Pergamon

Tetrahedron, Vol. 53, No. 27, pp. 9043-9056, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00615-7

Diastereoselective Manipulations of Bicyclo[m.1.0]alkane Derivatives. 3. Nucleophilic Additions to the Carbonyl Carbon of (1*R*,8*R*)-Bicyclo[6.1.0]nonan-2,6-dione 2-(2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal

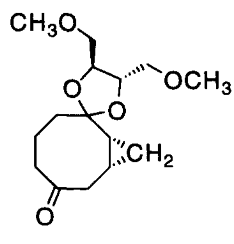
Eugene A. Mash,* Kalpana S. Nimkar, and James A. Baron

Department of Chemistry, The University of Arizona, Tucson, Arizona 85721-0041

Abstract: Conformations of the title compound were studied using a Monte Carlo search technique. Two principal conformational motifs were observed for the bicyclic carbocycle in which both faces of the carbonyl appear susceptible to nucleophilic attack. The title compound was synthesized in eight steps from *cis*-1,5-cyclooctanediol. Additions of nucleophiles (e.g., CH_3Li) to the title compound gave adducts in good yields, but with low levels of diastereoselectivity, in agreement with computational prediction. © 1997 Elsevier Science Ltd.

In an effort to develop a general synthetic approach to natural products which contain medium or large carbocyclic rings, we have undertaken studies of the conformations and reactivities of bicyclo[m.1.0]alkane derivatives.[1,2] We recently reported that nucleophilic additions to the carbonyl carbons of bicyclo[m.1.0]alkan-2-ones[3] exhibit high diastereoselectivity when $m \geq 6$.[2] This selectivity was attributed to a highly conserved local conformation for the α,β-cyclopropyl ketone functional group array in which approach to one face of the carbonyl is blocked by the transannular atoms of the larger ring.[1,2]

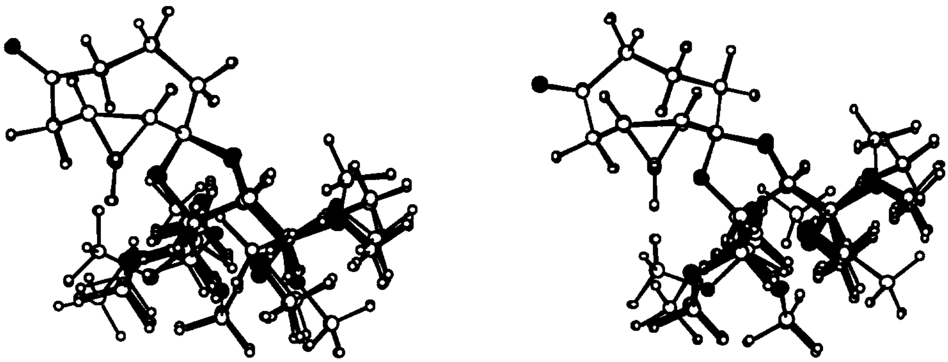
Of potential interest for the construction of natural products which contain eight-membered carbocycles is dione-monoketal 1. This compound, which is derivable from 1,5-cyclooctanediol (*vide infra*), may afford opportunities for stereocontrolled manipulation of reactive centers at multiple positions on the eight-membered ring. Furthermore, it presents an opportunity to further test the utility of conformational analysis of medium ring carbocycles as a predictive tool for chemical reactivity.[1,2,4] Presented herein are results of a computational study of the conformations of β,γ-cyclopropyl ketone 1, a synthesis of this ketone, and a study of additions of nucleophiles to its carbonyl carbon.



1

Conformations of Ketone 1

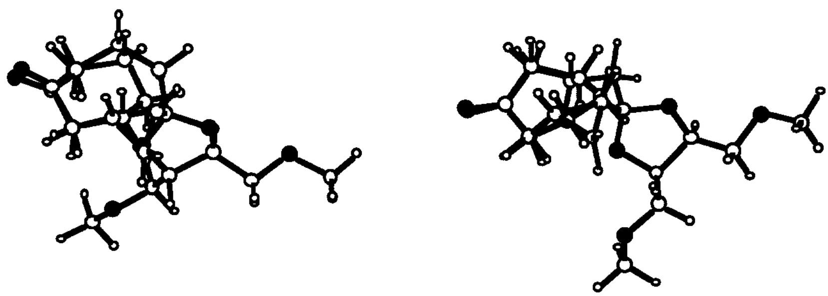
The conformational ensemble for 1 was obtained using a Monte Carlo search strategy and the MM2* force field resident in BATCHMIN v4.0.[5] There were found 226 conformers within 20 kJ and 8 conformers within 5 kJ of the global minimum. Owing to the rigidity of the cyclopropane ring, two conformational motifs of the bicyclo[6.1.0]nonanone substructure were predominant (Figure 1). Overlay **1A** is comprised of conformers which represent 75% and overlay **1B** is comprised of conformers which represent 23% of the conformer population at 195 K. The remaining 2% of the population exhibited other conformational motifs for the bicyclo[6.1.0]nonanone substructure.[6]



1A **1B**

Fig. 1. Overlays of the conformers of (1*R*,8*R*)-bicyclo[6.1.0]nonan-2,6-dione 2-(2*S*,3*S*)-1,4-di-*O*-methyl-1,2,3,4-butanetetrol ketal (**1**).

In each overlay both faces of the carbonyl appear sterically accessible to nucleophilic attack. The spatial arrangements of the atoms in the vicinity of the carbonyls of **1A** and **1B** resemble the chair and twist-boat conformers of cyclohexanone, respectively (Figure 2).[7] Summarized in Table 1 are important angles and distances for conformer **1-1** (representing **1A**), chair cyclohexanone, conformer **1-5** (representing **1B**), and twist-boat cyclohexanone.[8]



1-1/chair cyclohexanone **1-5**/twist-boat cyclohexanone

Fig. 2. Overlays of conformers **1-1** and **1-5** with with chair and twist-boat cyclohexanones, respectively.

Table 1. **Angles and Distances for Representative (1*R*,8*R*)-Bicyclo[6.1.0]nonan-2,6-dione 2-(2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal Conformers 1-1 and 1-5, Chair Cyclohexanone, and Twist-Boat Cyclohexanone.**

	1-1	Chair	**1-5**	Twist-boat
Angle, degrees				
H_{ax}-C-C=O	131 132	107	98 117	88
C-C(=O)-C	119	116	118	116
Distance from Carbonyl Carbon to Hydrogen, Å (proximal carbonyl face)				
H_α (axial)	2.16 (*Re*) 2.17 (*Re*)	2.14	2.14 (*Re*) 2.16 (*Si*)	2.15
H_β (axial)	2.57 (*Si*) 2.87 (*Si*)	2.83	2.61 (*Re*) 2.84 (*Si*)	2.74

