

On the Reaction of (Dibromomethyl)lithium with Bicyclic and Tricyclic Ketones

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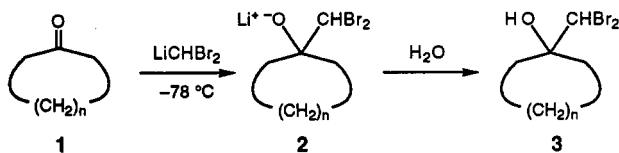
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Many literature examples show that the reaction of a simple cyclic ketone with (dibromomethyl)lithium at $-78\text{ }^{\circ}\text{C}$, followed by low-temperature hydrolysis of the resulting lithium alkoxide **33**, gives the corresponding dibromomethyl alcohol. We have found that the reaction of a bicyclic or tricyclic ketone with (dibromomethyl)lithium under comparable conditions provides a dibromomethyl alcohol and/or an α -bromo aldehyde. The latter product appears to result from an intramolecular displacement reaction in **33** to give a bromo epoxide, which then rearranges stereospecifically to the α -bromo aldehyde. The product ratios obtained in all of these reactions seem to be determined by the steric interactions in **33** between the alkoxide and dibromomethyl groups and the hydrogens that are *syn* to them at the carbons which are β to the original carbonyl carbon. As these steric interactions increase, the proportion of α -bromo aldehyde in the product mixture increases. If **33** obtained from any cyclic ketone is warmed to $10\text{ }^{\circ}\text{C}$ before it is hydrolyzed, then the only product isolated is the α -bromo aldehyde.

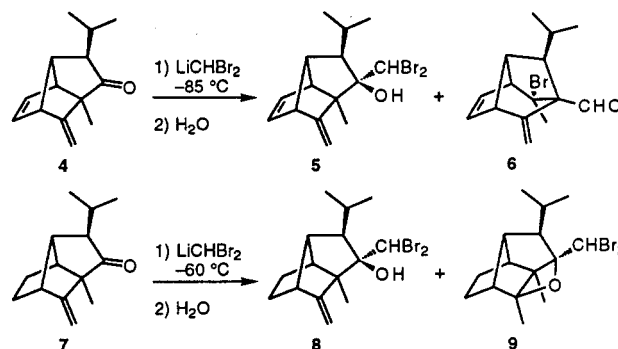
Introduction

Treatment of a cyclic ketone **1** with (dibromomethyl)lithium at $-78\text{ }^{\circ}\text{C}$ in tetrahydrofuran, followed by acid hydrolysis at low temperature of the resulting lithium alkoxide salt **2**, gives the corresponding dibromomethyl alcohol **3** in good yield.¹ For simple cyclic ketones, the success of this reaction is not dependent on the size of the

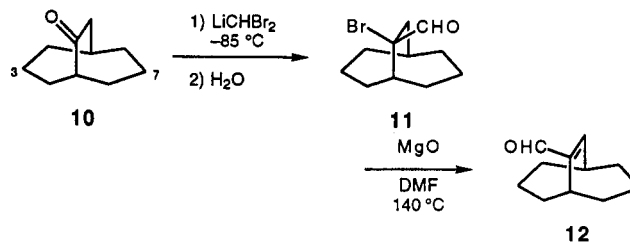


ring. Thus, the reaction of (dibromomethyl)lithium under these conditions with cyclopentanone (**1**, $n = 2$), cyclohexanone (**1**, $n = 3$), or cycloheptanone (**1**, $n = 4$) gives the corresponding dibromomethyl alcohol **3** in yields of 82, 91, and 76%, respectively.^{1b}

Because the products of these reactions are valuable synthetic intermediates for the ring expansion of cyclic ketones² and for the preparation of bromo olefins,³ the reactions of (dibromomethyl)lithium with more complex cyclic ketones containing five-membered⁴ and six-membered⁵ rings have been studied. In all of these cases, with the exceptions of ketones **4** and **7**, the only products that have been reported are the corresponding dibromomethyl alcohols. Ketone **4** gave the expected product **5** in 63% yield and **6** in 13% yield, whereas ketone **7** afforded alcohol **8** in 62% yield and **9** in 6% yield.^{4c} In view of all of these



examples, we were surprised to find that the reaction of (dibromomethyl)lithium with bicyclo[3.3.2]decan-9-one⁶ (**10**) at $-85\text{ }^{\circ}\text{C}$ provides 9-bromobicyclo[3.3.2]decane-9-carboxaldehyde (**11**) as the only isolated product in 89% yield. The structure of **11** was firmly established by heating **11** with magnesium oxide in *N,N*-dimethylformamide for



1 h at $140\text{ }^{\circ}\text{C}$ to give bicyclo[3.3.2]dec-9-ene-9-carboxaldehyde (**12**) in 86% yield. The formation of **11** from **10** is especially striking since Nicolaou and his co-workers have reported that the reaction of (dibromomethyl)lithium

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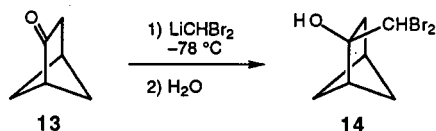
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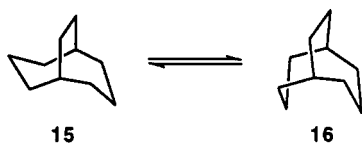
with bicyclo[2.1.1]hexan-2-one (13) at $-78\text{ }^{\circ}\text{C}$ gives only 2-(dibromomethyl)bicyclo[2.1.1]hexan-2-ol (14) in 95% yield.^{4e}



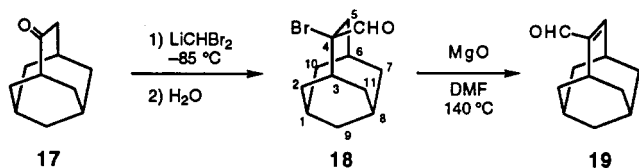
We have explored the reactions of (dibromomethyl)lithium with a variety of bicyclic and tricyclic ketones in an attempt to define the structural features which cause ketones 10 and 12 to react so differently with this reagent.

Results and Discussion

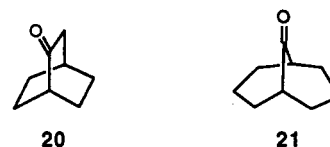
Experimental observations⁷ and molecular mechanics calculations⁸ have led to the conclusion that bicyclo[3.3.2]decane exists primarily in an equilibrium between the eclipsed boat-chair (15) and twin twist-chair (16) conformations. Consequently, it was of interest to determine



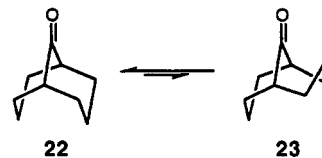
the influence on the reaction of (dibromomethyl)lithium with ketone 10 if the mobility of the three-carbon bridges in 10 were restricted. In effect, this could be accomplished by connecting C-3 and C-7 of 10 with a methylene group to give homoadamantan-4-one⁹ (17). Reaction of ketone 17 with (dibromomethyl)lithium at $-85\text{ }^{\circ}\text{C}$ provides 4-bromohomoadamantan-4-carboxaldehyde (18) as the only isolated product in 88% yield. Dehydrobromination of 18 with magnesium oxide in DMF gives homoadamantan-4-ene-4-carboxaldehyde (19) in 68% yield.



