A Short, Enantioselective Synthesis of the AB-Ring Substructure of the Brevetoxins via *endo*-Selective Alkynol Cycloisomerization

Mark M. Gleason and Frank E. McDonald*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113

Received April 2, 1997

Introduction

The brevetoxin family of marine natural products is of considerable interest due to their biological activities as potent neurotoxins, as well as the relatively complex polycyclic ether skeletons of these compounds.[1] The brevetoxin-type structures generally possess a *trans*−*syn*−*trans* arrangement of fused cyclic ethers, except for ring A in which the terminal alkyl substituent is *anti*, as represented in the simplest member of this family, hemibrevetoxin B (**1**).[2] We have considered a unique synthetic approach to hemibrevetoxin which features cyclization of an alkynyl alcohol **B** to the isomeric enol ether **A** (Figure 1), but this strategy requires regioselective formation of endocyclic products rather than the kinetically favored exocyclic isomers.

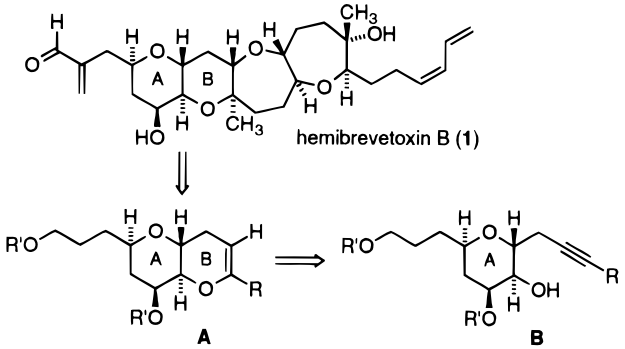
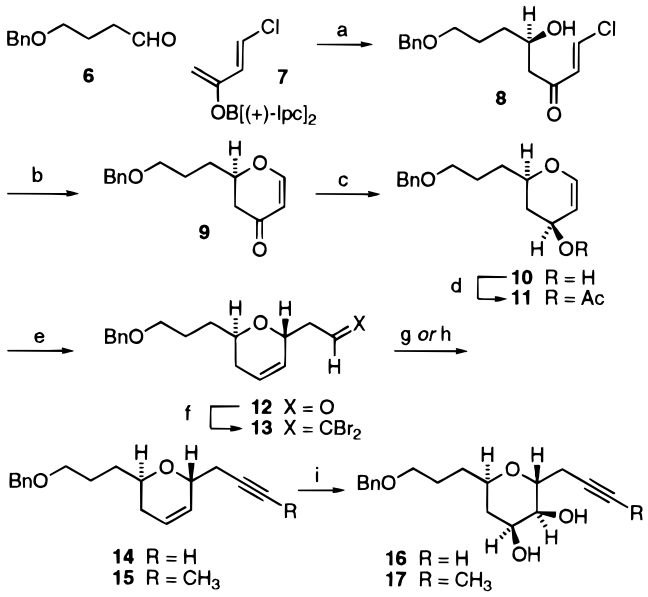


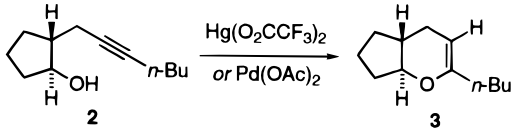
Figure 1. Retrosynthetic analysis of brevetoxins via alkynol cyclization.

Riediker and Schwartz have shown that the alkynyl alcohol **2** undergoes endocycloisomerization to give bicyclic dihydropyran **3** under mercury(II)-, or palladium(II)-promoted reaction conditions (eq 1), but endocyclic regioselectivity is observed only when the alcohol and alkyne-containing chains are placed in a *trans*-relationship on the cyclic ring.[3] We have developed mechanistically unique group(VI)-metal-promoted procedures in which terminal alkyne-containing alcohols **4** undergo cyclizations to endocyclic enol ethers **5** via vinylidene carbene intermediates (eq 2).[4] In this paper we present an enantioselective synthesis of the AB-ring substructure of the brevetoxin natural products via the application of alkynol cycloisomerization methodology.

