An Approach to the Stereoselective Synthesis of *syn*- and *anti*-1,3-Diol Derivatives. Retention of Configuration in the Mitsunobu Reaction

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The Mitsunobu reaction typically proceeds with inversion of configuration at the hydroxyl center. However, with a series of hindered alcohols, the intramolecular version of the Mitsunobu reaction afforded exclusively the product of retention of configuration. A mechanistic rationale for this observation is discussed, wherein this atypical stereochemical outcome is attributed to steric congestion at the reaction center.

Introduction

During the studies directed toward the total synthesis of tirandamycin A[1−3] and B[4] and the pheromone of the male swift moth *Hepialus hecta L*,[5] it was demonstrated that the 2,6-dioxabicyclo[3.3.1]nonane ring system of these natural products, e.g., **5**, could be synthesized by peracid oxidation of *anti*-furfuryl alcohol derivative **1b** and subsequent acid-catalyzed ketalization of the resulting pyranone **2b** (Scheme 1). To our surprise, oxidation and acid treatment of the diastereomeric *syn*-alcohol **1a** afforded bicyclic lactone **3a**, rather than the anticipated diastereomeric ketal, via a novel acid-catalyzed rearrangement of pyranone intermediate **2a**.[1] This rearrangement was remarkable since both furfuryl alcohol **1a** and its diastereomer **1b** underwent oxidation-rearrangement in a completely stereoselective manner to yield a single product, lactone **3a**.[1,5]

We previously reported[1] that the rearrangement described above is general for furfuryl analogues and appears to possess potential as an approach to the stereoselective synthesis of acyclic 1,3,5-triol derivatives (Scheme 2).[6] The synthetically challenging 1,3,5-triol moiety occurs in a variety of biologically important natural products, most notably the macrolide antibiotics erythromycin A,[7] rifamycin S,[8] lankamycin,[9] roflamycoin,[10] and streptovaricin A.[11] Because lactone **3b** could not be prepared by the rearrangement methodology (see Scheme 1), Mitsunobu inversion was investigated as a method for preparing triol **6b** via the corresponding lactone **3b**. The Mitsunobu reaction has been widely utilized in organic synthesis, most notably as a means of inverting stereochemistry at a secondary hydroxyl moiety.[12−15] In this paper, we report that the intramolecular Mitsunobu reaction of **3a** and structurally related bicyclic lactone analogues occurred with either retention or inversion of configuration depending on the steric environment of the secondary hydroxyl group. These remarkable results provided insight into the mechanism of the Mitsunobu reaction.

Results and Discussion

The hemiketal functionality of bicyclic lactone **3a** was protected as the methyl ether (*p*-TsOH, MeOH, rt), producing compound **7a** in high yield (Scheme 3). Subsequently, lactone **7a** was hydrolyzed with NaOH and

