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Stereochemistry of Electrophilic Attack on the Putative Carbanion Intermediate in the Base-Catalyzed Ketonization of 3,7-Dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol. Evidence against an S_E1 Mechanism for Ketonization

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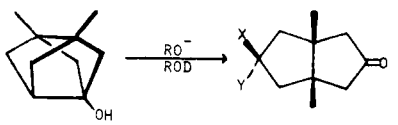
Abstract: The putative carbanion intermediate (**7**) in the base-catalyzed ketonization of 3,7-dimethyltricyclo[3.3.0.0^{3,7}]octan-1-ol (**1**) has been generated by oxidation of the epimeric hydrazines (**6**) in the presence of base. The hydrazines were synthesized by a five-step sequence starting from 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione (**3**). From either epimer of **6** deuterium capture in D_2O and in $(CH_2OD)_2$ by the carbanion **7** is nearly stereorandom, and ketalization of the carbonyl group in **7** has little effect on this result. The nearly stereorandom electrophilic attack on **7** contrasts with the essentially stereospecific incorporation of deuterium in the base-catalyzed ketonization of **1** to **2a**. The retention of configuration observed in the ketonization of **1** and the contrasting stereorandom deuterium capture by **7** are both most economically accommodated by an S_E2 mechanism for the transformation of **1** to **2a**, although an S_E1 process is not totally excluded.

Several years ago we reported that the base-catalyzed ketonization of the tricyclic alcohol **1** gives only **2a** and that this



1 **2a**, X = H, Y = D; **b**, X = D, Y = H

stereochemical outcome is independent of the solvent in which the reaction is run.[1] Subsequent studies[2] have shown that retention of configuration is apparently a general result for the base-catalyzed ketonization of polycyclic alcohols that do not contain cyclopropanol rings.[3]

The stereochemical course of the ketonization of polycyclic alcohols like **1** stands in marked contrast to the results obtained by Cram and co-workers[4] with acyclic alcohols. They observed retention only in solvents of low dielectric constant (e.g., *tert*-butyl alcohol), while inversion predominated in solvents of high dielectric constant and with good proton-donating ability (e.g., ethylene glycol). An S_E1 mechanism, involving the formation of a carbanion intermediate, nicely rationalizes the dependence of stereochemistry on solvent found in Cram's studies.[4]

There are two alternative explanations for the stereochemistry observed in the base-catalyzed ketonization of **1.** (a) The mechanism is S_E1, but for some reason electrophilic attack on the putative carbanion intermediate (**7**) proceeds with retention of configuration, independent of solvent.[5] (b) The mechanism is S_E2 with retention being a consequence of the cyclic transition state that is expected to be favored for a concerted reaction of this type.[6] In order to differentiate between these two possibilities, we have generated the putative S_E1 intermediate by an independent route and determined the stereochemistry of deuterium capture by **7.**

Results

Cram and co-workers have shown that oxidation of 2-phenyl-2-butylhydrazine in the presence of base generates the 2-phenyl-2-butyl carbanion and that the stereochemistry of protonation roughly parallels that observed when the same carbanion is formed from an alcohol by base-catalyzed ketonization.[7] Stille and co-workers have used hydrazine oxidation in base to generate several bicyclic carbanions.[8] Therefore, we chose to synthesize the epimeric hydrazines **6** as the precursors of the carbanion **7.**

The hydrazines **6** were prepared from 1,5-dimethylbicyclo[3.3.0]octane-3,7-dione (**3**)[9] by the route shown in Scheme I. The diketone **3** was refluxed in benzene with 1.5 equiv of ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid to give a mixture of **3** (7%), the desired monoketal (54%), and diketal (39%). Reduction of this mixture, followed by column chromatography on activity III basic alumina,[11] permitted the isolation of the epimeric hydroxyketals **4.** Partial separation of the slower moving **4a** from its *exo* isomer **4b** could be achieved, but only with inefficiency sufficient to render more practical the use of enriched mixtures in lieu of the pure epimers. With L-Selectride as the reducing agent, 88% epimerically pure **4a** could be obtained from **3** in 43% yield. Use of aluminum isopropoxide provided 73% epimerically pure **4b** in 27% yield. Since the diketal was recovered unchanged from these reductions and hydrolyzed back to **3** for recycling, the