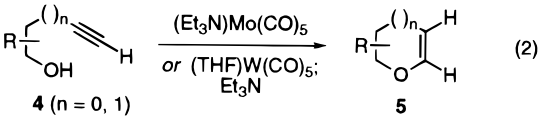
Scheme 1. Enantioselective Synthesis of Alkynyl Diols 16 and 17[a]



[a] Reagents and conditions: (a) **7**, Et_2O, −78 °C; then **6**, −5 °C (45%). (b) *i*-Pr_2NEt, TMSOTf, CH_2Cl_2, −78 to 20 °C (70%). (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, EtOH, −78 °C. (d) *i*-Pr_2NEt, Ac_2O, CH_2Cl_2 (82%, two steps). (e) $CH_2{=}CHOSi(t\text{-}Bu)(CH_3)_2$, $Cl_2Ti(O\text{-}i\text{-}Pr)_2$, −40 °C (79%). (f) PPh_3, Zn^0, CBr_4, CH_2Cl_2; then **12** (74%). (g) *n*-BuLi (2.1 equiv), THF, −78 to 20 °C; then H_2O (97%). (h) *n*-BuLi (2.1 equiv), THF, −78 to 20 °C; then CH_3I (95%). (i) Cat. $RuCl_3 \cdot 3H_2O$, $NaIO_4$, EtOAc:CH_3CN:H_2O (3:3:1), 0 °C, 5 min (47−54%).



(1)



(2)

Results and Discussion

Enantioselective Synthesis of A-Ring Alkynyl Diol Substrates. Compounds **16** and **17** represented projected substrates for the AB-ring substructure of hemibrevetoxin B and were prepared in relatively straightforward fashion, as shown in Scheme 1. The asymmetric aldol reaction of aldehyde **6**[5] and dienol borinate **7**[6] gave the secondary alcohol **8**, which underwent cyclization/dehydrohalogenation to afford dihydropyranone **9**. The enantiomeric excess was determined to be approximately

(1) (a) Catterall, W. A. *Science* **1988**, *242*, 50. (b) Trainer, V. L.; Edwards, R. A.; Szmant, A. M.; Stuart, A. M.; Mende, T. J.; Baden, D. G. In *Marine Toxins: Origin, Structure, and Molecular Pharmacology*; Hall, S., Strichartz, G., Eds.; ACS Symposium Series 418; American Chemical Society: Washington, DC, 1990; pp 166−175. (c) Shimizu, Y. *Chem. Rev.* **1993**, *93*, 1685. (d) Garson, M. *Chem. Rev.* **1993**, *93*, 1699. (e) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

(2) (a) Alvarez, E.; Candenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* **1995**, *95*, 1953. (b) Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1996**, *35*, 588. For syntheses of hemibrevetoxin B, see: (c) Nicolaou, K. C.; Reddy, K. R.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. (d) Kadota, I.; Jung-Youl, P.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777. (e) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365. (f) Mori, Y.; Yaegashi, Y.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557.

(3) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842.

(4) McDonald, F. E.; Bowman, J. L. *Tetrahedron Lett.* **1996**, *37*, 4675.

(5) (a) Kanao, M.; Hashimuze, T.; Ichikawa, Y.; Irie, K.; Isoda, S. *J. Med. Chem.* **1982**, *25*, 1358. (b) Baudouy, R.; Prince, P. *Tetrahedron* **1989**, *45*, 2067.

(6) (a) Price, C. C.; Pappalardo, J. A. *J. Am. Chem. Soc.* **1950**, *72*, 2613. (b) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413.

S0022-3263(97)00597-5 CCC: $14.00

90% ee by NMR analyses of both diastereomeric Mosher esters obtained from the aldol product **8**. The two-carbon side chain of the aldehyde **12** was introduced with excellent diastereoselectivity by $Cl_2Ti(O\text{-}i\text{-}Pr)_2$-promoted carba-Ferrier reaction[7] of (*tert*-butyldimethylsilyloxy-)ethene[8] with the allylic acetate **11** (generated by selective 1,2-reduction[9] of enone **9** and acylation). We could not detect the minor diastereomeric allylic acetates or diastereomeric aldehydes by ^1H NMR.

