Chemistry of A83543A Derivatives. 1. Oxidations and Reductions of A83543A Aglycon

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Received July 27, 1993•

A retro-biomimetic degradation of the A83543 tetracyclic ring system was investigated as one approach to obtaining putative polyketide-derived, late-stage biosynthetic precursors for the subsequent study of their cyclizations. However, initial studies revealed an unexpected chemical stability of the ring system that required the development of indirect methods to cleave the ring-forming bonds. Hydride reagents were especially useful for reductively cleaving the lactone and generating novel derivatives, whose structures and stereochemistries were determined by detailed NMR analyses correlated with results from molecular modeling. The latter were also used to rationalize the conformational behaviors and lack of reactivities exhibited by the macrocyclic lactone systems in the parent and 13,14-enone-reduced derivatives.

Several naturally occurring macrocyclic lactones and their derivatives are well-established agents of great commercial importance.[1] The isolation and structure determination of a new, structurally unique family of tetracyclic macrolides, denoted as the A83543 complex,[2] bears considerable promise because of the insecticidal activity of these compounds.[3] The practical importance and unique structural features of A83543A (1) (Figure 1) render this new natural product an attractive target for novel synthetic chemistry. The first asymmetric total syntheses of the optical antipodes of A83543A aglycon 2 and A83543A itself 1 have already been reported.[4ab]

It has been established that the biosynthesis of A83543A is consistent with the initial formation of a long-chain fatty acid assembled via a polyketide-derived pathway.[5a] The category of polyketides is frequently described in biosynthetic terms,[5b,c] due to the importance of this field of study for better understanding the nature of these intriguing compounds. In contrast to the monocyclic macrolide antibiotics, biosynthesis of the A83543 tetracyclic ring system requires the formation of three intramolecular carbon–carbon bonds in addition to lactonization (Scheme 1). However, the exact sequence of these three ring-forming reactions (lactonization, Diels–Alder, aldol) has not yet been established.[5a]

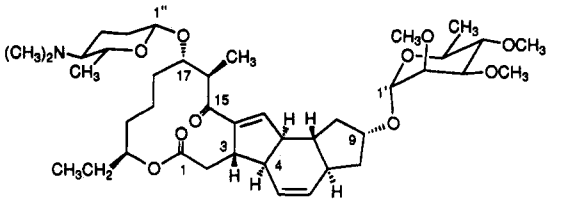

Figure 1. Structural formula of A83543A (1).

Although A83543A and (+)-ikarugamycin[6] both contain a 5,6,5-cis-anti-trans tricyclic ring system fused to a macrocyclic ring, they possess opposite absolute stereochemistries of their tricyclic systems, indicating important differences in their biogenetic pathways. The most likely explanation for this opposite stereochemistry is an opposite positioning of the diene relative to the dienophile during their respective intramolecular Diels–Alder reactions. Whether chemical or enzymatic in their origin, these differences between A83543 and ikarugamycin in the orientation of diene and dienophile during their biosyntheses are an interesting subject for further investigation.

A variety of mechanisms involved in the biosynthesis of natural products have often been successfully imitated by efficient laboratory syntheses of these diverse structures. The term "biomimetic synthesis" has been coined to describe those syntheses which are designed to parallel the processes taking place in nature.[5c] At the outset of this project, we proposed to reverse the postulated biosynthetic processes shown in Scheme 1 and to thereby carry out "retrobiomimetic" reactions of a 9,17-diprotected derivative of 2. The reasons for conducting such an exercise included the following: (a) to investigate the reversibility and stability of the ring system and the three ring-forming C–C bonds, (b) to provide substrates and purported intermediates for both microbiological and chemical studies to test the biosynthetic route and mechanisms of ring formation postulated above, (c) to

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• Abstract published in *Advance ACS Abstracts,* February 1, 1994.

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Scheme 1. Proposed Pathway for Biosynthesis of Tetracyclic Ring System

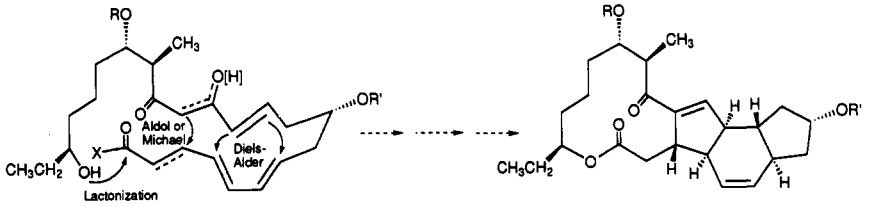

Table 1. ^{13}C NMR Data for A83543A Derivatives[a,b]

carbon	2	3	4	5	6	7	8	9	10	11	13[c]	14[c]	15	16	18	19
1	172.7	172.4	172.7	171.7	171.6	172.3	171.9	172.1	60.6	171.5	172.1	172.2	172.4	61.6	174.1	173.8
2	34.0	34.8	34.0	34.5	34.5	35.2	35.6	33.3	36.0	38.1	34.2	34.4	36.1	34.9	34.6	34.6
3	47.6	47.6	47.6	47.5	47.5	44.3	44.6	42.5	47.7	44.8	43.7	41.3	45.6	48.1	42.1	42.0
4	41.5	41.4	41.5	41.7	41.1	45.9	44.6	43.1	42.4	47.5	44.1	44.1	40.6	41.2	49.7	49.7
5	128.6	128.8	128.3	128.3	129.0	128.3	128.2	127.7	128.5	129.5	128.3	128.6	128.2	129.4	128.6	128.4
6	129.5	129.9	130.0	129.7	128.4	131.1	131.5	130.8	130.5	130.8	129.3	129.1	130.9	130.7	129.9	129.9
7	41.1	41.08	41.2	41.1	40.6	41.5	41.2	41.1	41.3	41.2	41.4	41.3	41.4	41.1	41.8	41.7
8	40.5	40.8	40.7	40.6	43.1	40.8	40.9	40.8	40.8	40.7	37.0	37.0	40.9	40.8	41.1	41.1
9	72.2	72.6	72.6	72.2	215.7	72.4	72.5	72.4	72.3	72.4	79.6	79.7	72.6	72.6	72.1	72.1
10	39.8	40.8	40.7	39.9	43.7	40.9	41.0	40.8	40.7	40.6	36.7	36.7	40.9	41.1	40.4	40.4
11	46.5	46.8	46.2	46.4	44.2	46.8	47.6	47.4	47.0	45.8	46.8	46.8	47.5	47.9	43.8	43.8
12	49.5	49.7	49.5	49.7	49.3	42.0	41.7	41.3	42.1	42.2	41.4	42.9	44.4	43.1	45.2	45.1
13	147.8	147.5	148.0	150.10	148.8	36.4	34.4	35.1	35.0	32.3	34.9	34.4	31.9	36.9	32.8	33.0
14	144.3	143.6	144.2	143.0	143.3	46.7	47.9	57.1	58.5	45.1	56.9	56.9	49.6	49.6	38.2	38.2
15	203.0	203.7	202.8	194.2	194.0	216.2	215.3	216.4	216.7	203.2	213.8	216.1	74.1	73.3	80.3	80.4
16	48.1	48.0	48.1	59.0	59.3	56.6	52.0	51.1	51.0	137.7	48.3	50.4	39.9	39.5	39.6	40.2
17	72.5	74.0	72.6	206.1	206.2	69.4	70.6	73.8	74.1	144.5	80.0	72.7	76.3	75.6	74.2	74.5
18	34.9	36.4	34.9	36.8	36.6	40.8	35.0	36.4	36.9	29.3	32.3	35.5	29.7	30.0	32.5	30.1
19	21.6	19.4	21.6	17.9	17.6	22.2	20.6	19.5	21.6	22.3	19.5	19.6	22.7	21.9	19.1	21.6
20	30.0	31.0	30.0	28.7	28.5	28.3	30.4	31.1	34.1	30.4	30.7	30.8	33.6	34.8	42.1	37.0
21	76.9	76.2	76.9	75.4	75.5	78.9	77.8	77.4	73.1	77.6	76.8	77.4	78.1	73.2	211.4	73.0
22	28.4	27.9	28.4	25.6	25.4	28.3	27.9	28.0	30.4	26.6	27.9	27.9	30.4	30.4	36.1	33.1
23	9.3	9.4	9.3	9.8	9.9	9.6	9.6	9.3	9.8	10.2	9.4	9.5	9.1	8.0	7.8	9.8
24	15.7	18.3	15.7	12.3	12.2	13.3	10.0	16.5	13.8	10.8	15.4	15.4	14.1	9.9	9.8	9.9

[a] All spectra were run in $CDCl_3$. [b] ^{13}C NMR chemical shifts (δ) for the TBDMS groups were very similar in all cases and can be exemplified by the values for compound 8: δ -3.86, -4.46, -4.72, and -4.77 ($4CH_3$ groups, $SiCH_3$); 17.99 and 18.09 (2 quart, C, Si-*C*(IV)); 25.75 and 25.88 (6 CH_3 groups, C(IV)-CH_3). [c] The carbon signals of the trifluoroacetate groups were not analyzed.

focus chemistry efforts exploring this new structure into learning the reactivity of its tetracyclic ring system, and (d) to explore approaches to novel related ring systems. Degradation of the aglycon was also perceived as a more chemically interesting and efficient route than total synthetic approaches to obtaining postulated intermediates occurring in the later stages of the biosynthetic pathway.

To investigate this retrobiomimetic proposal and to explore potentially useful structural modifications of A83543 derivatives, we initiated a study of the chemical behavior of A83543A aglycon (**2**) under a number of chemical conditions frequently employed in organic synthesis. Furthermore, since the 12-membered lactone ring of A83543 is fused to a rigid 5-membered ring, this uncommon situation posed a number of important questions regarding the conformation and reactivity of the substrates and the stereochemistries of the products formed.

Results and Discussion

The success of retro Diels–Alder processes, as applied to interesting chemical transformations of steroids, indicated a possible analogy that might lead to the cleavage of two of the three ring-forming bonds within the A83543A skeleton (C(4)–C(12) and C(7)–C(11) bonds). However, because of the ease of elimination of the 17-oxygen functionality and the thermodynamic stability of the 5,6,5-tricyclic *as*-hydrindacene ring system,[6b] a variety of retro Diels–Alder approaches, including thermal reactions, Lewis acid catalysis, and the PTAD-based methodology[7f-h] produced no satisfactory results. Attempts to carry out retro Michael reactions (cleavage of the C(3)–C(14) bond) under basic catalysis conditions also failed. Most unexpectedly, all efforts to hydrolyze the lactone to the corresponding seco acid under conditions that typically hydrolyze a lactone functionality failed with the A83543 molecule. These preliminary investigations clearly demonstrated the unanticipated chemical stability of the tetracyclic ring system and directed future efforts to indirect methods for cleaving the various bonds involved in ring formation.

