A-Ring Oxygenation Studies in Bridgehead Hydroxyl-Substituted *trans*-Tricyclo[9.3.1.0^{3,8}]pentadecan-14-one Congeners of Taxol

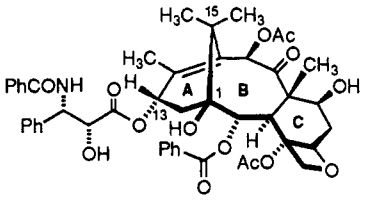
Steven W. Elmore[1] and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

Received April 22, 1993

The ready availability of **5** has prompted examination of a convenient means for carbonyl transposition in its A-ring. Attempts to implement such chemistry directly on **5** and its silyl-protected derivative suffer from a kinetic proclivity for transannular capture of the enolate anion. This undesirable process was circumvented by reduction of the C9 carbonyl following conversion to silyl enol ether **8**. Once the resulting 9α-alcohol was protected as its MOM ether, the enolates of **10a** and **10b** could be efficiently oxygenated at C13 by treatment with the Davis sulfonyl oxaziridine despite severe steric congestion in that locale. The resultant α-alcohol **11a** could be epimerized to the 13β-isomer by exposure to potassium hexamethyldisilazide. Remarkably, **11a** is prone to autoxidation, although the yield of diketone **12** is capricious. A preferred route to this key intermediate involves periodinane oxidation of **11a**. Reduction of **12** and its O-silylated derivative has provided the targeted compounds **15** and **16**, respectively. The conformational features of various intermediates are discussed in the light of NMR studies and MM2 calculations.

Previous contributions from this laboratory[2] have reported the design and development of a unique strategy for incorporating the C-1 bridgehead hydroxyl substituent in taxol (**1**).[3] More specifically, these studies demonstrated the feasibility of transforming the simple β,γ-unsaturated

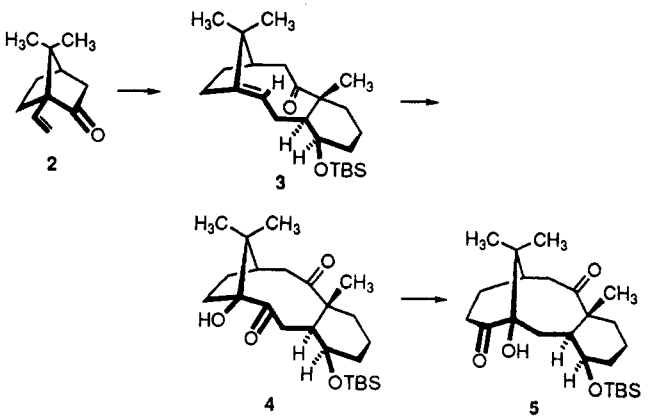


1

ketone **2**, readily available in enantiomerically pure condition from (+)-camphor,[4] into **3** (Scheme I). This substance serves as a convenient precursor to the crucial intermediate **4**, which experiences efficient 1,2-migration of the *gem*-dimethyl-substituted bridge when exposed to (*t*-BuO)$_3$Al in benzene at rt. Such α-ketol rearrangements are equilibrium controlled,[5] and the success of this isomerization rests on the greater thermodynamic stability of the *trans*-tricyclo[9.3.1.0^{3,8}]pentadecane isomer **5** relative to **4**.[2]

In a continuation of these exploratory studies, we have set out to uncover means for adjusting the oxidation level in ring A of **5**, with particular attention being paid to translocation of the carbonyl group to the C-13 position

Scheme I



(taxol numbering). The A-ring in taxol and taxusin is recognized to be sterically blockaded by the syn C-15 methyl substituent,[6] the presence of which severely limits the approach of reagents to this region of the molecule. However, if compounds more highly functionalized than **4** are to serve as viable precursors of taxol (**1**), regio- and stereocontrolled chemical modification of the A-ring must be developed. This fundamental problem is addressed in the present report.

Results

Of the various methods that were considered for the introduction of oxygen at C-13, the sulfonyl oxaziridine methodology popularized by Davis[7] seemed particularly qualified and was therefore explored in depth. Following silylation of the tertiary hydroxyl group in **5**[2d] to give **6**, it was immediately made evident that the deprotonation of this diketone under kinetically controlled conditions

(1) Chemistry Department Fellow, 1988-1989; National Needs Fellow, 1991-1992; Graduate Fellow of the ACS Organic Division sponsored by the Eli Lilly Co.

(2) (a) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277. (b) Paquette, L. A.; Combrink, K. D.; Elmore, S. W. *J. Am. Chem. Soc.* **1991**, *113*, 1335. (c) Paquette, L. A.; Elmore, S. W.; Combrink, K. D.; Hickey, E. R.; Rogers, R. D. *Helv. Chim. Acta* **1992**, *75*, 1755. (d) Paquette, L. A.; Combrink, K. D.; Elmore, S. W.; Zhao, M. *Helv. Chim. Acta* **1992**, *75*, 1772.

(3) Wani, W. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(4) Fisher, N.; Opitz, G. *Organic Syntheses*, Wiley: New York, 1973; Collect. Vol. V, p 877.

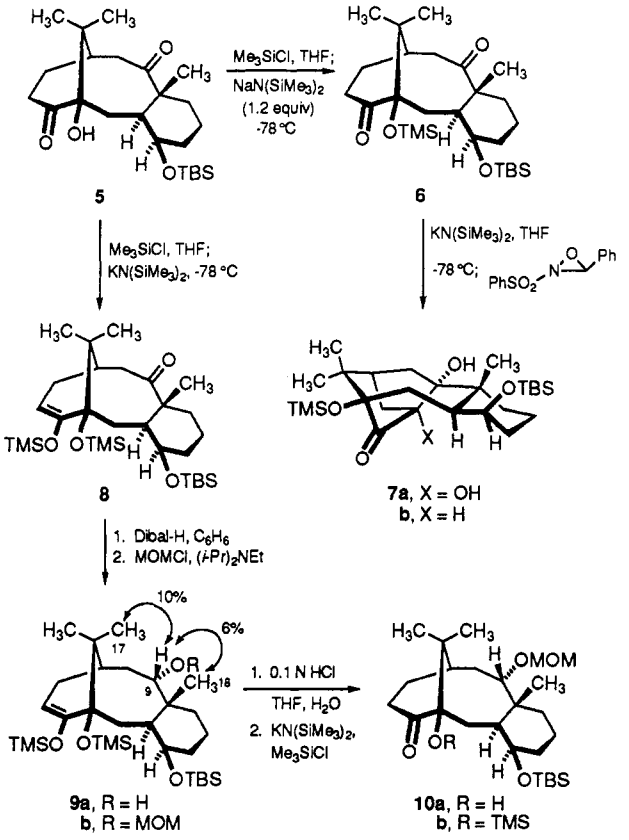
(5) (a) Nickon, A.; Nishida, T.; Frank, J.; Muneyuki, R. *J. Org. Chem.* **1971**, *36*, 1075. (b) Lin, T.; Nickon, A. *J. Am. Chem. Soc.* **1970**, *92*, 3496. (c) Nickon, A.; Lin, Y. *J. Am. Chem. Soc.* **1969**, *91*, 6861. (d) Nickon, A.; Nishida, T.; Lin, Y. *J. Am. Chem. Soc.* **1969**, *91*, 6860.

(6) (a) Lythgoe, B. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. 10, p 597 ff. (b) Suffness, M.; Cordell, G. A. *The Alkaloids*; Bross, A., Ed.; Academic Press: New York, 1985; Vol. 25, p 1 ff. (c) Blechert, S.; Guenard, T. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1990; Vol. 39, p 195 ff. (d) Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465. (e) Paquette, L. A. *Studies in Natural Products Chemistry*, Rahman, A. U., Ed.; Elsevier: Amsterdam, 1992; Vol. 11, p 3 ff.

(7) Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

0022-3263/93/1958-4963$04.00/0

Scheme II



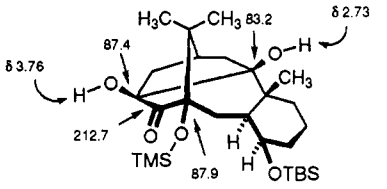
5 6 8 7a, X = OH b, X = H

9a, R = H b, R = MOM 10a, R = H b, R = TMS

occurs at C-13 to the virtual exclusion of C-10. As shown in Scheme II, the sequential treatment of **6** with potassium hexamethyldisilazide and N-(phenylsulfonyl)oxaziridine resulted in conversion to the transannularly cyclized product **7a** in rather low yield (36%). Amounts of **7b** were also isolated. The structural features of **7a** were established on the strength of a complete chemical shift profile of its constituent protons and carbons as defined by exhaustive ^{1}H decoupling, 2D COSY, and C/H correlation experiments. The existence of a transannular connectivity was subsequently demonstrated by selective INEPT irradiation of the two well-defined hydroxyl protons (see Figure 1).