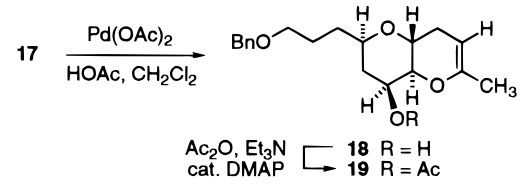
Application of the Corey−Fuchs alkynylation procedure[10] to aldehyde **12** afforded the alkyne products **14** and **15**. Alkene dihydroxylation of **14** or **15** with osmium tetraoxide catalysis (*N*-methylmorpholine *N*-oxide cooxidant) was sluggish and provided a low yield (<20%) of diols **16** and **17**. However, the ruthenium-catalyzed procedure developed by Shing[11] was much more effective for chemo- and stereoselective dihydroxylation of the alkene, affording product **16** in 54% yield (69% based on recovered **14**) as a 4:1 mixture of diastereomers *in only 5 min* at 0 °C. Similar results were obtained with the terminal alkyne substrate **15**.

Cyclization Studies. Reaction of the terminal alkynyl diol **16** with $(THF)W(CO)_5$ at room temperature failed to produce the expected bicyclic oxacarbene product, and little of the substrate **16** was recovered.[12] However, Lewis acidic reagents permitted cyclization under thermodynamic conditions. Reaction of the alkynyl diol **17** with mercuric trifluoroacetate provided the desired bicyclic enol ether **18**, albeit in only 16% yield. Treatment of **17** with palladium(II) acetate gave a better yield of product **18** (42%), which could be isolated in pure form after silica gel chromatography. This reaction was optimized by addition of acetic acid and molecular sieves (3 Å), which exhibited rate acceleration (reaction was complete after approximately 1 h by thin layer chromatography) and an increase in the isolated yield of enol ether **18** to 52%. Acylation of the secondary alcohol of **18** confirmed the structure of this bicyclic product (Scheme 2).

Conclusion

We have accomplished a short and highly stereoselective synthesis of the AB-fused bispyran system corresponding to many of the brevetoxin natural products.

Scheme 2. Endocyclization of Alkynyl Diol 17



Most other routes reported for synthesis of this substructure begin with the carbohydrate starting material D-mannose[2b−d] and thus require considerable functional group manipulation sequences including deoxygenation reactions. In contrast, our approach sets one stereocenter in an asymmetric aldol reaction, with the remaining chiral centers arising from substrate-induced stereocontrol. We are currently studying reiterative applications of metal-catalyzed alkynol *endo*-cyclizations to the synthesis of brevetoxin-type polycyclic ether structures.

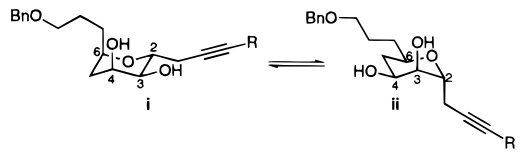
Experimental Section

(*E*,5*R*)-8-(Benzyloxy)-1-chloro-5-hydroxyoct-1-en-3-one (8). (+)-Ipc_2BCl (4.698 g, 14.65 mmol) was dissolved in dry Et_2O (29 mL) and chilled to 0 °C under N_2. *N*,*N*-Diisopropylethylamine (2.55 mL, 14.64 mmol) was added followed by *β*-chlorovinyl ketone **7** (1.544 g, 14.77 mmol) via cannula in dry Et_2O (5 mL). After 1.5 h at 0 °C, the mixture was chilled to −78 °C. Aldehyde **6** (2.40 g, 13.5 mmol) was added via cannula in Et_2O (5 mL). After 1.5 h at −78 °C, the mixture was transferred to a freezer (−5 °C) for 18 h. The mixture was warmed to 0 °C for 30 min, diluted with Et_2O, and washed with 3 N HCl and saturated $NaHCO_3$. The aqueous layers were extracted with Et_2O and the combined organic layers were added to MeOH (17 mL) and pH 7 buffer (28 mL) at 0 °C. Hydrogen peroxide (30 wt %, 15 mL) was added and the biphasic mixture was stirred at 0 °C for 30 min. The layers were separated, and the organic layer was washed with 10% $Na_2S_2O_5$. The aqueous layers were extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (pentane:Et_2O = 2:1) to give alcohol **8** (1.75 g, 45%). This compound is an unstable colorless solid which appears to eliminate water upon standing: $[\alpha]^{23}_D = -21.8$ ($CHCl_3$, $c = 1.56$); IR (thin film) 3390 (br), 3064, 1659, 1594 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (6 H, m), 6.53 (1 H, d, $J = 13.5$ Hz), 4.51 (2 H, s), 4.15−4.07 (1 H, m), 3.52 (2 H, t, $J = 6.0$ Hz), 2.67 (2 H, d $J = 6.0$ Hz), 1.84−1.52 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.1, 138.1, 137.4, 132.5, 128.2, 127.5, 127.5, 72.8, 70.0, 67.2, 47.7, 33.7, 25.8; HRMS (EI) calcd for $C_{15}H_{20}O_3Cl$ [(M + H)$^+$] 283.1101, found 283.1102.

