Convergent Synthesis of Polyether Ionophore Antibiotics: Protective Manipulation and Synthesis of Monensin A[1]

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Abstract: The protective manipulation and synthesis of the polyether antibiotic monensin is described. The hydroxyl groups and the carboxylic acid of monensin are protected, and its spiroketal is equilibrated to provide naturally derived, advanced targets for comparison to the synthetic materials. The total synthesis of these targets from spiroketal acids **3ax** and **3eq** and tricyclic glycal **4** by a highly convergent ester enolate Claisen rearrangement is described. Finally, the deprotection of each to monensin is described.

After we prepared spiroketal acids **3ax** and **3eq** and tricyclic glycal **4**[2] (Scheme I) for the final ester enolate Claisen rearrangement that will form the monensin skeleton (**2ax** and **2eq**), it became important to have available reference material for the stereochemical evaluation of the outcome of this strategically crucial reaction. On the basis of earlier experience with such coupling reactions,[3] both isomers at the C-12 position could be expected and the availability of a natural derivative would facilitate the identification of the desired isomer.

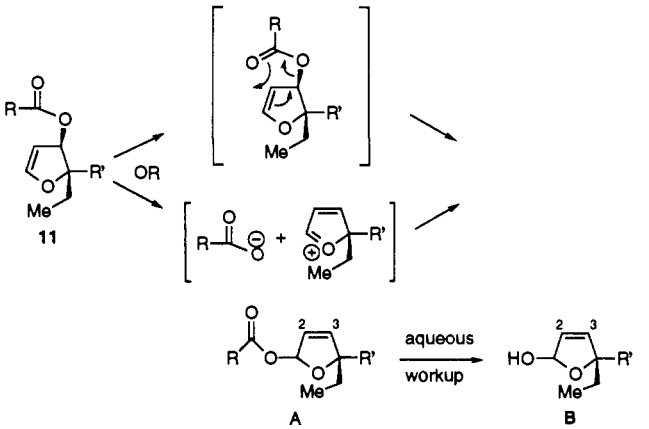
In addition, the previous efforts yielded the two spiroketal isomers of the left-side acid (**3eq** and **3ax**), both of which were to be utilized in the Claisen rearrangement. Both spiroketal isomers of protected, naturally derived monensin were therefore required for comparison purposes. Armed with the knowledge that the spiroketal of the left-side portion underwent equilibration to a mixture of isomers when the secondary hydroxyl was protected,[2] we were hopeful that a similarly protected, naturally derived monensin substrate would undergo equilibration, producing both of the desired targets **2eq** and **2ax**.

When a survey of the literature on the protection of monensin provided only nonselective methodology,[4] a simple scheme was developed which efficiently served our purposes. The free acid lactol of monensin acid **1** (Scheme II) was first converted to the methyl ketal with acidic methanol and methyl orthoformate. Conversion of the acid to the methyl ester was less straightforward. Treatment of the acid with diazomethane at this stage, when the C-7 or C-26 alcohols were unprotected, led to several products other than the expected methyl ester.[5] An attempt to use standard DCC coupling conditions[6] gave the monensin *N*-acylurea[7] as a major byproduct in addition to the methyl ester. The use of a literature modification of this procedure,[7] which prescribed the addition of DMAP·HCl, decreased the amount of *N*-acylurea produced and afforded methyl ester–methyl ketal **5** in good yield.

Selective protection of the C-26 primary hydroxyl was readily achieved with SEMCl (**6**), and then the remaining secondary alcohol at C-7 was protected as the MOM ether (**7ax**). As expected,[2,8] this spiroketal ester underwent acid-catalyzed equilibration under the conditions used for introduction of the methyl ketal, and the resulting separable mixture of naturally (**7ax**) and unnaturally (**7eq**) configured spiroketals was obtained in a ratio of 3.6:1. Reduction of each methyl ester to the alcohol followed, and then silylation with TBSCl gave both fully protected monensin derivatives **2eq** and **2ax**.

Concurrent with these degradative studies on monensin, an investigation of the crucial ester enolate Claisen rearrangement was carried out. The initial attempt under standard conditions gave poor results. Esterification of the acid chloride of **3eq** with the lithium alcoholate of the right-side tricyclic glycal **4** followed by enolization with LDA at −78 °C, silylation with TMSCl, warming, and aqueous workup gave a complex mixture of products. The major identifiable product was the silylated glycal which was recovered in 50% yield. The one-pot, multistep nature

(1) No reprints of this paper are available.
(2) Ireland, R. E.; Armstrong, J. D., III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* Preceding paper in this issue.
(3) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294. Ireland, R. E.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3279–3285.
(4) Agtarap, A.; Chamberlain, J. W.; Pinkerton, M.; Steinrauf, L. *J. Am. Chem. Soc.* **1967**, *89*, 5737–5739.
(5) Some of the byproducts may have been methyl ethers, the products of methylation of the hydrogen-bonded alcohols, similar to a case reported by Evans for polyether ionophore X-206. See: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526.
(6) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475–4478.
(7) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.
(8) In their syntheses of monensin, both Still and Kishi used acid-catalyzed equilibrations of the spiroketal to obtain one spiroketal from a mixture. In their cases, the C-7 hydroxyl was unprotected, allowing hydrogen bonding to occur. See: (a) Cai, D.; Still, W. C. *J. Org. Chem.* **1988**, *53*, 4643–4644. (b) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L. J.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262–263.
(9) Ireland, R. E.; Habich, D. *Chem. Ber.* **1981**, *114*, 1418–1427.
(10) This material was available from an aborted alternative right-side glycal synthesis. Its preparation is described in the supplementary material.
(11) Monitoring of the esterification reaction by silica gel or alumina TLC proved useless because the product ester apparently decomposed by a Ferrier rearrangement. See: Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 570–575. Wittman, M. D.; Halcomb, R. J.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 1979–1981. Intermediate **A** was not isolated from this reaction mixture but was observed by NMR under different reaction conditions (see footnote 12). Neutral aqueous workup of this reaction following attempted Claisen rearrangement provided hydrolyzed lactol **B**. This isolated compound had distinguishing H2 and H3 resonances in a multiplet centered at 5.81 ppm, quite different from the olefinic protons of the starting glycal.



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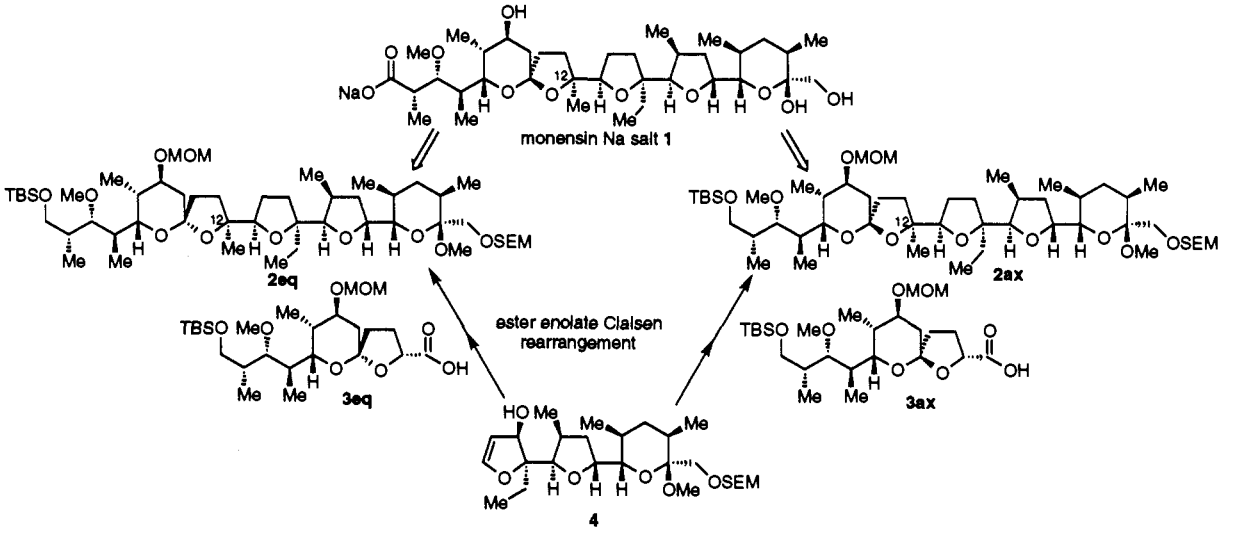
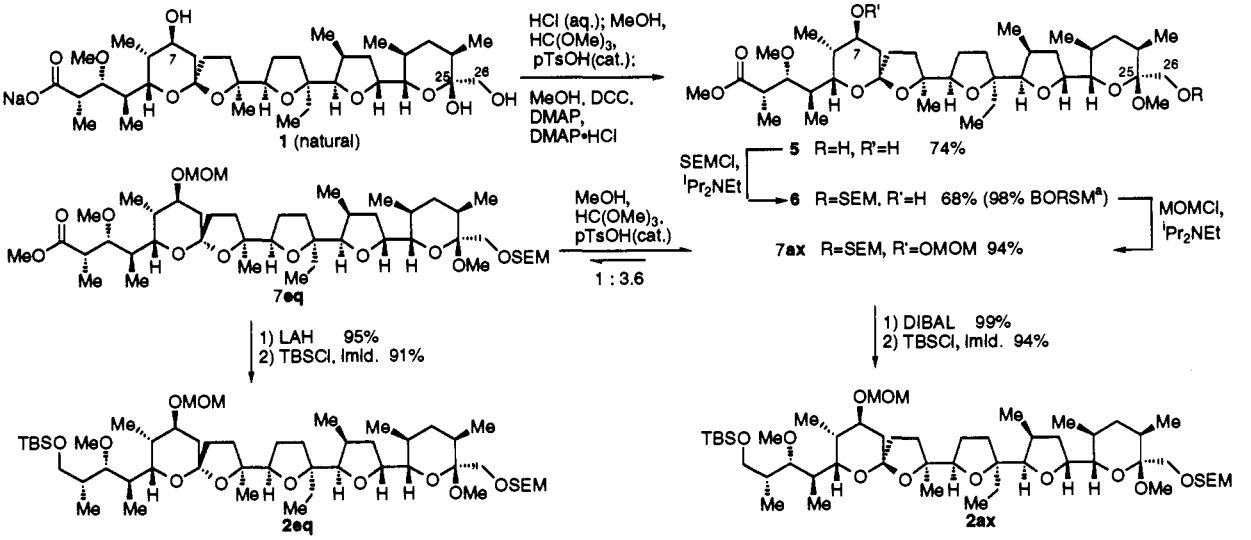
Scheme I