The pervasiveness of the unwanted transannular bonding warranted that it be curtailed from the outset. To this end, **5** was converted efficiently (83%) into **8** provided that the twofold silylation was performed at −78 °C and, most importantly, that potassium counterions were utilized. Reduction of **8** with DIBAL-H in benzene proceeded exclusively via the "carbonyl down" conformer to furnish the stereochemically homogeneous alcohol **9a**, which exists however as a 1:1 mixture of conformational isomers that exchange rather slowly on the NMR time scale at room temperature. As a consequence, two distinct sets of sharp signals are clearly evident under these conditions. Proton cosaturation studies proved particularly conducive to the detection of this atropisomeric interconversion. For example, saturation of the doublet of doublets centered at δ 3.21 followed by a 20-s delay resulted in efficient energy transfer to the doublet appearing at δ 4.19. These signals correspond to the C-9 carbinol proton absorptions in the axial and equatorial conformers, respectively.

Protection of the hydroxyl group in **9a** as the methoxymethyl ether[8] caused **9b** to adopt the single low-energy conformation that projects the ether substituent equatorially. In this case, irradiation of either the C17 or C18 methyl singlet elicited an NOE enhancement of significant magnitude (see formula), thereby signaling the relatively close spatial proximity of these three centers.



irradiate	observe
δ 3.76 (s)	83.7 (s) J_3
	87.4 (s) J_2
	212.7 (s) J_3
δ 2.73 (s)	87.4 (s) J_3
	83.2 (s) J_2

Figure 1. Key observations from selective INEPT measurements on **7a**. All assignments are based on complete decoupling experiments in tandem with C/H correlation and NOE studies.

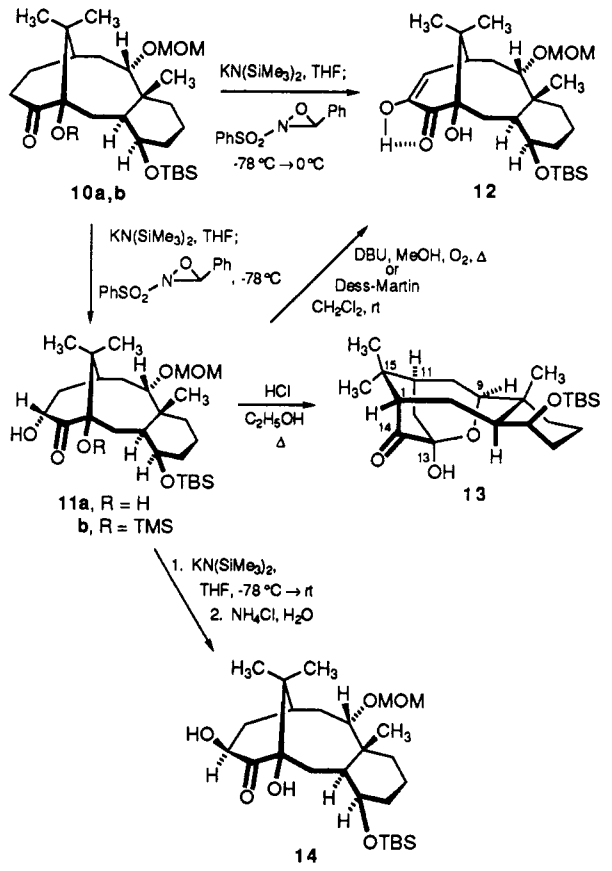
Acid hydrolysis of **9b** to give **10a** provided added insight into the remarkable interdependence of functional group distribution and conformation in this ring system. Thus, **10a** exists as a mixture of several conformers at ambient temperature, such that its high-field ^{1}H NMR spectrum is characterized by very broad absorptions under these conditions. When C_6D_5Br solutions of this α-ketol were heated to 420 K in the probe of a 250-MHz spectrometer, coalescence occurred to give an exceptionally well-defined spectrum amenable to first-order analysis.

Once **10a** was in hand, it was possible to effect its α-oxygenation without risk of competing intramolecular aldolization. As before, those experiments involving KN(SiMe$_3$)$_2$ as base proved to be the most efficacious. In the event, **11a** was isolated in 71% yield following exposure to excess oxaziridine reagent at low temperature (Scheme III). No additional enhancement in the extent of product formation was observed when the bridgehead hydroxyl was protected as in **10b** (73% yield of **11b**). These oxidations proved to be highly endo selective. At 25 °C, **11a** is constituted of a 3:1 mixture of conformational isomers that interconvert slowly on the NMR time scale, a conclusion that was corroborated by means of ^{1}H cosaturation experiments. The major diol conformer exhibits a well-separated although broadened downfield doublet at δ 5.45 (J = 9.7 Hz) due to the C13 carbinol proton and an upfield doublet at δ 2.85 (J = 6.0 Hz) arising from the C*H*(OMOM) array at C9. These absorptions are more highly deshielded and shielded, respectively, than those exhibited by the minor conformer (δ 4.34 and 4.17, respectively). The most discernible difference between the conformers is revealed in the coupling constant of the upfield methine signal, which at 9.4 Hz for the less prevalent species is compatible only with pseudoaxial projection of its OMOM substituent. The reduction in the magnitude of J to 6.0 Hz in the major conformer is in agreement only with a pseudoequatorial disposition of this functional group.

The preceding observations prompted parallel studies in which the oxidation reaction mixtures were allowed to

(8) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

Scheme III



warm to 0 °C prior to workup. Under these circumstances, the diosphenol **12** was produced. However, the yield of **12** when starting from **10a** proved to be capricious. Particularly exasperating were the precipitous decreases in efficiency that were prevalent as the reaction scale was increased. Consequently, a two-step sequence mediated by **11a** was developed and currently is the recommended route to **12**.

When heated with DBU in methanol, **11a** undergoes spontaneous autoxidation to give **12** in 56% yield. Deoxygenation of the solvent only slowed this process and did not result in the onset of other chemical changes.[9] Efficiency and convenience in producing **12** were both served by oxidizing **11a** with the Dess–Martin periodinane reagent.[10]

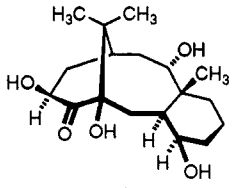
At this juncture, the acid-promoted removal of the MOM protecting group was explored. A rather remarkable series of changes occurred that culminated in the formation of **13**. The absence of a C1 hydroxyl was quite evident from the lack of those IR bands and ^{1}H NMR signals that characteristically arise from a strongly hydrogen-bonded α-ketol system. A ^{13}C line at the appropriate shift for an oxygen-bearing C1 carbon was also not evident. On the other hand, a C1 proton could be clearly observed as a broadened doublet (J = 13.0 Hz) at δ 2.64. Furthermore, C/H correlation and DEPT data convincingly established C1 to be the doublet appearing at 55.2 ppm. Importantly, the presence of an acetal connectivity was corroborated by the following key experiments where only quaternary carbons were observed in the selective INEPT spectrum:

Irradiate	Observe	
H11 (m, δ 1.21)	C13	91.8 ppm
	C15	36.6 ppm
H9 (br d, J = 11.7 Hz, δ 3.70)	C13	91.8 ppm

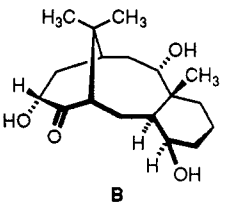
A plausible, although unsubstantiated, pathway for arrival at **13** consists of initial α-ketol rearrangement and subsequent S_N1 ionization at C1 with ensuing loss of the proton at C14 to generate a bridgehead enol that undergoes ketonization. Once the MOM group is cleaved, intramolecular 1,2-addition of the liberated C9 hydroxyl to the C13 carbonyl occurs in order to reduce nonbonded steric compression.

As noted above, attempts to accomplish the α-ketol rearrangement of **11a** under thermodynamic conditions[8] (DBU in hot methanol) resulted instead in autoxidation.[11] When **11a** was exposed alternatively to 2 equiv of KN(SiMe$_3$)$_2$ and its dipotassium salt was allowed to warm to room temperature prior to quenching with NH_4Cl, no α-ketol rearrangement was again seen. Instead, kinetically controlled protonation occurred on the α-face of the A-ring to deliver the conformationally rigid C13 epimer **14**.

MM2 calculations[12] performed on the four isomers **A–D** (with the ethereal substituents approximated as free hydroxyls to achieve simplification) indicated a small energetic preference to exist in favor of the C13 keto tautomers. Perhaps relevant to the problem was the added

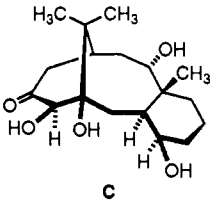


A

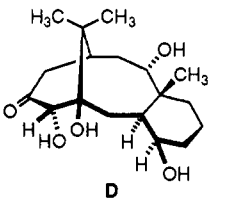


B

E_T	**A**	**B**
axial C9-OH	60.9 kcal/mol	60.4 kcal/mol
equat. C9-OH	61.0 kcal/mol	60.6 kcal/mol



C



D

E_T	**C**	**D**
axial C9-OH	58.9 kcal/mol	59.7 kcal/mol
equat. C9-OH	59.0 kcal/mol	60.1 kcal/mol

finding that the global minimum energy conformation in all four examples contains an axially oriented hydroxyl group at C9 (Figure 2).