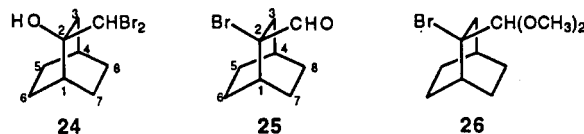
Given the strikingly different outcomes of the reaction of (dibromomethyl)lithium at low temperature with ketone 13, in which the carbonyl carbon is present in two five-membered rings, and ketones 10 and 17, in which the carbonyl carbon resides in two seven-membered rings, we investigated the reaction of (dibromomethyl)lithium under comparable conditions with bicyclic ketones in which the carbonyl carbon is located in two six-membered rings. Although bicyclo[2.2.2]octan-2-one¹⁰ (20) and bicyclo[3.3.1]nonan-9-one (21) both satisfy this condition, these two ketones provide significantly different environments for the carbonyl group. Both theoretical calculations and experimental results indicate that bicyclo[2.2.2]octane has



a broad energy minimum for twisting around the C-1 to C-4 axis, and so the eclipsed and twisted conformers are similar in energy.¹¹ On the other hand, ketone 21 has been shown to exist at room temperature in a 78:22 equilibrium between the chair-chair (22) and chair-boat (23) conformations, respectively.¹²

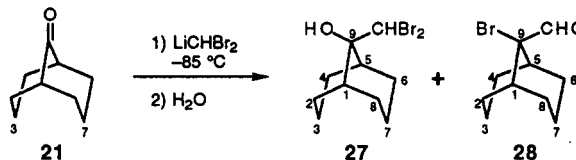


Treatment of ketone 20 with (dibromomethyl)lithium at $-85\text{ }^{\circ}\text{C}$ gives 2-(dibromomethyl)bicyclo[2.2.2]octan-2-ol (24) and 2-bromobicyclo[2.2.2]octane-2-carboxaldehyde (25) in yields of 62 and 20%, respectively. The products were separated readily by column chromatography on silica gel. Brown and his co-workers have noted previously that α -bromo aldehydes "are exceedingly reactive and cannot be stored as such for any length of time".¹³ Consequently, in order to prepare a suitable derivative of 25 for elemental



analysis, we employed the method of Taylor and Chiang to convert 25 to the corresponding dimethyl acetal 26 by reacting the α -bromo aldehyde with trimethyl orthoformate that had been adsorbed on the acidic montmorillonite clay K-10.¹⁴ Except for aldehydes 11 and 18, we were able to use this method for preparing the dimethyl acetals of all of the α -bromo aldehydes that were obtained in this study.

Reaction of (dibromomethyl)lithium with ketone 21 at $-85\text{ }^{\circ}\text{C}$ provides 9-(dibromomethyl)bicyclo[3.3.1]nonan-9-ol (27) and 9-bromobicyclo[3.3.1]nonane-9-carboxaldehyde (28) in yields of 52 and 36%, respectively.



In order to probe the influence of the mobile three-carbon bridges in 21 on the course of this reaction, we also examined the reaction of (dibromomethyl)lithium with adamantanone (29). In principle, this rigid tricyclic ketone can be obtained from 21 by joining C-3 and C-7 of 21 with a methylene bridge. Treatment of adamantanone with

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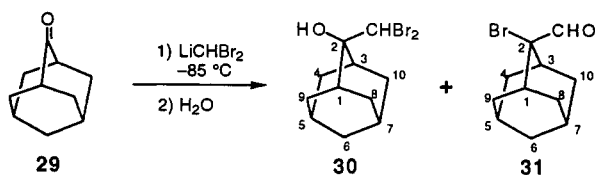
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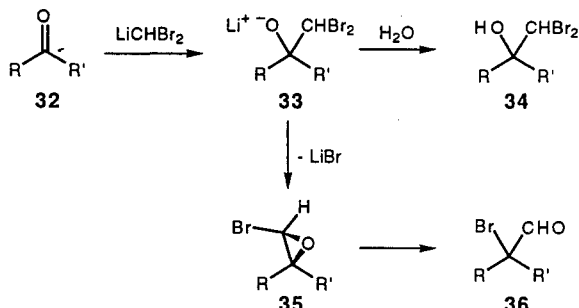
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(dibromomethyl)lithium at $-85\text{ }^{\circ}\text{C}$ affords 2-(dibromomethyl)adamantan-2-ol (**30**) and 2-bromoadamantane-2-carboxaldehyde (**31**) in yields of 58 and 18%, respectively.

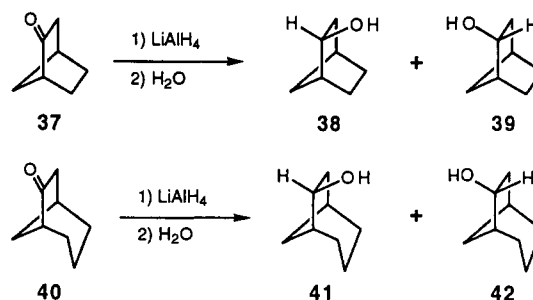


We believe that all of the reactions of cyclic ketones with (dibromomethyl)lithium can be explained by a common reaction mechanism. Attack of (dibromomethyl)lithium on ketone **32** gives lithium alkoxide **33**. If the

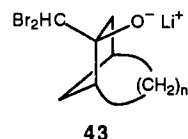


reaction temperature is maintained at $-85\text{ }^{\circ}\text{C}$, then **33** is stable for monocyclic ketones and for bicyclic ketones in which R and R' provide minimal steric congestion about the original carbonyl carbon. Consequently, hydrolysis at low temperature of **33** derived from any of these ketones affords the corresponding dibromomethyl alcohol **34**. However, as R and R' increase in size, then the enhanced proximity of the alkoxide and dibromomethyl groups in **33** promotes an intramolecular displacement reaction to give bromo epoxide **35**. Such an epoxide is known to rearrange readily to the corresponding α -bromo aldehyde **36**.¹⁵ The energy barrier for **33** \rightarrow **35** must be relatively low, since we have found that if the lithium alkoxide species **33** obtained from any cyclic ketone is warmed to $+10\text{ }^{\circ}\text{C}$ before it is hydrolyzed, then the only product obtained is **36**. The similar reactivities of the structurally related ketones **10** and **17** (and of **21** and **29**) with (dibromomethyl)lithium suggest that the important steric interactions in **33** are those between the alkoxide and dibromomethyl groups and the hydrogens *syn* to them at the carbons which are β to the original carbonyl carbon.