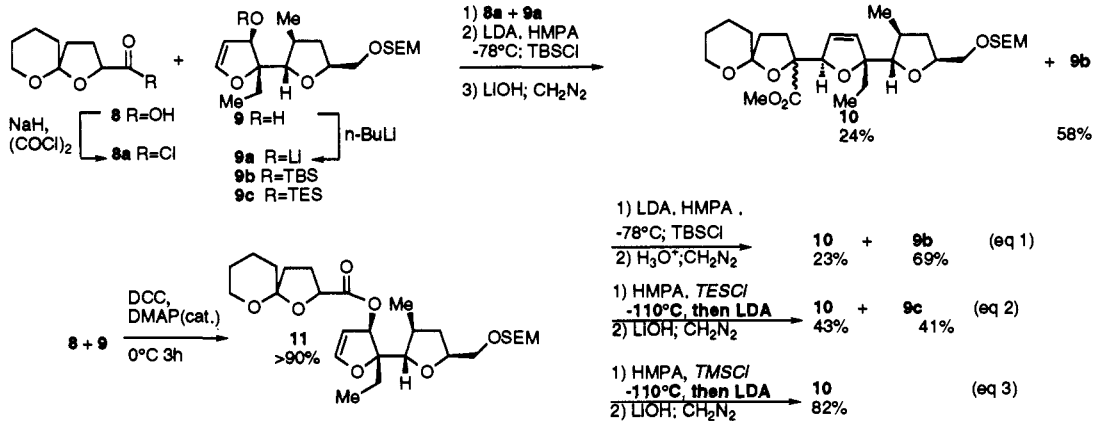


Scheme II



[a] Based on recovered starting material.

Scheme III

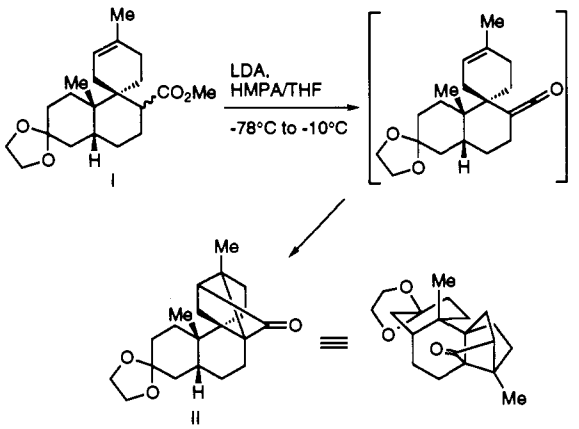


of this reaction made identification of the problematic step(s) difficult. Since the synthetic monensin subunits were too valuable to consume in a study of this Claisen reaction, it was decided that spiroketal acid **8**[9] and bicyclic glycal **9**[10] would be employed as model substrates for this work (Scheme III).

Repetition of the above conditions on the model system gave only a 24% yield of coupled rearranged methyl esters **10**. The majority of the glycal was again recovered as its TBS ether **9b**. This result seemed to indicate that the initial esterification was not proceeding to completion. Attempts to follow the ester formation under these conditions were prevented by the instability of the ester, which may be a consequence of its propensity to undergo Ferrier-type rearrangement.[11] The ester formed under these basic conditions proved unstable to silica gel TLC, and any

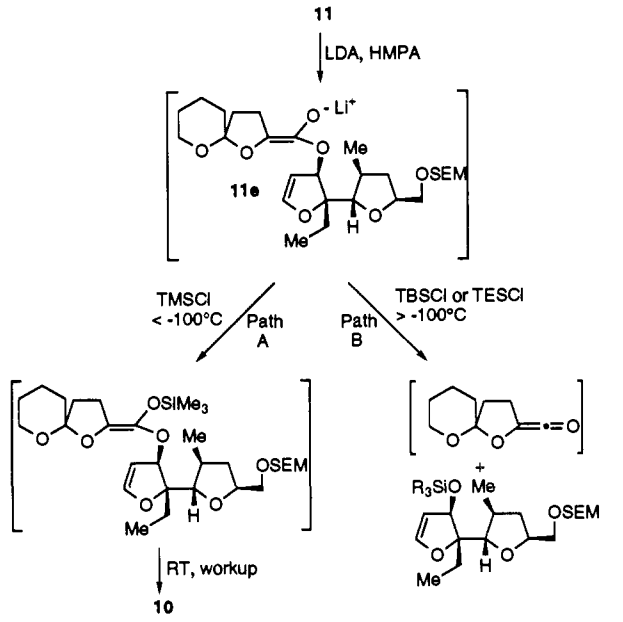
attempt to effect purification by silica gel, Florisil, or alumina chromatography or even simple aqueous workup led to decomposition. In an effort to carry out esterification under conditions which might permit ester isolation, standard neutral carbodiimide coupling[6] was explored. After some experimentation, it was found that treatment of a mixture of acid **8** and glycal **9** with excess DCC and catalytic DMAP at 0 °C for 3 h and then dilution with hexane and filtration gave ester **11** in greater than 90% yield. Extended reaction times or higher reaction temperatures led to significant amounts of Ferrier-type rearrangement,[12] but the neat product ester proved to be moderately stable.

With ester **11** in hand, we next investigated the Claisen rearrangement. Enolization of ester **11** with LDA at −78 °C and then trapping of the enolate with TBSCl again led to a low yield of product esters **10** and a large amount of silyl glycal **9b** (eq 1, Scheme III). This apparent partial fragmentation of ester **11** was interpreted as an undesired reaction pathway *following enolization or silylation* not as decomposition of unenolized ester in the reaction workup. The latter case would give Ferrier-type rearranged glycal, which was not isolated in a significant amount. This interpretation limited the problem to one of two possibilities: either the enolate was fragmenting before silylation or the silyl ketene acetal was fragmenting before rearrangement. Earlier work pointed toward the first possibility: an acetate enolate[13] had shown evidence of a side reaction in the form of an α-elimination that led to ketene formation, and enolization of sterically congested ester I clearly generated a ketene which was intramolecularly trapped as cyclobutanone II.[14]



This type of fragmentation would account for the recovery of the glycal portion from the attempted Claisen rearrangement on preformed ester **11**. The avoidance of this undesired reaction pathway apparently required rapid trapping of the enolate as its silyl ketene acetal. The temperature was therefore lowered to −110 °C to extend the life of the enolate, and a more reactive silylating agent, TESCl, was used. This doubled the yield of rearranged ester, but a considerable amount of fragmented silylated glycal was still produced (eq 2, Scheme III). The use of the even more reactive TMSCl further extended this approach, the yield again doubled to a very satisfactory 82%, and no silylated glycal was recovered (eq 3, Scheme III). A working hypothesis is illustrated in Scheme IV. At higher temperatures, with less reactive silylating agents, the enolate apparently favors path B and eliminates to give the ketene and glycalate which is then silylated. The lack of recovery of the acid portion is probably due

Scheme IV



to the numerous products the ketene can form.[15] At lower temperatures, with highly reactive trapping agents, the enolate favors expected path A.

