold Jones reagent, using the inverse addition procedure[22] (7.64 g, 68%): bp 73–76 °C (0.2 mmHg) as a colorless oil; IR (film) 3500–2500, 3292, 2118, 1705 cm^{-1}; mass spectrum, *m/e* (relative intensity) 112 (0.2), 111 (3), 97 (13), 94 (8), 70 (100), 60 (37); ^1H NMR ($CDCl_3$) δ 1.84 (quintet, 2 H, C_3, *J* = 7.1 Hz), 1.99 (t, 1 H, C≡CH, *J* = 2.6 Hz), 2.29 (td, 2 H, $C{\equiv}CCH_2$, *J* = 7.1, 2.6 Hz), 2.52 (t, 2 H, CH_2COOH, *J* = 7.1 Hz), 11.58 (s, 1 H, COOH).

Preparation of (*R,S*)-13-(*tert*-Butyldimethylsiloxy)-5,8-tetradecadiynoic Acid ((*R,S*)-10). Ethylmagnesium bromide (200 mmol) in dry THF (≈20 mL) was cooled to 5 °C and a solution of 5-hexynoic acid (1.01 g, 9.0 mmol) in dry THF (5 mL) was added dropwise over 15 min. The solution was warmed to 20 °C and stirred at 20 °C for 2 h. The solution was then cooled to 0 °C and freshly prepared CuBr (57 mg, 0.4 mmol) was added in one portion. The mixture was stirred at 0 °C for 15 min, followed by the dropwise addition of racemic tosylate **7** (3.28 g, 8.0 mmol) in THF (10 mL). The mixture was warmed to 20 °C over several hours, stirred at 20 °C for 16 h, and poured into ice water (50 mL). The mixture was acidified to pH 3 with 6 M HCl and extracted with ether (3 × 60 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo at 20 °C, to yield crude racemic **10** (3.3 g, >100%) as

a yellow oil. The oil was unstable and gradually decomposed to brown tars, even when stored at −30 °C. Consequently, the crude material was carried through to the next step without further purification. IR and ^{1}H NMR spectra of the crude material were taken to confirm that coupling had occurred: IR (film) 3600–2500, 2238, 1713, 1256 cm^{-1}; mass spectrum of methyl ester (CH_2N_2), CI, m/e 365 (M + 1); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H, CH_3Si), 0.88 (s, 9 H, $C(CH_3)_3$), 1.13 (d, 3 H, CH_3, J = 6.1 Hz), 1.48–1.67 (m, 4 H, C_{11} and C_{12}), 1.84 (quintet, 2 H, C_3, $J \simeq$ 7.0 Hz), 2.20 (m, 2 H, C_{10}), 2.29 (m, 2 H, C_4), 2.52 (t, 2 H, CH_2COOH, J = 7.0 Hz), 3.10 (quintet, 2 H, $C{\equiv}CCH_2C{\equiv}C$, J = 2.1 Hz), 3.82 (m, 1 H, C_{13}).

Preparation of (*S*)-(+)-13-(*tert*-Butyldimethylsiloxy)-5,8-tetradecadiynoic Acid ((*S*)-(+)-10) and (*R*)-(−)-10. (*S*)- and (*R*)-**10** were prepared exactly as described for racemic **10**. Due to the instability of these compounds, the crude products were used directly in the next step. The yields of crude material were comparable to that obtained for racemic **10** and the major product in each case was chromatographically identical by TLC or GLC to the racemic material.

Preparation of (*R*,*S*)-13-(*tert*-Butyldimethylsiloxy)-(5*Z*,8*Z*)-5,8-tetradecadienoic Acid ((*R*,*S*)-11). P-2 nickel (3.0 mmol) was prepared from $Ni(OAc)_2{\cdot}6H_2O$ (0.75 g, 3.0 mmol), 1 M ethanolic $NaBH_4$ solution (3.0 mL, 3.0 mmol), and ethylenediamine (0.54 mL, 8.1 mmol) in 95% EtOH (30 mL) under H_2. Crude racemic acid **10** (2.0 g, ≈4.8 mmol) was added in one portion and the mixture was stirred for 4 h, monitoring the progress of the reaction by GLC of the methyl esters (CH_2N_2). The intermediate enynes were clearly seen. At the end of the 4-h period, the reduction was complete. The mixture was filtered through a 5-mm pad of charcoal and the charcoal was rinsed with a few milliliters of ethanol. The filtrate was poured into cold brine (100 mL), extracted with ether (3 × 75 mL), dried ($MgSO_4$), and concentrated in vacuo. The last traces of solvent were removed by pumping at high vacuum (0.1 mmHg) for 3 h, yielding crude diene (*R*,*S*)-**11** (2.15 g). This was carried through immediately to the next step to minimize decomposition.