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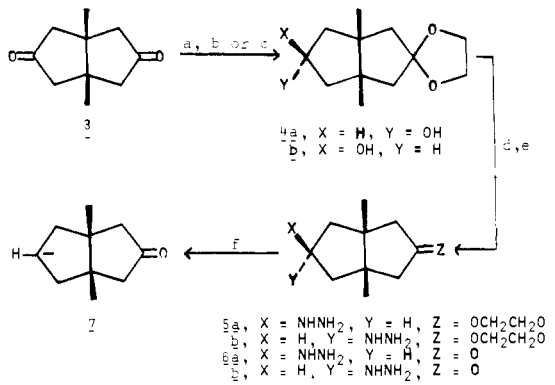
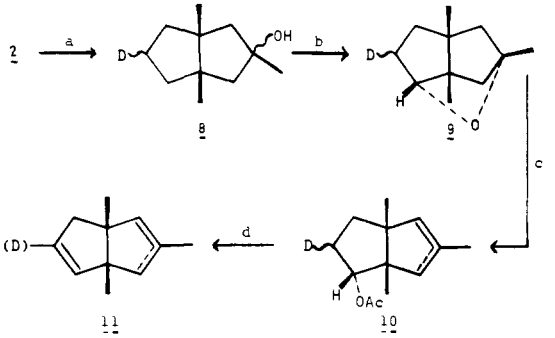
Scheme I



[a] (a) 1.5 equiv $(CH_2OH)_2$, TsOH, PhH, reflux, Dean-Stark. (b) $LiB[CH(CH_3)CH_2CH_3]_3H$, THF, −78°. (c) $Al[OCH(CH_3)_2]_3$, $(CH_3)_2CHOH$, reflux. (d) TsCl, Py. (e) N_2H_4, reflux. (f) KIO_4, 4 equiv RO^- in ROD.

Scheme II



[a] (a) CH_3Li, ether. (b) $Pb(OAc)_4$, $CaCO_3$, PhH. (c) Ac_2O, BF_3, ether. (d) 500°.

yields of **4a** and **4b** based on diketone consumed were considerably higher than those reported above.

The stereochemistry of the hydroxyketals **4** was suggested by the stereoselectivity of the reductions and by the fact that the methyl protons in the compound assigned the endo configuration (**4a**) appeared at higher field than the methyl protons in the molecule assigned the exo configuration (**4b**). This stereochemical assignment was confirmed by Eu(fod)$_3$ shift reagent studies.

The hydroxyketals **4** were converted in 82% yield to the tosylates, which were refluxed in anhydrous hydrazine for 1 h. The reaction mixtures were poured into deionized water, 1 M in NaOH, and the alkylhydrazines **5** extracted into CH_2Cl_2. The use of deionized water proved essential, since trace amounts of metals catalyzed the decomposition of the hydrazines in basic solution, resulting in greatly reduced yields. The crude hydrazines were obtained in 84% yield on evaporation of the CH_2Cl_2. They were converted to the oxalate salts for purification by recrystallization and for storage.

The transformation of **4** to **5** proved stereospecific. Since the displacement of tosylate by hydrazine is therefore indicated to proceed by an S_N2 mechanism, it is certainly reasonable to assume inversion of configuration in this reaction. With the stereochemistry of the hydroxyketals **4** assigned, the configurations of the hydrazines **5** are thus established.

The ketal group was removed from **5** by stirring the oxalate salts for 8 h in deionized water. Monitoring the deketalization by NMR showed the reaction to be complete. For carbanion generation in D_2O deketalization was accomplished in this solvent, and to the resulting solution of **6** was added an NaOD solution and KIO_4. For carbanion generation in $(CH_2OD)_2$ the aqueous solution of the oxalate salt of **6** was made 1 M in NaOH and **6** was extracted into CH_2Cl_2. This solution of **6** was dried and partially evaporated. Since polymerization of **6** was observed in concentrated solutions, $(CH_2OD)_2$ was added before removal of the CH_2Cl_2 was completed. The $(CH_2OD)_2$ solution of **6** was then oxidized.

Oxidations were carried out at 25-35 °C, using 1 mol of KIO_4 and at least 4 mol of base for each mol of hydrazine (**6**). For reactions in D_2O, where solutions of the oxalate salt of **6** were employed for carbanion generation, an additional 2 equiv of base was added to neutralize the acidic protons provided by the oxalic acid. Oxidation of **5** in both D_2O and $(CH_2OD)_2$ was also carried out, in order to test the effect of carbonyl group ketalization on the stereochemistry of deuterium incorporation. Since solutions of the oxalate salt of **5** were used in these reactions, an additional 2 equiv of base was again added.