The hydrolysis of **1** to its aglycon **2** was most efficiently performed by sulfuric acid in dilute ethanol. Best yields were obtained when a basic quench of the acidic reaction medium before workup was avoided. The 12-5-6-5 tetracyclic system proved to be very stable toward the strongly acidic conditions of hydrolysis. The identity of unchanged tetracyclic structure was confirmed by NMR spectroscopy (Tables 1 and 2; see also ref 2). Both hydroxy groups of A83543A aglycon were subsequently protected

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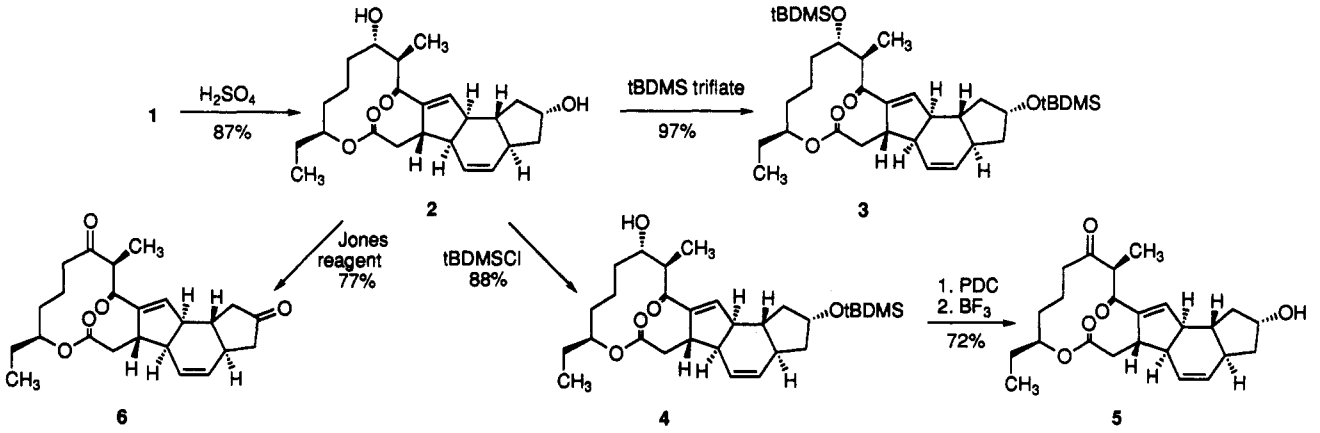
Table 2. ^{1}H NMR Data for A83543A Derivatives[a,b]

no.	2	3	4	5	6	7	8	9	10	11	13	14	15	16	18	19
1									3.52					3.73		
1									3.47					3.65		
2	3.18 dd (13.0, 4.0)	3.05	3.11	3.24 dd (13.2, 2.8)	3.23 dd (13.3, 4.0)	2.67	2.67 dd (13.1, 2.6)	2.46	1.90	2.43	2.59 dd (13.8, 5.1)	2.55	2.62 dd (14.8, 4.0)	1.75	2.69 dd (14.6, 5.8)	2.68 dd (14.6, 5.8)
2	2.44 dd (13.0, 2.8)	2.43	2.40	2.43	2.46	2.67	2.37	2.46	1.37	2.02 dd (16.2, 11.4)	2.45	2.55	2.45 dd (14.8, 5.4)	1.75	2.40	2.31 dd (14.6, 12.2)
3	3.02	3.03	3.00	3.00	3.10	2.04	2.12	2.18	2.16	2.45	2.26	2.22	2.52	2.18	2.08	2.08
4	3.47	3.48	3.44	3.04	3.12	2.56	2.36	2.84	2.03	2.18	2.80	2.83	2.06	2.04	2.28	49.71
5	5.81 ddd (10.0, 2.4, 2.4)	5.77 ddd (9.8, 2.7, 2.4)	5.75 ddd (10.0, 2.5, 2.5)	5.79 bdd (9.8, 2.5)	5.86 ddd (9.8, 2.4, 2.4)	5.64 ddd (9.5, 3.0, 3.0)	5.60 bdd (9.8, 2.6)	5.78 bdd (9.7, 2.7)	5.67 bdd (9.9, 2.3)	5.67 ddd (10.0, 2.5, 2.5)	5.83 ddd (10.0, 2.8, 2.3)	5.82 ddd (10.0, 2.5, 2.3)	5.53 ddd (10.0, 2.8, 2.4)	5.71 ddd (10.0, 2.4, 2.4)	5.69 ddd (9.8, 3.4, 3.4)	5.67 ddd (9.8, 3.4, 3.0)
6	5.93 bd (10.0)	5.88 bd (9.8)	5.87 bd (10.0)	5.90 bd (9.8)	5.94 bd (9.8)	5.88 bd (9.5)	5.87 bd (9.8)	5.87 bd (9.7)	5.80 bd (9.9)	5.88 bd (10.0)	5.92 bd (10.0)	5.89 bd (10.0)	5.75 bd (10.0)	5.82 bd (10.0)	5.79 bd (9.8)	5.79 bd (9.8)
7	2.28	2.27	2.27	2.26	2.40	2.20	2.22	2.16	2.18	2.20	2.21	2.22	2.22	2.22	2.19	2.19
8α	1.90 dd (12.0, 7.0)	1.84 dd (12.8, 7.2)	1.81	1.87 dd (9.1, 2.9)	1.97 dd (20.0, 7.8)	1.80	1.80	1.77	1.74 dd (12.6, 6.9)	1.80	2.08 dd (13.9, 6.6)	2.06 dd (13.9, 6.6)	1.80	1.77	1.76	1.77
8β	1.48	1.43	1.42	1.47	2.47	1.42	1.42	1.40	1.40	1.48	1.63	1.63	1.42	1.42	1.44	1.43
9	4.47	4.36	4.34	4.44		4.37	4.37	4.34	4.32	4.37	5.40	5.39	4.38	4.33	4.35	4.35
10α	2.38 dd (13.0, 6.0)	2.24	2.23	2.36	2.55	2.23	2.25	2.12	2.15	2.22	2.50	2.48	2.27	2.25	2.23	2.23
10β	1.26	1.27	1.26	1.25	1.91 dd (20.0, 7.3)	1.20	1.19	1.10	1.04	1.18	1.29	1.27	1.10	1.12	1.12	1.12
11	0.98	0.92	0.91	0.94	1.45	1.07	0.95	1.06	1.02	1.05	1.27	1.21	0.99	1.06	1.04	1.04
12	2.92	2.91	2.87	2.87	2.95	2.22	2.32	2.16	2.10	2.23	2.24	2.24	1.78	1.77	2.17	2.16
13	6.82 bs	6.84 bs	6.79	6.96	6.90	2.20	2.17	1.20	2.30	2.28	2.45	2.38	1.27	1.44	1.76	1.72
13						1.55	1.55	2.40	1.27	1.54	1.32	1.35	1.55	1.44	1.48	1.57
14						3.55	3.64	2.82	2.93	3.92	2.92 bq (9.5)	2.89 bq (9.3)	1.84	1.78	2.41	2.42
15													3.77 bd (4.1)	3.75	4.37 bd (10.2)	4.26 bd (10.7)
16	3.22 dq (12.0, 6.9)	3.22	3.19	4.25 q (6.8)	4.23 q (6.8)	2.40	2.55	2.81	2.89		3.16 dq (10.4, 6.8)	2.78	1.64	1.65	1.74	1.74
17	3.70	3.87	3.66			3.97	4.28	3.80	3.80	6.80 dd (10.8, 5.0)	5.22	3.80	3.74	3.78	3.65	3.64
18	1.53	1.65	1.56	2.61	2.65	1.80	1.56	1.70	1.38	2.37	1.77	1.60	1.55	1.79	1.43	1.50
18	1.53	1.44	1.45	2.37	2.35	1.42	1.56	1.40	1.38	2.10	1.77	1.60	1.26	1.43	1.43	1.36
19	1.63	1.56	1.65	1.75	1.75	1.82	1.78	1.68	1.50	1.78	1.56	1.65	1.30	1.37	1.64	1.48
19	1.28	1.08	1.29	1.65	1.75	1.44	1.18	1.10	1.28	1.70	1.56	1.17	1.03	1.37	1.49	1.27
20	1.54	1.69	1.60	1.60	1.53	1.84	1.80	1.80	1.52	1.73	1.78	1.35	1.73	1.52	2.38	1.46
20	1.49	1.27	1.43	1.49	1.53	1.62	1.52	1.22	1.35	1.73	1.33	1.28	1.45	1.25	2.38	1.33
21	4.72	4.67	4.69	4.83	4.83	4.83	4.86	4.76	3.48	4.58	4.83	4.77	4.65	3.51		3.51
22	1.50	1.53	1.50	1.56	1.47	1.58	1.61	1.53	1.41	1.68	1.53	1.55	1.77	1.45	2.37	1.79
22	1.50	1.53	1.50	1.43	1.47	1.58	1.61	1.53	1.41	1.54	1.53	1.55	1.45	1.45	2.37	1.41
23	0.82 t (7.0)	0.84 t (7.5)	0.81 t (7.0)	0.82 t (7.4)	0.81 t (6.5)	0.89 t (7.6)	0.88 t (7.6)	0.85 t (7.6)	0.90 t (7.5)	0.87 t (7.5)	0.86 t (7.5)	0.85 t (7.5)	0.91 t (7.5)	0.95 t (7.5)	1.03 t (7.5)	0.92 t (7.8)
24	1.23 d (6.9)	1.20 d (6.9)	1.21 d (7.0)	1.32 d (6.7)	1.32 d (6.8)	1.24 d (7.0)	1.02 d (6.8)	1.08 d (6.6)	1.05 d (7.0)	1.73 bs	1.12 d (6.7)	1.16 d (6.7)	0.89 d (6.8)	0.91 d (6.8)	0.95 d (6.9)	0.96 d (7.3)

[a] All spectra were run in $CDCl_3$; chemical shifts are reported in ppm (δ) downfield from internal TMS; proton–proton coupling constants measured in Hz are shown in parentheses. [b] ^{1}H NMR chemical shifts for the TBDMS groups were very similar in all cases and can be exemplified by the values for compound 8: δ −4.77 (s), −4.72 (s), −4.46 (s), and −3.86 (s) (4 CH_3 groups, $SiCH_3$); 0.85 (s) and 0.88 (s) (6 CH_3 groups, C(IV)-CH_3).

Scheme 2. Protection and Oxidation of Hydroxyl Groups



in the form of the TBDMS ether 3.[8a] Although 2 when stored at room temperature, even in the absence of light, showed considerable signs of decomposition, this did not occur with 3. Milder silylation conditions[8] resulted in the efficient formation of the C(9)-mono-O-protected compound 4, presumably due to the steric hindrance around C(17). The 17-hydroxy group in 4 was oxidized with PDC[9] which, after deprotection of the C(9) hydroxyl group, furnished the diketo-alcohol 5. On the other hand, oxidation of A83543A aglycon 2 with Jones reagent[10] gave the beautifully crystalline triketone 6 in a satisfactory yield.

NOE irradiation of the olefinic C(13)-H in 5 and 6 resulted in each case in a strong response (>10%) at the C(16)-H, similar to that for compounds 2 and 3. This suggested an unchanged *R* configuration at C(16) for both oxidation products. All NMR data (collected for a $CDCl_3$ solution of 6) indicated the presence of only one isomer. Molecular modeling of compound 6 (Monte Carlo searches, see Experimental Section) resulted in a set of low-energy conformers whose common feature was coplanarity of the C(16)-H with both the C(15) and C(17) carbonyl groups. According to the stereochemical requirement for carbonyl enolization,[11] such a conformation could prevent enolization toward C(16). In addition, the 16α-H was found to be located in a sterically shielded region. Analogous Monte Carlo calculations performed for the 16*S* epimer of compound 6 furnished structures with higher energy (difference in energy between global minima found for 6 and 16-*epi*-6: ΔE = 0.77 kcal/mol).

Diisobutylaluminum hydride has been reported to reduce conjugated enones in either a 1,2- or a 1,4-fashion; the reaction outcome is strongly dependent on the enone's structure. Also, DIBALH is known to react with most lactones, including hindered ones.[12a,d] Surprisingly, compound 2 did not react at all, even with a substantial excess of DIBALH. Strong complexation of the bulky dialkylaluminum hydride with the electron-donating oxygen atoms on the macrocyclic ring may have occurred, forming a steric hindrance that drastically reduced the expected reactivity of the carbonyl groups. These results further established the surprising stability of the macrocyclic lactone ring system.

