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Olefin Metathesis−Iodoetherification−Dehydroiodination Strategy for Spiroketal Subunits of Polyether Antibiotics

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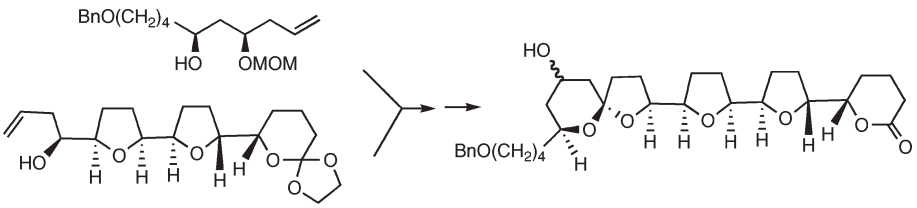

The convergent synthesis of two pentacyclic analogues of the polyether monensin A is described. Although different with respect to the configuration of the alcohol at the 3 position of the six-membered ring of the spiroketal subunit, the configuration at the acetal center in both structures is unchanged and is consistent with the anomeric effect. The key synthetic steps are the coupling of two complex segments via an olefin metathesis, and the subsequent conversion of a dihydroxyalkene to the spiroketal through an iodoetherification−dehydroiodination sequence. The compatibility of these transformations with a variety of functional groups makes the overall strategy appropriate for highly substituted frameworks.

Introduction

The polyether antibiotics, of which monensin **1** is a well-known example, are known for a variety of different biological effects (Figure 1).[1] Their ability to mediate ion transport across biological membranes, which in part has been related to their mode of action, has inspired structure activity and computational investigations.[2] As part of a program on complex spiroketals, we have been developing an unusual olefination−iodoetherification−spiroketalization strategy.[3−5] To test the feasibility of this methodology for the polyether antibiotics, we targeted the monensin analogue **2**. Mimetics like **2** that have unnatural substitution patterns are of interest in that such modifications may alter the natural configuration at the spiroketal center, leading to pronounced effects on overall molecular shape and consequently cation binding.[2] In this context, the spiroketal configuration in monensin is believed to be thermodynamically favored by the anomeric effect in the six-membered ring and hydrogen bonding between the ring alcohol and the

(1) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Vols. 1 and 2.

(2) (a) Peyrat, J.-F.; Figadère, B.; Cave, A. *Tetrahedron Lett.* **1995**, *36*, 7653–7656. (b) Wang, X.; Erickson, S. D.; Iimori, T.; Still, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 4128–4137. (c) Li, G.; Still, W. C. *Tetrahedron Lett.* **1993**, *34*, 919–922.

(3) (a) Li, X.; Li, J.; Mootoo, D. R. *Org. Lett.* **2007**, *9*, 4303–4306. (b) Tony, K. A.; Li, X.; Dabideen, D.; Li, J.; Mootoo, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1165–1169. (c) Li, J.; Li, X.; Mootoo, D. R. *Nat. Prod. Commun.* **2008**, *3*, 1771–1780.

(4) Reviews on spiroketals: (a) Favre, S.; Vogel, P.; Gerber-Lemaire, S. *Molecules* **2008**, *13*, 2570. (b) Raju, B. R.; Saika, A. K. *Molecules* **2008**, *13*, 1942–2038. (c) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406–4440. (d) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227–225. (e) Brimble, M. A.; Furkert, D. P. *Curr. Org. Chem.* **2003**, *7*, 1461–1484.

(5) Recent syntheses of complex spiroketals: (a) Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2002**, *43*, 1–2. (b) Crimmins, M. T.; Katz, J. D.; Washburn, D. G.; Allwein, S. P.; McAtee, L. F. *J. Am. Chem. Soc.* **2002**, *124*, 5661–5663. (c) Holson, E. B.; Roush, W. R. *Org. Lett.* **2002**, *4*, 3719–3723. (d) Tsang, K. I.; Brimble, M. A.; Bremner, J. B. *Org. Lett.* **2003**, *5*, 4425–4427. (e) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569–572. (f) Liu, J.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 2273–2276. (g) Statsuk, A. V.; Liu, D.; Kozmin, S. *J. Am. Chem. Soc.* **2004**, *126*, 9546–9547. (h) Takaoka, L. R.; Buskmelter, A. J.; LaCruz, T. E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2005**, *127*, 528–529. (i) Potuzaz, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *127*, 13796–13797. (j) Nicolaou, K. C.; Frederick, M. O.; Petrovic, G.; Cole, K. P.; Loizidou, E. Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 2609–2615. (k) Zhou, X.-T.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 1787–1790. (l) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 279–282. (m) Evans, D. A.; Dunn, T. B.; Kvrnø, L.; Beauchemin, A.; Raymer, B.; Olhava, E. J.; Mulder, J. A.; Juhl, M.; Kagechika, K.; Favor, D. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 4698–4703.

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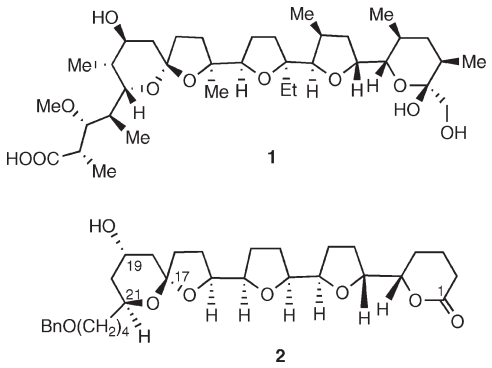
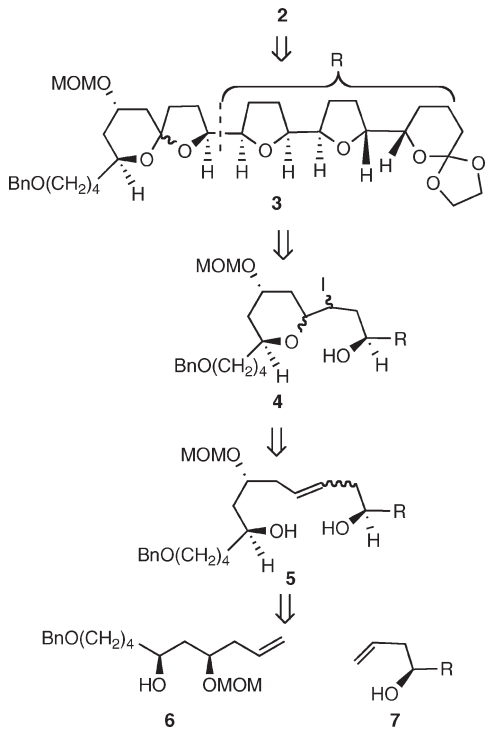


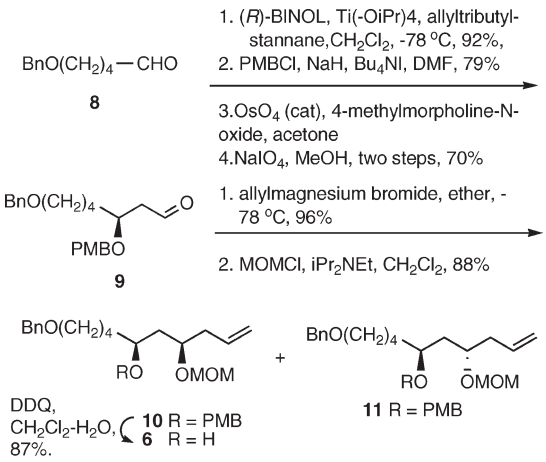
FIGURE 1. Simplified monensin mimetics.