Having defined the required reaction conditions for the model system, we then reinvestigated the synthetically relevant system. Esterification of glycal **4** with spiroketal acid **3eq** (Scheme V) was attempted first. Spiroketal isomer **3eq** was the major product of synthesis of the left side[2] and therefore more readily available. Experimentation showed these larger components to be somewhat less reactive, and higher concentration and temperature were required to obtain about a 75% yield in the esterification step.

Subsequent Claisen rearrangement under the modified conditions above led to a 58% yield of an inseparable mixture of product methyl esters in a ratio of 1:2.6 and 27% yield of silylated glycal **4a**. Desilylation of silyl ether **4a** cleanly afforded starting glycal which was used in subsequent rearrangements. When the unsaturated ester mixture was subjected to hydrogenation over palladium on carbon, a complex mixture of products was obtained that probably was the result of the Lewis acid catalyst. Hydrogenation over neutralized Raney nickel was clean, and reduction with lithium aluminum hydride furnished separable alcohols **12a** and **12b** in 14% and 37% yield, respectively, over the multistep sequence. With the carbon skeleton of monensin now fully assembled, only functional group manipulation and deprotection remained. Unfortunately, the expectation that the required deoxygenation of hindered alcohols **12a** and **12b** would be troublesome proved correct.[16] Intermolecular displacement of the derived triflate with halides or hydride failed. An acceptable method proved to be the use of a Barton thiocarbonate-based radical deoxygenation[17] procedure which resulted in the formation of the desired methyl-bearing compounds **2eq** and **2b** in mediocre yields. Comparison of each of these diastereoisomers to the naturally derived material described above showed that the minor diastereoisomer possessed the correct C-12 configuration and was therefore assigned **2eq**.

In a similar sequence, acid **3ax** was coupled to the glycal, rearranged, and reduced to give alcohols **13a** and **13b** in a 1:2

(12) The accumulation of Ferrier reaction products (structure A, footnote 11) in these reactions could be easily monitored by ^{13}C NMR. The resonances for C2 and C3 were found at 125 and 139 ppm, positions similar to the resonances of the corresponding carbons in product esters **10** (~127 and 138 ppm).

(13) Ireland, R. E.; Mueller, R. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

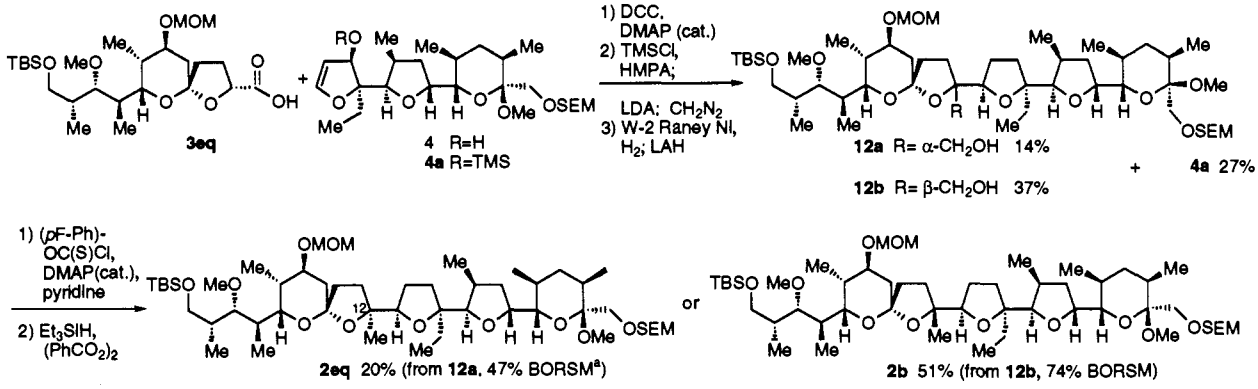
(14) Ireland, R. E.; Aristoff, P. A. *J. Org. Chem.* **1979**, *44*, 4323–4331. Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisrivongs, S. *J. Org. Chem.* **1984**, *49*, 1001–1013.

(15) For an account of the reactivity and various facile reactions of ketenes, see: Patai, S. *The Chemistry of Ketenes, Allenes, and Related Compounds*; John Wiley and Sons: New York, 1985; Chapters 7 and 8.

(16) A structurally similar methyl ester was found to be extremely resistant to nucleophilic attack. See: Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285–3294.

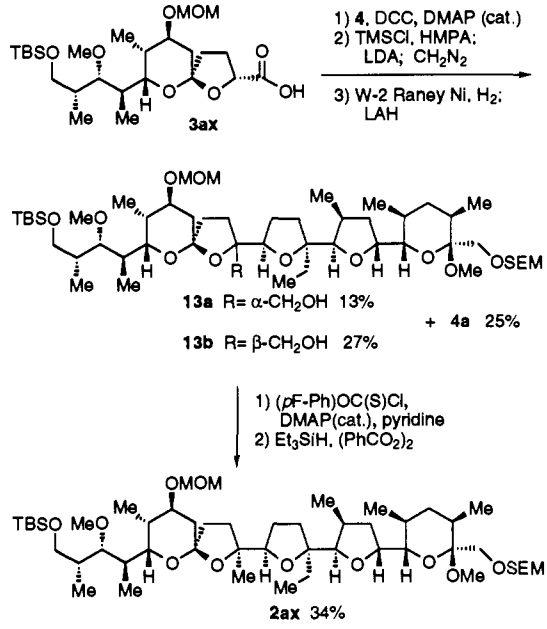
(17) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron* **1991**, *32*, 7187–7190.

Scheme V



[a] Based on recovered starting material.

Scheme VI



ratio (Scheme VI). As in the first case, minor alcohol **13a** was shown to have the correct configuration at C-12 after deoxygenation and comparison to the naturally derived material. Both spiroketal isomers **3eq** and **3ax** of the left-side acid can therefore be utilized in this convergent process for the synthesis of crucial monensin intermediates **2eq** and **2ax**. For the completion of this synthesis, polyethers **2eq** and **2ax** must be deprotected.

First, removal of the TBS ethers of **2eq** and **2ax** (Scheme VII) with TBAF gave alcohols **14eq** and **14ax**. Oxidation of each of these alcohols to the acids and esterification with diazomethane gave methyl esters **7eq** and **7ax**. Hydrolysis of the MOM and SEM ketals without adversely affecting the two monensin ketals then presented a challenge. Removal of the MOM ether was best accomplished by the treatment of each tetraketal **7eq** and **7ax** with several equivalents of dimethylboron bromide followed by hydrolytic workup.[18] This procedure gave a mixture of two major products, in which the C-25 methyl ketal was completely hydrolyzed. Reketalization of this mixture from each cleavage experiment led not only to the reestablishment of the C-25 methyl ketal but also to the equilibration of the hydroxyl–spiroketal portion to the system with the hydrogen-bonded axial C-9 oxygen substituent. The major product in each case was alcohol **6**, in which the MOM ether was removed, and the minor product diol **5**, in which both the MOM and SEM ethers were removed. The use of additional dimethylboron bromide in an attempt to complete the deprotection resulted in lower overall yields and increased decomposition.[19] Although the yield for the deprotection of **7eq** is somewhat low (55% yield of combined **5** + **6**), it should be noted that the starting material can be easily equilibrated to spiroketal isomer **7ax** (as in Scheme II), which is more efficiently deprotected (74% combined yield). An interesting note is the increased yield in the removal of the MOM in these substrates over that of the less complex left-side portion.[2]

Each of these products was then carried on to monensin. Hydrolysis of the methyl ester of methyl ester–methyl ketal **6** followed by removal of the SEM ether with CsF in HMPA and hydrolysis of the methyl ketal[8a] gave monensin, Na salt in good yield.

This completes a total synthesis of monensin. Even though the original obstacles associated with the construction of spiroketal acids **3eq** and **3ax** and tricyclic glycal **4** have been efficiently overcome,[2] the final stages of the synthesis leave much to be desired. The observation that the ester enolate Claisen rearrangement is a useful reaction for the union of two large subunits justifies the use of this reaction sequence in convergent strategies. For maximum efficiency, control of the stereochemical outcome of this process must be improved. Equally frustrating is the deoxygenation of the C-12 hydroxymethyl group, and a more efficient method will be necessary if this overall synthetic approach is to meet program goals. Both of these problems are currently under investigation; results will be forthcoming.