Precedent exists as well for acid-promoted α-ketol rearrangements. Notwithstanding, **11a** was affected neither by Lewis acids such as aluminum tri(*tert*-butoxide)[2] nor by Brönsted acids such as HCl in ethanol or TsOH in benzene below 60 °C. Above this temperature, the complete transformation of **11a** into **13** was again seen. As

(9) Nakamura, H.; Vasudevan, S.; Kim, M.; Brock, C. P.; Watt, D. S. *J. Org. Chem.* **1992**, *57*, 2223.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.

(11) The autoxidation of α-hydroxy ketones under basic conditions has been previously recognized. See, for example: (a) Clarke, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 4629. (b) Kupchan, S. M.; McLean, S.; Milne, G. W. A.; Slade, P. *J. Org. Chem.* **1962**, *27*, 147.
(12) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Burkett, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society, Washington, D.C., 1982, Monograph 177. The actual program used was MODEL version KS 2.96 (K. Steliou private communication).

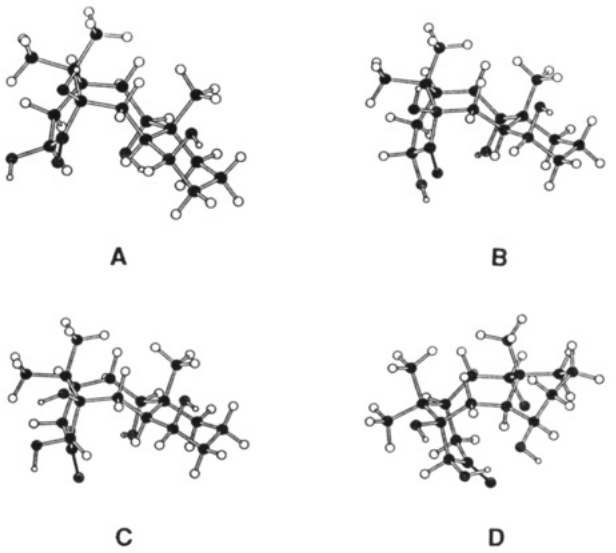


Figure 2. Global minimum-energy conformations of **A**–**D** having the C9 hydroxyl projected axially (Chem 3-D output).

a consequence, an alternative strategy for realizing our original objectives was necessarily developed.

With the availability of **12** in six convenient steps from **5**, we proceeded to consider a suitable means for the regiocontrolled reduction of this intermediate. Various attempts to utilize the existing bridgehead hydroxyl for directing 1,2-reduction to C14 as with $NaBH(OAc)_3$[13] only returned unreacted starting material. The Luche reagent ($NaBH_4$–$CeCl_3$)[14] also proved to be insufficiently reactive. We conjectured that the ease of deprotonation of **12** and the unusual level of steric encumbrance surrounding C14 combined to make reduction difficult. As a result, a heightened reactivity level such as that present in $LiAlH_4$ was considered necessary. Further, no overreduction was anticipated at C13 since this functionality will have been rapidly transformed into its enolate anion at −78 °C by this reagent and transiently protected from nucleophilic attack. As matters turned out, the yield of **15** was 97% based upon recovered starting material (Scheme IV).

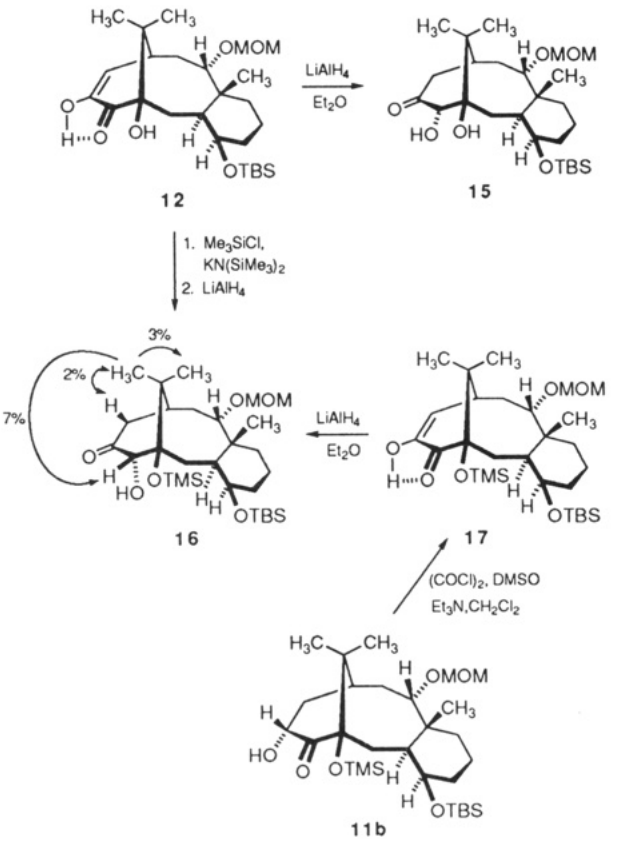
In order to streamline matters and eliminate problems encountered earlier during incorporation of the bridgehead siloxy functionality, the bissilylation of **12** was explored. Treatment of **12** with more than 2 equiv each of $KN(SiMe_3)_2$ and Me_3SiCl afforded the desired intermediate. Direct reduction with $LiAlH_4$ produced exclusively **16**, the stereochemistry of which was ascertained by NOE methods (see formula). This very desirable product was also converged upon by Swern oxidation[15] of **11b** to give **17** and reduction of this α-diketone with $LiAlH_4$. The production of **16** in this fashion marked the completion of this phase of our synthetic studies.

Discussion and Summary

The *trans*-tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system that is characteristic of many taxane diterpenes holds considerable fascination from a chemical reactivity standpoint. The unique approach toward taxusin[16] and taxol[2] being undertaken in these laboratories is one designed around the tactic of elaborating the necessary framework early in the synthetic venture. As a consequence, the subsequent functionalization reactions that need be applied to these intermediates often prove revealing of unusual reactivity patterns.[2,17] One might surmise, for example, that a rapid means for accessing 13-hydroxy 14-ketones such as **11** and **14** would involve direct oxidation of the silyl enol ethers **8** and **9**. However, these systems are unaffected by MCPBA under buffered and nonbuffered conditions, even at room temperature. Prolonged exposure resulted only in gradual decomposition. When recourse was made to the more reactive dimethyldioxirane reagent,[18] no reaction was again observed up to 0 °C. At 20–25 °C, cleavage of the trimethylsilyl groups was seen and **5** was isolated in 55% yield. Although the smaller TMS groups are attacked by this powerful oxidant, the larger OTBS group positioned at C4 remained unscathed. These reagents presumably require a trajectory orthogonal to the enol ether double bond to engage the π-linkage in chemical reaction. In **8** and **9**, this type of encounter is effectively blocked by the C16 methyl group. The area on the underside of these molecules is no less congested.

Perhaps for reasons already presented in other contexts,[19] the corresponding enolate anions are not similarly disadvantaged. Experimental findings of this type warrant that both classes of reactive intermediate be carefully

Scheme IV



(13) (a) Evans, D. A.; DiMare, M. *J. Am. Chem. Soc.* **1986**, *108*, 2476. (b) Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (c) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273.

(14) (a) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(15) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(16) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354.

(17) (a) Pegg, N. A.; Paquette, L. A. *J. Org. Chem.* **1991**, *56*, 2461. (b) Paquette, L. A.; Zhao, M.; Friedrich, D. *Tetrahedron Lett.* **1992**, *33*, 7311.

(18) (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847. (b) Adam, W.; Chan, Y. Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800. (c) Guertin, K. R.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 715.

(19) Hutchinson, J. H.; Li, D. L. F.; Money, T.; Palme, M.; Agharhimi, M. R.; Albizati, K. *Can. J. Chem.* **1991**, *69*, 558.

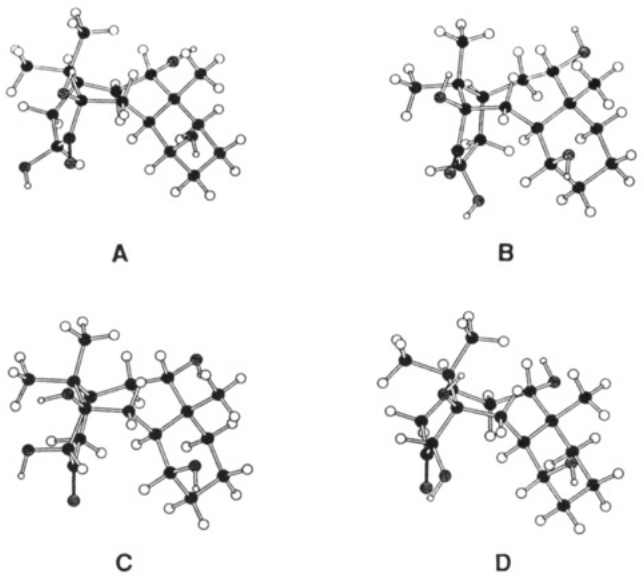


Figure 3. Global minimum-energy conformations of **A–D** having the C9 hydroxyl projected equatorially (Chem 3-D output).

scrutinized in those circumstances where synthetically useful reactivity is marginal or nonexistent.