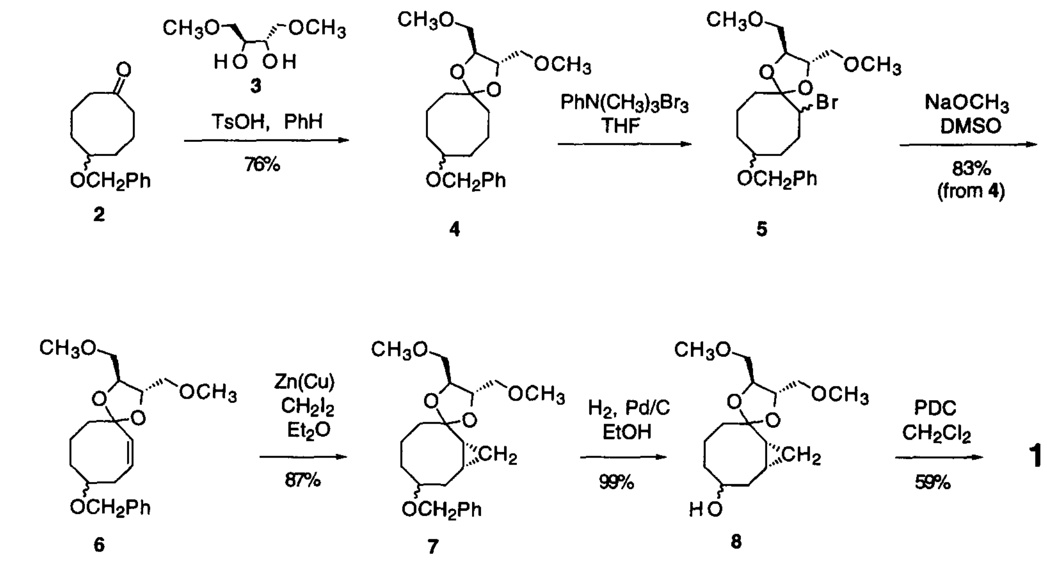
For **1-1** the H_{ax}-C-C=O torsion angles are 131° and 132°, while the C-C(=O)-C angle is 119°. These angles are larger than the corresponding angles in the chair conformer of cyclohexanone. The distances from the carbonyl carbon (*Re* face) to the axial α-hydrogens (2.16 and 2.17 Å) are comparable to the corresponding distance in chair cyclohexanone (2.14 Å). Assuming a Bürgi-Dunitz trajectory,[9] somewhat less torsional strain would be expected for attack at the *Re* face of **1-1** than for equatorial attack on chair cyclohexanone. Greater asymmetry is reflected in the distances from the carbonyl carbon (*Si* face) to the axial β-hydrogens (2.57 and 2.87 Å for **1-1** versus 2.83 Å for chair cyclohexanone). Somewhat more steric strain would be expected for nucleophilic attack at the *Si* face of **1-1** due to the closer proximity of one H_β.

The situation for **1-5** is similar. One H_{ax}-C-C=O torsion angle is 117° and the other 98°, while the C-C(=O)-C angle is 118°. These angles are larger than the corresponding angles in the twist-boat conformer of cyclohexanone. The distances from the carbonyl carbon to the axial α-hydrogens (2.14 Å to the *Re* face and 2.16 Å to the *Si* face) are comparable to the corresponding distance in twist-boat cyclohexanone (2.15 Å). The distances from the carbonyl carbon to the axial β-hydrogens (2.61 Å to the *Re* face and 2.84 Å to the *Si* face) bracket the corresponding distance in twist-boat cyclohexanone (2.74 Å). Slightly more torsional and steric strain would be expected for nucleophilic attack at the *Re* face of **1-5**.

From these qualitative arguments, it would seem reasonable to postulate that additions of nucleophiles to the carbonyl of ketone **1** would exhibit modest diastereoselectivity, perhaps comparable to that observed for conformationally anchored cyclohexanone derivatives.[10] A more quantitative prediction of diastereoselectivity for additions of nucleophiles to **1** would require evaluation of competing transition states. Work toward this goal is in progress.

Synthesis of Ketone 1

The synthesis of ketone **1** is outlined in Scheme 1. Ketalization of 5-(benzyloxy)cyclooctanone (**2**)[11] using the enantiomerically pure diol (2*S*,3*S*)-1,4-di-*O*-methyl-1,2,3,4-butanetetrol (**3**)[12] provided ketal **4** in 76% yield. Bromination of **4** with phenyltrimethylammonium tribromide[13] produced a mixture of α-bromoketal diastereomers **5**. Elimination with sodium methoxide in DMSO produced a mixture of chromatographically inseparable diastereomeric ene ketals **6** in 83% yield from **4**. The diastereomer ratio for **6** was approximately 1:1 as determined by ^{13}C NMR spectroscopy.[14] Treatment of **6** with an excess of the Simmons-Smith reagent[15] gave, in 87% yield, a mixture of cyclopropyl ketal diastereomers **7**. Debenzylation using hydrogen and palladium-on-charcoal provided epimeric alcohols **8**. Oxidation of **8** with pyridinium dichromate provided the target ketone **1** in 59% yield. The ratio of diastereomers arising from the Simmons-Smith cyclopropanation was >20:1 as determined from the ^{13}C NMR spectra of compounds **7**, **8**, and **1**. The stereochemistry of **1** was confirmed as 1*R*,8*R* by a single crystal X-ray diffraction study of a derivative (*vide infra*). The yield of **1** from **2** was 32% over 6 steps.

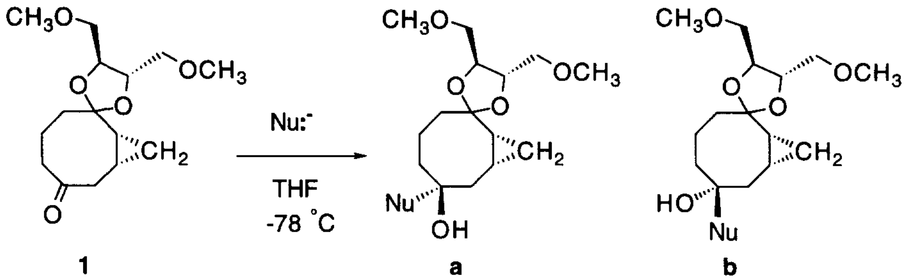


Scheme 1. Synthesis of (1*R*,8*R*)-Bicyclo[6.1.0]nonan-2,6-dione 2-(2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (**1**).

Additions of Nucleophiles to Ketone 1

Ketone **1** was subjected to attack by various nucleophiles under conditions which favor kinetic control. Results are summarized in Table 2. In all cases diastereomeric products arising from attack of the nucleophile at opposite faces of the carbonyl were observed. These diastereomers differed in polarity (except for **8a/8b**) and were isolated by column chromatography and characterized spectroscopically.

Table 2. Additions of Nucleophiles to Ketone **1**.