(2*R*)-2-[3-(Benzyloxy)-1-propyl]-2,3-dihydro-4*H*-pyran-4-one (9). Alcohol **8** (505.9 mg, 1.789 mmol) was dissolved in dry CH_2Cl_2 (3 mL) and chilled to −78 °C under N_2. Addition of *N*,*N*-diisopropylethylamine (0.25 mL, 1.4 mmol) was followed by dropwise addition of TMSOTf (0.38 mL, 2.0 mmol). After 5 min, the mixture was allowed to warm to 20 °C and was stirred for 1 h. The mixture was diluted with CH_2Cl_2 and was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (pentane:EtOAc = 3:1) to give **9** (318.6 mg, 70%) as a colorless oil; $[\alpha]^{23}_D = +94.7$ ($CHCl_3$, c = 0.530); IR (thin film) 1675, 1596 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (6 H, m), 5.40 (1 H, d, $J = 6.9$ Hz), 4.51 (2 H, s), 4.46−4.37 (1 H, m), 3.52 (2 H, t, $J = 5.4$ Hz), 2.53 (1 H, dd, $J = 17$, 13 Hz), 4.42 (1 H, dd, $J = 16.7$, 3.3 Hz), 1.92−1.69 (4 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6, 163.1, 138.3, 128.4, 127.6, 107.0, 79.3, 73.0, 69.5, 41.9, 31.3, 25.1; HRMS (EI) calcd for $C_{15}H_{18}O_3$ (M^+) 246.1256, found 246.1262. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.57; H, 7.43.

(2*R*,4*S*)-4-Acetoxy-2-(3-(benzyloxy)-1-propyl)-3,4-dihydro-2*H*-pyran (11). Pyrone **9** (674 mg, 2.74 mmol) was dissolved in anhydrous EtOH (57 mL), and $CeCl_3 \cdot 7H_2O$ (1.2692 g, 3.41

(7) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.
(8) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, *18*, 3791.
(9) Luche, J.-L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848.
(10) (a) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3796. (b) Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schreiber, S. L. *J. Org. Chem.* **1992**, *57*, 5060.
(11) (a) Shing, T. K. M.; Tai, V. W.-F.; Tam. E. K. W. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2312. (b) Shing, T. K. M.; Tam, E. K. W.; Tai, V. W.-F.; Chung, I. H. F.; Jiang, Q. *Chem. Eur. J.* **1996**, *2*, 50.
(12) We attribute the failure of this relatively general cyclization reaction to an unfavorable conformational equilibrium in compounds **16** and **17**. Although conformation **i**



has the *trans*-diequatorial relationship of propargyl and hydroxyl substituents required for cyclization, a *cis*-1,3-diaxial interaction is present between the C4-hydroxyl group and the C6-side chain. This interaction is avoided in conformation **ii**, but now the C2-propargyl and C3-hydroxyl substituents are in a *trans*-diaxial configuration. The vinylidene carbene arising from **16** apparently decomposes (possibly by an intermolecular reaction leading to polymerization) at a faster rate than the conformational interconversion required for cyclization.

mmol) was added. The mixture was stirred until the $CeCl_3 \cdot 7H_2O$ was dissolved, and the resulting solution was chilled to −78 °C. A solution of $NaBH_4$ (250 mg, 6.56 mmol) in EtOH (20 mL) was added dropwise over 15 min. After stirring for 1 h at −78 °C, the reaction was quenched by addition of acetone (4 mL). After warming to 20 °C, the mixture was concentrated and the residue was dissolved in H_2O and Et_2O. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give crude alcohol **10** as a yellow oil (430 mg). Typically, the crude alcohol **10** was acetylated without prior purification, as this compound was highly unstable, extremely acid-sensitive, and rapidly decomposed even in a freezer. An analytical sample was purified by silica gel chromatography (Et_2O:Et_2NH = 99:1) and characterized as follows: yellow oil; $[\alpha]^{23}_D = +55$ (CH_2Cl_2, $c = 0.456$); IR (thin film) 3369 (br), 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (5 H, m), 6.36 (1 H, dd, J = 6.2, 1.1 Hz), 4.72 (1 H, dt, J = 6.2, 1.9 Hz), 4.51 (2 H, s), 4.47−4.37 (1 H, m), 3.96−3.88 (1 H, m), 3.53−3.45 (2 H, m), 2.14 (1 H, ddt, J = 13, 6.5, 1.6 Hz) 1.83−1.54 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 138.4, 128.3, 127.6, 105.4, 74.5, 72.9, 69.9, 63.2, 38.1, 31.7, 25.3; HRMS (EI) calcd for $C_{15}H_{20}O_3$ $(M)^+$ 248.1412, found 248.1423.