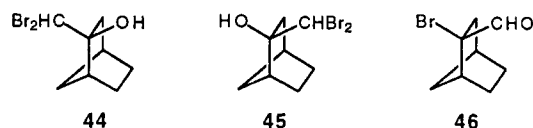
These observations encouraged us to examine the behavior of bicyclo[2.2.1]heptan-2-one (**37**) and bicyclo[3.2.1]octan-6-one¹⁶ (**40**) with (dibromomethyl)lithium under comparable conditions. In ketone **37**, the carbonyl carbon resides in a five-membered ring and a six-membered ring, whereas in ketone **40**, the carbonyl carbon is present in a five-membered ring and a seven-membered ring. Reduction of **37** with lithium aluminum hydride gives a 90:10 mixture of 2-*endo*- and 2-*exo*-bicyclo[2.2.1]heptan-2-ol (**38** and **39**, respectively).¹⁷ Reduction of **40** with lithium aluminum hydride affords a 95:5 mixture of 6-*endo*- and 6-*exo*-bicyclo[3.2.1]octan-6-ol (**41** and **42**, respectively).¹⁸ Consequently, the attack of (dibromomethyl)lithium on **37** and **40** should occur predominantly from the



sterically less-hindered *exo* face of the carbonyl carbon in both ketones. Therefore, ketones **13**, **37**, and **40** provide an opportunity to determine the consequences of modifying the environment of the lithium alkoxide moiety in **43** from a five- to a six- to a seven-membered ring while the surroundings of the dibromomethyl group remain relatively constant.

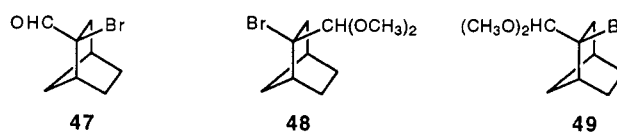


Reaction of ketone **37** with (dibromomethyl)lithium at $-85\text{ }^{\circ}\text{C}$ provides a mixture of 2-*exo*-(dibromomethyl)bicyclo[2.2.1]heptan-2-*endo*-ol (**44**), 2-*endo*-(dibromomethyl)bicyclo[2.2.1]heptan-2-*exo*-ol (**45**), and 2-*exo*-bromobicyclo[2.2.1]heptane-2-*endo*-carboxaldehyde (**46**)



in yields of 66, 4, and 12%, respectively. The stereochemical assignments of the substituents in α -bromo aldehyde **46** result from the following arguments:

(1) If the reaction mixture resulting from the addition of (dibromomethyl)lithium to ketone **37** is warmed to $10\text{ }^{\circ}\text{C}$ before it is hydrolyzed, then **46** and 2-*endo*-bromobicyclo[2.2.1]heptane-2-*exo*-carboxaldehyde (**47**) are obtained in an overall yield of 81% and in a ratio of $>95:5$,



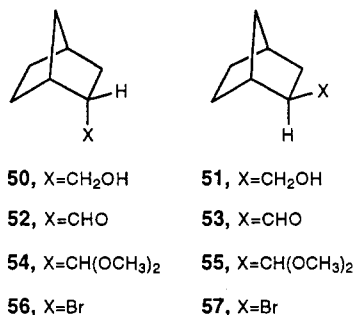
respectively. Treatment of the mixture of **46** and **47** with trimethyl orthoformate adsorbed on K-10 clay gives a mixture of the corresponding dimethyl acetals **48** and **49**. The difference in the ¹³C NMR chemical shifts of the two methoxy groups in **48** is δ 1.8, whereas this difference is only δ 0.8 in **49**. For purposes of comparison, a commercially available 75:25 mixture of the 2-*endo*- and 2-*exo*-bicyclo[2.2.1]heptanemethanols (**50** and **51**, respectively) was oxidized to a 75:25 mixture of the 2-*endo*- and 2-*exo*-bicyclo[2.2.1]heptanecarboxaldehydes (**52** and **53**, respectively), which was then converted to a 75:25 mixture of the 2-*endo* and 2-*exo*-(dimethoxymethyl)bicyclo[2.2.1]heptanes (**54** and **55**, respectively). The difference in the ¹³C NMR chemical shifts of the two methoxy groups within **54** and **55** are δ 0.8 and δ 0.3, respectively. Consequently, we

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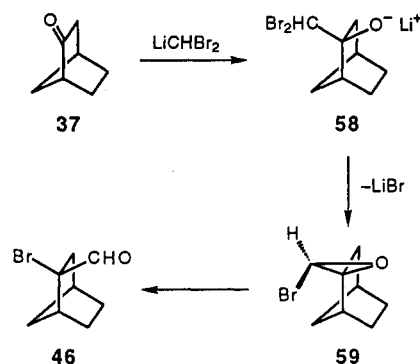
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conclude that the dimethoxymethyl groups in 48 and 49 are *endo* and *exo*, respectively.

(2) If the effects of the -Br and -CHO substituents on the chemical shifts of the carbons in bicyclo[2.2.1]heptane are assumed to be independent and additive, then the ¹³C NMR spectra of 46 and 47 can be calculated from an analysis of the ¹³C NMR spectra of aldehydes 52 and 53, the 2-*endo*- and 2-*exo*-bromobicyclo[2.2.1]heptanes (56 and 57, respectively), and the parent hydrocarbon. The ¹³C NMR spectra of 53,¹⁹ 56,²⁰ and 57²⁰ have been reported previously. A summary of the observed and calculated spectra for 46 and 47 is included in the Experimental Section. The excellent agreement between the trends in the calculated and observed values for all of the carbons in 46 and 47 provides further support for the stereochemical assignments of the substituents in these α -bromo aldehydes.

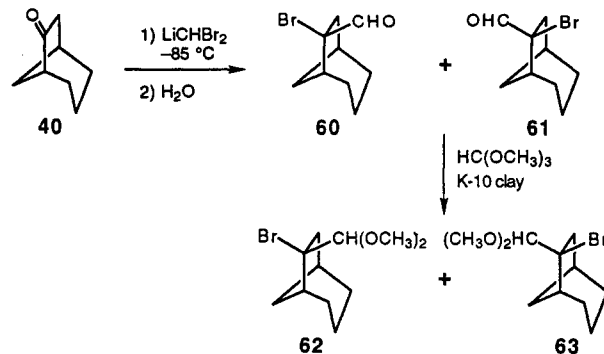
The formation of 46 in the reaction of (dibromomethyl)-lithium with ketone 37 can be accounted for by the initial attack of the nucleophile on the less-hindered face of the carbonyl carbon of 37 to give lithium alkoxide 58, which then undergoes an intramolecular displacement reaction



to give bromo epoxide 59. The rearrangement of 59 to 46 occurs stereospecifically so that the bromine atom in 46 ultimately resides on the same face of the original carbonyl carbon that was attacked by the nucleophile.

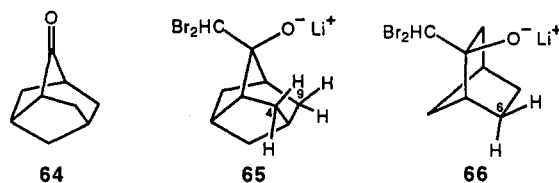
Reaction of ketone 40 with (dibromomethyl)lithium at -85 °C affords a mixture of 6-*exo*-bromobicyclo[3.2.1]octane-6-*endo*-carboxaldehyde (60) and 6-*endo*-bromobicyclo[3.2.1]octane-6-*exo*-carboxaldehyde (61) in a ratio of 95:5, respectively. Consistent with the stereochemical assignments of the substituents in 60, the difference in the ¹³C NMR chemical shifts of the two methoxy groups in dimethyl acetal 62 is δ 1.9.

