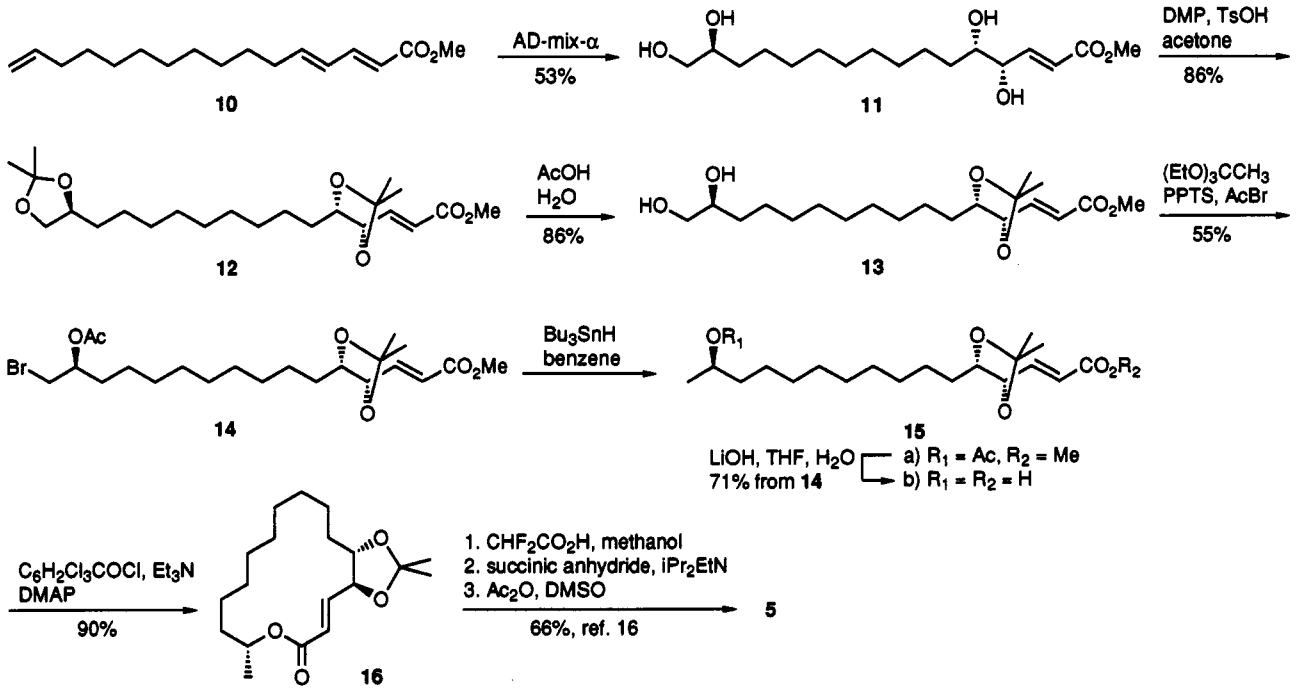
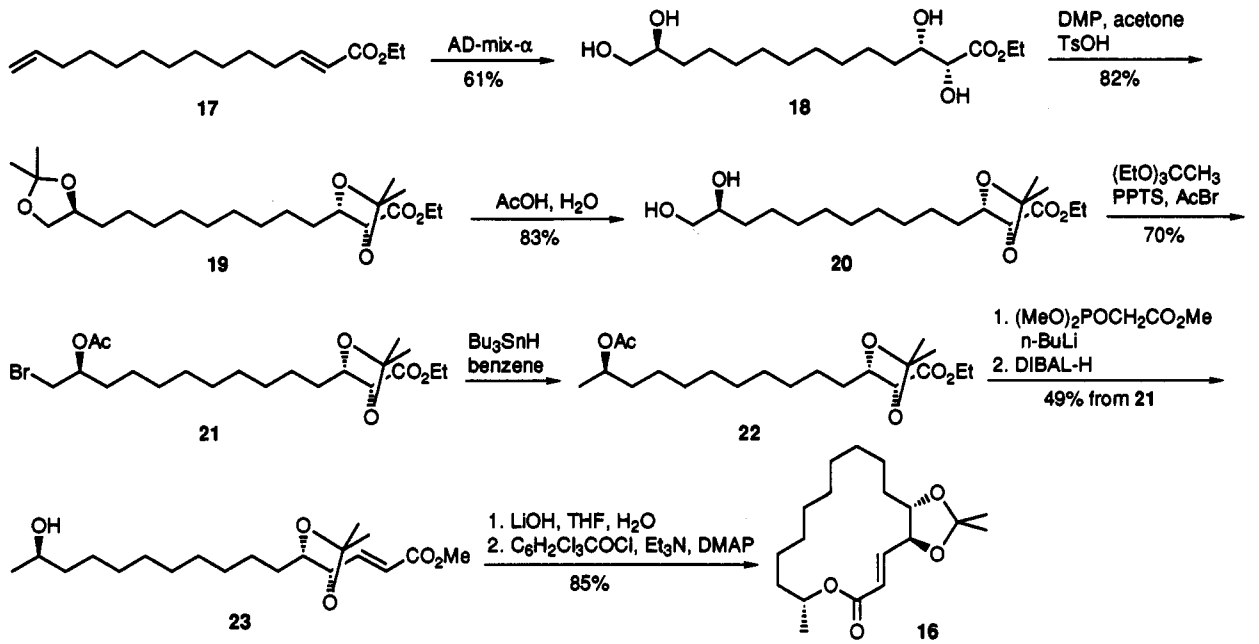
Scheme II



Scheme III



methyl (4*S*,5*S*,15*S*)-4,5,15,16-tetrahydroxyhexadec-2-enoate (**11**) in 53% yield. This tetrol was converted to the bis-acetonide derivative **12** in 86% using dimethoxypropane in acidic acetone. Selective hydrolysis (acetic acid/water) of the less sterically hindered acetonide at positions 15,16 afforded the monoacetonide **13** in 86% yield. The free diol within **13** was converted to the corresponding bromoacetate **14** in 55% yield by treatment with triethyl orthoacetate and catalytic amounts of PPTS followed by acetyl bromide. Debromination with tributyltin hydride afforded the methylcarbinol derivative **15a**. Hydrolysis of both esters within **15a** using LiOH in aqueous THF produced (4*S*,5*S*,15*R*)-trihydroxyhexadec-2-enoic acid-4,5-acetonide (**15b**) in 71% combined yield for both steps. Yamaguchi lactonization[20] of this hydroxy acid using 2,4,6-trichlorobenzoyl chloride and triethylamine (to generate the mixed anhydride) followed by treatment with (dimethylamino)pyridine, furnished the crystalline lactone **16** in 90% yield. Lactone **16** was found to be identical with the compound described by Tatsuta,[16] who had already converted it in 66% yield to (−)-A26771B (**5**) via a three-step sequence, including acid-catalyzed hydrolysis of the acetonide, selective succinylation of the hydroxyl at position 5, and Swern oxidation of the remaining alcohol at position 4.

A key feature in the above-described synthesis is relatively low reactivity of the electron-deficient double bond at position 2 of triene **10** toward the AD reagent. This allowed for clean, regioselective formation of tetrol **11** from an achiral precursor having the entire 16-carbon skeleton of the target macrolide **5**. Another characteristic

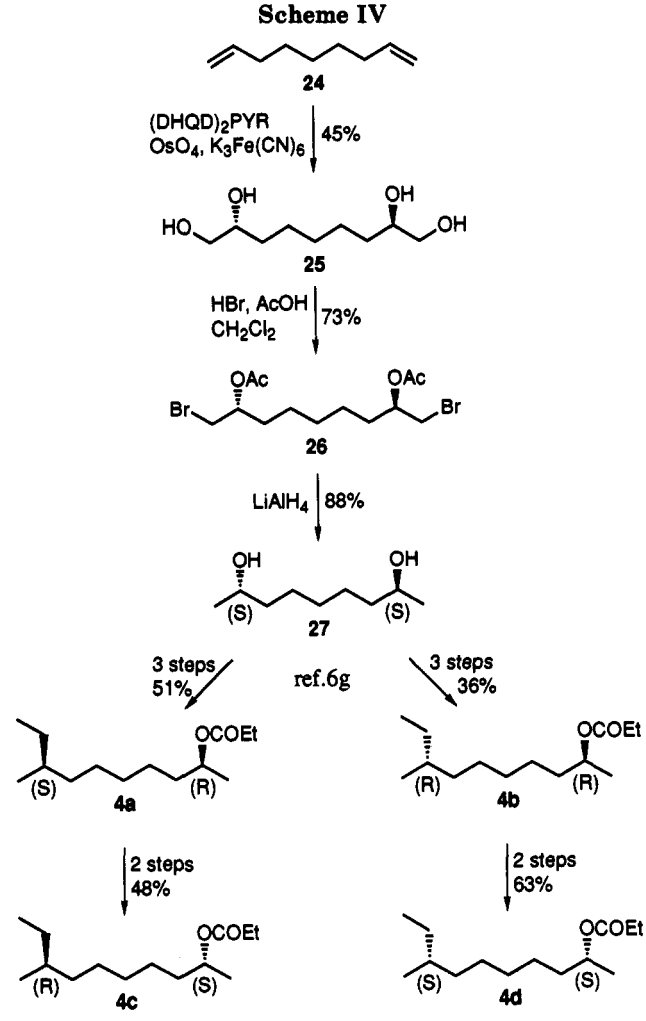
(20) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