The crude alcohol **10** (ca. 2.7 mmol), dried by azeotropic evaporations from toluene (3×), was dissolved in dry CH_2Cl_2 (14 mL) under N_2. Addition of *N*,*N*-diisopropylethylamine (2.9 mL, 17 mmol) was followed by addition of DMAP (2−3 mg) and Ac_2O (0.78 mL, 11 mmol) at 20 °C. After 16 h, the mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated. Purification by silica gel chromatography (pentane:Et_2O = 2:1, 1% Et_2NH) gave acetate ester **11** (685 mg, 82%): colorless oil; $[\alpha]^{23}_D = +23$ (CH_2Cl_2, $c = 0.526$); IR (thin film) 1734, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (5 H, m), 6.43 (1 H, d, J = 6.2 Hz), 5.38 (1 H, dddd, J = 8.7, 6.7, 1.9, 1.7 Hz), 4.72 (1 H, dt, J = 6.3, 1.9 Hz), 4.50 (2 H, s), 4.02−3.94 (1 H, m), 3.53−3.44 (2 H, m), 2.23 (1 H, ddt, J = 13, 6.6, 1.8 Hz), 2.04 (3 H, s), 1.83−1.62 (5 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 146.6, 138.4, 128.3, 127.6, 100.8, 74.1, 72.8, 69.7, 65.6, 33.3, 31.3, 25.3, 21.2; HRMS (EI) calcd for $C_{17}H_{22}O_4$ (M^+) 290.1518, found 290.1546. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.36; H, 7.58.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-5,6-dihydro-2-(formylmethyl)-2*H*-pyran (12). Acetate **11** (801 mg, 2.76 mmol), dried by azeotropic evaporation from toluene (3×), was dissolved in dry toluene (25 mL) and chilled to −40 °C under N_2. Addition of (*tert*-butyldimethylsiloxy)ethene (603.3 mg, 3.81 mmol) via cannula in toluene (5 mL) was followed by dropwise addition of $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ (3.0 mL, 2 M solution in CH_2Cl_2, 6.1 mmol, prepared by adding an equimolar amount of $TiCl_4$ to a solution of $Ti(O\textit{i}\text{-}Pr)_4$ in CH_2Cl_2 at 0 °C, followed by warming to 20 °C). After 1 h at −40 °C, the reaction was quenched by addition of saturated $NaHCO_3$ (5 mL). After warming to 20 °C, the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (pentane:EtOAc = 3:1) to give aldehyde **12** (598.4 mg, 79%, single isomer by ^1H NMR after chromatography). This compound is a colorless oil which slowly decomposed upon freezer storage after ca. 2 weeks: $[\alpha]^{23}_D = -59.9$ ($CHCl_3$, $c = 1.15$); IR (thin film) 2858, 2734, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (1 H, d, J = 3.3 Hz), 7.37−7.27 (5 H, m), 5.91−5.84 (1 H, m), 5.68 (1 H, br d, J = 10.2 Hz), 4.82−4.73 (1 H, m), 4.50 (2 H, s), 3.66−3.60 (1 H, m), 3.52−3.42 (2 H, m), 2.72 (1 H, ddd, J = 16, 9.0, 3.3 Hz), 2.50 (1 H, dd, J = 16, 4.5 Hz), 2.07−1.55 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.0, 138.5, 128.3, 127.8, 127.6, 127.4, 125.4, 77.2, 72.8, 70.0, 67.8, 47.8, 31.7, 30.3, 25.8; HRMS (EI) calcd for $C_{17}H_{22}O_3$ (M^+) 274.1569, found 274.1562.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-2-(3,3-dibromo-2-propenyl)-5,6-dihydro-2*H*-pyran (13). Dry CH_2Cl_2 (11 mL) was added to triphenylphosphine (1.410 g, 5.38 mmol) and zinc dust (349.5 mg, 5.35 mmol) under N_2, and the suspension was chilled to 0 °C. Carbon tetrabromide (1.832 g, 5.44 mmol) was added and the mixture was stirred at 20 °C for 66 h. Aldehyde **12** (467 mg, 1.70 mmol), dried by evaporation from toluene (3×), was added via cannula in dry CH_2Cl_2 (8 mL). After 40 h, the mixture was poured into pentane (30 mL), and the solvents were decanted from the resulting residue. The residue was dissolved in CH_2Cl_2 (5 mL), poured into pentane (30 mL) again, and decanted. This process was repeated four times. The solvents were evaporated and the residue was purified by silica gel chromatography (pentane:Et_2O = 5:1) to give dibromoolefin **13** (546.8 mg, 74%): colorless oil; $[\alpha]^{23}_D = -42.9$ (CH_2Cl_2, $c = 0.750$); IR (thin film) 3029, 2914, 2855, 1093 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.27 (5 H, m), 6.52 (1 H, t, J = 6.9 Hz), 5.90−5.83 (1 H, m), 5.70−5.64 (1 H, m), 4.52 (2 H, s), 4.30−4.22 (1 H, m), 3.70−3.61 (1 H, m), 3.57−3.45 (2 H, m), 2.48−2.38 (1 H, ddd, J = 15.3, 9.2, 6.9, Hz), 2.32−2.23 (1 H, ddd, J = 15.4, 7.2, 4.7 Hz), ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 135.4, 128.3, 128.3, 127.6, 127.5, 125.3, 89.8, 72.8, 70.7, 70.2, 67.7, 37.7, 32.0, 30.5, 25.9; HRMS (EI) calcd for $C_{18}H_{22}O_2{}^{79}Br^{81}BrH$ $[(M + H)^+]$ 431.0044, found 431.0020.