JOC*Note*

A Practical Synthesis of the F-Ring of Halichondrin B via Ozonolytic Desymmetrization of a C_2-Symmetric Dihydroxycyclohexene

Lei Jiang, Joseph R. Martinelli, and Steven D. Burke*

Department of Chemistry, University of Wisconsin−Madison, 1101 University Avenue, Madison, Wisconsin 53706-1396

burke@chem.wisc.edu

Received August 9, 2002

Abstract: C_2-symmetric dihydroxycyclohexene **1** was desymmetrized via a one-pot Criegee ozonolysis/acylation protocol to afford acetal-lactone **2**. Installation of the allyl side chain on the convex face of the bicyclic system and subsequent reduction provided the desired tetrahydrofuran **4** with the correct relative and absolute stereochemistries. Simple functional group manipulations led to the desired F-ring module **3** of halichondrin B.

Halichondrin B (Figure 1) is the most potent member of the halichondrin family of anticancer agents isolated from marine sponges.[1] The mechanism of action involves the binding of the vinca domain of tubulin, resulting in the inhibition of tubulin polymerization and tubulin dependent GTP hydrolysis.[2] On the basis of its potential as an antitumor agent, the National Cancer Institute has recommended halichondrin B for stage A preclinical trials.[2d,3] Synthetically, halichondrin B possesses a number of interesting structural features including a contiguous C1−C54 carbon chain containing 32 stereocenters, a unique 2,6,9-trioxatricyclo[3.3.2.0^{3,7}]decane "cage" ring system, and a 22-membered macrolactone with a *trans*-2,5-disubstituted THF ring (F-ring). Synthetic efforts have been devoted to halichondrin B by several groups,[4]

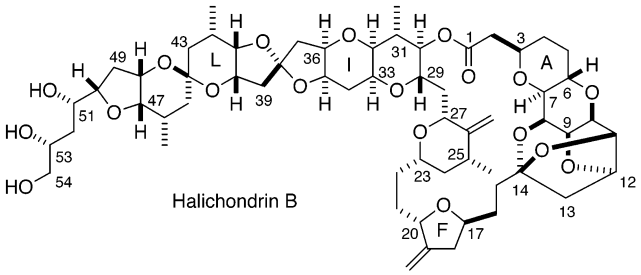
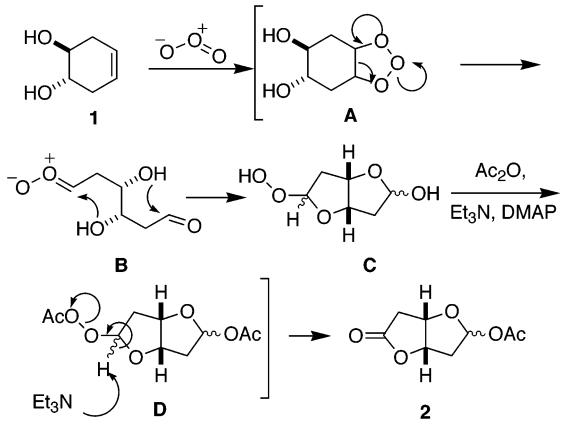


FIGURE 1. Structure of halichondrin B.

SCHEME 1. Mechanism for the Proposed One-Pot Ozonolysis/Terminus Differentiation



highlighted by Kishi's total synthesis.[5a] We have recently reported an efficient synthesis of the F-ring module[5] of halichondrin B via a palladium-mediated, ligand-controlled desymmetrization of a C_2-symmetric diol diacetate.[4i] Herein, we present an alternative, practical route for the same segment of halichondrin B.

Ozone is a versatile oxidizing agent that has been used extensively in organic synthesis as a result of the seminal work of Rudolf Criegee, initiated over 50 years ago.[6] In

* To whom correspondence should be addressed.

(1) For isolation, see: (a) Hirata, Y.; D. *Pure Appl. Chem*. **1986**, *58*, 701. (b) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rutzler, K. C. *J. Med. Chem*. **1991**, *34*, 3339. (c) Pettit, G. R.; Ichihara, Y.; Wurzel, G.; Williams, M. D.; Schmidt, J. M.; Chapuis, J. C. *J. Chem. Soc., Chem. Commun*. **1995**, 383. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem*. **1993**, *58*, 2538. (e) Pettit, G. R.; Gao, F.; Doubek, D. L.; Boyd, M. R.; Hamel, E.; Bai, R.; Schmidt, J. M.; Tackett, L. P.; Rutzler, K. C. *Gazz. Chim. Ital*. **1993**, *123*, 371. (f) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett*. **1994**, *35*, 9435.

(2) For biological activities, see: (a) Hamel, E. H. *Pharmacol. Ther*. **1992**, *55*, 31. (b) Bai, R.; Paull, K. D.; Herald, C. L.; Malspeis, L.; Pettit, G. R.; Hamel, E. H. *J. Biol. Chem*. **1991**, *266*, 15882. (c) Luduena, R. F.; Roach, M. C.; Prasad, V.; Pettit, G. R. *Biochem. Pharmacol*. **1993**, *45*, 421. (d) Pettit, G. R. *Pure Appl. Chem*. **1994**, *66*, 2271.

