equatorial approach of $^{17}OH^-$ in the axial ester than by axial approach in the equatorial ester, presumably for steric reasons. No simple correlation was found between results for different axial and equatorial leaving groups; however, for a poor leaving group (OC_6H_5, OC_6H_4OMe-*p*) the spread of the retention/inversion ratio between axial and equatorial isomers is greater than for a better leaving group ($OC_6H_4NO_2$-*p*). The stereochemical outcome of these reactions is quite different from that in the hydrolysis of the six-membered ring in cAMP that proceeds with inversion at phosphorus[33] presumably because one of the oxygen atoms of the ring is always in the apical position[24] needed for the leaving group.

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Investigations on Transition-State Geometry in the Aldol Condensation

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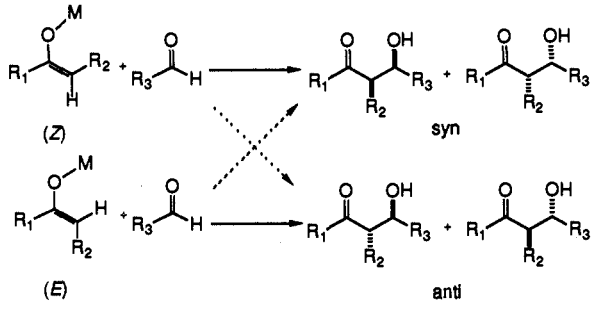
Abstract: Model compounds **1** and **2** have been studied to elucidate the relative orientation of enolate and carbonyl moieties in the aldol reaction. The syntheses of these compounds have been achieved from a common precursor derived from fragmentation of adamantane. Models of the limiting transition structures reveal that the cyclization must proceed through either a synclinal or antiperiplanar orientation of the aldehyde with respect to the enolate. Cyclizations of **1** were unexpectedly sluggish due to slow deprotonation of the tertiary center. The cyclization of **2** was very rapid and was studied as a function of enolate type (metal counterion), base type, solvent, and additive. The reactions of metal enolates showed an increasing preference for the syn product **5** with increasing cation coordinating ability ($K^+ < Na^+ < Li^+ < MgBr^+$). Attempted cyclization via boron and stannous enolates failed. The type of base and the choice of solvent had negligible effects on the selectivity. However, in the presence of strong cation-complexing agents, the model showed a strong preference for reaction via an antiperiplanar orientation of reactants giving the anti product **6** with high selectivity. The origin of the selectivities and the implication for enolate and transition structures are discussed.

Introduction and Background

The aldol reaction has developed into one of the most powerful and selective carbon–carbon bond forming reactions in synthetic organic chemistry.[1] Motivated by an interest in the total synthesis of polypropionate- and polyacetate-derived natural products such as macrolide and polyether antibiotics,[2] many research groups have developed methods that allow for stereoselective construction of β-hydroxy carbonyl compounds.[3] The efforts of Evans,[4] Masamune,[5] Mukaiyama,[6] Paterson,[7] Corey,[8] and others[9] in developing

Scheme I



a strategy based on chiral auxiliaries and additives have allowed the synthesis of each of the four possible aldol products in virtually enantiomerically pure form (Scheme I).[9,7]

The underlying factors responsible for controlling the stereoselectivity in the aldol condensation have also been the subject of numerous investigations.[1,10-12] The aldol reaction succeeds

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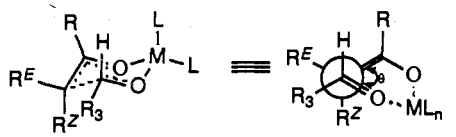

Figure 1. Zimmerman–Traxler transition structure for aldol reactions.

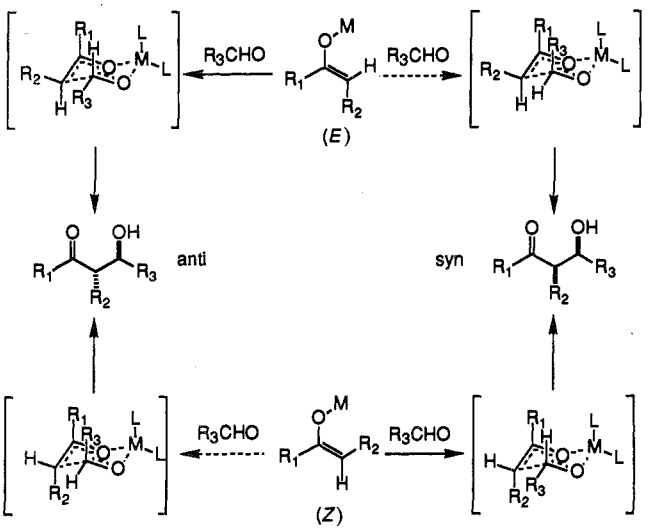

Figure 2. Chairlike transition-structure models for formation of the possible products from *Z*- and *E*-enolates.

with a wide variety of metals (e.g., B, Li, Na, K, Sn, Zr, Zn, Hg, and others), and the stereochemical outcome is often dependent on the nature of the metal, size of the substituents on the reactants, and the reaction conditions. This dependence can be classified into three main groups: (1) type 1, in which the product syn/anti ratios reflect the *E*/*Z* ratio of the enolate, (2) type 2, in which the reaction is syn-selective regardless of enolate geometry, and (3) type 3 reactions, in which the reaction is anti-selective regardless of enolate geometry.

In type 1 reactions, which employ group I, II, or III metals as the counterions, *Z*-enolates give predominantly syn products while *E*-enolates give predominantly anti products (Scheme I). This correlation is stronger for *Z*-enolates than for *E*-enolates. Steric bulk of substituents has a marked influence on these reactions: the previous trend is stronger when R_1 and R_3 are sterically demanding, while the normal *Z*-syn, *E*-anti trend is reversed when R_2 is very large. The correlation is also stronger and the steric effects are more important for boron enolates than for enolates of other metals in groups I–III. These reactions have been suggested to occur via a closed or chairlike transition structure.

Type 2 reactions, which are syn-selective, encompass a wide range of enol derivatives, including enol silane additions to aldehydes (promoted by various Lewis acids[13] and fluoride[14]), enol stannanes,[15] zirconium enolates,[16] stannous enolates,[17] α-stannyl[18] and α-mercurio ketones,[19] and enol borates.[20] Proposals for both open (extended) transition structures and closed, boatlike transition structures have been advanced, but there is still much disagreement.

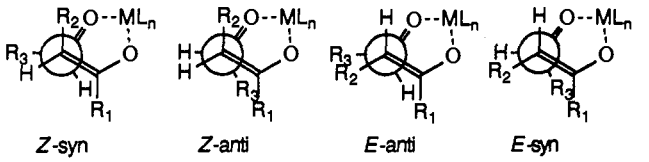

Figure 3. Skewed transition-structure models for aldol reactions of *Z*- and *E*-enolates.

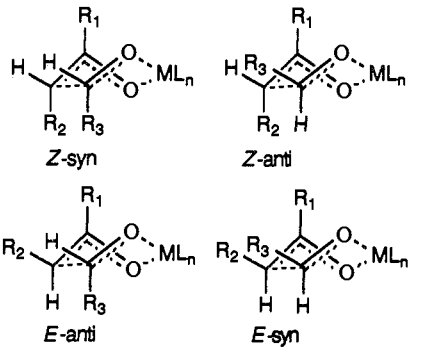

Figure 4. Boat transition-structure models for aldol reactions of *Z*- and *E*-enolates.

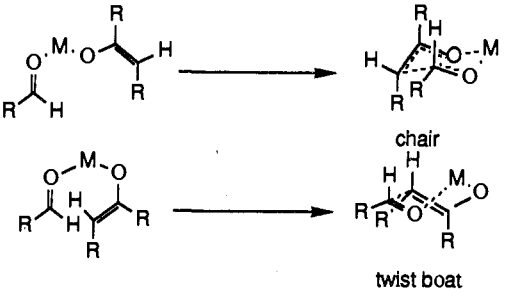

Figure 5. Preferred chair (*Z*-enolate) and twist-boat (*E*-enolate) transition states for aldol reactions of enol borates.

Finally, type 3 reactions, which afford anti products independent of enolate geometry, have recently been developed with use of ketene acetals[21] and ketene thioacetals.[22] Both open and closed transition structures have been proposed.

Transition-Structure Hypotheses. A number of transition-structure hypotheses have been formulated to explain the stereochemical course of the various types of aldol reactions. In the reactions of group I–III metal enolates, the first transition structure proposed was the "pericyclic" model suggested by Zimmerman and Traxler[23] in 1957 (Figure 1). This "closed", chairlike transition structure implies a synclinal[24] orientation between the enolate and carbonyl moieties with complexation of both reactants to the metal counterion. This chelation enforces a gauche arrangement of the reacting carbon–carbon and carbon–oxygen double bonds, implying a dihedral angle of 60°. In this chairlike arrangement, the aldehyde substituent R_3 prefers to take up an equatorial position for steric reasons, especially when R_1 is large, leading to the observed trend that *Z*-enolates afford predominantly syn-aldol adducts while *E*-enolates tend to give anti products (Figure 2).

As mentioned previously, *Z*-enolates exhibit a greater inherent stereoselectivity compared to *E*-enolates.[1,10c] This trend is not easily explained by the Zimmerman–Traxler model, and the basic transition structure has been modified to account for this ob-

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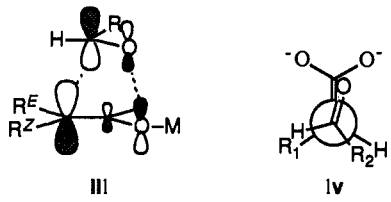


III IV

Figure 6. Anh–Thanh model (iii) and the Mulzer model (iv) for aldol reactions.

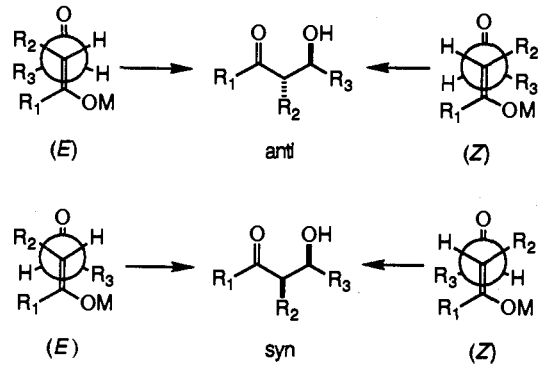


Figure 7. Acyclic or "open" transition-structure model for aldol reactions.

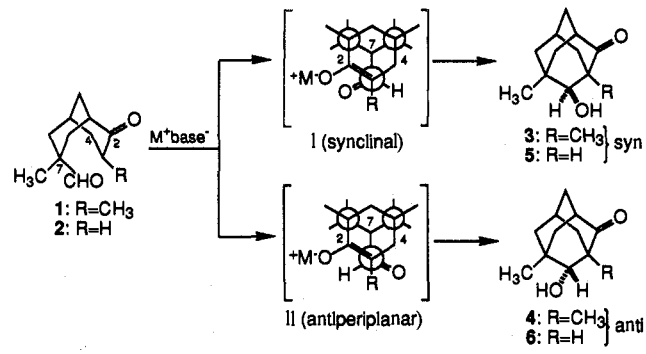
servation. Both Dubois[10c] and Heathcock[1c] have proposed a skewing of the idealized 60° dihedral angle about the forming carbon–carbon bond in the chairlike transition structure toward 90°. As shown in Figure 3, the preferred transition structure for the *Z*-enolate suffers no serious steric interactions, while in the transition structure leading to anti-aldol products, R_3 is now quite near R_1. However, for the *E*-enolate, *both* transition structures suffer steric interactions, leading to diminished stereoselectivity.

Evans[1a,25] has suggested that the diastereomeric boat transition structures may become important when there are significant steric interactions between groups on the forming bond (Figure 4). Evans' model predicts that an increase in the size of R_2 in the case of a *Z*-enolate would lead to a higher proportion of the anti-aldol product because the boat now becomes an alternative to the chair. On the other hand, for an *E*-enolate, an increase in the size of R_2 would have little effect on the stereoselectivity of the reaction.

Hoffmann[26a] has proposed that *E*-enol borates react via a twist-boat transition structure, whereas the *Z*-enol borates react via the normal chair transition structure. Unlike enol borinates, enol borates belong of the type 2 classification, affording syn-aldol products regardless of the enol geometry (Figure 5). Semiempirical calculations by Gennari[26b] support this hypothesis. A similar twist-boat/chair hypothesis was advanced by Nakamura and Kuwajima in the reaction of titanium enolates.[26c,d]

Anh and Thanh[27] have suggested that the stereochemistry of the aldol reaction can be explained by assuming that only directionality and frontier orbital interactions play essential roles in determining the transition structure. Their model places the enolate and carbonyl moieties essentially in parallel planes with a torsional angle of about 30° (Figure 6). Earlier, Mulzer[28] proposed that HOMO (enolate)–LUMO (aldehyde) interactions are responsible for the syn selectivity observed for lithium salts of acid dianions. He proposed a synperiplanar transition structure with essentially a 0° dihedral angle (Figure 6). Both of these authors highlight the pseudopericyclic nature of the transition structures implied by the FMO interactions.