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-5,6-dihydro-2-(2-propynyl)-2*H*-pyran (14). Dibromoolefin **13** (358 mg, 0.832 mmol) was dissolved in dry THF (6 mL) and chilled to −78 °C under N_2. *n*-Butyllithium (2.5 M in hexanes, 0.70 mL, 1.8 mmol) was added dropwise. After 1.5 h, the mixture was warmed to 20 °C. After an additional hour, the reaction was quenched by addition of H_2O (4 mL). The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography (pentane:Et_2O = 8:1) gave alkyne **14** (220 mg, 97%): colorless oil; $[\alpha]^{23}_D = -87$ (CH_2Cl_2, $c = 0.576$); IR (thin film) 3307, 2119 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (5 H, m), 5.93−5.82 (2 H, m), 4.51 (2 H, s), 4.37−4.32 (1 H, m), 3.72−3.64 (1 H, m), 3.57−3.45 (2 H, m), 2.50 (1 H, ddd, J = 16.5, 7.0, 2.7 Hz), 2.40 (1 H, ddd, J = 16.6, 7.0, 2.7 Hz), 2.08−1.57 (6 H, m), 2.02 (1 H, t, J = 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.3, 127.8, 127.6, 127.4, 125.3, 81.0, 72.8, 70.8, 70.2, 70.0, 68.1, 31.7, 30.4, 25.8, 24.3; HRMS (EI) calcd for $C_{18}H_{22}O_2$ (M^+) 270.1620, found 270.1633.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-2-(2-butynyl)-5,6-dihydro-2*H*-pyran (15). Dibromoolefin **13** (547 mg, 1.27 mmol) was dissolved in dry THF (8.5 mL) and chilled to −78 °C under N_2. *n*-BuLi (1.1 mL, 2.8 mmol, 2.5 M in hexanes) was added dropwise. After 1.5 h, the mixture was warmed to 20 °C for an additional 1.5 h. The mixture was chilled to −78 °C and methyl iodide (0.158 mL, 2.54 mmol) was added. After 1 h at −78 °C, the mixture was warmed to 20 °C for 2 h and quenched with H_2O. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Purification by silica gel chromatography (pentane:Et_2O = 4:1) gave alkyne **15** (455 mg, 95%): colorless oil; $[\alpha]^{23}_D = -89.8$ (CH_2Cl_2, $c = 0.668$); IR (thin film) 3031, 2918, 2856, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.24 (5 H, m), 5.87−5.85 (2 H, s), 4.29−4.25 (1 H, m), 3.71−3.62 (1 H, m), 3.52 (2 H, ddd, J = 9.3, 6.3, 3.0 Hz), 2.49−2.29 (2 H, m), 2.05−1.55 (6 H, m), 1.79 (3 H, dd, J = 5.2, 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.4, 128.3, 127.6, 127.5, 124.9, 77.3, 75.6, 72.8, 71.3, 70.2, 68.0, 31.8, 30.5, 25.9, 24.7; HRMS (EI) calcd for $C_{15}H_{19}O_2$ $[(M - C_4H_5)^+]$ 231.1385, found 231.1402. Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found: C, 80.04; H, 8.47.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-3,4-dihydroxy-2-(2-propynyl)-3,4,5,6-tetrahydro-2*H*-pyran (16). Alkene **14** (67.7 mg, 0.25 mmol) was dissolved in EtOAc (1.5 mL) and MeCN (1.5 mL) and chilled to 0 °C. $RuCl_3 \cdot 3H_2O$ (6.9 mg, 0.026 mmol) and $NaIO_4$ (91.4 mg, 0.43 mmol) were combined, dissolved in H_2O (0.5 mL), and added to the alkene solution. After 5 min, the reaction was quenched by addition of saturated $Na_2S_2O_5$ (3 mL). After stirring for 10 min at 20 °C, the aqueous layer was extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel chromatography (EtOAc) to give starting material (12 mg) and diol **16** as a 3:1 mixture of isomers (35.9 mg, 47% combined). This mixture was characterized as follows: colorless oil; $[\alpha]^{23}_D = +12$ (CH_2Cl_2, $c = 0.492$); IR (thin film) 3660−3140 (br), 2120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, major isomer) δ 7.33−7.28 (5 H, m), 4.49 (2 H, s), 4.06 (1 H, ddd, J = 7.3, 7.2, 3.6 Hz), 3.92−3.83 (1 H, m), 3.77 (1 H, dt, J = 6.6, 3.3 Hz), 3.60−3.46 (3 H, m), 2.84 (1 H, br d, J = 6.3 Hz), 2.70 (1 H, br d, J = 6.7 Hz), 2.46 (2 H, dd, J = 7.4, 2.5 Hz), 2.05 (1 H, t, J = 2.6 Hz), 1.84−1.53 (6 H, m); ^{13}C NMR (75 MHz, $CDCl_3$, major isomer) δ 138.4, 128.3, 127.7, 127.5, 79.9, 74.0, 72.8, 70.9, 69.9, 69.7, 69.1, 66.0, 34.8, 31.6, 25.9, 20.2; HRMS (EI) calcd for $C_{18}H_{24}O_4$ (M^+) 304.1674, found 304.1695.