of the AD reaction, i.e. the relatively low reactivity of *Z*-disubstituted alkenes, as compared with their *E*-isomers,[21] allowed for the convenient use of an nonpurified **10** (a 9:1 mixture of 4*E*/4*Z* isomers) as a substrate for the production of enantiomerically pure **11**. Nevertheless, we examined an alternative approach to **5** (Scheme III) that starts with diene **17** rather than triene **10**, with the extra double bond being added on a later stage of the synthesis. Reaction of **17** (easily prepared in 82% yield by a Wittig olefination of dodec-11-enal) with AD-mix-α, followed by recrystallization from ethyl acetate, afforded enantiomerically pure methyl (2*R*,3*S*,13*S*)-2,3,13,14-tetrahydroxytetradec-2-enoate (**18**) in 61% yield. Partial protection of this tetrol at the 2,3 positions was carried out as described in the previous approach via formation of the bis-acetonide **19** in 82% yield, followed by selective hydrolysis to give the monoacetonide **20** in 83% yield. The free diol within **20** was converted to the corresponding bromoacetate **21** in 70% yield. Debromination with tributyltin hydride to give **22**, followed by a one-pot, two-carbon homologation procedure, using a Horner–Emmons reagent and DIBAL-H,[22] furnished the unsaturated ester **23** in 49% combined yield for both steps. The latter was obtained as a 92:8 mixture of the *E* and *Z* isomers. Ester hydrolysis with LiOH in aqueous THF followed by Yamaguchi lactonization, as described above, afforded lactone **16** (in 85% yield) possessing pure *E*-geometry.[23] This crude lactone was found (by ^{1}H NMR) to be contaminated with 1.5% of the 15*S* epimer,[16] but a single recrystallization from acetone/ethanol/water produced enantiomerically pure **16**.

WCR Sex Pheromones. The sex pheromone emitted by the female western corn rootworm (WCR), *Diabrotica virgifera virgifera* LeConte, was isolated and identified as 8-methyldec-2-yl propanoate (**4**).[24] Although racemic **4** may be easily prepared,[25] the synthesis of any of the four stereoisomers **4a–d** has been reported to involve many steps, including difficult separation procedures. As is usually the case with aliphatic carbon skeletons which contain essentially noninteracting asymmetric carbon atoms, synthesis of these isomers requires the preparation and cross-coupling of two different chiral building blocks, each containing an appropriate asymmetric center.[26]

Starting with a symmetrical substrate, nona-1,8-diene (**24**) (Scheme IV), and dihydroxylating both double bonds with the same stereoselectivity, using (DHQD)$_2$–PYR,[7b] followed by recrystallization from acetone, generated enantiomerically pure (*R*,*R*)-1,2,8,9-tetrahydroxynonane (**25**) (in 45% yield). Bifunctional chirons having C_2 symmetry, such as **25**, are very useful intermediates, as they do not require selective identification of either end of the molecule. Desymmetrization by modifying any one of the two ends produces a single diastereomer, that may be specifically manipulated. Thus, using the above-described method, tetrol **25** was converted to the bis(bromo acetate) **26** in 73% yield, without interrupting its C_2 symmetry. Finally, reduction of **26** with LiAlH$_4$ furnished (*S*,*S*)-2,8-dihydroxynonane (**27**) in 88% yield.

Scheme IV



We have recently synthesized all four isomers of the WCR pheromones **4a–d** using enzymic methods to produce the same C_2 (*S*,*S*) chiron **27** and then employing copper-mediated cross-coupling methods and alcohol inversion techniques to manipulate its asymmetric centers.[6g] For example, isomers **4a** or **4b** are produced directly from the (*S*,*S*) chiron while isomers **4c** and **4d** are generated from the first two, respectively, by inversion of the carbinol center. Alternatively, isomers **4c** and **4d** may be prepared in a shorter route from the (*R*,*R*) enantiomer of **27**, starting with nonadiene **24** and using AD-mix-α instead of the (DHQD)$_2$–PYR/OsO$_4$/K$_3$Fe(CN)$_6$ mixture. This flexibility of choosing an appropriate catalyst with either enantioselectivity represents a major advantage of the AD methodology over the enzymic approach.

Conclusion

A very convenient, general, asymmetric synthesis of the methylcarbinol functionality from monosubstituted alkenes has been achieved, using the Sharpless asymmetric dihydroxylation reaction. The advantages of this method were demonstrated by highly efficient, asymmetric syntheses on enantiomerically pure natural products. All four stereoisomers of the WCR sex pheromone **4** are prepared in six steps form 1,8-nonadiene. For example, isomers **4a** and **4b** are synthesized in 14.7 and 10.4% overall yield, respectively. Similarly, a highly efficient synthesis of antibiotic (−)-A26771B (**5**) is described. The two alter-

(21) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.
(22) (a) Takacs, J. M.; Helle, M. A.; Seely, F. L. *Tetrahedron Lett.* **1986**, *27*, 1257. (b) Ikemoto, N.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 2524.
(23) Mori, K.; Sakai, T. *Liebigs Ann. Chem.* **1988**, 13.
(24) Guss, P. L.; Tumlinson, J. H.; Sonnet, P. E.; Proveaux, A. T. *J. Chem. Ecol.* **1982**, *8*, 545.
(25) Abrams, S. R.; Shaw, A. C. *J. Chem. Ecol.* **1987**, *13*, 1927.
(26) (a) Mori, K.; Watanabe, H. *Tetrahedron* **1984**, *40*, 299. (b) Sonnet, P. E.; Carney, R. L.; Henrick, C. *J. Chem. Ecol.* **1985**, *11*, 1371. (c) Ferreira, J. T. B.; Simonelli, F. *Tetrahedron* **1990**, *46*, 6311.

native approaches employ achiral starting materials, thus representing the first synthesis of this naturally occurring macrolide where the chiral centers have been generated by asymmetric induction. The first approach (Scheme II) transforms dodecenal into enantiomerically pure **5** in 11 steps and 4.1% overall yield, while the second one (Scheme III) achieves the same transformation in 12 steps and 6.6% overall yield. In comparison, the Tatsuta synthesis[16] converts D-glucose into **5** in 21 steps (not counting the additional steps associated with the convergent nature of the synthetic scheme) and 4.4% overall yield. The Quinkert approach[18] is also 21 steps long, starting from methoxymethyl phenyl ether, with 2.9% overall yield.

Experimental Section

General Methods: ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 and 100 MHz, respectively. Infrared spectra were measured neat. Positive ion mass spectra, using the fast ion bombardment (FIB) technique, were obtained on a VG ZAB-VSE double focusing, high-resolution mass spectrometer equipped with either a cesium or sodium ion gun. Optical rotations were measured in a 1-dm (1 mL) cell using Autopol III automatic polarimeter. TLC was performed on glass sheets precoated with silica gel (Merck, Kieselgel 60, F254, Art. 5715). Column chromatographic separations were performed on silica gel (Merck, Kieselgel 60, 70–230 mesh, Art. 9385) at atmospheric pressure. THF was dried by distillation over sodium benzophenone ketyl. (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) was purchased from Aldrich.