Scheme II



In addition to cyclic transition structures, "open" or extended transition structures have been proposed. Yamamoto[29] has invoked an acyclic transition structure with an antiperiplanar orientation of enolate and carbonyl moieties to explain the syn selectivity of zirconium and tin enolates independent of enolate geometry (Figure 7). The transition structures leading to anti aldol products are destabilized relative to those leading to syn by virtue of a gauche steric interaction between R_2 and R_3. Gennari[22] also invokes an open transition-structure model with an antiperiplanar disposition of reactants to explain the anti selectivity seen in aldol reactions of thioester silyl ketene acetals.

A recent ab initio molecular orbital analysis of the transition structures for various aldol reactions has been reported by Houk.[30] These calculations support the ideas of (1) an open transition structure for a metal-free enolate (no FMO stabilization), (2) a closed transition structure for lithium enolates with distorted attack angles[31] due to the short bonds to lithium and narrow angles, and (3) a close balance of chair and twist-boat closed transition structures for enol borinates and borates depending on substituents on the enolate and on boron.

Model Design. The ability to *rationally* design new stereoselective reactions or modify existing methods must ultimately lie in an accurate understanding of the origin of stereogenesis and the elements that govern stereocontrol. The transition structures depicted previously contain a wide variety of orientations of the enolate and carbonyl moieties in order to explain the stereochemical features of the products observed; they cannot all be correct. Furthermore, these transition-structure hypotheses are based on data obtained from *intermolecular* aldol reactions. Thus, the orientation of the enolate and carbonyl groups can only be *assumed*, since the intermolecular nature of the reactions makes it impossible to unambiguously assign the relative disposition of the reactants in the transition structure. We therefore decided to investigate the transition-structure geometry in the aldol reaction utilizing a model system designed to explicitly address the following questions: (1) is there a general orientational preference for the reactants in each of the three types of aldol reactions, (2) is there an intrinsic preference for the orientation of the reacting double bonds in the aldol condensation,[32] and (3) is the orientation of reactants dependent upon experimentally controllable factors such as metal counterion, additives, solvent, and temperature?

Selection of an appropriate model for the study is crucial and must overcome several problems: (1) forcing the reactants into conformations that correspond to open and closed transition states without introducing any extraneous steric bias, (2) making the reaction irreversible so product ratios reflect kinetically controlled aldol reactions, (3) the necessity for unambiguous electrophilic and nucleophilic components, and (4) making the model amenable

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(26) (a) Hoffmann, R. W.; Ditrich, K.; Froesch, S. *Tetrahedron* **1985**, *41*, 5517. (b) Gennari, C.; Todeschini, R.; Beretta, M. G.; Favini, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 612. (c) Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1983**, 3343. (d) Nakamura, E.; Kuwajima, I. *Acc. Chem. Res.* **1985**, *18*, 181.
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(31) (a) Bürgi, H. B.; Schefter, E.; Dunitz, J. D. *Tetrahedron* **1975**, *31*, 3089. (b) Bürgi, H. B.; Dunitz, J. D.; Shefter, E. *J. Am. Chem. Soc.* **1973**, *95*, 5065.
(32) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413.

to investigation of the various types of enolates and reaction conditions.

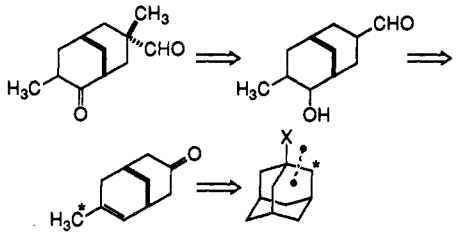
The model systems, **1** and **2** (Scheme II), were selected on the basis of the previous considerations.[33] Foremost among them was the decision to employ an intramolecular aldol reaction, thus allowing for a direct deduction of transition-structure geometries by correlation with product ratios. Inspection of molecular models reveals that the aldehyde is constrained to two limiting reactive geometries, i and ii, which correspond to synclinal (closed transition structure) or antiperiplanar (open transition structure) orientations, respectively. Reactions through these limiting conformations leads to the diastereomeric alcohols **3** (**5**) and **4** (**6**), thus providing a measure of the synclinal/antiperiplanar preference in the transition structure. The nearly symmetrical nature of the starting keto aldehyde should minimize steric bias and thus allow for evaluation of the nature and magnitude of any orientational preference between the reactants under various conditions. Formation of the highly stable adamantane skeleton should ensure kinetic control in the reaction. The aldehyde is nonenolizable and can serve only as the electrophilic component in the cyclization, thus assuring unambiguous electrophilic and nucleophilic components in the cyclization. Finally, there was no apparent reason that these models would be incompatible with any of the variety of conditions that we planned to utilize in our investigations.

Nevertheless, we recognized several potential problems with the model systems. The product alcohols **3** (**5**) and **4** (**6**) are diastereomers, and their ground-state energies cannot be assumed equal. If this energy difference manifests itself in the competing transition states, the product distribution may reflect this steric component. However, the general facility of aldol reactions at low temperatures coupled with the presumably large negative $\Delta H°$ upon forming the very stable adamantane skeleton suggests that the cyclizations of **1** and **2** should proceed via an eductlike (early) transition structure. Thus, the contribution of any ground-state energy difference in the products is expected to be insignificant.

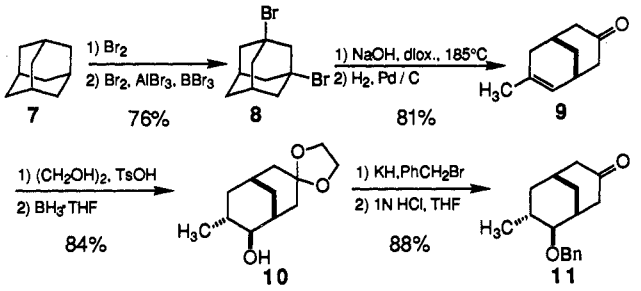
A more serious problem, however, is a potential steric bias in the starting keto aldehydes **1** and **2**. Although nearly symmetrical, there does exist a hybridization difference between the sp^2 ketone carbon (C(2)) and the sp^3-hybridized C(4) carbon. This difference may alter the steric environment around the aldehyde to such an extent as to bias one transition structure relative to the other due to this asymmetry. We felt this would make a fairly small contribution to the overall energy difference between the open and closed transition structures in these cyclizations.

Finally, a valid and important criticism of these models is that their intramolecular nature restricts conformational space to such an extent that there could be geometries available in intermolecular aldol reactions that are inaccessible in our system. For example, reaction via a boat conformation is not geometrically possible in our model system, yet these conformations have been put forward in some cases. Therefore, this model may not reflect the geometrical preferences for reactants in all intermolecular aldol reactions, and any extrapolation of the results obtained in this study to intermolecular aldol reactions must be done with caution. *However, we feel that it is even more tenuous to draw conclusions about the relative merits of competing transition structures in intermolecular reactions where selectivities of even 100/1 at −78 °C constitute only 1.8 kcal/mol.* It is, at best, naive to assume that this energy difference, corresponding to ca. 10% of the overall activation energy, is uniquely localized in a single feature as is implied by the existing models. Thus, a clear shortcoming of this system is also its strength in that we can excise with high accuracy exclusively the contribution of geometrical orientation, which must also be operative in the intermolecular systems. In sum, we felt the positive aspects of these structures far outweighed the problems and would provide us with the best possible method for *determination of the role the metal counterion and other variables play in determining the preference for an open or closed transition structure in the aldol condensation.*[34]

Scheme III



Scheme IV



Results

Model 1. Synthesis. Model system **1** proved to be more difficult to synthesize than was first anticipated.[34b] A brief retrosynthetic analysis is shown in Scheme III. The bicyclic skeleton can arise from a fragmentation of a suitable adamantane derivative, leading back to readily available adamantane as the starting material. Since adamantane contains 10 of the 12 carbons in **1**, much of the strategy centers around proper functionalization.

The synthesis of model system **1**, which ultimately proved successful, began with sequential 1,3-bromination of adamantane (Scheme IV). Adamantane was first monobrominated[35] in excellent yield by treatment with bromine at 150 °C and then subjected to the conditions[36] for dibromination to provide crystalline 1,3-dibromide **8** in a 76% overall yield. Fragmentation of the dibromide with 1 M NaOH/dioxane in a steel bomb at 185 °C[37] afforded the bicyclic *exo*-methylene ketone in 78% yield. This olefin was easily isomerized to the more stable endocyclic olefin by use of hydrogen and 5% palladium on charcoal[38] to produce ketone **9** in 98% yield.

The ketone was protected by treatment with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid. The olefin was hydroborated with BH_3/THF,[39] which, after oxidative workup with alkaline hydrogen peroxide, afforded alcohol **10** in 84% yield for the two steps. Alcohol **10** was obtained as a single stereoisomer, and although the stereochemistry of the hydroboration was not rigorously established at this stage, examination of models suggested a preference for exo face attack. Note the configuration of these centers is of no consequence, as both stereocenters are destroyed in subsequent reactions. Formation of the benzyl ether by treatment with KH and benzyl bromide followed by removal of the ketal by use of 1 N HCl in THF afforded ketone **11** in 88% combined yield.

The next step in the plan was to homologate the ketone function into an aldehyde. Unfortunately, many of the common direct methods failed.[40-42] In considering an indirect approach, we were

(33) For aldol cyclization of a related bicyclo[3.3.1]nonane system, see: Bishop, R.; Parker, W.; Stevenson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 565.

(34) (a) For a preliminary report, see: Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032. (b) Henke, B. R. Ph.D. Thesis, University of Illinois, 1989.

(35) Baughmann, G. L. *J. Org. Chem.* **1964**, *29*, 238.

(36) Stetter, H.; Schwarz, M.; Hirschhorn, A. *Chem. Ber.* **1959**, *92*, 1629.

(37) Gagneux, A. R.; Meier, R. *Tetrahedron Lett.* **1969**, 1365.

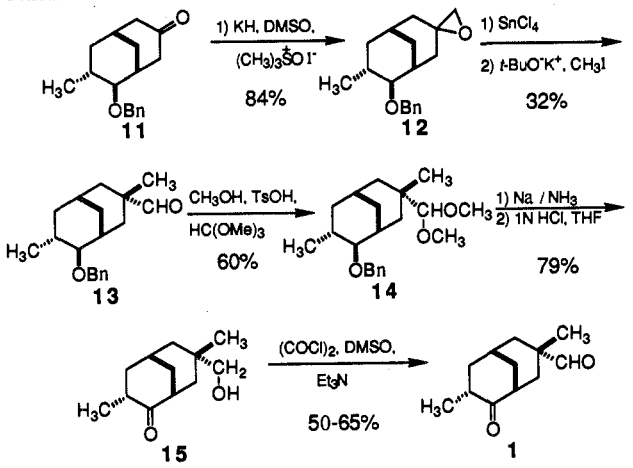
(38) Kimoto, K.; Imagawa, T.; Kawanisi, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3698.

(39) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses Via Boranes*; Wiley-Interscience: New York, 1975.

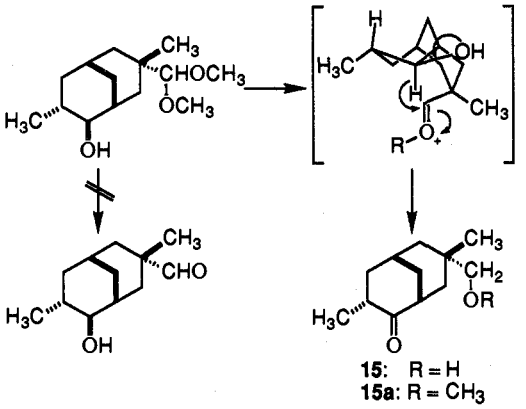
(40) Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.

(41) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Chem. Commun.* **1977**, 314.

Scheme V



Scheme VI



attracted to the sulfur-based ylides developed by Corey.[43] Treatment of ketone **11** with dimethyloxosulfonium methylide cleanly afforded epoxide **12** in 86% yield as a single diastereomer, presumably that arising from methylene addition to the exo face (Scheme V). Treatment with either boron trifluoride etherate or tin tetrachloride in methylene chloride gave the desired aldehyde in 45–65% as an inseparable mixture of epimers.[43,44] This reaction is capricious and must be done such that the neat Lewis acid is added at such a rate that the temperature of the reaction is maintained below −60 °C.[45]

Alkylation of the aldehyde was achieved by deprotonation with potassium *tert*-butoxide in *tert*-butyl alcohol/THF followed by addition of methyl iodide[46] to afford **13** as a single diastereomer in 64% yield. This result was pleasing since direct alkylation of aldehydes is often problematical due to competing aldol reaction.[47] The configuration of the alkylated aldehyde was again not rigorously proven at this time, but as previously, models indicated a strong preference for exo attack of the electrophile. This assumption was later verified by the successful cyclization of model system **1**.