Experimental Part

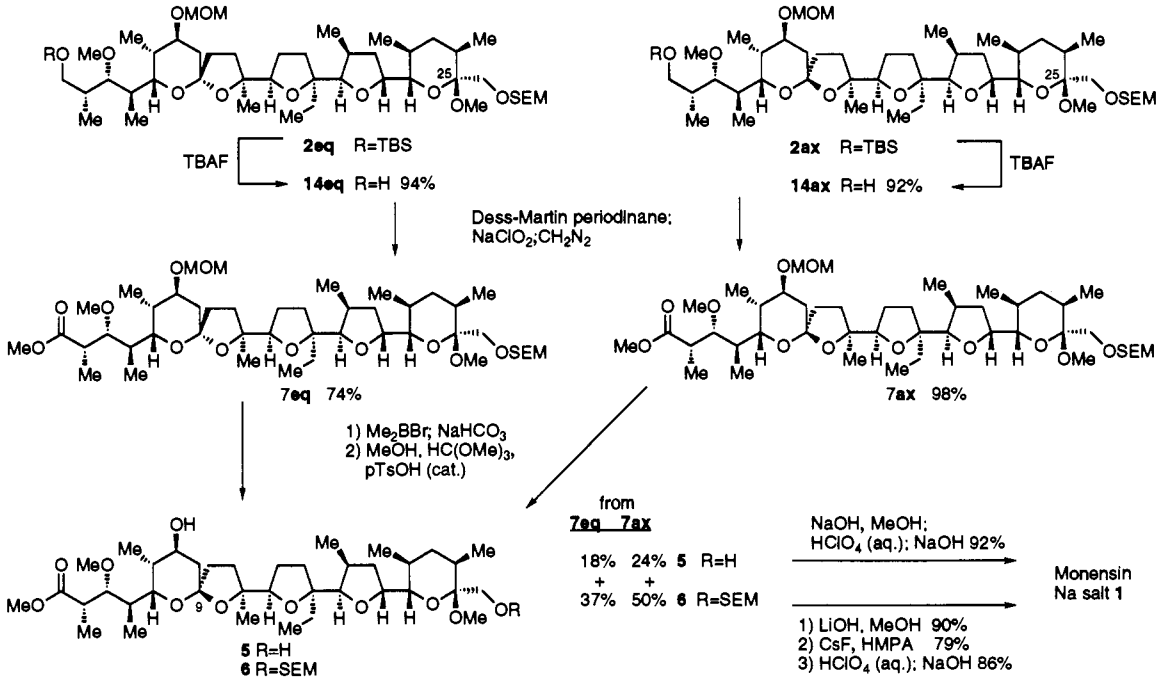
The scheme and experimental details for the preparation of model glycal **9** are contained in the supplementary material. General experimental methods have been reported previously.[2] All ^1H NMR J values are reported in hertz.

Monensin Methyl Ketal Methyl Ester (5). To a solution of 1.0 g (1.49 mmol) of monensin, Na salt (Sigma) in 10 mL of THF and 5 mL of water was added concentrated HCl to achieve pH 2. Following dilution with ether and separation, the aqueous layer was extracted with ether and the combined organics were dried over $MgSO_4$. Evaporation gave monensin acid, which was then dissolved in 20 mL of dichloromethane, and 9 mL of MeOH, 1 mL of $HC(OMe)_3$ and 5 mg of TsOH were added. After 1.5 h, the solution was diluted with hexane and filtered through silica gel (3 × 5 cm), washing with ethyl acetate. Following evaporation, the residue was dissolved in 20 mL of dichloromethane, and 0.327 g (2.68 mmol) of DMAP, 0.354 g (2.23 mmol) of DMAP·HCl, and 1.81 mL (4.7 mmol) of MeOH were added. Then, 0.461 g (2.23 mmol) of DCC was added in 3 mL of dichloromethane over 5 min. After 6 h, the solvent was evaporated and the residue chromatographed on silica gel (5 × 12 cm, 30% ethyl acetate/hexane) to give 0.766 g (74%) of monensin methyl ketal methyl ester (**5**): $[\alpha]^{23}_D$ +64° (c 1.21, $CHCl_3$); IR (neat) 3500, 2950, 1734, 1455, 1370, 1090, 1045 cm^{-1}; ^1H NMR δ 0.820 (m, 15H),

(18) Guindon, Y.; Yoakin, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912–3920.

(19) The attempted deprotection of the bis-MOM (instead of the MOM–SEM) analog was similar; much decomposition occurred in an attempt to completely deprotect with $BBrMe_2$.

Scheme VII



0.935 (d, 3H, J = 6.9), 1.14 (d, 3H, J = 6.9), 1.21–1.98 (m, 20H), 1.28 (s, 3H), 2.21(m, 2H), 2.58 (m, 2H), 3.21 (s, 3H), 3.28, (s, 3H), 3.33 (m, 3H), 3.62 (m, 2H), 3.65 (s, 3H), 3.87 (m, 2H), 4.02 (d, 1H, J = 9), 4.24 (m, 1H); ^{13}C NMR δ 8.2, 11.5, 12.4, 12.8, 16.1, 16.8, 17.8, 25.1, 27.6, 28.8, 32.4, 32.6, 32.9, 33.6, 34.8, 35.1, 36.1, 36.3, 37.2, 37.4, 39.4, 41.3, 48.7, 52.1, 58.6, 64.0, 68.3, 71.7, 77.2, 78.0, 82.0, 83.9, 86.1, 86.4, 88.0, 99.6, 107.9, 176.1. Anal. Calcd for $C_{38}H_{66}O_{11}$: C, 65.30; H, 9.52. Found: C, 65.36; H, 9.46.

Monensin Alcohol 6 (from Monensin Methyl Ketal Methyl Ester (5)). To a solution of 0.435 g (0.601 mmol) of diol **5** in 4 mL of dichloromethane and 0.825 mL (4.73 mmol) of ^{i}Pr$_2$NEt at 0 °C was added 0.524 g (2.96 mmol) of SEMCl. After 30 min (prolonged reaction times gave significant amounts of the bis-SEM ether), 2 mL of saturated sodium bicarbonate was added and the mixture allowed to warm and stir for 10 min. The mixture was extracted with ether and dried over $MgSO_4$. Chromatography of the residue on silica gel (2.5 × 12 cm, 20–40% ethyl acetate/hexane) gave 0.352 g (68%) of mono-SEM ether **6** and 0.0885 g (20%) of the starting diol: $[\alpha]^{23}_D$ +51.2° (c 1.65, $CHCl_3$); IR (neat) 3505, 2925, 1730, 1450, 1370, 1240, 1090, 1040 cm^{-1}; ^{1}H NMR δ –0.01 (s, 9H), 0.895 (m, 17H), 0.98 (d, 3H, J = 6.9), 1.18 (d, 3H, J = 6.9), 1.20–2.21 (m, 22H), 2.62 (m, 1H), 3.22 (s, 3H), 3.32 (s, 3H), 3.30–3.70 (m, 7H), 3.69 (s, 3H), 3.80 (dd, 1H, J = 10.4, 3.4), 3.98 (m, 2H), 4.20 (m, 1H), 4.66 (AB q, 2H, J = 2.4, 6.6); ^{13}C NMR δ –1.0, 8.6, 11.4, 12.4, 12.9, 16.3, 16.5, 18.0, 18.5, 24.2, 28.7, 30.0, 31.3, 32.0, 33.6, 34.6, 35.2, 35.5, 35.8, 37.4, 37.0, 39.0, 41.4, 48.5, 52.3, 58.6, 65.5, 68.3, 69.6, 71.8, 77.5, 77.8, 82.0, 82.3, 85.3, 87.0, 88.6, 95.6, 99.8, 107.7, 176.2. Anal. Calcd for $C_{44}H_{80}O_{12}Si$: C, 63.73; H, 9.72. Found: C, 63.68; H 9.62.