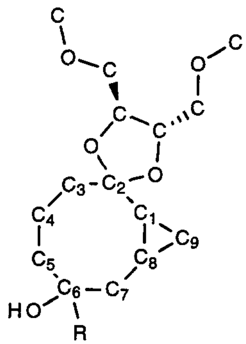


Entry	Nucleophile	Products	Yield, %	Diastereomer Ratio[a]	α[b]
1	$LiAlH_4$[c]	**8a,8b**	95	2:1[d]	1.00
2	CH_3Li	**9a,9b**	80[e]	4.0:1	1.50
3	*n*-C_4H_9Li	**10a,10b**	72[e]	3.2:1	1.15
4	*t*-C_4H_9Li	**11a,11b**	55[f]	1:1.2	1.19
5	CH_2=CHMgBr	**12a,12b**	73	2.8:1	1.18
6	C_6H_5Li	**13a,13b**	84	3.9:1	1.57
7	*p*-C_6H_5-C_6H_4MgBr	**14a,14b**	76	2.0:1	1.31
8	*n*-$C_4H_9C{\equiv}CLi$	**15a,15b**	88	4.9:1	1.09

[a]Ratio of isolated more polar to less polar diastereomer. [b]Ratio of R_f's on analytical tlc plates; see experimental for solvent systems. [c]Diethyl ether was used as solvent. [d]Chromatographically inseparable; diastereomer ratio determined by ^{13}C NMR analysis. [e]Starting material (15%) was also recovered. [f]Starting material (19%) was also recovered.

While the chemical yields for the reactions of nucleophiles with β,γ-cyclopropyl ketone **1** were good, the observed diastereoselectivities were low, ranging from 1:1.2 for *tert*-butyllithium (Table 2, entry 4) to 4.9:1 for 1-lithiohexyne (entry 8). Less sterically demanding nucleophiles generally exhibited higher diastereoselectivities (compare entries 2-4 and 8). In the case of 4-biphenylmagnesium bromide (entry 7), a 2:1 preference for attack at the *Si* face of the carbonyl was confirmed by unambiguous assignments of structure to the products. The less polar diastereomer was crystalline and was shown to possess structure **14a** by single crystal X-ray analysis. Structure **14b** was assigned to the corresponding more polar diastereomer. In keeping with these assignments, structures **9a-15a** and **9b-15b** were assigned to the less polar and more polar product diastereomers, respectively, on the basis of chromatographic mobility and the consistent trends in the chemical shifts of comparable carbons observed in the ^{13}C NMR spectra (Table 3). Shading indicates the upfield signal for each diastereomeric pair. The signal for C_8 in each of the less polar diastereomeric products appears significantly upfield relative to the signal for C_8 in the corresponding more polar diastereomeric products. The signals for C_4 and C_6 in each of the less polar diastereomeric products appear downfield relative to the corresponding signals in the more polar diastereomeric products. Significant chemical shift differences are also observed for C_5 and C_7 when R = alkene, arene, or alkyne. Signals arising from the more remote carbons, C_1, C_2, C_3, and C_9, are less strongly affected by the configuration at C_6. Thus, a modest preference for addition of carbon nucleophiles to the *Si* face of **1** exists.

Table 3. Selected ^{13}C NMR Chemical Shift Values for Alcohols **9-15**.



	C_9	C_8	C_4	C_1	C_5 and C_7		C_3	C_6	C_2
9a	5.5		18.0	23.8	37.7	40.1	41.7	74.0	111.5
9b	5.5	13.4		23.8	37.8	40.4	41.7		111.5
10a	5.5		17.4	23.9	37.7	40.7	41.7	75.6	111.6
10b	5.5	12.9		23.8	39.3	40.6	41.8		111.5
11a	5.6		18.7	24.0	34.9	38.8	42.0	78.5	112.0
11b	6.1	14.2		24.4	33.9	38.7	41.5		111.4
12a	5.5		17.2	23.8		38.2	41.5	75.8	111.5
12b	5.6	12.7		23.7	36.0		41.7		111.4
13a	5.8		17.4	24.0		39.8	41.3	77.1	111.8
13b	5.2	12.5		23.7	37.7		41.8		111.4
14a	5.7		17.6	24.1		39.8	41.4	77.1	111.8
14b	5.6	12.7		23.8	38.0		41.9		111.5
15a	5.2		17.6	23.7	38.4		41.1	71.3	111.4
15b	5.3	13.2		23.4		40.8	41.4		111.4

These results stand in sharp contrast to the uniformly high diastereoselectivities reported for additions of nucleophiles to the α,β-cyclopropyl ketone, bicyclo[6.1.0]nonan-2-one.[2] The high diasteroselectivities observed for this ketone were attributed to exposure of one face of the carbonyl to nucleophilic attack due to local conformational anchoring by the conjugated α,β-cyclopropyl carbonyl functional group array. As previously discussed, computational studies indicate that non-conjugated β,γ-cyclopropyl ketone **1** exists as a collection of low-energy conformers in which both faces of the carbonyl appear susceptible to nucleophilic attack. In accord with the Hammond postulate, high levels of diastereoselection are not to be anticipated, and experimental results have confirmed this expectation.

EXPERIMENTAL SECTION

All reactions were performed in flame-dried glassware under argon. Reaction mixtures were stirred magnetically. Hygroscopic liquids and solutions of reactive intermediates were transferred via syringe. Reaction product solutions were concentrated using a rotary evaporator at 30-40 mm Hg. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from CaH_2. Analytical thin-layer chromatography was performed on Merck glass-backed pre-coated plates (0.25 mm, silica gel 60, F-254). Visualization of spots was effected by treatment of the plate with a 2.5% solution of *para*-anisaldehyde in ethanol containing 6% H_2SO_4 and 2% acetic acid followed by charring on a hot plate. Gravity-driven column chromatography was performed on Merck silica gel 60 (70-230 mesh). Optical rotations were measured at 589 nm. NMR spectra were recorded in $CDCl_3$ solution. Proton and ^{13}C magnetic resonance spectra were recorded at 250.1 MHz and 62.9 MHz, respectively, using tetramethylsilane (0 ppm) and the center line of the chloroform-*d* triplet (77.0 ppm) as internal standards. Mass spectral analyses were carried out by the Mass Spectrometry Laboratory in the Department of Chemistry at the University of Arizona. X-ray crystallographic analyses were carried out by the Molecular Structure Laboratory in the Department of Chemistry at the University of Arizona. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

5-(Benzyloxy)cyclooctanone (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (4). A solution of 5-(benzyloxy)cyclooctanone (**2**)[11] (6.94 g, 29.9 mmol), 1,4-di-*O*-methyl-L-threitol (**3**)[12] (8.96 g, 59.7 mmol), and *p*-toluenesulfonic acid (0.57 g, 3 mmol) in dry benzene (500 mL) was heated to reflux under a Dean-Stark trap for 3 h, then cooled to room temperature and diluted with ether. The organic layer was washed with sat aq $NaHCO_3$ (2 x 300 mL), sat aq NaCl (300 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel 60 (250 g) eluted with 15% EtOAc/hexanes to give **4** (8.21 g, 22.5 mmol, 76%) as colorless oil homogeneous by tlc (R_f 0.09, 20% EtOAc/hexanes).