Following oxidation of **5**, the ketal group was removed from the product by stirring it in THF containing aqueous H_2SO_4. The deuterium content of the ketone **2** was then determined by mass spectrometry. When **6** was oxidized, the exchangeable deuterium was removed from the positions α to the carbonyl group in **2** prior to mass spectrometric analysis. Control experiments established that stirring the ketone for 2 h in methanol containing sodium methoxide effected complete removal of the exchangeable deuterium.

Mass spectrometry indicated that the incorporation of a single nonexchangeable deuterium in **2** was 90-95% for oxidations in D_2O and 82-83% for oxidations in $(CH_2OD)_2$. The percentage of deuterium incorporation did not depend significantly on whether **5** or **6** was oxidized, nor did it increase when the oxidation was carried out with as many as 20 equiv of base present. The latter observation suggests that the less than quantitative incorporation of deuterium is not due to a competitive free-radical pathway for decomposition of the presumed[7] alkyldiimide intermediate in the oxidations.[12] Instead, it would appear that there is an isotope effect associated with proton capture by the carbanion. Stille has also reported the observation of such apparent isotope effects for deuterium capture by carbanions formed via hydrazine oxidations in base.[8]

The stereochemistry of deuterium incorporation in **2** was determined by the method used previously,[1] which is outlined in Scheme II. Methyllithium converted **2** to a 1:1 mixture of epimeric alcohols (**8**). Although the epimers have been separated and identified by shift-reagent studies,[13] the mixture can be used for the next step, since both epimers undergo lead tetraacetate oxidation to the tricyclic ether **9.** Epimerizations in lead tetraacetate oxidations have been observed with other alcohols.[14]

A qualitative indication of the stereochemistry of deuterium incorporation could be gleaned from the NMR spectrum of the endo isomer of the alcohol **8** in the presence of shift reagents[13] or from the splitting of the methine proton signal in the NMR spectrum of **9.**[1] However, a much more quantitative assay was obtained by opening the tricyclic ether **9** to the mixture of endo acetates **10.** The methyl group added to **2** provided the desired regioselectivity in the ether cleavage by boron trifluoride-acetic anhydride,[15] and a mixture of two double-bond isomers resulted from deprotonation of the tertiary carbocation intermediate. The isomers were not separated but were pyrolyzed together at 500 °C in a well-seasoned flow system to yield a mixture of the two expected bicyclo[3.3.0]-octadienes (**11**). Acetate pyrolysis was anticipated to result in cis elimination,[16] so the difference between the deuterium content of **10** and **11** yielded the amount of endo deuterium present in **10.** Mass spectrometry demonstrated that the deuterium content remained constant throughout the conversion of **2** to **10;** consequently, it was assumed that the stereochem-

Table I. Stereochemistry of Deuterium Incorporation in **2** on Hydrazine Oxidation in the Presence of Base

hydrazine	stereochemistry (**a**:**b**)	solvent/base	product (**2a**:**2b**)
6	85:15	D_2O/NaOD	45:55
	36:64		40:60
5	80:20		42:58
6	82:18	$(CH_2OD)_2$/	49:51
	27:73	$KO(CH_2)_2OD$	55:45
	27:73		55:45
5	87:13		42:58

ical disposition of deuterium in the two compounds was identical. The reliability of this method for determining the stereochemistry of deuterium incorporation in **2** has been previously demonstrated on samples known by NMR techniques to contain predominantly endo deuterium.[1,13]

The results of this analysis of the stereochemistry of deuterium incorporation in **2** are shown in Table I. Inspection of this data shows that the stereochemistry of capture of deuterium by **7** is nearly random in both D_2O and $(CH_2OD)_2$ and does not depend critically on which hydrazine epimer is used to generate **7**. Moreover, nearly stereorandom deuterium capture is observed whether the carbonyl group in **7** is free or protected as the ethylene ketal.

Discussion

The lack of stereoselectivity in deuterium capture by **7** stands in stark contrast to the essentially stereospecific deuterium incorporation observed when **2a** is formed by base-catalyzed ketonization of **1**. It is tempting to conclude, therefore, that **7** is not an intermediate in the base-catalyzed ketonization of **1**, thus excluding an S_E1 mechanism for this reaction. However, an S_E1 mechanism for the ketonization of **1** is still possible, provided that the putative carbanion intermediate formed from **1** is solvated differently from the carbanion generated by basic oxidation of **6** and that deuterium capture is faster than interconversion of the two carbanions.

