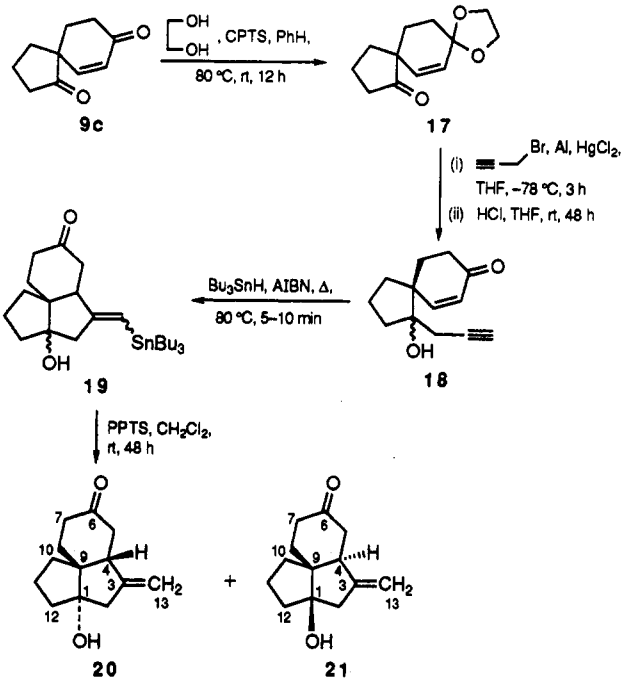
Scheme V



H-4 appeared as a doublet of doublets at 3.19 ppm (J = 2.14 and 1.96 Hz), shifted downfield with reference to that of compound **21**. In the ^{13}C NMR the characteristic difference was in the chemical shifts[10] of the ring junction carbons C-1 and C-9. For compounds **20** and **21** these carbons resonated at 91.07 (C-1) and 57.56 (C-9) ppm, and 88.22 (C-1) and 53.29 (C-9) ppm, respectively.

Thus, radical cyclization of compound **18** leads to *cis*- and *trans*-tricyclo[7.3.0.0^{4,9}]-1-hydroxy-3-methylidene-6-oxododecanes **21** and **20**, respectively. Compounds like **20** and **21** have been used as precursors for the synthesis of triquinane derivatives.[11]

In summary, the methodology outlined in path A provides a convenient method for the stereocontrolled synthesis of angularly fused tricyclic systems. More significantly, all the compounds underwent facile stereocontrolled radical cyclization, and the formation of a single diastereomer in each case is indicative of the extent of the stereocontrol observed during the cyclization.

The high degree of diastereoselectivity of the vinyl radical cyclization can be explained by an arguement analogous to that used to explain the stereoselectivity of hexenyl radical cyclization.[12] Beckwith *et al.*, Rajanbabu *et al.*, and Houk *et al.* used favorable modes of orbital overlap and steric interactions to explain the stereochemical outcome of this type of cyclization. In our case, the unfavorable mode of orbital overlap eliminates one chair and one boat transition state out of four possible transition states. Examination of the remaining chair and boat transition states with the aid of molecular models revealed a higher degree of steric crowding in the boat-like transition state than in the chair-like transition state. This arguement is in accordance with experimental observations. The combined effects of the steric factor and the favorable mode of orbital overlap result in the formation of single diastereomer via a single chair-like transition state (Figure 1).

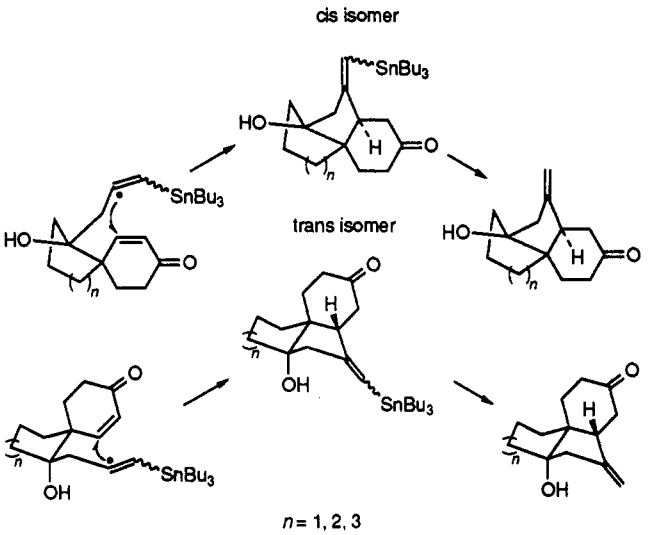
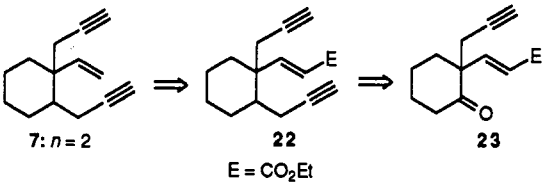


Figure 1.

Scheme VI



Attention was then focused on the reaction sequences detailed in path B (Scheme I). For the 5-*exo*-*trig* cyclization, the first step in the sequential radical cyclization, we envisaged an α,β-unsaturated ester group (compound **22**, Scheme VI) as a radical acceptor instead of an α,β-unsaturated keto group. (The use of the ester rather than the ketone eliminates the need for protection of the carbonyl during the addition of the organometallic reagent (see path A). Ketone **23** was synthesized as follows: Alkylation of 2-formylcyclohexanone with propargyl bromide gave a 75:25 mixture of C- and O-alkylated products **5** (n = 2) and **24**, which were separated by vacuum distillation. Wittig olefination of the C-alkylated product (**5**, n = 2) (1.3 equiv of (carbethoxyethyl)triphenylphosphonium bromide, 1.5 equiv of potassium carbonate, CH_2Cl_2/water (1:1), room temperature, 2 h)[13] gave compound **23** in 60% yield (Scheme VII). Addition of a propargylaluminum sesquibromide solution to ketone **23** gave alcohol **25** in 85% yield as a single diastereomer as evidenced by spectral data. Radical cyclization of compound **25** (2.2 equiv of tributyltin hydride, AIBN, 80 °C, 10 min) gave the stannyl adduct (the IR spectrum shows the disappearance of the C≡C—H stretching frequency and a shift in the carbonyl frequency from 1710 to 1730