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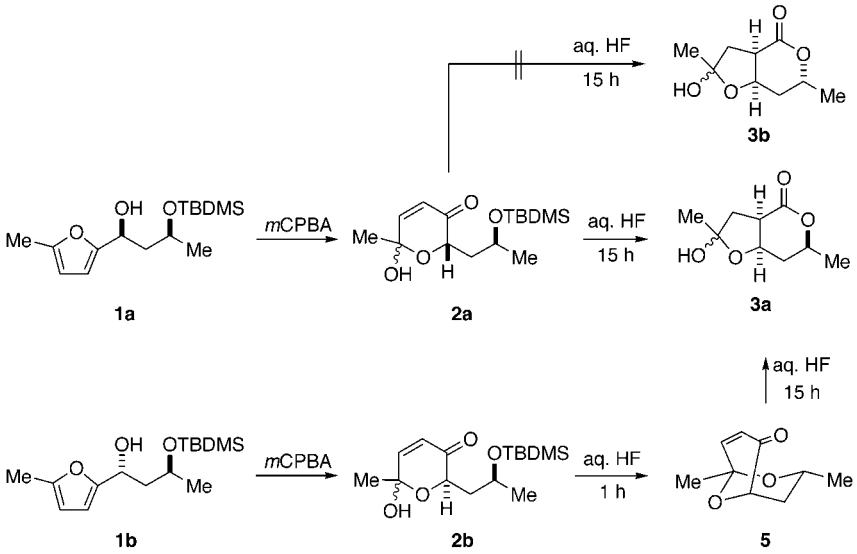
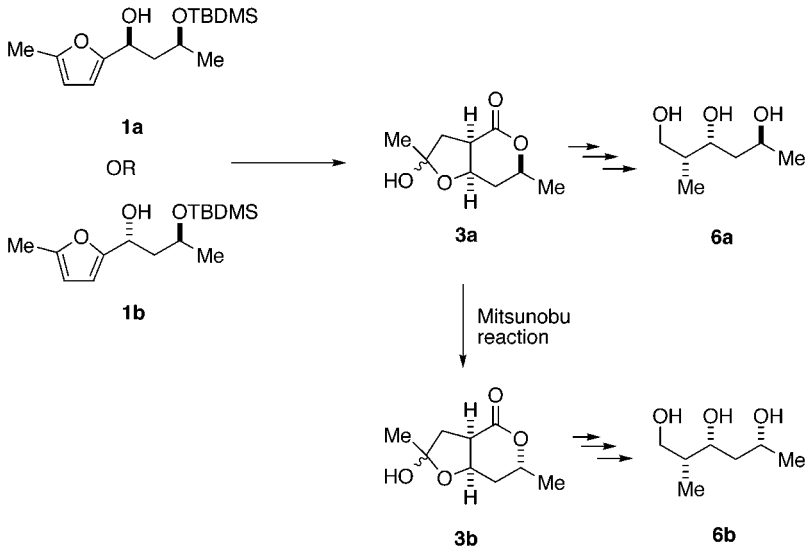
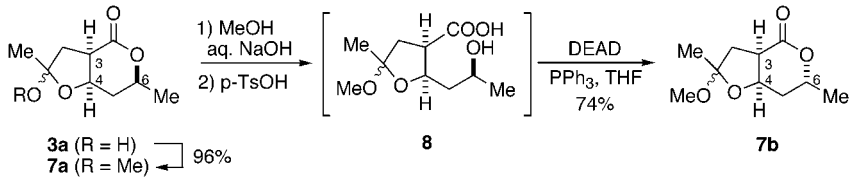
Scheme 1



Scheme 2



Scheme 3



then treated with *p*-TsOH to form hydroxyacid **8** in situ. As anticipated from the accepted mechanism of the Mitsunobu reaction, hydroxyacid **8** underwent stereospecific relactonization with inversion of configuration to provide bicyclic lactone **7b**. The relative stereochemistry of lactone **7b** was verified by ^{1}H and ^{13}C NMR spectroscopy. No trace of lactone **7a** was observed in the crude product.

To determine the generality of the intramolecular Mitsunobu inversion, the Mitsunobu reaction of lactones **10a** and **13a** was investigated (Scheme 4). The hydroxyl function at C-6 is more sterically hindered in these derivatives, and the effect of this steric factor on the lactonization process was unknown. Bicyclic lactones **10a** and **13a** were prepared from lactones **9** and **12**, respectively. Hydrolysis of lactones **10a** and **13a** with NaOH, followed by acidification gave hydroxyacids **11** and **14**, respectively. However, under the conditions of the Mitsunobu reaction (PPh_3, DEAD, buffer solution, pH ~6),[16,17] both systems yielded only starting lactone, the product of retention of stereochemistry, rather than the inverted diastereomers **10b** and **13b**. This unexpected stereochemical result indicated that steric bulk adjacent to the C-6 reaction center influenced whether retention or inversion of configuration was observed in the Mitsunobu lactonization.