Attempted hydrogenolysis of the benzyl ether with 5% palladium on charcoal under a variety of conditions led only to decomposition. Therefore, the aldehyde moiety of **13** was protected as a dimethyl acetal by treatment with *p*-toluenesulfonic acid in methanol (60% yield). Removal of the benzyl group with use of sodium in ammonia now occurred in quantitative yield. Hydrolysis of the resulting hydroxy acetal with 1 N HCl in THF afforded keto alcohol **15** instead of the expected hydroxy aldehyde. Formation of **15** can be explained by an intramolecular hydride transfer from the alcohol to the putative oxocarbenium ion intermediate (Scheme VI). Isolation of small amounts of ether **15a** provides further support for this mechanism.[48] This process allowed us to confirm the stereochemistry of the hydroboration, since only an endo hydrogen atom is in the correct orientation for intramolecular delivery to the protonated aldehyde. Fortunately, this hydride transfer did not alter the synthetic plan since oxidation of the resulting keto alcohol can also provide model system **1**.

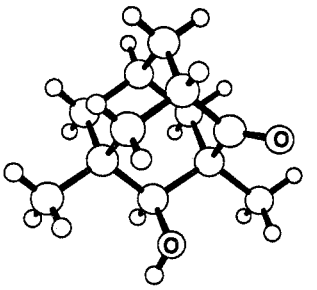
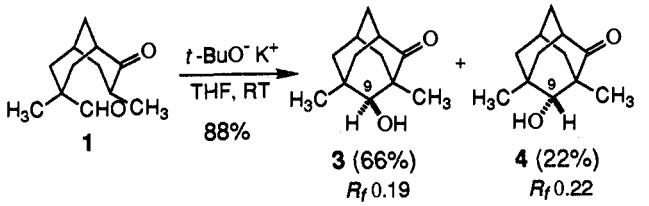


Figure 8. Chem 3D representation of syn adduct **3**.

Scheme VII



The anticipated (and hoped for!) lability of **1** toward aldol closure limited the choice of oxidation methods applicable to **15**. For example, oxidation with pyridinium dichromate,[49] DMSO/DCC,[50] and NCS/Me_2S[51] resulted in either no reaction or cyclization of keto aldehyde **1** under the reaction conditions. Swern oxidation[52] led to incomplete reaction and cyclization of the product under the reaction conditions. Ultimately, we found that quenching the reaction at temperatures below −25 °C with a pH 7 buffer solution suppressed the cyclization of product keto aldehyde. Workup then provided crude **1** along with 20–30% unreacted starting material. Purification of **1** also proved problematic as extensive cyclization occurred on chromatography with silica gel, basic alumina, and neutral alumina at room temperature and also upon attempted distillation. However, column chromatography on activity IV neutral alumina with use of a jacketed column cooled with circulating 2-propanol (−40 °C or below) afforded keto aldehyde **1** in 50–60% yield, free from starting material and cyclization products as judged by ^{1}H NMR analysis. Keto aldehyde **1** proved reasonably stable in the absence of acid or base and could be stored for up to 1 week at −20 °C under argon without decomposition.

Assignment of Aldol Adducts and Analytical Methods. As a prelude to our cyclization studies, the configuration of the diastereomeric aldol adducts needed to be assigned. Treatment of **1** with potassium *tert*-butoxide in THF at room temperature provided a 3/1 mixture of aldol adducts **3** and **4** (Scheme VII), which were separated by silica gel column chromatography. The

(42) (a) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 448. (b) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, 3535. (c) Kluge, A. F.; Cloudsdale, I. S. *J. Org. Chem.* **1979**, *44*, 4847. (d) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822.

(43) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(44) Rickborn, B.; Gerkin, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 1693.

(45) Recent optimization of this reaction allows for 85% yields reproducibly on a multigram scale: Lee, W. Unpublished results from these laboratories.

(46) (a) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**, 491. (b) Letourneux, Y.; Büjüktür, G.; Ryzlak, M. T.; Banerjee, A. K.; Gut, M. *J. Org. Chem.* **1976**, *41*, 2288.

(47) (a) March, J. *Advanced Organic Chemistry*; John Wiley and Sons: New York, 1977; pp 422, 423. (b) Fleming, I. *Chimia* **1980**, *34*, 265.

(48) For recent discussions of intramolecular hydride transfer, see: (a) Mills, O. S.; Watt, C. I. F.; Whitworth, S. M. *J. Chem. Soc., Perkin Trans. 2* **1990**, 487. (b) Sherrod, M. J.; Menger, F. M. *Tetrahedron Lett.* **1990**, *31*, 459.

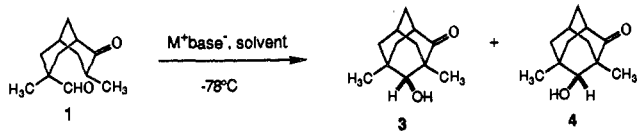
(49) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(50) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661.

(51) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.

(52) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

Table I. Cyclization of Model **1**[a]



entry	base[b]	solvent	temp, °C	time, h	syn (3)/anti (4)[c]	$\Delta\Delta G^{\ddagger}$
1	LiHMDS	THF	−55	6	71/29	0.35
2	NaHMDS	THF	−55	6.5	65/35	0.24
3	KHMDS	THF	−55	6	43/57	−0.11
4	LiHMDS	THF/HMPA	−55	6.5	36/64	−0.22
5	Bu_2BOTf/Et_3N	CH_2Cl_2	−20	10	NR	
6	$Sn(OTf)_2$/NMM	CH_2Cl_2	−20	10	NR	

[a] All cyclizations were performed with 1.1 equiv of base at −78 °C. [b] HMDS = hexamethyldisilazide. [c] Average of at least three runs within ±3%.

less polar, minor diastereomer was an oil that exhibited a ^1H chemical shift of 3.15 ppm for the methine proton H–C(9). The more polar major diastereomer was a crystalline solid whose ^1H NMR spectrum contained a resonance at 3.49 ppm for the H–C(9) proton. Models indicated the H–C(9) proton in the anti isomer **4** should be in the shielding cone[53] of the ketone and thus should be farther upfield than H–C(9) of the syn isomer. On the basis of this and the order of elution on TLC, we tentatively assigned the more polar diastereomer as the syn isomer.

To further support this assignment, ^1H NMR experiments using the lanthanide shift reagent $Eu(fod)_3$[54] were performed. However, these studies were inconclusive and in fact suggested the opposite assignment. The discrepancy was finally resolved by submitting the crystalline, major diastereomer to X-ray crystallographic analysis, which allowed us to unambiguously establish it indeed as the syn diastereomer (Figure 8).

Given the lability of **1** during purification, we initially felt that cyclization would be rapid at −78 °C, making careful monitoring of the cyclizations unnecessary. However, the inconsistent product ratios obtained from initial cyclization experiments caused us to question this hypothesis. Indeed, when the cyclization of **1** with lithium hexamethyldisilazide was followed by ^1H NMR, we discovered that the cyclization was surprisingly slow, requiring over 5 h for completion at −60 °C. Thus, an analytical method for monitoring the reactions also needed to be developed. Although gas chromatography could be used to resolve the diastereomeric syn- and anti-aldol adducts, keto aldehyde **1** cyclized to an extent of 70% or more on all GC columns used. The cyclizations could be monitored by HPLC by use of a 5-mm alumina column immersed in a −10 °C bath. Under these conditions, keto aldehyde **1** cyclized to an extent of only 10–20%.

Cyclizations of Model 1. The results of cyclization of model system **1** with various bases are collected in Table I. The reactions were prohibitively slow at −78 °C and consequently were run at −55 °C. That the cyclizations were operating under kinetic control was demonstrated by observing no equilibration when pure **3** or **4** was independently subjected to the reaction conditions. Inspection of the first three entries in Table I reveals that the syn selectivity decreases as the counterion changes from Li^+ to Na^+ to K^+, which parallels the decrease in coordination ability of the cation.[55] Although the selectivity for Li^+ is not high (ca. 2.5/1) and the selectivity change in going to K^+ not large (71/29 to 43/57, corresponding to a $\Delta\Delta G^{\ddagger}$ of 0.51 kcal/mol at −55 °C), the trend is definite and reproducible. The use of hexamethylphosphoric triamide (HMPA)[56] in cyclizations where lithium hexamethyldisilazide is the base produced a mildly anti-selective reaction (entry 4). Discussion of these trends is presented in

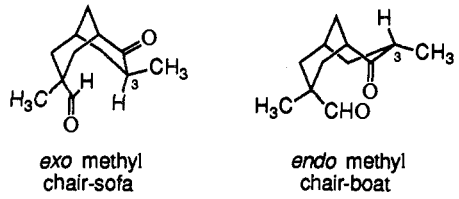


Figure 9. Preferred conformations of **1**, with different configuration of the C(3) methyl group.

conjunction with the results with model system **2**. Attempted enolate formation and subsequent aldol reaction with use of dibutylboron triflate as described by Evans[3c] led to no reaction after 10 h, even at −20 °C. Attempted cyclizations via a tin(II) enolate with use of stannous trifluoromethanesulfonate and *N*-methylmorpholine as described by Mukaiyama[57] also were unsuccessful.

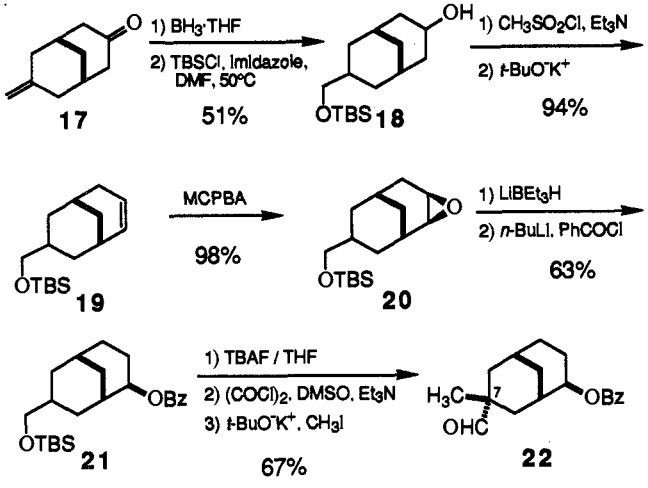
The long reaction time required for these cyclizations combined with the inability to effect a boron- or tin-mediated aldol reaction was of concern. We felt that, once formed, the enolate should undergo rapid aldol reaction considering the intramolecular nature of the reaction and the stability of the product alcohols. Therefore, we suspected that the steric crowding around H–C(3) must prohibit rapid enolate formation. Although the configuration of the C(3) methyl group is not known (epimerization is possible during either of the final two steps in the synthesis), either configuration makes the H–C(3) proton difficult to access. If the C(3) methyl group is in the exo configuration, then MM2 calculations[58] reveal that the bicyclo[3.3.1]nonane ring system adopts the chair-sofa conformation,[59] placing the H–C(3) proton endo, where it is shielded by the ring system and the formyl group (Figure 9). If the C(3) methyl group is endo, then the most stable conformation of the bicyclo[3.3.1]nonane is a chair-boat, which avoids steric interactions of the C(3) methyl with the formyl group. In this conformation, the H–C(3) proton is shielded by the C(9) methylene bridge. Convinced that this steric hindrance was the origin of the aforementioned problems, we abandoned our investigations on model system **1** in favor of model system **2**, in which the methyl group at C(3) was replaced by a proton.

Model 2. Synthesis. The most expedient method for construction of model system **2** was to modify the existing synthesis of model system **1**. Our synthetic approach to **2** was designed to use the C(10) olefinic carbon in the fragmentation product as a latent formyl group rather than use the ketone moiety. Unfortunately, this required a carbonyl 1,2-transposition of the C(3) ketone in compound **17**.