It might be argued, for instance, that in the ketonization of **1** by an S_E1 mechanism the carbanionic center would be generated in proximity to the carbonyl group, which could provide some stabilization for the negative charge. Deuterium capture by such a carbonyl stabilized carbanion might occur with endo stereochemistry for the same reason that a cyclic transition state is expected to be preferred in an S_E2 mechanism.[6]

In an S_E1 mechanism a carbanion is generated in the rate-determining step. Therefore, in the carbonyl stabilized carbanion version of the S_E1 mechanism for ketonization of **1** to **2a**, the putative intermediate must have the bond between the carbonyl and carbanionic centers sufficiently broken that rebonding does not occur. However, the data reported in Table I require that these centers must remain in sufficiently close proximity for their interaction to result in stereospecific endo capture of deuterium by the carbanion. Although the existence of such an intermediate is not precluded, we feel that the available experimental data are more economically accommodated by an S_E2 mechanism.

The stereospecific incorporation of deuterium with retention of configuration in the base-catalyzed ketonization of **1** and the contrasting, nearly stereorandom, deuterium capture by **7** are both expected, if the transformation of **1** to **2a** proceeds by an S_E2 mechanism. The operation of such a mechanism in this reaction seems not unreasonable, since the putative carbanion formed in an S_E1 process would be a much higher energy intermediate than the benzylic carbanions generated in the ketonizations studied by Cram.[4] An S_E2 mechanism should at least be considered as a possibility for the ketonization of other polycyclic alcohols,[2,3] where carbanions would also represent intermediates of relatively high energy.

Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are reported uncorrected. IR spectra were obtained on a Beckman Acculab-4 spectrometer and were calibrated with a polystyrene film. NMR spectra were obtained on Varian EM-360A and EM-360L spectrometers, using Me_4Si as an internal standard. Exact mass measurements were made on an AEI-MS9 mass spectrometer, interfaced to a PDP-12 computer, using perfluorokerosene mass standards. Isotopic ratio measurements were carried out on the same instrument and also on a Searle Scientific Research Instruments spectrometer, equipped with a chemical ionization source. Control studies showed that, when the same sample was run on both instruments, comparable isotopic ratios were obtained. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N.Y. All solvents were distilled, and reactions were carried out under atmospheres of nitrogen or argon.

1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione Monoethylene Ketal. Diketone **3**[9] (8.7 g, 52 mmol), ethylene glycol (4.87 g, 78 mmol), and *p*-toluenesulfonic acid (0.915 g) were dissolved in 100 mL of dry benzene in a 150-mL round-bottom flask, equipped with a Dean-Stark trap. The reaction mixture was refluxed for 5 h, cooled, and dried over potassium carbonate, and the benzene was evaporated at reduced pressure, leaving 11.72 g of liquid residue. Careful integration of the NMR spectrum of the product mixture showed it to contain **3** (7%), monoketal (54%), and diketal (39%). The NMR ($CDCl_3$) of the monoketal showed δ 1.13 (s, 6 H), 1.76 (d, 2 H, J = 14 Hz), 2.11 (s, 4 H), 2.19 (d, 2 H, J = 14 Hz), 3.85 (s, 4 H). The NMR ($CDCl_3$) of the diketal showed δ 1.04 (s, 6 H), 1.76 (d, 4 H, J = 14 Hz), 2.19 (d, 4 H, J = 14 Hz), 3.85 (s, 8 H).