SCHEME 1. Retrosynthetic Analysis



anomeric oxygen.[4,6−9] On this basis, we speculated that the simplified analogue **2**, in which the relative configuration at C-19 and C-21 of the six-membered ring is the same as in **1**, would favor the analogous spiroketal configuration. Retrosynthetically, we envisaged a convergent strategy in which alkene precursors **6** and **7** are coupled via a metathesis protocol to give the dihydroxyalkene **5**. Regioselective iodoetherification of **5** gives iodo-tetrahydropyran **4**, which when exposed to silver triflate leads to spiroketal **3**. Thus, the alkene in **5** is the functional equivalent of an alkyne.[10]

SCHEME 2. Synthesis of Alkene 6



Protecting group removal in **3** and spiroketal equilibration provides **2** (Scheme 1).

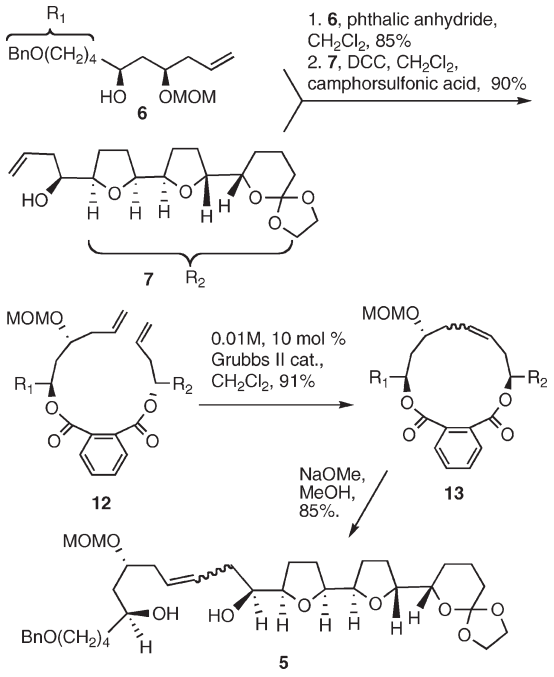
Results and Discussion

The tetracyclic homoallylic alcohol **7** was available from an earlier investigation.[11] The synthesis of the less complex alkene partner **6** started from commercially available 5-benzyloxypentanal **8**[12] (Scheme 2). Thus Keck allylation on **8** using (*R*)-1, 1′-bi-2-naphthol (BINOL) provided the derived homoallylic alcohol, which showed an enantiomeric excess of greater than 95% by analysis of the α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester derivatives.[13,14] Alcohol protection as the PMB ether followed by oxidative cleavage of the alkene provided aldehyde **9**. Unfortunately, the synthesis of the required *syn* diol derivative **6**, through the reaction of a variety of achiral and chiral allylating agents with **9**, was not highly selective.[15] The most practical route to **6** was to separate the 1:1 mixture of products from the reaction of **9** with allylmagnesium bromide, as the MOM derivatives **10** and **11**, and remove the PMB ether in the *syn* diol precursor **10**. The stereochemistry of **10** and **11** was assigned through analysis of the corresponding acetonides (Supporting Information).[16]

Although a cross metathesis (CM) on **6** and **7** provides a direct route to **5**, we opted for a ring-closing metathesis (RCM) strategy on a mixed phthalate derivative **12**,[17] because the CM of such type I metathesis partners is expected to lead to substantial homodimer formation (Scheme 3).[18] Thus, **12** was obtained, from the DCC-mediated coupling of

(6) Fukuyama, T.; Akasaka, K.; Karanewsky, D. S.; Wang, C.-L.; Schmid, G.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 262–263.
(7) Cai, D.; Still, W. C. *J. Org. Chem.* **1988**, *53*, 4643–4644.
(8) (a) Ireland, R. E.; Armstrong, J. D. III; Lebreton, J.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7152–7166. (b) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166–7172.
(9) Lutz, W. K.; Winkler, F. K.; Dunitz, J. D. *Helv. Chim. Acta* **1971**, *54*, 1103–1108.
(10) The strategy may be compared with the Au(I)-promoted spiroketalization of dihydroxyalkynes: Liu, B.; De Brabander, J. K. *Org. Lett.* **2006**, *8*, 4907–4910.
(11) Dabideen, D.; Mootoo, D. R. *Tetrahedron Lett.* **2003**, *44*, 8365–8368.
(12) Nagaoka, H.; Miyakoshi, T.; Kasuga, J.; Yamada, Y. *Tetrahedron Lett.* **1985**, *26*, 5055–5056.
(13) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467–8468.
(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. Curran, D. P.; Sui, B. *J. Am. Chem. Soc.* **2009**, *131*, 5411–5413.
(15) Danishefsky, S. J.; DeNinno, M. P.; Phillips, G. B.; Zelle, R. E.; Lartey, P. A. *Tetrahedron* **1986**, *42*, 2809–2819. Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109–4117. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404.
(16) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17.
(17) Fan, G.-T.; Hus, T.-S.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2000**, *41*, 6593–6597.
(18) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900–1923.

SCHEME 3. Synthesis of Dihydroxyalkene 5



the phthalate half-ester from **6**, and homoallylic alcohol **7**. RCM on **12** using Grubbs II catalyst afforded **13** in 91% yield as an inseparable 4:1 mixture of alkene isomers of undetermined configuration. Cleavage of **13** with NaOMe provided the required dihydroxyalkene **5** in 70% overall yield from **7**.