In summary, the reactions of (dibromomethyl)lithium at low temperature with ketones 13, 37, and 40 show that as *n* in 43 is increased from 1 to 2 to 3 there is an increasing



preference for the formation of the α -bromo aldehyde product. When the lithium alkoxide moiety is *syn* to a five-membered ring in 43, the only product obtained is the corresponding dibromomethyl alcohol. The alcohol is also favored over the α -bromo aldehyde by a margin of 85:15 when the lithium alkoxide group is *syn* to a six-membered ring in 43. However, if the lithium alkoxide moiety is *syn* to a seven-membered ring in 43, then the α -bromo aldehyde is the sole product.

These observations suggest that if the steric interaction between the lithium alkoxide group and the *syn*-hydrogen on the carbon β to the quaternary center in 43 were to be increased, then the proportion of α -bromo aldehyde in the product mixture would increase also. We have examined this alternative by comparing the reaction at low temperature of (dibromomethyl)lithium with ketone 37 and noradamantan-2-one²¹ (64). In both ketones, the carbonyl carbon is present in both a five-membered ring and a six-membered ring. Since it is known that nucleophiles attack the face of the carbonyl carbon in 64 that is *syn* to the five-membered ring,²² then (dibromomethyl)lithium should react with 64 to give 65. MM2 calculations and molecular models clearly show that the lithium



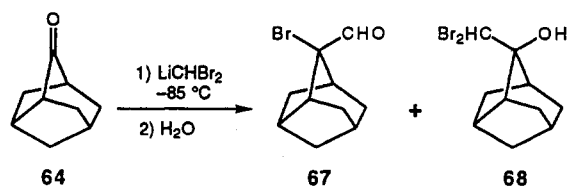
alkoxide moiety in 65 is significantly closer to the *syn*-hydrogens at C-4 and C-9 of 65 than is the case for the interaction of the same group with the *syn*-hydrogen at C-6 in 66. Consequently, a greater proportion of α -bromo aldehyde should result from the reaction of (dibromomethyl)lithium with 64 than with 37. Consistent with this prediction, treatment of 64 with (dibromomethyl)lithium at -85 °C gives 2-*exo*-bromonoradamantan-2-*endo*-carboxaldehyde (67) and 2-*exo*-(dibromomethyl)noradamantan-2-*endo*-ol (68) in yields of 75 and 19%, respectively.

Our analysis of the reaction at low temperature of (dibromomethyl)lithium with cyclic ketones also leads to the prediction that if the steric congestion in 33 were reduced, then the proportion of dibromomethyl alcohol in the product mixture would increase. We have studied this alternative by comparing the reactions at low temperature of (dibromomethyl)lithium with ketone 29 and

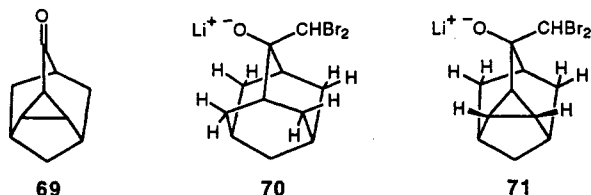
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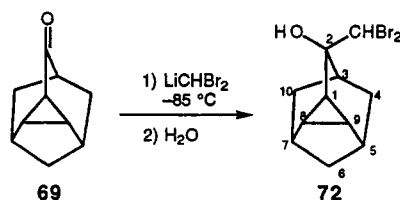
(21) We are indebted to Professor Alex Nickon of The Johns Hopkins University for supplying us with a generous sample of noradamantan-2-*exo*-ol which was oxidized to noradamantan-2-one with chromic acid.
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8,9-didehydroadamantan-2-one²³ (69). Attack of (dibromomethyl)lithium on 29 and 69 would give 70 and 71, respectively. MM2 calculations and molecular models clearly show that the steric interactions of both the lithium



alkoxide and the dibromomethyl groups with the hydrogens flanking them are more severe in 70 than they are in 71. Consequently, a greater proportion of the product resulting from the reaction of (dibromomethyl)lithium with 69 should be dibromomethyl alcohol than is the case for 29. Consistent with this prediction, treatment of 69 with (dibromomethyl)lithium at $-85\text{ }^{\circ}\text{C}$ gives 2-(dibromomethyl)-8,9-didehydroadamantan-2-ol (72) as the only isolated product in 81% yield.



Experimental Section

All melting points are uncorrected. The ¹H and ¹³C NMR spectra were obtained with CDCl₃ as the solvent and are referenced to an internal standard of tetramethylsilane. Attached proton tests for the resonances in the ¹³C NMR spectra utilized JVERT or DEPT pulse sequences. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE. Unless indicated otherwise, all starting materials and reagents are commercially available.

General Procedure for the Reaction of (Dibromomethyl)lithium with Ketones. A solution of lithium diisopropylamide was prepared by the addition of *n*-butyllithium (2.6 mL of a 1.54 M solution in hexane, 4.0 mmol) to a stirred solution of diisopropylamine (0.64 mL, 4.6 mmol, freshly distilled from CaH) in anhydrous tetrahydrofuran (10 mL, freshly distilled from sodium benzophenone ketyl) which was maintained at $-78\text{ }^{\circ}\text{C}$ under N₂. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min, and then at $0\text{ }^{\circ}\text{C}$ for 15 min, before it was cooled again to $-78\text{ }^{\circ}\text{C}$. This solution was added at a rate of approximately 0.5 mL/min *via* a motor-driven syringe pump to a stirred solution of the ketone (2.0 mmol) and CH₂Br₂ (1.39 g, 8.0 mmol, distilled from P₂O₅) in anhydrous ether (4.0 mL, freshly distilled from sodium benzophenone ketyl) that was maintained at $-85\text{ }^{\circ}\text{C}$ under N₂. After the addition was complete, the resulting dark solution was stirred for 1 h at $-85\text{ }^{\circ}\text{C}$, and then it was poured into a stirred mixture of ice (10 mL) and ether (20 mL). After the ice had melted, 10% aqueous HCl was added slowly to the resulting mixture until the aqueous layer was acidic (about 3 mL). The layers were separated, and the aqueous layer was extracted with

ether (2 × 10 mL). The organic layer and extracts were combined, washed with H₂O (10 mL) and brine (10 mL), and dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave a dark oil which was flash column chromatographed on Merck 7747 silica gel with CH₂Cl₂/petroleum ether. In all cases, the α -bromo aldehyde product eluted before the dibromomethyl alcohol product. Unreacted ketone, if present, usually eluted after the dibromomethyl alcohol product.

If the general procedure is altered so that the reaction mixture is allowed to warm slowly from $-85\text{ }^{\circ}\text{C}$ to $+10\text{ }^{\circ}\text{C}$ before it is quenched with water, then the only product isolated from the reaction of (dibromomethyl)lithium with any ketone we studied is the corresponding α -bromo aldehyde.