Throughout the present and earlier investigations,[2,16,17] no evidence has surfaced that the C9 carbonyl experiences any measurable degree of enolization, notwithstanding forcing conditions at times. This inertness contrasts with reports by both Holton[20] and Winkler[21] that describe the direct generation in related compounds of such enolate anions which, however, undergo uncommon C-silylation at C10 with β-stereoselectivity. The factors that govern these modulations in reactivity are undoubtedly conformational in nature. However, the means for controlling these phenomena *on demand* remain incompletely appreciated at this time.

One conformational consequence of the stereochemical orientation of a C9 substituent is the associated topography of ring B. All published X-ray data on taxanes[22] reveal the preferred ring B conformation to be as depicted in Figure 3. Indeed, the α-oriented MOM substituent in the present examples is believed to lock the structures into an identical eight-membered ring conformation. An awareness of this reduction in structural flexibility could prove useful as attempts are made to functionalize these intermediates further. The small preference shown by MM2 calculations for the axial C9 conformers (Figure 2) appears to be the result of hydrogen bonding interactions operating in ring A that outweigh energy considerations elsewhere in the molecule. A deviation from the expected C-ring chair conformation is seen for **D** in Figure 2. The twist-boat is probably an artifact of intramolecular hydrogen bonding between the hydroxyls at C-4 and C-14.

A key element underlying the successful construction of **15** was the use of sulfonyl oxaziridines as the agents of choice for oxidizing the C13 enolates. In the study detailed here, the formation of α-hydroxy ketones in this manner led to generation of the chemically differentiated α-diketones **12** and **17**. The next logical step of regiocontrolled reduction conveniently afforded the transformed isomers. The consequences of interchanging the keto and hydroxyl groups in the context of taxane-like compounds remain to be demonstrated. Regioselectivity should certainly be well accommodated, as we hope to demonstrate in future undertakings.

(20) Holton, R. A. Presented at the 202nd National Meeting of the American Chemical Society, San Francisco, CA, April 9, 1992.

(21) Winkler, J. D.; Lee, C. S.; Rubo, L.; Muller, C. L.; Squattrito, P. J. *J. Org. Chem.* **1989**, *54*, 4491.

(22) (a) Taxusin: Ho, T. I.; Lee, G. H.; Peng, S. M. *Acta Crystallogr.* **1987**, *C43*, 1378. (B) Taiwanan: Ho, T. I.; Lin, Y. C.; Lee, G. H.; Peng, S. M. *Acta Crystallogr.* **1987**, *C43*, 1380. (c) Baccatin, V.: Castellano, E. E.; Hodder, O. J. R. *Acta Crystallogr.* **1973**, *B29*, 2566. (c) Taxagifine: Chauvière, D.; Pascard, D.; Picot, F.; Potier, P.; Prange, T. *J. Chem. Soc., Chem. Commun.* **1982**, 495.

Experimental Section

General Considerations. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230–400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H (300 MHz) and ^{13}C NMR (75 MHz). The high-resolution and fast-atom-bombardment mass spectra were obtained at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

(4*R*,4a*S*,6*R*,10*R*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-dodecahydro-12a,13,13-trimethyl-6(trimethylsiloxy)-6,10-methanobenzocyclodecene-7,12-dione (6). A cold (−78 °C), magnetically stirred solution of **5** (100 mg, 0.237 mmol) in dry THF (20 mL) was blanketed with N_2 and treated sequentially and dropwise with trimethylsilyl chloride (0.30 mL, 2.37 mmol) and sodium hexamethyldisilazide (0.37 mL of 1 M in THF, 0.360 mmol). The reaction mixture was stirred for several hours at −78 °C, allowed to warm to 0 °C, and quenched with water. The separated organic layer was washed with water and brine, the washings were extracted with CH_2Cl_2, and the combined organic solutions were dried and concentrated. The residue was purified by flash chromatography on triethylamine-pretreated silica gel (elution with 5% ethyl acetate in petroleum ether) to give 110 mg (94%) of **6** as a white solid: mp 121–123 °C; IR ($CHCl_3$, cm^{-1}) 1707, 1681, 1470, 1462, 1260, 1218, 1210, 1110; ^{1}H NMR (300 MHz, C_6D_6) δ 3.60 (d, J = 2.6 Hz, 1 H), 2.83 (dd, J = 12.6, 4.4 Hz, 1 H), 2.69 (dd, J = 16.2, 9.7 Hz, 1 H), 2.30 (m, 1 H), 2.18–2.04 (m, 2 H), 1.76–1.55 (series of m, 6 H), 1.48–1.09 (series of m, 3 H), 1.42 (s, 3 H), 1.07 (s, 3 H), 1.04–0.80 (series of m, 2 H), 0.93 (s, 9 H), 0.80 (s, 3 H), 0.37 (s, 9 H), 0.07 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 216.0, 212.3, 87.3, 77.1, 51.8, 44.7, 43.2, 42.6, 42.4, 38.1, 37.4, 35.3, 34.4, 29.9, 26.0, 23.6, 22.5, 18.4, 18.3, 16.0, 3.0, −4.1, −5.0; MS m/z (M^+) calcd 494.3234, obsd 494.3227; $[\alpha]^{23}_D$ +20.7° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{27}H_{50}O_4Si_2$: C, 65.53; H, 10.18. Found: C, 65.41; H, 10.20.

(2*S*,3a*R*,5*R*,6a*S*,7*R*,10a*R*,10b*R*)-4-(*tert*-Butyldimethylsiloxy)dodecahydro-3a,10b-dihydroxy-10a,11,11-trimethyl-5-(trimethylsiloxy)-2,5-methanobenz[*e*]azulen-4(1*H*)-one (7a). A cold (−78 °C) solution of **6** (45 mg, 88 μmol) in THF (5 mL) was blanketed with N_2 and stirred vigorously while a similarly cold solution of potassium hexamethyldisilazide in toluene (0.19 mL of 0.5 M, 96.7 μmol) was introduced dropwise via syringe. After 15 min at this temperature, a solution of 1-phenyl-*N*-(phenylsulfonyl)oxaziridine (35 mg, 0.132 mmol) in cold (−78 °C), dry THF (0.5 mL) was transferred into the reaction vessel via cannula. This mixture was stirred at −78 °C for 3 h, allowed to warm to room temperature overnight, and poured into saturated $NaHCO_3$ solution. The separated organic phase was washed with water and brine, and all aqueous portions were extracted three times with $CHCl_3$. The combined organics were dried and concentrated to leave a residue that was subjected to chromatography on silica gel (elution with 17% ethyl acetate in petroleum ether). The least polar product was identified as **7a** (16 mg, 36%), followed by 9 mg of an unknown substance, and finally 18 mg (41%) of **7b**.

For **7a**: colorless oil: IR ($CHCl_3$, cm^{-1}) 3563, 3486, 1709, 1250, 1214; ^{1}H NMR (300 MHz, C_6D_6) δ 3.87 (m, 1 H), 3.75 (s, 1 H), 2.83 (dd, J = 4.5, 11.7 Hz, 1 H), 2.72 (s, 1 H), 2.56 (dd, J = 2.6, 16.4 Hz, 1 H), 2.52 (dd, J = 4.5, 11.7 Hz, 1 H), 1.91 (dd, J = 8.1, 15.3 Hz, 1 H), 1.82 (m, 1 H), 1.70–1.50 (series of m, 3 H), 1.40–1.22 (series of m, 6 H), 1.32 (s, 3 H), 0.96 (s, 3 H), 0.93 (s, 9 H), 0.72

(s, 3 H), 0.35 (s, 9 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.7, 87.9, 87.4, 83.2, 75.9, 47.1, 46.1, 42.9, 41.6, 41.0, 40.3, 39.2, 34.6, 32.6, 26.2, 25.9, 20.5, 18.2, 18.0, 17.8, 2.8, −4.5, −4.9; MS *m/z* (M^+) calcd 510.3197, obsd 510.3197; $[\alpha]^{22}_D$ −29.0° (*c* 0.91, $CHCl_3$).