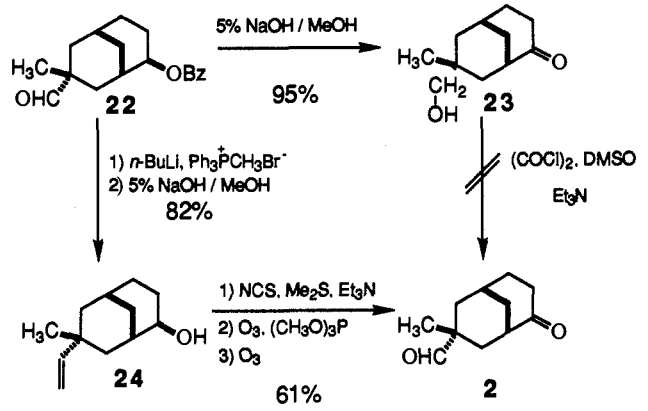
The new route began by treatment of ketone **17** with an excess of BH_3/THF[39] to provide a single diol in 50–60% yield after

(53) Johnson, C. E., Jr.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.
(54) For a review of lanthanide shift reagents and techniques, see: *Lanthanide Shift Reagents in Stereochemical Analysis*; Morrill, T. C., Ed.; VCH: New York, 1986.
(55) (a) Kebarle, P. *Ann. Rev. Phys. Chem.* **1977**, *28*, 445. (b) Morris, D. C. F. *Struct. Bonding (Berlin)* **1968**, *4*, 63. (c) Schade, C.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1987**, *27*, 169.
(56) House, H. O.; Prabhu, A. V.; Phillips, W. V. *J. Org. Chem.* **1976**, *41*, 1209.
(57) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353.
(58) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. Since this publication, numerous modifications and additional parameters have appeared. We thank Prof. Clark Still for providing the MACROMODEL (2.0) program.
(59) For previous studies concerning chair-boat equilibria in bicyclo[3.3.1]nonane systems, see: Peters, J. A.; Baas, J. M. A.; van de Graaf, B.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1978**, *34*, 3313 and references cited therein.

Scheme VIII



Scheme IX



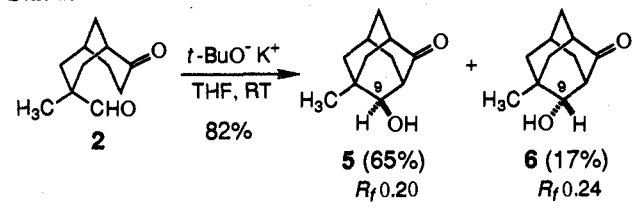
oxidation with alkaline hydrogen peroxide (Scheme VIII). The primary alcohol was selectively protected as the *tert*-butyldimethylsilyl ether to afford alcohol **18** in 51% overall yield for the two steps. Formation of the mesylate followed by elimination with potassium *tert*-butoxide in THF produced olefin **19** in 94% yield. Epoxidation with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 buffered with $NaHCO_3$ produced a single epoxide **20** in 98% yield. Previous examples of epoxidation in bicyclo[3.3.1]-nonane systems[60] suggested we had indeed obtained the desired *exo*-epoxide.

Treatment of epoxide **20** with $LiBEt_3H$ in THF[61] provided a single alcohol in 72% yield with complete regiocontrol. Since this reduction should be stereoelectronically controlled through trans-diaxial opening of the epoxide,[62] we were confident that the regiochemistry of the opening was in the desired sense. Formation of the benzoate ester **21** was achieved in 90% yield by treatment of the alcohol with *n*-BuLi followed by acylation with benzoyl chloride. Deprotection of the silyl ether with tetrabutylammonium fluoride in THF[63] followed by Swern oxidation[52] provided an epimeric mixture of aldehydes. Alkylation of this mixture with potassium *tert*-butoxide in *tert*-butyl alcohol/THF followed by addition of methyl iodide afforded **22** as a single stereoisomer in 67% overall yield for the three steps. By analogy to model system **1**, we assumed the methylation at C(7) occurred from the desired exo face.

The benzoate ester **22** was hydrolyzed by treatment with 5% NaOH in methanol/Et_2O to produce keto alcohol **23** in 95% yield. Apparently, the same facile intramolecular hydride transfer ob-

(60) Schaefer, J. P.; Endres, L. S.; Moran, M. D. *J. Org. Chem.* **1967**, *32*, 3963.
(61) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486.
(62) Fürst, A.; Scotoni, R. Jr. *Helv. Chim. Acta* **1953**, *36*, 1332, 1410.
(63) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1981.

Scheme X



served in the synthesis of **1** also occurs under basic conditions (Scheme IX). However, Swern oxidation of **23** followed by quenching at −25 °C and column chromatography on activity IV neutral alumina at low temperature, as described in the synthesis of **1**, provided a substantial amount of cyclized material. It appeared that keto aldehyde **2** was considerably more labile than **1**, a property that boded well for an accelerated cyclization rate but compounded the already significant purification problems. Further deactivation of the neutral alumina chromatographic support suppressed the problem of cyclization during chromatography but due to the diminished activity failed to cleanly separate **2** from starting keto alcohol **23**.

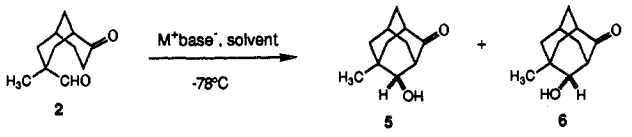
Clearly, we were constrained to an oxidation method that would generate keto aldehyde **2** without contamination from starting material or reagents. On the basis of our experiences with model system **1**, we felt alternative alcohol oxidation methods would be ineffective, so other aldehyde precursors were considered. Of the possible transformations available, we reasoned that ozonolysis[64] of a suitable olefinic precursor might provide a mild and clean method for generation of the requisite aldehyde. Olefination of aldehyde **22** with methylidenetriphenylphosphorane[65] provided the desired alkene in 90% yield, in which the aldehyde was "protected" as a vinyl group (Scheme IX). Subsequent hydrolysis of the benzoate ester with 5% NaOH/MeOH provided alcohol **24** in 91% yield. Oxidation of the alcohol under Corey–Kim conditions[51] led to formation of the desired ketone **25** in 94% yield. Ozonolysis at −78 °C in CH_2Cl_2 followed by reduction with trimethyl phosphite provided model system **2** without any traces of cyclized material. However, the reduction of the hindered ozonide was extremely slow with 1 equiv of trimethyl phosphite. Use of an excess increased the reduction rate but provided keto aldehyde **2** contaminated with the excess trimethyl phosphite, which was inseparable under the moderated chromatographic conditions. This problem was solved by resubjecting the reaction mixture containing keto aldehyde **2** and excess trimethyl phosphite to a *second* ozonolysis at −78 °C, which oxidized the remaining trimethyl phosphite to the much more polar trimethyl phosphate. Purification of this second ozonolysis mixture by low-temperature column chromatography on activity V neutral alumina provided pure keto aldehyde **2** in 55–70% yield.

Assignment, Analysis, and Controls. The configuration of the aldol adducts was again established by cyclization of **2** with potassium *tert*-butoxide in THF at room temperature, which provided the two epimeric keto alcohols **5** and **6** in a 3/1 ratio (Scheme X). These compounds were separated, and the stereostructure of each was assigned on the basis of the similarities in product ratio, polarity, and spectroscopic data with aldol adducts **3** and **4** from model system **1**.

It was immediately evident that model system **2** was much more reactive than model system **1**. Monitoring of the reaction of **2** with lithium hexamethyldisilazide in THF at −78 °C by ^1H NMR indicated complete consumption of starting material in less than 30 min. This increased kinetic lability avoided the necessity of finding an analytical method for monitoring the cyclizations. Thus, the protocol adopted for these reactions was to stir the reaction mixture (~0.01 M in substrate along with cyclododecane as an internal standard) for 30–60 min at −78 °C after addition of the appropriate base and any additives followed by quenching at −78 °C with a 1/1 mixture of methanol and pH 7 buffer solution. *All*

(64) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1978; Vol. 1.
(65) Schlosser, M.; Christmann, K. F. *Liebigs Ann. Chem.* **1967**, *708*, 1.

Table II. Effect of Metal Cation and Base Type in the Cyclization of Model System **2**[a]



entry	M^+	B[b]	solvent	yield,[d] %	syn (**5**)/ anti (**6**)[c,d]	$\Delta\Delta G^{\ddagger}$[e]
1	K	HMDS	THF	73	59/41	0.14
2	Na	HMDS	THF	69	67/33	0.27
3	Li	HMDS	THF	87	87/13	0.74
4	MgBr	HMDS	THF	94	96/4	1.23
5	Me_2Al	HMDS	THF	85	70/30	0.33
6[f]	K	HMDS	THF	*g*	75/25[f]	0.43
7	K	*t*-BuO	THF	89	65/35	0.24
8	Na	*t*-BuO	THF	91	67/33	0.27
9	Li	*t*-BuO	THF	99	83/17	0.62
10	K	H	THF	80	72/28	0.37
11	Bu_2BOTf	Et_3N	*h*	NR		
12	$Sn(OTf)_2$	*i*	CH_2Cl_2	NR		

[a] All cyclizations were performed with 1.1 equiv of base at −78 °C. [b] HMDS = hexamethyldisilazide. [c] Average of at least three runs within ±3%. [d] Ratios and yields were calculated on the basis of independently determined response factors vs cyclododecane. [e] Calculated at 195 °K. [f] Thermodynamic ratio, run at room temperature. [g] Yield not determined. [h] Dichloromethane or diethyl ether. [i] *N*-Methylmorpholine or *N*-ethylpiperidine.

cyclizations were proven to be under kinetic control by separately subjecting pure syn and anti alcohols to the reaction conditions and observing no equilibration. However, if the cyclizations with either potassium or sodium hexamethyldisilazide were warmed to room temperature for 1 h prior to quenching, we discovered that equilibration had occurred, indicating that retroaldol reaction could occur in the cyclizations. Interestingly, no retroaldol was observed at room temperature when lithium hexamethyldisilazide was employed as the base.

Cyclization Results of Model 2. Base and Counterion. The initial series of experiments probed the effect of the metal counterion (mono-, di-, and trivalent) and type of base (amide, alkoxide) on the stereochemical course of the cyclization (Table II). Entries 1–4 show the counterion-selectivity dependence for a given base, hexamethyldisilazide, in solvent THF. The data obtained parallel that from model system **1** (Table I) in that syn selectivity increases with the coordinating ability of the cation. *It is noteworthy that of all the entries, MgBrHMDS (entry 4) afforded the most syn-selective reaction (96/4).* The poor selectivity with the dimethylaluminum amide[66a] was surprising in light of the high selectivities observed in inter-[66b] and other intramolecular cases (see Discussion). Changing the base type had little effect, as seen from comparison of entries 1–3 with 7–10.

Cyclization under thermodynamic control (entry 6) with potassium hexamethyldisilazide resulted in a modest syn selectivity (75/25). This was demonstrated to be the thermodynamic equilibrium by separately subjecting pure syn- and anti-aldol adducts **5** and **6** to these same conditions and observing equilibration to the same 75/25 ratio. This corresponds to a $\Delta\Delta G°$ of 0.65 kcal/mol at 25 °C or 0.43 at −78 °C. The energy difference between **5** and **6** was found to be 0.6 kcal/mol by molecular mechanics calculation. The origin of this slight syn preference is unclear as is its contribution to the product ratios under kinetic control.

Finally, as with model system **1**, we were unable to induce cyclization of **2** via a boron enolate using a variety of methods.[3c,e,67] Successful generation of the boron enolate of ketone **25** (Scheme XI) was proved by trapping with propionaldehyde (66% yield),

Scheme XI

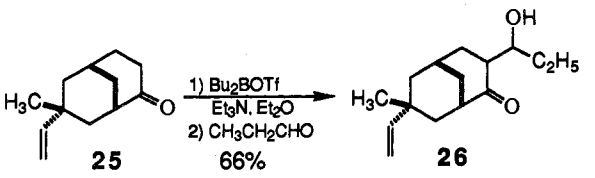


Table III. Effect of Solvent in the Cyclization of Model System **2**[a]

entry	base	solvent	yield,[b] %	syn (**5**)/ anti (**6**)[b,c]	$\Delta\Delta G^{\ddagger}$
1	$LiN(TMS)_2$	THF	87	87/13	0.74
2	$LiN(TMS)_2$	hexane	88	87/13	0.74
3	$LiN(TMS)_2$	toluene	84	87/13	0.74
4	$LiN(TMS)_2$	Et_2O	96	90/10	0.85
5	$LiN(TMS)_2$	DME	84	70/30	0.33
6	$KN(TMS)_2$	THF	73	59/41	0.14
7	$KN(TMS)_2$	toluene	90	89/11	0.81

[a] All reactions were performed with 1.1 equiv of base at −78 °C. [b] Ratios and yields were calculated on the basis of independently determined response factors vs cyclododecane. [c] Average of at least three runs within ±3%.

which suggested that the lack of cyclization in **2** was not due to an inability to form the enolate. In addition, cyclization attempts with use of an excess of boron reagent and base also failed. The lack of cyclization has important implications concerning the geometric requirements of the boron aldol reaction and are discussed in the following text. Similar problems were encountered upon attempted reaction via a stannous enolate under a variety of conditions.[57]

Solvent Effects. We next examined the effect of solvent on the stereochemical course of cyclization. The results are collected in Table III. With lithium hexamethyldisilazide as the base, the product distribution was unaffected by a change in solvent polarities ranging from hexane to THF. However, the use of DME resulted in a lowering of syn selectivity. With potassium hexamethyldisilazide as base, the solvent effect was much larger (entries 6 and 7). For this base in toluene, the reaction became much more syn-selective, remarkably comparable to the corresponding lithium base in the same solvent.