General Procedure for the Preparation of a Dimethyl Acetal of an α -Bromo Aldehyde. Trimethylorthoformate (0.75 mL) was stirred briefly with K-10 montmorillonite clay (0.5 g) at room temperature. Any excess liquid was adsorbed onto filter paper. To the resulting reagent was added a solution of the α -bromo aldehyde (100 mg) in hexanes (2.0 mL). The reaction mixture was stirred for 2 h at room temperature and then it was filtered. The filter cake was rinsed with more hexanes, and this material was combined with the original filtrate. This solution was washed with saturated aqueous NaHCO₃ (10 mL) and then dried over anhydrous Na₂SO₄. Evaporation of the solvent at reduced pressure provided the crude dimethyl acetal.

Reaction of Bicyclo[3.3.2]decan-9-one (10) with (Dibromomethyl)lithium. Treatment of 10⁶ (152 mg, 1.0 mmol) with LiCHBr₂ according to the general procedure provided 255 mg of a brown oil. Flash column chromatography of this material gave 37 mg of 10 and 166 mg of 11 (89% yield based on 76% conversion of 10) as a pale yellow solid: mp $87\text{--}89\text{ }^{\circ}\text{C}$; ¹³C NMR δ 190.8 (CHO), 78.9 (C-9), 42.2 (C-1), 38.3 (C-10), 33.0 (C-5), 31.4 (t), 30.9 (t), 30.7 (t), 28.7 (t), 22.2 (C-3 or C-7), 21.1 (C-3 or C-7); ¹H NMR δ 9.26 (s, 1 H), 3.12 (dd, $J = 16$ and 4 Hz, 1 H), 2.69 (m, 1 H), 2.46–2.22 (m, 3 H), 2.03–1.52 (m, 7 H), 1.52–1.20 (m, 4 H); IR ν (CHCl₃) 2920, 2720, 1728 cm⁻¹; HRMS calcd for C₁₁H₁₇BrO 244.046, found 244.043. This aldehyde could not be converted cleanly to its dimethyl acetal by the general procedure. Consequently, 11 was transformed into the corresponding α,β -unsaturated aldehyde.

Bicyclo[3.2.2]dec-9-ene-9-carboxaldehyde (12). MgO (31 mg) was added to a stirred solution of 11 (139 mg, 0.57 mmol) in DMF (2.5 mL). The reaction mixture was heated to $140\text{ }^{\circ}\text{C}$ and stirred at this temperature for 1 h. The reaction was allowed to cool to room temperature. It was then treated with 10% aqueous HCl (2.5 mL), diluted with H₂O (10 mL), and extracted with ether (4 × 10 mL). The combined ether extracts were washed sequentially with brine (5 mL), saturated aqueous NaHCO₃ (5 mL), and brine (5 mL), and then dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure gave a black oil which was Kugelrohr distilled ($80\text{ }^{\circ}\text{C}$ at 0.8 torr) to provide 81 mg (86% yield) of 12 as a colorless oil: ¹³C NMR δ 193.5 (CHO), 157.5 (C-10), 148.7 (C-9), 33.8 (C-5), 27.9 (C-1), 27.5 (C-2 and C-8, or C-4 and C-6), 27.3 (C-2 and C-8, or C-4 and C-6), 22.3 (C-3 and C-7); ¹H NMR δ 9.37 (s, 1 H), 6.90 (dd, $J = 8.9$ and 1.5 Hz, 1 H), 3.28–3.23 (m, 1 H), 2.87–2.78 (m, 1 H), 2.10–1.20 (m, 12 H); IR ν (CHCl₃) 2950, 1675, 1641 cm⁻¹. Anal. Calcd for C₁₁H₁₆O: C, 80.44; H, 9.82. Found: C, 80.58; H, 9.85.

Reaction of 4-Homoadamantanone (17) with (Dibromomethyl)lithium. Treatment of 17⁹ (329 mg, 2.0 mmol) with LiCHBr₂ according to the general procedure gave 605 mg of a brown oil. Flash column chromatography of this material gave 70 mg of 17 and 356 mg of 18 (88% yield based on 79% conversion of 17) as a low-melting pale yellow solid: ¹³C NMR δ 191.3 (CHO), 80.8 (C-4), 41.8 (C-5), 40.2 (C-3), 38.5 (t), 35.9 (t), 35.8 (t), 34.9 (t), 32.2 (t), 31.0 (C-6), 26.9 (C-1 or C-8), 26.7 (C-1 or C-8); ¹H NMR δ 9.29 (s, 1 H), 3.21 (ddm, $J = 16.5$ and 4.2 Hz, 1 H), 2.61–2.38 (m, 2 H), 2.31 (dd, $J = 16.5$ and 3.6 Hz, 1 H), 2.28–1.61 (m, 8 H), 1.57 (s, 2 H), 1.35 (d, $J = 13$ Hz, 2 H); IR ν (CHCl₃) 2919, 2855, 1727 cm⁻¹. This aldehyde could not be converted cleanly to its dimethyl acetal by the general procedure. Consequently, 18 was transformed into the corresponding α,β -unsaturated aldehyde.

Homoadamant-4-ene-4-carboxaldehyde (19). MgO (61 mg) was added to a stirred solution of 18 (300 mg, 1.17 mmol) in DMF (5 mL). Treatment and workup of the reaction mixture according

(23) (a) Murray, R. K., Jr.; Morgan, T. K., Jr.; Babiak, K. A. *J. Org. Chem.* 1975, 40, 1079. (b) Karlovic, G.; Majerski, Z. *J. Org. Chem.* 1978, 43, 746.

to the procedure employed for 11 → 14 provided a black oil which was Kugelrohr distilled (90 °C at 0.8 torr) to provide 141 mg (68% yield) of 19 as a colorless oil: ^{13}C NMR δ 193.2 (CHO), 161.7 (C-5), 152.9 (C-4), 36.1 (C-9), 32.9 (C-2 and C-11, or C-7 and C-10), 32.6 (C-2 and C-11, or C-7 and C-10), 32.6 (C-6), 29.0 (C-1 and C-8 coincident), 26.1 (C-3); ^1H NMR δ 9.31 (s, 1 H), 7.07 (dd, $J = 8.6$ and 1.4 Hz, 1 H), 3.14–3.06 (m, 1 H), 2.74–2.60 (m, 1 H), 2.20–1.40 (m, 12 H); IR ν (CHCl_3) 2930, 1675, 1645 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.98; H, 9.11.

Reaction of Bicyclo[2.2.2]octan-2-one (20) with (Dibromomethyl)lithium. Treatment of 20¹⁰ (248 mg, 2.0 mmol) with LiCHBr_2 according to the general procedure gave 514 mg of a brown oil. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of unreacted 20, 24, and 25 in a ratio of 10:65:25, respectively. Flash column chromatography of this material gave 25 mg of 20, 334 mg of 24 (62% yield based on 90% conversion of 20) as a pale yellow solid [mp 44–46 °C (recrystallized from hexanes)]; ^{13}C NMR δ 75.9 (C-2), 61.4 (CHBr_2), 42.1 (C-3), 33.6 (C-1), 26.1 (C-4), 24.2 (C-5 or C-8), 23.8 (C-5 or C-8), 21.5 (C-6 or C-7), 21.4 (C-6 or C-7); ^1H NMR δ 5.94 (s, 1 H), 2.36 (s, 1 H), 2.14–1.97 (m, 2 H), 1.85–1.20 (m, 10 H). Anal. Calcd for $\text{C}_8\text{H}_{14}\text{Br}_2\text{O}$: C, 36.27; H, 4.74. Found: C, 36.39; H, 4.72.], and 78 mg of 25 (20% yield based on 90% conversion of 20) [^{13}C NMR δ 191.6 (CHO), 73.9 (C-2), 35.5 (C-3), 32.4 (C-1), 25.6 (C-4), 25.0 (t), 23.6 (t), 23.1 (t), 22.3 (t); ^1H NMR δ 9.29 (s, 1 H), 2.78 (dt, $J = 15.5$ and 2.6 Hz, 1 H), 2.30–2.12 (m, 1 H), 2.07–1.90 (m, 1 H), 1.81–1.08 (m, 8 H); IR ν (CHCl_3) 2946, 2872, 1725 cm^{-1}].