For **7b**: colorless oil; IR (CCl_4, cm^{-1}) 3608, 1715, 1248, 1128, 1120, 1088, 1034, 1021; ^{1}H NMR (300 MHz, C_6D_6) δ 3.89 (m, 1 H), 2.79 (dd, *J* = 15.6, 11.7 Hz, 1 H), 2.60 (m, 2 H), 2.12 (td, *J* = 4.4, 12.2 Hz, 1 H), 1.88 (br dd, *J* = 2.4, 12.2 Hz, 1 H), 1.80 (m, 1 H), 1.54 (m, 2 H), 1.50–1.27 (series of m, 6 H), 1.26 (s, 3 H), 1.00 (s, 3 H), 0.94 (s, 9 H), 0.95–0.80 (series of m, 2 H), 0.82 (s, 3 H), 0.38 (s, 9 H), 0.03 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (300 MHz, C_6D_6) ppm 211.2, 88.2, 86.0, 75.9, 60.9, 47.1, 46.5, 45.4, 42.4, 40.3, 40.0, 35.3, 34.4, 33.9, 26.2, 26.0, 20.7, 18.2, 18.0, 17.5, 3.1, −4.5, −4.9; MS *m/z* (M^+) calcd 494.3247, obsd 494.3250; $[\alpha]^{21}_D$ −35.5° (*c* 1.11, $CHCl_3$).

(4*R*,4a*S*,6*R*,10*R*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-1,3,4,-4a,5,6,9,10,11,12a-decahydro-12a,13,13-trimethyl-6,7-bis(trimethylsiloxy)-6,10-methanobenzocyclodecen-12(2*H*)-one (8). A solution of **5** (878 mg, 2.08 mmol) and freshly distilled trimethylsilyl chloride (2.60 mL, 20.7 mmol) in dry THF (100 mL) was cooled to −78 °C under N_2 and treated via syringe with potassium hexamethyldisilazide in toluene (10.40 mL of 0.5 M, 5.20 mmol). After 1 h, another equivalent amount of base was introduced, to be followed 1 h later by a third identical quantity. The reaction mixture was allowed to warm slowly to rt and quenched with saturated NH_4Cl solution (20 mL). The separated organic phase was washed with water and brine, dried, and concentrated in vacuo. The residue was purified by chromatography on triethylamine-treated silica gel (elution with 20:1 petroleum ether–ethyl acetate) to give 972 mg (83%) of **8** as a colorless solid: mp 94–96 °C; IR ($CHCl_3$, cm^{-1}) 1687, 1650, 1255, 1100; ^{1}H NMR (300 MHz, C_6D_6) δ 4.65 (d, *J* = 5.4 Hz, 1 H), 3.91 (d, *J* = 2.7 Hz, 1 H), 2.65 (m, 1 H), 2.37–2.21 (m, 3 H), 1.98–1.65 (series of m, 3 H), 1.68 (s, 3 H), 1.48–1.06 (series of m, 6 H), 1.07 (s, 6 H), 0.96 (s, 9 H), 0.95 (m, 1 H), 0.27 (s, 9 H), 0.23 (s, 9 H), 0.15 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 215.9, 151.1, 103.3, 82.8, 76.1, 52.6, 42.8, 42.4, 41.5, 40.7, 40.1, 37.1, 34.8, 30.9, 29.0, 26.1, 24.9, 18.3, 17.4, 16.1, 2.7, 0.6, −4.1, −4.6; MS *m/z* (M^+) calcd 566.3642, obsd 566.3636; $[\alpha]^{23}_D$ −180.9° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{30}H_{58}O_4Si_3$: C, 63.55; H, 10.31. Found: C, 63.63; H, 10.32.

(4*R*,4a*S*,6*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-1,2,3,4,4a,5,6,9,10,11,12,12a-dodecahydro-12a,13,13-trimethyl-6,7-bis(trimethylsiloxy)-6,10-methanobenzocyclodecen-12-ol (9a). A nitrogen-blanketed solution of **8** (324 mg, 0.571 mmol) in anhydrous benzene (40 mL) was treated dropwise with diisobutylaluminum hydride in hexanes (0.69 mL of 1 M, 0.690 mmol), stirred for 30 min, and quenched with a 1:1 mixture of saturated $NaHCO_3$ and brine solutions. The separated organic phase was washed with water, 1 M HCl, and brine prior to drying and solvent evaporation. Column chromatography of the residue on silica gel (elution with 10:1 petroleum ether–ethyl acetate) furnished 304 mg (94%) of **9a** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3504, 1256, 890, 839, 762, 753; ^{1}H NMR (300 MHz, C_6D_6) δ 4.77 (dd, *J* = 4.7, 2.8 Hz, 0.5 H), 4.70 (dd, *J* = 2.7, 4.9 Hz, 0.5 H), 4.14 (d, *J* = 8.3 Hz, 0.5 H), 4.00 (m, 1 H), 3.21 (dd, *J* = 7.9, 11.2 Hz, 0.5 H), 2.65 (dd, *J* = 10.0, 16.2 Hz, 0.5 H), 2.50 (m, 0.5 H), 2.48–2.44 (m, 1 H), 2.38–2.26 (series of m, 1 H), 2.20–2.10 (series of m, 1 H), 1.99–1.64 (series of m, 6 H), 1.56–0.82 (series of m, 5 H), 1.44 (s, 1.5 H), 1.32 (s, 1.5 H), 1.24 (s, 1.5 H), 1.21 (s, 3 H), 1.20 (s, 1.5 H), 1.01 (s, 4.5 H), 1.07 (s, 4.5 H), 0.37 (s, 4.5 H), 0.34 (s, 4.5 H), 0.30 (s, 4.5 H), 0.28 (s, 4.5 H), 0.26 (s, 1.5 H), 0.24 (s, 1.5 H), 0.17 (s, 1.5 H), 0.15 (s, 1.5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 154.4, 151.8, 102.4, 101.9, 82.5, 82.4, 81.1, 78.6, 75.6, 75.2, 43.6, 43.5, 43.2, 42.3, 42.2, 42.1, 41.4, 41.2, 40.3, 39.0, 38.7, 36.9, 35.4, 35.0, 32.6, 32.4, 31.0, 30.5, 29.6, 26.4, 26.2, 26.1, 24.4, 23.1, 20.9, 20.4, 18.4, 16.73, 16.67, 3.2, 2.8, 0.74, 0.71, −3.7, −4.1, −4.4, −5.0; FAB MS *m/z* (M^+ + 1) calcd 569.39, obsd 569.50; $[\alpha]^{21}_D$ −52.1° (*c* 1.1, $CHCl_3$). Anal. Calcd for $C_{30}H_{60}O_4Si_3$: C, 63.32; H, 10.63. Found: C, 62.83; H, 10.62.

(4*R*,4a*S*,6*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-1,2,3,4,4a,5,6,9,10,11,12,12a-dodecahydro-12-(methoxymethoxy)-12a,13,13-trimethyl-6,7-bis(trimethylsiloxy)-6,10-methanobenzocyclodecene (9b). A solution of **9a** (124 mg, 0.220 mmol) and diisopropylethylamine (1.90 mL, 10.9 mmol) in THF (20 mL) was cooled to 0 °C and treated dropwise with chloromethyl methyl ether (0.41 mL, 5.40 mmol) via syringe. The reaction mixture was allowed to warm slowly to rt during 16 h and diluted with water. The organic phase was washed with water, saturated $NaHCO_3$ solution, water, and brine. All of the aqueous washings were extracted three times with $CHCl_3$, and the collective organic solutions were dried and concentrated. The residue was purified by silica gel chromatography (elution with 10:1 petroleum ether–ethyl acetate) to give 127 mg (95%) of **9b** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 1260, 1090, 1045, 900, 845; ^{1}H NMR (300 MHz, C_6D_6) δ 4.69 (m, 1 H), 4.59 (ABq, *J* = 6.7 Hz, Δν = 42.1 Hz, 2 H), 4.20 (br d, *J* = 6.3 Hz, 1 H), 4.02 (m, 1 H), 3.24 (s, 3 H), 2.41 (m, 1 H), 2.23 (dd, *J* = 6.1, 15.3 Hz, 1 H), 1.94 (m, 2 H), 1.79 (m, 4 H), 1.60 (m, 1 H), 1.56–1.10 (series of m, 3 H), 1.50 (s, 3 H), 1.42 (s, 3 H), 1.19 (s, 3 H), 1.03 (s, 9 H), 1.10–0.85 (series of m, 2 H), 0.31 (s, 9 H), 0.26 (s, 9 H), 0.21 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 151.9, 102.6, 96.2, 83.3, 79.8, 76.3, 55.6, 43.5, 42.1, 41.9, 41.4, 37.6 (2 C), 35.2, 32.7, 32.2, 30.3, 26.2, 25.3, 21.1, 18.4, 16.6, 3.1, 0.72, −3.7, −4.5; FAB MS *m/z* (M^+ + 1) calcd 613.49, obsd 613.50; $[\alpha]^{23}_D$ +2.0° (*c* 2.5, $CHCl_3$).