Iodoetherification of **5** using iodonium dicollidine perchlorate (IDCP) in dichloromethane provided an inseparable mixture of at least three iodocyclization products in the ratio of 5:3:1 in 86% yield (Scheme 4). The complexity of the NMR data for the iodocyclization product did not allow for the distinction between **4** or **14**. On the basis of the expected preference for the 6-*exo*-*trig* mode of cyclization versus the other cyclization pathways, we believe the major iodocyclization product to be THP **4**.[19] Exposure of the iodocyclization product to silver triflate in the presence of 2,4,6-collidine gave a 2:1 inseparable mixture of spiroketals **3** in 65% yield. The gross structure of **3** was determined by H/H and C/H 2D NMR, but complete stereochemical analysis was not possible at this stage because of the complexity of the spectral data. Regarding the mechanism of the transformation of **4** (or **14**) to **3**, we presume that the formation of **3** proceeds via the oxocarbenium ion **15** (or **16**). The latter may arise directly from cleavage of the C−I bond and a hydride shift, or indirectly through dehydroiodination to an initially formed enol ether, which is subsequently protonated.

To remove the MOM and orthoester protecting groups and possibly equilibrate the spiroketal mixture in a single step, **3** was next exposed to aqueous HCl in THF. The crude product was completely hydrolyzed to a mixture of dihydroxyacids, which was treated with DCC to give a 1:3 mixture of **2**:**17** in a combined yield of 72% from **3**. Interestingly, re-exposure of **2** to the reaction conditions gave a similar ratio of **2** and **17**. The structures were assigned through detailed

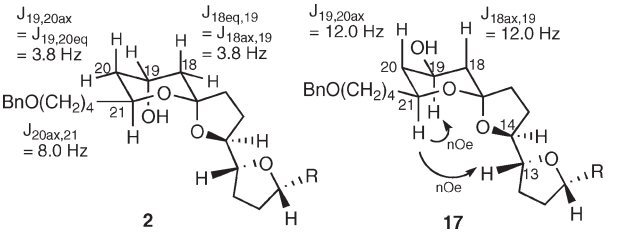
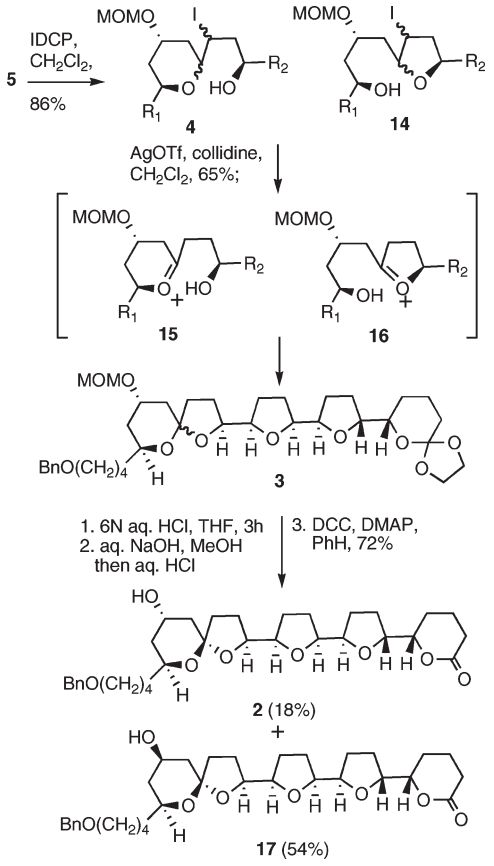


FIGURE 2. ^{1}H NMR analysis of **2** (d_6-benzene) and **17** (d_6-DMSO).

SCHEME 4. Monensin Spiroketal Analogues



analysis of TOCSY, NOESY, and HSQC data for **2** and **17** and their acetate derivatives in DMSO and, or benzene solutions (Figure 2). Surprisingly the configuration of the alcohol in the six-membered ring (i.e., at C-19) in the major isomer **17** was found to be inverted relative to the starting spiroketal **3**. Thus, a strong NOE between H-19 and H-21 indicated a *syn* diaxial-like relationship between H-19 and H-21, which meant that H-19 assumed an axial-like orientation on the six-membered ring. Large J values assigned to $J_{18ax,19}$ and $J_{19,20ax}$ in the signal for H-19 (δ 3.80 ppm, apparent tt, $J_{18eq,19} = J_{19,20eq} = 4.5$, $J_{18ax,19} = J_{19,20ax} = 12.0$ Hz) suggested a diaxial relationship between H-19 and protons on H-18 and H-20, which corroborated the NOE data and pointed to the chair conformation shown. Similar J values were extracted from the H-19 signal of the derived acetate **17-OAc** (δ 5.58 ppm, apparent tt, $J_{18eq,19} = J_{19,20eq} = 4.8$, $J_{18ax,19} = J_{19,20ax} = 11.5$ Hz). The anomeric configuration at the spiroketal carbon was assigned on the basis of a NOE between H-21 and one of the carbinol protons in the

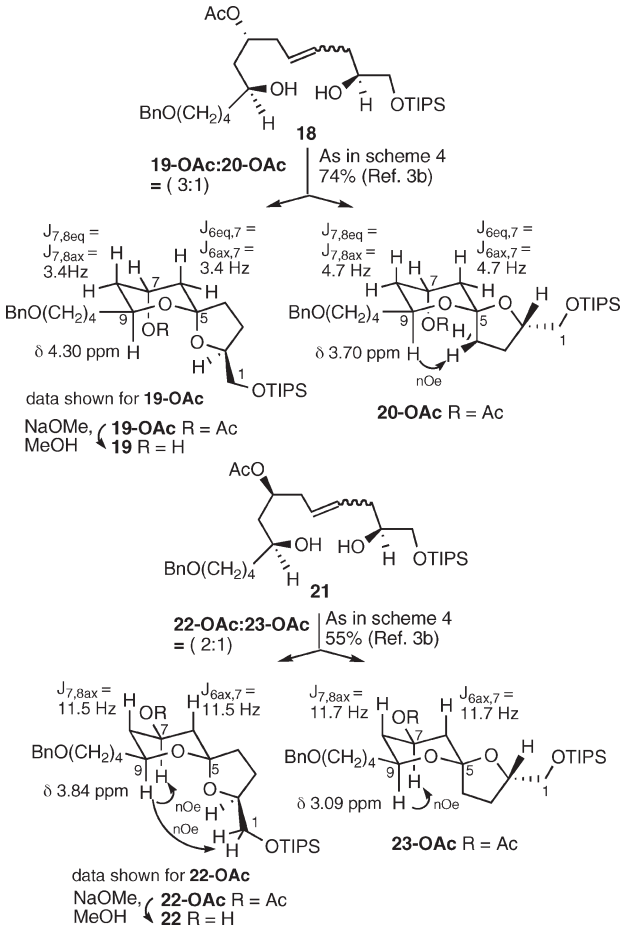
(19) Bedford, S. B.; Bell, K. E.; Bennet, F.; Haynes, C. J.; Knight, D. W.; Shaw, D. E. *Perkin Trans. 1* **1999**, 2142–2153.