(3) (a) Personal correspondence with Ernest Hamel, M.D., Ph.D., Senior Investigator, Laboratory of Molecular Pharmacology, Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute, NIH. Dr. Hamel informed us that halichondrin B was effective in vivo against human tumors transplanted into immunodeficient nude mice. (b) Personal correspondence with Michael R. Boyd, M.D., Ph.D., Chief, Laboratory of Drug Discovery Research and Development, NCI Cancer Research Center, Frederick, MD. Dr. Boyd shared with us his data and slides that resulted in the NCI Decision Network Committee's selection of halichondrin B for drug development.

(4) For synthetic effort from the Burke group, see: (a) Burke S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett*. **1994**, *35*, 703. (b) Burke S. D.; Jung, K. W.; Lambert, W. T.; Phillips, J. R.; Klovning, J. J. *J. Org. Chem*. **2000**, *65*, 4070. (c) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett*. **1991**, *32*, 3961−3964. (d) Burke S. D.; Zhang, G.; Buchanan, J. L. *Tetrahedron Lett*. **1995**, *36*, 7023. (e) Burke S. D.; Phillips, J. R.; Quinn, K. J.; Zhang, G.; Jung, K. W.; Buchanan, J. L.; Perri, R. E. In *Anti-infectives: Recent Advances in Chemistry and Structure−Activity Relationships*; Bentley, P. H., O'Hanlon, P. J., Eds.; Royal Society of Chemistry: Cambridge, UK, 1997; p 73. (f) Burke S. D.; Quinn, K. J.; Chen, V. J. *J. Org. Chem*. **1998**, *63*, 8626. (g) Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem*. **1998**, *63*, 6770. (h) Austad, B. C.; Hart, A. C.; Burke, S. D. *Tetrahedron* **2002**, *58*, 2011. (i) Jiang, L.; Burke, S. D. *Org. Lett*. **2002**, *4*, 3411. For a complete listing of synthetic efforts toward halichondrin B from other groups, see ref 4i.

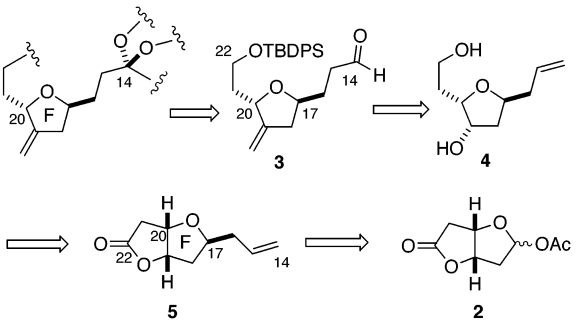
(5) For synthetic efforts toward the F-ring module of halichondrin B, see: (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc*. **1992**, *114*, 3162. (b) Horita, K.; Nagasawa, M.; Hachiya, S.; Yonemitsu, O. *Synlett* **1994**, 40−43. (c) Horita, K.; Sakurai, Y.; Nagasawa, M.; Yonemitsu, O. *Chem. Pharm. Bull*. **1997**, *45*, 1558−1572.

(6) . For reviews, see: (a) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1; 1982; Vol. 2. (b) Odinokov, V. N.; Tolstikov, G. A. *Russ. Chem. Rev*. **1981**, *50*, 636.

(7) Criegee, R.; Banciu, A.; Kaul, H. *Chem. Ber*. **1975**, *108*, 1642.

10.1021/jo026302w CCC: $25.00
Published on Web 12/31/2002

SCHEME 2. Retrosynthetic Analysis



1975, he reported the intramolecular trapping of carbonyl oxide with a hydroxyl group in a favorable position.[7] Later, Schreiber described a modified workup procedure for the ozonolysis of cyclic alkenes to afford a variety of open-chain products with differentiated terminal functionality,[8] including an acetal-ester. We envisioned that the application of Schreiber's protocol to a substrate with two hydroxyl groups at the appropriate positions would lead to the formation of a bicyclic acyloxy acetal-lactone. The proposed mechanism of this transformation is shown in Scheme 1. Fragmentation of the primary ozonide **A** leads to the desymmetrized intermediate **B** with one carbonyl terminus and a carbonyl oxide at the other end. Intramolecular five-membered hemiacetal formation with the appropriate hydroxyls would be followed by acylation to give **D**, and elimination of acetic acid would furnish the bicyclic acyloxy acetal-lactone **2**.

Retrosynthetically (Scheme 2), the F-ring of halichondrin B is viewed as a bridge between C1−C13 and C23−C36 subunits of the molecule. C14 and C22 are envisioned as the points of the attachment via structure **3**. Aldehyde **3** should be readily accessible from **4** via straightforward transformations. Lactone **5** should be available from the bicyclic hemiacetal derivative **2** via a Lewis acid promoted allylation reaction, which was expected to occur preferentially from the convex face of the bicyclic ring, thereby providing the desired stereochemistry at C17.