Additives. We have also investigated the dependence of cyclization stereochemistry on various additives that are known to influence the stereochemical outcome of enolate reactions (Table IV). Comparison of entries 1 and 2 shows that addition of 5 equiv of LiCl had no effect on the stereochemical course of addition with lithium hexamethyldisilazide in THF. However, addition of HMPA resulted in a large change in selectivity, resulting in a slightly anti-selective reaction. An even larger reversal was observed upon sequestering the cation with a macrobicyclic cryptand[68] (compare entries 4 and 5 and entries 6 and 7). Initial experiments with 18-crown-6[69] showed that deprotonation and cation complexation were competitive at −78 °C. To assure complete complexation of the cation, the cryptand was mixed with the base alone at room temperature and then added to a cold solution of **2**. In this way, *cyclization of the potassium enolate in the presence of 2 equiv of Kryptofix 222*[70] *in toluene resulted in a product ratio of 98/2, favoring the anti isomer.* The overall reversal is more dramatic in toluene where competitive solvation of the cation is less important.

Discussion

Before the implications of the stereochemical information provided by these studies are analyzed, it is valuable to frame the results in the context of other intramolecular aldol reactions. In

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(68) Lehn, J.-M. *Acc. Chem. Res.* **1978**, *11*, 49 and references cited therein.

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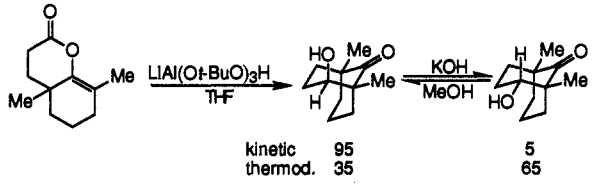
(70) Kryptofix 222 is the Aldrich tradename for 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.0]hexacosane.

Table IV. Effect of Additives in the Cyclization of Model System **2**[a]

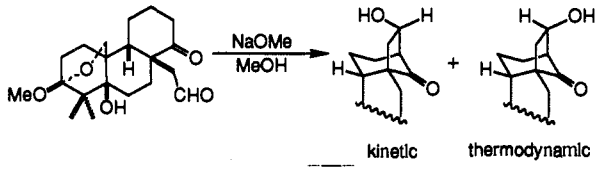
entry	base	solvent	additive (equiv)	yield,[b] %	syn (**5**)/anti (**6**)[b,c]	$\Delta\Delta G^{\ddagger}$
1	$LiN(TMS)_2$	THF	none	87	87/13	0.74
2	$LiN(TMS)_2$	THF	LiCl (5)	96	87/13	0.74
3	$LiN(TMS)_2$	THF	HMPA (5)	78	42/58	−0.13
4	$KN(TMS)_2$	THF	none	73	59/41	0.14
5	$KN(TMS)_2$	THF	Kryptofix 222 (2)	79	9/91	−0.90
6	$KN(TMS)_2$	toluene	none	90	89/11	0.81
7	$KN(TMS)_2$	toluene	Kryptofix 222 (2)	69	2/98	−1.51

[a] All reactions were performed with 1.1 equiv of base at −78 °C. [b] Ratios and yields were calculated on the basis of independently determined response factors vs cyclododecane. [c] Average of at least three runs within ±3%.

Scheme XII



Scheme XIII



contrast to the large number of stereodefined intermolecular aldol reactions, there are fewer examples of *stereodefined intramolecular reactions*. Intramolecular aldol reactions have found considerable application in the synthesis of bridged and fused polycyclic terpenoids.[71] However, in the majority of examples, the stereochemical issues are secondary to ring formation and often the hydroxyl group is eliminated or removed and thus the aldol stereochemistry not determined.[72] Furthermore, in only a handful of those cases where the aldol product was desired and the stereochemistry determined has the kinetic nature of the reactions been established. Interestingly, products derived from both synclinal and antiperiplanar transition structures have been found under kinetic control. For example, in developing the reductive aldol protocol, Martin[73] demonstrated that the high selectivity for the axial alcohol (synclinal transition structure) is kinetically derived as the equatorial alcohol dominates at thermodynamic equilibrium (Scheme XII). The magnitude and sense of selectivity in these reactions has been observed often.[74]

On the other hand, in a synthesis of enmein, Fujita[75] obtained a single adduct arising from intramolecular aldol reaction through an open transition structure (antiperiplanar) and demonstrated that this reaction was under kinetic control (Scheme XIII). Reaction under thermodynamic control gave the opposite aldol epimer. Open transition structures have been proposed for similar intramolecular aldol condensations under protic conditions, but

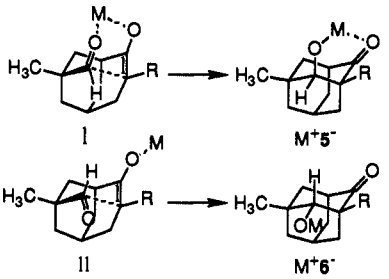


Figure 10. Open and closed transition structures and corresponding products.

kinetic control was not established.[76]

The data from model system **2** cyclizations show that the relative dispositions of reactants in the transition structure of the aldol condensation are dependent upon the metal counterion, solvent, and certain additives. When the counterion dependence from Table II is addressed, the results indicate an increase in syn selectivity with more strongly coordinating counterions ($K^+ < Na^+ < Li^+$).[77] One of the more surprising results was the significant component of anti products from open transition structures in reactions of alkali-metal enolates. Both the dramatic increase in enolate M–O bond length[78] and decrease in solvation enthalpy[56] in the series Li^+, Na^+, K^+ conspire to disfavor chelated transition structures. As these enolates may be in low aggregation states (see the following discussion), the expected hyperreactivity of such species could well explain their indifference to preorganization, even in nonpolar solvents. Moreover, in light of the distorted geometry found by Houk[30] in the transition structure for lithium enolate aldolization, it is not surprising that lithium was not extremely selective here. The rigid bicyclic skeleton might impose a mechanical restriction to optimization of the smaller angles required for lithium.[79] Insofar as the chelation must carry over into the aldolate, it should also be pointed out that the syn product is an axial 3-alkoxycyclohexanone (Figure 10).

The maximum syn selectivity for aldolization was found with $MgBr^+$, a cation often used when chelation in difunctional molecules is desired.[80] Indeed, this chelating ability has already been invoked in the superior selectivity for magnesium enolates (ketones[10c] and thioamides[81]) in the intermolecular aldol reaction. The high kinetic selectivity may be explained by a fortuitous combination of lower reactivity,[82] Lewis acidity, and appropriate

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(79) Preliminary molecular mechanics and semiempirical calculations of these fitted transition structures are in agreement with this hypothesis: Geissler, H. Unpublished results.

(80) For examples of the use of $MgBr_2$ in chelation-controlled reactions, see: (a) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1987**, *109*, 8117. (b) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, 1879.

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bond lengths. In this regard, it is interesting that the Mg–O bond length in a dimeric enolate (1.95 Å)[83] is exactly in the range found for the Li–O bond length in various enolate aggregates (1.9–2.0 Å).[84] It is also noteworthy that in the X-ray crystal structure the O–Mg bond is perpendicular to the enolate plane,[83] a condition required for aldol reactions of **2**. In addition, it was surprising that the reaction of the aluminum enolate was not highly selective. The Raphael–Martin aldol reactions[73,74] (presumably of aluminum enolates) give the "synclinal product" selectively. Similarly, the intermolecular reactions of dimethylaluminum enolates are highly selective examples of type 1 condensations.[66b] Nonetheless, the trend is clear that the cation plays an important organizational role in orienting the reactive double bonds. Thus, *there exists a strong preference for reaction through a closed transition structure with a synclinal orientation of reactants as the coordination ability of the metal counterion increases.* An important corollary to this conclusion is that *even in the presence of coordinating counterions the open transition structures are energetically accessible.*

Interestingly, we saw little stereochemical dependence on the base in the cyclizations. The primary role of the base used in intermolecular aldol reactions of acyclic enolates is to establish the enolate geometry.[1c,5b,11a,12a,85] However, in recent years the role of the base in the stereochemical outcome of the aldol addition itself has been recognized. Enantioselective enolate alkylations and aldol reactions employing chiral amine bases implicate a crucial role of the base in the structure and reactions of the enolates.[84] Crystallographic analyses of heteroaggregates have lent credence to the notions of base involvement in enolate chemistry.[84] Unfortunately, there are no studies to date on the effect of the base on the aggregate structure of enolates in solution.[86] The negligible effect of the base type observed in these reactions raises the interesting question as to whether aggregates are at all involved.

The nature of the solvent also had little effect on the stereochemical outcome of the reaction of lithium enolates. Cyclizations in the nonpolar solvent hexane were identical with the results in THF, indicating that the change in solvents of this polarity range does not affect the coordinating ability of the lithium ion. However, when the solvent was changed to DME, an interesting drop in syn selectivity was observed. The origin of this erosion in selectivity can be interpreted in terms of either monomeric or higher order structures. As a monomer, the change may simply be a competitive coordination of the lithium by the chelating solvent DME (perhaps displacing a ligated amine), resulting in a decreased preference for reaction through the closed (chelating) transition structure. Alternatively, the drop in selectivity may reflect a change in the aggregation state of the enolate in DME. Jackman[87a] has shown that lithioisobutyrophenone in solution exists as a tetramer in THF (and solvents that are less polar than THF), but in DME the major species is a dimer. Moreover, it is known that the reactivity of lithium enolates in alkylation reactions is highly dependent on their aggregation state.[87b] These and other[88–90] studies involving organolithium compounds indicate that

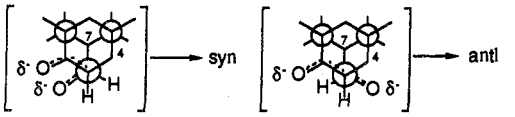

Figure 11. Charge distribution in the two competing transition states in the aldol cyclization of **2**.

the aggregated species may be the true reactive intermediates.

The effect of solvent on the course of reaction of the potassium enolate merits brief mention. In contrast to the lack of sensitivity of the lithium enolate to changes in solvent, the potassium enolate reacted with enhanced syn selectivity in toluene compared to THF. This can explain the diminished solvating power of toluene that results in a lesser ability to separate charged species.[91] Thus, Coulombic forces should be much more important in toluene, and the coordination ability of the potassium ion should be enhanced compared to that of lithium. In other words, the higher ionic character of the potassium enolate renders it more sensitive to changes in the medium.

Certain additives are also known to alter the course of reactions through changes in aggregation state,[87a,c] cation sequestering,[68,87a] and changes in the reaction medium itself.[84] As mentioned previously, alkali-metal enolates are highly aggregated under the conditions typical for synthetic reactions.[87d] Furthermore, Jackman[87c] has demonstrated that the addition of LiCl to lithioisobutyrophenone results in a replacement of one of the enolates in the tetramer with a chloride ion, thus altering the aggregate structure. This change was shown to affect both the rate and the regiochemistry of alkylation of this enolate.[87a,b] Comparison of entries 1 and 2 in Table IV shows that addition of 5 equiv of LiCl had no effect on the stereochemical course of addition with lithium hexamethyldisilazide in THF. This provides further support for the intermediacy of monomeric enolates in these aldol reactions.

On the other hand, hexamethylphosphoric triamide (HMPA) produced a dramatic change in the selectivity of the cyclizations to afford a slightly anti-selective reaction (Table I, entry 4 and Table IV, entry 3). This change can be explained by the decreased coordinating ability of the counterion in the presence of HMPA. House[56] demonstrated that addition of 4 equiv of HMPA to the lithium enolate of acetophenone caused a significant upfield shift of C(1) of the enolate in the ^{13}C NMR. The shielding of this carbon is due to selective solvation of the lithium cation and charge separation. Further, Jackman[87a] has observed a similar change upon addition of HMPA to lithioisobutyrophenone. On the basis of these results, we explain the loss in syn selectivity in terms of an increased preference for reaction through an open transition state caused by a change in coordination ability of the cation. The cation-solvating ability of HMPA attenuates the coordinating potential of Li^+ such that reaction through an open transition structure is as energetically favorable as reaction through a closed transition structure.