7-Hydroxy-1,5-dimethylbicyclo[3.3.0]octane-3-one Ethylene Ketal. A. By Reduction with L-Selectride to Yield Predominantly the Endo Isomer (4a). To a round-bottom flask were added 5.89 g of ketal mixture and 10 mL of dry tetrahydrofuran (THF). The solution was cooled to −78 °C, and 24.6 mL of a 1 M solution of L-Selectride (1.3 equiv based on the carbonyl estimated to be present in the ketal mixture) was slowly added. The solution was stirred at −78 °C for 3 h, and then 18 mL of 3 M NaOH was added, followed by 23 mL of 30% hydrogen peroxide. The peroxide was added slowly enough so that the vigorous reaction that occurred as the organoborane was oxidized did not become violent. The solution was then allowed to warm to room temperature and extracted with five 50-mL portions of CH_2Cl_2. The organic extracts were washed with water and dried over magnesium sulfate. Removal of solvent under reduced pressure gave 5.1 g of a mixture of diketal, **4a, 4b,** and diols. This mixture was separated by column chromatography on 130 g of basic alumina (Woelm), deactivated to activity III.[11] The column was eluted with a benzene–chloroform solvent gradient. Diketal was eluted with pure benzene. Fractions enriched in **4b** preceded those enriched in **4a**. After combination of the latter fractions, 2.5 g (43% from **3**) of a mixture of 88% **4a** and 12% **4b** was obtained. The NMR spectrum of **4a** ($CDCl_3$) showed δ 0.97 (s, 6 H), 1.73–3.05 (m, 9 H), 3.87 (s, 2 H), 3.88 (s, 2 H), 4.22 (m, 1 H).

Exact mass. Calcd for $C_{12}H_{20}O_3$: 212.1423. Found: 212.1418.

B. By Reduction with Aluminum Isopropoxide to Yield Predominantly the Exo Isomer (4b). Aluminum isopropoxide was prepared by the method described by Fieser and Fieser.[17] To 3.64 g (1.3 equiv) of this reagent in 32 mL of 2-propanol was added 4.57 g of ketal mixture. The solution was heated at reflux for 2.5 h and then poured into 150 mL of water. The aqueous mixture was extracted with three 100-mL portions of CH_2Cl_2, and the organic extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate. Solvent removal under reduced pressure afforded 3.5 g of product mixture, which was chromatographed as described above. Combination of fractions enriched in **4b** yielded 1.24 g (27% from **3**) of a mixture containing 27% **4a** and 73% **4b**. The NMR spectrum ($CDCl_3$) of **4b** showed δ 1.10 (s, 6 H), 1.39–3.05 (m, 9 H), 3.89 (s, 4 H), 4.34 (m, 1 H).

Tosylate of 4. To 2.373 g (11.2 mmol) of a mixture of **4a** and **4b** in 30 mL of dry pyridine was added 15.7 mmol of recrystallized tosyl chloride. The reaction mixture was stirred for 48 h at ambient temperature. Following the addition of 0.3 mL of water, stirring was continued for an additional 20 min. The reaction mixture was then poured into 130 mL of ether, which was extracted with three 70-mL

portions of 1 M HCl, washed with saturated sodium carbonate solution, and dried over magnesium sulfate. Solvent removal at reduced pressure yielded 3.374 g (82%) of a mixture of exo and endo tosylates. The ratio of the resonances for the bridgehead methyl groups in the epimeric mixture was the same as that in the mixture of **4a** and **4b** from which the tosylates were formed. The NMR spectrum ($CDCl_3$) of the endo tosylate showed δ 0.93 (s, 6 H), 1.65–2.37 (m, 8 H), 2.52 (s, 3 H), 3.91 (s, 4, H), 5.04 (m, 1 H), 7.41 (d, 2 H, J = 8 Hz), 7.87 (d, 2 H, J = 8 Hz). The spectrum ($CDCl_3$) of the exo isomer showed δ 1.08 (s, 6 H), 1.50–2.37 (m, 8 H), 2.48 (s, 3 H), 3,84 (s, 4 H), 5.07 (m, 1 H), 7.41 (d, 2 H, J = 8 Hz), 7.87 (d, 2 H, J = 8 Hz).

Exact mass. Calcd for $C_{19}H_{26}O_5S$: 366.1466. Found: 366.1482.

7-Hydrazino-1,5-dimethylbicyclo[3.3.0]octan-3-one Ethylene Ketal (5). A mixture of 3.374 g (9.22 mmol) of the tosylate of **4** and 25 mL of hydrazine (Baker 95%, dried over NaOH and distilled under reduced pressure[18]) was refluxed for 1 h. After cooling to ambient temperature, the hydrazine solution was poured into 50 mL of deionized water, 1 M in NaOH, which was extracted with three 50-mL portions of CH_2Cl_2. The organic extracts were washed twice with 50-mL portions of deionized water and dried over anhydrous sodium carbonate. Solvent removal at reduced pressure yielded 1.750 g (84%) of a mixture of hydrazine epimers. The ratio of the upfield to the downfield methyl resonance was the inverse of that in the tosylate mixture from which the hydrazines were prepared. The NMR spectrum (CH_2Cl_2) of the exo hydrazine (**5a**) showed δ 1.05 (s, 6 H), 1.35–2.33 (m, 8 H), 3.04 (broad s, 3 H), 3.32 (m, 1 H), 3.91 (s, 4 H). The spectrum (CH_2Cl_2) of the endo isomer showed δ 1.02 (s, 6 H), 1.43–2.32 (m, 8 H), 3.06 (broad s, 3 H), 3.33 (m, 1 H), 3.91 (s, 4 H).