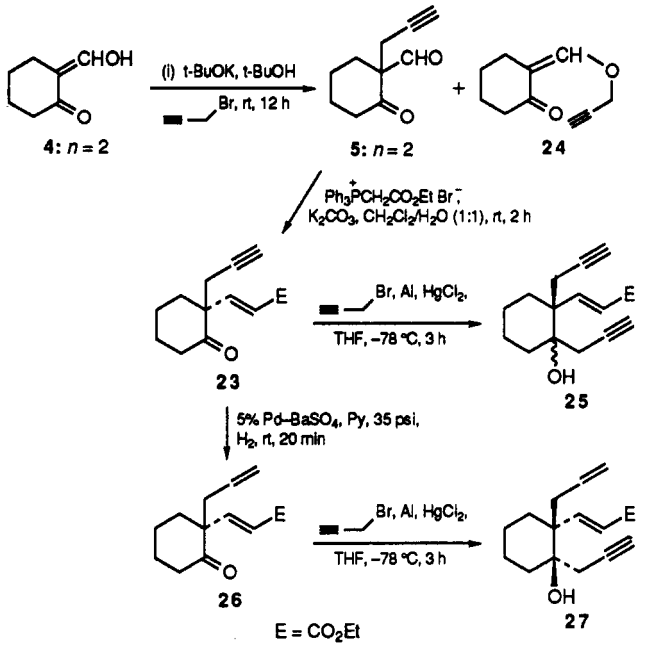
(10) Metzger, P.; Casaderall, E.; Pouet, H. *J. Org. Mag. Reson.* **1982**, *19*, 229.

(11) (a) Ihara, M.; Kotosi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2963. (b) Ihara, M.; Kawaguchi, A.; Ueda, H.; Chihiro, M.; Fukumoto, K.; Kametani, H. *J. Chem. Soc., Perkin Trans 1* **1987**, 1331.

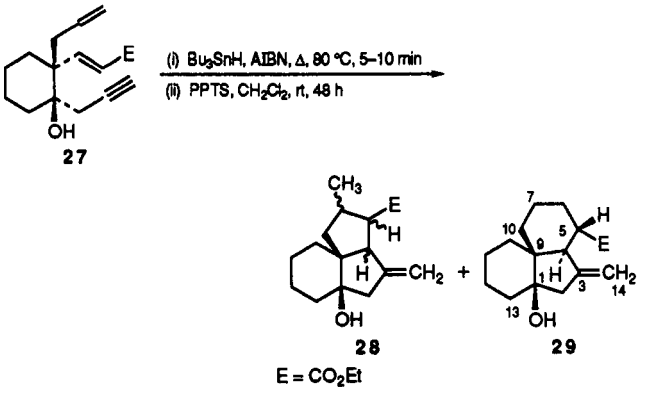
(12) (a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545. (b) RajanBabu, T. V.; Fukunaga, T.; Reddy, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 1759, 256. (c) RajanBabu, T. V. *J. Am. Chem. Soc.* **1987**, *109*, 609. (d) Beckwith, A. L. J.; Scheisser, C. H. *Tetrahedron Lett.* **1985**, 373. (e) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (f) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondom, N. G.; Nagase, S. *J. Org. Chem.* **1986**, 2874. (g) Houk, K. N.; Spellmeyer, D. C. *J. Org. Chem.* **1987**, *52*, 959.

(13) Ganesh Raj, S. P.; Janardhanam, S.; Rajagopalan, K. *Synth. Commun.* **1989**, 1341.

Scheme VII



Scheme VIII



cm^{-1}). Protiodestannylation followed by column chromatography afforded a liquid whose IR spectrum indicated that the cyclization had occurred. However, ^{1}H NMR showed it to be a mixture of products. Separation by column chromatography proved to be very difficult, and the yield after destannylation was only 20%. Repeating the radical cyclization of compound **25** with only 1.1 equiv of tributyltin hydride also resulted in a mixture of products after protiodestannylation.

Even though it was possible to effect the cyclization of compound **25**, the very poor yield and the difficulty encountered in separating products proved to be deterrents. The complications are obviously due to the indiscriminate addition of tributyltin radical [(n-Bu)$_3$Sn$^\bullet$] to all the available sites and the cyclization of the resulting radical in a random fashion without any stereocontrol. In order to achieve the required cyclization via path B it is imperative that the initial addition of tributyltin radical [(n-Bu)$_3$Sn$^\bullet$] to compound **25** be made regiospecific. Compound **27** can in principle can be expected to undergo regiospecific radical addition and sequential radical cyclization (Scheme VII).

Reduction of compound **23** gave compound **26** in 95% yield. Compound **26** could also be alternatively prepared in 60% yield by hydrostannylation of the triple bond and then destannylation. Addition of a propargylaluminum sesquibromide solution to ketone **26** gave alcohol **27** in 85% yield as a single diastereomer as evidenced by HPLC and spectral data. The stereochemical features of compound **27** indicated in Scheme VII were obtained by chemical studies.[14]

Radical cyclization of compound **27** (Scheme VIII) under neat conditions gave the cyclized stannyl adduct which was subjected to protiodestannylation. Column chromatography of the crude material gave two compounds in a 95:5 ratio in 75% combined yield. The minor compound showed IR absorptions at 3600 (OH), 3080 (C=CH$_2$), 1735 (COOEt), and 1640–50 (C=C) cm^{-1}, indicating that the cyclization had taken place. However, the ^{1}H NMR spectrum showed it to be a mixture of isomers. The characteristic peaks for the *gem*-vinyl protons at 4.9–5.0 ppm were present, and the methyl group appeared as a doublet at around 1 ppm. The above observations are indicative of the fact that the minor product arises from a 5-*exo*-5-*exo*-*trig* cyclization pathway. On the basis of its spectral data, the minor product was assigned structure **28**. The major product was found to be homogeneous by TLC, and its IR spectrum showed absorptions at 3600 (OH), 3080 (C=CH$_2$), 1735 (COOEt), and 1650 (C=C) cm^{-1}. The ^{1}H NMR spectrum showed the complete disappearance of the olefinic protons of the starting material and the appearance of the signals at 4.62 and 4.81 ppm due to the *gem*-vinyl protons at C-14. The NMR also showed a doublet at 2.87 ppm (J = 11.72 Hz) due to proton H-4 and a doublet of triplets at 2.42 ppm (J = 8.31 and 3.41 Hz) due to proton H-5. These assignments were further substantiated by irradiation studies. Irradiation of the doublet of triplets at 2.42 ppm (H-5) simplified the doublet at 2.87 ppm (H-4) to a singlet. Similarly, irradiation of the doublet at 2.87 ppm (H-4) simplified the doublet of triplets at 2.42 ppm (H-5). In the ^{13}C NMR spectrum, the vinyl carbons resonated at 149.28 ppm (C-3) and 105.57 ppm (C-14), and the methine carbons resonated at 50.68 ppm (C-4) and 40.87 ppm (C-5). The indicated stereochemical relationship between H-4 and H-5 was based on mechanistic considerations and confirmed by differential NOE studies. Differential NOE study of proton H-4 caused no positive enhancement of H-5 and vice versa. From the above spectral data, it was evident that the major product arises via a 5-*exo*-6-*endo*-*trig* cyclization, and it was assigned structure **29**. A survey of the literature[15] showed that there are few examples of α-carbonyl-centered radicals favoring 6-*endo* cyclization rather than 5-*exo* cyclization, thereby implying that product **29** was formed from the cyclization of the *endo*-oriented carbonyl under kinetic control. The probable mechanism for the formation of compound **29** is detailed in Scheme IX. The second cyclization, the cyclization of carbonyl-stabilized radical **29b** to alkyl radical **31**, seems to be an unfavorable process, but the cyclization is still exothermic and fast because a σ-bond is formed at expense of a π-bond.