Spectral data for **4**: $[\alpha]^{24}_D$ 3.5° (*c* 0.85, $CHCl_3$); IR (neat) cm^{-1} 2929, 1451, 1366, 1027; ^1H NMR δ 1.50-2.10 (13, m), 3.38 (3, s), 3.39 (3, s), 3.49 (4, m), 3.89 (2, t), 4.48 (2, s), 7.26-7.33 (5, m); ^{13}C NMR δ 19.2, 19.3, 33.2, 33.9, 35.8, 36.6, 59.3 (x 2), 69.9, 73.1, 76.7, 76.8, 78.1, 113.0, 127.1, 127.3, 128.1, 138.1; MS (EI) *m/z* (relative intensity) 273 (9), 258 (24), 229 (17), 215 (22), 187 (73), 115 (86), 91 (100); HRMS (FAB+) calcd for $C_{21}H_{33}O_5$ (M+H) 365.2328, found 365.2334.

Anal. Calcd for $C_{21}H_{32}O_5$: C 69.20, H 8.85; found: C 69.30, H 8.88.

5-(*RS*)-5-(Benzyloxy)cyclooct-2-en-1-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (6). A solution of ketal **4** (7.88 g, 21.6 mmol) in dry THF (50 mL) was cooled to 0 °C and phenyltrimethylammonium tribromide (8.94 g, 23.8 mmol) was added in one portion. The mixture was allowed to attain room temperature and was vigorously stirred for 17 h. The mixture was then poured into 5% aq K_2CO_3 solution and was extracted with ether (5 x 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel 60 (250 g) eluted with 15% EtOAc/hexanes to give α-bromoketal **5** (9.32 g, 21.0 mmol, 97%) as colorless oil (R_f 0.25, 20% EtOAc/hexanes, two elutions). ^{13}C NMR indicated this product is a mixture of diastereomers.

To a well-stirred solution of α-bromoketal **5** (8.88 g, 20.0 mmol) in DMSO (10 mL) at room temperature was added sodium methoxide (5.41 g, 100 mmol). After 72 h, the resulting thick brown slurry was poured into sat aq NaCl solution (400 mL) and the mixture was extracted with hexanes (5 x 75 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel 60 (60 g) eluted with 10% EtOAc/hexanes to give **6** (6.22 g, 17.1 mmol, 86%) as a colorless oil homogeneous by tlc (R_f 0.61, 20% EtOAc/hexanes, five elutions).

Spectral data for **6**: IR (neat) cm^{-1} 3025, 1652, 1494, 1391, 1352; ^1H NMR δ 1.40-2.00 (6, m), 2.68 (2, m), 3.37 (3, s), 3.39 (3, s), 3.40-3.65 (6, m), 3.87-4.00 (2, m), 4.50 (2, s), 5.60-5.80 (2, m), 7.31-7.33 (5, m); ^{13}C NMR δ 17.3, 17.4, 29.0, 29.1, 29.8, 29.9, 40.1, 59.1, 59.2, 70.0, 72.9, 73.0, 73.6, 73.7, 76.7, 76.9, 77.3, 77.6, 78.9, 79.1, 110.1, 125.5, 127.1, 127.2, 128.1, 128.4, 128.6, 136.3, 136.4, 138.8. ^{13}C NMR indicated this product is a mixture of two diastereomers in approximately a 1:1 ratio.

Anal. Calcd for $C_{21}H_{30}O_5$: C 69.59, H 8.34; found: C 69.60, H 8.40.

(1*R*,6*RS*,8*R*)-6-(Benzyloxy)bicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (7). A suspension of zinc-copper couple[15] (10.66 g, 164.1 mmol) in ether (300 mL, freshly distilled from P_2O_5) was heated to reflux and diiodomethane (6.61 mL, 22.0 g, 82.1 mmol) and a small crystal of iodine were added. After two h a solution of ene ketal **6** (5.95 g, 16.4 mmol) in ether (80 mL) was added dropwise, and heating was continued for 18 h. The mixture was then cooled in an ice bath and sat aq K_2CO_3 (80 mL) was added dropwise. The brown solid residue was removed by filtration and was washed with methylene chloride (400 mL). The organic phase was separated, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel 60 (150 g) eluted with 20% EtOAc/hexanes to give **7** (5.38 g, 14.3 mmol, 87%) as a colorless oil homogeneous by tlc (R_f 0.64, 20% EtOAc/hexanes, five elutions).

Spectral data for **7**: IR (neat) cm^{-1} 3051, 2985, 1730, 1355, 1195; ^1H NMR δ 0.21-0.29 (1, m), 0.53-0.68 (1, m), 1.03-1.22 (2, m) 1.55-1.83 (5, m), 2.07-2.23 (4, m), 3.33 (3, s), 3.37 (3, s), 3.42-3.43 (2, m), 3.49-3.54 (2, m), 3.78-3.86 (2, m), 4.39-4.58 (2, m), 7.26-7.33 (5, m); ^{13}C NMR δ 5.2, 5.8, 10.3, 13.5, 14.9, 17.2, 23.5, 23.7, 28.0, 29.4, 30.3, 31.3, 41.8, 41.9, 59.4 (x 2), 69.9, 70.1, 73.3, 73.5, 75.6, 75.9, 78.2, 78.3, 78.8, 79.0, 111.7, 127.2, 127.4, 128.2, 139.3. ^{13}C NMR indicated this product is a mixture of two diastereomers in approximately a 1:1 ratio.

Anal. Calcd for $C_{22}H_{32}O_5$: C 70.18, H 8.57; found: C 69.89, H 8.53.

(1*R*,6*RS*,8*R*)-6-Hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (8). To a well-stirred solution of benzyl ether **7** (2.32 g, 6.18 mmol) in absolute ethanol (30 mL) was added 10% Pd/C (50 mg). The reaction flask was evacuated and flushed with H_2 gas five times. The mixture was then stirred under H_2 (1 atm) at room temperature for 10 h. The catalyst was removed by centrifugation. Volatiles were removed *in vacuo* and the residue was chromatographed on silica gel 60 (30 g) eluted with 40% EtOAc/hexanes to give **8** (1.75 g, 6.11 mmol, 99%) as a colorless oil homogeneous by tlc (R_f 0.12, 40% EtOAc/hexanes).

Spectral data for **8**: IR (CH_2Cl_2) cm^{-1} 3453, 3051, 2929, 1454, 1264, 1194, 1136, 1092, 981, 852, 779; ^1H NMR δ 0.13-0.29 (1, m), 0.42-0.58 (1, m), 0.93-1.10 (2, m), 1.38-1.92 (9, m), 2.35 (1, bs), 3.29 (3, s), 3.30

(3, s), 3.34-3.44 (4, m), 3.70-3.81 (2, m); ^{13}C NMR δ 5.2, 5.7, 9.7, 13.6, 17.4, 20.5, 23.4, 23.8, 32.1, 32.4, 34.2, 34.6, 41.8, 41.9, 59.4 (x 2), 71.3, 71.5, 73.3, 73.4, 75.6, 75.7, 79.0, 111.6, 111.8. ^{13}C NMR indicated this product is a mixture of two diastereomers in approximately a 1:1 ratio.