Preparation of (*R*,*S*)-13-Hydroxy-(5*Z*,8*Z*)-5,8-tetradecadienoic Acid ((*R*,*S*)-12). Crude racemic acid **11** (1.90 g) was stirred at 20 °C for 16 h in 25 mL of AcOH:H_2O:THF (3:1:1). The solvents were removed in vacuo at 20 °C and the residue was flash chromatographed on silica gel (2.5 cm ID × 20 cm) and eluted with hexane:EtOAc:AcOH (140:60:2) to yield hydroxy acid (*R*,*S*)-**12** (0.55 g, 53% from tosylate **7**) as a viscous oil: IR (solution, $CHCl_3$) 3550–2500, 3020, 1711 cm^{-1}; mass spectrum of methyl ester (CH_2N_2), CI, m/e 255 (M + 1); ^{1}H NMR ($CDCl_3$) δ 1.21 (d, 3 H, CH_3, J = 6.3 Hz), 1.28–1.53 (m, 4 H, C_{11} and C_{12}), 1.71 (quintet, 2 H, C_3, J = 7.0 Hz), 2.00–2.18 (m, 4 H, C_4 and C_{10}, allylic), 2.12 (s, 2 H, OH), 2.37 (t, 2 H, CH_2COOH, J = 7.0 Hz), 2.80 (t, 2 H, C_7, bisallylic, $J \simeq$ 6.5 Hz), 3.78–3.89 (m, 1 H, C_{13}), 5.30–5.48 (m, 4 H, olefin).

Preparation of (*S*)-(+)-13-Hydroxy-(5*Z*,8*Z*)-5,8-tetradecadienoic Acid ((*S*)-(+)-12) and (*R*)-(−)-12. (*S*)- and (*R*)-**12** were prepared exactly as described for racemic **12**. The intermediate TBDMS-protected dienes **11** were not isolated. Pure (*S*)-**12** was recovered in 48% yield from tosylate (*S*)-**7**, while pure (*R*)-**12** was obtained in 51% yield from (*R*)-**7**. Both gave ^{1}H NMR spectra identical with racemic **12**.

Preparation of (*R*,*S*)-13-Methyl-(5*Z*,8*Z*)-5,8-tridecadienolide (I). A solution of racemic hydroxy acid **12** (0.50 g, 2.08 mmol) and dry triethylamine (distilled from P_2O_5, 3.0 g, 30 mmol) in dry acetonitrile (dried with 3-Å molecular sieve, 200 mL) was added dropwise under argon via a high-dilution head to a refluxing solution of 2-chloro-1-methylpyridinium iodide (2.5 g, 10 mmol) in dry acetonitrile (200 mL) over a 24-h period. Reflux was continued for an additional 2 h. The mixture was then cooled to 20 °C and concentrated under reduced pressure. Water (150 mL) was added to the residue and the mixture was extracted with pentane (3 × 100 mL). The combined pentane extracts were washed with water (1 × 50 mL), dried ($MgSO_4$), concentrated under reduced pressure, and flash chromatographed on silica gel (2.5 cm ID × 17 cm) eluting with hexane:EtOAc (60:1), giving racemic macrolide I (208 mg, 47%): IR (film) 3009, 1731 cm^{-1}; mass spectrum, m/e (relative intensity) 222 (8), 180 (14), 140 (16), 126 (11), 106 (19), 93 (49), 79 (100), 67 (59), 55 (26), 41 (36); ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 3 H, CH_3, J = 6.1 Hz), 1.33–1.77 (m, 6 H, C_3, C_{10}, C_{11}, C_{11}', C_{12}, C_{12}'), 1.83 (m, 1 H, C_3'), 1.98 (m, 1 H, C_4), 2.20–2.43 (m, 3 H, C_4', C_7, C_{10}'), 2.27 (ddd, 1 H, C_2, J = 14.5, 8.2, 3 Hz), 2.40 (ddd, 1 H, C_2', J = 14.5, 10, 3 Hz), 3.15 (ddd, C_7', J = 15.1, 9.5, 9.5 Hz), 5.03 (dqd, 1 H, C_{13}, J = 10, 6.1, 2.8 Hz), 5.27 (m, 1 H, C_5), 5.40 (m, 3 H, C_6, C_8, C_9). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.65; H, 9.98. Found: C, 75.88; H, 9.97.