(14) After compound **27** was completely saturated, attempts at lactonization failed. The failure of the lactonization indicates that the OH and carbethoxy groups are probably in a trans relationship.

(15) (a) Clive, D. L. J.; Cheshire, D. R. *J. Chem. Soc., Chem. Commun.* **1987**, 1520. (b) Curran, D. P.; Chang, C. T. *J. Org. Chem.* **1989**, *54*, 3140. (c) Porter, N. A.; Chang, U. H. T.; Magmin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3354. (d) Birkhofer, H.; Beckhaus, H. D.; Ruchardt, C. In *Substituent Effects in Radical Chemistry*; Viehe, H. G., Jaunousek, Z., Merenyi, R., Eds.; Reiedel: Boston, 1986; p 199. Sustmann, R. *ibid.*, p 143. (e) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157.

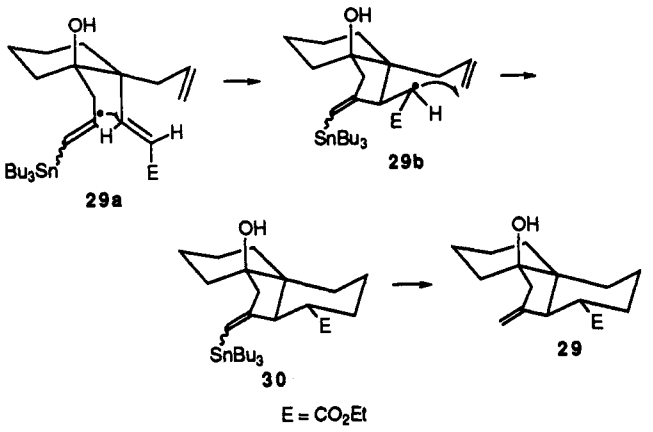
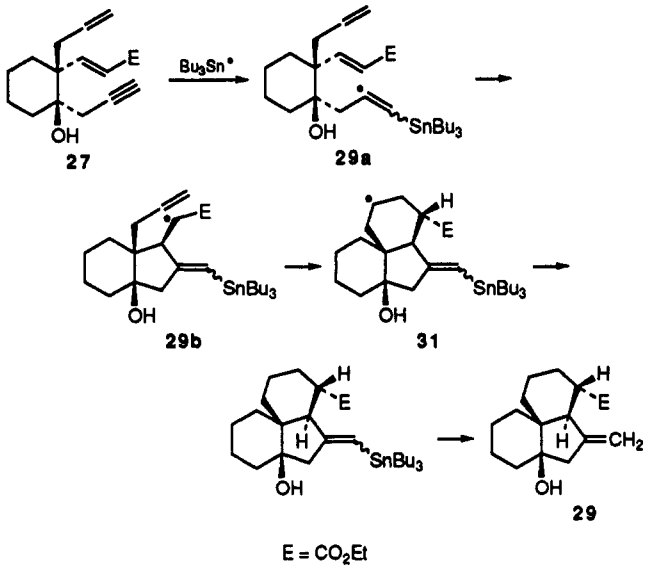


Figure 2.

Scheme IX



The formation of a single diastereomer **29** can be explained by an arguement similar to that used to explain the stereochemistry of the cyclizations of **13**, **16**, **20**, and **21**: favorable orbital overlap and steric interactions in a single chair-like transition state model (Figure 2). The transition state of the first step (**29a** → **30**) in the sequential radical cyclization was based on our previous studies,[3] and the transition state for the second step (**29b** → **30**, the 6-*endo* cyclization) is chair-like because of the geometric constraints caused by the resonance interaction between the radical and the ketone.[15b,c] Thus for path B, we observed a C–C–C bond formation in a single step leading to a functionalized tricyclic system.

In summary, two pathways for the stereocontrolled synthesis of angularly fused tricyclic carbocycles from 2-formylcycloalkanones are described. These two pathways are potential routes for the construction of naturally occurring compounds. Via path A in the case of six- and seven-membered rings, a high degree of stereocontrol was observed for both the propargylaluminum sesquibromide addition to the ketones and the radical cyclization; but in the case of five-membered ring, the addition of the propargylaluminum sesquibromide was nonselective. However, the mixture underwent smooth radical cyclization to produce a single diastereomer in each case. Via path B, the propargylation was 95% stereoselective, and the angularly fused tricyclic system was obtained in a single step via sequential radical cyclization with the major product arising from a *5-exo-6-endo-trig* cyclization. Finally, it was demonstrated that the applicability of this methodology for the stereocontrolled synthesis of [*n.n.n*] systems depends upon the starting material framework. Further studies are in progress.

Experimental Section

All boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 598 spectrophotometer. ^{1}H NMR spectra were recorded either at 400 or at 90 MHz. ^{13}C NMR spectra were recorded either at 100.6 or at 22.5 MHz as indicated. Chemical shifts are reported in ppm (δ) with Me_4Si as a standard, and coupling constants are expressed in hertz. Percent NOE enhancements were obtained by integrating the affected resonance relative to the irradiated resonance in the difference spectrum. Mass spectra were recorded on a GCMS QP 1000 A spectrometer and a JEOL JMS-DX 303 HF mass spectrophotometer. Elemental analysis were performed with a Perkin-Elmer 240 B elemental analyser. HPLC studies were carried out on a Shimadzu LC-4A and LC-5A instruments with a Zorbax ODS column with a UV-detector and methanol–water (3:2) or acetonitrile–water (3:2) as the solvent at a flow rate of 4 μl/min. Thin-layer chromatograms were developed on glass plates coated with silica gel-G (ACME) of 0.25-mm thickness and were visualized with iodine. Column chromatography was carried out either with SiO_2 (silica gel, ACME, 100–200 mesh) or with neutral Al_2O_3 (alumina, ACME, washed with ethyl acetate and activated). For experiments requiring anhydrous conditions, glassware were thoroughly dried in an oven, cooled, and assembled under a stream of N_2. The organic extracts of crude products were dried over anhydrous magnesium sulfate. Solvents were reagent grade and were purified according[16] to the literature procedure prior to use, and n-Bu_3SnH was prepared[17] according to the literature procedure.