(2*R*,6*R*)-6-[3-(Benzyloxy)-1-propyl]-2-(2-butynyl)-3,4-dihydroxy-3,4,5,6-tetrahydro-2*H*-pyran (17). Alkene **15** (143

mg, 0.503 mmol) was dissolved in EtOAc (3.0 mL) and MeCN (3.0 mL) and chilled to 0 °C. $RuCl_3 \cdot H_2O$ (7 mg, 0.03 mmol) and $NaIO_4$ (199 mg, 0.930 mmol) were dissolved in H_2O (1 mL) and added to the alkene solution. After 5 min, the reaction was quenched by addition of saturated aqueous $Na_2S_2O_5$ (5 mL). After stirring for 10 min, the aqueous layer was extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by chromatography (100% EtOAc) to give starting material (31.5 mg) and diol **17** (87 mg, 54%, 69% based on recovered starting material) as a 4:1 mixture of diastereomers. This mixture was characterized as follows: colorless oil; $[\alpha]^{23}_D = +33.1°$ (CH_2Cl_2, $c = 3.50$); IR (thin film) 3640−3130 (br), 2931, 2858, 2244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, major diastereomer) δ 7.32−7.27 (5 H, m), 4.49 (2 H, s), 4.01 (1 H, ddd, $J = 7.5$, 7.2, 3.3 Hz), 3.87−3.79 (2 H, m), 3.55−3.45 (3 H, m), 2.84 (1 H, br d, $J = 6.2$ Hz), 2.72 (1 H, br d, $J = 6.8$ Hz), 2.42−2.39 (2 H, m), 1.80−1.47 (6 H, m), 1.76 (3 H, t, $J = 2.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, major diastereomer) δ 138.4, 128.3, 127.6, 127.5, 78.3, 74.8, 74.4, 72.8, 69.9, 69.5, 69.2, 65.9, 34.8, 31.7, 25.9, 20.4, 3.5; HRMS (EI) calcd for $C_{19}H_{26}O_5$ (M^+) 318.1831, found 318.1821.