(*S*,*S*)-Dihydroxycyclohexene **1**[9] was synthesized from known (*S*,*S*)-4,5-dihydroxy-octa-1,7-diene[10] via a ring-closing metathesis (RCM) reaction with use of Grubbs' catalyst[11] (Scheme 3). Initially, attempted ozonolysis of the C_2-symmetric cyclohexene diol **1** with Schreiber's conditions gave a mixture of acyloxy acetal-lactone, hemiacetal-lactone, and a small amount of bis-hemiacetal. Employment of excess acetic anhydride and addition of DMAP gave a more satisfactory result, allowing the isolation of the desired acyloxy acetal-lactone **2a,b** in 75% yield as a separable (4:1) mixture of diastereomers. This mixture was subjected to Lewis acid promoted allylation to give an isolable (1:2) mixture of the allylation products.[12] NOE experiments on both minor product *epi*-**5** and major product **5** were performed to identify the desired product (Figure 2). The H_b of the minor product showed

SCHEME 3

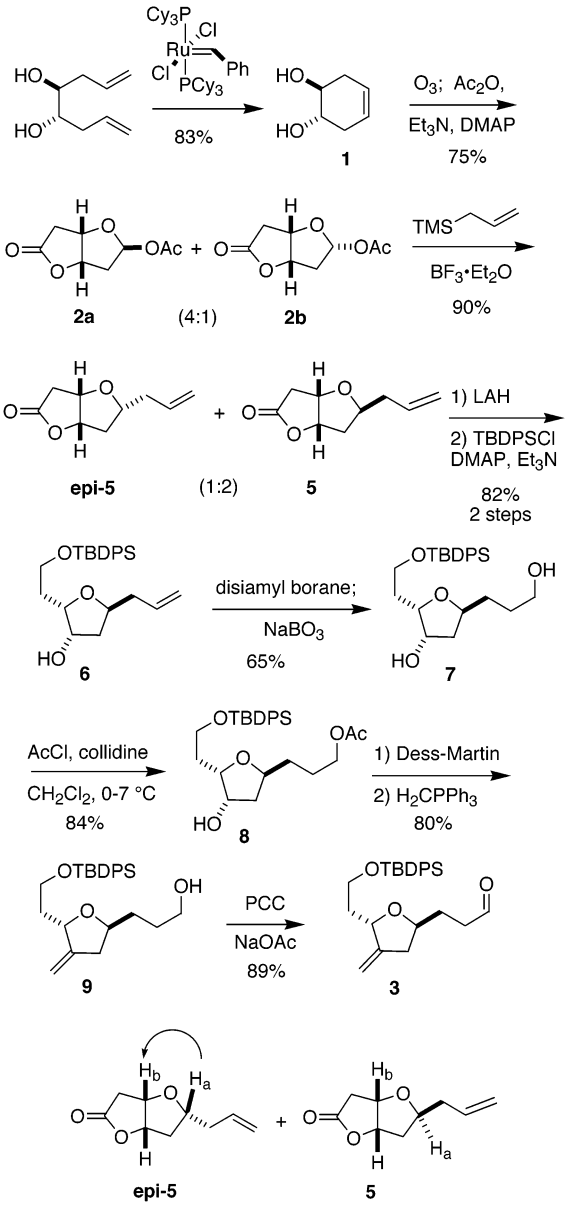


FIGURE 2. NOE study on compounds *epi*-**5** and **5**.

significant NOE when H_a was irradiated, while major product did not show any enhancement between H_a and H_b. It is important to note that **5**, with electrophilic functionality at C22, can be viewed as a potential coupling partner with C23 of the middle fragment of halichondrin B. Lactone **5** was initially treated with 9-BBN to functionalize the double bond, but lactone reduction occurred at the same time. To avoid this complication, lactone **5** was reduced with lithium aluminum hydride to provide the corresponding diol **4**. Selective silylation was achieved following Hernandez's procedure to give *tert*-butyldiphenylsilyl (TBDPS) ether **6**.[13] Subsequent hydroboration of the terminal alkene pro-

(8) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(9) Suemune, H.; Hasegawa, A.; Sakai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 55.

(10) Koert, U.; Stein, M.; Wagner, H. *Chem. Eur. J.* **1997**, *3*, 1170.

(11) For a recent review, see: Grubbs, R. H.; Trnka, T. M. *Acc. Chem. Res.* **2001**, *34*, 18.