Monensin Methyl Ester 7ax (from Alcohol 6). To a solution of 0.190 g (0.211 mmol) of alcohol **6** in 1 mL of dichloromethane and 0.551 mL (3.16 mmol) of ^{i}Pr$_2$NEt was added 0.160 mL (2.11 mmol) of MOMCl. After 3 days, 1 mL of saturated sodium bicarbonate was added and the mixture allowed to stir for 10 min. The mixture was extracted with ether and dried over $MgSO_4$. Chromatography of the residue on silica gel (2.5 × 12 cm, 20% ethyl acetate/hexane) gave 0.322 g (94%) of ether **7ax** as a colorless oil: $[\alpha]^{23}_D$ +66.7° (c 1.08, $CHCl_3$); IR (neat) 2950, 1740, 1460, 1375, 1245, 1110, 1050, 840 cm^{-1}; ^{1}H NMR δ –0.017 (s, 9H), 0.883 (m, 17H), 0.97 (d, 3H, J = 6.6), 1.16 (d, 3H, J = 6.6), 1.20 (s, 3H), 1.28–2.21 (m, 21H), 2.62 (m, 1H), 3.20 (s, 3H), 3.29 (s, 3H), 3.33 (s, 3H), 3.35–3.64 (m, 8H), 3.68 (s, 3H), 3.88 (d, 1H, J = 11.1), 3.92 (d, 1H, J = 4.5), 4.19 (m, 1H), 4.56 (AB q, 2H, J = 1.8, 6.9), 4.71 (d, 1H, J = 6.9); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ –1.0, 8.5, 11.1, 12.4, 13.1, 16.3, 16.6, 18.1, 18.5, 24.4, 28.7, 29.9, 31.4, 32.1, 32.8, 33.6, 34.1, 34.6, 35.5, 35.7, 37.2, 37.6, 40.6, 41.0, 48.5, 52.2, 55.4, 58.5, 65.5, 68.4, 69.6, 74.8, 77.6, 77.8, 82.1, 82.6, 85.4, 86.6, 87.5, 94.2, 95.6, 9.7, 106.1, 176.3. Anal. Calcd for $C_{46}H_{84}O_{13}Si$: C, 63.27; H, 9.70. Found: C, 63.42; H, 9.67.

Monensin Methyl Ester 7eq (from Ester 7ax). A stirred solution of 0.738 g (0.844) of ester **7ax** in 16 mL of CH_2Cl_2 was treated with 14.6 mL of MeOH, 1.6 mL of $HC(OMe)_3$, and 20 mg of TsOH at room temperature. After 6 h, saturated sodium bicarbonate was added and the product was isolated by extraction with ether. Chromatography of the crude product on silica gel (4 × 12 cm, 20% ethyl acetate/hexane) gave 0.563 g (76%) of recovered ester **7ax**. Further elution provided 0.156 g (21%) of ester **7eq** as an oil: $[\alpha]^{23}_D$ +36.3° (c 1.12, $CHCl_3$); IR (neat) 2980, 1740, 1460, 1370, 1250, 1150, 1040, 920, 840 cm^{-1}; ^{1}H NMR δ 0.01 (s, 9H), 0.86–0.97 (m, 18H), 1.12 (s, 3H), 1.18 (d, 3H, J = 6.9), 1.23–2.35 (m, 23H), 2.61 (m, 1H), 3.24 (s, 3H), 3.33 (s, 3H), 3.36 (s, 3H), 3.38–3.67 (m, 7H), 3.69 (s, 3H), 3.74 (m, 1H), 4.01 (d, 1H, J = 3.3), 3.87 (dd, 1H, J = 7.5 and 7.5), 4.23 (m, 1H), 4.63 (s, 2H), 4.68 (s, 2H); ^{13}C NMR δ –1.0, 8.5, 11.6, 12.5, 12.9, 16.3, 16.5, 18.0, 18.4, 20.7, 27.8, 29.7, 30.9, 33.6, 33.7, 34.2, 34.6, 35.2, 35.5, 35.7, 36.3, 37.5, 37.7, 41.1, 48.4, 52.0, 55.7, 58.8, 65.4, 69.6, 72.3, 76.7, 77.9, 82.6, 83.7, 84.7, 85.0, 86.7, 94.8, 95.6, 99.7, 107.6, 176.4. Anal. Calcd for $C_{46}H_{84}O_{13}Si$: C, 63.27; H, 9.70. Found: C, 63.41; H, 9.61.

Monensin Alcohol 14ax (from Methyl Ester 7ax). To a solution of 0.250 g (0.307 mmol) of ester **7ax** in 3 mL of dichloromethane at –78 °C was added 1.22 mL (1.22 mmol) of 1.0 M DIBAL in hexane. After 10 min, the solution was allowed to warm to 0 °C and 4 mL of 0.5 M potassium sodium tartrate was added and the mixture allowed to stir for 10 min. The mixture was extracted with ether and dried over $MgSO_4$. Chromatography of the residue on silica gel (2.5 × 12 cm, 40% ethyl acetate/hexane) gave 0.238 g (99%) of alcohol **13ax** as a colorless oil: $[\alpha]^{23}_D$ +50.0° (c 1.22, $CHCl_3$); IR (neat) 3480, 2940, 1455, 1370, 1245, 1045, 835 cm^{-1}; ^{1}H NMR δ –0.012 (s, 9H), 0.88–0.99 (m, 23H), 1.22 (s, 3H), 1.25–2.38 (m, 22H), 3.21 (s, 3H), 3.33 (s, 3H), 3.34 (s, 3H), 3.4–3.6 (m, 10H), 3.95 (d, 1H, J = 3.6), 4.03 (dd, J = 1.2, 10.2), 4.19 (m, 1H), 4.59 (d, 1H, J = 6.9), 4.66 (AB q, 2H, J = 2.4, 6.9), 4.75 (d, 1H, J = 6.9); ^{13}C NMR δ –1.0, 8.6, 11.1, 12.5, 12.9, 16.4, 16.6, 18.1, 18.5, 24.6, 28.8, 29.9, 31.4, 32.0, 32.7, 33.6, 34.0, 34.6, 34.5, 35.7, 35.9, 37.0, 37.6, 40.7, 48.5, 55.7, 58.8, 65.5, 68.0, 68.9, 69.6, 75.7, 77.6, 77.9, 81.3, 82.8, 85.5, 86.7, 87.8, 94.5, 95.6, 99.8, 106.1. Anal. Calcd for $C_{45}H_{84}O_2Si$: C, 63.95; H, 10.02. Found: C, 64.05; H, 9.91.

Monensin Alcohol 14eq (from Methyl Ester 7eq). A solution of 0.155 g (0.180 mmol) of ester **7eq** in 2 mL of ether was added to 13.4 mg (0.35 mmol) of $LiAlH_4$ in 2 mL of ether at 0 °C. After 10 min, 0.5 mL of water was added followed by 1 mL of 2 M NaOH and Na_2SO_4. The mixture was filtered through Celite, and the solids were washed with ether. Chromatography of the crude product on silica gel (2.5 × 6 cm, 30% ethyl acetate/hexane) gave 0.143 g (95%) of the alcohol as a colorless oil: $[\alpha]^{23}_D$ +34.8° (c 1.71, $CHCl_3$); IR (neat) 3480, 2960, 2880, 1450, 1370, 1245, 1150, 1035, 940, 835 cm^{-1}; ^{1}H NMR δ –0.04 (s, 9H), 0.86–0.96 (m, 23H), 1.11 (s, 3H), 1.25–2.38 (m, 22H), 3.22 (s, 3H), 3.34 (s,

3H), 3.35 (s, 3H), 3.40–3.65 (m, 9H), 3.71 (m, 1H), 3.86 (dd, 1H, J = 7.2), 4.01 (d, 1H, J = 3.3), 4.21 (m, 1H), 4.63 (s, 2H), 4.67 (s, 1H); ^{13}C NMR δ –1.0, 8.5, 11.5, 12.3, 12.8, 16.4, 16.5, 18.0, 18.5, 20.6, 27.9, 29.8, 30.9, 33.4, 33.6, 34.3, 34.6, 35.4, 35.5, 35.7, 36.0, 36.3, 37.1, 47.7, 48.4, 56.1, 58.2, 66.5, 68.1, 69.7, 73.2, 77.4, 78.1, 78.7, 80.9, 83.7, 84.3, 85.1, 86.7, 95.6, 95.8, 99.7, 107.5. Anal. Calcd for $C_{45}H_{84}O_2Si$: C, 63.95; H, 10.02. Found: C, 64.13; H, 10.19.