Anal. Calcd for $C_{15}H_{26}O_5$: C 62.92, H 9.15; found: C 63.30, H 9.43.

(1*R*,8*R*)-Bicyclo[6.1.0]nonan-2,6-dione 2-(2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butane-tetrol Ketal (1). To a well-stirred solution of alcohol **8** (1.63 g, 5.70 mmol) in dry CH_2Cl_2 (25 mL) was added PDC (4.29 g, 11.4 mmol) in one portion. After 7 h the mixture was diluted with ether and filtered. The filtrate was concentrated in *vacuo* and the residue was chromatographed on silica gel 60 (30 g) eluted with 20% EtOAc/hexanes to give **1** (0.94 g, 3.5 mmol, 59%) as a colorless oil homogeneous by tlc (R_f 0.12, 40% EtOAc/hexanes).

Spectral data for **1**: $[\alpha]^{24}_D$ -20.0° (*c* 15.5, ether); IR (CH_2Cl_2) cm^{-1} 3453, 2926, 1733, 1455, 1373, 1136, 1266, 1195, 1092, 958, 850, 735; ^{1}H NMR δ 0.39-0.48 (1, m), 0.72-0.81 (1, m), 1.00-1.17 (1, m), 1.31-1.42 (1, m), 1.57-1.71 (1, m), 1.79-2.05 (3, m), 2.41-2.81 (4, m), 3.36 (3, s), 3.42 (3, s), 3.47 (2, d, J = 4.8 Hz), 3.55 (2, d, J = 4.9 Hz), 3.84-3.90 (1, m), 3.96-4.01 (1, m); ^{13}C NMR δ 7.13, 13.3, 18.5, 23.5, 40.8, 41.3, 42.1, 59.3 (x 2), 72.9, 73.0, 75.5, 78.9, 110.5, 214.7. ^{13}C NMR indicated this product is a single diastereomer (>20:1).

Anal. Calcd for $C_{15}H_{24}O_5$: C 63.36, H 8.51; found: C 63.19, H 8.73.

(1*R*,6*RS*,8*R*)-6-Hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketals (8a and 8b). To a well-stirred suspension of $LiAlH_4$ (43 mg, 1.1 mmol) in ether (3 mL) at 0 °C was added a solution of **1** (110 mg, 0.39 mmol) in ether (1.5 mL) dropwise. After 20 min the reaction was quenched by successive additions of water (43 μL), 4N NaOH (43 μL), and water (129 μL). After stirring for 40 min, the white precipitate was removed by filtration. Volatiles were removed by distillation at atmospheric pressure to give a mixture of alcohols **8a** and **8b** as a colorless oil homogeneous by tlc (R_f 0.12, 40% EtOAc/hexanes). The yield was 106 mg (0.37 mmol, 95%). Spectral data were as given above.

General Procedure for Nucleophilic Additions. A three-necked flask was charged with THF (3-5 mL) and the nucleophile (ca 3 equiv) and cooled in a dry ice/isopropanol bath. A solution of ketone **1** (1 equiv) in THF (1 mL) was added dropwise and the reaction mixture was allowed to warm to the room temperature gradually. The reaction was then quenched by addition of sat aq NH_4Cl solution (2-3 mL) and the mixture was extracted with ether (4 x 20 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel 60 eluted with mixtures of EtOAc/hexanes to afford products.

(1*R*,6*S*,8*R*)-6-Hydroxy-6-methylbicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (9a) and (1*R*,6*R*,8*R*)-6-Hydroxy-6-methylbicyclo[6.1.0]-nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (9b). From ketone **1** (110 mg, 0.39 mmol) and methyllithium (0.4 M solution in ether, 2.8 mL, 1.1 mmol) was obtained a mixture of starting material (17 mg, 15%) and less polar and more polar diastereomeric alcohols **9a** and **9b**, respectively. The yield of **9a**, a pale yellow oil homogeneous by tlc (R_f 0.18, 40% EtOAc/hexanes), was 18 mg (0.05 mmol, 16%). The yield of **9b**, a white solid, mp 71-73 °C, homogeneous by tlc (R_f 0.12), was 72 mg (0.22 mmol, 64%).

Spectral data for **9a**: $[\alpha]^{23}_D$ -36.2° (*c* 1.05, $CHCl_3$); ^1H NMR δ 0.29-0.31 (1, m), 0.64-0.66 (1, m), 0.80-2.09 (11, m), 1.19 (3, s), 3.41 (3, s), 3.44 (3, s), 3.50-3.58 (4, m), 3.87-3.91 (2, m); ^{13}C NMR δ 5.5, 11.8, 18.0, 23.8, 29.1, 37.7, 40.1, 41.7, 59.4 (x 2), 73.3, 73.4, 74.0, 75.6, 78.9, 111.5; HRMS (FAB+) calcd for $C_{16}H_{29}O_5$ (M+H) 301.2015, found 301.2012, calcd for $C_{16}H_{27}O_4$ (M+H-H_2O) 283.1909, found 283.1913.

Spectral data for **9b**: $[\alpha]^{23}_D$ -26.6° (*c* 3.35, $CHCl_3$); IR (neat) cm^{-1} 3051, 2927, 2304, 1420, 1264, 1088, 948, 895, 737; ^1H NMR δ 0.17-0.29 (1, m), 0.45-0.58 (1, m), 0.61-0.72 (1, m), 0.90-1.06 (1, m), 1.20 (3, s), 1.41-1.76 (8, m), 2.04 (1, bs), 3.29 (3, s), 3.32 (3, s), 3.34-3.46 (4, m), 3.72-3.84 (2, m); ^{13}C NMR δ 5.5, 13.4, 16.2, 23.8, 29.2, 37.8, 40.4, 41.7, 59.3 (x 2), 73.2, 73.3, 73.6, 75.6, 78.7, 111.5.

(1*R*,6*S*,8*R*)-6-Butyl-6-hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (10a) and (1*R*,6*R*,8*R*)-6-Butyl-6-hydroxybicyclo[6.1.0]-nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (10b). From ketone **1** (110 mg, 0.39 mmol) and *n*-butyllithium (1.2 M solution in hexanes, 0.95 mL, 1.1 mmol) was obtained a mixture of starting material (16 mg, 15%) and less polar and more polar diastereomeric alcohols **10a** and **10b**, respectively. The yield of **10a**, a pale yellow oil homogeneous by tlc (R_f 0.23, 40% EtOAc/hexanes), was 22 mg (0.064 mmol, 17%). The yield of **10b**, a pale yellow oil homogeneous by tlc (R_f 0.20), was 71 mg (0.21 mmol, 55%).