(12) When the allylation was performed on pure **2b**, a 5:1 (**5**:*epi*-**5**) mixture of diastereomers was obtained, suggesting partial involvement of an ion pair mechanism rather than solely through the oxonium ion that would be derived from either substrate diastereomer. Varying the reaction temperature did not affect stereoselectivity.

ceeded uneventfully with disiamyl borane, and oxidative workup with $NaBO_3$[14] gave primary alcohol **7**. Selective monoacylation of the primary hydroxyl with AcCl/2,6-lutidiene furnished the secondary alcohol **8**. Dess−Martin periodinane[15] oxidation was followed by a one-pot Wittig methylenation/deacylation reaction giving the primary alcohol **9**.[16] Buffered PCC oxidation provided **3**, the desired F-ring segment of halichondrin B, which was identical with the substance provided via the alternate sequence.[4i]

In summary, a one-pot ozonolysis/acylation desymmetrization reaction has been employed to provide bicyclic acyloxy acetal-lactones **2a,b**, which contain a tetrahydrofuran nucleus ideally functionalized for conversion in eight steps to the C14−C22, F-ring segment **3** of halichondrin B. Segment couplings and completion of the synthesis are underway.

Experimental Section

General Procedures. The solvents used in reactions were dried prior to use. All other reagents were used as received without purification. All moisture-sensitive reactions were performed in flame-dried and/or oven-dried glassware under a positive pressure of nitrogen unless otherwise noted. Thin-layer chromatography was carried out with glass TLC plates precoated with silica gel 60 F254. Flash column chromatography was accomplished with silica gel 60 (230−400 mesh). High-resolution mass spectra (HRMS) with electrospray ionization (ESI) were measured with a TOF analyzer. Proton nuclear magnetic resonance spectra were recorded in deuterated solvents at either 300 or 500 MHz. Carbon nuclear magnetic resonance spectra were recorded in deuterated solvents at 75 MHz. Infrared spectra were measured on an FT-IR spectrometer equipped with a DTGS detector. Optical rotations, for which concentrations (*c*) are reported in g/100 mL, were measured on a digital polarimeter at room temperature with a Na lamp.

Preparation of Cyclohex-4-ene-1,2-diol (1). To a refluxing solution of (*S*,*S*)-4,5-dihydroxy-octa-1,7-diene[10] (0.54 g, 3.8 mmol) in 330 mL of benzene was added Grubbs' catalyst (0.16 g, 0.02 mmol) in 50 mL of benzene via syringe pump over a period of 1 h. The solution was stirred at reflux for 4.5 h. After the reaction mixture was cooled to room temperature, *N*-methyl morpholine *N*-oxide (0.2 g, 1.6 mmol) was added and the reaction mixture was stirred for an additional 2 h, then, the resulting dark solution was filtered through a pad of silica gel and the filtrate was concentrated in vacuo. FCC (50% hexanes/Et_2O) furnished 0.36 g (3.16 mmol, 83%) of the cyclic diol **1** as a crystalline solid. ^{1}H NMR (CD_3OD) δ_H 5.55−5.52 (m, 2H), 3.63−3.57 (m, 2H), 2.50−2.35 (m, 2H), 2.10−1.95 (m, 2H); ^{13}C NMR (CD_3OD) δ_C 125.3 (2 × CH), 72.4 (2xCH), 34.0 (2 × CH_2); IR (KBr pellet) 3346, 3043, 2932, 2898, 2838, 1657, 1441, 1349, 1278, 1056, 680 cm^{-1}; $[\alpha]^{24}_D$ +99.0° (*c* 1.0, $CHCl_3$); mp reported 100−102 °C,[9] observed 99−101 °C.

Preparation of Lactone-Acetates 2a and 2b. A solution of diol **1** (0.44 g, 3.8 mmol) in ethyl acetate (190 mL) at −78 °C was purged with ozone until the solution turned blue. The system was then purged with N_2 for approximately 10 min or until the blue color disappeared. To this solution were added slowly (approximately 30 min each) via syringe pump Ac_2O (2.36 g, 23.2 mmol) and Et_3N (3.8 g, 38.0 mmol), and stirring was continued at −78 °C for 10 min prior to the addition of DMAP (0.2 g, 1.8 mmol). The reaction mixture was allowed to warm to room temperature and stir overnight. It was then quenched with $NaHCO_3$ and extracted with ethyl acetate (3 × 100 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated. FCC (Et_2O) furnished 0.52 g (2.85 mmol, 75%) of fused lactones **2a** and **2b** (**2a**/**2b** = 4/1) as crystalline solids. **2a**: ^{1}H NMR ($CDCl_3$) δ_H 6.36 (dd, *J* = 6.0, 2.0 Hz, 1H), 5.09 (ddd, *J* = 6.0, 4.0, 2.0 Hz, 1H), 4.83 (td, *J* = 4.0, 2.0 Hz, 1H), 2.75−2.65 (m, 2H), 2.56 (ABMX, *J* = 15.5, 7.5, 2.0 Hz, 1H), 2.40 (ABMX, *J* = 15.5, 7.0, 2.0 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$) δ_C 174.4 (C), 170.0 (C), 98.0 (CH), 82.1 (CH), 78.9 (CH), 39.3 (CH_2), 35.4 (CH_2), 20.9 (CH_3); IR (thin film) 3029, 2988, 2969, 2941, 1773, 1725, 1386, 1255, 1190, 1154, 1118, 1012 cm^{-1}; $[\alpha]^{24}_D$ −142.5° (*c* 0.88, $CHCl_3$); HRMS (ESI) calculated for $C_9H_{14}O_6Na$ ($MNaMeOH^+$) 241.0688, found 241.0689; mp 68−70 °C. **2b**: ^{1}H NMR ($CDCl_3$) δ_H 6.39 (d, *J* = 4.5 Hz, 1H), 5.19 (t, *J* = 6.0 Hz, 1H), 5.0 (dt, *J* = 6.0, 1.0 Hz, 1H), 2.83 (ABX, *J* = 19.0, 6.0 Hz, 1H), 2.73 (ABX, *J* = 19.0, 1.0 Hz, 1H), 2.53 (AB, *J* = 15.0 Hz, 1H), 2.28 (ABMX, *J* = 15.0, 6.0, 4.5 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 173.8 (C), 170.1 (C), 98.3 (CH), 81.7 (CH), 80.0 (CH), 39.1 (CH_2), 37.3 (CH_2), 21.2 (CH_3); IR (KBr pellet) 3028, 2929, 2899, 1774, 1728, 1380, 1254, 1174, 1062, 1110 cm^{-1}; $[\alpha]^{24}_D$ −23.3° (*c* 0.18, $CHCl_3$); HRMS (ESI) calculated for $C_9H_{14}O_6Na$ ($MNaMeOH^+$) 241.0688, found 241.0679; mp 61−63 °C.