Consequently, we turned our attention to combinations of $LiAlH_4$ and strongly coordinating additives. Compound 2 reacted with $LiAlH_4$–pyridine[13a] (lithium tetrakis(dihydro-*N*-pyridyl)aluminate) in THF to give, after 9α-O-silylation, the 13,14β-dihydro derivative 7. The stereochemistry at C(14) in 7 was established at a later stage by NMR spectral comparisons (see Tables 1 and 2). No products of lactone reductive cleavages were observed in this reaction. Preferential 1,4-addition of hydrogen to the enone moiety of 2 thus paralleled other *in vivo* and *in vitro* reductions by dihydropyridines.[13b] Clearly, in the case of compound 2, the general problem[14] of 1,2- vs 1,4-reduction mode is further complicated by the presence of the lactone functionality, by complexation phenomena, by the presence of hydroxyl protons, and by strong, but difficult to predict, steric effects. For example, cation complexation to the carbonyl oxygen of an enone system is known to enhance the 1,2-reduction mode, but on the other hand, cation complexing additives are known to substantially increase the amount of 1,4-reduction.[14a] In the case of A83543A derivatives, these effects are clearly contradictory, and the problem of selective and controlled reduction of the 13-en-15-one and/or lactone groups at that moment remained unsolved.

Reaction of compound 3 with $NaBH_4$ in ethanol smoothly afforded the 13,14β-dihydro derivative 8. Although earlier reports[14b] showed that sodium borohydride can reduce 2-cyclopentenones to saturated alcohols with good selectivity, the reaction seems to depend strongly on the structure and chemical nature of the enone system. Recently, an analogous reduction leading to unsaturated, allylic alcohols was reported.[14c] The stereochemistry at C(14) of compound 8 was determined by NMR methods and further substantiated by correlations with molecular modeling studies. The 14β-H configuration was confirmed at a later stage by chemical transformations of compound 8.

(8) (a) Corey, E. J.; Cho, H.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. (b) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817.
(9) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.
(10) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
(11) Pollack, R. M. *Tetrahedron* **1989**, *45*, 4913.
(12) (a) Winterfeldt, E. *Synthesis* **1975**, 617. (b) Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1976**, 3865. (c) Antus, S.; Gottsegen, A.; Nogradi, M. *Synthesis* **1981**, 574. (d) Ley, S. V.; Santafianos, D.; Blaney, W. M.; Simmonds, M. S. J. *Tetrahedron Lett.* **1987**, *28*, 221.
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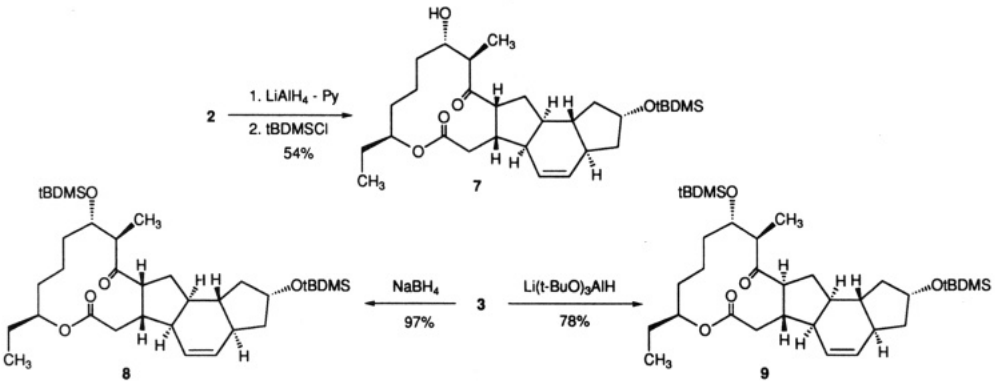
Scheme 3. Hydride Reductions of Enone



Conformational investigations of macrolactone compounds have been the focus of a number of studies.[15] The complexity of macrolactone conformational space is such that macrolides have served as working examples[15b] for the development of contemporary molecular modeling methods. As recent literature indicates,[15a] one very effective way to determine low-energy structures of a 12-membered lactone is internal coordinate Monte Carlo searching.[15b] This method was applied throughout the present study, as implemented in the MacroModel V 3.5a program.[16] The MM2* force field was used for conformational energy minimizations.[16,17]

A Monte Carlo conformational search was carried out for compound **8**, as described in the Experimental Section (the 9α-OMe derivative was used rather than the 9α-OTBDMS to save computational time). This search resulted in a set of conformers, seven of which were located within 1.44 kcal/mol from the found global energy minimum (GEM) structure. Four lowest energy conformers were within 0.96 kcal/mol from the GEM; except for different rotamers of the 21-ethyl side chain and the 17-*O*-TBDMS group, they corresponded to a single conformer, identical with the GEM (see Figure 2).

Some interatomic distances found for the GEM were of strategic importance in the determination of stereochemistry at C(14) in **8**: 14H–17H = 2.09 Å, 14H–13βH = 2.33 Å, 14H–3H = 2.44 Å, 14H–13αH = 2.72 Å. The fifth lowest conformer (ΔE = 1.24 kcal/mol) was significantly different: 14H–11H = 2.24 Å, 14H–3H = 2.28 Å, 14H–17H = 2.31 Å, 14H–13βH = 2.41 Å. Experimental NOE responses determined for compound **8** in $CDCl_3$ at 500 MHz, upon irradiation at the 14β-H, were: 17H (15%), 13β-H (8%), 3β-H (5%), 13α-H (4%), 16-H (2%), 11β-H (2%), and 24-Me (2%). These results are in excellent agreement with the expected NOE values based upon molecular modeling. The GEM structure found for **8** very clearly explains the strongly deshielded position of the 14β-H in the proton spectra, due to its placement in the deshielding cone of the C(15) carbonyl and to its proximity to the C(1) carbonyl oxygen.

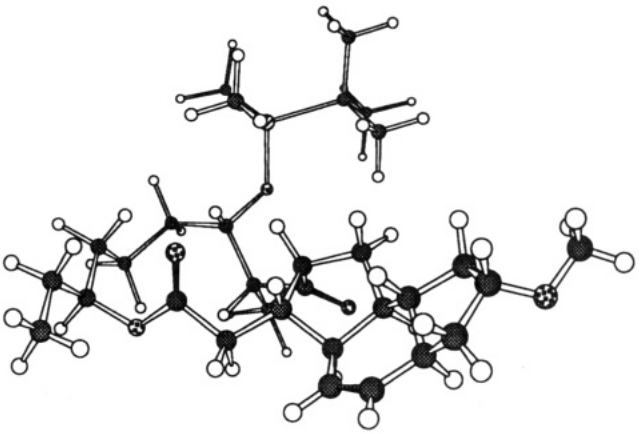


Figure 2. Perspective view of the lowest energy macrolactone ring conformer of compound **8**.

The efficient transformations of compound **3** to **8** and compound **2** to **7**, although selective, did not give access to the 13,14α-dihydro derivatives. The marked differences in reactivity between borohydrides and alkoxyaluminohydrides[14a] prompted us to react compound **3** with Li(t-BuO)$_3$AlH. This reaction provided compound **9**, epimeric to **8** at C(14), selectively and in good yield. We also noticed for the first time the unusual stability toward epimerization of the C(14) stereocenter. The structure of compound **9** was corroborated by NMR data (see Tables 1 and 2).

Attempts to use lithium aluminum hydride for selective reductions of **3** were not successful. The reaction required some excess of the reducing agent to proceed (see Experimental Section), and the high reducing potential of $LiAlH_4$ lowered the selectivity. Compound **9** (33%) was isolated together with compound **10** (33%). Evidently, the enolate formed from **3** during conjugate reduction[14] was stable under the reaction conditions which reductively opened the lactone group; the C(15) carbonyl group was then regenerated upon workup. This observation shed some light on the stability of C(15) enolates (vide infra). The structure of compound **10** followed from comparison of NMR data for **9** and **10** (see Tables 1 and 2).

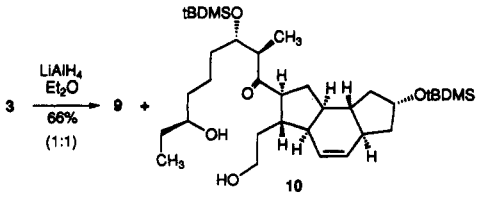
The conformations of compound **9** were determined by Monte Carlo searches. Conformational diversity of **9** was found to be much greater than for **8**, with seven lowest energy conformers being within 0.97 kcal/mol from the GEM. However, the two lowest energy conformers were within 0.35 kcal/mol of each other and differed only slightly

(15) (a) Saunders, M.; Houk, K. N.; Wu, Y.-D.; Still, W. C.; Lipton, M.; Chang, G.; Guida, W. C. *J. Am. Chem. Soc.* **1990**, *112*, 1419. (b) Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (c) Still, W. C.; MacPherson, L. J.; Harada, T.; Callahan, J. F.; Rheingold, A. L. *Tetrahedron* **1984**, *40*, 2275. (d) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *23*, 3981. (e) Matsushima, T.; Nakajima, N.; Yonemitsu, O.; Hata, T. *Tetrahedron Lett.* **1991**, *32*, 5133.

(16) (a) MacroModel V 3.5X: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440. (b) See also: *MacroModel V 3.5X: Release Notes, Primer, User Manual, and BatchMin 3.5 User Manual*; Department of Chemistry, Columbia University: New York, NY 10027; April 1992.

(17) Bowen, J. P.; Allinger, N. L. Molecular Mechanics: The Art of Parametrization. In *Reviews In Computational Chemistry: Advances*; Lipkowitz, K. B., Boyd, D. B., Eds.; VCH Publishers: New York, 1991; Chapter 3, pp 81–97 and references cited therein.

Scheme 4. Reductive Cleavage of A83543 Lactone



in their torsional angles at C(18) and C(19). The GEM found for compound 9 was lower in conformational energy than the GEM found for 8 by 3.20 kcal/mol.

At this point, it was useful to compare the conformational features of compounds 8 and 9 with their 17α-methoxy analogues in order to examine the influence that the steric bulk of the C(17) substituents exerted on the conformation of the macrolactone ring. Toward this end, the 9,17-dimethoxy analogues of compounds 8 and 9 were investigated by the Monte Carlo method. For 13,14β-dihydro derivatives, the bulky substituent at C(17) clearly stabilizes the conformers similar to the GEM structure of this compound; i.e., many fewer conformers of a different type are found within 3 kcal/mol of GEM. However, in the 13,14α-dihydro and 13,14-unsaturated series, bulky substituents at C(17) favor a different conformation of the lactone ring, with a 17α-pseudoaxial orientation of the substituent, unlike the 17α-methoxy derivative. Clearly, the compounds considered here adopt quite specific preferred conformations as a consequence of the existing asymmetric centers, a fact recognized in the field of polyketide chemistry.[18] In addition, the effect of nonligating substituents exerted by preorganizing the macrocycle structure can create an efficient mechanism for a "conformational lock" of a particular conformation.[19] On the other hand, substituents on a flexible ring that show high barriers to rotation participate in a "local conformation problem",[20a] a subject of dynamic NMR studies. We found a number of low-energy conformers of compounds 6, 8, and 9, differing only in the rotation angles of the 17-*O*-TBDMS and/or 21-ethyl groups, but possessing identical structures of the macrolactone ring. This is yet another example of the stabilizing effect of large, flexible, nonchelating substituents. Such molecular modeling results should be considered in planning searches for more potent derivatives of biologically active macrolactones. It has been proposed[20b] that stable conformers of flexible structures bind much stronger to receptors or are much better ionophores[20c,d] than unstable ones. Such preorganization enhances binding both entropically and enthalpically.[21]

Having established the stereochemistry at C(14) in compounds 8–10 and having estimated the conformational preferences of both types of C(14) epimers, we subsequently investigated the possibility of epimerization at C(14) for compounds 8 and 9. The difference found in conformational energy between 8 and 9 (ΔE = 3.20 kcal/mol, vide supra) suggested a substantial thermodynamic driving force for epimerization of 8 to 9. Numerous methods that have been used for epimerization of ketones were evaluated (see Experimental Section), but they all gave either unchanged substrates or secondary products 11–14. It is important to note that none of these products was epimerized at C(14) (see Tables 1 and 2).