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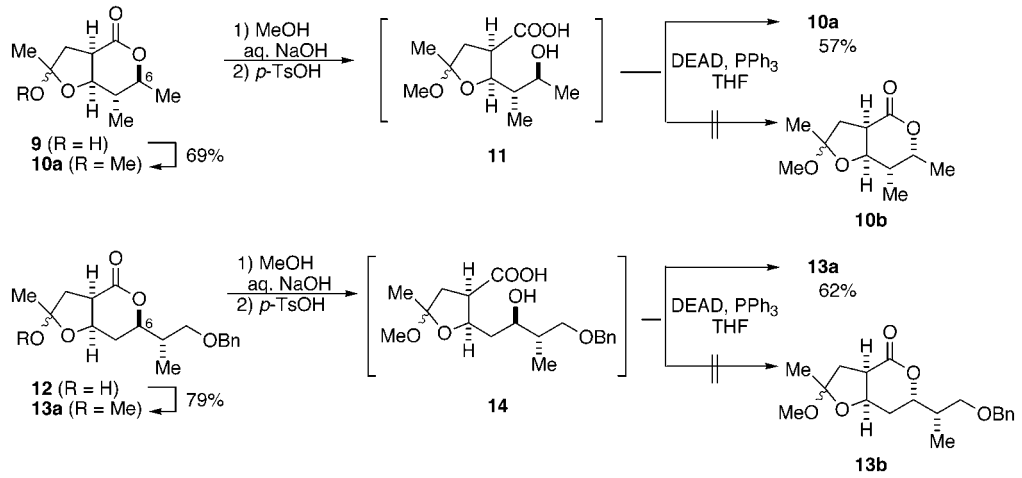
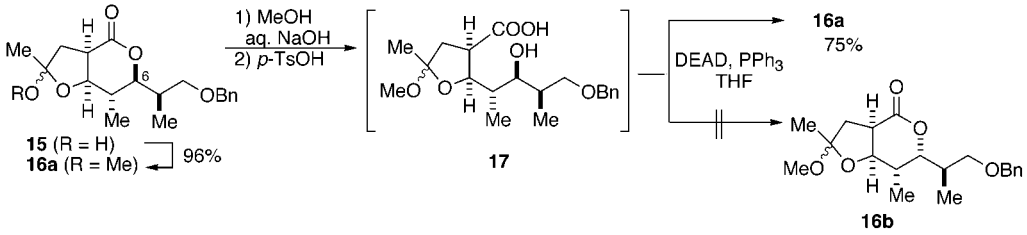
Scheme 4



Scheme 5



The generality of the hydrolysis-Mitsunobu lactonization process was investigated also with highly hindered lactone **16a** (Scheme 5). As expected on the basis of the results from lactones **10a** and **13a** (Scheme 4), complete retention of configuration was observed for relactonization of hydroxyacid **17** as summarized in Scheme 5.

Retention of configuration in the Mitsunobu reaction has been reported previously.[15,18−23] In most instances, retention of configuration has been attributed to gross deviations in the intended mechanistic pathway involving S_N2' or S_N1 processes during the Mitsunobu reaction of allylic alcohols[15,18−20,23] or neighboring group participation.[21,22] Neither of these situations exists in these systems. Lactonization under Mitsunobu conditions has been shown to occur generally with complete stereospecificity.[17,21,24] In one instance, Fleming observed retention of configuration during generation of a five-membered lactone, but this result was attributed to formation of a carbocation intermediate,[19] which again is not probable in these systems.

Lactonization with retention of stereochemistry with hindered alcohols such as **11**, **14**, and **17** can be attributed to preferential closure of an acyloxyphosphonium intermediate (e.g., **20**, Scheme 6). Although the mechanism of the Mitsunobu reaction has been extensively studied,[13,14,25−27] we have recently demonstrated the intermediacy of acyloxyphosphonium salts in the Mitsunobu process.[28] The Mitsunobu reaction proceeds through an equilibrium (Scheme 6) of acyloxyphosphonium salt **20** and alkoxyphosphonium salt **21**. If the C-6 hydroxyl function is not sterically hindered (e.g., **8**, Scheme 6), then carboxylate displacement from phosphonium salt **19** occurred with *inversion* of configuration to afford lactone **7b**. On the other hand, if the hydroxyl moiety is highly hindered, e.g., **11**, then carboxylate displacement cannot occur (**21**) and the competing lactonization with *retention* of configuration via acyloxyphosphonium salt **20** was observed.