Preparation of Compound 5. To a solution of lactone-acetates **2a** and **2b** (0.44 g, 2.4 mmol) in CH_3CN (25 mL) at 0 °C was added trimethylallylsilane (0.69 g, 6.0 mmol) followed by $BF_3{\cdot}Et_2O$ (0.4 g, 2.9 mmol). The reaction mixture was stirred at 0 °C for 20 min then warmed to room temperature and stirred for an additional 2 h. The reaction was quenched with a saturated solution of NH_4Cl, extracted with EtOAc (3 × 50 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated. FCC (50% hexanes/Et_2O) furnished 0.36 g (2.14 mmol, 90.0%) of *epi*-**5** and **5** as colorless oils. *epi*-**5**: ^{1}H NMR ($CDCl_3$) δ_H 5.74 (ddt, *J* = 17.0, 11.0, 7.0 Hz, 1H), 5.13−5.03 (m, 2H), 4.99 (ddd, *J* = 7.0, 4.0, 2.0 Hz, 1H), 4.51 (app q, *J* = 4.0 Hz, 1H), 4.01 (quin, *J* = 7.0 Hz, 1H), 2.70 (d, *J* = 3.0 Hz, 2H), 2.45−2.24 (m, 3H), 1.93 (ABMX, *J* = 14.0, 8.0, 2.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 175.4 (C), 133.7 (CH), 117.8 (CH_2), 84.5 (CH), 79.4 (CH), 78.5 (CH), 39.7 (CH_2), 37.5 (CH_2), 36.4 (CH_2); IR (thin film) 3077, 2978, 2928, 2867, 1780, 1642, 1350, 1157, 1073, 917 cm^{-1}; $[\alpha]^{24}_D$ −38.6° (*c* +19.0, $CHCl_3$); HRMS (ESI) calculated for $C_9H_{12}O_3Na$ (MNa^+) 191.0684, found 191.0676. **5**: ^{1}H NMR ($CDCl_3$) δ_H 5.76 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1H), 5.14−5.05 (m, 3H), 4.80 (ddd, *J* = 4.5, 1.5, 1.0 Hz, 1H), 4.14 (d app q, *J* = 11.0, 6.0 Hz, 1H), 2.74 (ABX, *J* = 18.5, 6.0 Hz, 1H), 2.65 (ABX, *J* = 18.5 1.0 Hz, 1H), 2.39−2.29 (m, 3H), 1.72 (ABX, *J* = 14.0, 10.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 176.0 (C), 133.6 (CH), 117.8 (CH_2), 84.7 (CH), 77.7 (CH), 77.5 (CH), 38.8 (CH_2), 38.2 (CH_2), 36.6 (CH_2); IR (thin film) 3077, 2978, 2929, 2872, 1772, 1646, 1340, 1176, 1150, 1068, 1034, 901 cm^{-1}; $[\alpha]^{24}_D$ +48.4° (*c* 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_9H_{12}O_3Na$ (MNa^+) 191.0684, found 191.0694.