(4*R*,4a*S*,6*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-dodecahydro-6-hydroxy-12-(methoxymethoxy)-12a,13,13-trimethyl-6,10-methanobenzocyclodecen-7(1*H*)-one (10a). A solution of **9b** (236 mg, 0.385 mmol) and 0.1 N HCl (10 mL) in THF (30 mL) was stirred at rt for 16 h and diluted with brine. The separated organic phase was washed with water and brine, dried, and concentrated. Flash chromatographic purification of the residue (silica gel, elution with 10:1 petroleum ether–ethyl acetate) afforded 170 mg (95%) of **10a** as a colorless solid: mp 98–100 °C; IR ($CHCl_3$, cm^{-1}) 3508, 1697, 1258, 1146, 1032; ^{1}H NMR (250 MHz, 420 K, C_6D_5Br) δ 4.41 (ABq, *J* = 6.1 Hz, Δν = 26.0 Hz, 2 H), 3.64 (br d, *J* = 9.6 Hz, 1 H), 3.46 (m, 1 H), 3.12 (s, 3 H), 2.45 (m, 1 H), 2.33 (m, 1 H), 2.17–1.93 (series of m, 3 H), 1.86 (m, 1 H), 1.70–1.45 (series of m, 4 H), 1.42 (m, 1 H), 1.35–0.95 (series of m, 6 H), 1.12 (s, 3 H), 1.06 (s, 3H), 0.78 (s, 3 H), 0.75 (s, 9 H), −0.11 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (63 MHz, 420 K, C_6D_5Br) ppm (several peaks remain broad under these conditions; observed are the following) 216.9, 99.3 83.6, 76.5, 57.6, 44.7, 43.6, 43.2, 41.1, 38.5, 36.8, 31.9, 29.6, 27.8, 24.4, 21.6, 19.9, 18.1, −2.6, −3.0; FAB MS *m/z* (M^+ + 1) calcd 469.33, obsd 469.50; $[\alpha]^{21}_D$ +54.0° (*c* 2.2, $CHCl_3$). Anal. Calcd for $C_{26}H_{48}O_5Si$: C, 66.62; H, 10.32. Found: C, 66.70; H, 10.30.

(4*R*,4a*S*,6*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-dodecahydro-12-(methoxymethoxy)-12a,13,13-trimethyl-6-(trimethylsiloxy)-6,10-methanobenzocyclodecen-7(1*H*)-one (10b). A solution of **10a** (47 mg, 0.10 mmol) and freshly distilled trimethylsilyl chloride (0.13 mL, 1.0 mmol) was cooled to −78 °C under N_2 while potassium hexamethyldisilazide in toluene (0.42 mL of 0.5 M, 0.21 mmol) was introduced dropwise via syringe. After 1 h, the reaction mixture was poured into saturated $NaHCO_3$ solution, the separated aqueous layer was washed with water and brine, and the aqueous phases were back-extracted with ethyl acetate. The organic solutions were dried and evaporated to leave a residue, chromatography of which on silica gel (gradient elution with hexanes to 10:1 petroleum ether–ethyl acetate) provided 11 mg (18%) of **9b** and 42 mg (77%) of **10b** as a colorless solid: mp 101–102 °C; IR ($CHCl_3$, cm^{-1}) 1705, 1249, 1146, 1111, 1087, 1036, 841; ^{1}H NMR (300 MHz, C_6D_6) δ 4.54 (ABq, *J* = 6.8 Hz, Δν = 36.3 Hz, 1.33 H), 4.33 (ABq, *J* = 6.0 Hz, Δν = 67.3 Hz, 0.67 H), 4.11 (br d, *J* = 9.7 Hz, 0.67 H), 3.66 (m, 1 H), 3.40 (m, 0.33 H), 3.22 (s, 2 H), 3.14 (s, 1 H), 2.85 (br d, *J* = 6.6 Hz, 0.33 H), 2.55 (m, 0.67 H), 2.45–2.13 (series of m, 2 H), 1.99–1.35 (series of m, 10 H), 1.35–0.90 (series of m, 3.67 H), 1.34 (s, 2 H), 1.30 (s, 2 H), 1.17 (s, 1 H), 1.15 (s, 1 H), 0.99 (s, 9.33 H), 0.88 (s, 2 H), 0.49 (s, 3 H), 0.40 (s, 6 H), 0.14 (s, 1H), 0.13 (s, 2 H), 0.04 (s, 3 H); ^{13}C NMR (63 MHz, C_6D_6) ppm 213.8, *213.0*, 97.7, *96.5*, 88.3, 87.2, *86.6*, *81.1*, 78.4, *74.4*, 56.4, *55.7*, 44.7, 44.4, 43.8, *43.7*, 42.0, *41.3*, *40.8*, *39.3*, *39.1*, 38.9, 38.8, *38.7*, *37.7*, *36.3*, *35.1*, 34.9, *32.3*, 30.6, *30.2*, *28.6*, 26.9, *26.2*, 24.1, *23.6*, 22.3, 20.7, *19.7*, 18.4, *18.3*, 16.34, *16.26*, 3.4, *3.2*, *−3.7*, −4.0, −5.0 (underlined signals are for the major confomer); MS *m/z* (M^+) calcd 540.3665, obsd 540.3652; $[\alpha]^{22}_D$ +70.5° (*c* 3.1, $CHCl_3$).

(4*R*,4a*S*,6*R*,8*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)dodecahydro-6,8-dihydroxy-12-(methoxymethoxy)-12a,-13,13-trimethyl-6,10-methanobenzocyclodecen-7(1*H*)-one (11a). A cold (−78 °C) solution of potassium hexamethyldisilazide

(4.5 mL of 0.5 M in toluene, 2.23 mmol) in dry THF (20 mL) was treated dropwise via cannula with **10a** (298 mg, 0.636 mmol) dissolved in THF (20 mL). After 30 min, a solution of the oxaziridine (330 mg, 1.91 mmol) in THF (5 mL) was also introduced. Reaction was allowed to proceed for 30 min, at which point the reaction mixture was diluted with saturated NH_4Cl solution and ether, and allowed to warm to rt. The separated organic phase was washed with water and brine, and the combined aqueous solutions were extracted with ether. The organic solutions were dried and evaporated to leave an oily solid, chromatography of which on silica gel (gradient elution with 20:1 to 5:1 petroleum ether–ethyl acetate) led to the isolation of **11a** (220 mg, 71%) as a colorless solid: mp 148–151 °C; IR (CCl_4, cm^{-1}) 3524, 1698, 1256, 1148, 1100, 1036; ^1H NMR (300 MHz, C_6D_6) δ 5.45 (br t, J = 9.7 Hz, 0.75 H), 4.45 (ABq, J = 6.1 Hz, $\Delta\nu$ = 52.7 Hz, 1.5 H), 4.48 (ABq, J = 6.8 Hz, $\Delta\nu$ = 35.7 Hz, 0.5 H), 4.34 (br t, J = 9.6 Hz, 0.25 H), 4.17 (d, J = 9.4 Hz, 0.25 H), 4.07 (s, 0.75 H), 2.85 (d, J = 6.0 Hz, 0.75 H), 2.69 (dd, J = 11.0, 16.3 Hz, 0.75 H), 5.04 (ddd, J = 1.0, 8.7, 13.2 Hz, 0.75 H), 2.38 (dd, J = 5.6, 16.1 Hz, 0.25 H), 2.20–1.90 (series of m, 1.25 H), 1.85–1.64 (series of m, 4.75 H), 1.60–1.49 (series of m, 2.75 H), 1.39–1.20 (series of m, 2 H), 1.36 (s, 0.75 H), 1.35 (s, 0.75 H), 1.20–0.78 (series of m, 1.75 H), 1.18 (s, 2.25 H), 1.12 (s, 2.25 H), 0.97 (s, 6.75 H), 0.94 (s, 2.25 H), 0.89 (s, 2.25 H), 0.83 (s, 0.75 H), 0.70 (s, 2.25 H), –0.02 (s, 0.75 H), –0.05 (s, 3 H); ^{13}C NMR (76 MHz, C_6D_6) ppm *217.7*, 217.3, *98.0*, 96.1, *88.2*, 83.5, *82.9*, 80.3, *77.8*, 74.1, *73.6*, 72.6, *56.7*, 55.7, *44.8*, *44.6*, 44.4, *42.0*, *41.8*, 41.2, 40.5, 39.7, 39.6, *39.0*, *38.9*, 38.1, 36.1, *35.1*, *34.9*, 34.7, 30.7, 29.9, *29.1*, *27.1*, *26.1*, 26.0, 23.6, *22.1*, *20.5*, 20.0, *18.3*, 18.2, *16.3*, 16.1, *–4.3* (1 C), *–4.9*, –5.1 (underlined signals are for the major conformer); MS m/z (M^+) calcd 484.3219, obsd 484.3237; $[\alpha]^{21}_D$ +19.1° (*c* 1.6, $CHCl_3$). Anal. Calcd for $C_{26}H_{48}O_6Si$: C, 64.42; H, 9.98. Found: C, 64.61; H, 10.02.