General Procedure for the Synthesis of Spirodiones 9a–c. 2-(Hydroxymethylene)cycloalkanones (0.1 mol) and powdered KOH (250 mg) were suspended in methyl vinyl ketone (0.25 mol) under N_2 at rt. The mixture became homogeneous in about 1 h. The reaction was allowed to stir for an additional 6 h, after which time the excess methyl vinyl ketone was removed in vacuo. The brown residue was taken up in 150 mL of CH_2Cl_2, washed with 2 × 40 mL of buffer solution (1 molar aqueous potassium dihydrogen phosphate) and brine, and dried. The solvent was removed in vacuo. The residue was pure enough to be used as such for the next step.

The residue obtained in the previous step was dissolved in 250 mL of benzene, and 200 mg of methanesulfonic acid was added. The solution was heated at reflux for 10 h under N_2 with a Dean–Stark apparatus to remove water. The mixture was cooled to rt. Sodium acetate (2 g) was added, and the solvent was removed in vacuo. The dark brown residue was taken up in 200 mL of CH_2Cl_2, and the solution was washed once each with saturated sodium bicarbonate, water, and brine and dried. Removal of the solvent gave a liquid residue, which was distilled in vacuo.

Spiro[5.5]undec-7-ene-1,9-dione (9a).[6] The reaction of 2-formylcyclohexanone gave compound **9a** in 70% yield: bp 140 °C (0.05 Torr), lit. bp 92–94 °C (0.015 Torr).

Spiro[6.5]dodec-8-ene-1,10-dione (9b).[6] The reaction of 2-formylcycloheptanone gave compound **9b** in 75% yield: bp 116–117 °C (0.1 Torr), lit. bp 122 °C (0.13 Torr).

Spiro[4.5]dec-6-ene-1,8-dione (9c).[6] The reaction of 2-formylcyclopentanone gave compound **9c** in 80% yield: bp 104–105 °C (0.1 Torr), lit. bp 60 °C (0.01 Torr).

General Procedure for Propargylation of Ketones[3] 9a, 11, 14, 17, 23, and 26. An aluminum amalgam was prepared from aluminum foil (0.0361 mol, 3 equiv) and a catalytic amount of mercuric chloride (10 mg) in 15 mL of dry THF by vigorously stirring the mixture at rt for 1 h under a N_2 atmosphere. A solution of propargyl bromide (0.0361 mol, 3 equiv) in 25 mL of

(16) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: New York, 1988.
(17) Szammer, J.; Otovos, L. *Chem. Ind.* **1988**, 764.

dry THF was slowly added to the stirred suspension at such a rate so as to maintain the temperature between 30–40 °C. After the addition, stirring was continued until a dark grey solution was obtained (ca. 1 h). The propargyl sesquialuminum bromide solution thus obtained was added to a solution of the ketone (0.0120 mol, 1 equiv) in 100 mL of dry ether at −78 °C under a N_2 atmosphere. The reaction mixture was stirred at −78 °C for 3 h, poured into ice–water, and extracted with 4 × 25 mL of ether. The combined ether extracts were washed with brine, dried, and concentrated. The propargylated compounds obtained from **23** and **26** were subjected to column chromatography (silica gel, 150 g) with hexane–ethyl acetate to give pure propargyl carbinols. But the compounds obtained from **11**, **14**, and **17** were subjected to deketalization without purification.

Deketalization. The crude acetal was dissolved in 10% HCl in THF (1:3) and was stirred at rt for 48 h. Ether (50 mL) was added, and the organic layer was washed with saturated sodium bicarbonate solution and water and dried. The solvent was removed in vacuo, and the residual liquid was subjected to column chromatography (silica gel, 150 g) with hexane–ethyl acetate to give the propargyl carbinol.

9-Hydroxy-9-(3′-prop-1′-ynyl)spiro[5.5]undec-7-ene (10). The addition of the propargyl aluminum sesquibromide solution (1.1 equiv) to compound **9a** by means of the general procedure gave compound **10** in 70% yield: IR (CCl_4) 3560, 3300, 2100, 1700 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.8–5.7 (q, 2H), 2.1 (t, 1H), 2.52–1.18 (m, 15H).

General Procedure for the Selective Ketalization[7] of the Enone Carbonyl of Spirodiones 9a–c. According to the procedure of Paquette *et al.*,[7] a round-bottomed flask was charged with spirodione (0.03 mol, 1 equiv), collidinium *p*-toluenesulfonate (CPTS, 0.004 mol, 0.125 equiv), ethylene glycol (0.045 mol, 1.5 equiv), and 125 mL of benzene. The reaction mixture was refluxed for 14 h with a Dean–Stark apparatus to remove the water formed in the reaction. The reaction mixture was cooled, washed with 2 × 40 mL of sodium bicarbonate solution and 2 × 25 mL of water, and dried. The solvent was completely removed in vacuo, and the residue was chromatographed over neutral alumina with hexane–ethyl acetate as eluent.

Synthesis of Ketal 11. The treatment of spirodione **9a** with ethylene glycol and CPTS for 12 h gave enone ketal **11** in 70% yield: R_f = 0.52 (1:10, AcOEt–hexane); IR (CCl_4) 1700, 1620 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.7 (q, 2H), 4.0 (s, 4H), 2.6–1.4 (m, 12H).

Synthesis of Ketal 14. The ketalization of spirodione **9b** gave enone ketal **14** in 75% yield: R_f = 0.5 (1:10, AcOEt–hexane); IR (CCl_4) 1700, 1620 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.6 (q, 2H), 4.0 (s, 4H), 2.8–1.6 (m, 14H).

Synthesis of Ketal 17. The ketalization of spirodione **9c** gave enone ketal **17** in 70% yield: R_f = 0.48 (1:10, AcOEt–hexane); IR (CCl_4) 1740, 1615 cm^{-1}; ^1H NMR (90 MHz, CCl_4) δ 5.7 (q, 2H), 4.1 (s, 4H), 2.4–1.4 (m, 10H).