Spectral data for **10a**: $[\alpha]^{23}_D$ -37.5° (*c* 1.31, $CHCl_3$); ^1H NMR δ 0.23-0.31 (1, m), 0.59-0.70 (1, m), 0.83-0.95 (2, m), 1.06-1.20 (4, m), 1.35-1.42 (8, m), 1.52-1.68 (2, m), 1.73-1.81 (4, m), 3.38 (3, s), 3.40 (3, s), 3.47-3.55 (4, m), 3.87-3.91 (2, m); ^{13}C NMR δ 5.5, 11.7, 14.1, 17.4, 23.3, 23.9, 25.2, 36.6, 37.7, 40.7, 41.7, 59.4 (x 2), 73.3, 73.5, 75.6, 75.7, 78.8, 111.6; HRMS (FAB+) calcd for $C_{19}H_{35}O_5$ (M+H) 343.2484, found 343.2496, calcd for $C_{19}H_{33}O_4$ (M+H-H_2O) 325.2379, found 325.2392.

Spectral data for **10b**: $[\alpha]^{23}_D$ -26.2° (*c* 3.20, $CHCl_3$); IR (neat) cm^{-1} 3050, 2970, 1314, 1090, 973, 739, 705; ^1H NMR δ 0.21-0.30 (1, m), 0.50-0.58 (1, m), 0.60-0.70 (1, m), 0.85 (3, t, J = 7.0 Hz), 1.00-1.10 (1, m), 1.16-1.85 (15, m), 3.31 (3, s), 3.34 (3, s), 3.41-3.50 (4, m), 3.76-3.88 (2, m); ^{13}C NMR δ 5.5, 12.9, 14.1, 15.9, 23.2, 23.8, 25.2, 35.0, 39.3, 40.6, 41.8, 59.3 (x 2), 73.2, 73.3, 75.1, 75.6, 78.7, 111.5; HRMS (FAB+) calcd for $C_{19}H_{35}O_5$ (M+H) 343.2484, found 343.2483, calcd for $C_{19}H_{33}O_4$ (M+H-H_2O) 325.2379, found 325.2369.

(1*R*,6*S*,8*R*)-6-(1,1-Dimethyl)ethyl-6-hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (11a) and (1*R*,6*R*,8*R*)-6-(1,1-Dimethyl)ethyl-6-hydroxybicyclo[6.1.0]-nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (11b). From ketone **1** (169 mg, 0.59 mmol) and *tert*-butyllithium (1.6 mL of a 1.5 M solution in pentane, 2.4 mmol) was obtained a mixture of less polar and more polar diastereomeric alcohols **11a** and **11b**, respectively, and recovered ketone **1**. Column chromatography gave **11a** and an inseparable mixture of **11b** and **1**. The yield of **11a**, a pale-yellow oil homogeneous by tlc (R_f 0.32, 40% EtOAc/hexanes), was 60 mg (0.18 mmol, 30%). The mixture of **11b** and ketone **1** was taken up in absolute ethanol under argon at 0 °C and treated with sodium borohydride (20 mg, 0.53 mmol). After stirring for 15 min at 0 °C, seven drops of glacial acetic acid were added and the mixture was transferred to a separatory funnel containing ether (50 mL). The resulting organic layer was washed with 1% aq HCl (20 mL), sat aq $NaHCO_3$ (20 mL), then dried ($MgSO_4$), filtered, and concentrated. Column chromatography gave **11b** and a mixture of **8a** and **8b**. The yield of **11b**, a pale-yellow oil homogeneous by tlc (R_f 0.27, 40% EtOAc/hexanes) was 51 mg (0.15 mmol, 25%). The yield of **8a** and **8b**, a colorless oil homogeneous by tlc (R_f 0.11, 40% EtOAc/hexanes) was 32 mg (0.11 mmol, 19%).

Spectral data for **11a**: $[\alpha]^{23}_D$ -19.3° (c 5.59, $CHCl_3$); IR (neat) cm^{-1} 3506, 2961, 1464, 1404, 1148, 1098; ^1H NMR δ 0.22-0.31 (1, m), 0.56-0.65 (1, m), 0.93 (9, s), 0.80-2.17 (11, m), 3.38 (3, s), 3.40 (3, s), 3.42-3.58 (4, m), 3.81-3.98 (2, m); ^{13}C NMR δ 5.6, 12.2, 18.7, 24.0, 26.2, 31.2, 34.9, 38.8, 42.0, 59.4 (x 2), 73.5, 73.6, 75.8, 78.5, 79.0, 112.0; HRMS (FAB+) calcd for $C_{19}H_{35}O_5$ (M+H) 343.2484, found 343.2487, calcd for $C_{19}H_{33}O_4$ (M+H-H_2O) 325.2379, found 325.2338.

Spectral data for **11b**: $[\alpha]^{23}_D$ -16.7° (c 6.53, $CHCl_3$); IR (neat) cm^{-1} 3489, 2963, 1472, 1387, 1140, 1080; ^1H NMR δ 0.18-0.26 (1, m), 0.50-0.61 (1, m), 0.85-2.00 (10, m), 1.01 (9, s), 2.25 (1, d, J = 15 Hz), 3.32-3.50 (4, m), 3.38 (3, s), 3.41 (3, s), 3.80-3.98 (2, m); ^{13}C NMR δ 6.1, 14.2, 16.0, 24.4, 26.8, 32.2, 33.9, 38.7, 41.5, 59.4, 59.5, 73.3, 75.7, 78.2, 78.7, 111.4; HRMS (FAB+) calcd for $C_{19}H_{35}O_5$ (M+H) 343.2484, found 343.2477, calcd for $C_{19}H_{33}O_4$ (M+H-H_2O) 325.2379, found 325.2360.

(1*R*,6*S*,8*R*)-6-Hydroxy-6-vinylbicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (12a) and (1*R*,6*R*,8*R*)-6-Hydroxy-6-vinylbicyclo[6.1.0]-nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (12b). From ketone **1** (100 mg, 0.35 mmol) and vinylmagnesium bromide (1.0 M solution in THF, 1.1 mL, 1.1 mmol) was obtained a mixture of less polar and more polar diastereomeric alcohols **12a** and **12b**, respectively. The yield of **12a**, a pale yellow oil homogeneous by tlc (R_f 0.19, 40% EtOAc/hexanes), was 20 mg (0.06 mmol, 19%). The yield of **12b**, a white solid, mp 68-69 °C, homogeneous by tlc (R_f 0.16), was 57 mg (0.19 mmol, 54%).

Spectral data for **12a**: $[\alpha]^{23}_D$ -30.1° (c 0.95, $CHCl_3$); ^1H NMR δ 0.29-0.36 (1, m), 0.62-0.71 (1, m), 1.10-1.31 (4, m), 1.70-1.92 (7, m), 3.37 (3, s), 3.41 (3, s), 3.47 (2, d, J = 4.6 Hz), 3.54 (2, d, J = 5.5 Hz), 3.81-3.86 (2, m), 5.15 (1, d, J = 11.9 Hz), 5.20 (1, d, J = 18.5 Hz), 6.06 (1, dd, J = 18.5 and 11.9 Hz); ^{13}C NMR δ 5.5, 11.4, 17.2, 23.8, 35.5, 38.2, 41.5, 59.3 (x 2), 73.2, 73.4, 75.6, 75.8, 78.9, 111.5, 111.9, 145.1; HRMS (FAB+) calcd for $C_{17}H_{29}O_5$ (M+H) 313.2015, found 313.2029, calcd for $C_{17}H_{27}O_4$ (M+H-H_2O) 295.1909, found 295.1917.