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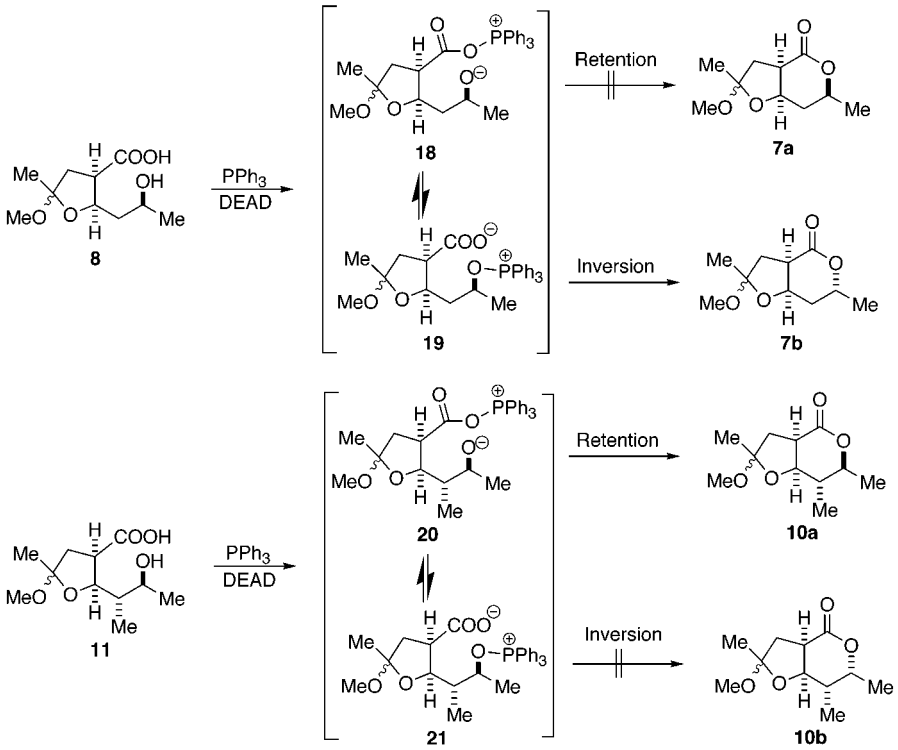
Scheme 6



Conclusion

The change in stereochemical outcome of the Mitsunobu reaction with highly hindered alcohol derivatives offers valuable insight into the mechanism of this important process, namely, that acyloxyphosphonium salt intermediates can play a critical role in the lactonization process. Additional studies relating to the generality of this process are underway and will be reported in due course.

Experimental Section

General Methods. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on either a 200- or 400-MHz spectrometer in C_6D_6 unless otherwise noted. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared spectra were recorded as solutions in CCl_4. Band positions are given in reciprocal centimeters (cm^{-1}), and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Thin-layer chromatography (TLC) was performed with the compounds being identified in one or more of the following manners: UV (254 nm), iodine, or vanillin/sulfuric acid charring. Melting points are corrected.

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl. Methanol (MeOH) was stored over molecular sieves. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted. Glassware used in the reactions described below was dried for a minimum of 12 h in an oven at 120 °C and assembled under an atmosphere of nitrogen. The syntheses of compounds **3a**, **9**, **12**, and **15** have been previously reported.[1,2,5]