The structure of elimination product 11 was determined by NMR and correlated with results from Monte Carlo conformational searches. The lowest energy conformers found for 16,17(*Z*)-11 and 16,17(*E*)-11 were compared. The experimental NOE value detected at 14β-H upon irradiation of the olefinic 17-H (NOE >10%) unequivocally indicated the 16,17(*E*) configuration of 11. Furthermore, the GEM structure for (*E*)-11 corresponded very well with the strongly deshielded position of the 14β-H in proton spectra of 11 and with the relatively shielded position of the 24-methyl protons in these spectra. Even though the *Z* isomer of 11 possessed a lower conformational energy (ΔE = 0.84 kcal/mol), the rotamer of the intermediate 15-en-15-ol that could lead[22] to (*E*)-11 was energetically preferred over the rotamer leading to (*Z*)-11 by some 30 kcal/mol!

The puzzling stability of 8 and 9 toward enolization must be kinetic in origin and must result either from (a) complete lack of enolization toward C(14) or (b) preferential reaction of the enol(ate)s with protons on only one face of the enol double bond, with this face being determined by the shape of the substrate molecule. To shed more light on this problem, we conducted deuteriation experiments (see Experimental Section). Under basic conditions, compound 8 easily enolized toward C(14) and C(16), while compound 9 did not enolize toward C(14) at all. The lack of enolization of 9 toward C(14) could be explained either by the stereoelectronic requirement[11,22] or by the relatively hindered position of 14α-H (Figure 3). Assuming that the calculated conformational energy difference between 8 and 9 is correct, a rationale for the observed stability of the C(14) stereocenter in 8 was still lacking.

Enolate reactions taking place within macrocyclic rings have been extensively studied by computational methods.[15cd,23] It is also known that the MacroModel program is not suitable[16] for structure determination of complex lithium enolates,[24] even though such attempts have recently been reported.[23b] Rather, we thought that determination of the preferred conformations of 14-en-15-ols might provide useful insights into the steric limitations and relative stabilities of these species.

Our further analysis was based on the fact that in the energetically preferred set of conformations for compound 8, including the GEM structure, the C(15) carbonyl was oriented "outward" from the macrolactone ring, but for the epimeric compound 9, the C(15) carbonyl orientation was "inward" toward the ring. Thus, assuming in each case comparable accessability to base of the C(14)-protons,

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(22) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Elmsford: New York, 1983.

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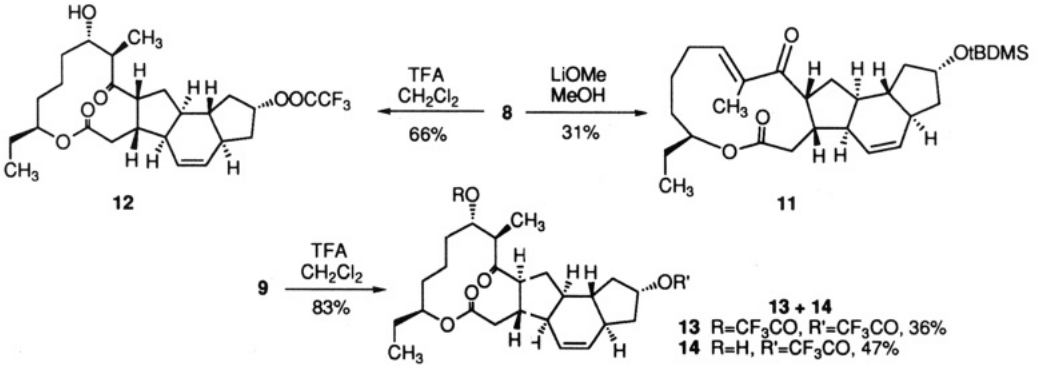
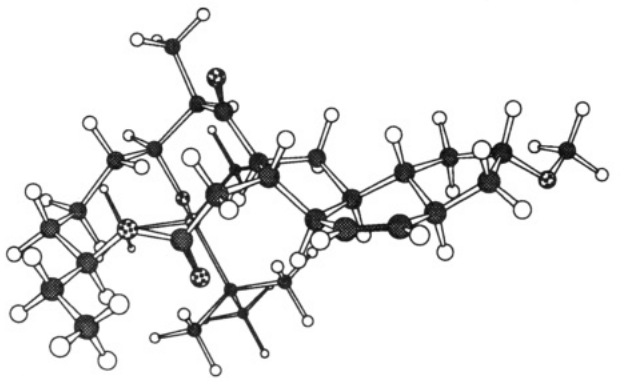
(24) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

Scheme 5. Acylation of 13,14-Dihydro Products





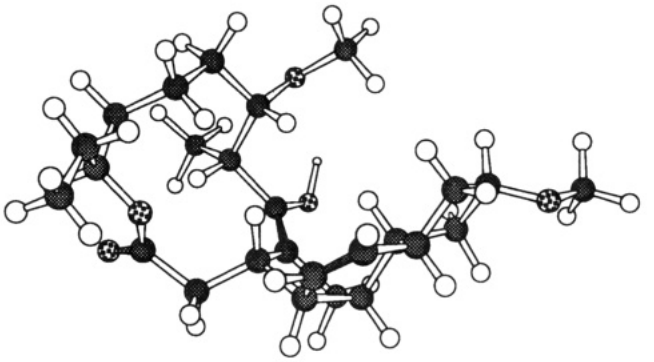


Figure 3. Perspective view of the lowest energy macrolactone ring conformer of compound **9**.

the enol(ate) initially formed from **8** should be the "outward" one (Figure 4a), while that formed from **9** should be "inward 15-O" enol(ate) (Figure 4b). Both enols were subjected to Monte Carlo conformational searches. The "inward" isomer was found to possess a much lower conformational energy ($\Delta E = 3.02$ kcal/mol). In addition, the structure of the enol shown in Figure 4b resembles very closely the conformation of 9,17-dimethoxy analogue of compound **3** and the GEM conformation of **9** (see Figure 3). This conformation of the "inward" enol is substantially different from the GEM conformation of **8** (see Figure 2).

Possibly, ketone **9** is not susceptible to enolization toward C(14) at all, and it is the thermodynamically preferred epimer (under thermodynamic conditions,[25] no reaction of **9** was observed). In the case of ketone **8**, enolization gives rise to enol species which presumably cannot equilibrate to give the more stable "inward" type of structures due to the necessity of a complete reorganization of the macrolactone ring (compare Figure 4a and b). Clearly, factors other than purely steric ones are responsible for the protonation of the "outward" type of enol structures exclusively from the β face. The energy barrier between **8** and **9** is too high to overcome under the conditions (and reaction times) employed because it would require too substantial a reorganization of the macrolactone ring at the enol(ate) stage of the reaction. Although base-promoted interconversions of similar structures have been reported during a total synthesis, a retro-Aldol mechanism is most likely involved in that case.[4] These contrasting results offer additional support for the involvement of different mechanisms in each case.

Structures resembling those shown in Figure 4 may also arise during the conjugate reductions of the 13-en-15-one

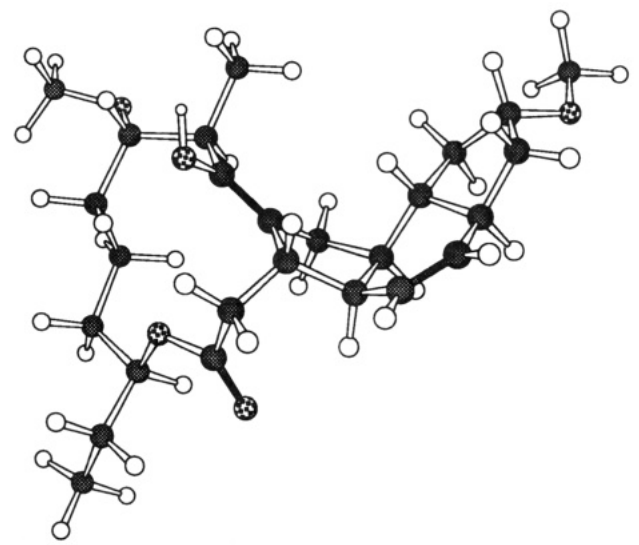


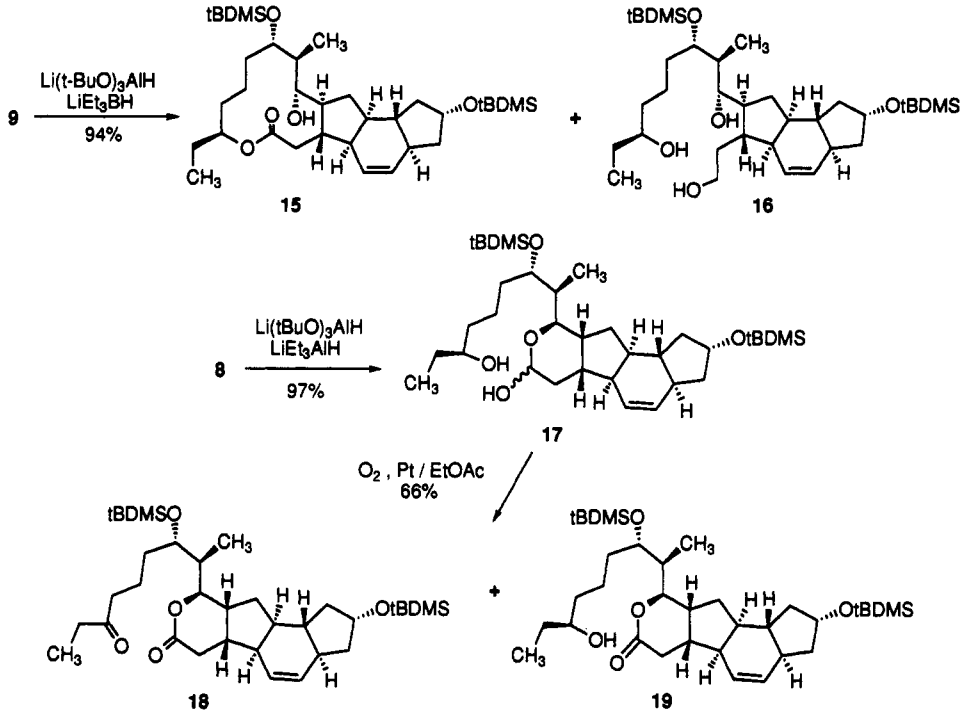
Figure 4. Perspective views of the lowest energy conformers of (a) the "outward enol" and (b) the "inward enol".

system. The fact that Li(t-BuO)$_3$AlH is a much stronger complexing agent[14a] than borohydride implies an intramolecular donation of a proton (originating from a water molecule initially chelating the alkoxyalumino complex of the enol) to the enol double bond during the mild quenching procedure, exclusively leading to the 14α-ketone **9**. The result of reduction with lithium tetrakis(dihydro-*N*-pyridyl)aluminate in the presence of an excess of pyridine leading to compound **7** appears to corroborate this proposed explanation.

Finally, we have further investigated the lack of reactivity of the lactone function toward DIBALH and MeOLi (vide supra). A number of methods for "nonhydrolytic" cleavage of lactones are known.[26] We were interested in methods for preserving the 21-hydroxy group in its original *S* configuration. To our knowledge, the method reported

(25) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979.

Scheme 6. Reductive Cleavage of 13,14-Dihydro Products



by Corey et al.[27] is best suited for such macrolactone cleavages. However, even the improved procedure, using LiOOH in the presence of 2-hydroxyethyl sulfide,[27b] furnished no lactone hydrolysis products. Compound **3** also did not react with sodium thiomethoxide or sodium thiophenoxide.[28] This lack of reactivity of the C(1) carbonyl group toward some nucleophiles other than hydride may be only partially rationalized by its hindered arrangement (see Figures 2–4).

Lithium triethylborohydride is one of the strongest known donors of nucleophilic hydride ion.[29] In the presence of aluminum trialkoxides, $LiEt_3BH$ is capable of reductively cleaving THF rings.[29c] On the other hand, lithium tri-*tert*-butoxyaluminohydride, besides being a hydride donor, shows some Lewis acidity (electrophilicity).[14a,30] Both compounds **8** and **9** did not react with $Li(t\text{-}BuO)_3AlH$ in anhydrous ether; however, addition of $LiEt_3BH$ to the reaction mixture in each case resulted in a fast reaction, although leading to different products.