1-Hydroxy-1-(3′-prop-1′-ynyl)spiro[5.5]undec-7-ene-9-one (12). Compound **11** was propargylated with the propargyl sesquialuminum bromide solution by means of the general procedure. Deketalization followed by chromatography gave compound **12** in 80% yield: R_f = 0.75 (1:5, AcOEt–hexane); IR (CCl_4) 3580, 3300, 2100, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 10.74, 1.46, 1H), 5.96 (d, J = 10.74, 1H), 2.71 (br s, 1H), 2.62 (dd, J = 17.09, 2.44, 1H), 2.26 (dd, J = 17.09, 2.44, 1H), 2.16 (dd, J = 2.93, 2.44, 1H), 2.5 –1.2 (m, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 199.68 (s), 154.51 (d), 129.25 (d), 80.34 (s), 73.60 (s), 72.65 (d), 42.64 (s), 33.56 (t), 33.39 (t), 32.73 (t), 28.28 (t), 28.04 (t), 21.43 (t), 21.22 (t); MS *m/z* 218 (M^+). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31; Found: C, 77.22; H, 8.29.

1-Hydroxy-1-(3′-prop-1′-ynyl)spiro[6.5]dodec-8-ene-10-one (15). Compound **14** was propargylated with propargyl sesquialuminum bromide solution by means of general procedure. Deketalization followed by chromatography gave compound **15** in 75% yield: R_f = 0.7 (1:5, AcOEt–hexane); IR (CCl_4) 3560, 3300, 2100, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, J = 10.75, 1.46, 1H), 5.96 (d, J = 10.75, 1H), 2.58 (dd, J = 16.6, 2.44, 1H), 2.26 (dd, J = 16.6, 2.44, 1H), 2.13 (dd, J = 2.93, 2.44, 1H), 2.5–1.42 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 193.64 (s), 154.20(d), 128.60 (d), 80.40 (s), 76.12 (s), 72.63 (d), 45.60 (s), 35.49 (t), 34.06 (t), 32.21 (t), 29.74 (t), 27.75 (t), 27.63 (t), 21.98 (t), 20.81 (t); MS *m/z* 232 (M^+). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; Found: C, 77.54; H, 8.70.

1-Hydroxy-1-(3′-prop-1′-ynyl)spiro[4.5]dec-6-ene-8-one (18). Compound **17** was propargylated with propargyl sesquialuminum bromide solution by means of the general procedure. Deketalization followed by chromatography gave compound **18** in 90% yield: R_f = 0.5 (1:5, AcOEt–hexane); IR (CCl_4) 3560, 3300, 2100 cm^{-1}. However, spectral data showed that **18** was a 1:1 mixture of isomers, and their separation proved to be difficult: ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 10.74, 1.96, 1H), [6.68 (dd, J = 10.74, 1.96, 1H], 5.99 (d, J = 10.25, 1H), [5.93 (d, J = 10.64, 1H], 2.58–1.69 (m, 28H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.73 (199.54), 154.30 (153.96), 128.89 (128.22), 82.83 (82.47), 80.33 (80.15), 72.22 (71.89), 50.68 (50.06), 37.92 (35.46), 37.20 (37.07), 34.21 (32.82), 28.31 (28.13), 27.32 (26.97), 19.55 (19.29), MS *m/z* 204 (M^+). Analysis of mixture **18**, calcd for $C_{13}H_{16}O_2$: C, 76.64; H, 7.90. Found: C, 76.61; H, 7.89.

General Procedure for Radical Cyclization and Protiodestannylation. A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar was charged with analar N_2, propargylated carbinol (0.0021 mol), tributyltin hydride (0.0022 mol), and azobis(isobutyronitrile) (AIBN, 0.0001 mol). The entire assembly was lowered into an oil bath maintained between 75–85 °C, and the mixture was stirred. After an induction period of less than 5 min, an exothermic reaction occurred (a small amount of gas was produced), and the reaction was allowed to stir for another 10 min, at which point TLC showed that the reaction was complete (also by IR). The crude vinylstannane thus obtained was suitable for protiodestannylation.

To a solution of crude vinylstannane in 30 mL of CH_2Cl_2 was added pyridinium *p*-toluenesulfonate (PPTS, 2 equiv), and the reaction mixture was stirred at rt for 48 h or until TLC analysis showed complete disappearance of starting material and the formation of a polar product. The solvent was removed under reduced pressure, and the residue was thoroughly extracted with 10 × 25 mL of hexane–ethyl acetate (2:3). The combined extracts were concentrated under reduced pressure, and the crude product was chromatographed (silica gel) with hexane–ethyl acetate as the eluent to give the destannylated product.

Tricyclo[7.4.0.0^{4,9}]-1-hydroxy-3-methylidene-6-oxotridecane (13). Radical cyclization of **12** and then destannylation gave **13** in 80% yield: R_f = 0.75 (1:5, AcOEt–hexane); IR (CCl_4) 3600, 3080, 1700, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.05 (d, J = 1.95, 1H), 4.95 (d, J = 1.95, 1H), 2.78 (d, J = 17.09, 1H), 2.67 (br s, 1H), 2.4 (d, J = 17.09, 1H), 2.63–1.47 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 213.39 (s), 150.09 (s), 109.29 (t), 79.48 (s), 46.92 (d), 45.37 (s), 44.84 (t), 42.49 (t), 42.46 (t), 36.46 (t), 35.12 (t), 31.80 (t) 22.62 (t), 21.40 (t); MS *m/z* 220 (M^+). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; Found: C, 76.25; H, 9.13.

Tricyclo[8.4.0.0^{4,9}]-1-hydroxy-3-methylidene-6-oxotridecane (16). Radical cyclization of **15** (5 min) and then destannylation gave **16** in 75% yield: R_f = 0.72 (1:5, AcOEt–hexane); IR (CCl_4) 3580, 3080, 1705, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (d, J = 1.92, 1H), 4.69 (dd, J = 2.44, 1.95, 1H), 2.54 (br s, 1H), 2.55–1.44 (m, 19H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.53 (s), 149.68 (s), 106.22 (t), 82.27 (s), 50.60 (d), 49.48 (t), 48.30 (s), 40.30 (t), 38.69 (t), 36.91 (t), 34.88 (t), 30.25 (t) 27.73 (t), 22.24 (t), 22.33 (t); MS *m/z* 234 (M^+). Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.33; H, 9.21.

***cis*- and *trans*-Tricyclo[6.4.0.0^{4,9}]-1-hydroxy-3-methylidene-6-oxododecane (20 and 21).** Radical cyclization of **19** (10 min) and then destannylation gave compounds **20** and **21** in 80% combined yield as a mixture of isomers. The isomers were separated by column chromatography with hexane–ethyl acetate as the eluent.