Preparation of (*S*)-(+)-13-Methyl-(5*Z*,8*Z*)-5,8-tridecadienolide ((*S*)-(+)-I) and (*R*)-(−)-I. (*S*)-(+)-I was prepared in 37% yield, following the cyclization procedure for racemic I: $[\alpha]^{32}_D$ +41.8° (*c* 0.958, $CHCl_3$).

(*R*)-(−)-I was similarly prepared in 33% yield: $[\alpha]^{34}_D$ −43.4° (*c* 0.737, $CHCl_3$).

Synthesis of II. Preparation of 4-(*tert*-Butyldimethylsiloxy)-1-butyne (14). The *tert*-butyldimethylsilyl ether of **13** was prepared by the standard procedure[16] in 94% yield: bp 45–46 °C (2.5 mmHg); IR (film) 3318, 2124, 1258 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6 H, CH_3Si), 0.92 (s, 9 H, $C(CH_3)_3$), 1.98 (t, 1 H, C_1, J = 2.5 Hz), 2.42 (tt, 2 H, C_3, J = 7, 2.5 Hz), 3.76 (t, 2 H, C_4, J = 7 Hz); mass spectrum, CI, m/e 185 (M + 1). Anal. Calcd for $C_{10}H_{20}OSi$: C, 65.15; H, 10.94. Found: C, 65.16; H, 11.10.

Preparation of 5-(*tert*-Butyldimethylsiloxy)-2-pentyn-1-yl *p*-Toluenesulfonate (16). Tosylate **16** was prepared, via alcohol **15**, by the procedure described for the synthesis of **6** and **7**. The yield from **14** was 83% (as an oil, one spot on TLC, hexane:EtOAc, 4:1): IR (film) 2242, 1600, 1340, 1256 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6 H, CH_3Si), 0.83 (s, 9 H, $C(CH_3)_3$), 2.31 (tt, 2 H, C_4, J = 7.1, 2.2 Hz), 2.45 (s, 3 H, CH_3), 3.60 (t, 2 H, C_5, J = 7.1 Hz), 4.68 (t, 2 H, C_1, J = 2.2 Hz), 7.35 (d, 2 H, tosyl, J = 8 Hz), 7.80 (d, 2 H, tosyl, J = 8 Hz). Anal. Calcd for $C_{18}H_{28}O_4SSi$: C, 58.66; H, 7.66. Found: C, 58.70; H, 7.72.

Preparation of 3,6-Dodecadiyne-1,11-diol (18). A solution of EtMgBr (38 mmol) in ≈40 mL of dry THF was prepared. Alkyne **5** (7.91 g, 35 mmol) in dry THF (20 mL) was added dropwise over 30 min, during which time the temperature rose to 30 °C and H_2 was evolved. The solution was stirred at 20–30 °C for 2 h, cooled to 0 °C, and CuBr (400 mg, 2.8 mmol) was added. The resulting suspension was stirred for 15 min, and tosylate **16** (12.5 g, 34 mmol) in dry THF (20 mL) was added dropwise over 20 min. The mixture was warmed to 20 °C over 2 h, stirred for 16 h, and poured into water (100 mL) containing 10 g of NH_4Cl. The resulting mixture was extracted with ether (3 × 75 mL) and the combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. A 100-mg portion of the residue was removed for analysis and a solution of a few crystals of *p*-toluenesulfonic acid in dry MeOH (75 mL) were added to the remainder. The resulting solution was stirred at 20 °C for 2 h and then concentrated in vacuo at 0 °C. The residue was taken up in ether (100 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash chromatography (hexane:EtOAc, 2:3) yielded 4.36 g of **18** (66%) as a yellow oil, which rapidly darkened on standing: IR (film) 3700–3050, 2220, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3 H, C_{12}, J = 6.0 Hz), 1.50–1.68 (m, 6 H, OH, C_9, C_{10}), 2.15–2.23 (m, 2 H, C_8), 2.45 (tt, 2 H, C_2, J = 6.0, 2.2 Hz), 3.15 (quint, 2 H, C_5, J = 2.2 Hz), 3.72 (t, 2 H, C_1, J = 6.0 Hz), 4.86 (m, 1 H, C_{11}); mass spectrum, m/e (relative intensity) 194 (0.1), 103 (44), 91 (100), 77 (51), 71 (44).