For the 3,14-trans compound **9**, only reduction occurred, leading to compounds **15** and **16**. The stereochemistry at C(15) in **15** and **16** is based on the expected mode of hydride approach to the C(15) carbonyl in compound **9** (see Figure 3). The relatively small coupling observed for the 15β-H in compound **15** is in agreement with a conformation of the macrolactone ring in which the steric interaction of the bulky C(16) center with the proximate five-membered ring is minimal.

In the case of 3,14-cis compound **8**, the reaction cleanly furnished the mixture of lactoles **17**, which was further oxidized to compounds **18** and **19**, using molecular oxygen in the presence of a platinum catalyst.[31] Selectivity toward compound **19** in the last reaction probably can be improved (see Experimental Section).

The results of molecular modeling for compound **8** (Figure 2) and consideration of the steric biases involved in possible hydride donor approaches indicated that the configuration at C(15) of the initially formed C(15) alcohol should be 15β-OH (or 15*R*), which corresponds to 15β-O in **17**. This was positively verified by NMR analysis and Monte Carlo searches performed for compound **19**. The structure found as the GEM (in vacuum) showed a good correlation of coupling constants calculated by MacroModel with values extracted from the NMR spectra of compound **19**.[32]

	found (Hz)	calcd (Hz)
3β-2αH	12.2	12.2
3β-2βH	5.8	4.3
15α-14βH	10.7	10.6
15α-16αH	ca. 1	1.4

A similar coupling pattern was found for all conformers within approximately 3 kcal/mol of the GEM structure.

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The 15β-O configuration was supported by the coupling observed for 15α-H. No realistic conformation for the 15α-O epimer was found that showed a large coupling between 14β-H and 15-H. In the lowest energy conformation, a hydrogen bond between the 21-OH and C(1) carbonyl fixes the side chain into a folded arrangement, with C(18) "inward", as reflected by its high-field position in the carbon spectrum. All spectral and modeling evidence indicated that the lactone ring of **19** is a boat with the 15α-H and 2α-H in flagpole positions. Repeated modeling with the input structures possessing artificially introduced chair lactone rings repeatedly furnished the same set of boatlike low-energy conformers. Compound **18** showed very close spectral similarity to **19**.

A few comments are appropriate for the NMR results presented in Tables 1 and 2. The assignment of C(5) and C(6) is based on the NOE enhancement observed for the C(5)-H upon irradition of the 3β-H in compounds **3**, **6**, **8**, and **9**. The assignment of the proton and carbon signals of the 5,6,5-tricylic system posed no major problems other than signal overlapping in some cases. Also, it was facilitated by the characteristic coupling pattern, observed best in COSY spectra, for the C(8), C(9), and C(10) protons. In a few cases, Karplus–Altona-type calculations[32] of coupling constants, based on molecular modeling, were very helpful in the stereochemical assignments of protons (e.g., C(8) and C(10) protons of compound **6**). Most difficult were the assignments of protons and carbons within the C(18)–C(20) region as the result of strong overlapping in the COSY spectra, even at 500 MHz. Importantly, the coupling observed for the C(2) protons was diagnostic in the verification of the low-energy conformations determined by MacroModel together with NOEDS results. This approach was possible due to the conformationally well-defined position of the 3β proton and to the very limited conformational mobility of the ring junction between the 12-membered lactone and the 5-membered ring. For other more flexible systems with large variations in conformational populations, more complex approaches have been developed which, however, also rely on the computer-aided generation of conformer structures.[33]

Summary

In summary, the hydrolysis, oxidation, and reduction of O-protected derivatives of the A83543A aglycon (**2**) resulted in several unexpected results. Efficient methods of synthesis of both epimeric 13,14-dihydro derivatives were developed, and the enolization phenomena of these compounds were studied. The combined use of molecular modeling and NMR techniques was indispensable in gaining insights into the very complex conformational behavior of the 12-membered lactones fused to a five-membered ring. The stereochemistries at C(14) and C(15) of new reduction products were successfully established. Further results of chemical modifications of the A83543 family of compounds will be reported in due course.

Experimental Section

General. Unless otherwise noted, materials and solvents were obtained from commercial suppliers and used without further purification. Pyridine was dried over KOH, distilled, and then redistilled from P_2O_5 immediately prior to use. Absolute methanol was prepared from commercial reagent by distillation from $Mg(OMe)_2$. Anhydrous solvents and solutions were added using syringes. Chromatography was carried out using Kieselgel 60 (E. Merck, Darmstadt), 230–400 mesh, according to the procedure described by Still.[34] Reactions and chromatography fractions were analyzed by TLC, using 5- × 10-cm glass plates covered with a 0.25-mm layer of silica gel 60 F_{254} (E. Merck, Darmstadt, Art. No. 5719). UV light and H_2SO_4–anisaldehyde solution followed by heating were used for visualization. Mixtures of 10–50% EtOAc in hexanes were used as TLC solvents, unless otherwise noted. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 241 polarimeter for 1% solutions in the solvents indicated at 24 °C, using a 50-mm optical cell. IR spectra were recorded for samples in dry $CHCl_3$ solutions on a Nicolet 510 P FT IR spectrophotometer. UV spectra were obtained using a Shimadzu UV-2101 PC spectrophotometer in the solvents indicated. NMR spectra were recorded on either a General Electric QE-300, Bruker AMX-500, or Varian Unity-500 spectrometer in $CDCl_3$ (7.26 ppm and 77.0 ppm) or in other solvents, as indicated. Two-dimensional NMR experiments:[35] C,H-HETCOR,[35b] HMQC,[35c] COSY-90,[35b] and DQF-COSY[35b] were carried out using standard software and published pulse sequences. In addition to one-dimensional NMR experiments, the HETCOR and COSY spectra were routinely analyzed for each compound reported in Tables 1 and 2. NOE difference spectra[34a] were recorded on a Varian Unity-500 spectrometer with the following parameters: sweep width of 8000 Hz; 90° pulse; mixing time 1.5 s; four steady-state pulses; 16 transients were acquired. Mass spectra were recorded on Finnigan-MAT 731 (EI) and/or VG ZAB-2SE (FAB) mass spectrometers. Elemental analyses were determined with a CEC 440 elemental analyzer. For some new compounds, combustion analysis was not obtained due to either the presence of somewhat labile protecting groups or the consumption of the small amount of product in biological tests and bioconversion experiments. In these cases, purity was ascertained by both proton and ^{13}C NMR spectra and high-resolution mass spectral analysis on samples obtained by preparative chromatographic purification.

Modeling. Molecular modeling was carried out using the MacroModel V 3.5a program, cooperating with the BatchMin V 3.5 auxiliary program. A Silicon Graphics IRIS INDIGO-Elan workstation was used for structure input, structure analysis, simple minimizations, and communication with a CRAY-2 supercomputer. Input structures were based on a crystal structure of A83543A, modified accordingly. For 13,14-dihydro compounds **8** and **9**, conformational investigation was carried out on both the 17-*O*-TBDMS and 17-OMe derivatives in each case to estimate the influence of the bulk of the 17-substituent on macrolactone conformation. Internal coordinate Monte Carlo conformational searches were performed on a CRAY-2 supercomputer, using standard procedures of the MacroModel V 3.5 program with manual Monte Carlo setup, introducing 8–13 rotatable bonds, and using a limit of 1200–1500 calculated structures. As the closure bond, either the C(19)–C(20) or the C(1)–sp^3O bond was chosen, with a closure distance of 1.0–4.0 Å. No geometrical constraints were applied. Energy minimizations were carried out using the MM2* force field and PRCG or FMNR minimizers. The quality of force field parameters employed in calculations was controlled using the ECalc procedure. All of the investigated compounds were minimized in vacuum, and some of them were also minimized in chloroform and/or water media.

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Output from the CRAY-2 was subsequently analyzed by repeated manual minimizations using the SGI workstation to eliminate any *de facto* identical conformers and/or to analyze different conformers showing very close values of conformational energy. Final energy gradients were brought to values much smaller than 0.01 kJ/Å-mol for each minimized structure.

A83543A Aglycon (2). A sample of A83543A (1) (8.50 g, 11.61 mmol; 97% pure by HPLC) was dissolved in EtOH (100 mL). Water (100 mL) was added, and upon stirring, to this solution was added 4 N H_2SO_4 (aq) solution (200 mL). The reaction mixture was heated to reflux, under a nitrogen atmosphere, for 4.5 h. It was then cooled to room temperature, diluted with toluene (250 mL) and EtOAc (300 mL), and brine (300 mL) was added. After extraction, the phases were separated. The water layer was extracted once more with EtOAc (100 mL). The combined organic layers were washed successively with diluted brine (3×) and 5% aqueous $NaHCO_3$ (2×) and then dried over anhyd $MgSO_4$ and concentrated in vacuo. The residue was purified on a flash SiO_2 column (250 g; EtOAc). After concentration to dryness of the chromatographically pure fractions, A83543A aglycon (2) was obtained as a glassy solid (4.08 g, 87%). This product, $[\alpha]_{589} = -145.6°$ (MeOH), $[\alpha]_{589} = -131.7°$ ($CHCl_3$), was homogeneous by TLC (in EtOAc) and by ^1H- and ^{13}C-NMR ($CDCl_3$, 300 MHz); data (see Tables 1 and 2) are in agreement with those reported[2] for acetone-d_6 solutions.

9α,17α-Bis-*O*-(TBDMS) Ether of A83543A Aglycon (3). A83543A aglycon (2) (1.10 g, 2.73 mmol) was dissolved in dry CH_2Cl_2 (30 mL), and 2,6-lutidine (redistilled, 1.40 mL, 1.29 g, 12 mmol) was added, followed by TBDMS triflate (1.30 mL, 1.48 g, 5.60 mmol). After 45 min of stirring at room temperature under nitrogen, the reaction mixture was concentrated in vacuo. The residue was taken up into toluene (100 mL), and the solution was rinsed successively with brine, diluted brine, and 5% aqueous $NaHCO_3$ (3×). The organic layer was dried over anhyd K_2CO_3 and concentrated in vacuo. The residue was purified on a flash column of SiO_2 (100 g; toluene). Pure fractions furnished the 9α,17α-bis-*O*-(TBDMS) derivative of A83543A aglycon (3) as a colorless semisolid (1.678 g, 97%): $[\alpha]_{589} = -82.9°$ (MeOH); IR 3018, 2965, 2931, 1716, 1658, 1258, 1052, 837 cm^{-1}; UV $\epsilon_{244} = 9100$ (EtOH); NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB H^+) 155, 227, 309, 329, 461, 499, 573, 631; HR FAB (MH^+) calcd for $C_{36}H_{63}O_5Si_2$ *m/z* 631.4214, found *m/z* 631.4205.

9α-*O*-TBDMS Ether of A83543A Aglycon (4). A83543A aglycon (2) (41.0 mg, 0.102 mmol) was dissolved in dry CH_2Cl_2 (50 mL), and 2,6-lutidine (redistilled, 39.3 mg, 0.366 mmol) was then added, immediately followed by TBDMSCl (22.6 mg, 0.150 mmol). The reaction mixture was stirred under nitrogen at room temperature for 16 h, and toluene (120 mL) was then added. The resulting solution was washed with 5% aqueous $NaHCO_3$ (3×), dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was passed through a short SiO_2 column (5 g; CH_2Cl_2) to afford pure 9α-*O*-TBDMS derivative of A83543A aglycon (4) as a glassy, colorless solid (46.5 mg, 88%): $[\alpha]_{589} = -138.8°$ (MeOH); IR 3600, 3028, 2965, 2931, 1715, 1659, 1606, 1463, 1373, 1259, 1051, 896, 837 cm^{-1}; UV $\epsilon_{244} = 9900$ (EtOH); NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; EI MS *m/z* 57, 75, 95, 113, 155, 169, 182, 213, 253, 275, 329, 387, 404, 459, 498, 516; HR EI (M^+) calcd for $C_{30}H_{48}O_5Si$ *m/z* 516.3269, found *m/z* 516.3271.