The preference for the open transition structure in the absence of coordinating cations was clearly demonstrated in the reaction of a "naked" enolate generated by sequestering of the metal cation with a potassium-selective complexing agent. Indeed, *reactions in the presence of 2 equiv of the macrobicyclic cryptand Kryptofix 222 resulted in a product ratio of 98/2 favoring the anti isomer.* While crown ethers have no measurable effect on the bulk structure of lithium enolates,[56,87a] lithium complexing agent cryptand 211 has a profound effect, shifting the resonance for C(2) nearly 8 ppm upfield.[87a] This is believed to correspond to the free

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(91) Reichardt, C. *Solvent and Solvent Effects in Organic Chemistry*, 2nd ed.; VCH: New York, 1988.

enolate separated from the sequestered lithium ion. Thus, reactions of these types of enolates are interpreted to proceed via monomeric, metal free anions. The highly anti-selective aldol cyclization under these conditions can be explained by the preference for reaction through an open transition structure. We believe this preference is due to the more favorable charge distribution in the transition structure leading to the anti product relative to that leading to syn product. In the absence of cations to stabilize the negatively charged oxygens in the synclinal transition structure, the minimization of electrostatic repulsion dominates (Figure 11).

The extreme anti selectivity observed with the metal-free enolate casts doubt on the importance of HOMO–LUMO interactions as proposed by Mulzer.[28] It is more likely that the high threo selectivity observed with acid *dianions* in the presence of cation complexing agents is due to enhanced chelation of one of the cations in a synperiplanar transition structure as proposed by Houk.[30]

These results coupled with the results from Table II clearly show the importance of the cation in determining the preference for double-bond topicity in the aldol reaction; the change from a syn/anti ratio of 96/4 (Table I, entry 4) to 2/98 (Table IV, entry 7) represents a $\Delta\Delta G^{\ddagger}$ of 2.74 kcal/mol at −78 °C. In addition, the ability to obtain either a highly syn-selective or anti-selective reaction just by changing conditions indicates that there is minimal steric bias in the substrate, thus allaying some of our concerns about intrinsic design flaws. This conclusion is supported by the small equilibrium energy difference found for the products as well (Table II, entry 6).

The lack of cyclization of model system **2** via either boron or stannous enolates was disappointing, but nonetheless provides valuable insight. Several explanations can by offered for this failure. Trivially, the enolate derivatives may not have formed due to the presence of the formyl group (not rigorously proven for **2**). Assuming the enolate did form, *then the failure to close implies that in aldol reactions of boron enolates simultaneous coordination of both oxygens with the boron must occur for the reaction to proceed.* The much more nucleophilic lithium, sodium, or potassium enolates do not require this assembly and react readily via open transition structures as well. Apparently, the coordination of the boron provides the necessary activation of the enolate (by ate complex formation) and the aldehyde (by Lewis acid polarization) to effect addition. This may not be geometrically possible in **2** as the optimized theoretical transition-structure bond lengths for the boron enolate were significantly shorter than for lithium.[30,79] In addition, the C=C—O—B torsion angle is close to 90°, the theoretical maximum on the rotational curve.[21]

In addition to the obvious implications of this study to understanding the stereochemical details of the aldol condensation, it also serves as a mechanistic tool for gaining insight into the behavior of the various enolate reagents. The aldomerization of glycoaldehyde phosphate to hexose-2,4,6-triphosphate and pentose-2,4-diphosphate (formose reaction) has been exhaustively studied by Eschenmoser.[92] Remarkably, allose 2,4,6-triphosphate and ribose 2,4-diphosphate are the dominant kinetic products in 2 M sodium hydroxide. These products are elegantly rationalized by a synclinal transition structure that minimizes 1,5-interactions. The study of the aqueous aldol reaction in models related to **2** is underway.

The second ramification impinges on the important and emerging field of catalytic asymmetric aldol reactions.[93] The remarkable findings of Hayashi and Ito in the aldol reaction of isocyanoacetates with aldehydes using their ferrocenyl–gold catalyst have been reinterpreted by Togni and Pastor in terms of a transition structure in which the electrophile is not coordinated. Thus, to rationalize the major isomer, it is proposed that the aldehyde residue is aligned antiperiplanar to the ammonium enolate (Figure 12). This is precisely what would be predicted for the lack of a coordinating cation. The synthesis of the appropriate silyl enol ether derivative of **2** to generate the ammonium enolate (and examine the Mukaiyama aldol reaction[13] in general) is underway. The stereochemical studies of an intramolecular silyl enol ether/acetal model have been completed[34b] and will be reported separately.

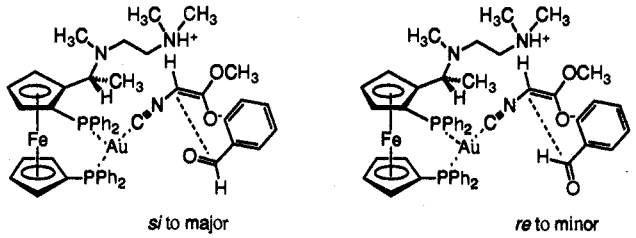

Figure 12. Proposed transition structures for the Hayashi–Ito aldol reaction.

Conclusions

The syntheses of the two model systems **1** and **2** designed to study the preference of an open versus closed transition structure in the intramolecular aldol reaction have been described. The cyclizations of these compounds as various enolate derivatives under different conditions have revealed several important trends. Regarding counterion effects, the reactions with a strongly coordinating metal counterion such as Mg^{2+} showed a strong preference for reaction through a closed transition structure in which the metal counterion could coordinate to both oxygen atoms. This transition structure requires a synclinal orientation of reactants. However, reactions of a "naked" enolate, in which the metal counterion has been sequestered, showed a strong preference for reaction via an open transition structure in which dipole moments of the enolate and aldehyde moieties are minimized. This transition structure requires an antiperiplanar orientation of reactants.

Effects of other experimental variables were also investigated. Choice of base type and solvent were found to have little effect on the stereochemical course of these cyclizations. Additives such as HMPA and cryptands favored cyclization through an open transition structure. The origin of this effect is formulated as the ability of these additives to effectively attenuate the coordinating power of the cation present in the cyclizations. The attenuation of the Lewis acidity results in reaction through the open transition structure, which minimizes electrostatic repulsion of the partially negatively charged oxygens in the transition structure. Cyclizations via boron and stannous enolates were unsuccessful, presumably due to the inability of the metals in these enolates to simultaneously coordinate the aldehyde oxygen. It is certain that the factors controlling the course of these aldol reactions are also operating in intermolecular versions and should be taken into consideration. However, because of the restricted nature of this model, direct application of these analogies should be done with caution.

Experimental Section

General Methods. ^1H NMR and ^{13}C NMR were recorded on Varian XL-200 (200-MHz ^1H, 50.4-MHz ^{13}C), General Electric QE-300 (300-MHz ^1H, 75.5-MHz ^{13}C), Nicolet NTC-360 (360-MHz ^1H), or General Electric GN-500 (500-MHz ^1H, 125.8-MHz ^{13}C) spectrometers with deuteriochloroform with tetramethylsilane (TMS, $\delta = 0.00$ for ^1H) or chloroform ($\delta = 7.26$ for ^1H, 77.06 for ^{13}C) as an internal reference unless otherwise stated. Chemical shifts are given (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened), and exch (D_2O exchangeable). Coupling constants, J, are reported (Hz). Infrared spectra were recorded on either a Perkin-Elmer 1320 IR or an IBM FTIR-32 spectrophotometer. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong), m (medium), w (weak), and br (broad). Mass spectra were obtained on a Varian MAT CH-5 spectrometer with ionization voltages of 70 and 10 eV. Data are reported in the form m/e (intensity relative to base = 100).

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Elemental combustion analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, phosphomolybdic acid, vanillin, or sulfuric acid/ethanol. Solvents for extraction and chromatography were technical grade and were distilled from the indicated drying agents: hexane, dichloromethane ($CaCl_2$); ether ($CaSO_4/FeSO_4$) or ethyl acetate (K_2CO_3). Column chromatography was performed by the method of Still[94] with 32–63-mm silica gel (Woelm) and neutral or basic alumina of the indicated activity (Brinkmann). Analytical gas chromatography was performed on either a Varian 3700 or a Hewlett-Packard 5890 gas chromatograph equipped with a variable-temperature program and flame ionization detector. The columns used were a Hewlett-Packard 50-m OV-17 capillary column (column A), Hewlett-Packard 50-m HP-101 capillary column (column B), Hewlett-Packard 50-m Carbowax 20M capillary column (column C), Hewlett-Packard 50-m HP-1 column (column D), or a 5% silicon SE-30 on 60–80 Chromosorb G (6 ft by $^1/_8$ in.) column (column E); injector temperature was either 270 or 225 °C (Carbowax only), detector temperature was 300 °C, and flow rates were approximately 30 mL/min for H_2 and N_2 and 100 mL/min for air. Temperature programs are reported in the following form: initial temperature (time(min)), temperature ramp rate (deg/min), final temperature (time(min)). High-pressure liquid chromatography (HPLC) was performed on a Perkin-Elmer Series 1 LC pump with a Hewlett-Packard 1037A refractive index detector with use of a 25 × 4.6 mm column of alumina (Excalibur, 5 mm). Retention times (t_R) and integrated ratios were obtained from a Hewlett-Packard 3390A recorder. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Bulb to bulb distillations were done on a Büchi GKR-50 Kugelrohr; boiling points (bp) refer to air bath temperatures and are uncorrected. Methyllithium, *n*-butyllithium, and vinyllithium were titrated according to the method of Gilman.[95] Stereochemical notation used in the experimental section is the system described by Brewster.[96]

1-Bromoadamantane. A dry 100-mL three-necked flask was fitted with an efficient reflux condenser and an addition funnel. A Dewar cold finger was cooled to −78 °C and placed on top of the reflux condenser. Bromine (37 mL, 0.770 mol) was added to adamantane (15.0 g, 0.11 mol) at room temperature with magnetic stirring over a period of 10 min. The reaction was gradually warmed to 105 °C over a period of 3 h, during which time copious amounts of HBr were evolved. After being heated another 2 h at 105 °C, the reaction mixture was cooled to room temperature and poured into 1 L of ice–water, and 200 mL of CCl_4 was added. With rapid stirring and external cooling (ice bath), the excess Br_2 was quenched by slow addition of solid $NaHSO_3$ until the red color disappeared. The resulting bilayer was separated and the aqueous layer extracted with CCl_4 (2 × 200 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated, and the yellow residue was recrystallized from hot methanol to afford 20.73 g (88%) of 1-bromoadamantane as white plates. Data: mp 117–118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 2.38 (m, 6 H), 2.09 (m, br, 3 H), 1.72 (m, 6 H); ^{13}C NMR (50.4 MHz, $CDCl_3$) 49.37, 35.58, 32.65.

1,3-Dibromoadamantane (8). A dry 250-mL three-necked flask was fitted with an efficient reflux condenser; on top of the reflux condenser was placed a cold (−78 °C) Dewar cold finger. Aluminum tribromide (590 μL, 0.0654 M solution in Br_2) was added to a solution of dry Br_2 (50 mL, 0.96 mol) and BBr_3 (9.66 mL, 38.54 mmol). The resulting mixture was magnetically stirred, and 1-bromoadamantane (20.73 g, 96.36 mmol) was added in one portion. The reaction was gradually heated to 85 °C for 90 min, during which time copious amounts of HBr were evolved. The reaction mixture was then cooled to room temperature and poured into 1 L of ice–water, and CCl_4 (200 mL) was added. With rapid stirring and external cooling (ice bath), the excess Br_2 was quenched by slow addition of solid $NaHSO_3$ until the red color disappeared. The resulting bilayer was separated and the aqueous layer extracted with CCl_4 (2 × 200 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated, and the light tan residue was recrystallized from hot methanol to afford 24.41 g (87%) of **8** as white plates. Data for **8**: mp 110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 2.87 (m, 2 H), 2.26 (m, 10 H), 1.70 (m, 2 H); ^{13}C NMR (50.4 MHz, $CDCl_3$) 62.26, 59.03, 47.04, 35.08, 33.58.

7-Methylidenebicyclo[3.3.1]nonan-3-one (17). A suspension of **8** (12.00 g, 40.79 mmol) in 260 mL of 1 M NaOH/dioxane (1/1) in a steel bomb was heated to 185 °C (oil bath temperature) for 16 h and then cooled to room temperature. The resulting brown solution was partitioned between EtOAc (400 mL) and water (200 mL) and the aqueous layer extracted with EtOAc (2 × 300 mL). The organic layers were combined, dried (K_2CO_3), and concentrated, and the tan residue was recrystallized from petroleum ether to afford 10.22 g (83%) of **17** as a light yellow amorphous solid. Data for **17**: mp 157–158 °C; ^{1}H NMR (200 MHz, $CDCl_3$) 4.80 (m, 2 H, C=CH_2), 2.66–2.24 (m, 10 H), 1.94 (m, 2 H); ^{13}C NMR (50.4 MHz, $CDCl_3$) 211.15 (*C*=O), 141.77 (*C*=CH_2), 114.75 (C=*C*H_2), 47.41, 41.44, 32.12, 30.85; GC t_R = 12.68 min, 110 (2), 5, 175 (15), column B.