Bicyclic Enol Ether (18). Alkynyl diol **17** (34.9 mg, 0.110 mmol) was dried by evaporation from toluene (3×), dissolved in dry CH_2Cl_2 (1.5 mL), and added to 3 Å molecular sieves (43 mg, flame dried) via cannula. Acetic acid (0.013 mL, 0.23 mmol), followed by $Pd(OAc)_2$ (15.9 mg, 0.071 mmol), was added and the mixture was stirred under N_2 at 20 °C for 2.5 h (reaction was complete by thin layer chromatography (pentane:Et_2O = 2:1) after ca. 1 h). The mixture was filtered through silica gel (1 cm) eluting with EtOAc. The solvents were concentrated and the residue was purified by silica gel chromatography (pentane:Et_2O = 2:1, 1% Et_2NH) to give enol ether **18** as a colorless oil (18.4 mg, 52%). $[\alpha]^{23}_D = +7.5$ (CH_2Cl_2, $c = 0.348$); IR (thin film) 3459 (br), 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.24 (5 H, m), 4.50 (2 H, s), 4.44 (1 H, d, $J = 5.7$ Hz), 4.22−4.19 (1 H, m), 3.96 (1 H, ddd, $J = 9.9$, 9.8, 6.3 Hz), 3.90−3.83 (1 H, m), 3.53−3.44 (3 H, m), 2.40−1.90 (6 H, m), 1.78−1.58 (3 H, m), 1.74 (3 H, t, $J = 1.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.2, 138.6, 128.3, 127.6, 127.4, 94.1, 76.4, 72.8, 72.2, 70.2, 65.3, 59.8, 33.3, 29.2, 27.4, 27.1, 19.4; HRMS (EI) calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1851.

Bicyclic Enol Ether Acetate Ester (19). Alcohol **18** (12.2 mg, 0.0383 mmol) was dissolved in Et_3N (1.0 mL) under N_2. DMAP (1 mg), followed by Ac_2O (0.015 mL, 0.16 mmol), was added and the mixture stirred at 20 °C for 16 h. The volatiles were evaporated under reduced pressure and the residue was purified by silica gel chromatography (pentane:Et_2O = 2:1, 1% Et_2NH) to give acetate **19** (13.5 mg, 97%): colorless oil; $[\alpha]^{23}_D = +51°$ (CH_2Cl_2, $c = 0.314$); IR (thin film) 1740, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.27 (5 H, m), 5.35 (1 H, dt, $J = 3.3$, 3.2 Hz), 4.50 (2 H, s), 4.41 (1 H, d, $J = 4.8$ Hz), 3.98 (1 H, ddd, $J = 9.8$, 9.5, 6.2 Hz), 3.93−3.86 (1 H, m), 3.58 (1 H, dd, $J = 9.9$, 3.3 Hz), 3.53−3.44 (2 H, m), 2.21−1.92 (4 H, m), 2.07 (3 H, s), 1.76−1.55 (4 H, m), 1.70 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 150.6, 138.5, 128.3, 127.6, 127.5, 93.1, 74.3, 72.9, 71.9, 69.9, 67.2, 60.8, 32.1, 28.9, 27.5, 27.0, 21.4, 19.4; HRMS (EI) calcd for $C_{21}H_{28}O_5$ 360.1937, found 360.1928.

Acknowledgment. This research was supported by the National Science Foundation Early Career Development Program (CHE−9501608). F.E.M. also acknowledges support from the Alfred P. Sloan Foundation and Lilly Research Laboratories. M.M.G. was an American Chemical Society Organic Division Graduate Fellow, sponsored by Glaxo Research Laboratories.

Supporting Information Available: ^1H NMR spectra of new compounds **8**−**19** (12 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.

JO970597+