Preparation of Substrates: 2-(Dec-9-enyl)-1,3-dioxolane (6a) was prepared in 90% yield by mixing undec-10-enal with excess ethylene glycol and catalytic amounts of *p*-toluenesulfonic acid in benzene and refluxing overnight with continuous removal of water: ^1H NMR δ 5.81 (m, 1H), 4.99 (br d, *J* = 17.2 Hz, 1H), 4.93 (br d, *J* = 10.4 Hz, 1H), 4.84 (t, *J* = 4.8 Hz, 1H), 3.96 (m, 2H), 3.84 (m, 2H), 2.02 (m, 2H), 1.64 (m, 2H), 1.45–1.20 (m, 12 H). **Ethyl undec-10-enoate (6b)** was purchased from Aldrich. **Dodec-11-enenitrile (6c)** was prepared in two steps from undec-10-en-1-ol in 85% yield: first formation of the tosylate ester with *p*-toluenesulfonyl chloride and pyridine and then treatment with KCN in DMSO at 100 °C for 1 h: ^1H NMR δ 5.81 (m, 1H), 4.99 (m, 1H), 4.93 (m, 1H), 2.33 (t, *J* = 7.1 Hz, 2H), 2.04 (m, 2H), 1.65 (m, 2H), 1.44 (m, 2H), 1.39 (m, 2H), 1.29 (br, 8H); HRMS (FAB) calcd for $C_{12}H_{22}N$ $(M + H)^+$ 180.1752, found 180.1745. **Dodec-11-en-2-one (6d)** was prepared in two steps from undec-10-enal in 80% yield: first treatment with methylmagnesium bromide and then oxidation with PCC in dichloromethane: ^1H NMR δ 5.77 (m, 1H), 4.97 (br d, *J* = 17.1 Hz, 1H), 4.90 (br d, *J* = 11.2 Hz, 1H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.11 (s, 3H), 2.01 (br q, *J* = 6.9 Hz, 2H), 1.54 (m, 2H), 1.35 (m, 2H), 1.26 (br s, 8H); HRMS (FAB) calcd for $C_{12}H_{22}ONa$ $(M + Na)^+$ 205.1568, found 205.1560. **Undec-10-enyl *tert*-butyldimethylsilyl ether (6e)** was prepared in 92% yield from undec-10-enol by treatment with *tert*-butyldimethylchlorosilane and imidazole in DMF: ^1H NMR δ 5.80 (m, 1H), 4.98 (dq, *J* = 17.2, 1.8 Hz, 1H), 4.92 (dq, *J* = 10.2, 1.8 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.03 (br q, *J* = 7.7 Hz, 2H), 1.50 (m, 2H), 1.36 (m, 2H), 1.27 (br s, 10H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 139.19, 114.06, 63.33, 33. 80, 32.86, 29.56, 29.41, 29.11, 28.92, 25.96, 25.77, −5.29; IR (neat) 2927.3, 2855.5, 1641.2, 1466.8, 1255.0 cm^{-1}. **Methyl (*E,E*)-hexadeca-2,4,15-trienoate (10)** was prepared as follows: Compound **6c** (3.58 g, 20 mmol) was dissolved in dry toluene (40 mL). DIBAL-H (1 M in hexane, 24 mL, 24 mmol) was added dropwide at 0 °C, and the mixture was stirred at the same temperature for 3 h and then at 10 °C for 1 h and finally worked up with 3 N HCl and hexane. The organic layer was concentrated and purified on a silica gel column (using 40:1 hexane/ethyl acetate), affording dodec-11-enal (3.12 g, 86%): ^1H NMR δ 9.76 (t, *J* = 2.0 Hz, 1H), 5.79 (m, 1H), 4.98 (br d, *J* = 17.2 Hz, 1H), 4.92 (br d, *J* = 11.6 Hz, 1H), 2.41 (dt, *J* = 7.6, 2.0 Hz, 2H), 2.03 (q, *J* = 7.2 Hz, 2H), 1.62 (m, 2H), 1.37 (m, 2H), 1.28 (br s, 10 H). A solution of methyl(diethylphosphono)crotonate (1.18 g, 5 mmol) in dry THF (5 mL) was added dropwise to a cold (−78 °C) solution of LDA (1.5 M in hexane, 3.35 mL, 5 mmol) in THF (10 mL) and the mixture was stirred for 10 min. A solution of dodec-11-enal (800 mg, 5 mmol) in THF (5 mL) was added dropwise and the mixture was stirred at same temperature for 1 h, allowed to warm to room temperature over 20 min, and then worked up with saturated aqueous ammonium chloride and ether. Purification over a silica gel column afforded compound **10** (580 mg, 44%) which was found to contain 8–10% (by NMR) of the (2*E*,4*Z*) isomer. This mixture was used in the AD reaction without further purification: ^1H NMR δ 7.26 (dd, *J* = 15.6, 10.0 Hz, 1H), 6.14 (m, 2H), 5.82 (m, 2H), 4.99 (dq, *J* = 17.2, 2.0 Hz, 1H), 4.92 (dq, *J* = 11.4, 1.1 Hz, 1H), 3.73 (s, 3H), 2.16 (br q, *J* = 7.2 Hz, 2H), 2.03 (br q, *J* = 8.0 Hz, 2H), 1.40 (m, 4H), 1.27 (br, 10 H); ^{13}C NMR δ 167.68, 145.37, 144.91, 139.13, 128.20, 118.56, 114.06, 51.32, 33.76, 32.95, 29.44, 29.40, 29.35, 29.12, 29.07, 28.87, 28.63; HRMS (FAB) calcd for $C_{17}H_{29}O_2$ $(M + H)^+$ 265.2168, found 265.2175.

Ethyl Tetradeca-2,13-dienoate, (17). A solution of triethyl phosphonoacetate (2.23 g, 10 mmol) in THF (5 mL) was added dropwise to a cold (0 °C) mixture of NaH (60% in mineral oil, 400 mg, 10 mmol) in dry THF (20 mL), and the mixture was stirred for 20 min at the same temperature. A solution of dodec-11-enal (960 mg, 6 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred at the same temperature for 20 min and then worked up with saturated aqueous ammonium chloride. The crude organic extract was purified on a short silica gel column (using 40:1 hexane/ethyl acetate) to give pure **17** in the form of a colorless oil (1.24 g, 82%): ^1H NMR δ 6.96 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.81 (m, 2H), 4.99 (dq *J* = 18.7, 1.6 Hz, 1H), 4.93 (dq, *J* = 10.1, 1.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 2.19 (qd, *J* = 7.0, 1.5 Hz, 2H), 2.04 (q, *J* = 6.8 Hz, 2H), 1.44 (m, 2H), 1.37 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.28 (br s, 10 H); ^{13}C NMR 166.72, 149.40, 139.12, 121.14, 114.07, 60.04, 33.76, 32.15, 29.41, 29.32, 29.08, 29.87, 27.97, 14.23; HRMS (FAB) calcd for $C_{16}H_{29}O_2$ $(M + H^+)$, 253.2168, found 253.2163.

General Method of Dihydroxylation. Monosubstituted alkenes **6** were dihydroxylated following the general procedure described by Sharpless.[7] Enantiomeric purity was determined by conversion of the diol into a bis-Mosher's ester followed by HPLC analysis using a chiral Pirkle 1A column (with 66:1 hexane/2-propanol).

2-[(*R*)-9,10-Dihydroxydecyl]-1,3-dioxolane (7a). Asymmetric dihydroxylation of **6a** (212 mg, 1 mmol) produced **7a** (230 mg, 93%, 89% ee) in the form of a white solid. Recrystallization from cold ether afforded enantiomerically pure **7a** (156 mg, 98% ee): mp 61–63 °C; ^1H NMR δ 4.84 (t, *J* = 4.8 Hz, 1H), 3.97 (m, 2H), 3.85 (m, 2H), 3.67 (m, 1H), 3.62 (dd, *J* = 11.1, 2.7 Hz, 1H), 3.41 (dd, *J* = 11.1, 7.7 Hz, 1H), 2.98 (br s, 2H), 1.65 (m, 2H), 1.41 (m, 4H), 1.29 (br s, 10 H); ^{13}C NMR δ 104.63, 72.28, 66.71, 64.77, 33.86, 33.08, 29.57, 29.45, 29.40, 29.35, 25.51, 24.00; IR (KBr) 3374.3, 2917.4, 2850.9, 1470.6, 1407.6 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{26}O_4Na$ $(M + Na)^+$, 269.1729, found 269.1720.

Ethyl (*R*)-10,11-Dihydroxyundecanoate (7b). Asymmetric dihydroxylation of **6b** (217 mg, 1.02 mmol) produced **7b** (240 mg, 96%, 90% ee). Recrystallization from cold ether afforded enantiomerically pure **7b** (173 mg, >98% ee): mp 58–59 °C; ^1H NMR δ 4.12 (q, *J* = 7.1 Hz, 2H), 3.68 (m, 1H), 3.64 (br d, *J* = 11.0 Hz, 1H), 3.42 (dd, *J* = 11.0, 7.9 Hz, 1H), 2.92 (br s, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 1.61 (m, 2H), 1.42 (m, 2H), 1.30 (br s, 10H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR δ 174.00, 72.26, 66.74, 60.19, 34.32, 33.05, 29.50, 29.32, 29.11, 29.02, 25.48, 24.88, 14.20; IR (KBr) 3486.1, 3255.2, 2925.7, 2852.3, 1734.3, 1470.6 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{26}O_4Na$ $(M + Na)^+$ 269.1729, found 269.1733.

(*R*)-11,12-Dihydroxydodecanenitrile (7c). Asymmetric dihyroxylation of **6c** (179 mg, 1 mmol) produced **7c** (200 mg, 94%, 87% ee). Recrystallization from cold ether afforded enantiomerically pure **7c** (183 mg, 97% ee): mp 63–64 °C; ^1H NMR δ 3.63 (m, 2H), 3.40 (t, *J* = 9.0 Hz, 1H), 3.20 (br d, *J* = 9.3 Hz, 2H), 2.35 (t, *J* = 7.1 Hz, 2H), 1.65 (m, 2H), 1.43 (m, 4H), 1.30 (br s, 10 H); ^{13}C NMR δ 119.87, 72.24, 66.77, 33.01, 29.55, 29.31, 29.16, 28.65, 28.56, 25.50, 25.26, 17.06; IR (KBr) 3478.0, 3239.2, 2920.8, 2851.2, 2247.0, 1467.9 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{23}O_2NNa$ $(M + Na)^+$, 236.1626, found 236.1624.

(*R*)-11-Oxododecane-1,2-diol (7d). Asymmetric dihyroxylation of **6d** (182 mg, 1 mmol) produced **7d** (215 mg, 99%, 86% ee). Recrystallization from cold ether afforded enantiomerically

pure **7d** (174 mg, 97% ee): mp 68–69 °C; ^{1}H NMR δ 3.71 (m, 1H), 3.66 (dd, J = 11.0, 3.0 Hz, 1H), 3.44 (dd, J = 11.0, 7.6 Hz, 1H), 2.42 (t, J = 7.4 Hz, 2H), 2.14 (s, 3H), 2.04 (br, 2H), 1.56 (m, 2H), 1.44 (br s, 3H), 1.29 (br s, 9H); ^{13}C NMR δ 72.24, 66.81, 43.75, 33.11, 29.86, 29.47, 29.24, 29.06, 25.44, 23.76; IR (KBr) 3378.2, 3281.5, 2929.7, 2849.4, 1707.9 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{24}O_3Na$ (M + Na)$^+$ 239.1623, found 239.1633.