tris-THF residue, presumed to be H-13. Such a NOE is not possible for the opposite acetal configuration. Consistent with this analysis is the absence of any NOEs between H-19 or H-21 and any of the methylene protons in the proximal THF ring. In the case of the minor spiroketal **2**, the signals for H-19 (δ 4.10 ppm, apparent dquintet, $J_{18eq,19} = J_{18ax,19} = J_{19,20ax} = J_{19,20eq}$ = ca. 3.8, $J_{19,OH}$ = 10.0 Hz) and H-21 (δ 4.18 ppm, apparent tdd, $J_{20eq,21} = J_{21,22}$ = ca. 2.2, $J_{21,22'}$ = 7.5, $J_{20ax,21}$ = 8.0 Hz) indicated relatively small J values for H-19 and the protons on C-18 and C-20, and a J value of 8.0 Hz between H-21 and one of the H-20 protons. This data is in agreement with the stereochemistry at C-19 and C-21 and the six-membered ring conformation as illustrated. The J values for H-19 in **2-OAc** (δ 5.15 ppm, apparent quintet, J = 3.0 Hz) also supported an equatorial-like positioning of H-19. Unfortunately, the NOESY data for **2** or **2-OAc** were not helpful in assigning the configuration at the spiroketal carbon. The anomeric configuration was subsequently assigned by comparison with the NMR data for simpler spiroketal analogues (vide infra).

To probe the configurational inversion observed at C-19 in the transformation of THP-iodide **4** to the spiroketal **17** and obtain simpler spiroketal analogues as reference compounds for assigning the stereochemistry of **2** and **17**, we investigated the spiroketalization protocol on substrates **18** and **21** (Scheme 5). A cross metathesis strategy using an excess of the more easily accessible alkene partner was practical for the preparation of these precursors. These results and the transformation of **18** and **21** to spiroketal mixtures **19-OAc**:**20-OAc** (3:1) and **22-OAc**:**23-OAc** (2:1) have been previously reported. The stereochemical assignment of the spiroketal products is detailed here. For **20-OAc**, (the minor isomer from **18**), a J value of 4.7 Hz for H-7 and each of the protons at C-6 and C-8 and a NOE between H-9 and H-4 suggested an equatorial-like orientation of the substituent at C-7 and the nonanomeric spiroketal configuration in the conformation shown. The configuration at C-7 of the major isomer **19-OAc** was similarly established from J data, and the spiroketal configuration inferred, on the assumption of its diastereomeric relationship to **20-OAc**. The deshielding of H-9 in **19-OAc** by the axial anomeric oxygen relative to the corresponding proton in **20-OAc** (δ 4.30 vs 3.70) corroborated the relative configuration at the spiroketal carbons in **19-OAc** and **20-OAc**.[20] The stereochemistry of **22-OAc** and **23-OAc**, the spiroketals from **21**, was determined in a similar fashion as described for **19-OAc** and **20-OAc**. The configuration at C-7 was assigned from vicinal J values and the configuration at the spiroketal carbons was based on NOEs between H-9 and CH_2-1 in the major anomeric product **22-OAc**. As for **19-OAc**/**20-OAc**, the downfield shift of H-9 in **22-OAc** relative to **23-OAc** supported the assignment at the spiroketal carbons.

To assign the acetal configuration in the monensin-like spiroketal **2-OAc**, the ^{1}H and ^{13}C chemical shifts for the carbinols on the six-membered ring and the acetal carbon were compared to the corresponding signals in **19-OAc** and **20-OAc**, the model spiroketals for the two anomers of **2-OAc** (Supporting Information). Thus the data for **2-OAc** very closely matched that for **19-OAc** but not **20-OAc**, and accordingly the acetal center in **2-OAc** (and therefore **2**) was assigned the anomeric configuration. The data for the deacetylated analogues **2** and **19** were also in excellent agreement. Of additional note, the ^{1}H NMR for the alcohols **2** and **19** showed a characteristic sharp doublet for the hydroxyl proton (i.e., δ 3.97, d, J = 10.0 Hz), which is consistent with the intramolecular hydrogen bond that is believed to stabilize such anomeric spiroketals with an axial alcohol at C-19/C-7.[9] Interestingly, the signals for the OH protons were not easily discernible in the spectra of the C-19/C-7 epimeric alcohols **17** and **22**. Similarly, closer matching of the NMR data for the other monensin analogue **17-OAc** to the model spiroketal **22-OAc** compared to the anomeric partner **23-OAc** provided independent support for the configuration that was earlier assigned to the spiroketal carbon in **17-OAc**.

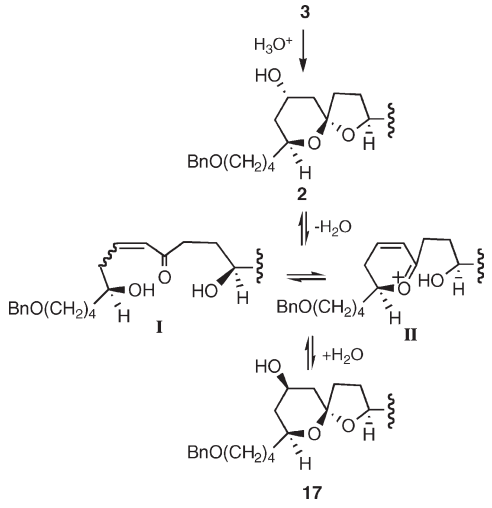
SCHEME 5. Synthesis and Stereochemical Analysis of Model Spiroketals



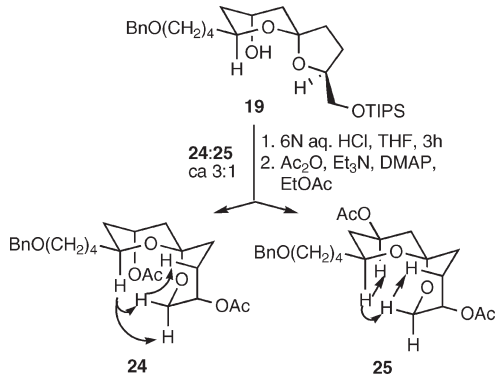
As indicated earlier, because of difficulty in assigning stereochemistry in **3**, the product of the silver-mediated spiroketalization of the monensin substrate **4**, it was not clear whether the loss of configurational integrity at C17 that was observed in the transformation of **4** → **3** → **17** (and **2**) had occurred in the initial spiroketalization step or the subsequent acid-mediated protecting group removal step. That the configuration at C7 was preserved in the spiroketalization of **18** and **21** suggests that the former is unlikely. A more plausible explanation is that inversion at C19 occurs in the acid-promoted reaction on **3**, via an elimination−addition sequence involving an intermediate enone **I** or related

(20) Ireland, R. E.; Daub, J. P. *J. Org. Chem.* **1983**, *48*, 1303–1312.