(*R*,*S*)-(1*l*,5*l*)-3-Methylbicyclo[3.3.1]non-2-en-7-one (9). A suspension of **17** (4.88 g, 32.49 mmol) and 5% Pd/C (400 mg) in 100 mL of absolute ethanol was placed on an atmospheric-pressure hydrogenation apparatus, flushed three times with H_2 gas, and then magnetically stirred under an atmosphere of H_2 until the isomerization was complete as determined by GC analysis (30–90 min). The solution was then gravity-filtered through coarse filter paper, rinsing with portions of ethanol to remove the catalyst. The filtrate was concentrated and distilled to afford 4.83 g (99%) of **9** as a clear, colorless oil. Data for **9**: bp 72 °C (0.10 Torr); ^{1}H NMR (200 MHz, $CDCl_3$) 5.42 (m, 1 H, C=C*H*), 2.66–2.25 (m, 10 H), 1.95 (m, 2 H), 1.59 (s, 3 H); ^{13}C NMR (50.4 MHz, $CDCl_3$) 212.50 (*C*=O), 133.05 (*C*=CH), 124.83 (C=*C*H), 47.34, 46.73, 37.58, 31.31, 30.44, 23.37; GC t_R = 12.15 min, 110 (2), 5, 175 (15), column B.

(*R*,*S*)-(1*l*,5*l*)-7-(Ethylenedioxy)-3-methylbicyclo[3.3.1]non-2-ene (27). A magnetically stirred solution of **9** (4.83 g, 32.15 mmol), ethylene glycol (3.60 mL, 64.30 mmol), and trimethyl orthoformate (7.03 mL, 64.30 mmol) in 150 mL of toluene was treated with 100 mg of *p*-toluenesulfonic acid at room temperature, and the resulting solution was heated to reflux for 90 min. After being cooled to room temperature, the reaction mixture was partitioned between Et_2O (150 mL) and saturated aqueous $NaHCO_3$ solution (150 mL), and the aqueous layer was extracted with Et_2O (2 × 150 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification by column chromatography (hexane/EtOAc (15/1)) afforded 5.51 g (88%) of **27** as a clear, colorless oil. An analytical sample was prepared by Kugelrohr distillation. Data for **27**: bp 105 °C (1.50 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 5.46 (d, J = 6.0, 1 H, C=C*H*), 3.95 (m, 1 H, OCH_2), 3.86 (m, 1 H, OCH_2), 3.78 (m, 1 H, OCH_2), 3.72 (m, 1 H, OCH_2), 2.38 (s, br, 1 H, C=CHC*H*), 2.23 (m, 2 H), 1.85–1.71 (m, 6 H), 1.63 (s, 3 H, CH_3), 1.56 (d, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 134.56 (*C*=CH), 124.09 (C=*C*H), 109.03 (*O*CO), 64.77 (O*C*H_2), 62.71 (O*C*H_2), 41.76, 39.18, 36.53, 31.15, 29.25 (C=C-H*C*), 27.73, 23.35 (*C*H_3); IR (CCl_4) 2923 (s), 2824 (w), 2678 (w), 1454 (w), 1429 (m), 1374 (m), 1356 (w), 1339 (w), 1300 (w), 1269 (w), 1238 (w), 1146 (s), 1090 (s), 1040 (m), 1019 (m), 972 (m), 947 (w), 930 (w), 853 (m), 831 (w); MS (70 eV) 194 (M^+, 53), 179 (23), 150 (10), 132 (11), 112 (75), 107 (18), 106 (13), 93 (66), 92 (13), 91 (14), 87 (20), 86 (11), 59 (100), 43 (13); R_f 0.45 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{12}H_{18}O_2$ (MW 194.27): C, 74.19; H, 9.34. Found: C, 74.19; H, 9.31.

(*R*,*S*)-(1*l*,2*u*,3*l*,5*u*)-7-(Ethylenedioxy)-2-hydroxy-3-methylbicyclo-[3.3.1]nonane (10). A magnetically stirred solution of **27** (5.40 g, 27.80 mmol) in 100 mL of THF was cooled to 0 °C, and then a 1.0 M solution of BH_3·THF complex (42 mL, 42.00 mmol) was added dropwise over a period of 15 min. The reaction mixture was allowed to warm to room temperature, was stirred 1 h, and then was cooled to 0 °C, and the excess BH_3·THF was destroyed by careful addition of water until no more H_2 evolution was observed. A mixture of 30 mL of 10% aqueous NaOH solution and 15 mL of 30% aqueous H_2O_2 solution was added slowly over 5 min, and the resulting heterogeneous mixture was allowed to warm to room temperature, was rapidly stirred for 1 h, and then was heated to 40 °C for 20 min to ensure complete oxidation. The mixture was then poured into brine and extracted with Et_2O (3 × 150 mL). The organic layers were combined, dried (K_2CO_3), and concentrated, and the residue was distilled to afford 5.33 g (90%) of **10** as a clear, colorless, viscous oil that later solidified. Data for **10**: bp 125 °C (0.05 Torr); mp 53–54 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.93 (m, 2 H, OCH_2), 3.78 (m, 2 H, OCH_2), 3.65 (d, J = 9.44, 1 H, C*H*OH), 2.16 (m, 1 H, HOCHC*H*), 1.99–1.88 (m, 4 H), 1.74 (m, 1 H), 1.62 (m, 3 H), 1.36 (m, 2 H), 1.13 (m, 1 H), 0.97 (d, J = 6.1, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 108.81 (*O*CO), 76.62 (*C*HOH), 64.19 (O*C*H_2), 62.79 (O*C*H_2), 41.76, 40.07, 38.59, 33.47, 30.75, 26.96, 25.88, 19.19 (*C*H_3); IR (CCl_4) 3629 (w), 3358 (w, br), 2928 (s), 2872 (s), 1458 (w), 1429 (w), 1372 (w), 1350 (w), 1316 (w), 1239 (w), 1148 (m), 1090 (m), 1030 (m), 1001 (w), 961 (w), 908 (w), 853 (w); MS (70 eV) 212 (M^+, 11), 141 (20), 140 (11), 139 (100), 124 (11), 122 (20), 117 (10), 113 (17), 110 (53), 109 (12), 108 (13), 107 (17), 106 (16), 103 (40), 99 (32), 97 (12), 95 (26), 92 (14), 88 (10), 87 (51), 86 (49), 73 (11), 59 (19), 43 (16); R_f 0.30 (hexane/EtOAc (1/1)). Anal. Calcd for $C_{12}H_{20}O_3$ (MW 212.43): C, 67.89; H, 9.50. Found: C, 68.06; H, 9.44.

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(95) Gilman, H.; Haubein, A. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515.
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(*R,S*)-(1*l*,2*u*,3*l*,5*u*)-2-(Benzyloxy)-7-(ethylenedioxy)-3-methylbicyclo[3.3.1]nonane (28). A 35% suspension of KH in mineral oil was washed with hexane (3 × 10 mL). The solvent was removed in vacuo to obtain an accurate weight (2.0 g, 50.1 mmol), and then the solid was slurried with 80 mL of DME. The magnetically stirred slurry was cooled to 0 °C, and then a solution of **9** (5.32 g, 25.06 mmol) in 10 mL of DME was added dropwise over 5 min. The resulting light yellow solution was warmed to room temperature, and then tetrabutylammonium iodide (925 mg, 2.51 mmol) was added in one portion. After this addition was complete, benzyl bromide (4.47 mL, 37.59 mmol) was added neat via syringe over a 1-min period. The resulting milky white solution was heated to 55 °C for 1 h and then was cooled to 0 °C and the excess KH quenched by addition of water. The reaction mixture was poured into brine (100 mL) and extracted with Et_2O (3 × 100 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification by gradient silica gel column chromatography (hexane/EtOAc (10/1, 8/1, 5/1, 1 column volume each)) afforded 6.68 g (88%) of **28** as a clear, colorless oil. An analytical sample of **28** was obtained by Kugelrohr distillation. Data for **28**: bp 130 °C (0.05 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 (m, 5 H, *H*Ar), 4.52 (m, 2 H, ArCH_2O), 3.92 (m, 2 H, OCH_2), 3.82 (m, 2 H, OCH_2), 3.49 (d, J = 10.0, 1 H, *CH*OH), 2.20 (s, br, 2 H), 2.00 (m, 1 H), 1.83–1.61 (m, 6 H), 1.39 (m, 1 H), 1.18 (m, 1 H), 1.03 (d, J = 6.2, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 139.06 (*C*Ar), 128.28 (*C*Ar), 128.02 (*C*Ar), 127.43 (*C*Ar), 108.10 (O*C*O), 83.88 (*C*HO), 70.65 (ArCH_2O), 64.12 (OCH_2), 62.81 (OCH_2), 41.76, 40.91, 35.10, 31.15, 30.71, 27.22, 25.81, 19.50 (CH_3); IR (CCl_4) 3067 (w), 3033 (w), 2928 (s), 2872 (s), 1497 (w), 1456 (w), 1429 (w), 1368 (m), 1348 (w), 1240 (w), 1206 (w), 1148 (m), 1121 (w), 1092 (s), 1071 (s), 1042 (m), 1028 (w), 965 (m), 945 (w), 858 (w); MS (70 eV) 302 (M^+, 5), 211 (65), 201 (12), 200 (74), 196 (21), 168 (36), 139 (19), 121 (100), 99 (17), 91 (37), 87 (39), 86 (63); R_f 0.65 (hexane/EtOAc (1/1)); GC t_R = 13.62 min, 75 (2), 20, 275 (10), column A. Anal. Calcd for $C_{19}H_{26}O_3$ (MW 302.41): C, 75.46; H, 8.67. Found: C, 75.55; H, 8.70.

(*R,S*)-(1*l*,2*u*,3*l*,5*u*)-2-(Benzyloxy)-3-methylbicyclo[3.3.1]nonan-7-one (11). A magnetically stirred solution of ketal **28** (6.50 g, 21.50 mmol) in 30 mL of THF at room temperature was treated with 30 mL of 1 M aqueous HCl, and the resulting homogeneous mixture was stirred for 3 h at room temperature. The mixture was then slowly poured into 100 mL of saturated aqueous $NaHCO_3$ solution and extracted with Et_2O (3 × 125 mL). The organic layers were combined, dried (K_2CO_3), and concentrated, and the residue was distilled to afford 5.35 g (96%) of **11** as a clear colorless oil. Data for **11**: bp 150 °C (0.50 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 7.30 (m, 5 H, *H*Ar), 4.50 (d, J = 11.0, 2 H, ArCH_2O), 2.86 (d, J = 8.8, 1 H, *CH*OH), 2.55–2.33 (m, 5 H), 2.24 (m, 1 H), 2.03 (m, 1 H), 1.71 (m, 1 H), 1.59 (m, 1 H), 0.93 (d, J = 6.6, 3 H, CH_3), 0.73 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 211.85 (*C*=O), 138.45 (*C*Ar), 128.40 (*C*Ar), 127.83 (*C*Ar), 127.65 (*C*Ar), 85.93 (*C*HO), 70.99 (ArCH_2O), 50.31, 48.75, 36.81, 32.60, 30.00, 28.04, 26.67, 19.25 (CH_3); IR (CCl_4) 3067 (w), 3033 (w), 2953 (s), 2928 (s), 2863 (m), 1713 (s), 1497 (w), 1458 (m), 1420 (w), 1360 (m), 1289 (w), 1231 (w), 1206 (w), 111 (m), 1090 (s), 1073 (s), 1028 (w), 976 (w), 943 (w); MS (70 eV) 258 (M^+, 3), 187 (66), 149 (15), 131 (11), 121 (10), 107 (15), 93 (13), 92 (21), 91 (100); R_f 0.25 (hexane/EtOAc (4/1)); GC t_R = 12.80 min, 75 (2), 20, 275 (10), column A. Anal. Calcd for $C_{17}H_{22}O_2$ (MW 258.36): C, 79.03; H, 8.58. Found: C, 78.81; H, 8.38.