Methoxy Bicyclic Lactone 7a. A solution of *p*-TsOH (77.0 mg, 0.410 mmol) in 5 mL of MeOH was added to a solution of bicyclic lactone **3a** (760 mg, 4.07 mmol) in 5 mL of MeOH at 25 °C. After 30 min at 25 °C, the reaction was neutralized with 5% $NaHCO_3$ solution. The MeOH was evaporated in vacuo, and the remaining crude mixture was extracted with 3 × 30 mL of EtOAc. The combined organic layers were washed with 10 mL of saturated NaCl and 10 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave a 3:1 mixture of anomers of methoxy bicyclic lactone **7a** (784 mg, 96%) as a white solid. The anomers were separated by chromatography, with only the major anomer **7a** being used for subsequent chemistry. High R_f product (**7a-major**): mp 61−62 °C; R_f = 0.48, 50% EtOAc/hexane; IR (CCl_4) 2987 (m), 2962 (m), 1743 (s), 1387 (s), 1212 (s), 1106 (s), 1075 (s); ^{1}H NMR (C_6D_6) δ 0.93 (d, 3H, J = 6.3), 1.13−1.30 (m, 1H), 1.25 (s, 3H), 1.63−1.74 (m, 1H), 2.24−2.44 (m, 2H), 2.77 (ddd, 1H, J = 15.9, 8.7, 6.7), 3.04 (s, 3H), 3.50−3.66 (m, 1H), 4.02 (dt, 1H, J = 8.7, 8.0); ^{13}C NMR (C_6D_6) δ 20.7, 20.8, 36.7, 41.1, 42.6, 48.3, 71.5, 73.4, 107.4, 172.4; LRMS (EI) 200 ((M^+), 3), 185 (16), 169 (100), 112 (17), 109 (16); HRMS (EI) calcd for $C_{10}H_{16}O_4$ 200.1048 (M^+), found 200.1063. Low R_f product (**7a-minor**): mp 98−100 °C; R_f = 0.38, 50% EtOAc/hexane; IR (CCl_4) 2987 (m), 2956 (m), 1743 (s), 1381 (s), 1212 (s), 1143 (s), 1068 (s); ^{1}H NMR (C_6D_6) δ 0.95 (d, 3H, J = 6.3), 1.20 (s, 3H), 1.78−1.21 (m, 4H), 2.50−2.61 (m, 1H), 2.98 (s, 3H), 3.43−3.56 (m, 1H), 4.10 (dt, 1H, J = 9.7, 8.0); ^{13}C NMR (C_6D_6) δ 20.8, 20.9, 38.4, 40.6, 42.4, 48.5, 70.5, 75.2, 108.2, 171.3; HRMS (EI) calcd for $C_9H_{13}O_3$ 169.0865 ((M^+) − OCH_3), found 169.0862.

Methoxy Bicyclic Lactone 7b. A solution of NaOH (0.260 mL of 20% w/v, 1.30 mmol) was added to a solution of the methoxy bicyclic lactone **7a** (217 mg, 1.10 mmol) in 2 mL of MeOH at 25 °C. After the addition was complete, the solution was heated at 70 °C for 1.5 h. The MeOH was evaporated in vacuo to provide a carboxylate. This crude salt was dissolved in 5 mL of THF, and 235 mg (1.30 mmol) of *p*-TsOH in 5 mL of THF was added. The reaction mixture of acid **8** was treated with a preformed solution of PPh_3 and DEAD (formed by addition of 228 μL (1.30 mmol) of DEAD to a solution of 341 mg (1.30 mmol) of PPh_3 in 5 mL of THF at 25 °C). After the mixture was stirred for 24 h at 25 °C, the reaction mixture was neutralized with 5% $NaHCO_3$ solution and extracted with 3 × 50 mL of EtOAc. The combined organic layers were washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 160 mg (74%) of methoxy bicyclic lactone **7b** as an oil. No trace of diastereomeric lactone **7a** was observed in either the ^{1}H or ^{13}C NMR spectrum of the product

(<5%). R_f = 0.46, 50% EtOAc/hexane; IR (CCl_4) 2985 (m), 2961 (m), 1748(s), 1382 (m), 1220 (s), 1186 (m), 1073 (m); ^{1}H NMR (C_6D_6) δ 0.86 (d, 3H, J = 6.3), 1.19 (m, 1H), 1.24 (s, 3H), 1.58 (m, 1H), 2.36 (m, 2H), 2.64 (m, 1H), 3.04 (s, 3H), 3.41 (m, 1H), 3.94 (m, 1H); ^{13}C NMR (C_6D_6) δ 20.7, 20.8, 36.7, 40.1, 46.5, 50.4, 69.9, 71.4, 104.8, 174.3. HRMS (EI) calcd for $C_{10}H_{16}O_4$ 200.1045 (M^+), found 200.1063.