Spectral data for **12b**: $[\alpha]^{23}_D$ -38.9° (c 2.7, $CHCl_3$); IR (neat) cm^{-1} 3033, 2981, 2884, 1264, 1135, 1093, 929, 895; ^1H NMR δ 0.29-0.36 (1, m), 0.53-0.68 (1, m), 0.70-0.82 (1, m), 1.10-1.31 (5, m), 1.46-1.90 (6, m), 3.38 (3, s), 3.41 (3, s), 3.46-3.52 (4, m), 3.81-3.86 (2, m), 5.06 (1, d, J = 11.9 Hz), 5.25 (1, d, J = 18.5 Hz), 6.06 (1, dd, J = 18.5 and 11.9 Hz); ^{13}C NMR δ 5.6, 12.7, 15.6, 23.7, 36.0, 37.9, 41.7, 59.3 (x 2), 73.2, 73.3, 75.3, 75.6, 78.7, 111.4, 111.9, 145.3; HRMS (FAB+) calcd for $C_{17}H_{29}O_5$ (M+H) 313.2024, found 313.2029, calcd for $C_{17}H_{27}O_4$ (M+H-H_2O) 295.1909, found 295.1916.

(1*R*,6*S*,8*R*)-6-Hydroxy-6-phenylbicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (13a) and (1*R*,6*R*,8*R*)-6-Hydroxy-6-phenylbicyclo[6.1.0]-nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (13b). From ketone **1** (111 mg, 0.39 mmol) and phenyllithium (1.8 M solution in ether, 0.58 mL, 1.1 mmol) was obtained a mixture of less polar and more polar diastereomeric alcohols **13a** and **13b**, respectively. The yield of **13a**, a pale yellow oil homogeneous by tlc (R_f 0.11, 25% EtOAc/hexanes), was 24 mg (0.065 mmol, 17%). The yield of **13b**, a pale yellow oil homogeneous by tlc (R_f 0.07), was 95 mg (0.26 mmol, 67%).

Spectral data for **13a**: $[\alpha]^{23}_D$ -35.6° (c 1.05, $CHCl_3$); ^1H NMR δ 0.38-0.47 (1, m), 0.66-0.79 (1, m), 0.80-1.31 (3, m), 1.37-2.38 (8, m), 3.37 (3, s), 3.41 (3, s), 3.44-3.59 (4, m), 3.87-3.91 (2, m), 7.21-7.36 (3, m), 7.47-7.51 (2, m); ^{13}C NMR δ 5.8, 11.9, 17.4, 24.0, 36.3, 39.8, 41.3, 59.4 (x 2), 73.4, 73.6, 75.8, 77.1, 79.0, 111.8, 125.6, 126.9, 128.0, 148.0; HRMS (FAB+) calcd for $C_{21}H_{31}O_5$ (M+H) 363.2171, found 363.2162, calcd for $C_{21}H_{29}O_4$ (M+H-H_2O) 345.2066, found 345.2079.

Spectral data for **13b**: $[\alpha]^{23}_D$ -29.5° (*c* 4.0, $CHCl_3$); IR (neat) cm^{-1} 3581, 3051, 2984, 2927, 2303, 1696, 1444, 1264, 1090, 965; ^1H NMR δ 0.23-0.38 (1, m), 0.45-0.61 (1, m), 0.80-1.33 (3, m), 1.53-2.41 (8, m), 3.30 (3, s), 3.31 (3, s), 3.40-3.48 (4, m), 3.76-3.86 (2, m), 7.15-7.28 (3, m), 7.47-7.50 (2, m); ^{13}C NMR δ 5.2, 12.5, 15.9, 23.7, 37.7, 37.9, 41.8, 59.3 (x 2), 73.1 (x 2), 75.6, 76.6, 78.7, 111.4, 125.5, 126.7, 127.9, 148.2; HRMS (FAB+) calcd for $C_{21}H_{31}O_5$ (M+H) 363.2171, found 363.2185, calcd for $C_{21}H_{29}O_4$ (M+H-H_2O) 345.2066, found 345.2075.

(1*R*,6*S*,8*R*)-6-[4-(1,1'-Biphenyl)]-6-hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (14a) and (1*R*,6*R*,8*R*)-6-[4-(1,1'-Biphenyl)]-6-hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (14b). From ketone **1** (109 mg, 0.38 mmol) and 4-biphenylmagnesium bromide, prepared by addition of 4-bromobiphenyl (448 mg, 1.92 mmol) to a mixture of magnesium shavings (57 mg, 2.4 mmol) and a crystal of iodine in THF (3 mL) at reflux, was obtained a mixture of less polar and more polar diastereomeric alcohols **14a** and **14b**, respectively. The yield of **14a**, a white solid, mp 81 °C, homogenous by tlc (R_f 0.17, 37% EtOAc/hexanes), was 42 mg (0.10 mmol, 26%). The yield of **14b**, a pale yellow oil homogenous by tlc (R_f 0.13, 37% EtOAc/hexanes), was 82 mg (0.19 mmol, 50%).

Spectral data for **14a**: $[\alpha]^{23}_D$ -4.63° (*c* 0.36, Et_2O); IR (neat) cm^{-1} 3441, 2925, 1492, 1440, 1195, 1143, 1090; ^1H NMR δ 0.38-0.45 (1, m), 0.69-0.80 (1, m), 1.15-1.90 (7, m), 2.07-2.40 (4, m), 3.39 (3, s), 3.42 (3, s), 3.40-3.51 (2, m), 3.52-3.60 (2, m), 3.85-3.98 (2, m), 7.30-7.62 (9, m); ^{13}C NMR δ 5.7, 12.0, 17.6, 24.1, 36.5, 39.8, 41.4, 59.5 (x 2), 73.4, 73.7, 75.8, 77.1, 79.0, 111.8, 126.1, 126.8, 127.0, 127.2, 128.7, 139.8, 140.8, 147.2; HRMS (FAB+) calcd for $C_{27}H_{35}O_5$ (M+H) 439.2484, found 439.2431, calcd for $C_{27}H_{33}O_4$ (M+H-H_2O) 421.2379, found 421.2383.

Spectral data for **14b**: $[\alpha]^{23}_D$ -26.4° (*c* 1.4, Et_2O); IR (neat) cm^{-1} 3441, 2925, 1484, 1440, 1300, 1090; ^1H NMR δ 0.31-0.36 (1, m), 0.49-0.56 (2, m), 1.13-1.25 (2, m), 1.60-2.21 (9, m), 2.37-2.43 (1, m), 3.40 (6, s), 3.45-3.60 (2, m), 3.84-3.98 (2, m), 7.31-7.35 (1, m), 7.42 (2, t, J = 7.5), 7.56-7.66 (6, m); ^{13}C NMR δ 5.6, 12.7, 16.0, 23.8, 38.0, 38.1, 41.9, 59.4, 59.5, 73.3, 75.8, 76.7, 78.9, 111.5, 126.1, 126.8, 127.0, 127.1, 128.7, 139.8, 140.7, 147.3; HRMS (FAB+) calcd for $C_{27}H_{35}O_5$ (M+H) 439.2484, found 439.2465, calcd for $C_{27}H_{33}O_4$ (M+H-H_2O) 421.2379, found 421.2397.