Monensin Ether 2ax (from Alcohol 14ax). To a solution of 0.400 g (0.508 mmol) of alcohol **14ax** in 6 mL of DMF were added 0.173 g (2.54 mmol) of imidazole and 0.191 g (1.27 mmol) of TBSCl. After 2 h, the solution was poured into 20 mL of water and 25 mL of ether. The mixture was extracted with ether and dried over $MgSO_4$. Chromatography of the residue on silica gel (2.5 × 12 cm, 10% ethyl acetate/hexane) gave 0.430 g (94%) of silyl ether **2ax** as a colorless oil: $[\alpha]^{23}_D$ +46.7° (c 1.37, $CHCl_3$); IR (neat) 2920, 1460, 1375, 1245, 1050, 835 cm^{-1}; ^{1}H NMR δ –0.005 (s, 9H), 0.014 (s, 6H), 0.86 (s, 9H), 0.87 (m, 20H), 0.99 (d, 3H, J = 6.9), 1.23 (s, 3H), 1.25–2.22 (m, 22H), 3.22 (s, 3H), 3.31 (s, 3H), 3.34 (s, 3H), 3.20–3.67 (m, 10H), 3.97 (d, 1H, J = 4.5), 4.03 (d, 1H, J = 11.1), 4.21 (m, 1H), 4.58 (d, 1H, J = 6.9), 4.68 (AB q, 2H, J = 2.4, 6.6), 4.77 (d, 1H, J = 6.9); ^{13}C NMR δ –5.0, –5.12, –1.0, 8.5, 11.2, 11.9, 13.4, 16.3, 16.6, 18.0, 18.4, 18.6, 24.8, 26.2, 28.8, 29.8, 31.4, 31.8, 32.7, 33.5, 33.6, 34.6, 35.5, 35.7, 35.8, 36.8, 37.6, 40.8, 48.5, 55.5, 57.9, 65.4, 66.7, 69.6, 69.7, 75.0, 77.6, 77.8, 78.3, 88.3, 85.4, 86.6, 87.8, 94.3, 95.6, 99.7, 106.0. Anal. Calcd for $C_{51}H_{98}O_{12}Si_2$: C, 63.84; H,10.29. Found: C, 63.66; H, 10.43.

Monensin Ether 2eq (from Alcohol 14eq). Treatment of 0.143 g (0.169 mmol) of alcohol **14eq** in a manner similar to that described above for compound **14ax** and chromatography on silica gel (2.5 × 6 cm, 5–10% ethyl acetate/hexane) gave 0.147 g (91%) of ether **2eq**. Crystallization from MeOH gave colorless needles, mp 121–122 °C: $[\alpha]^{23}_D$ +28.1° (c 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ –0.003 (s, 9H), 0.01 (s, 3H), 0.02 (s, 3H), 0.81–0.96 (m, 23H), 0.86 (s, 9H), 1.11 (s, 3H), 1.24–2.38 (m, 22H), 3.22 (s, 3H), 3.31 (s, 3H), 3.33 (s, 3H), 3.39–3.72 (m, 10H), 3.86 (dd, 1H, J = 7.2), 4.01 (d, 1H, J = 3.3), 4.21 (m, 1H), 4.61 (s, 2H), 4.68 (AB q, 2H, J = 7.2); ^{13}C NMR δ –5.1, –1.0, 8.5, 11.2, 11.8, 13.2, 16.4, 16.5, 18.0, 18.5, 18.6, 20.7, 26.3, 27.8, 29.8, 31.0, 33.3, 33.6, 34.3, 34.6, 35.3, 35.6, 35.8, 36.3, 37.2, 37.7, 48.4, 55.8, 58.2, 65.5, 66.8, 69.7, 73.6, 76.9, 77.4, 78.1, 79.0, 83.8, 84.7, 85.1, 86.7, 94.9, 95.6, 99.7, 107.6. Anal. Calcd for $C_{51}H_{98}O_{12}Si_2$: C, 63.84; H,10.29. Found: C, 63.87; H, 10.21.

Model Claisen Methyl Esters 10 (from Acid 8 and Glycal 9). To a solution of 0.100 g (0.278 mmol) of glycal **9**[10] and 0.052 g (0.278 mmol) of acids **8**[9] (2 diastereomers, racemic) in 1.0 mL of CH_2Cl_2 at 0 °C was added 0.003 g (0.0278 mmol) of DMAP followed by 0.063 g (0.307 mmol) of DCC in 0.5 mL of CH_2Cl_2 over 20 min. After 3.5 h, the solution was diluted with 4 mL of hexane, filtered through Celite, and evaporated to give a residue (0.167 g, 107%) which was estimated by ^{1}H and ^{13}C NMR to contain the desired ester, <5% of the unreacted glycal, and the DMAP. To a solution of this residue in 1.0 mL of THF and 0.2 mL of HMPA at –78 °C was added 0.180 mL of TMSCl (1.42 mmol, freshly distilled from CaH_2). After the solution was cooled to approximately –105 °C (EtOH/ $N_{2(liquid)}$, bath temperature –110 °C), a solution of LDA (0.855 mmol, prepared in 1.0 mL of THF and 0.2 mL of HMPA) was added dropwise through a –78 °C cooling jacket. After 5 min at –100 °C, the solution was allowed to slowly warm to 25 °C and stir for 12 h. Following quenching with 2 mL of a 1 M solution of LiOH in water, the biphasic mixture was stirred vigorously for 5 min, then diluted with ether, and acidified to pH <3 with concentrated HCl. The solution was diluted and extracted with ether, and the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in ether and treated with excess ethereal diazomethane. Following evaporation, chromatography of the residue on silica gel (2.5 × 12 cm, 30% ethyl acetate/hexane) gave 0.1234 g (82%) of an inseparable mixture of four diastereomeric, unsaturated methyl esters in a ratio of 2.8:1.5:1:1.8, as estimated by ^{1}H and ^{13}C NMR IR (neat) 2950, 1735, 1460, 1375, 1245 cm^{-1}; ^{1}H NMR of mixture: δ 0.01 (s), 3.68, 3.69, 3.70, 3.72 (4 s), 4.92, 5.00, 5.10, 5.14 (4 m, 2.8:1.5:1:1.8), 5.7–5.9 (m); ^{13}C NMR of mixture: δ –1.1, 8.8, 9.0, 9.1, 9.3, 62.0, 62.1, 65.2, 66.1, 70.6, 78.4, 89.8, 95.2, 95.7, 95.9, 96.0, 107.2, 107.3, 107.5, 107.6, 127.2, 127.3, 127.4, 128.2, 133.6, 133.8, 134.0, 172.8, 173.6, 173.65, 173.7, 174.1. Anal. Calcd for $C_{28}H_{48}O_8Si$: C, 62.19; H, 8.96. Found: C, 62.24; H, 8.95.

Claisen Alcohols 12a and 12b (from Acid 3eq and Glycal 4). To a solution of 0.078 g (0.155 mmol) of glycal **4**[2] and 0.079 g (0.155 mmol) of acid **3eq**[2] in 0.2 mL of CH_2Cl_2 at 25 °C was added 0.062 mL of a 0.5 M solution of DMAP in CH_2Cl_2 (0.031 mmol) followed by 0.233 mL of a 0.8 M solution of DCC in CH_2Cl_2 (0.186 mmol) over 50 min. The solution was then cooled to 0 °C and stirred for 2.5 h. Following dilution with 2 mL of hexane, the solution was filtered through Celite and evaporated to give a residue which was estimated by ^{1}H and ^{13}C NMR to contain the desired ester and 20–25% of the unreacted glycal. To a solution of this residue in 1.8 mL of THF and 0.3 mL of HMPA at –78 °C was added 0.118 mL of TMSCl (0.930 mmol, freshly distilled from CaH_2). After the solution was cooled to approximately –105 °C (EtOH/ $N_{2(liquid)}$, bath temperature –110 °C), 0.542 mL of a 1.0 M solution of LDA (0.542 mmol) in 9:1 THF/HMPA was added dropwise through a –78 °C cooling jacket. After 5 min at –100 °C, the solution was allowed to slowly warm to 25 °C and stir for 12 h. Following quenching with 0.5 mL of a 1 M solution of LiOH in water, the biphasic mixture was stirred vigorously for 5 min, then diluted with ether, and acidified to pH <3 with concentrated HCl. The solution was diluted and extracted with ether, and the combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was dissolved in ether and treated with excess ethereal diazomethane. Following evaporation, chromatography of the residue on silica gel (2.5 × 12 cm, 18% ethyl acetate/hexane) gave, first, 0.024 g (27%) of the TMS ether of the glycal (converted to glycal by desilylation with TBAF in THF) followed by 0.090 g (58%) of an inseparable mixture of two diastereomeric, unsaturated methyl esters in a ratio of 2.6:1, as estimated by ^{1}H and ^{13}C NMR. The unsaturated methyl esters were dissolved in a slurry of approximately 0.300 g of W-2 Raney nickel (washed with 5 × 2 mL of water to give pH 7) in ethyl acetate and stirred vigorously under an atmosphere of hydrogen for 1.5 h. Following filtration, the resulting inseparable mixture of diastereomeric saturated esters was dissolved in ether and added to a solution of 0.005 g (0.141 mmol) of LAH in 1 mL of ether at 0 °C. After 10 min, 1 drop of water, 1 drop of aqueous 15% NaOH, 2 drops of water, and 1 g of $MgSO_4$ were added in succession. Filtration and evaporation gave a separable mixture of alcohols **12a** and **12b**. Chromatography of the mixture on silica gel (1.5 × 12 cm, 20% ethyl acetate/hexane) gave first, 0.0576 g (66% from the unsaturated esters) of the apolar alcohol (later assigned **12b**) followed by 0.0204 g (23% from the unsaturated esters) of the polar alcohol (later assigned **12a**). Apolar alcohol: $[\alpha]^{23}_D$ +36.8° (c 0.95, $CHCl_3$); IR (neat) 3485, 2925, 1460, 1375, 1250, 1085, 1030, 835, 770 cm^{-1}; ^{1}H NMR δ 0.00 (s, 9H), 0.01 (s, 3H), 0.03, (s, 3H), 0.76–0.98 (m, 23H), 3.24 (s, 3H), 3.32 (s, 3H), 3.34 (s, 3H), 3.3–3.8 (m, 13H), 3.98 (d, 1H, J = 3.9), 4.23 (m, 1H), 4.61 (s, 2H), 4.67 (s, 2H); ^{13}C NMR δ –5.0, –1.0, 8.5, 11.5, 11.6, 13.0, 16.4, 16.6, 18.1, 18.4, 18.6, 25.8, 26.3, 28.7, 30.3, 30.6, 33.6, 34.4, 34.6, 35.4, 35.7, 35.8, 36.2, 37.2, 37.5, 48.6, 55.9, 58.5, 65.5, 66.8, 67.1, 69.6, 74.2, 76.5, 77.0, 77.5, 79.2, 81.1, 85.9, 87.4, 88.6, 94.9, 95.6, 99.8, 107.6; FAB HRMS M + Na calcd for $C_{51}H_{98}O_{13}Si_2Na$ 997.6444, found 997.6401.