Methoxy Bicyclic Lactone 10a. A solution of *p*-TsOH (17.0 mg, 0.090 mmol) in 3 mL of MeOH was added to a solution of bicyclic lactone **9** (18.8 mg, 0.940 mmol) in 3 mL of MeOH at 25 °C. After 30 min at 25 °C, the reaction was neutralized with 5% $NaHCO_3$ solution. The MeOH was evaporated in vacuo, and the remaining crude mixture was extracted with 3 × 10 mL of EtOAc. The combined organic layers were washed with 10 mL of saturated NaCl and 10 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 139 mg (69%) of a 2:1 mixture of anomeric methoxy bicyclic lactone **10a** as a colorless oil. The diastereomers were separated by chromatography, with only the major anomer **10a** being used for subsequent chemistry. High R_f product (**10a-major**): R_f = 0.69, 50% EtOAc/hexane; IR (CCl_4) 2986 (s), 2938 (s), 1746 (s), 1381 (s), 1209 (s), 1147 (s), 1026 (s); ^{1}H NMR (C_6D_6) δ 0.66 (d, 3H, J = 6.7), 0.93 (d, 3H, J = 6.3), 1.23 (s, 3H), 1.14−1.35 (m, 1H), 2.34 (m, 2H), 2.87 (m, 1H), 3.02 (s, 3H), 3.31 (m, 1H), 3.51 (t, 1H, J = 9.0); ^{13}C NMR (C_6D_6) δ 14.6, 18.2, 20.5, 41.4, 41.6, 42.8, 48.2, 75.9, 80.4, 107.1, 172.1; LRMS (EI) 214 ((M^+), 1), 183 (100), 182 (96), 165 (25), 137 (24), 136 (28), 107 (28); HRMS (EI) calcd for $C_{11}H_{18}O_4$ 214.1248 (M^+), found 214.1248. Low R_f product (**10a-minor**): R_f = 0.49, 50% EtOAc/hexane; IR (CCl_4) 2987 (s), 2937 (s), 1743 (s), 1383 (s), 1338 (s), 1195 (s), 1068 (s); ^{1}H NMR (C_6D_6) δ 0.72 (d, 3H, J = 6.7), 0.97 (d, 3H, J = 6.3), 1.19 (s, 3H), 1.49 (m, 1H), 1.69 (m, 1H), 2.62 (m, 2H), 2.95 (s, 3H), 3.26 (m, 1H), 3.55 (t, 1H, J = 9.5); ^{13}C NMR (C_6D_6) δ 14.6, 18.2, 20.8, 41.0, 42.5, 48.5, 48.8, 75.1, 82.3, 107.9, 171.0.

Methoxy Bicyclic Lactone 10a Prepared by the Mitsunobu Reaction. A solution of NaOH (0.084 mL of 20% w/v, 0.42 mmol) was added to a solution of the methoxy bicyclic lactone **10a** (from above experimental) (60 mg, 0.28 mmol) in 5 mL of MeOH at 25 °C. After addition was completed, the solution was heated at 70 °C for 1.5 h. The MeOH was evaporated in vacuo to provide a carboxylate. This crude salt was dissolved in 5 mL of THF, and 61 mg (0.34 mmol) of *p*-TsOH in 5 mL of THF was added. The reaction mixture of acid **11** was treated with a preformed solution of PPh_3 and DEAD (formed by addition of 69 μL (0.28 mmol) of DEAD to a solution of 31 mg (0.28 mmol) of PPh_3 in 5 mL of THF at 25 °C). After the mixture was stirred for 24 h at 25 °C, the reaction mixture was neutralized with 5% $NaHCO_3$ solution and extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 99 mg (57%) of methoxy bicyclic lactone **10a** as an oil. The product of the Mitsunobu reaction was identical by IR, ^{1}H and ^{13}C NMR spectroscopy to the spectra of the starting material, bicyclic lactone **10a**, described in the above experimental.