Comparable processing of **10b** (30 mg, 55.3 μmol) gave 22 mg (73%) of **11b** as a 2:1 mixture of conformational isomers; ^1H NMR (300 MHz, C_6D_6) δ 5.31 (m, 0.66 H), 4.49 (ABq, J = 7.4 Hz, $\Delta\nu$ = 35.9 Hz, 0.66 H), 4.45 (ABq, J = 6.3 Hz, $\Delta\nu$ = 28.6 Hz, 1.34 H), 4.29 (t, J = 9.6 Hz, 0.34 H), 4.13 (d, J = 9.3 Hz, 0.34 H), 3.63 (m, 0.66 H), 3.54 (m, 1 H), 3.24 (s, 2 H), 3.20 (s, 1 H), 2.83 (d, J = 6.2 Hz, 0.66 H), 2.60 (dd, J = 10.9, 16.3 Hz, 0.66 H), 2.47 (m, 0.66 H), 2.26 (dd, J = 6.0, 15.9 Hz, 0.34 H), 2.10–1.40 (series of m, 9 H), 1.38–0.77 (series of m, 7.34 H), 1.34 (s, 1 H), 1.28 (s, 1 H), 1.12 (s, 2 H), 1.11 (s, 2 H), 0.98 (s, 6 H), 0.97 (s, 3 H), 0.86 (s, 2 H), 0.81 (s, 1 H), 0.45 (s, 6 H), 0.39 (s, 3 H), 0.12 (s, 2 H), 0.06 (s, 1 H), 0.02 (s, 1 H), 0.02 (s, 2 H), 0.01 (s, 1 H).

(4*R*,4a*S*,6*R*,10*S*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-1,2,4,4a,5,6,10,11,12,12a-decahydro-6,8-dihydroxy-12-(methoxymethoxy)-12a,13,13-trimethyl-6,10-methanobenzocyclodecen-7(1*H*)-one (12). A. Oxidation of 10a. Into a cold (–78 °C) solution of potassium hexamethyldisilazide (0.37 mL of 0.5 M in toluene, 0.188 mmol) in dry THF (2 mL) was introduced a solution of **10a** (22 mg, 47 μmol) in THF (3 mL). After 15 min, the oxaziridine (24 mg, 0.141 mmol) dissolved in THF (1 mL) was added dropwise via cannula, and the reaction mixture was allowed to warm to rt during 4 h and then quenched with saturated NH_4Cl solution. The separated organic layer was washed with 1 M HCl, water, and brine prior to drying and concentration. The residue was chromatographed on silica gel (gradient elution from 20:1 to 3:1 petroleum ether–ethyl acetate) to afford 19 mg (82%) of **12** as a colorless solid: mp 57–59 °C; IR ($CHCl_3$, cm^{-1}) 3487, 1672, 1654, 1391, 1256, 1146, 1086, 1032; ^1H NMR (300 MHz, C_6D_6) δ 5.66 (d, J = 6.6 Hz, 1 H), 5.55 (s, 1 H), 4.49 (ABq, J = 6.8 Hz, $\Delta\nu$ = 23.0 Hz, 2 H), 4.02 (dd, J = 2.7, 11.7 Hz, 1 H), 3.44 (m, 1 H), 3.19 (s, 3 H), 3.10 (s, 1 H), 2.25 (m, 1 H), 2.17 (dd, J = 3.7, 15.5 Hz, 1 H), 2.10–1.57 (series of m, 5 H), 1.53–0.88 (series of m, 6 H), 1.29 (s, 3 H), 1.28 (s, 3 H), 1.04 (s, 3 H), 0.97 (s, 9 H), 0.11 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.7, 148.2, 124.8, 97.3, 84.2, 80.1, 73.2, 55.8, 43.1, 41.5, 40.1, 37.9, 34.7, 31.9, 30.5, 29.6, 26.1, 26.0, 21.2, 19.8, 18.2, 16.4, –4.3, –4.9; MS m/z (M^+) calcd 482.3065, obsd 482.3055; $[\alpha]^{22}_D$ +106.0° (*c* 1.16, $CHCl_3$).

B. Autoxidation of 11a. A solution of **11a** (12 mg, 20.6 μmol) in methanol (2 mL) was treated with 2 drops of DBU and stirred at rt overnight, heated at reflux for 2 h, concentrated, and placed directly atop a microcolumn of silica gel. Gradient elution from hexanes to 10:1 petroleum ether–ethyl acetate furnished 6 mg (56%) of **12**.

C. Periodinane Oxidation of 11a. To a solution of the Dess–Martin periodinane (282 mg, 0.665 mmol) in dry CH_2Cl_2 (30 mL) under N_2 was added via cannula a solution of **11a** (248 mg, 0.512 mmol) in CH_2Cl_2 (30 mL). After 10 min, a milky white precipitate appeared and the reaction was complete. The mixture was poured into a separatory funnel containing ether and 1 M NaOH, and the organic phase was separated and washed with 1 M NaOH, water, $NaHSO_3$ solution (2×), and brine. After drying and concentration, the residue was purified by silica gel chromatography (elution with 5:1 petroleum ether–ethyl acetate) to give 210 mg (85%) of **12**.

(1*S*,3*R*,5*S*,7*S*,8a*S*,9*R*,12a*R*)-9-(*tert*-Butyldimethylsiloxy)-dodecahydro-3-hydroxy-6,6,12a-trimethyl-1,5:3.7-dimethanol*H*-2-benzoxecin-12-one (13). A solution of **11a** (22 mg, 45 μmol) in absolute ethanol (5 mL) was treated with 3 drops of concentrated HCl and slowly warmed to 50 °C. The reaction mixture was partitioned between water and ethyl acetate. The organic phase was washed with brine and dried. The residue was subjected to chromatography on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to furnish 12 mg (64%) of **13** as a colorless solid: mp 131–133.5 °C; IR ($CHCl_3$, cm^{-1}) 3492, 1709, 1256, 1188, 1148, 1086, 1041, 988; ^1H NMR (300 MHz, C_6D_6) δ 5.18 (s, 1 H), 3.70 (br d, J = 11.7 Hz, 1 H), 3.58 (ddd, J = 3.0, 2.5, 2.5 Hz, 1 H), 3.25 (m, 1 H), 2.64 (br d, J = 13.0 Hz, 1 H), 2.06–1.87 (series of m, 5 H), 1.77 (ddddd, J = 13.0, 13.0, 13.0, 3.5, 3.5 Hz, 1 H), 1.58–1.43 (series of m, 3 H), 1.32–1.07 (series of m, 3 H), 0.94 (s, 9 H), 0.93 (s, 3 H), 1.02–0.80 (m, 1 H), 0.77 (s, 3 H), 0.58 (s, 3 H), –0.05 (s, 3 H), –0.06 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.2, 91.8, 81.3, 76.6, 55.2, 41.1, 39.6, 38.7, 36.6, 34.4, 32.6, 28.5, 26.0, 25.8, 23.0, 22.7, 18.4, 18.2, 17.6, –4.4, –5.0; MS m/z (M^+) calcd 422.2852, obsd 422.2842; $[\alpha]^{23}_D$ –107.8° (*c* 0.78, CCl_4). Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20; H, 10.02. Found: C, 68.12; H, 10.00.

(4*R*,4a*S*,6*R*,10*R*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-dodecahydro-6,8-dihydroxy-12-(methoxymethoxy)-12a,13,-13-trimethyl-6,10-methanobenzocyclodecen-7(1*H*)-one (14). To a cold (–78 °C) solution of potassium hexamethyldisilazide (0.45 mL of 0.5 M in toluene, 0.227 mmol) in dry THF (2 mL) was introduced **11a** (36 mg, 0.074 mmol) as a solute in THF (3 mL). After 30 min, the reaction mixture was allowed to warm to rt and quenched with saturated NH_4Cl solution. The separated organic phase was washed with brine, dried, and evaporated to leave a residue which was chromatographed on silica gel (elution with 5:1 petroleum ether–ethyl acetate) to give 16 mg (45%) of **14** as a colorless solid: mp 142–145 °C; IR ($CHCl_3$, cm^{-1}) 3690, 3523, 1698, 1459, 1391, 1260; ^1H NMR (300 MHz, C_6D_6) δ 4.45 (ABq, J = 6.9 Hz, $\Delta\nu$ = 49.0 Hz, 2 H), 4.16 (s, 1 H), 4.00 (d, J = 8.4 Hz, 1 H), 3.70 (m, 1 H), 3.27 (s, 1 H), 3.18 (d, J = 10.1 Hz, 1 H), 3.11 (s, 3 H), 2.60 (dd, J = 9.6, 10.1 Hz, 1 H), 2.06 (dd, J = 5.6, 16.1 Hz, 1 H), 2.00–1.63 (series of m, 7 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.35 (m, 3 H), 1.30–1.13 (m, 2 H), 1.20 (s, 3 H), 0.98 (s, 9 H), 0.09 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 221.2, 96.1, 82.0, 78.5, 75.4, 68.8, 55.5, 46.2, 41.4, 40.9, 40.4, 39.0, 36.9, 36.6, 35.0, 30.6, 30.5, 26.0, 23.2, 20.1, 18.3, 16.1, –4.2, –5.0; MS m/z (M^+) calcd 484.3219, obsd 484.3215; $[\alpha]^{21}_{2D}$ +11.7°(*c* 1.40, $CHCl_3$). Anal. Calcd for $C_{26}H_{48}O_6Si$: C, 64.42; H, 9.98. Found: C, 64.50; H, 9.99.