For purification and storage **5** was converted to the oxalate salt by dissolving the crude hydrazine in the minimum amount of ethanol and slowly adding a solution of ethanol saturated with anhydrous oxalic acid. After the addition of 1 molar equiv of oxalic acid, the ethanol was cooled to −20 °C to complete crystallization. The oxalate salt was filtered and recrystallized from a mixed solvent of methanol-ethanol-ether. The epimeric composition of the salt was not significantly altered by recrystallization. The NMR spectrum of the salt in D_2O was similar to that of the hydrazine, except that the broad singlet centered at δ 3.05 was absent.

Anal. Calcd for $C_{14}H_{24}O_6N_2$: C, 53.15; H, 7.65; N, 8.85; O, 30.34. Found: C, 53.43; H, 8.05; N, 8.71; O, 30.01.

Oxidation of 7-Hydrazino-1,5-dimethylbicyclo[3.3.0]octan-3-one (6) in D_2O. To 13 mL of D_2O was added 1.7 g (5.4 mmol) of the oxalate salt. The solution was stirred at ambient temperature for 8 h, and the hydrolysis of the ketal was monitored by NMR. Hydrolysis was signaled by disappearance of the ketal resonance and the concomitant appearance of a singlet at δ 3.55 for ethylene glycol. To the solution of ketone **6** was added 23 mL of D_2O, in which 0.776 g (33.7 mmol) of clean sodium had previously been dissolved at low temperature, followed by 1.25 g (5.4 mmol) of potassium periodate. Effervescence was noted immediately on mixing. The mixture was stirred for 10 min at ambient temperature, and the product ketone **2** extracted with three 40-mL portions of pentane. The organic extracts were washed with water, dried over magnesium sulfate, and evaporated at reduced pressure. Yields of ketone ranged from 70 to 90%, with the lower yields probably being due to the volatility of **2**. The NMR spectrum ($CDCl_3$) of the ketone[10] lacked the singlets at δ 2.22 and 2.25 for the protons α to the carbonyl group, and the singlet at δ 1.73 integrated for only 5 H relative to the 6 H singlet at δ 1.08. The four exchangeable deuteriums were removed from **2**-d_5 by stirring the ketone in 12 mL of methanol, 1 M in sodium methoxide, for 2 h. To the methanol solution was added 25 mL of water containing 12 mmol of HCl, and the ketone was extracted with three 40-mL portions of pentane. The organic extracts were washed with three 35-mL portions of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to yield 80% of recovered **2**-d_1. Although the ketone appeared very clean by NMR, for mass spectral analysis samples were sublimed at reduced pressure or subjected to preparative GLC. Both methods gave samples of **2** with mp 138–144°C, whose mass spectra showed them to be 90–93% d_1, with no d_2 species detectable.

Oxidation of 7-Hydrazino-1,5-dimethylbicyclo[3.3.0]-octan-3-one Ethylene Ketal (5) in D_2O. The oxalate salt of **5** (5.6 mmol) was added to 35 mL of D_2O in which 0.74 g (32.2 mmol) of sodium followed by 1.29 g (5.6 mmol) of potassium periodate had previously been dissolved. After stirring for 10 min, the product was extracted with pentane, as described above. After the organic phases were washed and dried, solvent removal at reduced pressure gave 0.99 g (90%) of a clear liquid. The NMR spectrum ($CDCl_3$) of the ethylene ketal of **2** showed δ 1.01 (s, 6 H), 1.26–2.31 (m, 5 H), 1.81 (s, 2 H), 1.83 (s, 2 H), 3.86 (s, 4 H).

Exact mass. Calcd for $C_{12}H_{19}DO_2$: 197.1524. Found: 197.1538.