Preparation of 11-Oxo-3,6-dodecadiynoic Acid (19). Chromium trioxide (12.0 g, 120 mmol) was dissolved in 120 mL of 3.5 M H_2SO_4 (420 mmol) and cooled to −5 °C. A solution of diol **18** (4.30 g, 22.2 mmol) in acetone (250 mL) was added dropwise over 4 h. When the addition was complete, the mixture was warmed to 20 °C over 45 min, then poured into water (400 mL), and extracted with ether (4 × 150 mL). The combined ether extracts were washed with brine (3 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was flash chromatographed (hexane:EtOAc:AcOH, 75:75:1) to yield 1.83 g (40%) of **19** as a highly unstable oil: IR (film) 3700–2400, 2240, 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.79 (quint, 2 H, C_9, J = 6.75 Hz), 2.12 (s, 1 H, COOH), 2.17 (s, 3 H, C_{12}), 2.23 (tt, 2 H, C_8 J = 6.75, 2.2 Hz), 2.58 (t, 2 H, C_{10}, J = 6.75 Hz), 3.18 (quint, 2 H, C_5, J = 2.2 Hz), 3.38 (t, 2 H, C_2, J = 2.2 Hz).

Preparation of 11-Hydroxy-3,6-dodecadiynoic Acid (20). Keto acid **19** (1.8 g, 8.7 mmol) was dissolved in 25 mL of absolute EtOH and cooled to −20 °C. $NaBH_4$ (0.456 g, 12 mmol) was added in one portion and the solution was warmed to 0 °C over 15 min

and then cooled to -20 °C again. The reaction mixture was slowly acidified with 3.5 N HCl, brine (25 mL) was added, and the solution was extracted with ether (4 × 25 mL). The combined ether extracts were washed with brine (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to give an orange oil, which rapidly darkened in color. This was used immediately, without purification, in the next step. An analytical sample of ≈50 mg was removed: IR (film) 3650–2400, 2235, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 3 H, C_{12}, J = 6.3 Hz), 1.48–1.72 (m, 4 H, C_9, C_{10}), 2.10 (s, 2 H, COOH, OH), 2.15–2.23 (m, 2 H, C_8), 3.15 (quint, 2 H, C_5, J = 2.25 Hz), 3.32 (t, 2 H, C_2, J = 2.25 Hz), 3.87 (m, 1 H, C_{11}); mass spectrum of methyl ester (CH_2N_2), m/e (relative intensity) 222 (0.2), 203 (3), 129 (45), 105 (45), 91 (100), 77 (51), 45 (35).

Preparation of 11-Hydroxy-(3*Z*,6*Z*)-3,6-dodecadienoic Acid (21). P-2 nickel (4 mmol) was made by the standard procedure[20] in 95% EtOH (30 mL). The crude acid **20** was added and the mixture was stirred under H_2 for 5 h. The solution was then filtered with suction through 5 mm of activated charcoal, rinsing several times with EtOH. The filtrate was concentrated in vacuo at 20 °C. Ether (20 mL) was added and the solution was acidified to pH 3 with 2 M HCl. The ether layer was separated and the aqueous portion was extracted with ether (3 × 20 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to yield 1.53 g of crude product. Flash chromatography (hexane:EtOAc:AcOH, 75:75:1) yielded 0.66 g of **21** (≈35% from **19**): IR (film) 3650–2400, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (d, 3 H, C_{12}, J = 6.3 Hz), 1.37–1.52 (m, 4 H, C_9, C_{10}), 2.00–2.15 (m, 2 H, C_8), 2.82 (t, 2 H, C_5, J = 6.0 Hz), 3.17 (m, 2 H, C_2), 5.32–5.48 (m, 2 H, C_6, C_7) 5.53–5.65 (m, 2 H, C_3, C_4); mass spectrum of methyl ester (CH_2N_2), m/e (relative intensity) 92 (68), 91 (69), 79 (100), 74 (68).