The structure of **14a** was confirmed by single crystal X-ray analysis.

(1*R*,6*S*,8*R*)-6-(1-Hexynyl)-6-hydroxybicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (15a) and (1*R*,6*R*,8*R*)-6-(1-Hexynyl)-6-hydroxy-bicyclo[6.1.0]nonan-2-one (2*S*,3*S*)-1,4-Di-*O*-methyl-1,2,3,4-butanetetrol Ketal (15b). From ketone **1** (110 mg, 0.39 mmol) and 1-lithiohexyne, prepared from lithium diisopropylamide (1.5 M solution in hexanes, 0.63 mL, 0.95 mmol) and 1-hexyne (152 mL, 110 mg, 1.3 mmol), was obtained a mixture of less polar and more polar diastereomeric alcohols **15a** and **15b**, respectively. The yield of **15a**, a pale yellow oil homogeneous by tlc (R_f 0.35, 40% EtOAc/hexanes), was 21 mg (0.057 mmol, 15%). The yield of **15b**, a pale yellow oil homogeneous by tlc (R_f 0.32), was 104 mg (0.28 mmol, 73%).

Spectral data for **15a**: $[\alpha]^{23}_D$ -21.7° (*c* 2.75, $CHCl_3$); ^1H NMR δ 0.22-0.31 (1, m), 0.52-0.68 (1, m), 0.75-2.10 (15, m), 0.85 (3, t, J = 7.0 Hz), 2.12 (2, t, J = 6.7 Hz), 3.34 (3, s), 3.35 (3, s), 3.43-3.49 (4, m), 3.80-

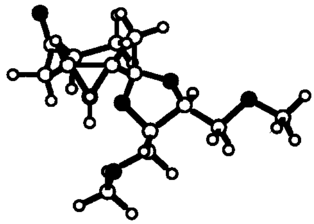
3.84 (2, m); ^{13}C NMR δ 5.2, 10.9, 13.4, 17.6, 18.2, 21.6, 23.7, 30.6, 38.4, 39.4, 41.1, 59.3 (x 2), 71.3, 73.2, 73.3, 75.6, 78.9, 82.9, 85.0, 111.4; HRMS (FAB+) calcd for $C_{21}H_{35}O_5$ (M+H) 367.2484, found 367.2485, calcd for $C_{21}H_{33}O_4$ (M+H-H_2O) 349.2379, found 349.2389.

Spectral data for **15b**: $[\alpha]^{23}_D$ -17.8° (*c* 9.6, $CHCl_3$); IR (neat) cm^{-1} 3448, 3051, 2927, 1630, 1453, 1376, 1293, 1264, 1089, 974, 852, 738; ^1H NMR δ 0.25-0.32 (1, m), 0.53-0.59 (1, m), 0.75-2.10 (15, m), 0.81 (3, t, J = 7.0 Hz), 2.11 (2, t, J = 6.8 Hz), 3.28 (3, s), 3.31 (3, s), 3.37-3.45 (4, m), 3.76-3.79 (2, m); ^{13}C NMR δ 5.3, 13.2, 13.4, 15.7, 18.1, 21.7, 23.4, 30.7, 37.4, 40.8, 41.4, 59.2 (x 2), 71.0, 73.1 (x 2), 75.6, 78.7, 83.2, 85.0, 111.4; HRMS (FAB+) calcd for $C_{21}H_{35}O_5$ (M+H) 367.2484, found 367.2491, calcd for $C_{21}H_{33}O_4$ (M+H-H_2O) 349.2379, found 349.2376.

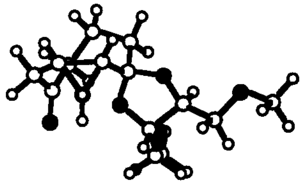
Acknowledgment. Partial support of this research by Research Corporation, by the Elsa U. Pardee Foundation, by the E. I. DuPont de Nemours Company, and by the University of Arizona through the Materials Characterization Program and the Office of the Vice President for Research are gratefully acknowledged. Assistance from Dr. Michael Bruck of the Molecular Structure Laboratory is gratefully acknowledged.

REFERENCES AND NOTES

1. Mash, E. A.; Gregg, T. M.; Stahl, M. T.; Walters, W. P. *J. Org. Chem.* **1996**, *61*, 2738-2742.
2. Part 2: Mash, E. A.; Gregg, T. M.; Kaczynski, M. A. *J. Org. Chem.* **1996**, *61*, 2743-2752.
3. Enantiomerically enriched bicyclo[m.1.0]alkan-2-ones **1** are readily prepared from 2-cycloalken-1-one ketals; see (a) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679-692. (b) Mash, E. A.; Torok, D. S. *J. Org. Chem.* **1989**, *54*, 250-253. Mash, E. A.; Math, S. K.; Arterburn, J. A. *J. Org. Chem.* **1989**, *54*, 4951-4953. (c) Yeh, S.-M.; Huang, L.-H.; Luh, T.-Y. *J. Org. Chem.* **1996**, *61*, 3906-3908.
4. (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981-3996. (b) Still, W. C. In *Current Trends in Organic Synthesis*; Pergamon Press: Tokyo, Japan, 1982; pp 233-246.
5. (a) *BATCHMIN, 4.0*; Columbia University: New York, 1993. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comp. Chem.* **1990**, *11*, 440-467.
6. Conformers with carbonyls disposed so that the *Re* face is clearly more exposed to attack include **1**-11 (0.6%), **1**-18 (0.3%), **1**-19 (0.3%), **1**-29 (0.1%), **1**-36 (0.1%), **1**-43 (0.1%), and **1**-45 (0.1%). Conformer **1**-40 (0.1%) is the lowest energy conformer in which the *Si* face is clearly more exposed to attack.



conformer 11



conformer 40

7. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994, pp 731-737 and references cited in therein.
8. The conformational ensemble for cyclohexanone was obtained using a Monte Carlo search strategy and the MM2* force field resident in BATCHMIN v4.0.
9. (a) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563-1572. (b) Bürgi, H.-B. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 460-473.
10. Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521-546.
11. 5-(Benzyloxy)cyclooctanone (**2**) can be prepared in large quantities in two steps from *cis*-1,5-cyclooctanediol; see McMurry, J. E.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 10167-10173.
12. Schmidt, M.; Amstutz, R.; Crass, G.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1691-1707.
13. Marquet, A.; Jacques, J. *Bull. Soc. Chim. Fr.* **1962**, 90-96.
14. Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183-2186.
15. Preparation of zinc-copper couple: Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825-1826.

(*Received in USA* 21 *February* 1997; *accepted* 21 *May* 1997)