Preparation of Compound 6. To a suspension of LAH (200 mg, 4.28 mmol) in 10 mL of THF at 0 °C was added a solution of lactone **5** (360 mg, 2.14 mmol) in THF (10 mL). The resulting mixture was stirred for 2 h at which point TLC showed the reaction was complete. The reaction was cautiously quenched with saturated NH_4Cl. The aqueous layer was extracted with EtOAc (4 × 40 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated. FCC (EtOAc) furnished diol **4** (0.35, g 2.03 mmol, 95%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ_H 5.78 (ddt, *J* = 13.5, 10.0, 8.0 Hz, 1H), 5.13−5.02 (m, 2H), 4.36−4.23 (m, 2H), 3.97 (td, *J* = 7.0, 3.0 Hz, 1H), 3.92−3.80 (m, 1H), 3.77−3.67 (m, 1H), 2.65 (br, 1H), 2.53−2.17 (m, 3 H), 2.06 (ABMX, *J* = 13.5, 6.0, 1.0 Hz, 1H), 1.99−1.86 (m, 2 H), 1.78 (ABMX, *J* = 14.0, 10.0, 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ_C 134.4 (CH), 117.2 (CH_2), 82.3 (CH), 76.6 (CH), 73.5 (CH), 60.3 (CH_2), 40.4 (CH_2), 40.1 (CH_2), 31.3 (CH_2); IR (thin film) 3434, 3077, 2929, 1635, 1558, 1456, 1339, 1260, 1200, 1063, 999, 914 cm^{-1}; $[\alpha]^{24}_D$ −8.9° (*c* 1.3, $CHCl_3$); HRMS (ESI) calculated for $C_9H_{16}O_3Na$ (MNa^+)195.0997, found 195.0968.

To a mixture of alcohol **4** (130 mg, 0.75 mmol), DMAP (3.7 mg, 0.03 mmol), and Et_3N (83 mg, 0.83 mmol) in CH_2Cl_2 (7 mL)

(13) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 99.
(14) Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *J. Org. Chem.* **1989**, *54*, 5930.
(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
(16) Sharma, G. V. M.; Vepachedu, S. R.; Chandrasekhar, S. *Synth. Commun.* **1990**, *20*, 3403.

was added TBDPSCl (236 mg, 0.83 mmol). The reaction mixture was stirred at room temperature overnight, then it was quenched with H_2O and extracted with diethyl ether (3 × 40 mL), and the combined organics were dried with Na_2SO_4 and concentrated. FCC (50% Et_2O/hexanes) afforded 262 mg (0.64 mmol, 86%) of silyl ether **6** as an oil. **^{1}H NMR** ($CDCl_3$) δ_H 7.69−7.63 (m, 4H), 7.56−7.33 (m, 6H), 5.80 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H), 5.14−5.02 (m, 2H), 4.43−4.38 (m, 1H), 4.32 (dq, J = 10.0, 6.0 Hz, 1H), 3.99 (ddd, J = 10.0, 6.5, 3.0 Hz, 1H), 3.77 (ABMX, J = 10.0, 4.5, 3.5 Hz, 1H), 3.63 (ABMX, J = 10.0, 10.0, 3.0 Hz, 1H), 3.31 (br, 1H), 2.42−2.20 (m, 2H), 2.19−2.03 (m, 2H), 1.95−1.74 (m, 2H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 135.5 (4 × CH), 134.5 (CH), 132.6 (C), 132.5 (C), 129.9 (2 × CH), 127.8 (4 × CH), 117.0 (CH_2), 82.1 (CH), 76.5 (CH), 73.0 (CH), 61.3 (CH_2), 40.2 (CH_2), 40.1 (CH_2), 31.9 (CH_2), 26.7 (3 × CH_3), 19.0 (C); IR (thin film) 3448, 3071, 2929, 2857, 1640, 1428, 1082, 1008, 702 cm^{-1}; $[\alpha]^{24}_D$ +3.9° (*c* 3.5, $CHCl_3$); HRMS (ESI) calculated for $C_{25}H_{34}O_3SiNa$ (MNa^+) 433.2175, found 433.2158.

Preparation of Compound 7. To a solution of 2-methyl-2-butene (3.95 mL of 2.0 M, 7.9 mmol) was added 3.95 mL of THF to dilute the solution to 1.0 M. The resulting solution was cooled to 0 °C and BH_3·SMe_2 (2.0 mL of 2M, 4 mmol) was added. This mixture was allowed to stir at 0 °C for 1 h, then it was transferred to a solution of alkene **6** (550 mg, 1.34 mmol) in THF (10 mL) at 0 °C via cannula. The resulting mixture was allowed to stir overnight before it was quenched with a saturated solution of $NaBO_3$. The aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organics were dried with Na_2SO_4, filtered, and concentrated. FCC (EtOAc) furnished diol **7** (0.37 g, 0.86 mmol, 65%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.68−7.60 (m, 4H), 7.48−7.32 (m, 6H), 4.43−4.37 (m, 1H), 4.32−4.20 (m, 1H), 4.00 (ddd, J = 10.0, 5.0, 4.0 Hz, 1H), 3.76 (ABMX, J = 11.0, 5.0, 4.0 Hz, 1H), 3.70−3.55 (m, 3 H), 3.32 (d, J = 2 Hz, 1H), 2.62 (t, J = 5.0 Hz, 1H), 2.20−2.03 (m, 2H), 1.93−1.51 (m, 6H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 135.5 (4 × CH), 132.6 (C), 132.4 (C), 130.0 (2 × CH), 127.9 (4 × CH), 82.1 (CH), 77.4 (CH), 73.0 (CH), 62.9 (CH_2), 61.2 (CH_2), 41.0 (CH_2), 32.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 26.8 (3 × CH_3), 19.0 (C); IR (thin film) 3399, 3070, 2929, 2857, 1456, 1111, 1008, 701 cm^{-1}; $[\alpha]^{24}_D$ −1.7° (*c* 1.0, $CHCl_3$); HRMS (ESI) calculated for $C_{25}H_{36}O_4SiNa$ (MNa^+) 451.2281, found 451.2270.