Preparation of 11-Methyl-(3*Z*,6*Z*)-3,6-undecadienolide (II). A solution of hydroxy acid **21** (0.64 g, 3.1 mmol) and dry triethylamine (2.42 g, 24 mmol) in dry acetonitrile (200 mL) was added over 20 h via a fixed-rate addition funnel and a high-dilution head to a refluxing solution of 2-chloro-1-methylpyridinium iodide (3.18 g, 12.4 mmol) in dry acetonitrile (200 mL), under argon. The resulting solution was refluxed a further 2 h, cooled, and concentrated in vacuo. The residue was taken up in pentane (50 mL) and washed with water (50 mL). The aqueous phase was extracted twice more with pentane (25 mL) and the combined pentane extracts were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed (hexane:EtOAc, 40:1), yielding 45 mg (7.5%) of macrolide II: IR (film) 3010, 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, C_{12}, J = 6.25 Hz), 1.33 (m, 1 H, C_9), 1.51 (m, 1 H, C_9), 1.67 (m, 1 H, C_{10}), 1.76 (m, 1 H, C_{10}), 2.05 (ddt, 1 H, C_8, J = 13.75, 10.5, 9, 6.5 Hz), 2.44 (dddd, 1 H, C_8, J = 13.75, 6.5, 6.5, 6.5 Hz), 2.62 (dddd, 1 H, C_5, J = 13.75, 6.75, 6.75 Hz), 2.95 (dd, 1 H, C_2, J = 13.0, 7.5 Hz), 3.16 (dt, 1 H, C_5, J = 13.75, 9.9 Hz), 3.21 (dd, 1 H, C_2, J = 13.0, 9.5 Hz), 4.97 (dd, quartet, 1 H, C_{11}, J = 7.5, 6.25, 3 Hz), 5.29 (ddd, 1 H, C_7, J = 10.5, 6.5, 10.5 Hz), 5.49 (ddd, 2 H, C_3, C_6, J = 10.5, 9, 6.75 Hz), 5.63 (ddd, 1 H, C_4, J = 10.5, 9, 6.75 Hz); mass spectrum, m/e (relative intensity) 194 (3), 176 (4), 91 (42), 79 (100), 77 (39), 67 (36); high-resolution mass spectrum, calcd for $C_{12}H_{18}O_2$, 194.1306; found, 194.1306.

Synthesis of Macrolide III. Preparation of 7-((2-Methoxyethoxy)methoxy)-1-heptyne (25). 2-Heptyn-1-ol (**23**) was prepared in 95% distilled yield from 1-hexyne and paraformaldehyde, as described for **6**. Isomerization of **23** to the terminal alkyne **24**, as described for **7**, gave **24** in 46% distilled yield. Alcohol **24** was then protected as the (β-methoxyethoxy)methyl ether **25** in 95% yield:[25] bp 70–73 °C (0.2 mmHg); IR (film) 3295, 2118 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.67 (m, 6 H, C_4–C_6), 1.95 (t, 1 H, C_1, J = 2.5 Hz), 2.21 (tt, 2 H, C_3, J = 7, 2.5 Hz), 3.40 (s, 3 H, OCH_3), 3.57 (t, 2 H, C_7, J = 6.3 Hz), 3.58 (m, 2 H, OCH_2CH_2O), 3.70 (m, 2 H, OCH_2CH_2O), 5.72 (s, 2H, OCH_2O); mass spectrum, CI, m/e 201 (M + 1).

Preparation of 12-((2-Methoxyethoxy)methoxy)-1-(*tert*-butyldimethylsiloxy)-3,6-dodecadiyne (26). Diyne **26** was prepared from **25** (11.5 g, 57.5 mmol) and **16** (24 g, 65 mmol) as described for **17**.

The crude material (1 g) was removed for analysis, while the remainder was carried through directly to the next step: IR (film) 2234, 1255, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H, CH_3Si), 0.91 (s, 9 H, $(CH_3)_3C$), 1.38–1.68 (m, 6 H, C_9–C_{11}), 2.16 (tt, 2 H, C_8, J = 7, 2.4 Hz), 2.49 (tt, 2 H, C_2, J = 7.4 × 2.4 Hz), 3.11 (quint, 2 H, C_5, J = 2.4 Hz), 3.40 (s, 3 H, CH_3O), 3.53–3.60 (m, 4 H, OCH_2CH_2O, C_{12}), 3.68–3.75 (m, 4 H, OCH_2CH_2, C_1), 4.72 (s, 2 H, OCH_2O); mass spectrum, CI, m/e 397 (M + 1).