Polar alcohol: $[\alpha]^{23}_D$ +38.2° (c 1.44, $CHCl_3$); IR (neat) 3480, 2925, 1460, 1375, 1250, 1085, 1030, 835, 770 cm^{-1}; ^{1}H NMR δ 0.01 (s, 9H), 0.02, (s, 3H), 0.03 (s, 3H), 0.8–1.0 (m, 23H), 0.87 (s, 9H), 1.28–2.42 (m, 23H), 3.15–3.78 (m, 11H), 3.27 (s, 3H), 3.33 (s, 3H), 3.34 (s, 3H), 4.03 (m, 2H), 4.17 (d, 1H, J = 4.2), 4.31 (m, 1H), 4.61 (s, 2H), 4.68 (s, 2H); ^{13}C NMR δ –5.1, –1.0, 8.4, 11.5, 11.8, 13.3, 16.4, 16.9, 17.9, 18.5, 18.7, 26.3, 27.9, 28.8, 30.1, 31.4, 32.9, 33.3, 33.7, 34.1, 34.9, 35.1, 35.7, 35.9, 37.2, 37.3, 48.7, 55.9, 58.3, 64.1, 65.5 66.8, 69.9, 73.9, 76.7, 76.9, 77.0, 78.1, 78.9, 83.8, 84.4, 87.2, 94.9, 95.6, 99.7, 107.9; FAB HRMS M + Na calcd for $C_{51}H_{98}O_{13}Si_2Na$ 997.6444, found 997.6426.

Polyether 2b (from Alcohol 12b). To a solution of 0.010 g (0.0102 mmol) of alcohol **12b**, 0.005 mL (0.0615 mmol) of pyridine, and a trace of DMAP in 0.2 mL of dichloromethane was added 0.005 mL (0.0369 mmol) of *p*-fluorophenyl chlorothioformate. After 5 h, the solution was evaporated and the residue (containing some starting alcohol by TLC) dissolved in 1 mL of Et_3SiH. The solution was heated at reflux with 1 drop of a solution of AIBN (prepared by dissolving 0.1 g of AIBN in 1 mL of toluene) added every 0.5 h. After 1.5 h, the solution was cooled and evaporated to dryness and the residue purified by prepapative TLC (15% ethyl acetate/hexane) to give 0.0050 g (51%) of polyether **2b** as a colorless oil and 0.0027 g (23%) of the starting alcohol. **2b**: $[\alpha]^{23}_D$ +41.1° (c 0.5, $CHCl_3$); ^{1}H NMR δ 0.01 (s, 9H), 0.03 (s, 6H), 0.82–0.99 (m, 23H), 0.89 (s, 9H), 1.37 (s, 3H), 3.43 (s, 6H), 3.2–3.7 (m, 11H), 3.98 (d, 1H, J = 3.6), 4.23 (m, 1H), 4.62 (s, 3H), 4.69 (s, 2H); FAB HRMS M + Na calcd for $C_{51}H_{98}O_{12}Si_2Na$ 981.6494, found 981.6454.

Polyether 2eq (from Alcohol 12a). To a solution of 0.0157 g (0.0161 mmol) of alcohol **12a**, 0.006 mL (0.0805 mmol) of pyridine, and a trace of DMAP in 0.2 mL of dichloromethane was added 0.007 mL (0.0483 mmol) of *p*-fluorophenyl chlorothioformate. After 4 h, the solution was evaporated and the residue (containing some starting alcohol by TLC)

dissolved in 1 mL of Et_3SiH. The solution was heated at reflux with 1 drop of a solution of AIBN (prepared by dissolving 0.1g AIBN in 1 mL of toluene) added every 0.5 h. After 1.5 h, the solution was cooled and evaporated to dryness and the residue purified by prepapative TLC (two developments with 10% ethyl acetate/hexane) to give the impure product and 0.0043 g (27%) of the starting alcohol. Recrystallization of the impure product from MeOH gave 0.0050 g (20%) of pure polyether **2eq** as colorless needles, mp 121 °C (mixture mp 121 °C with naturally derived material). The compound was identical in all respects to the naturally derived material.

Claisen Alcohols 13a and 13b (from Acid 3ax and Glycal 4). To a solution of 0.085 g (0.170 mmol) of glycal **4**[2] and 0.082 g (0.163 mmol) of acid **3ax**[2] in 0.3 mL of CH_2Cl_2 at 25 °C was added 0.075 mL of a 0.5 M solution of DMAP in CH_2Cl_2 (0.038 mmol) followed by 0.278 mL of a 0.8 M solution of DCC in CH_2Cl_2 (0.221 mmol) over 30 min. The solution was then stirred at room temperature for 3 h. Following dilution with 3 mL of hexane, the solution was filtered through Celite and evaporated to give a residue which was estimated by ^1H and ^{13}C NMR to contain the desired ester and less than 10% of the unreacted glycal. Enolization and rearrangment of the crude intermediate ester followed by esterification in a manner similar to that described above and chromatography on silica gel (2.5 × 6 cm, 15% ethyl acetate/hexane) gave 0.021 g (25%) of the silated glycal followed by 0.080 g (50%) of the unsaturated esters. Hydrogenation and reduction followed by chromatography on silica gel (2.5 × 6 cm, 15–20% ethyl acetate/hexane) gave, first, 0.0355 g (27%) of the apolar alcohol (later assigned **13b**) followed by 0.0174 g (13%) of the polar alcohol (later assigned **13a**). Apolar alcohol: $[\alpha]^{23}_D$ +45.4° (*c* 1.1, $CHCl_3$); IR (neat) 3440, 2925, 1460, 1375, 1250, 1185, 1150, 1050, 840, 775 cm^{-1}; ^1H NMR δ 0.01 (s, 9H), 0.02 (s, 3H), 0.03 (s, 3H), 0.88 (s, 9H), 1.01 (d, 3H, *J* = 6.9), 1.17–2.40 (m, 22H), 3.26 (s, 3H), 3.32 (s, 3H), 3.35 (s, 3H), 3.42–3.67 (m, 10H), 3.77–3.82 (m, 2H), 3.97 (dd, 1H, *J* = 9.0 and 1.0), 4.16 (d, 1H, *J* = 4.2), 4.29 (m, 1H), 4.58 (d, 1H, *J* = 6.9), 4.68 (AB q, 2H, *J* = 6.9), 4.76 (d, 1H, *J* = 6.9); ^{13}C NMR δ −5.1, −1.0, 8.5, 11.2, 12.0, 13.5, 16.4, 16.9, 17.9, 18.5, 18.6, 26.3, 27.9, 29.0, 29.2, 30.3, 32.6, 33.0, 33.5, 33.7, 35.1, 35.7, 35.9, 37.0, 37.3, 39.8, 48.6, 55.6, 58.0, 65.5, 66.7, 66.8, 69.8, 70.1, 74.6, 76.8, 78.0, 78.4, 80.3, 83.9, 87.2, 88.2, 94.2, 95.6, 99.7, 106.4; FAB HRMS M + Na calcd for $C_{51}H_{98}O_{13}Si_2Na$ 997.6444, found 997.6487.