Treatment of 119 mg of 25 with $\text{HC}(\text{OCH}_3)_3$ and K-10 clay according to the general procedure provided 100 mg (69% yield) of 26 as a pale yellow solid. Recrystallization of this material from hexanes gave 26 as a white solid: mp 65–65.5 °C; ^{13}C NMR δ 109.6 [$\text{CH}(\text{OCH}_3)_2$], 76.2 (C-2), 59.3 (OCH_3), 57.9 (OCH_3), 42.3 (C-3), 33.6 (C-1), 25.7 (C-4), 25.2 (t), 24.3 (t), 24.1 (t), 23.8 (t); ^1H NMR δ 4.07 (s, 1 H), 3.69 (s, 3H), 3.62 (s, 3H), 2.36–1.98 (m, 2 H), 1.86–1.30 (m, 10 H). Anal. Calcd for $\text{C}_{11}\text{H}_{15}\text{BrO}_2$: C, 50.20; H, 7.28. Found: C, 50.40; H, 7.29.

Reaction of Bicyclo[3.3.1]nonan-9-one (21) with (Dibromomethyl)lithium. Treatment of 21 (250 mg, 1.8 mmol) with LiCHBr_2 according to the general procedure gave 485 mg of a brown oil. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of 27 and 28 in a ratio of 65:35, respectively. Flash column chromatography of this material provided 291 mg (52% yield) of 27 as a pale yellow solid [mp 77–79 °C; ^{13}C NMR δ 75.3 (C-9), 61.8 (CHBr_2), 35.8 (C-1 and C-5), 28.1 (C-2 and C-4, or C-6 and C-8), 28.0 (C-2 and C-4, or C-6 and C-8), 20.5 (C-3 or C-7), 19.8 (C-3 or C-7); ^1H NMR δ 6.45 (s, 1H), 2.40–2.02 (m, 5 H, containing a 1 H s at δ 2.07), 1.87–1.41 (m, 10 H). Anal. Calcd for $\text{C}_{10}\text{H}_{16}\text{Br}_2\text{O}$: C, 38.49; H, 5.17. Found: C, 38.61; H, 5.19.], and 151 mg (36% yield) of 28 as an off-white solid [mp 63–64 °C dec; ^{13}C NMR δ 190.9 (CHO), 82.0 (C-9), 34.9 (C-1 and C-5), 30.8 (C-2 and C-4, or C-6 and C-8), 28.4 (C-2 and C-4, or C-6 and C-8), 21.1 (C-3 or C-7), 20.5 (C-3 or C-7); ^1H NMR δ 9.29 (s, 1 H), 2.52–2.19 (m, 4 H), 2.12–1.38 (m, 10 H); IR ν (CHCl_3) 2930, 2822, 2720, 1721 cm^{-1}].

Treatment of 195 mg of 28 with $\text{HC}(\text{OCH}_3)_3$ and K-10 clay according to the general procedure provided 86 mg (37% yield) of 9-bromo-9-(dimethoxymethyl)bicyclo[3.3.1]nonane (73) as a yellow solid. Recrystallization of this material from hexanes gave 73 as a white solid: mp 94–96 °C; ^{13}C NMR δ 106.2 [$\text{CH}(\text{OCH}_3)_2$], 83.9 (C-9), 58.8 (OCH_3), 36.2 (C-1 and C-5), 29.83 (C-2 and C-4, or C-6 and C-8), 29.77 (C-2 and C-4, or C-6 and C-8), 20.4 (C-3 or C-7), 20.0 (C-3 or C-7); ^1H NMR δ 4.67 (s, 1 H), 3.70 (s, 6 H), 2.56–1.32 (m, 14 H). Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{BrO}_2$: C, 52.00; H, 7.64. Found: C, 51.86; H, 7.65.

Reaction of Adamantanone (29) with (Dibromomethyl)lithium. Treatment of 29 (300 mg, 2.0 mmol) with LiCHBr_2 according to the general procedure gave 600 mg of a brown oil. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of 30 and 31 in a ratio of 70:30, respectively. Flash column chromatography of this material provided 378 mg (58% yield) of 30 as a white solid [mp 89.5–90.5 °C (recrystallized from hexanes)]; ^{13}C NMR δ 76.5 (C-2), 60.8 (CHBr_2), 37.5 (C-6), 35.7 (C-1 and C-3), 33.7 (C-4 and C-9, or C-8 and C-10), 33.3 (C-4 and C-9, or C-8 and C-10), 26.6 (C-5 or C-7), 26.5 (C-5 or C-7); ^1H NMR δ 6.49 (s, 1 H), 2.32–2.17

(m, 4 H), 2.09 (s, 1 H), 1.92–1.53 (m, 10 H). Anal. Calcd for $\text{C}_{11}\text{H}_{16}\text{Br}_2\text{O}$: C, 40.77; H, 4.98. Found: C, 40.69; H, 4.94.], and 88 mg (18% yield) of 31 as a yellow oil [^{13}C NMR δ 190.9 (CHO), 81.2 (C-2), 37.8 (C-6), 36.0 (C-8 and C-10), 35.0 (C-1 and C-3), 33.8 (C-4 and C-9), 27.5 (C-5 or C-7), 26.8 (C-5 or C-7); ^1H NMR δ 9.26 (s, 1 H), 2.39 (bs, 4 H), 2.17–1.66 (m, 10 H); IR ν (CHCl_3) 2922, 2857, 2718, 1721 cm^{-1}].

Treatment of 152 mg of 31 with $\text{HC}(\text{OCH}_3)_3$ and K-10 clay according to the general procedure provided 145 mg (80% yield) of 2-bromo-2-(dimethoxymethyl)adamantane (74) as a white solid. Recrystallization of this material from hexanes gave 74 as a white solid: mp 103.5–105 °C; ^{13}C NMR δ 106.0 [$\text{CH}(\text{OCH}_3)_2$], 84.2 (C-2), 58.2 (OCH_3), 39.5 (C-6), 36.5 (C-1 and C-3), 35.3 (C-4 and C-9, or C-8 and C-10), 35.2 (C-4 and C-9, or C-8 and C-10), 27.1 (C-5 and C-7); ^1H NMR δ 4.70 (s, 1 H), 3.68 (s, 6 H), 2.65–1.56 (m, 14 H). Anal. Calcd for $\text{C}_{13}\text{H}_{21}\text{BrO}_2$: C, 53.99; H, 7.32. Found: C, 54.04; H, 7.34.