(*R*)-10,11-Dihydroxyundecyl *tert*-Butyldimethylsilyl Ether (7e). Asymmetric dihydroxylation of **6e** (284 mg, 1 mmol) produced **7e** (294 mg, 92%, 84% ee) in the form of a colorless oil: ^{1}H NMR δ 3.66 (m, 2H), 3.60 (t, J = 6.7 Hz, 2H), 3.42 (dd, J = 10.7, 7.6 Hz, 1H), 2.58 (br, 1H), 1.50 (m, 2H), 1.43 (m, 3H), 1.28 (br, 12H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR δ 72.32, 66.77, 63.32, 33.12, 32.83, 29.61, 29.53, 29.47, 29.39, 25.96, 25.75, 25.50, −5.28; IR (neat) 3372.3, 2927.6, 2855.1, 1462.9, 1387.6, 1360.5, 1255.0; HRMS (FAB) calcd for $C_{17}H_{38}O_3SiCs$ (M + Cs)$^+$ 451.1641, found 451.1643.

General Method of Bromoacetylation: Method A.[9] Diol 7 (1 mmol) was dissolved in dichloromethane (2 mL) at 0 °C. Solution of HBr (30% in acetic acid, 3 mmol) was slowly added and the mixture was stirred at 0 °C for 3 h and then at room temperature for 15 min. Water was added and the mixture was extracted with dichloromethane. The organic layer was washed with water and dried over sodium sulfate, and solvent was removed under reduced pressure. Filtration over a short silica gel or alumina column produced 8. The latter was found to be contaminated with approximately 3–4% of the isomeric bromo acetate.

Method B.[8] A solution of 7 (1 mmol), triethyl orthoacetate (1.5 mmol), and PPTS (5 mg) in methylene chloride (5 mL) was stirred at 40 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in methylene chloride (2 mL) and cooled to 0 °C, triethylamine (10 μL) and acetyl bromide (1.5 mmol) were added sequentially, and the mixture was stirred at same temperature for 2 h. A saturated solution of sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvent under reduced pressure followed by filtration over a silica gel column afforded 8. The latter was found to be contaminated with approximately 2–3% of the isomeric bromo acetate.

2-[(*R*)-9-Acetoxy-10-bromodecyl]-1,3-dioxolane (8a). Using method B, diol **7a** (97 mg, 0.39 mmol) was converted to **8a** (70 mg, 58%) in the form of a colorless oil: $[\alpha]_D$ +7.8° (c = 1.13, $CHCl_3$); ^{1}H NMR δ 4.98 (m, 1H), 4.83 (t, J = 4.8 Hz, 1H), 3.97 (m, 2H), 3.84 (m, 2H), 3.50 (dd, J = 10.8, 4.5 Hz, 1H), 3.42 (dd, J = 10.8, 5.4 Hz, 1H), 2.08 (s, 3H), 1.64 (m, 4H), 1.40 (m, 2H), 1.28 (br s, 10H); ^{13}C NMR δ 170.40, 104.59, 72.39, 64.84, 34.22, 33.83, 32.44, 29.42, 29.33, 29.21, 24.97, 23.98, 20.99; IR (neat) 2926.6, 2855.8, 1742.0, 1372.0, 1235.0 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{27}O_4BrCs$ (M + Cs)$^+$ 483.0147, found 483.0141.

Ethyl (*R*)-10-Acetoxy-11-bromoundecanoate (8b). Using method A, diol **7b** (50 mg, 0.20 mmol) was converted to **8b** (66 mg, 92%) in the form of a colorless oil: $[\alpha]_D$ +7.49° (c = 1.95, $CHCl_3$); ^{1}H NMR δ 4.99 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.51 (dd, J = 10.8, 4.6 Hz, 1H), 3.43 (dd, J = 10.8, 5.5 Hz, 1H), 2.28 (t, J = 7.5 Hz, 2H), 2.09 (s, 3H), 1.64 (m, 4H), 1.29 (br s, 10H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.77, 170.38, 72.36, 60.10, 34.27, 34.19, 32.41, 29.14, 29.05, 28.99, 24.95, 24.86, 20.98, 14.21; IR (neat) 2929.4, 2855.8, 1738.0, 1464.3, 1372.3 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{27}O_4BrCs$ (M + Cs)$^+$ 483.0147, found 483.0136.

(*R*)-11-Acetoxy-12-bromododecanenitrile (8c). Using method B, diol **7c** (72 mg, 0.34 mmol) was converted to **8c** (90 mg, 83%) in the form of a colorless oil: $[\alpha]_D$ +8.15° (c = 2.4, $CHCl_3$); ^{1}H NMR δ 4.99 (m, 1H), 3.51 (dd, J = 10.8, 4.6 Hz, 1H), 3.39 (dd, J = 10.8, 5.4 Hz, 1H), 2.34 (t, J = 7.1 Hz, 2H), 2.09 (s, 3H), 1.67 (m, 4H), 1.44 (m, 2H), 1.30 (br, 10H); ^{13}C NMR δ 170.43, 119.82, 72.36, 34.22, 32.43, 29.19, 28.56, 25.33, 24.96, 21.00, 17.08; IR (neat) 2928.0, 2855.5, 2244.6, 1740.8, 1461.5, 1426.7, 1236.4 cm^{-1}; HRMS calcd for $C_{14}H_{24}O_2NBrCs$ (M + Cs)$^+$ 450.0045, found, 450.0041.

(*R*)-12-Bromo-11-acetoxydodecan-2-one (8d). Using method A, diol **7d** (53 mg, 0.25 mmol) was converted to **8d** (71 mg, 90%) in the form of a colorless oil: $[\alpha]_D$ +7.77° (c = 2.57, $CHCl_3$); ^{1}H NMR δ 4.99 (m, 1H), 3.51 (dd, J = 10.8, 4.6 Hz, 1H), 3.43 (dd, J = 10.8, 5.5 Hz, 1H), 2.39 (t, J = 7.4 Hz, 2H), 2.11 (s, 3H), 2.07 (s, 3H), 1.67 (m, 2H), 1.58 (m, 2H), 1.28 (br s, 10 H); ^{13}C NMR δ 209.26, 170.41, 72.40, 43.69, 34.20, 32.42, 29.18, 29.15, 29.03, 24.96, 23.72, 20.99; IR (neat) 2928.4, 2855.2, 1741.4, 1716.2, 1462.6, 1371.6, 1236.1 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{25}O_3BrCs$ (M + Cs)$^+$ 453.0041, found 453.0022.

(*R*)-10-Acetoxy-11-bromoundecyl *tert*-Butyldimethylsilyl Ether (8e). Using method B, diol **7e** (100 mg, 0.31 mmol) was converted to **8e** (113 mg, 85%) in the form of a colorless oil: $[\alpha]_D$ +6.85° (c = 3.76, $CHCl_3$); ^{1}H NMR δ 4.99 (m, 1H), 3.59 (t, J = 6.5 Hz, 2H), 3.50 (dd, J = 11.0, 4.4 Hz, 1H), 3.42 (dd, J = 11.0, 5.6 Hz, 1H), 2.09 (s, 3H), 1.67 (m, 2H), 1.50 (m, 2H), 1.28 (br s, 12H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 170.40, 72.41, 63.25, 34.20, 32.82, 32.46, 29.44, 29.34, 29.25, 25.95, 25.73, 25.01, 21.00, −5.27; IR 2927.3, 2855.4, 1744.7, 1471.1, 1371.8, 1234.1 cm^{-1}; HRMS calcd for $C_{19}H_{39}O_3BrSiCs$ (M + Cs)$^+$ 555.0904, found 555.0911.

General Method of Debromination. To a solution of bromoacetate 8 (1 mmol) and AIBN (10 mg) in benzene (5 mL) was added tributyltin hydride (1.2 mmol) dropwise over 30 min, and the mixture was refluxed for an additional 1 h. Solvent was removed under reduced pressure, the residue was dissolved in methylene chloride (5 mL), iodine (3 mmol) was added, and the mixture was stirred at room temperature for 1 h and then washed with water. The organic layer was washed with 10% aqueous sodium thiosulfate, the solvent was removed, and the crude product was passed through a short bed of silica gel to give 9.

2-[(*S*)-10-Acetoxydecyl]-1,3-dioxolane (9a). Debromination of **8a** (58 mg, 0.19 mmol) produced **9a** (27 mg, 57%) in the form of a colorless oil: $[\alpha]_D$ +1.52° (c = 0.79, $CHCl_3$); ^{1}H NMR δ 4.90 (m, 1H), 4.84 (t, J = 4.8 Hz, 1H), 3.97 (m, 2H), 3.85 (m, 2H), 2.03 (s, 3H), 1.66 (m, 2H), 1.57 (m, 1H), 1.47 (m, 1H), 1.41 (m, 2H), 1.25 (br s, 10H), 1.20 (3H, d, J = 6.3 Hz); ^{13}C NMR δ 170.78, 104.65, 71.03, 64.79, 35.91, 33.86, 29.47, 29.38, 29.34, 25.34, 24.02, 21.36, 19.92; IR (neat) 2928.1, 2854.9, 1736.0, 1371.9, 1244.8 cm^{-1}; HRMS calcd for $C_{15}H_{29}O_4$ (M + H)$^+$ 273.2066, found 273.2068.