Methoxy Bicyclic Lactone 13a. A solution of *p*-TsOH (25.0 mg, 0.120 mmol) in 3 mL of MeOH was added to a solution of bicyclic lactone **12** (386 mg, 1.21 mmol) in 3 mL of MeOH at 25 °C. After 30 min at 25 °C, the reaction was neutralized with 5% $NaHCO_3$ solution. The MeOH was evaporated in vacuo, and the remaining crude mixture was extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 5 mL of saturated NaCl and 5 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 316 mg (79%) of a 2:1 mixture of anomeric methoxy bicyclic lactone **13a** as a colorless oil. The diastereomers were separated by chromatography, with only the major anomer **13a** being used for subsequent chemistry. High R_f product (**13a-major**): R_f = 0.67, 50% EtOAc/hexane; IR (CCl_4) 3031 (s), 2968 (s), 2937 (s), 1743 (s), 1493 (m), 1456 (s), 1381 (s), 1300 (s), 1212 (s), 1181 (s), 1075 (s); ^{1}H NMR (C_6D_6) δ 0.76 (d, 3H, J = 7.0), 1.24 (s, 3H), 1.37 (m, 1H), 1.91 (m, 2H), 2.38 (m, 2H), 2.65 (m, 1H), 3.04 (s, 3H), 3.24 (m, 2H), 3.82 (m, 1H), 3.97 (dt, 1H, J = 7.8, 8.9), 4.21 (d, 2H, J = 1.9), 7.08−7.24 (m, 5H); ^{13}C NMR (C_6D_6) δ 12.7, 20.7, 31.9, 37.8, 41.0, 43.0, 48.3, 71.2, 73.2, 73.6, 76.3, 107.5, 127.8, 128.3, 128.6, 139.3, 172.4; LRMS (EI) 303 ((M^+) − 31, 69), 173 (28), 160 (100), 159 (20), 145 (20), 127 (23), 113 (29), 105 (21); HRMS (EI) calcd for $C_{19}H_{26}O_5$ 303.1596 (M+), found 303.1613. Low R_f product (**13a-minor**): R_f = 0.58, 50% EtOAc/hexane; IR (CCl_4) 3031 (m), 2968 (s), 2908 (s), 1749 (s), 1497 (m), 1452 (s), 1378 (s), 1360 (s), 1200 (s); ^{1}H NMR (C_6D_6) δ 0.78 (d, 3H, J = 7.0), 1.16 (s, 3H), 1.38−1.65 (m, 2H), 1.79−2.01 (m, 2H), 2.42 (m, 1H), 2.98 (s, 3H), 3.11−3.32 (m, 2H), 3.73 (m, 1H), 4.02 (m, 2H), 4.19 (m, 2H), 7.03−7.24 (m, 5H); ^{13}C NMR (C_6D_6) δ 12.8, 20.9, 33.7, 37.9, 40.6, 42.8, 48.5, 71.3, 73.2, 75.5, 75.6, 108.2, 128.0, 128.2, 128.4, 139.1, 171.2.

Methoxy Bicyclic Lactone 13a Prepared by the Mitsunobu Reaction. A solution of NaOH (0.052 mL of 20% w/v, 0.26 mmol) was added to a solution of the major methoxy bicyclic lactone **13a** (From above experimental) (86 mg, 0.26 mmol) in 2 mL of MeOH at 25 °C. After addition was complete, the solution was heated at 70 °C for 3 h. The MeOH was evaporated in vacuo to provide a carboxylate. This crude salt was dissolved in 5 mL of THF, and 54 mg (0.26 mmol) of *p*-TsOH in 5 mL of THF was added. The reaction mixture of acid **14** was treated with a preformed solution of PPh_3 and DEAD (formed by addition of 45 μL (0.26 mmol) of DEAD to a solution of 68 mg (0.26 mmol) of PPh_3 in 3 mL of THF at 25 °C). After the mixture was stirred for 24 h at 25 °C, the reaction mixture was neutralized with 5% $NaHCO_3$ solution and extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 31 mg (62%) of methoxy bicyclic lactone **13a** as an oil. The product of the Mitsunobu reaction was identical by IR and ^{1}H and ^{13}C NMR spectroscopy to the spectra of the starting material, bicyclic lactone **13a**, described in the above experimental.