17-Keto Derivative of A83543A Aglycon (5). The 9α-*O*-TBDMS ether of A83543A aglycon (4) (46.5 mg, 0.090 mmol) was dissolved in dry CH_2Cl_2 (4 mL), and DMF (2 mL) was added. To this solution, stirred at room temperature under nitrogen, was added solid PDC (1.58 g, 4.20 mmol) in a few portions, and stirring at room temperature was continued. After 16 h, the reaction mixture was diluted with toluene (70 mL) and then extracted with brine (2×) and with 5% aqueous $NaHCO_3$ (2×). The organic layer was dried over anhydrous K_2CO_3, filtered, and concentrated in vacuo. The residue was purified on a flash SiO_2 column (5 g; CH_2Cl_2) to give the 17-keto-9α-*O*-TBDMS derivative of A83543A aglycon as a colorless semisolid (36.6 mg, 79%): ^1H-NMR ($CDCl_3$, 300 MHz) δ 6.93 (1H, bs), 5.85 (1H, bd, *J* = 9.5 Hz), 5.73 (1H, bdd, *J* = 9.5 Hz, 3.4 Hz), 4.79 (1H, m), 4.32 (1H, m), 4.21(1H, q, *J* = 6.8 Hz), 3.22 (1H, dd, *J* = 13.4, 3.0 Hz), 1.30 (3H, d, *J* = 6.8 Hz), 0.88 (9H, s), 0.81 (3H, t, *J* = 7.6 Hz), 0.04 (6H, bs).

The 9α-*O*-TBDMS derivative thus synthesized (36.6 mg, 0.071 mmol) was dissolved in toluene (15 mL), and H_2O (0.10 mL) was added. The mixture was stirred vigorously at room temperature for 10 min, and $BF_3{\cdot}Et_2O$ (0.10 mL) was then added. Stirring was continued for 15 min. The mixture was then diluted with toluene (50 mL) and washed with 5% $NaHCO_3$ (aq) (3×). The organic phase was dried over anhyd K_2CO_3 and then concentrated in vacuo. The residue was purified on a SiO_2 column (5 g; EtOAc) to give the pure product, 17-keto derivative of A83543A aglycon (5), as a colorless glassy solid (26.0 mg, 91%): IR 1716, 1665, 1607, 1440, 1377, 1231, 1165, 1005 cm^{-1}; NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB H^+) *m/z* 103, 119, 129, 141, 149, 155, 171, 243, 261, 273, 351, 383, 401; HR FAB (MH^+) *m/z* calcd for $C_{24}H_{33}O_5$ 401.2328, found *m/z* 401.2340.

9,17-Diketo Derivative of A83543A Aglycon (6). A83543A aglycon (2) (360 mg, 0.894 mmol) was dissolved in acetone (50 mL), and the solution was cooled to 0 °C. Jones reagent[10] was then added slowly, until the reddish-brown coloration persisted. 2- Propanol (2 mL) was then added, the reaction mixture was diluted with brine (50 mL), and toluene (100 mL) was added. After repeated extraction, the layers were separated. The organic layer was washed successively with diluted brine and with 5% aqueous $NaHCO_3$, dried over anhyd Na_2SO_4, and concentrated in vacuo. The residue was additionally purified on a SiO_2 short column (10 g; 50% EtOAc in hexanes). Concentration of pure fractions gave the 9,17-diketo A83543A aglycon (6) (274 mg, 77%): needles (MeOH); mp = 198–199.5 °C; $[\alpha]_{589} = -178.7°$ (MeOH); IR 1745, 1717, 1667, 1378, 1163, 1052; UV $\epsilon_{247} = 9300$ (EtOH); NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB H^+) *m/z* 119, 142, 155, 183, 259, 291, 399. Anal. Calcd for $C_{24}H_{30}O_5$: C, 71.97; H, 8.05. Found: C, 71.99; H, 7.80.

Attempted Reaction of A83543A Aglycon with DIBALH. Carefully dried A83543A aglycon (2) (81 mg, 0.201 mmol) was dissolved in dry toluene (10 mL), and the solution was cooled to 0 °C under N_2. The DIBALH solution in hexanes (1.0 M, 1.2 mL, 1.2 mmol) was then slowly added. Stirring was continued for 1 h at 0 °C and then overnight at room temperature. After 16 h, a pale yellow precipitate was formed. The solid was filtered (by TLC, the filtrate did not contain any A83543A-derived products). The solid was washed twice with hexanes and dissolved in dry DMF (3 mL). DMAP (52 mg, 0.43 mmol) and TBDMSCl (70 mg, 0.46 mmol) were added, and stirring at room temperature was continued for 2 h. After the usual workup and purification, the 9,17-bis-*O*-(TBDMS) derivative of A83543A aglycon (3) (67 mg, 53%) was the only product recovered.

9α-*O*-TBDMS Ether of 13,14β-Dihydro A83543A Aglycon (7). To a mixture of dry THF (25 mL) and dry pyridine (1.50 mL, 18.5 mmol), which was stirred under nitrogen at room temperature, was added $LiAlH_4$ powder (80 mg, 2.10 mmol) in a few portions. Stirring at room temperature under nitrogen was continued for 30 min, and the mixture was then cooled to 0 °C. A solution of A83543A aglycon (104 mg, 0.258 mmol) in THF (5 mL) was slowly added. Stirring was continued at 0 °C under nitrogen for 1 h and then at room temperature for 1 h. Afterwards, the reaction mixture was diluted with Et_2O (150 mL) and cooled to 0 °C. The resulting solution was carefully quenched with saturated brine and washed with diluted brine (3×). The organic layer was dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo to give a colorless solid (101.5 mg, one major plus two minor components by TLC, only slight differences in polarity). This crude product was dissolved in dry CH_2Cl_2 (20 mL), and 2,6-lutidine (0.30 mL, 276 mg, 2.57 mmol) was added, followed by TBDMSCl (54.0 mg, 0.358 mmol). [Note: The 9-monoprotection reaction was chosen to help in chromatographic separation and, at the same time, to avoid the presence of two TBDMS groups. The 18 *tert*-butyl protons usually appear in NMR spectra as one, very high singlet, overwhelming the signals of other protons.] The reaction mixture was stirred under nitrogen, at room temperature. After 17 h, it was diluted with toluene (100 mL) and extracted successively with brine, diluted brine (2×), and 5% aqueous $NaHCO_3$. The combined extracts were dried over anhyd K_2CO_3, filtered, and concentrated in vacuo. The residue was chromatographed on a flash SiO_2 column (10 g; 10% Et_2O in CH_2Cl_2) to give the 9α-*O*-TBDMS ether of 13, 14β-dihydro A83543A aglycon (7) as a colorless semisolid (73 mg, 54%): $[\alpha]_{589} = -104.0°$ (EtOH); IR 3590, 3485, 3012, 2957, 2930, 2858, 1718, 1709 (sh), 1471, 1460, 1361, 1258, 1160, 1107, 1049, 961, 908, 837 cm^{-1}; NMR see Tables 1 and 2; MS (FAB Li^+) *m/z*

129, 161, 217, 257, 295, 313, 353, 413, 449, 525; HR FAB (MLI$^+$) calcd for $C_{30}H_{50}O_5SiLi$ m/z 525.3588, found m/z 525.3611.

9α,17α-Bis-*O*-(TBDMS) Ether of 13,14β-Dihydro A83543A Aglycon (8). The 9α,17α-bis-*O*-(TBDMS) ether of A83543A aglycon (3) (309 mg, 0.488 mmol) was dissolved in THF (5 mL), and EtOH (30 mL) was added. To this solution, stirred at room temperature, was added $NaBH_4$ (83 mg, 2.18 mmol). The reaction mixture was stirred at room temperature, and the progress of reaction was monitored by TLC. After 20 min, the solution was diluted with toluene (150 mL), and saturated brine was added. After extraction, the phases were separated, and the organic layer was washed successively with brine (2×), diluted brine, and aqueous $NaHCO_3$ (2×), dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was purified on a column (10 g SiO_2; 7% EtOAc in hexanes) to yield the 9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (8) (302 mg, 97%): needles (Et_2O); mp 112–113 °C; $[\alpha]_{589} = -94.7°$ (EtOH); IR 2957, 2930, 2884, 2858, 1716, 1705 (sh), 1473, 1463, 1258, 1107, 1054, 1006, 956, 893, 837 cm^{-1}; NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB Li$^+$) m/z 133, 161, 249, 281, 315, 449, 521, 589, 639 (MLi$^+$). Anal. Calcd for $C_{38}H_{84}O_5Si_2$: C, 68.30; H, 10.19. Found: C, 68.05; H, 10.19.

9α,17α-Bis-*O*-(TBDMS) Ether of 13,14α-Dihydro A83543A Aglycon (9). The 9α,17α-bis-*O*-(TBDMS) ether of A83543A aglycon (3) (660 mg, 1.046 mmol) was dissolved in dry Et_2O (80 mL). To this solution, vigorously stirred under nitrogen, at room temperature, was added in one portion Li(t-BuO)$_3$AlH (585 mg, 97%, 2.23 mmol). Stirring under these conditions was continued for 5 h, with TLC monitoring of the reaction progress. The reaction mixture was then cooled to 0 °C, carefully quenched with saturated brine, and diluted with Et_2O (50 mL). The solution was washed with 1 N aqueous H_2SO_4 and then succesively with diluted brine, 5% aqueous $NaHCO_3$ (2×), and water. The organic layer was dried over anhyd K_2CO_3 and concentrated in vacuo. The residue thus obtained was purified on a flash SiO_2 column (50 g; 5% EtOAc in hexanes) to give the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro-A83543A aglycon (9): white solid (519 mg, 78%); $[\alpha]_{589} = -40.6°$ (EtOH); IR 2957, 2931, 2858, 1718, 1701, 1473, 1463, 1258, 1175, 1106, 1059, 1005, 988, 837 cm^{-1}; NMR ($CDCl_3$, 300 MHz) see Tables 1 and 2; MS (FAB Li$^+$) m/z 161, 193, 227, 315, 389, 449, 525, 579, 639 (MLi$^+$). Anal. Calcd for $C_{38}H_{84}O_5Si_2$: C, 68.30; H, 10.19. Found: C, 68.20; H, 9.94.

9α,17α-Bis-*O*-(TBDMS) Ether of 13,14α-Dihydro A83543A Aglycon (9) and 9α,17(*S*)-Bis-*O*-(TBDMS) Ether of 13,14α-Dihydro-21(*S*)-hydroxy-1,21-seco-(3β-H)-3α-(2-hydroxyethyl) A83543A Aglycon (10). The 9α,17α-bis-*O*-(TBDMS) ether of A83543A aglycon (3) (502 mg, 0.796 mmol) was dissolved in dry Et_2O (50 mL). To this solution, cooled to 0 °C and vigorously stirred under nitrogen, was added $LiAlH_4$ (32 mg, 0.84 mmol, 4.2 equiv). The reaction was monitored by TLC. After 20 min, when a few percent of the substrate was still unreacted, the reaction mixture was immediately quenched at 0 °C with saturated brine. Et_2O (50 mL) was then added, and the mixture was successively washed with brine, 1 N H_2SO_4 (aq), diluted brine, and 5% aqueous $NaHCO_3$. The organic layer was subsequently dried over anhyd K_2CO_3, filtered, and concentrated in vacuo. The residue was separated on a flash SiO_2 column (75 g; mixtures of 2–20% Et_2O in CH_2Cl_2) to give (a) the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro-A83543A aglycon (9) (167.5 mg, 33%, identical by ^{1}H-NMR and ^{13}C-NMR with an authentic sample) and (b) the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro-21-(*S*)-hydroxy-1,21-seco-3β-H-3α-(2-hydroxyethyl) A83543A aglycon (10) (165 mg, 33%): IR 3590, 3460, 3009, 2957, 2930, 2896, 2859, 1696, 1471, 1463, 1258, 1107, 1049, 1006, 893, 837 cm^{-1}; NMR ($CDCl_3$, 300 MHz) see Tables 1 and 2; MS (FAB, Li$^+$) m/z 113, 133, 161, 185, 277, 313, 351, 397, 449, 511, 527, 545, 643; HR FAB (MLi$^+$) calcd for $C_{36}H_{68}O_5Si_2Li$ m/z 643.4765, found m/z 643.4741.