Ethyl (*S*)-10-Acetoxyundecanoate (9b). Debromination of **8b** (82 mg, 0.23 mmol) produced **9b** (47 mg, 74%) in the form of a colorless oil: $[\alpha]_D$ +1.02° (c = 2.34, $CHCl_3$); ^{1}H NMR δ 4.88 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.03 (s, 3H), 1.59 (m, 3H), 1.45 (m, 1H), 1.28 (br s, 10H), 1.25 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 173.82, 170.73, 71.04, 60.09, 35.84, 34.26, 29.31, 29.25, 29.10, 29.03, 25.31, 24.88, 21.33, 19.90, 14.20; IR (neat) 2977.4, 2931.1, 2856.1, 1736.4, 1463.9, 1372.1 cm^{-1}; HRMS calcd for $C_{15}H_{29}O_4$ (M + H)$^+$ 273.2066, found 273.2066.

(*S*)-11-Acetoxydodecanenitrile (9c). Debromination of **8c** (81 mg, 0.25 mmol) produced **9c** (54 mg, 89%) in the form of a colorless oil: $[\alpha]_D$ +0.78° (c = 2.57, $CHCl_3$); ^{1}H NMR δ 4.89 (m, 1H), 2.34 (t, J = 7.1 Hz, 2H), 2.03 (s, 3H), 1.65 (m, 2H), 1.46 (m, 3H), 1.29 (br s, 11H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 170.78, 119.82, 70.97, 35.85, 29.31, 29.16, 28.69, 28.59, 25.32, 21.37, 19.93, 17.09; IR (neat) 2928.2, 2855.5, 2244.6, 1734.8, 1460.9, 1371.6, 1245.3 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{25}O_2NCs$ (M + Cs)$^+$ 372.0940, found 372.0932.

(*S*)-11-Acetoxydodecan-2-one (9d). Debromination of **8d** (50 mg, 0.15 mmol) produced **9d** (29 mg, 80%) in the form of a colorless oil: $[\alpha]_D$ +1.45° (c = 1.38, $CHCl_3$); ^{1}H NMR δ 4.88 (m, 1H), 2.42 (t, J = 7.5 Hz, 2H), 2.14 (s, 3H), 2.03 (s, 3H), 1.56 (m, 3H), 1.42 (m, 1H), 1.28 (br s, 10H), 1.20 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 209.28, 170.74, 70.96, 43.72, 35.84, 29.30, 29.24, 29.06, 25.31, 23.75, 21.34, 19.90; IR (neat) 2929.7, 2855.2, 1735.1, 1712.8, 1371.3, 1244.7 cm^{-1}; HRMS calcd for $C_{14}H_{27}O_3$ (M + H)$^+$ 243.1960, found 243.1953.

(*S*)-10-Acetoxyundecyl *tert*-Butyldimethylsilyl Ether (9e). Debromination of **8e** (109 mg, 0.26 mmol) produced **9e** (68 mg, 77%) in the form of a colorless oil: $[\alpha]_D$ +1.00° (c = 3.40, $CHCl_3$); ^{1}H NMR δ 4.88 (m, 1H), 3.60 (t, J = 6.6 Hz, 2H), 2.03 (s, 3H), 1.50 (m, 4H), 1.24 (br s, 12H), 1.20 (d, J = 6.3 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 170.75, 71.0, 63.28, 35.89, 32.86, 29.49, 29.43, 29.41, 29.37, 25.95, 25.74, 25.36, 21.36, 19.92, −5.29; IR (neat) 2928.6, 2856.1, 1739.4, 1463.1, 1371.6, 1245.2 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{41}O_3Si$ (M + H)$^+$ 345.2825 (M + H)$^+$, found 345.2833.

Methyl (4*S*,5*S*,15*S*)-4,5,15,16-Tetrahydroxyhexadec-2-enoate (11). A mixture of **10** (520 mg, 2 mmol), AD-mix-α (5.6 g), and methanesulfonamide (190 mg, 2 mmol) in *tert*-butyl alcohol/water (1:1, 80 mL) was stirred at 0 °C for 24 h. Sodium

metabisulfite (6 g) was slowly added and the mixture was extracted with ethyl acetate to give 11 in the form of white solid. This crude product was recrystallized from ethyl acetate (352 mg, 53%): mp 111–112 °C; $[\alpha]_D$ −20.3° (c = 2.0, MeOH); ^{1}H NMR (CD_3OD) δ 7.02 (dd, J = 15.7, 4.7 Hz, 1H), 6.09 (dd, J = 15.7, 1.7 Hz, 1H), 4.16 (td, J = 4.6, 1.7 Hz, 1H), 3.72 (s, 3H), 3.54 (m, 2H), 3.46 (dd, J = 11.1, 4.4 Hz, 1H), 3.40 (dd, J = 11.1, 6.6 Hz, 1H), 1.47 (m, 4H), 1.31 (br s, 14H); ^{13}C NMR (CD_3OD) 168.56, 150.13, 121.76, 74.91, 74.88, 73.22, 67.35, 52.06, 34.40, 33.53, 30.82, 30.69, 30.66, 26.97, 26.67; HRMS (FAB) calcd for $C_{17}H_{32}O_6Cs$ (M + Cs)$^+$ 465.1253, found 465.1254.

Methyl (4*S*,5*S*,15*S*)-4,5,15,16-Tetrahydroxyhexadec-2-enoate Bis-Acetonide, (12). Tetrol 11 (175 mg, 0.53 mmol) was dissolved in a mixture of dimethoxypropane (DMP) (5 mL) and acetone (5 mL) together with and *p*-toluenesulfonic acid (2 mg), and the mixture was stirred at 60 °C for 1 h. Saturated aqueous sodium bicarbonate was added, and the mixture was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure afforded 12 (188 mg, 86%) in the form of a colorless oil: $[\alpha]_D$ −2.11° (c = 1.75, $CHCl_3$); ^{1}H NMR δ 6.88 (dd, J = 15.6, 5.6 Hz, 1H), 6.13 (dd, J = 15.6, 1.2 Hz, 1H), 4.15 (ddd, J = 7.1, 5.7, 1.4 Hz, 1H), 4.08 (m, 1H), 4.03 (t, J = 5.9 Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.50 (t, J = 7.1 Hz, 1H), 1.65 (m, 3H), 1.47 (m, 3H), 1.44 (s, 3H), 1.41 (s, 6H), 1.36 (s, 3H), 1.28 (br, 12H); ^{13}C NMR δ 166.43, 144.54, 122.07, 109.32, 108.52, 80.60, 80.16, 76.12, 69.49, 51.69, 33.56, 32.07, 29.58, 29.41, 29.38, 27.23, 26.92, 26.55, 25.93, 25.68; IR (neat) 2985.3, 2931.6, 2856.0, 1729.9, 1662.4 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{40}O_6Cs$ (M + Cs)$^+$ 545.1879; found 545.1887.

Methyl (4*S*,5*S*,15*S*)-4,5,15,16-Tetrahydroxyhexadec-2-enoate 4,5-Acetonide, (13). A solution of 12 (180 mg, 0.44 mmol) in acetic acid/water (1:1, 10 mL) was stirred at room temperature for 2 h. Solvents were removed under reduced pressure and the residue was purified by passing it through a short silica gel column using hexane/ethyl acetate (1:1) to give 13 (140 mg, 86%) in the form of a colorless oil: $[\alpha]_D$ −10.49° (c = 2.04, $CHCl_3$); ^{1}H NMR δ 6.88 (dd, J = 15.6, 5.6 Hz, 1H), 6.13 (dd, J = 15.6, 1.4 Hz, 1H), 4.15 (ddd, J = 7.1, 5.7, 1.3 Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.70 (m, 2H), 3.42 (dd, J = 11.0, 7.6 Hz, 1 H), 2.73 (br s, 2H), 1.60 (m, 2H), 1.45 (m, 4H), 1.44 (s, 3H), 1.41 (s, 3H), 1.28 (br s, 12H); ^{13}C NMR δ 166.52, 144.59, 122.02, 109.34, 80.62, 80.15, 72.26, 66.74, 51.73, 33.10, 32.05, 29.55, 29.34, 27.25, 26.58, 25.88, 25.50; IR (neat) 3403.9, 2985.7, 2928.5, 2854.2, 1728.3, 1661.6 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{36}O_6Cs$ (M + Cs)$^+$ 505.1566, found 505.1551.

Methyl (4*S*,5*S*,15*S*)-15-Acetoxy-16-bromo-4,5-dihydroxyhexadec-2-enoate 4,5-Acetonide (14). A solution of diol 13 (140 mg, 0.38 mmol), triethyl orthoacetate (107 μL, 0.56 mmol), and pyridinium *p*-toluenesulfonate (PPTS) (2 mg) in CH_2Cl_2 (1 mL) was stirred at 45 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (1 mL) and cooled to 0 °C, acetyl bromide (40 μL) was added, and the mixture was stirred at the same temperature for 2 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with CH_2Cl_2. Removal of the solvent under reduced pressure followed by chromatographic purification (silica gel, hexane/ethyl acetate 9:1) afforded 14 (100 mg, 55%) in the form of colorless oil: $[\alpha]_D$ −17.09° (c = 1.75, $CHCl_3$); ^{1}H NMR δ 6.88 (dd, J = 15.6, 5.6 Hz, 1H), 6.13 (dd, J = 15.6, 1.2 Hz, 1H), 4.99 (m, 1H), 4.15 (ddd, J = 7.1, 5.7, 1.3 Hz, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.59 (dd, J = 10.9, 4.6, Hz, 1H), 3.43 (dd, J = 10.9, 7.6 Hz, 1H), 2.09 (s, 3H), 1.67 (m, 2H), 1.59 (m, 2H), 1.47 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.29 (br s, 12H); ^{13}C NMR δ 170.40, 166.42, 144.53, 122.03, 109.31, 80.65, 80.09, 72.43, 51.72, 34.21, 32.44, 32.05, 29.55, 29.33, 29.21, 27.23, 26.59, 25.91, 24.99, 20.99; IR (neat) 2985.6, 2928.9, 2855.2, 1731.1, 1661.9 cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{37}O_6BrCs$ (M + Cs)$^+$ 609.0828, found 609.0828.