The ketal was hydrolyzed by dissolving the crude product in a mixture of 50 mL of THF and 50 mL of 6% H_2SO_4 and stirring for several hours. The ketone was extracted with four 40-mL portions of pentane, which were combined, washed with two 40-mL portions of water and then 50 mL of saturated sodium bicarbonate solution, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave 0.62 g (72%) of the ketone **2.** Mass spectral analysis showed this material to be 95% d_1 and 5% d_0.

Oxidation of 7-Hydrazino-1,5-dimethylbicyclo[3.3.0]octan-3-one (6) in Ethylene Glycol-*O,O'*-d_2. Deketalization of 1.2 g (3.8 mmol) of the oxalate salt of **5** was effected by stirring it for 8 h in 8 mL of deionized water. Then 8 mL of 2 M NaOH was added, and the ketohydrazine **6** was extracted with three 20-mL portions of CH_2Cl_2. The organic extracts were washed with 20 mL of deionized water, dried over sodium carbonate, and evaporated to a volume of 20 mL under reduced pressure. To this solution was added 36 mL of $(CH_2OD)_2$[19] in which 0.89 g (23.8 mmol) of potassium had previously been dissolved at low temperature. Removal of the CH_2Cl_2 was then completed. Potassium periodate (1.1 equiv) was added, and the solution was stirred at 30 °C for 2 h. The reaction mixture was diluted with 40 mL of water and extracted with three 25-mL portions of pentane. The organic extracts were washed with 50 mL of water, dried over magnesium sulfate, and evaporated under reduced pressure. The yield of **2**-d_5 isolated ranged from 15 to 25%. After exchange of deuterium α to the carbonyl, the mass spectrum of a sublimed sample of **2** indicated a mixture of 82% d_1 and 18% d_0.

Oxidation of 7-Hydrazino-1,5-dimethylbicyclo[3.3.0]octan-3-one Ethylene Ketal (5) in Ethylene Glycol-*O,O'*-d_2. To 40 mL of $(CH_2OD)_2$, in which 54 mmol of potassium had previously been dissolved at low temperature, was added 1.32 g (4.17 mmol) of the oxalate salt of **5,** followed by 1.1 equiv of potassium periodate. The reaction mixture was stirred at 35 °C for 5 h and worked up as described for the oxidation of **6,** affording the ketal of **2** in 51% yield. The ketal group was hydrolyzed, and the mass spectrum of the resulting ketone (**2**) showed it to be 83% d_1 and 17% d_0.

1,3,5-Trimethylbicyclo[3.3.0]octan-3-ol-7-d_1 (8). To 22 mL of 1.84 M methyllithium in ether at 0 °C was added 600 mg (4.0 mmol) of ketone **2** in 1 mL of ether. After stirring for 1 h, the solution was allowed to warm to room temperature, neutralized with 1 M HCl, and saturated with ammonium chloride. The aqueous phase was extracted with three 50-mL portions of ether, and the combined organic extracts were washed with water and dried over magnesium sulfate. Following solvent evaporation under reduced pressure, the oily residue was taken up in 1 mL of ether and added to a second 40-mmol batch of methyllithium in ether. Workup of this reaction afforded 620 mg (96%) of **8,** as a roughly 1:1 mixture of epimers. These epimers have previously been separated by preparative GLC at 140 °C on a 10 ft × 3/8-in. column of 20% Carbowax 20M on Chromosorb W and identified by shift reagent studies.[13] The NMR of the exo alcohol (CCl_4) showed δ 1.10 (s, 6 H), 1.23 (s, 3 H), 1.2–1.6 (m, 4 H), 1.61 (s, 6 H), while that of the endo isomer displayed δ 0.93 (s, 6 H), 1.29 (s, 3 H), 1.3–2.2 (m, 10 H). The NMR spectrum of the isomer mixture with which we worked showed the nonmethyl resonances integrating to approximately 9 H in each isomer, corresponding to the presence of one atom of deuterium.

Exact mass. Calcd for $C_{11}H_{19}DO$: 169.1575. Found: 169.1592.