Polar alcohol: $[\alpha]^{23}_D$ +33.3° (*c* 1.7, $CHCl_3$); IR (neat) 3420, 2920, 1460, 1375, 1245, 1185, 1150, 1060, 835, 775 cm^{-1}; ^1H NMR δ 0.02 (s, 9H), 0.02 (s, 3H), 0.03 (s, 3H), 0.80–0.98 (m, 23H), 0.86 (s, 9H), 1.19–2.48 (m, 23H), 3.29 (s, 3H), 3.32 (s, 3H), 3.35 (s, 3H), 3.39–3.68 (m, 12H), 4.05 (dd, 1H, *J* = 10.2, 1.2), 4.15 (d, 1H, *J* = 4.2), 4.29 (m, 1H), 4.65 (AB q, 2H, *J* = 6.9), 4.70 (s, 2H); ^{13}C NMR δ −5.10, −511, −0.97, 8.6, 11.3, 11.8, 13.2, 16.4, 16.9, 18.1, 18.5, 18.6, 26.3, 28.8, 28.9, 30.0, 31.0, 32.8, 33.0, 33.4, 34.0, 35.1, 35.6, 35.8, 36.9, 37.1, 38.7, 48.8, 55.8, 58.0, 64.7, 65.6, 66.3, 68.8, 69.9, 75.6, 76.8, 77.7, 78.3, 84.5, 86.5, 88.5, 88.8, 94.8, 95.7, 99.8, 106.1; FAB HRMS M + Na calcd for $C_{51}H_{98}O_{13}Si_2Na$ 997.6444, found 997.6431.

Polyether 2ax (from Alcohol 13a). To a solution of 0.0130 g (0.0133 mmol) of alcohol **13a**, 0.006 mL (0.0805 mmol) of pyridine, and a trace of DMAP in 0.2 mL of dichloromethane was added 0.007 mL (0.0483 mmol) of *p*-fluorophenyl chlorothioformate. After 3 h, the solution was evaporated and the residue dissolved in 1 mL of Et_3SiH. The solution was heated at reflux with 1 drop of a solution of AIBN (prepared by dissolving 0.1g of AIBN in 1 mL of toluene) added every 0.5 h. After 1.5 h, the solution was cooled and evaporated to dryness and the residue purified by preparative TLC (two developments with 20% ethyl acetate/hexane) to give 0.0044 g (34%) of polyether **2ax**, identical in all respects to the naturally derived material.

Monensin Alcohol 14ax (from Polyether 2ax). To a solution of 0.112 g (0.120 mmol) of silyl ether **2ax** in 1 mL of THF was added 0.063 g (0.240 mmol) of TBAF·H_2O. After 6 h, the solution was diluted with hexane and filtered through a pad of silica gel, washing with 40% ethyl acetate in hexanes. Following evaporation, chromatography of the residue on silica gel (1.0 × 12 cm, 40% ethyl acetate/hexane) gave 0.090 g (92%) of alcohol **14ax** as a colorless oil. Characteristics are identical to those given above.

Monensin Alcohol 14eq (from Polyether 2eq). Treatment of 0.106 g (0.11 mmol) of ether **2eq** in a manner similar to that described for ether **2ax** and chromatography of the residue on silica gel (2.5 × 6 cm, 30% ethyl acetate/hexane) gave 0.088 g (94%) of alcohol **14eq** as a colorless oil. Characteristics are identical to those given above.

Monensin Methyl Ester 7ax (from Alcohol 14ax). To a solution of 0.080 g (0.0981 mmol) of alcohol **14ax** in 0.8 mL of dichloromethane were added 0.079 mL (0.981 mmol) of pyridine and 0.075 g (0.176 mmol) of Dess–Martin periodinane. After 1 h, 2 mL of a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ was added and the mixture vigorously stirred for 10 min. The mixture was extracted with ether and dried over $MgSO_4$. Evaporation gave the crude aldehyde as a colorless oil. To a solution of the aldehyde in 0.8 mL of ^tBuOH and 0.3 mL of water were added 0.1 mL of 2-methyl-2-butene, 0.035 g (0.294 mmol) of NaH_2PO_4, and 0.018 g (0.196 mmol) of $NaClO_2$. After being stirred vigorously for 1 h, the mixture was extracted with ether and dried over $MgSO_4$. Following treatment with excess diazomethane, chromatography of the residue on silica gel (1.0 × 12 cm, 20% ethyl acetate/hexane) gave 0.0801 g (98%) of methyl ester **7ax** as a colorless oil. Characteristics are identical to those given above.

Monensin Methyl Ester 7eq (from Alcohol 14eq). Oxidation and esterification of 0.082 g (0.0975 mmol) of alcohol **14eq** in a manner similar to that described for alcohol **14ax** and chromatography on silica gel (2.5 × 6 cm, 20% ethyl acetate/hexane) gave 0.0629 g (74%) of ester **7eq** as an oil. Characteristics are identical to those given above.

Monensin Alcohol 6 and Monensin Methyl Ketal Methyl Ester (5) (from Monensin Methyl Ester 7ax). To a solution of 0.124 g (0.140 mmol) of ester **7ax** and 0.066 mL (0.630 mmol) of ether in 2 mL of CH_2Cl_2 at −78 °C was added dropwise 0.365 mL (0.59 mmol) of a solution of Me_2BBr in CH_2Cl_2 (1.58 M). After 30 min at −78 °C, 3 mL of a mixture of saturated sodium bicarbonate and THF (1:1) was added rapidly and the mixture was allowed to warm to room temperature. The crude product was isolated by extraction with ether and dissolved in 2 mL of CH_2Cl_2 containing 2 mL of MeOH/$CH(MeO)_3$ (10:1) and 0.1 mL of a solution of TsOH in MeOH (2.5 mg in 0.1 mL). After the mixture was stirred for 1 h at room temperature, saturated sodium bicarbonate was added and the mixture was extracted with ether. Chromatography of the crude product on silica gel (2.5 × 6 cm, 20–30% ethyl acetate/hexane) gave 0.0596 g (50%) of alcohol **6**. Characteristics are identical to those given above. Further elution gave 0.0247 g (24%) of ester **5**. Characteristics are identical to those given above.

Monensin Alcohol 6 and Monensin Methyl Ketal Methyl Ester (5) (from Monensin Methyl Ester 7eq). Similar treatment of 0.122 g (0.14 mmol) of ester **7eq** to that described above for ester **7ax** and chromatography on silica gel (2.5 × 6 cm, 20–30% ethyl acetate/hexane) gave 0.0427 g (37%) of alcohol **6**. Further elution gave 0.018 g (18%) of ester **5**.

Monensin Sodium Salt (from Methyl Ester 6). To a solution of 0.099 g (0.119 mmol) of ester **6** in 2 mL of MeOH was added 0.030 g of LiOH. After being stirred for 12 h, the solution was diluted with 4 mL of water. The mixture was extracted with ether and dried over $MgSO_4$. Evaporation gave the crude acid (0.087 g, 90%) as a colorless oil. To a solution of the acid in 2.5 mL of HMPA was added 0.243 g (1.54 mmol) of undried CsF (Aldrich) and the mixture heated to 115 °C for 20 h. Following cooling, the mixture was poured into 15 mL of 1.5% HCl and extracted with ether. The ether layers were washed with saturated NaCl and dried over $MgSO_4$. Evaporation gave the crude monensin methyl ketal, which was subjected to Still hydrolysis,[8a] giving 0.054 g (86%) of monensin sodium salt, identical to commercially obtained monensin, sodium salt (Sigma): TLC (R_f = 0.68, 2% acetic acid/ethyl acetate); $[\alpha]^{23}_D$ +72° (*c* 0.91, $CHCl_3$). ^1H NMR spectra of synthetic and commercial material are given in the supplementary material.

Monensin, Sodium Salt (from Methyl Ester Methyl Ketal 5). Ester **5** (0.094 g, 0.134 mmol) was subjected to Still hydrolysis,[8a] giving 0.085 g (92%) monensin, sodium salt, identical to commercially obtained monensin, sodium salt (Sigma) by the criteria of the above procedure.

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Supplementary Material Available: Experimental procedures and characterization data for the preparation of compound **9** and 1H NMR spectra of monensin sodium salt (22 pages). Ordering information is given on any current masthead page.