Methyl (4*S*,5*S*,15*R*)-15-Acetoxy-4,5-dihydroxyhexadec-2-enoate 4,5-Acetonide (15a). A solution of 14 (69 mg, 0.14 mmol), tributyltin hydride (0.046 mL, 0.17 mmol), and AIBN (5 mg) in benzene (1 mL) was refluxed for 1 h. Filtration of the reaction mixture over silica gel (hexane/ethyl acetate, 9:1) afforded crude 15a (75 mg, contaminated with traces of organotin compounds), which was taken to the next step without further purification. An analytical sample was prepared by treatment of the crude compound with iodine in CH_2Cl_2 and then with a mixture of DMP, acetone, and catalytic amounts of TsOH: $[\alpha]_D$ −10.97° (c = 1.75, $CHCl_3$). The ^{1}H NMR spectrum of 15a was found to be identical to the reported spectrum of the corresponding mixture of epimers at position 15.[16] HRMS (FAB) calcd for $C_{22}H_{38}O_6Cs$ (M + Cs)$^+$ 531.1723, found 531.1736.

(4*S*,5*S*,15*R*)-15-Acetoxy-4,5-Dihydroxyhexadec-2-enoic Acid 4,5-Acetonide (15b). The crude 15a (75 mg) was treated with a mixture of aqueous LiOH (0.2 M, 1 mL) and THF/H_2O (3:2, 4 mL) for 2 days, acidified with oxalic acid, and filtered over silica gel (hexane/acetone, 3:2) to give 15b (34 mg, 71% from 14): ^{1}H NMR δ 6.96 (dd, J = 15.6, 5.6 Hz, 1H), 6.14 (dd, J = 15.6, 1.6 Hz, 1H), 6.0 (br, 1H), 4.18 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 1.62 (m, 2H), 1.45 (s, 3H), 1.42 (s, 3H), 1.50–1.20 (m, 17H), 1.19 (d, J = 6.4 Hz, 3H).

(4*S*,5*S*,15*R*)-4,5-Dihydroxyhexadec-2-en-15-olide 4,5-Acetonide (16). A solution of acid 15b (34 mg, 0.1 mmol), triethylamine (0.032 mL, 0.23 mmol), and 2,4,6-trichlorobenzoyl chloride (50 mg, 0.2 mmol) in dry THF (1 mL) was stirred at room temperature for 1 h. The mixture was diluted with toluene (20 mL), filtered under argon, and added dropwise (over 6 h) to a hot (90 °C) solution of 4-(*N*,*N*-dimethylamino)pyridine (78 mg, 0.64 mmol) in toluene (10 mL). The mixture was stirred for an additional 1 h, filtered, concentrated, and passed through a short silica gel column with hexane/ethyl acetate, 19:1, affording 16 (29 mg, 90%) in the form of white, fine needles: mp 70–71 °C (lit.[22] 74–75 °C); $[\alpha]_D$ +6.82° (c = 1.05, $CHCl_3$), (lit.[22] +7.0°, c = 1.0, $CHCl_3$); ^{1}H NMR δ 6.89 (dd, J = 15.6, 6.8 Hz, 1H), 6.13 (dd, J = 15.6, 1.2 Hz, 1H), 5.03 (m, 1H), 4.13 (ddd, J = 8.2, 6.8, 1.0 Hz, 1H), 3.76 (td, J = 8.2, 5.3 Hz, 1H), 1.81 (m, 1H), 1.62 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.50–1.15 (br m, 14H), 1.26 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 165.52, 144.32, 123.66, 109.25, 80.86, 80.10, 71.21, 35.31, 31.05, 27.85, 27.27, 27.20, 26.96, 26.59, 26.48, 24.82, 23.33, 20.51.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-tetrahydroxytetradecanoate (18). A solution of 17 (1.14 g, 4.5 mmol), AD-mix-α (12.8 g), and methanesulfonamide (855 mg) in *tert*-butyl alcohol/water (1:1, 134 mL) was stirred at 0 °C for 24 h. Sodium metabisulfite (13.5 g) was added slowly and the mixture was extracted with ethyl acetate. Removal of the solvent under reduced pressure afforded 18 (1.12 g, 77%) in the form of a white solid. The latter was recrystallized from ethyl acetate (880 mg, 61%): mp 95–96 °C; $[\alpha]_D$ −11.13° (c = 2.75, MeOH); ^{1}H NMR δ (CD_3OD) δ 4.21 (qd, J = 7.2, 1.7 Hz, 2H), 4.04 (d, J = 2.8 Hz, 1H), 3.82 (td, J = 6.7, 2.8 Hz, 1H), 3.56 (m, 1H), 3.46 (dd, J = 11.1, 4.5 Hz, 1H), 3.40 (dd, J = 11.1, 6.6 Hz, 1H), 1.55 (m, 2H), 1.47 (m, 3H), 1.32 (br s, 13H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD) δ 174.73, 74.85, 73.69, 73.25, 67.39, 62.16, 34.43, 34.21, 30.83, 30.67, 26.91, 26.69, 14.51; HRMS (FAB) calcd for $C_{16}H_{32}O_6Na$ (M + Na)$^+$, 343.2097, found 343.2100.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-Tetrahydroxytetradecanoate Bisacetonide (19). Tetrol 18 (640 mg, 2 mmol) and *p*-toluenesulfonic acid acid (10 mg) were dissolved in a 1:1 mixture (20 mL) of 2,2-dimethoxypropane and acetone and stirred at 60 °C for 1 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvent under reduced pressure afforded 19 (650 mg, 82%) in the form of a colorless oil: $[\alpha]_D$ −2.64° (c = 4.63, $CHCl_3$); ^{1}H NMR δ 4.24 (qd, J = 7.2, 2.0 Hz, 2H), 4.14–4.01 (m, 4H), 3.50 (t, J = 7.2 Hz, 1H), 1.74 (m, 1H), 1.64 (m, 2H), 1.50–1.20 (m, 15H), 1.47 (br s, 3H), 1.44 (br s, 3H), 1.41 (br s, 3H), 1.35 (br s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 170.95, 110.64, 108.49, 79.15, 76.09, 69.46, 61.21, 33.54, 33.47, 29.58, 29.41, 29.37, 27.13, 26.90, 25.70, 25.60, 25.56, 14.12; IR (neat) 2984.4, 2928.4, 2854.7, 1758.2, 1730.7, 1454.1, 1368.7 cm^{-1}; Anal. Calcd for $C_{22}H_{40}O_6$, C, 65.97; H, 10.07. Found: C, 65.80; H, 9.81.

Ethyl (2*R*,3*S*,13*S*)-2,3,13,14-Tetrahydroxytetradecanoate 2,3-Acetonide (20). Compound 19 (400 mg, 1 mmol) was dissolved in a 1:1 mixture (10 mL) of acetic acid and water and stirred at room temperature for 2 h. Solvents were removed under reduced pressure, and the residue was passed through a short silica gel column using 1:1 hexane/ethyl acetate to give 20 (300 mg, 83%) in the form of a colorless oil: $[\alpha]_D$ −12.66° (c = 1.39, $CHCl_3$); ^{1}H NMR δ 4.24 (qd, J = 7.1, 2.2 Hz, 2H), 4.11 (m, 2H), 3.70 (m, 1H), 3.65 (dd, J = 11.0, 3.0 Hz, 1H), 3.43 (dd, J = 11.0, 7.6 Hz, 1H), 2.05 (br s, 2H), 1.70 (m, 2H), 1.50–1.20 (m, 16H), 1.47 (s, 3H), 1. 44 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 171.01, 110.65, 79.02, 72.23, 66.63, 61.26, 33.44, 33.01, 29.60,

29.47, 29.42, 29.38, 27.10, 25.55, 14.09; IR (neat) 3391.4, 2984.9, 2926.0, 2853.1, 1753.3, 1732.9, 1455.9 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{36}O_6Na$ $(M + Na)^+$ 383.2410, found 383.2408.

Ethyl (2*R*,3*S*,13*S*)-13-Acetoxy-14-bromo-2,3-dihydroxytetradecanoate 2,3-Acetonide (21). Compound **20** (262 mg, 0.81 mmol), triethyl orthoacetate (314 mg, 1.94 mmol), and PPTS (10 mg) were dissolved in methylene chloride (1 mL) and stirred at 45 °C for 1 h. Solvents were removed under reduced pressure, the residue was dissolved in methylene chloride (1 mL) and cooled to 0 °C, acetyl bromide (0.10 mL) was added, and the mixture was stirred at the same temperature for 2 h. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with methylene chloride. Removal of solvents under reduced pressure and purification over a silica gel column, using 9:1 hexane/ethyl acetate, afforded **21** (294 mg, 79%): $[\alpha]_D$ −17.62° (c = 2.02, $CHCl_3$); ^1H NMR δ 4.99 (m, 1H), 4.24 (qd, J = 7.2, 2.0 Hz, 2H), 4.11 (m, 2H), 3.51 (dd, J = 10.8, 4.4 Hz, 1H), 3.43 (dd, J = 10.8, 5.6 Hz, 1H), 2.09 (s, 3H), 1.67 (m, 4H), 1.50–1.20 (m, 14H), 1.46 (s, 3H), 1.44 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 170 .96, 170.38, 110.64, 79.16, 79.09, 72.42, 61.23, 34.19, 33.47, 32.44, 29.41, 29.33, 29.21, 27.14, 25.62, 24.98, 20.98, 14.14; IR (neat) 2984.3, 2927.0, 2853.5, 1742.7, 1459.9, 1370.5 cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{37}O_6BrCs$ $(M + Cs)^+$ 597.0825, found 597.0816.