Reaction of Bicyclo[2.2.1]heptan-2-one (37) with (Dibromomethyl)lithium. Treatment of 37 (220 mg, 2.0 mmol) with LiCHBr_2 according to the general procedure gave 482 mg of a dark oil. Analysis of this material by quantitative ^{13}C NMR spectroscopy showed that it consisted of a mixture of 44, 45, and 46 in a ratio of 85:5:10, respectively. Flash column chromatography of this material gave 376 mg (66% yield) of 44 as a yellow oil [^{13}C NMR δ 83.2 (C-2), 59.6 (CHBr_2), 45.9 (C-1), 45.8 (C-3), 38.7 (C-7), 37.7 (C-4), 27.2 (C-5), 22.9 (C-6); ^1H NMR δ 5.75 (s, 1 H), 2.55 (bs, 1 H), 2.45 (s, 1 H), 2.33 (bs, 1 H), 2.14–2.00 (m, 1 H), 1.84–1.72 (m, 1 H), 1.60–1.27 (m, 6 H). Anal. Calcd for $\text{C}_8\text{H}_{12}\text{Br}_2\text{O}$: C, 33.84; H, 4.26. Found: C, 33.83; H, 4.14.], 23 mg (4% yield) of 45 as a yellow oil [^{13}C NMR δ 83.5 (C-2), 57.2 (CHBr_2), 48.5 (C-1), 46.9 (C-3), 37.9 (C-7), 37.2 (C-4), 27.9 (C-5), 22.5 (C-6)] that was contaminated with 44, and 47 mg (12% yield) of 46 as a yellow oil [^{13}C NMR δ obsd (calcd) 191.8 (CHO), 75.4 (77.4) (C-2), 47.1 (49.0) (C-1), 40.5 (43.6) (C-3), 38.3 (37.4) (C-7), 38.0 (38.0) (C-4), 27.5 (27.8) (C-5), 25.0 (22.5) (C-6); ^1H NMR δ 9.52 (s, 1 H), 2.74 (bd, 1 H), 2.52 (dd, $J = 14.8$ and 2.5 Hz, 1 H), 2.40 (bs, 1 H), 2.22–2.00 (m, 2 H), 1.70–1.40 (m, 3 H), 1.28–1.40 (m, 2 H); IR ν (CHCl_3) 2970, 2879, 2833, 2729, 1721 cm^{-1}].

Treatment of 199 mg (1.8 mmol) of 37 with LiCHBr_2 according to the general procedure, but allowing the reaction mixture to warm to 10 °C before hydrolysis, gave 295 mg (81% yield) of a >95:5 mixture of 46 and 47. ^{13}C NMR for 47: δ obsd (calcd) 191.0 (CHO), 74.8 (78.3) (C-2), 43.8 (45.7) (C-1), 39.5 (42.0) (C-3), 36.7 (36.8) (C-4), 36.3 (37.1) (C-7), 28.8 (29.1) (C-5), 25.7 (24.1) (C-6).

Treatment of 122 mg of a mixture of 46 and 47 with $\text{HC}(\text{OCH}_3)_3$ and K-10 clay according to the general procedure provided 109 mg of a mixture of 2-*exo*-bromo-2-*endo*-(dimethoxymethyl)bicyclo[2.2.1]heptane (48) and 2-*endo*-bromo-2-*exo*-(dimethoxymethyl)bicyclo[2.2.1]heptane (49) as a pale yellow oil. Kugelrohr distillation of this material at 75 °C and 0.5 Torr gave 100 mg (65% yield) of a colorless oil that consisted of a mixture of 48 [^{13}C NMR δ 109.0 [$\text{CH}(\text{OCH}_3)_2$], 77.0 (C-2), 58.9 (OCH_3), 57.1 (OCH_3), 49.8 (C-1), 46.9 (C-3), 39.0 (C-7), 37.4 (C-4), 28.0 (C-5), 24.9 (C-6); ^1H NMR δ 3.96 (s, 1 H), 3.66 (s, 3 H), 3.60 (s, 3 H)] and 49 [^{13}C NMR δ 109.5 [$\text{CH}(\text{OCH}_3)_2$], 58.4 (OCH_3), 58.2 (C-1), 57.6 (OCH_3), 44.9 (C-3), 37.3 (C-4), 36.6 (C-7), 29.3 (C-5), 25.6 (C-6); ^1H NMR δ 4.64 (s, 1H), 3.55 (s, 3H), 3.54 (s, 3H)] in a ratio of ca. 90:10, respectively. Anal. of 48/49 mixture. Calcd for $\text{C}_{10}\text{H}_{17}\text{BrO}_2$: C, 48.21; H, 6.88. Found: C, 48.23; H, 6.71.

2-*endo*-Bicyclo[2.2.1]heptanecarboxaldehyde (52) and 2-*exo*-Bicyclo[2.2.1]heptanecarboxaldehyde (53). Anhydrous dimethyl sulfoxide (0.85 mL, 11 mmol) was added slowly to a stirred solution of oxalyl chloride (0.70 g, 5.5 mmol) in CH_2Cl_2 (15 mL) that was maintained at –78 °C under N_2 . At this point, a solution of a 75:25 mixture of 50/51 (634 mg, 5.0 mmol) in CH_2Cl_2 (5 mL) was added slowly to the reaction mixture. After the reaction mixture had been stirred for 20 min at –78 °C, triethylamine (3.6 mL) was added dropwise, and the resulting mixture was allowed to warm slowly to room temperature. The reaction then was quenched with H_2O (25 mL), and the aqueous and organic phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). These extracts were combined with the organic phase of the reaction mixture, and

the resulting solution was washed sequentially with 5% aqueous HCl (2 × 20 mL) and saturated aqueous NaHCO₃ (20 mL) and then dried over anhydrous MgSO₄. Evaporation of the solvent at reduced pressure provided 569 mg (92% yield) of a 75:25 mixture of **52** [¹³C NMR δ 204.9 (CHO), 53.9 (C-2), 40.2 (C-7), 38.9 (C-1), 37.4 (C-4), 29.4 (C-3 and C-5 coincident), 24.7 (C-6)] and **53** [¹³C NMR δ 203.1 (CHO), 54.6 (C-2), 38.2 (C-1), 36.2 (C-7), 36.2 (C-4), 30.2 (C-3), 29.5 (C-5 or C-6), 29.2 (C-5 or C-6)].

Treatment of 180 mg of a 75:25 mixture of **52:53** with HC(OCH₃)₃ and K-10 clay according to the general procedure provided 150 mg of a mixture of **54** [¹³C NMR δ 106.6 [CH(OCH₃)₂], 52.7 (OCH₃), 51.9 (OCH₃), 41.8 (C-2), 39.8 (C-7), 38.5 (C-1), 36.9 (C-4), 33.1 (C-3), 29.9 (C-5), 23.6 (C-6)] and **55** [¹³C NMR δ 107.2 [CH(OCH₃)₂], 52.7 (OCH₃), 52.4 (OCH₃), 44.3 (C-2), 38.2 (C-1), 36.6 (C-4), 36.0 (C-7), 33.4 (C-3), 30.0 (C-5 or C-6), 28.9 (C-5 or C-6)] as a colorless oil.