Note: Different reagent ratios and/or reaction temperature led to lower yields, gave less selectivity, and furnished byproducts of unidentified structure. For example, in an experiment for which ca. 10 equiv (ca. 2.5 molar equiv) of $LiAlH_4$ was used (0 °C/Et_2O/workup identical to that described above) were isolated (a) the 13,14α-dihydro-1,21-seco-3α-(2-hydroxyethyl) derivative 10 (33%) and (b) an unidentified compound (colorless semisolid, 40% mass of the organic substrate): ^{1}H-NMR ($CDCl_3$, 25 °C, 300 MHz, single component) δ 8.45 (1H, bs, D_2O exchangable), 5.84 (1H, bd, J = 9.5 Hz), 5.61 (1H, ddd, J = 9.5, 2.8, 2.8 Hz), 4.84 (1H, m), 4.41 (1H, m), 4.06 (1H, m), 3.02 (2H, m), 2.82 (1H, m), 2.67 (1H, dd, J = 16.2 Hz, 3.0 Hz), 2.57 (1H, dd, J = 16.2, 4.2 Hz), 2.36 (4H, m), 2.18 (1H, m), 1.80 (1H, m), 1.75–1.10 (15 H, m), 1.17 (3H, d, J = 7.0 Hz), 0.92 (18 H, s), 0.87 (3H, t, J = 7.8 Hz), 0.05 (12 H, bs); ^{13}C-NMR ($CDCl_3$, 30 °C, 300 MHz) δ 215.2 (s, broadened), 173.0 (s), 130.6 (d), 128.6 (d), 99.9 (s), 78.5 (d, broadened), 72.6 (d), 71.2 (d), 49.3 (d, broadened), 48.4 (d, broadened), 45.0 (d, broadened), 43.9 (d), 42.9 (d), 41.2(d), 41.1 (t), 41.0 (t), 36.5 (t), 35.2 (t), 33.5(t), 32.3 (t, broadened), 28.1 (t), 25.9 (q, 3C), 25.8 (q, 3C), 20.2 (t, broadened), 18.1 (s), 18.0 (s), 15.3 (q, broadened), 10.0 (q), −4.2 (q), −4.6 (q), −4.7 (q, 2C). This compound did not react with acetone-d_6 (1 day at rt; signals in carbon spectrum not broadened), with 5% D_2O/acetone-d_6 (3 days at rt), or with trifluoroacetic acid-d_1 (1 equiv) in 5% D_2O/acetone-d_6 (5 h, rt). A 50% excess of TFA caused only partial hydrolysis of the silyl groups.

Attempted Reaction of Lithium Methoxide with 12-Membered Lactones. 9α-*O*-TBDMS Ether of 13,14β-Dihydro-16,17(*E*)-didehydro-17-deoxy-9α-*O*-TBDMS A83543A Aglycon (11). General Procedure. A sample of the macrolactone 3, 8, or 9 (0.20 mmol) was dissolved in dry THF (2 mL), and dry methanol (10 mL) was added. The solution was cooled under nitrogen to 0 °C, and freshly cut lithium metal (10 mg, 1.44 mmol) was added. Stirring under nitrogen at 0 °C and TLC monitoring were continued for 1 h. The cooling bath was then removed, and the reaction mixture was stirred overnight at room temperature and under nitrogen. Afterwards, it was diluted with toluene (100 mL) and rinsed successively with brine, diluted brine, and water (2×). The organic phase was dried over anhyd K_2CO_3 and concentrated in vacuo. The residue was purified on a flash column (10 g; 5% EtOAc in hexanes, then 10% EtOAc in hexanes). Pure fractions thus obtained were concentrated to dryness and analyzed by NMR. When 9α,17α-bis-*O*-(TBDMS) A83543A aglycon (3) or its 13,14α-dihydro derivative 9 were used for this reaction, only unchanged substrates were recovered (82% and 75%, respectively). In the case of 13,14β-dihydro-9α,17α-bis-*O*-(TBDMS) A83543A aglycon (8), in addition to recovered substrate (45%), was isolated the 9α-*O*-(TBDMS) ether of 13,14β-dihydro-16,17(*E*)-didehydro-17-deoxy A83543A aglycon (11), a colorless semisolid (31 mg, 31%): IR 3016, 2965, 2930, 1718, 1676, 1257, 1049, 837 cm^{-1}; UV ϵ_{236} = 7800 (EtOH); NMR ($CDCl_3$, 300 MHz) see Tables 1 and 2; FAB (H$^+$) MS m/z 92, 135, 155, 174, 195, 363, 499; HR FAB (MH$^+$) for $C_{30}H_{49}O_4Si$ calcd m/z 501.3399, found m/z 501.3405.

Reaction of 12-Membered Lactones with LiOOH in THF–EtOH Medium. General Procedure. The 12-membered macrocyclic lactones 3, 8, or 9 (0.30 mmol) were dissolved in THF (15 mL). To this solution was added EtOH (5 mL), followed by LiOH monohydrate (0.90 g, 21.4 mmol). The mixture was stirred for 10 min, and then H_2O_2 (30% in H_2O, 3.2 g, 48 mmol), H_2O (3 mL), and 2-hydroxyethyl sulfide (5.0 g, 41 mmol) were added. Stirring at room temperature and TLC monitoring were continued for 6 days. Thin-layer chromatography did not indicate formation of any products of lactone cleavage. After the usual workup[27b] and flash column purification (a) in the case of 13, 14β-dihydro-9α,17α-bis-*O*-(TBDMS) A83543A aglycon (8), the substrate (74%) was recovered, (b) in the case of 13,14α-dihydro-9α,17α-bis-*O*-(TBDMS) A83543A aglycon (9), no reaction was observed after 3 days, but then decomposition to a large number of nonpolar products occurred, and (c) in the case of 9α,17α-bis-*O*-(TBDMS) A83543A aglycon (3), no lactone cleavage occurred.

Compound 3 also did not react with sodium amide (2.5 equiv) in THF for 22 h at room temperature. The same compound was completely inert toward either an excess of sodium thiophenoxide or sodium thiomethoxide, in etheral solvents.

Attempted C-14 Epimerization Reactions of Compounds 8 and 9. (a) Basic Conditions (Other Than Described Above). The 9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (8) (60 mg, 0.095 mmol) was dissolved in THF (5 mL). To this solution was added EtOH (5 mL), followed by solid LiOH–H_2O (162 mg, 3.9 mmol). The reaction mixture was stirred at room temperature under nitrogen for 1 h, and then it was diluted with toluene (50 mL). The resulting mixture was

successively extracted with brine, diluted brine, and water. The organic layer was dried over anhyd K_2CO_3 and concentrated in vacuo to give a solidifying substance (58 mg, 97%). Both the ^{1}H-NMR spectrum and the TLC chromatogram showed no changes in comparison with the substrate 8.

A sample of 13,14β-dihydro derivative 8 (58 mg, 0.092 mmol) was dissolved in EtOH (5 mL). This solution was treated with 5% KOH/EtOH solution (1 mL, 0.89 mmol KOH), under nitrogen at room temperature. After 20 min, the reaction mixture was diluted with toluene and worked up as described above to give a semisolid (50 mg, 86%), which was identical by NMR and TLC with compound 8.

Similarly, compound 8 was recovered unchanged after treating its solution in dry toluene with DMAP (5 equiv) at room temperature for 20 h.

The 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro A83543A aglycon (**9**) (40 mg, 0.063 mmol) was dissolved in THF (2 mL). To this solution was added EtOH (2 mL), followed by LiOH hydrate (130 mg, 3.1 mmol). The reaction mixture was stirred at room temperature under nitrogen for 30 min. Toluene (30 mL) was then added, and the resulting solution was extracted with diluted brine (3×). The organic phase was dried over anhyd K_2CO_3, filtered, and concentrated in vacuo to give a semisolid (30 mg, 75%). The ^{1}H-NMR spectrum of that sample indicated unchanged substrate 9.

Compound 9 also did not react with an excess of DMAP (toluene, room temperature, 16 h).

(b) Deuteriation Experiments. The 9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (**8**) (109 mg, 0.172 mmol) was dissolved in dry benzene (2 mL), and CD_3OD (5 mL) was added. To this solution, stirred at 15 °C (water bath) under nitrogen, was added Li metal (11 mg, 1.57 mmol). After the metal had completely reacted, stirring was continued for another 15 min. Benzene (50 mL) was then added, and the solution was washed with D_2O (3×). The organic layer was dried over anhyd $MgSO_4$, filtered, and evaporated in vacuo to give 2,2,14β-trideuterio-9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (**8-d_3**), a colorless semisolid (98 mg, 90%, homogenous by TLC). ^{1}H- and ^{13}C-NMR spectra of this material ($CDCl_3$ solution, 300 and 75 MHz, respectively), after careful analysis of integration, indicated incorporation of deuterium in position 14β (100%), in both C-2 positions (85% each), and in the 16α position (ca. 5%).

The 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro A83543A aglycon (**9**) (54 mg, 0.085 mmol) was dissolved in dry benzene (2 mL), and CD_3OD (4 mL) was added. To this solution, stirred at 15 °C under nitrogen, was then added Li metal (16 mg, 2.28 mmol). After the metal had reacted, the reaction mixture was stirred for another 20 min. It was then worked up with D_2O, analogous to the procedure described above. The substance isolated (51.5 mg, 95%, homogenous by TLC) was almost identical by NMR with the substrate **9**, except for incorporation of ca. 15% of deuterium, exclusively at both C-2 positions (based on ^{1}H-NMR integration analysis; $CDCl_3$, 300 MHz).

(c) Acidic Conditions. 9α-(Trifluoroacetoxy)-13,14β-dihydro A83543A Aglycon (12), 9α,17α-Bis(trifluoroacetoxy)-13,14α-dihydro A83543A Aglycon (13), and 9α-(Trifluoroacetoxy)-13,14α-dihydro A83543A Aglycon (14). The 9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (**8**) (20.0 mg, 0.032 mmol) was dissolved in CH_2Cl_2 (3 mL). To this solution was added trifluoroacetic acid (0.250 mL, 370 mg, 3.2 mmol). The reaction mixture was stirred at room temperature under a nitrogen atmosphere. After 16 h, Et_2O (60 mL) was added. The resulting solution was washed successively with diluted brine, 5% aqueous $NaHCO_3$ (2×), and water. The organic layer was then dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was purified on a flash SiO_2 column (5 g; 5% Et_2O in CH_2Cl_2) to give 9α-(trifluoroacetoxy)-13,14β-dihydro A83543A aglycon (**12**) as a white solid (10.5 mg, 66%); needles (Et_2O); mp 136–138 °C; ^{1}H-NMR (300 MHz, dry $CDCl_3$) δ 5.88 (1H, bd, J = 9.9 Hz), 5.73 (1H, ddd, J = 9.9, 2.6, 2.6 Hz), 5.43 (1H, m), 4.84 (1H, m), 4.03 (1H, m), 3.60 (1H, m), 2.70–1.10 (23 H, m), 1.25 (3H, d, J = 6.8 Hz), 0.89 (3H, t, J = 7.5 Hz); MS (FAB Li$^+$) m/z 161, 217, 257, 281, 313, 359, 394, 449, 507 (MLi$^+$); HR FAB (MLi$^+$) calcd for $C_{26}H_{35}O_6F_3Li$ m/z 507.2546, found m/z 507.2510.