Ethyl (2*R*,3*S*,13*R*)-13-Acetoxy-2,3-dihydroxytetradecanoate Acetonide (22). Compound **21** (294 mg, 0.63 mmol) and AIBN (10 mg) were dissolved in benzene (5 mL). A solution of tributyltin hydride (0.20 mL, 0.76 mmol) in benzene (1 mL) was added slowly over 10 min, and the mixture was refluxed for 60 min and then passed through a short silica gel column (with hexane/ethyl acetate, 9:1) to give crude **22** (210 mg, contaminated with traces of organotin compounds), which was taken to next step without further purification. An analytical sample of **22** was prepared as described above for compound **15a**: $[\alpha]_D$ −11.63° (c = 1.69, $CHCl_3$); ^1H NMR δ 4.89 (m, 1H), 4.25 (qd, J = 7.1, 2.2 Hz, 2H), 4.11 (m, 2H), 2.03 (s, 3H), 1.75–1.20 (m, 18H), 1.47 (br s, 3H), 1.44 (br s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H); ^{13}C NMR δ 170.97, 170.74, 110.65, 79.09, 70.99, 61.24, 35.86, 33.48, 29.44, 29.39, 27.14, 25.61, 25.31, 19.91, 14.13; HRMS (FAB) calcd for $C_{21}H_{38}O_6Na$ $(M + Na)^+$ 409.2566, found 409.2564.

Methyl (4*S*,5*S*,15*R*)-4,5,15-Trihydroxyhexadec-2-enoate 4,5-Acetonide (23). *n*-BuLi (2.5 M in hexane, 1.17 ml, 2.92 mmol) was added dropwise to a cold (−78 °C) solution of trimethyl phosphonoacetate (531 mg, 2.92 mmol) in dry CH_2Cl_2 (10 ml) and the mixture was stirred at the same temperature for 0.5 h. Solution of compound **22** (210 mg, crude) in CH_2Cl_2 (1 mL) was added slowly, the mixture was stirred for 1 h, and then DIBAL-H (1 M in hexane, 3 mL, 3 mmol) was added dropwise over 2 h. The mixture was stirred for 16 h, allowing it to warm up to room temperature, and then refluxed for 1 h and finally quenched with saturated aqueous NH_4Cl. It was then extracted with ether, filtered over Celite, and purified over a silica gel column (hexane/ethyl acetate, 4:1) to give **23** (110 mg, 49% from **21**). This product, which was found (by NMR) to be a 92:8 mixture of E/Z isomers, was taken to the next step without further purification: ^1H NMR δ 6.88 (dd, J = 15.6, 5.7 Hz, 1H), 6.13 (dd, J = 15.6, 1.4 Hz, 1H), 4.15 (ddd, J = 7.2, 5.7, 1.4 Hz, 1H), 3.78 (m, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 1.58 (m, 5H), 1.44 (s, 3H), 1.41 (s, 3H), 1.50–1.25 (br m, 14 H), 1.19 (d, J = 6.2 Hz, 3H); ^{13}C NMR δ 166.48, 144.58, 122.12, 109.34, 80.62, 80.18, 68.10, 51.72, 39.33, 32.08, 29.58, 29.51, 29.41, 29.38, 27.24, 26.60, 25.91, 25.73, 23.46 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{36}O_5Cs$ $(M + Cs)^+$ 489.1614, found 489.1623.

Conversion of 23 to 16. Compound **23** (110 mg, 0.31 mmol) was hydrolyzed to **15b** using LiOH in aqueous THF, as described above for compound **15a**. Following the above-described Yamaguchi lactonization procedure, the resultant hydroxy acid **15b** was converted to crystalline **16** (85 mg, 85% combined yield for both steps).

(*R*,*R*)-1,2,8,9-Tetrahydroxynonane (25). Sodium ferricyanide (9.88 g), K_2CO_3 (4.15 g), $(DHQD)_2$-PYR[7b] (80 mg) and OsO_4 (0.2 M in toluene, 0.1 mL) were mixed in *tert*-butyl alcohol/water (1:1, 200 mL), at 0 °C. Nona-1,8-diene (620 mg, 5 mmol) was added, and the mixture was stirred at 0 °C for 24 h and then quenched with sodium metabisulfite (15 g). The mixture was saturated with sodium chloride, extracted with 2-propanol, and dried over K_2CO_3. Removal of the solvent under reduced pressure and recrystallization from acetone afforded **25** (434 mg, 45%): mp 74–76 °C; $[\alpha]_D$ +19.08° (c = 2.10, MeOH); ^1H NMR (CD_3OD) δ 3.56 (m, 2H), 3.46 (dd, J = 11.1, 4.4 Hz, 2H), 3.40 (dd, J = 11.1, 6.6 Hz, 2H), 1.50 (m, 4H), 1.36 (br s, 6H); ^{13}C NMR δ 73.21, 67.36, 34.36, 30.87, 26.63; IR (KBr) 3485.6, 3385.8, 2928.3, 2853.6, 1473.4 cm^{-1}; HRMS (FAB) calcd for $C_9H_{20}O_4Na$ 215.1259, found 215.1259.

(*R*,*R*)-2,8-Diacetoxy-1,9-dibromononane (26). Compound **25** (460 mg, 2.4 mmol) was dissolved in methylene chloride (5 mL). A solution of HBr (30% in AcOH, 4.5 mL) was added dropwise at 0 °C and the mixture was stirred at same temperature for 1 h. Water was added and the mixture was extracted with ether, washed with brine, and dried over sodium sulfate. Solvent was removed under reduced pressure and the residue was passed through a silica gel or alumina columns, using hexane/ethyl acetate (19:1), affording **26** (704 mg, 73%). The latter was found to be contaminated with 3–4% of isomeric products: ^1H NMR δ 5.00 (m, 2H), 3.50 (dd, J = 10.8, 4.6 Hz, 2H), 3.43 (dd, J = 10.8, 5.4 Hz, 2H), 2.10 (s, 6H), 1.68 (br q, J = 6.8 Hz, 4H), 1.33 (br s, 6H); ^{13}C NMR δ 170.42, 72.23, 34.12, 32.31, 28.93, 24.82, 21.00; IR (neat) 2937.3, 2859.9, 1739.7, 1372.2, 1233.6 cm^{-1}; HRMS calcd for $C_{13}H_{22}O_4Br_2Cs$ $(M + Cs)^+$ 532.8939, found 532.8916.

(*S*,*S*)-2,8-Dihydroxynonane (27). Compound **26** (200 mg, 0.5 mmol) was dissolved in ether/THF (1:1, 5 mL). $LiAlH_4$ (114 mg, 3 mmol) was added slowly at 0 °C and the mixture was stirred at 0 °C for 2 h, and then refluxed for 16 h. The mixture was cooled to room temperature, quenched with wet ether, dried over sodium sulfate, filtered, and washed with ethyl acetate. Removal of solvents under reduced pressure followed by purification over a silica gel column, using 1:1 hexane/ethyl acetate, afforded **27** (70 mg, 88%). The latter was found to be contaminated with 3–4% of isomeric products. This compound was found to be identical (by $[\alpha]_D$, ^1H NMR, ^{13}C NMR, IR, and HRMS) to an authentic sample obtained from TBADH-catalyzed reduction of nonane-2,8-dione.[6g]

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of 7a–e, 8a–e, 9a–e, 11–14, 16, and 18–22 (50 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

A Mechanistic Study of 2-Vinylbenzimidazole Formation from 2-(2′-Haloethyl)benzimidazoles. Synthesis of Highly Electron-Rich Vinylic Compounds by General Base and Specific Acid–General Base Catalysis

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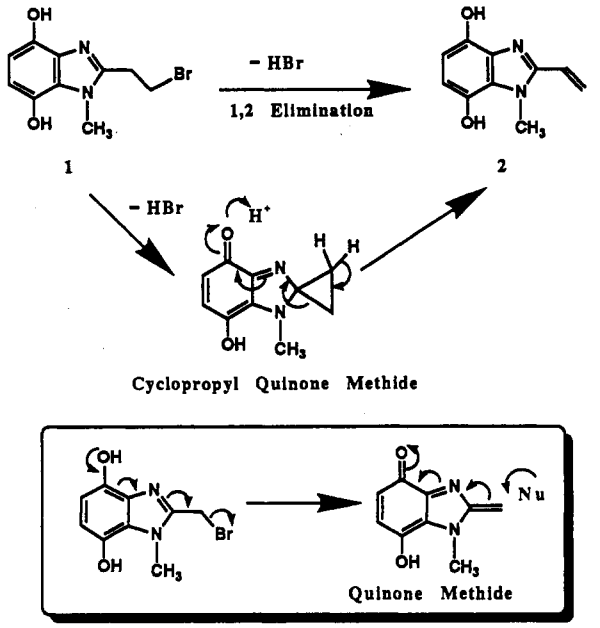
The mechanism of halide elimination from 2-(haloethyl)-1-methyl-4,7-dihydroxybenzimidazole was studied in aqueous buffer by means of a pH-rate profile, buffer dilution studies, and ^{13}C scrambling. It was anticipated that a spiro-fused cyclopropyl species could arise from the above benzimidazole derivative by loss of HX. However, the results of our studies were consistent with both the general base and the specific acid/general base-catalyzed 1,2-elimination of HX. Since the loss of the leaving group occurs in the same transition state as proton abstraction, the elimination mechanism is of the "E2" type. The specific acid/general base process permits facile elimination reactions in acidic (pH < 6) media. Thus, protonation of the benzimidazole nitrogen (specific acid) at low pH electrostatically favors proton abstraction by the general base (acetate and phosphate).