Trans Isomer 20: R_f = 0.52 (1:5, AcOEt–hexane); IR (CCl_4) 3600, 3060, 1705, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.09 (dd, J = 2.44, 1.96, 1H), 5.01 (dd, J = 2.44, 1.96, 1H), 3.19 (dd, J = 2.93, 2.44, 1H), 2.4–1.51 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.75 (s), 155.28 (s), 101.73 (t), 91.07 (s), 57.56 (s), 44.16 (d), 39.59 (t), 37.99 (t), 37.72 (t), 31.10 (t), 29.78 (t), 26.28 (t), 25.30 (t); MS *m/z* 206 (M^+). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.98. Found: C, 75.70; H, 8.98.

Cis Isomer 21: R_f = 0.49 (1:5, AcOEt–hexane); IR (CCl_4) 3600, 3060, 1705, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (d, J

= 1.96, 1H), 4.79 (d, J = 1.96, 1H), 2.72 (d, J = 16.11, 1H), 2.58–1.55 (m, 15H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 212.79 (s), 151.09 (s), 107.19 (t), 88.22 (s), 53.29 (s), 49.22 (d), 46.25 (t), 41.04 (t), 40.69 (t), 38.16 (t), 37.14 (t), 28.40 (t), 22.16 (t); MS m/z 206 (M^+). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.98. Found: C, 75.78; H, 8.98.

2-Formyl-2-(3′-prop-1′-ynyl)cyclohexanone (5). A solution of 2-formylcyclohexanone (25.0 g, 0.2 mol) in 40 mL of *tert*-butyl alcohol was added to a solution of potassium *tert*-butoxide [prepared from potassium metal (8.19 g, 0.21 mol)] in 350 mL of *tert*-butyl alcohol over a period of 30 min under a N_2 atmosphere. After the reaction mixture stirred for 30 min at rt, propargyl bromide (26.18 g, 0.22 mol) was added dropwise over a period of 1.5 h. The resulting mixture was stirred overnight at rt. The solid potassium iodide was filtered off, and *tert*-butyl alcohol was removed form the filtrate under reduced pressure. Water (150 mL) was added to the residue, and the mixture was extracted with 6 × 50 mL of ether. The combined extracts were washed with water and brine and dried. Concentration under reduced pressure and distillation of the residue afforded both C- and O-alkylated products.

O-Alkylated Product 24: 8.13 g, 25%; bp 60–64 °C at 0.5 Torr; IR (CCl_4) 3300, 1705, 1650 cm^{-1}.

C-Alkylated Product 5: 24.40 g, 75%; bp 75–80 °C at 0.5 Torr; IR (CCl_4) 3300, 1730, 1705 cm^{-1}; ^{1}H NMR (90 MHz, CCl_4) δ 9.5 (s, 1H), 2.6 (t, 1H), 2.5–1.8 (m, 10H); MS m/e 164 (M^+).

2-(2′-Carbethoxyvinyl)-2-(3′-prop-1′-ynyl)cyclohexanone (23). To a solution of compound **5** (15.0 g, 0.031 mol) in 60 mL of CH_2Cl_2 along with (carbethoxymethyl)triphenylphosphonium bromide (15.5 g, 0.04 mol, 1.3 equiv) in 60 mL of water was added potassium carbonate (6.2 g, 0.047 mol, 1.5 equiv) in small portions over a period of 10 min.[13] The resulting mixture was stirred for 2 h; the organic layer was separated, washed with 2 × 25 mL of water, and dried. Removal of the solvent gave a residue, which solidified on cooling. Digestion of the solid with petroleum ether (40–60 °C) gave a residue, which was chromatographed (silica gel) to afford compound **23** in 60% yield (4.2 g): R_f = 0.6 (1:20 AcOEt–hexane); IR (CCl_4) 3300, 1725, 1700, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 16.11, 1H), 5.82 (d, J = 16.11, 1H), 4.21 (q, J = 7.33, 2H), 2.55 (t, J = 1.95, 2H), 2.51–2.31 (m, 4H), 2.03 (dd, J = 2.93, 2.44, 1H), 1.89–1.68 (m, 4H), 1.30 (t, J = 7.33, 3H); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 206.80 (s), 165.20 (s), 148.09 (d), 122.64 (d), 79.44 (s), 71.16 (d), 62.41 (t), 53.48 (s), 39.17 (t), 35.71 (t), 26.68 (t), 26.26 (t), 21.01 (t), 13.78 (q); MS m/e 234 (M^+).

1,2-Bis(3′-prop-1′-ynyl)-2-(2′-carbethoxyvinyl)cyclohexan-1-ol (25). Propargylation of **23** with propargyl sesquialuminum bromide solution by means of the general procedure gave compound **25** in 85% yield: R_f = 0.75 (1:20, AcOEt–hexane); IR (CCl_4) 3580, 3300, 2100, 1710, 1640 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 17.09, 1H), 5.85 (d, J = 17.09, 1H), 4.20 (q, J = 7.32, 2H), 2.74 (dd, J = 16.6, 2.41, 1H), 2.66 (dd, J = 16.6, 2.44, 1H), 2.48 (d, J = 2.44, 2H), 2.33 (s, 1H), 2.13 (d(t), J = 2.44, 1H), 1.96 (d(t), J = 2.44, 1H), 2.10–1.40 (m, 8H), 1.13 (t, J = 7.32, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.58 (s), 150.20 (d), 121.96 (d), 81.09 (s), 81.05 (s), 73.51 (s), 72.57 (d), 71.07 (d), 60.47 (t), 46.45 (s), 32.77 (t), 29.08 (t), 27.43 (t), 22.36 (t), 22.09 (t), 20.57(t), 14.19 (q); MS m/z 274 (M^+). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08; Found: C, 74.44; H, 8.10.

Radical Cyclization of Compound 25. Compound **25** was subjected to the general procedure for radical cyclization (2.2 equiv of n-Bu_3SnH, 10 mmol) and destannylation (60 h) to afford the cyclized compound as part of an inseparable mixture: IR (CCl_4) 3580, 3080, 1740, 1650 cm^{-1}.