SCHEME 6. Proposed Mechanism for C-19/C-7 Epimerization



SCHEME 7. C7 Epimerization in Model Spiroketals



oxocarbenium ion **II** (Scheme 6). Similar observations have previously been reported.[21] Such a mechanism is also consistent with the observation that re-exposure of **2** under similar conditions leads to a mixture of **2** and **17**. To test this hypothesis, alcohol **19** (which is stereochemically analogous to **3**) was subjected to the identical acidic procedure that was applied to **3** (Scheme 7). Indeed, this reaction produced a mixture of rearranged [5.5.0] spiroketals **24** and **25** that were epimeric at C7.

Conclusion

The pentacyclic monensin analogues **2** and **17** were prepared in a convergent fashion from alkenol precursors **6** and **7**. Although different with respect to the configuration of the alcohol at the 3 position of the six-membered ring of the spiroketal, the configuration at the acetal center in both **2** and **17** is unchanged and is in line with the anomeric effect. This observation is relevant to the design of more finely tuned spiroketal containing ionophores. From a synthetic standpoint, attractive features are the alkenol precursors (which in general may be obtained via a variety of established stereoselective routes), the metathesis reaction for segment coupling, and the generation of the spiroketal linkage under nonacidic conditions. This strategy appears especially appropriate for highly functionalized substrates and may be relevant to the formation of spiroketals under kinetic conditions. However, in the present case, these features are negated by the highly acidic conditions required to remove the MOM protecting group in the initial spiroketal product. Therefore the synthetic scope can be maximized by judicious selection of alcohol protecting groups.

Experimental Section

Monensin Analogues (2 and 17). A solution of **3** (26 mg, 0.04 mmol), THF (0.8 mL) and 6 N HCl (0.2 mL) was stirred at rt for 3 h. The reaction mixture was then adjusted to pH 5 by addition of saturated aqueous $NaHCO_3$ and diluted with MeOH (0.8 mL). Aqueous 1 N NaOH (1.0 mL) was then added, and the mixture stirred at rt for 1 h. The pH of the mixture was then adjusted to 5 by carefully adding 3 N HCl. Most of the solvent was evaporated under reduced pressure, and the residual solution was extracted with diethyl ether. The ether extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude oil was dried by removal of the benzene−water azeotrope, and DCC (15 mg, 0.06 mmol) and DMAP (3 mg, 0.02 mmol) were added at 0 °C to the resulting benzene solution (1 mL). The reaction mixture was stirred for 3 h. The solvent was then evaporated in vacuo, and the residue was purified by FCC to afford 2:17 (16 mg, 72%) in a respective ratio of 1:3. Repeat FCC on the mixture afforded separated samples of **2** and **17**.

For **2**: $R_f = 0.30$ (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 0.80−2.10 (m, 28H), 3.3 (t, J = 6.1 Hz, 2H), 3.75 (m, 3H), 3.90 (m, 3H), 3.97 (d, J = 10.1 Hz, 1H, OH), 4.10 (dquintet, J = 3.8, 10.2 Hz, 1H), 4.18 (app tdd, J = 2.2, 2.5, 8.0 Hz, 1H), 4,32 (s, 2H), 7.24 (m, 3H), 7.32 (d, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 18.6, 23.2, 25.2, 28.0, 28.4, 28.6, 28.8, 28.9, 30.1, 30.7, 36.6, 39.1, 39.5, 39.6, 65.6, 65.7, 70.7, 73.3, 81.3, 81.7, 82.5, 83.1, 84.3, 107.6, 127.1−129.3 (aromatic carbons buried in C_6D_6 triplet), 139.9, 169.8. ESMS $(M + NH_4)^+$ 576.2. For **2-OAc**: $R_f = 0.85$ (10% MeOH in CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 1.00−2.25 (m, 31 H), 3.40 (t, J = 6.3 Hz, 2H), 3.79 (m, 2H), 3.90 (apparent q, J = 6.2 Hz, 1H), 4.02 (m, 2H), 4.12 (apparent q, J = 6.4 Hz, 1H), 4.31 (m, 1H), 4.45 (s, 2H), 5.15 (app quintet, J = 3.0 Hz, 1H), 7.27 (m, 3H), 7.45 (d, J = 7.2 Hz, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 18.6, 21.6, 23.1, 25.3, 28.4, 28.5, 28.9, 29.0, 29.5, 30.1, 30.7, 35.6, 36.3, 36.6, 40.1, 65.4, 68.1, 70.7, 73.3, 81.3, 81.7, 82.5, 82.8, 84.0, 105.8, 127.9−128.9 (aromatic carbons buried in C_6D_6 triplet), 139.9, 169.6, 170.3. FABHRMS calcd for $C_{34}H_{49}O_9$ $(M + H)^+$ 601.3377, found 601.3381.

For **17**: $R_f = 0.25$ (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 1.05 (m, 2H), 1.15 (m, 2H), 1.50 (m, 24H), 3.42 (t, J = 6.0 Hz, 2H), 3.85 (m, 3H), 3.95 (q, J = 6.4 Hz, 1H), 4.09 (m, 3H), 4.22 (app tt, J = 5.1, 11.2), 4.50 (s, 2H), 7.25 (m, 3H), 7.40 (d, J = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, C_6D_6) δ 18.5, 23.3, 25.1, 28.2, 28.8, 28.9, 29.1, 29.2, 30.1, 30.7, 36.7, 39.3, 41.9, 44.1, 65.9, 69.3, 70.7, 73.3, 81.3, 81.9, 82.6, 82.8, 83.5, 83.9, 107.6, 127.7−129.4 (aromatic carbons buried in C_6D_6 triplet), 139.9, 170.0. ^{1}H NMR (500 MHz, DMSO-d_6) δ 0.95 (q, 6.0 Hz, 1H, H-20ax), 1.21 (m, 1H, H-23), 1.25−1.95 (m, CH_2-3, 4, 7, 8, 11, 12, 15, 16, 18, H-20eq, CH_2-22, H-23′, CH_2-24, 24H), 2.30 (ddd, J = 7.0, 9.5, 17.0 Hz, H-2), 2.45 (ddd, J = 5.0, 6.0, 17.0 Hz, H-2′), 3.37 (t, J = 6.5 Hz, CH_2-25), 3.55 (m, 1H, H-21), 3.70 (m, 2H, H-13, 14), 3.80 (tt, J = 4.5, 12.0 Hz, 1H, H-19), 3.85 (m, 1H, H-9), 3.95 (m, 2H, H-6, 10), 4.30 (dt, J = 3.5, 12.0 Hz, H-5), 4.37 (s, 2H, $PhCH_2$). FABHRMS calcd for $C_{32}H_{47}O_8$ $(M + H)^+$ 559.3271, found 559.3282. For **17-OAc**: $R_f = 0.80$ (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 1.00−2.25 (m, 31H), 3.42 (t, J = 6.6 Hz, 2H), 3.80 (m, 1H), 3.93 (m, 2H), 4.05 (m, 3H), 4.46 (m, 2H), 5.58 (tt, J = 5.0, 11.5 Hz, 1H), 7.26 (m, 3H), 7.4