The 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro A83543A aglycon (**9**) (99 mg, 0.156 mmol) was dissolved in CH_2Cl_2 (2.5 mL). Trifluoroacetic acid (0.350 mL, 518 mg, 4.54 mmol) was then added, and the reaction mixture was stirred under nitrogen at room temperature. After 14 h, the solution was diluted with Et_2O (100 mL) and extracted successively with diluted brine (2×) and 5% aqueous $NaHCO_3$ (2×). The organic phase was dried over anhyd Na_2SO_4 and concentrated in vacuo. The residue was separated on a flash SiO_2 column (12 g; CH_2Cl_2, then 5% Et_2O in CH_2Cl_2) to give (a) 9α,17α-bis(trifluoroacetoxy)-13,14α-dihydro A83543A aglycon (**13**) as a white solid (34 mg, 36%) [needles (Et_2O); mp 141–144 °C and 168–169 °C; $[\alpha]_{589}$ = −7.2° (EtOH); IR 3025, 2971, 2938, 2873, 1780, 1719, 1461, 1387, 1352, 1338, 1228, 1160, 1075, 985, 873 cm^{-1}; NMR ($CDCl_3$, 300 MHz) see Tables 1 and 2; MS (FAB Li$^+$) m/z 133, 161 (100), 193, 281, 327, 359, 397, 449 (92), 507, 551, 603; HR FAB (MLi$^+$) calcd for $C_{28}H_{34}O_7F_6Li$ m/z 603.2369, found m/z 603.2306] and (b) 9α-(trifluoroacetoxy)-13,14α-dihydro A83543A aglycon (**14**) as a white solid (37 mg, 47%): needles (Et_2O); mp 176–179 °C and 206–207 °C; $[\alpha]_{589}$ = −70.0° (EtOH); IR 3620, 3485, 3025, 3020, 2971, 2936, 2870, 1778, 1717, 1459, 1388, 1352, 1220, 1172, 1072, 985 cm^{-1}; NMR ($CDCl_3$, 300 MHz) see Tables 1 and 2; MS (FAB Li$^+$) m/z 161 (100), 193, 245, 281, 313, 359, 393, 419, 449, 507 (88); HR FAB (MLi$^+$) calcd for $C_{26}H_{35}O_6F_3Li$ m/z 507.2546, found m/z 507.2526.

9α,17α-Bis-*O*-(TBDMS) Ether of 3,14α-Dihydro-15α-hydroxy-A83543A Aglycon (15) and 9α,17(*S*)-Bis-*O*-(TBDMS) Ether of 13,14α-Dihydro-15(*S*),21(*S*)-dihydroxy-1,21-seco A83543A Aglycon (16). The 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro A83543A aglycon (**9**) (265 mg, 0.419 mmol) was dissolved in dry Et_2O (60 mL), and lithium tri-*tert*-butoxyaluminohydride (97%, 161 mg, 0.615 mmol) was added in one portion. The reaction mixture was stirred under nitrogen at room temperature for 1 h. No changes were observed by TLC. Afterwards, $LiEt_3BH$ (1.0 M solution in THF, 0.90 mL, 0.90 mmol) was added, and stirring was continued for an additional 1 h. The reaction mixture was then cooled to 0 °C and carefully quenched with saturated brine. The ether phase was washed with 1 N aqueous H_2SO_4 and then with 5% aqueous $NaHCO_3$ (3×), dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was separated by flash column chromatography (25 g of SiO_2, 5% EtOAc in hexanes, then 20% EtOAC in hexanes) to furnish (a) the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro A83543A aglycon (**9**) (12 mg, 4%), identical with an authentic sample by ^{1}H-NMR, (b) the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro-15α-hydroxy-A83543A aglycon (**15**) as a colorless semisolid (52 mg, 19%) [$[\alpha]_{589}$ = −24.0° (CH_2Cl_2); IR 3625, 3500, 2957, 2930, 2858, 1719, 1472, 1463, 1389, 1257, 1158, 1052, 1006, 958, 894, 837 cm^{-1}; NMR (500 MHz, $CDCl_3$) see Tables 1 and 2; MS (FAB Li$^+$) m/z 161, 193, 281, 315, 345, 449, 547, 601, 623, 641 (MLi$^+$); HR FAB (MLi$^+$) for $C_{36}H_{66}O_5Si_2Li$ calcd m/z 641.4609, found m/z 641.4616. Anal. Calcd for $C_{36}H_{66}O_5Si_2$: C, 68.08; H, 10.47. Found: C, 68.08; H, 10.88], and (c) the 9α,17α-bis-*O*-(TBDMS) ether of 13,14α-dihydro-15(*S*),21(*S*)-dihydroxy-1,21-seco A83543A aglycon (**16**) as a colorless glassy solid (201 mg, 75%): $[\alpha]_{589}$ = −22.9° ($CHCl_3$); IR 3622, 3440, 3009, 2956, 2930, 2859, 1471, 1463, 1256, 1048, 1006, 894, 837 cm^{-1}; NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB Li$^+$) m/z 133, 167, 215, 299, 313, 357, 393, 449, 489, 525, 645 (MLi$^+$); HR FAB (MLi$^+$) for $C_{36}H_{70}O_5Si_2Li$ calcd m/z 645.4922, found m/z 645.4940. Anal. Calcd for $C_{36}H_{70}O_5Si_2$: C, 67.66; H, 11.04. Found: C, 67.90; H, 10.89.

9α,17α-Bis-*O*-(TBDMS) Ether of 13,14β-Dihydro-1,21(*S*)-dihydroxy-1,15β-oxo-1,21-seco-A83543A Aglycon (Mixture of C_1-Epimers) (17). The 9α,17α-bis-*O*-(TBDMS) ether of 13,14β-dihydro A83543A aglycon (**8**) (163 mg, 0.257 mmol) was dissolved in dry Et_2O (30 mL). To this solution, stirred at room temperature, was added Li(t-BuO)$_3$AlH (97%, 101 mg, 0.385 mmol). The reaction mixture was stirred at room temperature under nitrogen. After 30 min, TLC analysis (UV detection) showed *no reaction*. $LiEt_3BH$ (1.0 M in THF, 0.60 mL, 0.60 mmol) was then added, and stirring at room temperature was continued for another 30 min. Afterwards, the reaction mixture was diluted with Et_2O (100 mL), and the solution was cooled to 0 °C and slowly quenched with saturated brine. The organic layer was washed successively with 1 N aqueous H_2SO_4 and 5%

aqueous $NaHCO_3$ (2×), dried over anhyd K_2CO_3, and concentrated in vacuo. The residue was additionally purified on a short SiO_2 column (5 g; Et_2O–CH_2Cl_2 (1:1)) to give an inseparable mixture (homogenous by TLC in a number of solvents) of the 9α,17(*S*)-bis-*O*-(TBDMS) ether of 13,14β-dihydro-1α,21(*S*)-dihydroxy-1,15β-oxo-1,21-seco A83543A aglycon ((1*R*)-17) (70%) and the 9α,17(*S*)-bis-*O*-(TBDMS) ether of 13,14β-dihydro-1β,21(*S*)-dihydroxy-1,15β-oxo-1,21-seco A83543A aglycon ((1*S*)-17) (30%). (Note: the configurations at C-1 of compounds 17 were assigned based on the assumption that the lactole ring adopts a chair conformation with the C-15 alkyl substituent in an equatorial position. This was additionally corroborated by the proportion of C-1 epimers found, being in agreement with the anomeric effect.[22]) The mixture 17 was obtained as a colorless semisolid (160 mg, 97%): ^{1}H-NMR (pyridine-d_5, 300 MHz) δ 5.90–5.70 (2H, m), 5.53 (0.7 H, bs), 5.26 (0.3 H, bd, J = 9.5 Hz), 4.40–3.60 (4H, m). The remaining portion of the spectrum was obscured due to signal overlapping. In a "direct" C,H-HETCOR spectrum (pyridine-d_5), the proton resonating at 5.53 ppm correlated with a methine carbon at 91.8 ppm, and the proton at 5.26 ppm showed connectivity to a methine carbon at 92.7 ppm: ^{13}C-NMR (pyridine-d_5, 75 MHz) δ 130.71, 130.25, 129.65, 129.06, 92.73, 91.82, 75.45, 75.21, 73.70, 72.66, 72.07, 68.00, 48.39, 46.64, 45.90, 43.71, 43.07, 42.26, 41.63, 41.40, 41.35, 41.31, 41.18, 41.12, 41.03, 39.84, 39.79, 39.77, 39.60, 38.00, 37.92, 33.78, 33.75, 33.70, 32.86, 32.79, 32.14, 30.65, 30.57, 25.96, 25.82, 21.19, 20.66, 18.06, 18.04, 17.98, 10.65, 10.23, 8.49, −4.26, −4.35, −4.43, −4.77, −4.83. Anal. Calcd for $C_{36}H_{68}O_5Si_2$: C, 67.87; H, 10.76. Found: C, 68.03; H, 10.70.

9α,17(*S*)-Bis-*O*-(TBDMS) Ether of 13,14β-Dihydro-1,21-dioxa-1,15β-oxo-1,21-seco A83543A Aglycon (18) and 9α,17-(*S*)-Bis-*O*-(TBDMS) Ether of 13,14β-Dihydro-9α,17α-Bis-*O*-(TBDMS)-21(*S*)-hydroxy-1-oxa-1,15β-oxo-1,21-seco-A83543A Aglycon (19). The mixture of (14β-H)-21-hydroxy-1-lactoles epimeric at C-1 (17) (145 mg, 0.228 mmol) was dissolved in EtOAc (freshly distilled, 30 mL). To this solution was added 5% Pt/C (371 mg). Oxygen gas was then bubbled through the solution at room temperature at a moderate rate. Solvent (distilled EtOAc) was added periodically to maintain a ca. 30-mL volume of the reaction mixture. (TLC monitoring of the reaction progress proved to be difficult due to the identical TLC polarities of the 21-hydroxy lactoles 17 and the 21-hydroxy lactone 19). After 45 h, the catalyst was filtered, and the solution was concentrated in vacuo. The residue was separated on a flash SiO_2 column (12 g; 15% EtOAc in hexanes) to give (a) 9α,17-(*S*)-bis-*O*-(TBDMS) ether of 13,14β-dihydro-1,21-dioxa-1,15β-oxo-1,21-seco A83543A aglycon (18) as a colorless semisolid (38 mg, 26%) [NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB H$^+$) m/z 107, 127, 155, 189, 228, 265, 325, 369, 457, 573, 633 (MH$^+$); HR FAB (MH$^+$) calcd for $C_{36}H_{65}O_5Si_2$ m/z 633.4370, found m/z 633.4359] and (b) 9α,17(*S*)-bis-*O*-(TBDMS) ether of 13,14β-dihydro-21(*S*)-hydroxy-1-oxa-1,15β-oxo-1,21-seco A83543A aglycon (19), a colorless semisolid (58 mg, 40%): IR 3580, 3495, 3455, 2958, 2930, 2895, 2855, 1736, 1471, 1464, 1248, 1110, 1050, 1028, 996, 893, 838 cm^{-1}; NMR ($CDCl_3$, 500 MHz) see Tables 1 and 2; MS (FAB H$^+$) m/z 188, 232, 294, 338, 485, 503, 573, 617, 635 (MH$^+$); HR FAB (MH$^+$) calcd for $C_{36}H_{67}O_5Si_2$ m/z 635.4526, found m/z 635.4535.

Acknowledgment. We are indebted to our colleagues within the research laboratories of Eli Lilly and Co. and DowElanco who helped in the course of this project. In particular, we are very grateful to Lawrence C. Creemer, John L. Occolowitz and his associates, Jonathan W. Paschal, John D. Snoddy, James L. Vandygriff, and all members of the Physical Chemistry Support and Computer Support Groups whose experience and excellent technical assistance were invaluable for the realization of this project. We thank Professors Leo A. Paquette, William R. Roush, Edward C. Taylor, Paul A. Wender, Marvin J. Miller, and Mark Lipton for their many helpful discussions. J.G.M. thankfully acknowledges his participation in the Postdoctoral Program of Eli Lilly and Co.

Supplementary Material Available: Proton and ^{13}C spectra for compounds 3–5, 7, 10, 11, 14, 18, and 19 and proton spectra for compounds 12 and 13 (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.