2-(3′-Prop-1′-enyl)-2-(2′-carbethoxyvinyl)cyclohexanone (26). Method A. Compound **23** (1.17 g, 0.0057 mol) was dissolved in 15 mL of dry pyridine, and 40 mg of 5% Pd–$BaSO_4$ was added. The solution was hydrogenated at 35 psi hydrogen pressure for 20 min. Pyridine was removed by distillation under reduced pressure, and the residue was extracted with 4 × 25 mL of chloroform. The chloroform extracts were washed with cold 10% hydrochloric acid and water and dried. Removal of the solvent under reduced pressure followed by column chromatography over silica gel with 5% ethyl acetate–hexane gave compound **26** (1.12 g) in 95% yield: R_f = 0.75 (1:20, AcOEt–hexane); IR (CCl_4) 3040, 1710–1690, 1630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 16.11, 1H), 5.76 (d, J = 16.6, 1H), 5.69–5.58 (m, 1H), 5.07 (d, J = 2.45, 1H), 5.04 (d, J = 10.74, 1H), 4.2 (q, J = 7.33, 2H), 2.48–2.41 (m, 4H), 2.00–1.93 (m, 2H), 1.81–1.74 (m, 4H), 1.30 (t, J = 7.33, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.64 (s), 166.07 (s), 150.41 (d), 132.97 (d), 122.27 (d), 118.73 (t), 60.56 (t), 54.54 (s), 41.29 (t), 39.78 (t), 35.79 (t), 26.96 (t), 21.39 (t), 14.22 (q); MS m/e 236 (M^+). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.85. Found: C, 71.16; H, 8.86.

Method B. Subjecting compound **23** to the general procedure for radical cyclization with n-Bu_3SnH and then destannylation gave compound **26** in 60% yield. The spectral data were identical with those of the compound obtained by method A.

1-(3′-Prop-1′-ynyl)-2-(3′-prop-1′-enyl)-2-(2′-carbethoxyvinyl)cyclohexan-1-ol (27). Propargylation of compound **26** with propargyl sesquialuminum bromide solution by means of the general procedure gave compound **27** in 85% yield: R_f = 0.75 (1:20, AcOEt–hexane); IR (CCl_4) 3560, 3300, 3040, 2100, 1720, 1640, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 16.11, 1H), 5.70 (d, J = 16.11, 1H), 5.53–5.51 (m, 1H), 5.04 (d, J = 10.74, 1H), 5.01 (d, J = 3.41, 1H), 4.2 (q, J = 7.32, 2H), 2.55 (d, J = 7.81, 2H), 2.53 (dd, J = 16.85, 2.69, 1H), 2.43 (dd, J = 16.6, 2.46, 1H), 2.1 (dd, J = 2.93, 2.44, 1H), 2.08 (s, 1H), 1.99–1.32 (m, 8H), 1.30 (t, J = 7.32, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 166.56 (s), 152.20 (d), 134.15 (d), 121.22 (d), 117.70 (t), 80.37, 74.00 (s), 72.31 (d), 60.40 (t), 46.71 (s), 35.29 (t), 32.68 (t), 27.98 (t), 27.00 (t), 22.37 (t), 20.14 (t), 14.28 (q); MS m/z 276 (M^+). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.89; H, 8.77.

Radical Cyclization of Compound 27. Compound **27** was subjected to the general procedure for radical cyclization (10 min) and destannylation (48 h) to afford the cyclized compounds in 75% combined yield as a mixture of isomers. The isomers were separated by column chromatography.

Compound 28: R_f = 0.5 (1:20 AcOEt–hexane); IR (CCl_4) 3600, 3080, 1735, 1650–40 cm^{-1}. But the compound was found to be a mixture of isomers [by ^{1}H NMR (400 MHz)].

Compound 29: 0.421 g; R_f = 0.49 (1:20 AcOEt–hexane); IR (CCl_4) 3600, 3080, 1740, 1650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (dd, J = 2.44, 1.95, 1H), 4.62 (dd, J = 2.44, 1.95, 1H), 4.16 (m, 2H), 2.87 (d, J = 11.72, 1H), 2.70 (dd, J = 18.06, 1.95, 1H), 2.42 (d(t), J = 8.3, 3.41, 1H), 2.25 (d, J = 18.56, 1H), 2.04 (s, 1H), 1.93–1.3 (m, 14H), 1.24 (t, J = 7.33, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.26 (s), 149.28 (s), 105.57 (t), 78.87 (s), 60.18 (t), 50.68 (d), 46.10 (s), 42.32 (t), 40.87 (d), 33.35 (t), 30.29 (t), 24.85 (t), 24.75, (t) 23.57 (t), 20.40 (t), 20.22 (t), 14.08 (q); MS m/z 278 (M^+). Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.35; H, 9.41.

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A General Approach to Enantiomerically Pure Methylcarbinols. Asymmetric Synthesis of Antibiotic (−)-A26771B and the WCR Sex Pheromone

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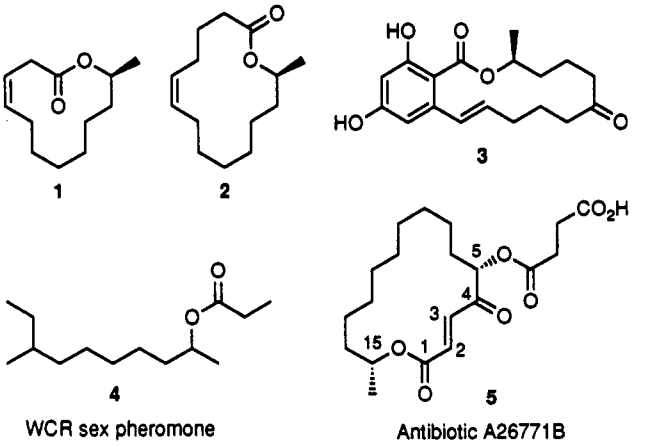
Either (*R*) or (*S*) enantiomerically pure methylcarbinol groups are conveniently produced from monosubstituted alkenes via the Sharpless asymmetric dihydroxylation (AD) reaction. The initial AD product, 1,2-dihydroxyalkane, obtained with predictable absolute configuration and high enantiomeric purity, is converted into 2-acetoxy-1-bromoalkane and then subjected to reductive debromination. These conditions are compatible with a variety of functional groups, including acetal, ester, nitrile, ketone, and silyl ether. The advantages of this method are demonstrated by highly efficient, asymmetric syntheses of enantiomerically pure natural products. All four stereoisomers of the WCR sex pheromone **4** are prepared in six steps form nona-1,8-diene in 10–15% overall yield. Similarly, a highly efficient formal total synthesis of antibiotic (−)-A26771B (**5**) is accomplished via two alternative approaches. The first one transforms dodec-11-enal into enantiomerically pure **5** in 11 steps and 4.1% overall yield, while the second achieves the same transformation in 12 steps and 6.6% overall yield.