(21) (a) Ikunaka, M.; Mori, K. *Agric. Biol. Chem.* **1987**, *51*, 565–571. (b) Smith, A. B. III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469–1471. (c) Reference 8a.

(d, $J = 7.2$ Hz, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 18.6, 21.3, 23.1, 25.3, 28.5, 28,7, 28.9 (two signals), 29.2, 30.2, 30.6, 36.5, 37.9, 39.3, 40.3, 68.9, 69.2, 70.7, 73.3, 81.3, 81.8, 82.5, 82.7, 83.5, 83.9, 107.2, 127.0−128.9 (aromatic carbons buried in C_6D_6 triplet), 140.1, 169.7, 169.9. FABHRMS calcd for $C_{34}H_{49}O_9$ $(M + H)^+$ 601.3377, found 601.3351.

Spiroketal Mixture (3). AgOTf (121 mg, 0.47 mmol) was added to a solution of **4** (90 mg, 0.12 mmol) and collidine (0.06 mL) in anhydrous CH_2Cl_2 (15 mL). The reaction mixture was stirred for 25 min at rt, poured into saturated aqueous $Na_2S_2O_3$ (10 mL), and extracted with CH_2Cl_2. The organic extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC of the residue afforded **3** (48 mg, 65%) as an inseparable mixture (2:1). $R_f = 0.36$ (60% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.22−2.17 (m, 28H), 3,20, 3.35 (both s, 1H, 2H respectively), 3.37 (apparent t, $J = 7.0$ Hz, 2H), 3.58 (m, 2H), 3.75 (m, 1H), 3.76−4.02 (m, 7H), 4.18 (m, 1H), 4.33 (m, 1H), 4.38, 4,40 (both s, 2H), 4.51, 4.73 (both ABq, $\Delta\delta = 0.01$, 0.12 ppm, $J = 8.5$, 6.5 Hz, 0.66H, 1.33H respectively), 7.24 (m, 3H), 7.37 (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 23.1, 23.3, 23.7, 27.7, 28.3, 28.7, 29.0, 29.2, 29.3, 29.4, 29.6, 30.7, 30.8, 31.0, 32.5, 36.2, 36.6, 36.8, 37.0, 37.1, 37.3, 40.2, 40.7, 55.6, 63.6, 64.9, 65.7, 70.2, 70.9, 71.0, 73.5, 77.6, 81.2, 82.4, 82.6, 82.7, 82.9, 84.1, 84.3, 95.6 (OCH_2O), 106.2 (spiroketal-major), 107.8 (spiroketal-minor), 120.2 (orthoester), 127.0−130.0 (several lines buried C_6D_6 triplet), 140.0. FABHRMS calcd for $C_{36}H_{55}O_{10}$ $(M + H)^+$ 647.3795, found 647.3794.

THP-Iodide (4). To a solution of **5** (85 mg, 0.13 mmol) and 4 Å MS (225 mg) in dry CH_2Cl_2 (18 mL) was added IDCP (100 mg, 0.21 mmol). The mixture was stirred at rt for 15 min, filtered through Celite into saturated aqueous $Na_2S_2O_3$ (20 mL), and extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), filtered, and evaporated in vacuo. FCC of the residue afforded **4** (86 mg, 86%) as an inseparable mixture. $R_f = 0.37$ (60% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.14−2.29 (m, 26H), 3.20, 3.21, 3.25 (all s, 3H), 3.39 (m, 2H), 3.61 (m, 2H), 3.76−3.91 (m, 9H), 4.11 (m, 1H), 4.20−4.52 (m, 6H), 7.20 (m, 3H), 7.35 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.9, 23.1, 23.1, 23.8, 26.0, 26.2, 26.4, 27.6, 27.9, 28.2, 28.3, 28.7, 28.8, 28.9, 29.3, 30.6, 30.7, 32.4, 33.8, 36.0, 36.2, 36.7, 36.8, 37.2, 37.3, 39.8, 40.1, 40.9, 41.5, 41.7, 55.6, 55.7, 63.7, 65.0, 70.2, 70.7, 71.0, 71.2, 73.1, 73.3, 73.4, 73.6, 75.0, 76.0, 76.2, 77.4, 77.4, 82.1, 82.2, 82.4, 82.6, 82.7, 83.1, 83.6, 83.7, 95.3, 95.7, 95.9, 120.1, 127.0−130.0 (several lines buried under C_6D_6 triplet), 140.0. FABHRMS calcd for $C_{36}H_{57}O_{10}I$ $(M + H)^+$ 775.2918, found 775.2920.

Dihydroxyalkene (5). Mixed phthalate-alkene **13** (75 mg, 0.10 mmol) was dissolved in MeOH (7 mL) and a ca. 1 M solution of NaOMe in MeOH (1.5 mL) was added. The mixture was stirred for 24 h at rt. The solvent was removed in vacuo, and the residue was dissolved in ether. The ethereal extract was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by FCC to afford recovered starting material **13** (7 mg) and **5** (48 mg, 85% based on recovered **13**). $R_f = 0.13$ (60% EtOAc/petroleum ether). ^{1}H NMR (500 MHz, C_6D_6, major isomer) δ1.40 (m, 3H), 1.60 (m, 4H), 1.71 (m, 8H), 1.88 (m, 6H), 2.07 (m, 1H), 2.22 (m, 1H), 2.28 (t, $J = 8.0$ Hz, 2H), 2.35 (m, 1H), 3.03 (br s, 1H), 3.21 (s, 3H), 3.41 (m, 3H), 3.58 (m, 2H), 3.74−3.94 (m, 7H), 3.97 (m, 1H), 4.18 (m, 1H), 4.20 (m, 1H), 4.41 (s, 2H), 4.47 (ABq, $\Delta\delta = 0.12$ ppm, $J = 7.0$ Hz, 2H), 5.57 (m, 1H), 5.62 (m, 1H), 7.16 (t, $J = 8.0$ Hz, 1H), 7.24 (t, $J = 8.0$ Hz, 2H), 7.38 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (75 MHz, C_6D_6, mixture) δ 21.9, 23.2, 25.9, 26.2*, 27.7, 28.3, 28.9, 29.2, 30.8, 32.4, 32.7*, 33.0*, 37.9, 38.7, 38.8, 42.8, 56.0, 63.7, 65.0, 70.9, 71.7, 73.5, 73.8*, 73.5, 77.4, 77.7, 82.2, 82.5, 82.8, 83.3, 95.9, 120.1, 127.9, 128.9, 129.0, 130.3, 140.0 (* indicates selected signals for minor isomer). FABHRMS calcd for $C_{36}H_{56}O_{10}Na$ $(M + Na)^+$ 671.3771, found 671.3770.