Methoxy Bicyclic Lactone 16a. A solution of *p*-TsOH (4.0 mg, 0.019 mmol) in 2 mL of MeOH was added to a solution of bicyclic lactone **15** (63 mg, 0.19 mmol) in 2 mL of MeOH at 25 °C. After 30 min at 25 °C, the reaction was neutralized with 5% $NaHCO_3$ solution. The MeOH was evaporated in vacuo, and the remaining crude mixture was extracted with 3 × 20 mL of EtOAc. The combined organic layers were washed with 5 mL of saturated NaCl and 5 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 60 mg (92%) of a 2:1 mixture of anomeric methoxy bicyclic lactone **16a** as a colorless oil. The anomers were separated by chromatography, with only the major anomer being used in subsequent chemistry. High R_f product (**16a-major**): R_f = 0.71, 50% EtOAc/hexane; IR (CCl_4) 3031 (m), 2970 (s), 2938 (s), 1749 (s), 1453 (s), 1380 (s), 1220 (s), 1187 (s), 1109 (s), 1068 (s); ^{1}H NMR (C_6D_6) δ 0.69 (d, 3H, J = 7.0), 0.73 (d, 3H, J = 6.7), 1.22 (s, 3H), 1.61 (m, 1H), 1.86 (m, 1H), 2.32 (d, 2H, J = 8.7), 2.77 (q, 1H, J = 8.7), 3.00 (s, 3H), 3.17 (dd, 1H, J = 5.7, 8.7), 3.49 (m, 2H), 3.95 (dd, 1H, J = 1.9, 10.7), 4.30 (s, 2H), 7.17−7.31 (m, 5H); ^{13}C NMR (C_6D_6) δ 8.6, 14.1, 20.4, 33.9, 37.6, 41.3, 42.9, 48.1, 72.1, 73.3, 77.9, 80.6, 107.1, 127.5, 127.8, 127.9, 139.1, 172.4; LRMS (EI) 317 ((M^+) − 31, 99), 160 (88), 159 (51), 91 (100). Low R_f product (**16a-minor**): R_f = 0.60, 50% EtOAc/hexane; IR (CCl_4) 3033 (m), 2974 (s), 2939 (s), 1748 (s), 1456 (s), 1382 (s), 1220 (s), 1189 (s), 1143 (m), 1099 (s), 1019 (s); ^{1}H NMR (C_6D_6) δ 0.75 (d, 3H, J = 6.9), 0.79 (d, 3H, J = 6.7), 1.16 (s, 3H), 1.58 (m, 1H), 1.72−1.89 (m, 2H), 2.45 (m, 1H), 2.95 (s, 3H), 2.98 (m, 1H), 3.18 (dd, 1H, J = 5.7, 8.9), 3.52 (m, 2H), 3.91 (dd, 1H, J = 1.9, 10.7), 4.31 (d, 2H, J = 3.4), 7.09−7.32 (m, 5H); ^{13}C NMR (C_6D_6) δ 8.8, 14.1, 20.7, 34.1, 38.4, 40.8, 42.8, 48.4, 72.1, 73.5, 77.0, 82.6, 107.9, 127.5, 127.8, 128.0, 140.4, 174.4; LRMS (EI) 317 ((M^+) − 31, 100), 160 (44), 91 (99), 82 (62).

Methoxy Bicyclic Lactone 16a Prepared from the Mitsunobu Reaction. A solution of NaOH (0.054 mL of 20% w/v, 0.27 mmol) was added to a solution of the major methoxy

bicyclic lactone **16a** (from the above experiment) (93 mg, 0.27 mmol) in 2 mL of MeOH at 25 °C. After addition was complete, the solution was heated at 70 °C for 1.5 h. The MeOH was evaporated in vacuo to provide a carboxylate. This crude salt was dissolved in 5 mL of THF, and 55 mg (0.26 mmol) of *p*-TsOH in 5 mL of THF was added. The reaction mixture of acid **17** was treated with a preformed solution of PPh_3 and DEAD (formed by addition of 47 μL (0.26 mmol) of DEAD to a solution of 70 mg (0.26 mmol) of PPh_3 in 5 mL of THF at 25 °C). After the mixture was stirred for 24 h at 25 °C, the reaction mixture was neutralized with 5% $NaHCO_3$ solution and extracted with 3 × 30 mL of EtOAc. The combined organic layers were washed with 10 mL of H_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue by flash chromatography (50% EtOAc/hexane) gave 70 mg (75%) of methoxy bicyclic lactone **16a** as an oil. The product of the Mitsunobu reaction was identical by IR and ^1H and ^{13}C NMR spectroscopy to the spectra of the starting material, bicyclic lactone **16a**, described in the above paragraph.

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Supporting Information Available: ^1H NMR spectra of compounds whose spectra have been reported in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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