Introduction

This laboratory has been involved with mechanistic studies of the formation and fate of benzimidazole-based quinone methides, inset of Chart I.[2] Quinone methide chemistry is of general interest since many naturally occurring quinones can form this alkylating species upon two-electron reduction and leaving group elimination.[3] Our interest in benzimidazole-based quinone methides stems from the success in designing both a new antitumor agent[4] and a new xanthine oxidase inhibitor[5] based on this ring system. We wondered if a "cyclopropyl quinone methide", analogous to the A-ring of CC1065,[6] can form by leaving group elimination from the hydroquinone species 1 in Chart I.[7] Like the quinone methide species, the cyclopropyl species should be an alkylating agent.[8] In the present article, we report on the elimination chemistry of 1.

Contrary to the above expectation, the elimination chemistry of 1 actually involves "E2-type" 1,2 elimination processes[9] rather than HBr elimination via the cyclopropyl species. A ^{13}C scrambling study was used to verify that the formation of 2 does not involve a symmetric intermediate, Chart I. We were intrigued by the facility of HBr elimination from 1, even in solutions with pH values far below neutrality. Strong base is usually employed in the preparation of 2-vinylbenzimidazoles by elimination.[10] Our indepth mechanistic study, which utilized a pH-rate profile and a Brønsted plot, revealed that the elimination mechanism involves general base-catalyzed proton abstraction from the C(1′)-position of the protonated benzimidazole as well as general base-catalyzed proton abstraction from the C(1′)-position of the neutral benzimidazole. Elimination by the first process (specific acid–general base catalysis) results in an energetically favorable transition state wherein anion development occurs on a positively charged system.

Chart I



Results and Discussion

Synthesis. The preparation of 1 and 2 and the ^{13}C-scrambling study are discussed below in conjunction with Charts II–IV. Preparation of 2 was carried out starting

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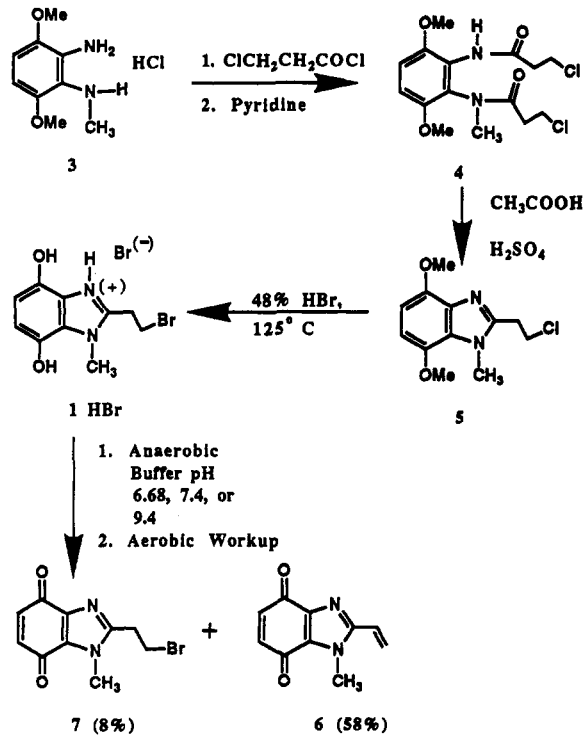
Chart II



with the known diamine hydrochloride **3**, Chart II. The acylation of **3** with 3-chloropropionyl chloride afforded the diacyl product **4**. Monoacylation of **3** was not possible even under mild conditions due to the high reactivity of this very electron-rich diamine.

Heating **4** in sulfuric acid/acetic acid afforded **5** as a result of monodeacylation of **4** followed by rapid closure to afford the imidazo ring. One-pot demethylation and exchange of chloride with bromide was possible by refluxing **5** in 48% HBr. The hydrobromide salt of **1** crystallized from this reaction in pure form. Reaction of **2** in anaerobic buffered solutions held at pH 6.68, 7.4, or 9.4 and then aerobic workup afforded the vinylic quinone **6** and a trace amount of **7** resulting from the oxidation of unreacted starting material. This range of pH values covers the pH range (5–9) of our kinetic study of elimination. The required incubation time of **2** in anaerobic buffer depends on pH and the concentration of buffer. At pH values above neutrality, the 1,2 HBr elimination from **1** is very slow and incubation times are up to 24 h. For example, a reaction run at pH 10 resulted in small amount of elimination along with substantial decomposition. At pH values lower than 7, in the presence of high buffer species (acetate or phosphate buffers > 0.2 M), eliminations are complete in a matter of hours. The specific acid-general base catalytic mechanism is responsible for the facile elimination below neutrality, whereas the less-favorable general base mechanism is responsible for elimination at high pH (*vide infra*, next section).

When the elimination of HBr from **2** was carried out in deuterated buffer (pD = 7.05 phosphate buffer), both **6** and **7** were found to have no deuterium incorporation at the C(1′) position (or at any other position). The absence of deuterium incorporation at this position indicates that proton abstraction in the course of 1,2 elimination of HBr from **1** must be irreversible.

The isolation of the alkene hydroquinone **2** was possible by treatment of **1** with sodium hydride in tetrahydrofuran,

Chart III

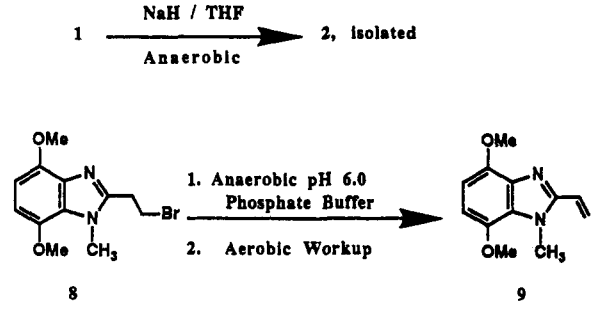


Chart III. Although **2** is rapidly oxidized to **6** in aerobic solutions, solid **2** could be stored in the air for a period of days.

In order to assess the role of the hydroquinone moiety on product formation, the methoxy derivative **8** was subject to HBr elimination in phosphate buffer, Chart III. The vinylic benzimidazole **9** was obtained in 75% yield. It is noteworthy that **9** was not obtained if oxygen was present during the incubation in phosphate buffer, perhaps due to the oxidation of **9**. The formation of **9** from **8** indicates that hydroxyl groups are not required for elimination to occur.

In order to dismiss the presence of the cyclopropyl intermediate on the elimination reaction path, we prepared the $^{13}C(1')$-labeled analogue of **16** from **10**, Chart IV. The reactions shown in Chart 4 afforded **16** without any scrambling of the label. Elimination of HBr from **16** in anaerobic buffer followed by aerobic workup afforded **17** and **18** also without scrambling of the label. The assessment of ^{13}C scrambling was possible from the ^{13}C–^{1}H coupling patterns of the compounds shown in Chart IV.

Kinetic Studies. The rates of HBr elimination from **1** were measured in aqueous buffer over the pH range of 5–9 at 30.0 ± 0.2 °C under strict anaerobic conditions. The progress of the reaction was monitored by following absorbance changes at 260 nm. All absorbance vs time(s) plots were fit to a first-order rate law for over five half-lives of the reaction. The observed first-order rate constants (k_{obsd}, s^{-1}) obtained from these plots were found to be highly dependent on the concentration of buffer employed to hold pH. Buffer catalysis contributed greatly below pH 7, but was not apparent much above this pH value.

The buffer dilution plots shown in Figure 1 were made in order to determine k_{lyate} values as well as the second-order rate constants for general acid and general base catalysis. Extrapolation of the k_{obsd} vs [buffer] plots shown in Figure 1 to zero buffer provided as the y-intercept the values of k_{lyate} (i.e. the term pertaining to catalysis by H^+, HO^-, and H_2O). Shown in Figures 2 is the plot of log k_{lyate} vs pH representing the pH-rate profile for HBr elimination from **1**. The +2 slope of this plot below pH 6 indicates that a total of two proton dissociations (or their equivalent) must be involved in the rate-determining step for elimination. Above pH 7, the acid dissociations are complete and therefore the k_{lyate} values are independent of pH.

When the bromide leaving group of **1** was changed to chloride (**1(Cl)**), rate constants for elimination decreased by 10-fold. Thus, the rate-determining step for alkene formation must involve halide elimination[11] as well as the two proton transfers indicated by the pH-rate profile. The mechanism for the conversion of **1** and **2** must