Mixed Phthalate Ester (12). To a stirred solution of alkenol **6** (0.381 g, 1.18 mmol, Supporting Information) in pyridine (15 mL) were added phthalic anhydride (0.524 g, 3.54 mmol) and DMAP (73 mg, 0.60 mmol). After 20 h the solution was filtered through a bed of Celite, and the solvent was removed under reduced pressure. The residue was purified by FCC to afford recovered **6** (104 mg) and the derived monophthalate ester (344 mg, 85%). $R_f = 0.50$ (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45−1.80 (m, 7H), 2.05 (m, 1H), 2.30 (m, 1H), 2.40 (m, 1H), 3.40 (s, 3H), 3.50 (m, 2H), 3.85 (m, 1H), 4.55 (ABq, $\Delta\delta = 0.05$ ppm, $J = 10.5$ Hz, 2H), 4.70 (s, 2H), 5.10 (m, 2H), 5.30 (m, 1H), 5.85 (m, 1H), 7.30 (m, 5H), 7.50 (m, 2H), 7.70 (m, 1H), 7.80 (m, 1H), 10.35 (br. s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 29.5, 34.1, 38.7, 55.5, 70.0, 72.8, 73.1, 74.2, 95.2, 117.7, 127.6, 127.7, 128.3, 128.8, 129.1, 130.8, 131.3, 132.8, 134.2, 138.3, 167.6, 169.9. FABHRMS calcd for $C_{27}H_{34}O_7Na$ $(M + Na)^+$ 493.2202, found 493.2205.

A stirred solution of alcohol **7**[11] (200 mg, 0.56 mmol), the acid from the previous step (335 mg, 0.713 mmol), DMAP (14 mg, 0.11 mmol), and camphorsulfonic acid (13 mg, 0.06 mmol) in anhydrous benzene (25 mL) at 5 °C was treated with DCC (260 mg, 1.12 mmol). After the mixture stirred for 19 h at rt, diethyl ether (50 mL) was added, and the mixture was filtered through Celite. Concentration of the filtrate and FCC of the residue afforded **12** (400 mg, 90% based on recovered starting material). $R_f = 0.58$ (30% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.59−1.98 (m, 21H), 2.21 (m, 1H), 2.49 (m, 2H), 2.69 (m, 1H), 2.75 (m, 1H), 3.26 (s, 3H), 3.37 (m, 2H), 3.59 (m, 2H), 3.74−3.97 (m, 7H), 4.10 (m, 1H), 4.38 (s, 2H), 4.60 (ABq, $\Delta\delta =$ 0.10 ppm, $J = 7.0$ Hz, 2H), 5.16 (m, 4H), 5.52 (m, 1H), 5.61 (m, 1H), 6.00 (m, 2H), 7.03 (m, 2H), 7.22 (m, 3H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.73 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 22.0, 22.9, 28.2, 28.5, 28.8, 28.9, 29.6, 30.6, 32.5, 35.1, 36.7, 39.7, 39.9, 55.9, 63.7, 65.0, 70.8, 73.5, 73.6, 75.2, 76.4, 77.5, 80.6, 82.3, 82.5, 83.0, 96.4, 117.8, 118.0, 120.2, 127.9, 129.4, 129.5, 130.9, 131.2, 133.6, 134.4, 134.8, 135.4, 140.0, 166.8, 167.3. FABHRMS calcd for $C_{46}H_{62}O_{12}Na$ $(M + Na)^+$ 829.4139, found 829.4136.

Cyclic Alkene (13). Grubb's II catalyst (68 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) was injected, at rt, into a degassed solution of diene **12** (360 mg, 0.40 mmol) in CH_2Cl_2 (40 mL). The mixture heated at reflux for 4 h and cooled to rt, at which time DMSO (0.2 mL) was added, and stirring was continued for 16 h. The solution was then concentrated in vacuo. FCC of the residue afforded **13** (280 mg, 91% based on recovered starting material) as an inseparable 4:1 mixture. $R_f = 0.42$ (40% EtOAc/petroleum ether); ^{1}H NMR, major isomer, (500 MHz, C_6D_6) δ 1.60−1.93 (m, 20H), 2.01 (m, 1H), 2.15 (m, 2H), 2.32 (m, 1H), 2.62 (m, 2H), 3.15 (s, 3H), 3.40 (t, $J = 7.0$ Hz, 2H), 3.58 (m, 2H), 3.74 (m, 2H), 3.86 (m, 2H), 3.95 (m, 4H), 4.40 (s, 2H), 4.48 (m, 2H), 5.48 (m, 2H), 5.58 (m, 2H), 7.01 (m, 2H), 7.23 (m, 3H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.61 (d, $J = 7.0$ Hz, 1H), 7.79 (d, $J = 7.0$ Hz, 1H); ^{13}C NMR, major isomer, (75 MHz, C_6D_6) δ 22.0, 23.5, 28.2, 28.4, 28.6, 28.8, 29.7, 30.7, 32.5, 34.4, 35.1, 37.5, 39.6, 55.9, 63.7, 65.0, 70.9, 73.5, 74.3, 76.0, 77.5, 81.2, 82.2, 82.5, 83.0, 96.7, 120.2, 127.9, 128.9, 129.1, 129.6, 130.5, 131.8, 132.5, 136.0, 140.0, 166.3, 168.0. FABHRMS (mixture) calcd for $C_{44}H_{59}O_{12}$ $(M + H)^+$ 779.4007, found 779.4009.