Preparation of 12-((2-Methoxyethoxy)methoxy)-3,6-dodecadiyn-1-ol (27). Crude alkyne **26** was dissolved in dry MeOH (200 mL) and *p*-toluenesulfonic acid (200 mg) was added. The solution was stirred for 2 h at 20 °C, then concentrated in vacuo without heating. The residue was dissolved in ether (125 mL), extracted with saturated $NaHCO_3$ (25 mL), washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed in three portions on silica gel (5 cm ID × 20 cm) eluting with hexane:EtOAc (1:3) to yield **27** (8.3 g, 54% from **25**): IR (film) 3420, 2218 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34–1.68 (m, 7 H, C_9–C_{11}, OH), 2.17 (tt, 2 H, C_8, J = 7, 2.5 Hz), 2.45 (tt, 2 H, C_2, J = 6.1, 2.5 Hz), 3.13 (quintet, 2 H, C_5, J = 2.5 Hz), 3.40 (s, 2 H, OCH_3), 3.48–3.65 (m, 4 H, OCH_2CH_2O, C_{12}), 3.65–3.77 (m, 4 H, OCH_2CH_2O, C_1), 4.72 (s, 2 H, OCH_2O); mass spectrum, CI, m/e 283 (M + 1).

Preparation of 12-((2-Methoxyethoxy)methoxy)-3,6-dodecadiynoic Acid (28). A solution of alcohol **27** (2.20 g, 7.8 mmol) in reagent acetone (100 mL) was added dropwise over 4 h to a solution of CrO_3 (3.12 g, 31.2 mmol) in 1.5 M H_2SO_4 (50 mL, 75 mmol) at 0 °C. When the addition was complete, the mixture was allowed to warm to 20 °C and was stirred an additional 2 h. Ether (100 mL) was added and the mixture was extracted with brine (3 × 75 mL). The ethereal solution was then concentrated in vacuo. The residue was taken up in ether (75 mL) and extracted with 0.5 M $NaHCO_3$ (3 × 30 mL). The combined basic extracts were acidified with 6 M HCl to pH 2 and extracted with ether (3 × 50 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo, yielding crude **28** (1.59 g, 69% crude yield). An analytical sample was withdrawn and the remainder was submitted directly to the next step: IR (film) 3600–2500, 2239, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.68 (m, 7 H, C_9–C_{11}, OH), 2.18 (tt, 2 H, C_8, J = 6.6, 2.4 Hz), 3.16 (quintet, 2 H, C_5, J = 2.4 Hz), 3.30 (t, 2 H, C_2, J = 2.4 Hz), 3.42 (s, 3 H, OCH_3), 3.58 (t, 2 H, C_{12}, J = 6.5 Hz), 3.53–3.63 (m, 2 H, OCH_2CH_2O), 3.66–3.75 (m, 2 H, OCH_2CH_2O), 4.73 (s, 2 H, OCH_2O).

Preparation of 12-Hydroxy-3,6-dodecadiynoic Acid (29). Crude acid **28** (1.50 g, 5.07 mmol) was stirred for 24 h at 20 °C in 27.5 mL of THF:H_2O:concentrated HCl (8:2:1). Ether (100 mL) was added and the mixture was extracted with brine (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was flash chromatographed on silica gel (2.5 cm ID × 20 cm) eluting with hexane:EtOAc:AcOH (25:75:1) to yield **29** (675 mg, 64%) as a viscous oil, which solidified on refrigeration: IR (film) 3600–2400, 2240, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–1.78 (m, 8 H, C_9–C_{11}, 2 OH), 2.16–2.27 (m, 2 H, C_8), 3.15 (quintet, 2 H, C_5, J = 2.4 Hz), 3.29 (t, 2 H, C_2, J = 2.4 Hz), 3.70 (t, 2 H, C_{12}, J = 6 Hz); mass spectrum of methyl ester (CH_2N_2), CI, m/e 223 (M + 1).

Preparation of 12-Hydroxy-(3*Z*,6*Z*)-3,6-dodecadienoic Acid (30). Diene **30** was prepared from **29** as described for the conversion of **20** to **21**. The resulting yellow oil was used without further purification: IR (film) 3600–2500, 3010, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (m, 4 H, C_9–C_{10}), 2.11 (s, 2 H, OH), 1.53–1.65 (m, 2 H, C_{11}), 2.02–2.11 (m, 2 H, C_8), 2.83 (t, 2 H, C_5, J = 6.4 Hz), 3.16 (d, 2 H, C_2, J = 6.4 Hz), 3.67 (t, 2 H, C_{12}, J = 6.8 Hz), 6.34–5.46 and 5.51–5.70 (m, 4 H, olefins); mass spectrum of methyl ester (CH_2N_2), CI, m/e 227 (M + 1).