Introduction

The methylcarbinol group, $CH_3CH(OH)C$, appears ubiquitously in many biochemicals and pharmaceuticals, including naturally occurring macrocyclic lactones[1] and pheromones.[2] This stereogenic center, which represents the "starter unit" in polyketide natural products, is found in either (*R*) or (*S*) configuration.[3] A reliable and widely used source of enantiomerically pure methylcarbinols for the synthesis of such target molecules is the "chiral pool" of natural products.[4] An alternative, time-tested source for many chiral building blocks is asymmetric synthesis via enzyme catalysis.[5] We have demonstrated the advantages of the latter approach by using *Thermoanaerobium brockii* alcohol dehydrogenase (TBADH) to catalyze the reduction of a broad range of methyl ketones to the corresponding methylcarbinols with excellent enantioselectivity.[6] We have also employed these alcohols in the total synthesis of natural products containing methylcarbinol, including ferrulactone II (**1**)[6e] (*S*)-(+)-(*Z*)-tetradec-5-en-13-olide (**2**)[6d] (*S*)-(−)-zearalenone (**3**)[6f] as well as all four isomers of 8-methyldec-2-yl propanoate (**4**), the sex pheromone emitted by the female western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte.[6g]



Here we report on a very convenient, general, asymmetric synthesis of the methylcarbinol functionality from monosubstituted alkenes using the Sharpless asymmetric dihydroxylation (AD) reaction.[7] We demonstrate the advantages of this method by the formal synthesis of all four stereoisomers of the WCR sex pheromone **4** and antibiotic (−)-A26771B (**5**) using achiral starting materials.

Results and Discussion

Our general approach to methylcarbinols is outlined in Scheme I. The AD reaction with monosubstituted alkenes

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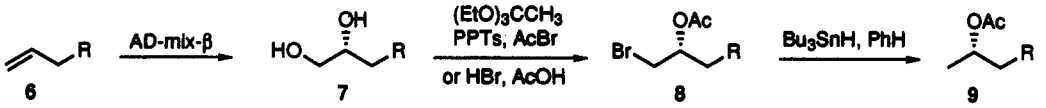
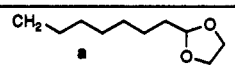
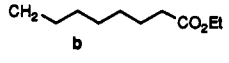
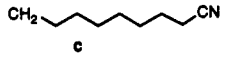
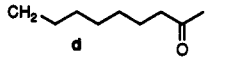
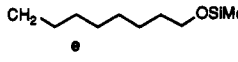
Scheme I



6 7 8 9

Table I

R	7: yield (%), ee (%)	8: yield (%)	9: yield (%)
 a	93, 89[a]	58	57
 b	96, 90[a]	96	74
 c	94, 87[a]	83	89
 d	99, 86[a]	90	80
 e	92, 84	85	77

[a] A single recrystallization of this diol from diethyl ether afforded a pure sample with enantiomeric excess greater than 97%.

6 is known to proceed with very high yields to give 1,2-dihydroxyalkanes 7, with predictable absolute configuration (AD-mix-α forms the 2*S* configuration while AD-mix-β produces the 2*R* stereochemistry) and high enantiomeric purity (80–98% ee).[7] In many cases, such high levels of enantiomeric enrichment allow for essentially pure enantiomers to be achieved by a single recrystallization of the crude diol. Selective deoxygenation of the primary hydroxyl group in 7 could thus give rise to enantiomerically pure methylcarbinol (Scheme I).

The five representative examples shown in Table I illustrate the generality and chemoselectivity of the method with respect to variety of functional groups. Diol 7 was converted to 2-acetoxy-1-bromoalkane 8, by treatment with triethyl orthoacetate and catalytic amounts of pyridinium *p*-toluenesulfonate (PPTS) followed by addition of acetyl bromide.[8] Alternatively, the same transformation was achieved using HBr in acetic acid.[9] Reductive removal of the primary bromide in 8 was carried out under mild conditions using tributyltin hydride.[10] For compounds having functional groups that are compatible with $LiAlH_4$, reduction with the latter reagent may proceed with higher yields to give the free alcohol of **9**.[11] As shown in Table I, the method is compatible with variety of functional groups, including acetal, ester, nitrile, ketone, and silyl ether. In all cases, the AD reaction proceeded with very high yields (92–99%) and with high enantiomeric excess (84–90%). In four out of the five examples, a single recrystallization of the diol (**7a–d**) afforded an enantiomerically pure compound. Diol **7e** was obtained as an oil. Conversion of 7 to 8 proceeded in satisfactory yields even with the acid-sensitive acetal substrate **7a** that was converted to **8a** in 58% yield. Similarly, the conditions for the debromination step with tin hydride were found to be compatible with these representative functional groups. To confirm that no racemization occurred at the secondary carbinol center throughout these transformations, compound **9a** (that was obtained from enantiomerically pure **7a**) was hydrolyzed in KOH/methanol to the corresponding secondary alcohol, which was then converted to its Mosher ester. ^1H NMR analysis of the latter indicated that its enantiomeric purity was fully retained.

We have recently demonstrated the advantages of the AD reaction with disubstituted alkenes in the synthesis of enantiomerically pure polyoxygenated natural product.[12] Here we illustrate the usefulness of the above described method in the asymmetric synthesis of antibiotic (−)-A26771B (**5**) and the four isomers of the WCR sex pheromone **4**, starting from achiral olefins.

Antibiotic A26771B. The sixteen-membered macrolide antibiotic A26771B (**5**) was isolated in 1977 from *Penicillium turbatum* and was found to be moderately active against Gram-positive bacteria, mycoplasma, and fungi.[13] This polyketide secondary metabolite[14] has attracted considerable synthetic efforts, yielding a number of alternative approaches to the racemic compound.[15] Synthesis of **5** in its naturally occurring form was also achieved, starting from enantiomerically pure compounds, including D-glucose,[16] D-glyceraldehyde,[17] and (*R*)-(+)-methyloxirane.[18] Here we present two alternative synthetic approaches to enantiomerically pure **5**, starting with achiral polyalkene precursors and using the above described methodology (Schemes II and III). In both cases the stereogenic carbinol centers, 5*S* and 15*R*, are introduced in a single AD step.

The starting material for the first approach (Scheme II), methyl (*E,E*)-hexadeca-2,4,15-trienoate (**10**) was prepared via a Wittig reaction of dodec-11-enal and methyl-(diethylphosphono)crotonate under basic conditions (LDA, THF).[19] Reaction of **10** with AD-mix-α and methanesulfonamide in a 1:1 mixture of *tert*-butyl alcohol/water followed by recrystallization from ethyl acetate afforded

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