(4*R*,4a*S*,6*R*,7*S*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-dodecahydro-6,7-dihydroxy-12-(methoxymethoxy)-12a,13,-13-trimethyl-6,10-methanobenzocyclodecen-8(2*H*)-one (15). To a cold (–78 °C), magnetically stirred suspension of lithium aluminum hydride (6 mg, 0.15 mmol) in dry ether (1 mL) was added a solution of **12** (14 mg, 29 μmol) in either (1 mL). The reaction mixture was stirred in the cold for 1 h, allowed to warm to rt, worked up in the alkaline manner recommended by Fieser, and filtered through Celite. Column chromatography of the residue after concentration (silica gel, gradient elution from 10:1 to 5:1 petroleum ether in ethyl acetate) returned 8 mg of **12** and gave 6 mg (43%, or 97% based on recovered **12**) of **15** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3601, 3500 (br), 1702, 1257; ^1H NMR (300 MHz, C_6D_6) δ 4.47 (ABq, J = 6.8 Hz, $\Delta\nu$ = 27.1 Hz, 2 H), 4.10 (br d, J = 2.6 Hz, 1 H), 4.03 (br s, 1 H), 3.99 (m, 1 H), 3.37 (s, 1 H), 3.18 (s, 3 H), 2.42 (dd, J = 7.7, 17.8 Hz, 1 H), 2.09 (d, J = 17.8 Hz, 1 H), 2.04–1.67 (series of m, 7 H), 1.56–0.79 (series of

m, 5 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.02 (s, 3 H), 1.00 (s, 9 H), 0.57 (m, 1 H), 0.18 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.5, 96.8, 82.8, 80.5, 80.1, 72.2, 55.7, 46.8, 41.8, 40.8, 40.7, 40.4, 36.4, 33.8, 33.4, 30.3, 29.8, 26.1, 23.5, 19.7, 18.3, 16.1, -4.2, -4.7; MS m/z ($M^+ - H_2O$) calcd 466.3116, obsd 466.3112; $[\alpha]^{21}_D$ -7.8° (c 0.56, $CHCl_3$).

(4*R*,4a*S*,6*R*,10*S*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)-2,3,4,4a,5,6,10,11,12,12a-decahydro-8-hydroxy-12-(methoxymethoxy)-12a,13,13-trimethyl-6-(trimethylsiloxy)-6,10-methanobenzocyclodecen-7(1*H*)-one (17). To a flame-dried flask fitted with a 5-mL pressure-equalizing funnel was added 1.5 mL of 0.50 M dimethyl sulfoxide in CH_2Cl_2 (0.75 mmol) and annydrous CH_2Cl_2 (2 mL). The funnel was charged with a solution of **11b** (70 mg, 0.126 mmol) in CH_2Cl_2 (4 mL). The flask was cooled to -78 °C, and 0.75 mL of 0.50 M oxalyl chloride in CH_2Cl_2 (0.377 mmol) was added dropwise via syringe during 5 min. After 15 min of stirring, the solution containing **11b** was introduced dropwise, to be followed 25 min later with triethylamine (0.11 mL, 0.789 mmol). The cold bath was removed, the solution was allowed to warm to rt and stirred there for 20 min, and brine was added. The separated organic phase was dried and concentrated to leave a yellow residue that was purified by column chromatography (silica gel, elution with 10:1 petroleum ether–ethyl acetate) to give **17** (50 mg, 72%) as a clear oil: IR ($CHCl_3$, cm^{-1}) 3468, 1731, 1682, 1660, 1462, 1251, 1092, 1032, 840; ^{1}H NMR (300 MHz, C_6D_6) δ 5.76 (s, 1 H), 5.63 (d, J = 6.5 Hz, 1 H), 4.51 (ABq, J = 6.8 Hz, $\Delta\nu$ = 23.7 Hz, 2 H), 4.00 (dd, J = 2.6, 11.6 Hz, 1 H), 3.50 (m, 1 H), 3.20 (s, 3 H), 2.32 (m, 1 H), 2.10–1.95 (series of m, 3 H), 1.85–1.55 (series of m, 5 H), 1.36–0.83 (series of m, 3 H), 1.29 (s, 3 H), 1.21 (s, 3 H), 1.00 (s, 12 H), 0.38 (s, 9 H), 0.16 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.3, 148.6, 122.7, 97.3, 84.8, 84.1, 74.1, 55.8, 43.0, 42.7, 40.4, 40.2, 38.0, 34.8, 31.9, 31.0, 30.6, 26.2, 21.6, 19.8, 18.3, 16.3, 3.0, -3.7, -5.0; FAB MS m/z (M^+ + 1) calcd 555.35, obsd 555.50; $[\alpha]^{21}_D$ +106.3° (c 0.52, $CHCl_3$).

(4*R*,4a*S*,6*R*,7*S*,10*S*,12*S*,12a*R*)-4-(*tert*-Butyldimethylsiloxy)dodecahydro-7-hydroxy-12-(methoxymethoxy)-12a,13,-13-trimethyl-6-(trimethylsiloxy)-6,10-methanobenzoylcyclodecen-8(2*H*)-one (16). A. Silylation–Reduction of 12. A nitrogen-blanketed solution of **12** (61 mg, 0.126 mmol) in dry THF (5 mL) was treated with freshly distilled trimethylsilyl chloride (0.16 mL, 1.26 mmol), cooled to -78 °C in advance of the addition of potassium hexamethyldisilazide (0.63 mL of 0.5 M in toluene, 0.314 mmol), and allowed to warm to rt. Two additional identical equivalents of base were required to complete the conversion to product. The reaction mixture was poured onto saturated $NaHCO_3$ solution and petroleum ether. The separated organic phase was dried and concentrated to leave a residue which was dissolved in ether (2 mL) and added dropwise via cannula to a stirred suspension of lithium aluminum hydride (8 mg, 0.211 mmol) in ether (1 mL) at -78 °C. This reaction mixture was stirred for 0 °C for 1 h and quenched with water. The organic layer was washed with brine, filtered through Celite, dried, and evaporated. Chromatography of the residue (silica gel, gradient elution with 10:1 to 5:1 petroleum ether–ethyl acetate) gave 34 mg (48%) of **16** as a clear oil: IR (CCl_4, cm^{-1}) 3484, 1702, 1250, 1091, 1032; ^{1}H NMR (300 MHz, C_6D_6) δ 4.49 (ABq, J = 6.8 Hz, $\Delta\nu$ = 27.6 Hz, 2 H), 4.12 (m, 1 H), 4.01 (s, 1 H), 4.00 (m, 1 H), 3.54 (d, J = 1.4 Hz, 1 H), 3.19 (s, 3 H), 2.41 (m, 1 H), 2.11 (d, J = 17.8 Hz, 1 H), 2.06 (dd, J = 3.7, 15.5 Hz, 1 H), 1.99–1.72 (series of m, 5 H), 1.47 (dd, J = 11.4, 13.7 Hz, 1 H), 1.39–1.14 (series of m, 3 H), 1.34 (s, 3 H), 1.26 (s, 3 H), 1.03 (s, 9 H), 1.00–0.83 (m, 1 H), 0.93 (s, 3 H), 0.50 (m, 1 H), 0.31 (s, 9 H), 0.23 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.9, 96.8, 85.0, 82.9, 79.7, 72.6, 55.8, 46.6, 43.2, 41.0, 40.5, 39.9, 36.3, 33.8, 32.8, 30.6, 30.4, 26.3, 24.1, 19.7, 18.2, 16.0, 2.6, -3.7, -4.7; MS m/z (M^+) calded 556.3614, obsd 556.3625; $[\alpha]^{21}_D$ -1.2° (c 1.8, $CHCl_3$).

B. Hydride Reduction of 17. Reduction of **17** (27 mg, 48.7 μmol) with lithium aluminum hydride (5 mg, 0.131 mmol) in anhydrous ether (2.5 mL) as described above afforded 18 mg (68%) of **16**, spectroscopically identical to the material obtained in part A.

Acknowledgment. We are grateful to the Bristol-Myers Squibb Co. for their financial support, to Dr. Dirk Friedrich for his assistance with the NMR experiments, and to Eugene Hickey, Scott Edmondson, and James Lanter for the molecular modeling studies.

Supplementary Material Available: 300-MHz ^{1}H and 75-MHz ^{13}C NMR spectra of those compounds lacking combustion data and tables of the final atomic coordinates for **A–D** in both conformations as shown in Figures 2 and 3 (25 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.