Preparation of Compound 8. To a solution of diol **7** (0.19 g 0.44 mmol) in dry CH_2Cl_2 (5 mL) was added collidine (235 mg, 2.2 mmol). The mixture was cooled to 0 °C, followed by the addition of a solution of acetyl chloride (36.3 mg, 0.46 mmol) in CH_2Cl_2 (1 mL) via syringe pump over a period of 10 min. After being stirred at this temperature for 2 h, the reaction mixture was allowed to warm to 7 °C and stirred overnight. The reaction was quenched with 5% HCl(aq) and EtOAc. The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. FCC (50% Et_2O/hexanes) gave pure acetate **8** (174 mg, 0.37 mmol, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ_H 7.68−7.59 (m, 4H), 7.46−7.34 (m, 6H), 4.39 (m, 1H), 4.23 (d app q, J = 7.0, 2.5 Hz, 1H), 4.07 (t, J = 6.5 Hz, 2H), 3.97 (ddd, 9.0, 5.0, 3.0 Hz, 1H), 3.77 (ABX_2, J = 10.0, 4.0 Hz, 1H), 3.62 (ABMX, J = 10.0, 10.0, 2.5 Hz, 1H), 3.29 (br, 1H), 2.19−2.04 (m, 2H), 2.02 (s, 3H), 1.92−1.24 (m, 6H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 171.1 (C), 135.5 (4 × CH), 132.6 (C), 132.4 (C), 129.9 (2 × CH), 127.8 (4 × CH), 81.8 (CH), 76.7 (CH), 73.0 (CH), 64.4 (CH_2), 61.3 (CH_2), 40.8 (CH_2), 32.3 (CH_2), 31.9 (CH_2), 26.7 (3 × CH_3), 25.3 (CH_2), 20.9 (CH_3), 18.9 (C); IR (thin film) 3455, 3061, 2945, 2908, 2868, 1727, 1464, 1439, 1367, 1349, 1225, 1109, 815, 702 cm^{-1}; $[\alpha]^{24}_D$ −1.1° (*c* 2.4, $CHCl_3$); HRMS (ESI) calculated for $C_{27}H_{38}O_5SiNa$ (MNa^+) 493.2396, found 493.2386.

Preparation of Compound 9. To a solution of alcohol **8** (90 mg, 0.19 mmol) in dry CH_2Cl_2 (3 mL) was added 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (180 mg, 0.4 mmol) at room temperature. The solution was stirred for 3 h until TLC showed completion of the reaction. It was diluted with Et_2O, filtered through a short pad of silica gel, and concentrated. Purification by FCC (50% Et_2O/hexanes) gave the corresponding ketone (84 mg, 0.18 mmol, 95%) as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.68−7.63 (m, 4H), 7.45−7.33 (m, 6H), 4.34−4.24 (m, 1H), 4.18 (dd, J = 8.0, 5.5 Hz, 1H), 4.14−4.03 (m, 2H), 3.86−3.70 (m, 2H), 2.61 (ABX, J = 18.0, 7.0 Hz, 1H), 2.21 (ABMX, J = 18.0, 7.0, 1.0 Hz, 1H), 2.03 (s, 3H), 1.96−1.59 (m, 6H), 1.01 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 216.4 (C), 171.0 (C), 135.5 (4 × CH), 133.6 (C), 133.5 (C), 129.6 (2 × CH), 127.6 (4 × CH), 76.0 (CH), 74.8 (CH), 64.0 (CH_2), 59.6 (CH_2), 42.4 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 26.8 (3 × CH_3), 24.8 (CH_2), 20.9 (CH_3), 19.2 (C); IR (thin film) 3070, 2955, 2857, 1744, 1739, 1472, 1428, 1363, 1239, 1182, 1111, 703 cm^{-1}; $[\alpha]^{24}_D$ −19.6° (*c* 1.9, $CHCl_3$); HRMS (ESI) calculated for $C_{27}H_{38}O_5SiNa$ (MNa^+) 493.2396, found 493.2386.