Reaction of Bicyclo[3.2.1]octan-6-one (40) with (Dibromomethyl)lithium. Treatment of **40**¹⁶ (221 mg, 1.78 mmol) with LiCHBr₂ according to the general procedure gave 368 mg of a brown-black oil. Analysis of this material by quantitative ¹³C NMR spectroscopy showed that it consisted of a mixture of **60** and **61** in a ratio of 95:5, respectively. Flash column chromatography of this material with 90:10 petroleum ether/CH₂Cl₂ provided 174 mg (45% yield) of a 95:5 mixture of **60/61** as a yellow oil. The major isomer showed: ¹³C NMR δ 189.8 (CHO), 77.0 (C-6), 47.4 (C-5), 38.3 (C-7 or C-8), 38.2 (C-7 or C-8), 34.9 (C-1), 31.2 (C-2), 28.3 (C-4), 17.2 (C-3); ¹H NMR δ 9.59 (s, 1 H), 2.78 (dd, *J* = 15.2 and 1.8 Hz, 1 H), 2.66 (bs, 1 H), 2.54–2.24 (m, 3 H), 1.86–1.13 (m, 7 H); IR ν (CHCl₃) 3030, 2946, 2863, 2729, 1720 cm⁻¹. The minor isomer showed: ¹³C NMR δ 190.7 (CHO), 73.8 (C-6), 39.7 (C-5), 37.1 (C-7 or C-8), 36.2 (C-7 or C-8), 35.2 (C-1), 31.9 (C-2), 30.2 (C-4), and 19.1 (C-3).

Treatment of 113 mg of a 95:5 mixture of **60/61** with HC(OCH₃)₃ and K-10 clay according to the general procedure provided 104 mg (76% yield) of 6-*exo*-bromo-6-*endo*-(dimethoxymethyl)bicyclo[3.2.1]octane (**62**) as a pale yellow solid (containing some of the minor isomer **63**). Recrystallization of this material from hexanes gave **62** as a white solid: mp 59–60 °C; ¹³C NMR δ 107.0 [CH(OCH₃)₂], 80.9 (C-6), 59.3 (OCH₃), 57.4 (OCH₃), 48.5 (C-5), 43.5 (C-7), 39.1 (C-8), 34.1 (C-1), 32.2 (C-2), 28.2 (C-4), 19.2 (C-3); ¹H NMR δ 4.22 (s, 1 H), 3.73 (s, 3H), 3.64 (s, 3H), 2.67–2.33 (m, 3 H), 2.09 (d, *J* = 15 Hz, 1 H), 1.77–1.38 (m, 8 H). Anal. Calcd for C₁₁H₁₉BrO₂: C, 50.20; H, 7.28. Found: C, 50.18; H, 7.16.

Reaction of Noradamantan-2-one (64) with (Dibromomethyl)lithium. Treatment of **64**^{21,22} (205 mg, 1.5 mmol) with LiCHBr₂ according to the general procedure gave 376 mg of a brown oil. Analysis of this material by ¹³C NMR spectroscopy showed that it consisted of a mixture of **67** and **68** in a ratio of 85:15, respectively. Flash column chromatography of this material gave 258 mg (75% yield) of **67** as a yellow semisolid [¹³C NMR δ 188.1 (CHO), 85.3 (C-2), 47.4 (C-1 or C-3), 43.9 (C-1 or C-3), 43.0 (t), 42.1 (t), 41.6 (t), 37.3 (C-5 or C-7), 35.4 (C-5 or C-7), 33.6 (t); ¹H NMR δ 9.49 (d, *J* = 0.7 Hz, 1 H), 3.03–2.91 (m, 1 H), 2.82–2.57 (m, 3 H), 2.23 (bs, 1 H), 1.97 (dm, *J* = 14 Hz, 1 H), 1.84–1.56 (m, 6 H); IR ν (CHCl₃) 2945, 2876, 2735, 1719 cm⁻¹] and 88 mg (19% yield) of **68** as a white solid [mp 84.5–85 °C (recrystallized from pentane); ¹³C NMR δ 85.2 (C-2), 60.4 (CHBr₂), 44.3 (C-1 or C-3), 43.7 (C-1 or C-3), 43.7 (t), 37.2 (t), 37.0 (C-5 or C-7), 36.2 (t), 34.8 (C-5 or C-7), 32.5 (t); ¹H NMR δ 5.92 (s, 1 H), 2.49–2.30 (m, 4 H, containing a 1 H s at δ 2.45), 2.18 (bs, 1 H), 2.13–1.95 (m, 2 H), 1.75–1.57 (m, 3 H), 1.52–1.33 (m, 3 H). Anal. Calcd for C₁₀H₁₄Br₂O: C, 38.74; H, 4.55. Found: C, 38.68; H, 4.61].

Treatment of 110 mg of **67** with HC(OCH₃)₃ and K-10 clay according to the general procedure provided 103 mg (78% yield) of 2-*exo*-bromo-2-*endo*-(dimethoxymethyl)noradamantane (**75**) as a yellow solid. Recrystallization of this material from hexanes gave **75** as a colorless solid: mp 84.5–85 °C; ¹³C NMR δ 106.8 [CH(OCH₃)₂], 87.8 (C-2), 59.3 (OCH₃), 57.1 (OCH₃), 50.8 (C-1 or C-3), 45.7 (C-1 or C-3), 44.0 (t), 43.2 (t), 38.5 (t), 37.1 (C-5 or C-7), 35.0 (C-5 or C-7), 34.1 (t); ¹H NMR δ 4.58 (s, 1 H), 3.63 (s, 3 H), 3.59 (s, 3 H), 2.94–1.15 (m, 12 H). Anal. Calcd for C₁₂H₁₈BrO₂: C, 52.38; H, 6.96. Found: C, 52.21; H, 6.99.

Reaction of 8,9-Didehydroadamantan-2-one (69) with (Dibromomethyl)lithium. Treatment of **69**²³ (296 mg, 1.5 mmol) with LiCHBr₂ according to the general procedure gave 726 mg of a brown oil. Analysis of this material by ¹³C NMR spectroscopy showed that it contained only 2-(dibromomethyl)-8,9-didehydroadamantan-2-ol (**72**). Column chromatography of this material on 60–200 mesh silica gel with CH₂Cl₂ as the eluent provided 519 mg (81% yield) of **72** as a white solid: mp 97–97.5 °C; ¹³C NMR δ 72.0 (C-2), 61.0 (CHBr₂), 53.7 (C-6), 36.0 (C-3), 31.1 (C-4 or C-10), 30.5 (C-5 or C-7), 30.3 (C-5 or C-7), 29.6 (C-4 or C-10), 29.4 (C-1), 27.8 (C-8 or C-9), 27.1 (C-8 or C-9); ¹H NMR δ 6.24 (s, 1 H), 2.36 (s, 1 H), 2.40–1.30 (complex m, 12 H). Anal. Calcd for C₁₁H₁₄Br₂O: C, 41.02; H, 4.38. Found: C, 41.19; H, 4.21.