Preparation of (3*Z*,6*Z*)-3,6-Dodecadienolide (III). Macrolide III was prepared in 27% yield (2.8% overall from 1-hexyne) by the method described for II: IR (film) 3010, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (m, 2 H, C_9), 1.46 (m, 2 H, C_{10}), 1.71 (m, 2 H, C_{11}), 2.05 (quartet, 2 H, C_8, J = 7.5 Hz), 2.91 (dd, 2 H, C_5, J ≈ 7.7 Hz), 3.09 (d, 2 H, C_2, J = 7.75 Hz), 4.11 (m, 2 H, C_{12}), 5.43–5.58 (m, 4 H, C_3, C_4, C_6, C_8); mass spectrum, m/e (relative intensity) 194 (9), 176 (3), 93 (44), 91 (41), 80 (41), 79 (100), 67 (47). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.47; H, 9.46.

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Registry No. (*R,S*)-**3**, 90134-40-0; (*S*)-(+)-**3**, 90192-96-4; (*R*)-(−)-**3**, 90192-97-5; (*R,S*)-**4**, 69177-44-2; (*S*)-(+)-**4**, 65756-08-3; (*R*)-(−)-**4**, 90192-98-6; (*R,S*)-**5**, 82679-36-5; (*S*)-(+)-**5**, 82729-82-6; (*R*)-(−)-**5**, 90192-99-7; (*R,S*)-**6**, 90134-41-1; (*S*)-(+)-**6**, 90193-00-3; (*R*)-(−)-**6**, 90193-01-4; (*R,S*)-**7**, 90134-42-2; (*S*)-(+)-**7**, 90193-02-5; (*R*)-(−)-**7**, 90193-03-6; **8**, 928-90-5; **9**, 53293-00-8; (*R,S*)-**10**, 90134-43-3; (*S*)-(+)-**10**, 90193-04-7; (*R*)-(−)-**10**, 90193-05-8; (*R,S*)-**11**, 90134-44-4; (*R,S*)-**12**, 90134-45-5; (*S*)-(+)-**12**, 90242-06-1; (*R*)-(−)-**12**, 90193-06-9; **13**, 927-74-2; **14**, 78592-82-2; **15**, 90134-46-6; **16**, 90134-47-7; **18**, 90134-48-8; **19**, 90134-49-9; **20**, 90134-50-2; **21**, 90134-51-3; **23**, 1002-36-4; **24**, 63478-76-2; **25**, 90134-52-4; **26**, 90134-53-5; **27**, 90134-54-6; **28**, 90134-55-7; **29**, 90134-56-8; **30**, 90134-57-9; (*R,S*)-I, 90134-38-6; (*S*)-(+)-I, 90192-94-2; (*R*)-(−)-I, 90192-95-3; II, 86583-51-9; III, 90134-39-7; 1-butyne, 107-00-6; (*R,S*)-methyloxirane, 16033-71-9; (*S*)-(−)-methyloxirane, 16088-62-3; (*R*)-(+)-methyloxirane, 15448-47-2; 1-hexyne, 693-02-7.

Synthesis of Two Fragments of the 14-Membered Macrolide Antibiotic Oleandomycin from D-Glucose

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Methyl 3-*O*-benzyl-7-*O*-(*tert*-butyldimethylsilyl)-2,4-di-*C*-methyl-2,4,6-trideoxy-α-D-*galacto*-heptopyranoside and methyl 2,4-di-*C*-methyl-3-*O*-((2-methoxyethoxy)methyl)-2,4,6-trideoxy-α-D-*galacto*-hexopyranoside, protected forms of the C_3–C_8 and C_9–C_{13} fragments, respectively, of the medically important 14-membered macrolide antibiotic oleandomycin were synthesized from D-glucose. Catalytic hydrogenation of the intermediate 4-*C*-methylene derivatives in the presence of 10% palladium on barium sulfate proceeded with high stereoselectivity, affording mainly galacto isomers. The C_3 hydroxy groups of these chiral fragments were protected with different groups in view of the planned ultimate glycosylation reactions.

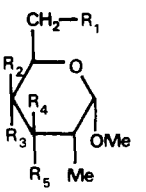
Considerable effort has been directed recently toward the total synthesis of the medically important macrolide antibiotics.[1] A recent paper[2] on the construction of the C_1–C_7 and C_8–C_{13} fragments of the aglycon of oleandomycin (**6**) prompts us to disclose results obtained in this field in our laboratories.