A suspension of methyltriphenylphosphonium bromide (90 mg, 0.25 mmol) in dry THF (1 mL) was treated with *n*-BuLi (0.1 mL, 0.25 mmol, 2.5 M solution in hexane) under N_2 at 0 °C. The resulting yellow solution was allowed to stir at room temperature for 30 min, then it was cooled to −78 °C. A solution of the ketone from above (28 mg, 0.06 mmol) in dry THF (0.5 mL) was added slowly and the reaction mixture was stirred at −78 °C for 2 h before it was allowed to warm to room temperature. Stirring was continued for 4 h before quenching with saturated aqueous NH_4Cl. The aqueous layer was extracted with Et_2O three times, and the combined organics were dried ($MgSO_4$) and concentrated. Purification by FCC (70% Et_2O/hexanes) gave pure **9** (20 mg, 0.048 mmol, 84%). ^{1}H NMR ($CDCl_3$) δ_H 7.70−7.63 (m, 4H), 7.45−7.31 (m, 6H), 4.94 (q, J = 3.0 Hz, 1H), 4.80 (q, J = 3.0 Hz, 1H), 4.66−4.58 (m, 1H), 3.95 (quin, J = 8.5 Hz, 1H), 3.87−3.71 (m, 2H), 3.62 (t, J = 6.0 Hz, 2H), 2.62 (ABM app X_3, J = 18.5, 6.0, 2.0 Hz, 1H), 2.31−2.18 (m, 2H), 1.90−1.51 (m, 6H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$) δ_C 151.5 (C), 135.6 (4 × CH), 134.0 (C), 133.9 (C), 129.5 (2 × CH), 127.6 (4 × CH), 104.8 (CH_2), 76.8 (CH), 76.6 (CH), 62.8 (CH_2), 60.7 (CH_2), 38.9 (CH_2), 38.2 (CH_2), 32.0 (CH_2), 29.6 (CH_2), 26.9 (3× CH_3), 19.2 (C); IR (thin film) 3478, 3152, 2946, 2909, 2865, 1466, 1439, 1390, 1365.0, 1248, 1196, 1110, 1049, 699 cm^{-1}; $[\alpha]^{24}_D$ −22.9° (*c* 1.2, $CHCl_3$) HRMS (ESI) calculated for $C_{26}H_{36}O_3SiNa$ (MNa^+) 447.2331, found 447.2310.

Preparation of Aldehyde 3. To a suspension of PCC (21.6 mg, 0.08 mmol) and sodium acetate (21.6 mg) in 1 mL of CH_2Cl_2 was added a solution of alcohol **9** (17 mg, 0.04 mmol) in 0.5 mL of CH_2Cl_2. The resulting mixture was stirred for an additional 3 h then diluted with diethyl ether and filtered through a pad of silica gel. FCC (30% hexanes/Et_2O) furnished 15 mg (0.036 mmol, 89%) of **3** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 9.74 (t, J = 1.5 Hz, 1H), 7.69−7.60 (m, 4H), 7.44−7.31 (m, 6H), 4.93 (q, J = 2.0 Hz, 1H), 4.81 (q, J = 2.0 Hz, 1H), 4.60−4.51 (m, 1H), 3.94 (quin, J = 6.5 Hz, 1H), 3.82−3.70 (m, 2H), 2.64 (ABM app X_3, J = 16.0, 7.0, 2.0 Hz, 1H), 2.53 (ABM_2X, J = 17.5, 7.0, 1.5 Hz, 1H), 2.45 (ABM_2X, J = 17.5, 7.0, 1.5 Hz, 1H), 2.23 ($ABXM_2R$, J = 16.0, 7.0, 2.0, 1.0 Hz, 1H), 1.80 (t, J = 7.0 Hz, 2H), 1.80−1.68 (m, 2H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 202.0 (CH), 151.3 (C), 135.6 (4 × CH), 133.9 (2 × C), 129.5 (2 × CH), 127.6 (4 × CH), 105.0 (CH_2), 76.5 (CH), 76.0 (CH), 60.7 (CH_2), 40.4 (CH_2), 38.5 (CH_2), 38.2 (CH_2), 27.5 (CH_2), 26.8 (3 × CH_3), 19.2 (C); IR (thin film) 3070, 2949, 2930, 2856, 1725, 1428, 1110, 1083 cm^{-1}; $[\alpha]^{24}_D$ −55.0 ° (*c* 0.5, $CHCl_3$); HRMS (ESI) calculated for $C_{26}H_{34}O_3SiNa$ (M + Na^+) 445.2175, found 445.2179. These data matched those of **3** prepared by an alternate route.[4i]

Acknowledgment. William D. Thomas is acknowledged for running the NOE experiment**.** We thank the NIH [Grant CA74394 (S.D.B.)] for generous support of this research. The NIH (1 S10 RR08389-01) and NSF (CHE-9208463) are acknowledged for their support of the NMR facilities of the University of Wisconsin−Madison Department of Chemistry.

Supporting Information Available: Spectra (^{1}H NMR, ^{13}C NMR) for compounds **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026302W