1,3,7-Trimethyl-9-oxatricyclo[4.2.1.0^{3,7}]nonane-5-d_1 (9). Crystals of lead tetraacetate (6.50 g, 15.0 mmol) were washed with acetic acid and dried under vacuum. Calcium carbonate (2.24 g, 22.4 mmol) was oven dried at 170 °C overnight. These reagents were heated in 10 mL of refluxing benzene for 15 min, and 635 mg (3.75 mmol) of **8** in 5 mL of benzene was then added slowly. The initial addition produced a vigorous reaction in which a white precipitate was formed. After 48 h at reflux, water was added, and the resulting mixture was filtered through a bed of Celite. The filter cake was rinsed with several 3-mL portions of CH_2Cl_2, and the combined organic phases were washed with water and dried over magnesium sulfate. Solvent removal under reduced pressure was carried out at 0 °C, because of the high volatility of the tricyclic ether **9.** The crude product was obtained in 51% yield. Purification was accomplished by chromatography on 10 g of activity II basic alumina, using 1:20 ether–pentane to elute the column. The

122 mg (20%) of material thus obtained was suitable for subsequent reactions in the sequence, but for analytical purposes the ether **9** was further purified by preparative GLC at 135 °C on the Carbowax column described above. the NMR spectrum ($CDCl_3$) of **9** showed δ 0.93 (s, 3 H), 0.97 (s, 3 H), 1.30 (s, 3 H), 1.55 (s, 4 H), 1.73 (broad s, 3 H), 3.98 (broad s, 1 H). The NMR spectrum of samples of **9** containing no deuterium showed one more proton in the broad singlet at δ 1.73,[13] and the methine proton appeared as a doublet with J = 4 Hz.[1]

Exact mass. Calcd for $C_{11}H_{17}DO$: 167.1418. Found: 167.1394.

***endo*-6-Acetoxy-1,3,5-trimethylbicyclo[3.3.0]oct-2-ene-7-d_1 and *endo*-8-Acetoxy-1,3,5-trimethylbicyclo[3.3.0]oct-2-ene-7-d_1 (10).** To 170 mg of the tricyclic ether **9** in a mixture of 4 mL of ether and 6.2 mL of freshly distilled acetic anhydride at 0 °C was added in 2 mL of ether 0.84 mL of boron trifluoride etherate, freshly distilled from calcium hydride. The reaction mixture was stirred for 22 h at 0 °C and then poured into 42 mL of ice water. The two-phase solution was stirred at room temperature for 2 h, and the product was then extracted with three 20-mL portions of ether. The organic extracts were washed with 10% sodium bicarbonate until neutral and then with several portions of water. After drying over magnesium sulfate, solvent removal under reduced pressure afforded 143 mg (67%) of crude product, which was purified by chromatography on 5 g of neutral alumina. Elution of the column with 22:1 hexane-ethyl acetate gave 88 mg (42%) of **10** as a 1:1 mixture of double bond isomers that was suitable for subsequent reactions. For analytical purposes **10** could be further purified by preparative GLC at 125 °C on the Carbowax column described above. An NMR spectrum ($CDCl_3$) of the mixture of double bond isomers showed δ 1.05 (m, 12 H), 1.2–2.7 (m, 10 H), 1.71 (m, 6 H), 2.11 (s, 6 H), 4.71 (s, 1 H), 4.81 (s, 1 H), 4.97 (m, 1 H), 5.11 (m, 1 H).

Exact mass. Calcd for $C_{13}H_{19}DO_2$: 209.1548. Found: 209.1536.

1,3,5-Trimethylbicyclo[3.3.0]octa-2,6-diene and -2,7-diene (11). The mixture of endo acetates (**10**) was dissolved in 1 mL of pentane and injected into a flow system pyrolysis apparatus[20] whose internal temperature was 500 °C. The pyrolysis column was washed with 2 mL of pentane, and the pyrolysate was recycled twice more. After each pyrolysis, an additional 2 mL of pentane was used to wash the column. The pentane solution was washed with saturated sodium bicarbonate until neutral and then with three portions of water. After drying over sodium sulfate, solvent removal under reduced pressure afforded a 1:1 mixture of the dienes **11**. No attempt was made to separate the double-bond isomers, but they were collected together by preparative GLC at 85 °C, using the Carbowax column described above. The NMR spectrum ($CDCl_3$) of the mixture showed δ 0.97 (s, 3 H), 1.01 (s, 3 H), 1.04 (s, 6 H), 1.67 (broad s, 6 H), 2.23 (broad s, 8 H), 5.08 (m, 2 H), 5.49 (m, 3.5 H).

Exact mass. Calcd for $C_{11}H_{15}D$: 149.1312. Found: 149.1294. Calcd for $C_{11}H_{16}$: 148.1250. Found: 148.1238.

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