Our synthetic strategy for the construction of the major part of the aglycon of oleandomycin (**6**), from carbohydrate precursors, Scheme I, is based on an aldol condensation reaction between fragments **2** and **4** to create the C_8–C_9 bond of intermediate **5**. The stereochemical complication resulting from this reaction will be of no consequence since the expected diasterochemical aldol mixture (**5**) will have to be oxidized at C_9 to a ketone. This step is planned to be carried out after removal of the unwanted oxygen atom of **5** at C_7 as performed in the recently reported Woodward synthesis of erythromycin A.[3]

We describe here the synthesis of two carbohydrates (**1** and **3**) comprising seven of the 10 asymmetric centers of the aglycon of oleandomycin (**6**).[4] These carbohydrates, with the required different protecting groups on their C_3 oxygen atom, are precursors of fragments **2** and **4**, respectively.

Results and Discussion

Synthesis of the Protected Form of the C_3–C_8 Fragment of the Aglycon of Oleandomycin. Selective tosylation of diol **7**, prepared in 10 steps from D-glucose[5,6] afforded **8**. Treatment of **8** in dimethyl sulfoxide solution with 1.5 equiv of potassium cyanide allowed chain extension and preparation of **9**. Reaction of **9** in dry toluene at room temperature with diisobutylaluminum hydride followed by lithium aluminum hydride reduction afforded



7, $R_1 = R_3 = OH$; $R_2 = R_4 = H$; $R_5 = OBn$
8, $R_1 = OTs$; $R_2 = R_4 = H$; $R_3 = OH$; $R_5 = OBn$
9, $R_1 = CN$; $R_2 = R_4 = H$; $R_3 = OH$; $R_5 = OBn$
10, $R_1 = CH_2OH$; $R_2 = R_4 = H$; $R_3 = OH$; $R_5 = OBn$
11, $R_1 = CH_2OSi\text{-}t\text{-}BuMe_2$; $R_2 = R_4 = H$; $R_3 = OH$; $R_5 = OBn$
12, $R_1 = CH_2OSi\text{-}t\text{-}BuMe_2$; $R_4 = H$; $R_2,R_3 = O$; $R_5 = OBn$
13, $R_1 = CH_2OSi\text{-}t\text{-}BuMe_2$; $R_5 = H$; $R_2,R_3 = O$; $R_4 = OBn$
14, $R_1 = CH_2OSi\text{-}t\text{-}BuMe_2$; $R_5 = H$; $R_2,R_3 = CH_2$; $R_4 = OBn$
15, $R_1 = CH_2OSi\text{-}t\text{-}BuMe_2$; $R_2 = R_5 = H$; $R_3 = Me$; $R_4 = OBn$
18, $R_1 = Br$; $R_2 = R_4 = H$; $R_3 = OBz$; $R_5 = OMEM$
19, $R_1 = R_2 = R_4 = H$; $R_3 = OBz$; $R_5 = OMEM$
20, $R_1 = R_2 = R_4 = H$; $R_3 = OH$; $R_5 = OMEM$
21, $R_1 = R_4 = H$; $R_2,R_3 = O$; $R_5 = OMEM$
22, $R_1 = R_5 = H$; $R_2,R_3 = O$; $R_4 = OMEM$
23, $R_1 = R_5 = H$; $R_2,R_3 = CH_2$; $R_4 = OMEM$
24, $R_1 = R_2 = R_5 = H$; $R_3 = Me$; $R_4 = OMEM$

the diol **10**. Selective protection of the primary hydroxy group of **10** by treatment with *tert*-butyldimethylsilyl chloride furnished **11**. Oxidation of **11** by pyridinium chlorochromate[7] gave the highly unstable ketone **12**. Isomerization of the axially oriented C_3 substituent of **12** was performed by sodium methoxide treatment,[5] leading

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(1) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585.
(2) Patterson, I. *Tetrahedron Lett.* **1983**, *24*, 1311.
(3) Woodward, R. B.; et al. *J. Am. Chem. Soc.* **1981**, *103*, 3210, 3213, and 3215.
(4) Hochstein, F. A.; Els, H.; Celmer, W. D.; Shapiro, B. L.; Woodward, R. B. *J. Am. Chem. Soc.* **1960**, *82*, 3225.

0022-3263/84/1949-2338$01.50/0