Bicyclic Spiroketal Alcohol (19). K_2CO_3 (10 mg) was added to a solution of **19-OAc** (10.0 mg, 0.018 mmol) in methanol (1 mL). The reaction mixture was stirred for 4 h at rt and neutralized with methanolic HCl. The mixture was diluted with CH_2Cl_2, and the suspension was filtered through Celite. The filtrate was evaporated in vacuo, and the residue was purified by FCC to give alcohol **19** (8.0 mg, 88%). $R_f = 0.25$ (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.03−1.18 (m, 21H), 1.25 (m, 2H), 1.38 (m, 2H), 1.48 (m, 1H), 1.53 (m, 1H), 1.60−1.74 (m, 6H), 1.80 (m, 3H), 1.87 (dd, $J = 7.0$, 10.0 Hz, 1H), 3.37 (t, $J = 6.2$ Hz, 2H), 3.65 (dd, $J = 6.5$, 9.6 Hz, 1H), 3.86 (dd, $J = 6.4$, 9.6 Hz, 1H), 3.97 (d, $J = 10.2$ Hz, 1H, OH), 4.10 (app dquintet, $J = 3.1$, 10.2 Hz, 1H), 4.19 (app quintet, $J = 5.0$ Hz,

1H), 4.23 (m, 1H), 4.38 (s, 2H), 7.20 (m, 3H), 7.34 (d, $J = 7.5$ Hz, 2H). ^{13}C NMR (125 MHz, C_6D_6) δ 12.7, 18.6, 23.3, 27.3, 30.9, 36.8, 39.2, 39.3, 39.5, 65.5, 65.7, 68.6, 70.8, 73.2, 82.6, 107.6, 127.9−128.9 (aromatic carbons buried in C_6D_6 triplet), 139.9. ESHRMS calcd for $C_{29}H_{54}NO_5Si$ $(M + NH_4)^+$ 524.3766, found 524.3773.

Bicyclic Spiroketal Alcohol (22). Application of the deacetylation procedure that was described for **19** to **22-OAc** (6.0 mg, 0.011 mmol) provided alcohol **22** (5.0 mg, 91%). $R_f = 0.25$ (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) $R_f = 0.25$ (20% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.05−1.17 (m, 21H), 1.01 (m, 1H), 1.36 (m, 3H), 1.47 (m, 3H), 1.54 (m, 1H), 1.62 (m, 3H), 1.74 (m, 1H), 1.82 (m, 1H), 1.85−2.00 (m, 3H), 3.36 (t, $J = 6.1$ Hz, 2H), 3.68 (dd, $J = 7.0$, 9.5 Hz, 1H), 3.81 (m, 1H), 3.94 (dd, $J = 5.8$, 9.5 Hz, 1H), 4.07 (app tt, $J = 4.7$, 11.2 Hz, 1H), 4.24 (quintet, $J = 6.6$ Hz, 1H), 4.37 (s, 2H), 7.12 (t, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 12.7, 18.6, 23.3, 28.2, 30.8, 36.7, 39.1, 41.7, 43.8, 66.0, 68.8, 69.2, 70.8, 73.4, 82.0, 107.4, 128.0−128.9 (aromatic carbons buried in C_6D_6 triplet), 139.8. ESHRMS calcd for $C_{29}H_{50}O_5SiNa$ $(M + Na)^+$ 529.3320, found 529.3330.

Bicyclic Spiroketals (24 and 25). A solution of **19** (4.0 mg, 0.008 mmol), THF (0.4 mL) and 6 N HCl (0.1 mL) was stirred at rt for 3 h following the identical conditions that were applied to **3**. The reaction was then diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The ether extract was dried (Na_2SO_4), filtered, and concentrated in vacuo. FCC (80% EtOAc/petroleum ether) of the crude product afforded two components (ratio ca. 3:1), which were individually dissolved in EtOAc (1 mL) and treated with acetic anhydride (0.05 mL), DMAP (1 mg), and Et_3N (0.1 mL). The reaction mixture was quenched with MeOH and evaporated in vacuo. FCC of the residue from the individual reactions afforded **24** (1.4 mg, 39%) and **25** (0.4 mg, 22%) respectively. For **24**: $R_f = 0.25$ (25% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.38 (m, 5H), 1.54 (m, 2H), 1.69 (m, 4H), 1.76 (s, 3H), 1.85 (s, 3H), 1.87 (dt, $J = 4.7$, 11.7 Hz, 1H), 2.17 (tt, $J = 4.5$, 11.5 Hz, 1H), 2.25 (dt, $J = 1,4$, 15.0 Hz, 1H), 3.44 (t, $J = 6.0$ Hz, 2H), 3.85 (dd, $J = 1.7$, 12.7 Hz, 1H), 3.90 (bd, $J = 1$ 12.7, 1H), 4.04 (m, 1H), 4.46 (s, 2H), 4.82 (bs, 1H), 5.12 (apparent q, $J = 3.6$ Hz, 1H), 7.25 (m, 5H). ^{13}C NMR (125 MHz, C_6D_6) δ 21.2, 21.5, 23.2, 23.3, 30.8, 31.2, 35.6, 36.4, 38.2, 62.6, 65.0, 67.5, 70.6, 73.4, 95.8, 127.0−129.0 (aromatic carbons buried in C_6D_6 triplet), 139.8, 170.3. ESHRMS calcd for $C_{24}H_{34}O_7Na$ $(M + Na)^+$ 457.2196, found 457.2199. For **25**: $R_f = 0.47$ (25% EtOAc/petroleum ether); ^{1}H NMR (500 MHz, C_6D_6) δ 1.32 (m, 2H), 1.44 (m, 2H), 1.55 (m, 1H), 1.67 (m, 5H), 1.79 (s, 3H), 1.84 (s, 3H), 1.89 (dt, $J = 4.2$, 13.3 Hz, 1H), 2.05 (m, 1H), 2.11 (tt, $J = 5.0$, 13.6 Hz, 1H), 2.29 (ddd, $J = 2.0$, 5.0, 12.1 Hz, 1H), 3.45 (m, 2H), 3.47 (m, 1H), 3.72 (ABq, $\Delta\delta = 0.16$ ppm, $J = 12.7$ Hz, 2H), 4.47 (bs, 1H), 4.80 (bs, 1H), 5.57 (ddd, $J = 3.0$, 9.5, 14.5 Hz, 1H), 7.25 (m, 5H). ^{13}C NMR (125 MHz, C_6D_6) δ 21.0 (two signals), 23.0, 23,1, 30.2, 30.5, 36.1, 37.8, 41.3, 62.2, 67.3, 67.9, 68.5, 70.4, 73.2, 97.1, 127.0−129.0 (aromatic carbons buried in C_6D_6 triplet), 169.6. ESHRMS calcd for $C_{24}H_{34}O_7Na$ $(M + Na)^+$ 457.2196, found 457.2198.

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Supporting Information Available: Synthetic procedures and characterization data, including ^{1}H and ^{13}C NMR and spectra for compounds **2**−**7**, **9**−**13**, and **17**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.