(*R,S*)-(1*l*,2*u*,3*l*,5*u*,7*l*)-2-(Benzyloxy)-3-methylbicyclo[3.3.1]nonane-spiro-7,2′-1′-oxacyclopropane (12). A 35% suspension of KH in mineral oil was washed with hexane (3 × 5 mL) and the solvent removed in vacuo to obtain an accurate weight (745 mg, 18.57 mmol). Dimethyl sulfoxide (15 mL) was added to the dry KH rapidly with magnetic stirring at room temperature; gas evolution was observed, and a clear, light yellow solution was obtained. After being stirred for 15 min, trimethyloxosulfonium iodide (4.08 g, 18.57 mmol) was added all at once. The resulting mixture was stirred for 5 min, and then **11** (4.00 g, 15.48 mmol) was added neat dropwise over 2 min. The reaction mixture was stirred at room temperature for 18 h, and then poured into water and extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc (6/1)) afforded 3.52 g (83%) of **12** as a clear, colorless oil. An analytical sample of **12** was obtained by Kugelrohr distillation. Data for **12**: bp 155 °C (0.30 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 7.34 (m, 5 H, *H*Ar), 4.50 (d, J = 11.2, 2 H, ArCH_2O), 3.41 (d, J = 10.3, 1 H, *CH*OH), 2.34 (s, 2 H, CCH_2O), 2.20 (m, 3 H), 2.08 (m, 1 H), 2.00 (d, J = 4.0, 1 H), 1.89 (m, 1 H), 1.70 (m, 1 H), 1.32 (m, 2 H), 1.18 (m, 2 H), 1.07 (d, J = 6.3, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 139.00 (*C*Ar), 128.30 (*C*Ar), 127.87 (*C*Ar), 127.43 (*C*Ar), 85.81 (*C*HO), 71.05 (ArCH_2O), 55.75 (*C*O), 48.31 (CH_2O), 40.57, 39.98, 35.29, 31.55, 31.38, 27.03, 25.86, 19.57 (CH_3); IR (CCl_4) 3067 (w), 3033 (m), 2930 (s), 2870 (s), 1497 (w), 1458 (m), 1426 (w), 1366 (m), 1206 (w), 1121 (m), 1096 (s), 1071 (s), 1028 (m), 1009 (w), 947 (m), 907 (m); MS (70 eV) 272 (M^+, 1), 93 (15), 92 (21), 91 (100), 79 (10); R_f 0.40 (hexane/EtOAc (4/1)); GC t_R = 18.55 min, 180 (2), 5, 250 (15), column D. Anal. Calcd for $C_{18}H_{24}O_2$ (MW 272.42): C, 79.37; H, 8.88. Found: C, 79.39; H, 9.05.

(*R,S*)-(1*l*,2*u*,3*l*,5*u*,7*x*)-2-(Benzyloxy)-7-formyl-3-methylbicyclo[3.3.1]nonane (29). A magnetically stirred solution of **12** (3.0 g, 11.0 mmol) in 50 mL of CH_2Cl_2 was cooled to −78 °C, and then freshly distilled $SnCl_4$ (1.29 mL, 11.01 mmol) was added neat dropwise to the reaction mixture *at a rate that kept the temperature of the solution below −60 °C.* The resulting light yellow solution was stirred for 10 min at −78 °C and then quenched by addition of 5 mL of saturated aqueous $NaHCO_3$ solution at a rate that kept the reaction temperature below −50 °C. The resulting mixture was allowed to warm to room temperature, poured into water, and extracted with Et_2O (3 × 100 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification by gradient silica gel column chromatography (hexane/EtOAc: 20/1, 2 column volumes; 10/1, 5/1, 1 column volume each) afforded 1.69 g (56%) of **29** as a clear, colorless oil. An analytical sample of **29** was obtained by Kugelrohr distillation. Data for **29**: bp 160 °C (0.05 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 9.58 (s, 1 H, *CH*O), 7.35 (m, 5 H, *H*Ar), 4.51 (m, 2 H, ArCH_2O), 2.88 (d, J = 10.4, 1 H, *CH*OCH_2Ar), 2.39 (m, 1 H, *CH*CHO), 2.20 (s, br, 2 H), 1.97 (m, 2 H), 1.79 (m, 1 H), 1.68 (m, 2 H), 1.52 (m, 1 H), 1.34 (m, 1 H), 1.10 (d, J = 13.3, 1 H), 1.02 (d, J = 6.2, 3 H, CH_3), 0.72 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 204.91 (*C*=O), 138.55 (*C*Ar), 128.38 (*C*Ar), 127.93 (*C*Ar), 127.60 (*C*Ar), 85.73 (*C*HO), 70.54 (ArCH_2O), 42.25 (*C*HC=O), 33.49, 32.71, 32.27, 31.90, 30.90, 27.63, 24.70, 19.33 (CH_3); IR (CCl_4) 2928 (s), 2863 (m), 2708 (w), 1728 (s), 1497 (w), 1459 (m), 1364 (w), 1264 (w), 1071 (s), 1028 (w), 997 (w), 909 (m); MS (70 eV) 272 (M^+, 8), 181 (42), 163 (22), 145 (12), 136 (10), 135 (30), 133 (12), 107 (12), 105 (15), 93 (32), 92 (81), 91 (100), 79 (11); R_f 0.44 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{18}H_{24}O_2$ (MW 272.42): C, 79.37; H, 8.88. Found: C, 79.62; H, 8.90.

(*R,S*)-(1*l*,2*u*,3*l*,5*u*,7*u*)-2-(Benzyloxy)-7-formyl-3,7-dimethylbicyclo[3.3.1]nonane (13). A solution of **29** (3.0 g, 11.0 mmol) in 5 mL of THF was added dropwise to a magnetically stirred solution of potassium *tert*-butoxide (2.47 g, 22.02 mmol) in 30 mL of 2-methyl-2-propanol at room temperature, and the resulting clear yellow solution was stirred for 5 min. Methyl iodide (1.71 mL, 27.53 mmol) was added neat dropwise to the reaction mixture, and the resulting milky yellow solution was stirred for 60 min at room temperature and then poured into 70 mL of water and extracted with Et_2O (3 × 100 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc (20/1)) afforded 1.98 g (63%) of **13** as a clear, colorless oil. Data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$) 9.42 (s, 1 H, *CH*O), 7.36 (m, 5 H, *H*Ar), 4.55 (d, J = 11.3, 2 H, ArCH_2O), 3.10 (d, J = 10.2, 1 H, *CH*OCH_2Ar), 2.38 (m, 1 H), 2.10 (m, 2 H), 1.96 (m, 1 H), 1.85 (m, 1 H), 1.59 (m, 1 H), 1.43 (m, 2 H), 1.11 (m, 1 H), 0.90 (s, 3 H, CH_3), 0.87 (d, J = 6.4, 3 H, CH_3), 0.56 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.77 (*C*=O), 138.83 (*C*Ar), 128.31 (*C*Ar), 128.0 (*C*Ar), 127.51 (*C*Ar), 84.33 (*C*HO), 70.81 (ArCH_2O), 44.41, 40.76, 37.74, 34.62, 31.87, 31.65, 27.80, 25.19, 18.97 (CH_3); IR (CCl_4) 3090 (w), 3067 (w), 3033 (w), 2955 (s), 2962 (s), 2896 (m), 2793 (w), 2691 (w), 1728 (s), 1497 (w), 1461 (m), 1372 (w), 1070 (s), 1028 (w), 978 (w), 909 (w); MS (70 eV) 162 (23), 149 (11), 107 (15), 93 (17), 92 (19), 91 (100), 65 (11), 55 (11), 43 (23), no M^+; R_f 0.13 (hexane/EtOAc (30/1)); GC t_R = 21.26 min, 170 (2), 5, 250 (7), column B. Anal. Calcd for $C_{19}H_{26}O_2$ (MW 286.43): C, 79.68; H, 9.15. Found: C, 79.38; H, 9.13.

(*R,S*)-(1*l*,2*u*,3*l*,5*u*,7*u*)-2-(Benzyloxy)-7-(dimethoxymethyl)-3,7-dimethylbicyclo[3.3.1]nonane (14). Trimethyl orthoformate (2.22 mL, 20.34 mmol), was added to a magnetically stirred solution of **13** (2.33 g, 8.13 mmol) in 30 mL of dry methanol at room temperature. A catalytic amount of *p*-toluenesulfonic acid (100 mg) was added, and the resulting solution was stirred at room temperature for 5 h and then was poured into a saturated $NaHCO_3$ solution (100 mL) and extracted with Et_2O (3 × 125 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc (25/1)) afforded 1.92 g (71%) of **14** as a clear colorless oil. An analytical sample of **14** was obtained by Kugelrohr distillation. Data for **14**: bp 150 °C (0.70 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 7.35 (m, 5 H, *H*Ar), 4.52 (d, J = 11.9, 2 H, ArCH_2O), 4.00 (s, 1 H, C*H*(OCH_3)$_2$), 3.52 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 3.07 (d, J = 9.7, 1 H, *CH*OCH_2Ar)), 2.13 (m, 1 H), 2.06 (m, 1 H), 1.91 (m, 1 H), 1.80 (m, 1 H), 1.69 (m, 3 H), 1.46 (m, 1 H), 1.28 (m, 2 H), 1.02 (d, J = 6.5, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 0.93 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 138.96 (*C*Ar), 128.33 (*C*Ar), 127.97 (*C*Ar), 127.45 (*C*Ar), 112.49 (O*C*HO), 86.69 (*C*HO), 70.16 (ArCH_2O), 58.91 (OCH_3), 58.47 (OCH_3), 39.88, 38.27, 37.23, 34.55, 32.37, 31.81, 26.42 (CH_3), 25.21, 24.91, 20.47 (CH_3); IR (CCl_4) 3067

(w), 3033 (w), 2926 (s), 2867 (m), 2830 (m), 1497 (w), 1455 (m), 1381 (w), 1370 (w), 1204 (w), 1130 (m), 1121 (s), 1109 (s), 1073 (s), 1028 (w), 988 (w), 922 (w); MS (70 eV) 162 (14), 107 (11), 93 (13), 91 (77), 75 (100), no M^+; GC t_R = 18.11 min, 120 (2), 10, 240 (15), column B. Anal. Calcd for $C_{21}H_{32}O_3$ (MW 332.48): C, 75.86; H, 9.70. Found: C, 75.97; H, 9.77.

(*R*,*S*)-(1*l*,2*u*,3*l*,5*u*,7*u*)-7-(Dimethoxymethyl)-3,7-dimethyl-2-hydroxybicyclo[3.3.1]nonane (30). A dry 100-mL three-necked flask equipped with a Dewar cold finger was cooled to −78 °C, and 50 mL of NH_3(g) was condensed into the flask. A solution of **14** (1.53 g, 4.60 mmol) in 10 mL of dry Et_2O was added to the magnetically stirred NH_3 solution. Sodium metal (423 mg, 18.41 mmol) was cleaned in dry ethanol and added in small pieces to the reaction mixture over 10 min, and then the cold bath was removed and the deep blue solution allowed to reflux for 45 min. The solution was then cooled to −78 °C and quenched by careful addition of small quantities of solid NH_4Cl until the blue color disappeared. The ammonia was allowed to evaporate off under a strong stream of N_2, and the remaining white solid was partitioned between water (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was adjusted to pH 3 by addition of 1 N HCl and then was extracted with CH_2Cl_2 (3 × 75 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification of the resulting yellow oil by silica gel column chromatography (hexane/EtOAc (3/1)) afforded 1.07 g (96%) of **30** as a clear, colorless oil. An analytical sample of **30** was obtained by Kugelrohr distillation. Data for **30**: bp 150 °C (0.25 Torr); ^{1}H NMR (300 MHz, $CDCl_3$) 3.93 (s, 1 H, C*H*$(OCH_3)_2$), 3.51 (s, 6 H, OC*H*$_3$), 3.34 (d, J = 8.7, 1 H, C*H*OH), 2.04 (m, 1 H), 1.87 (m, 2 H), 1.67 (m, 2 H), 1.57–1.40 (m, 5 H), 1.30 (m, 2 H), 1.04 (d, J = 6.4, 3 H, CH_3), 0.97 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 113.23 (*C*HO), 80.33 (*C*HOH), 58.67 (O*C*H$_3$), 39.41, 38.11, 36.50, 35.94, 35.16, 34.90, 26.65 (*C*H$_3$), 25.10, 23.92, 20.30 (*C*H$_3$); IR (CCl_4) 3623 (w), 2928 (s), 2870 (m), 2830 (m), 1456 (w), 1381 (w), 1186 (w), 1129 (m), 1107 (s), 1076 (s), 1021 (m), 988 (m), 926; MS (70 eV) 75 (100), no M^+; R_f 0.30 (hexane/EtOAc (3/1)); GC t_R = 23.98 min, 170 isothermal, column B. Anal. Calcd for $C_{14}H_{26}O_3$ (MW 242.36): C, 69.38; H, 10.81. Found: C, 69.34; H, 10.76.

(*R*,*S*)-(1*l*,3*x*,5*u*,7*u*)-3,7-Dimethyl-7-(hydroxymethyl)bicyclo[3.3.1]nonan-2-one (15). A magnetically stirred solution of **30** (1.16 g, 4.79 mmol) in 40 mL of THF was treated with 15 mL of 1 M aqueous HCl, and the resulting homogeneous solution was stirred at room temperature for 40 h. The reaction mixture was then poured into saturated aqueous $NaHCO_3$ solution (80 mL) and was extracted with Et_2O (3 × 75 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc (3/1)) afforded 800 mg (85%) of **15** as a clear, colorless, viscous oil that later solidified. Data for **15**: mp 68–70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 2.98 (dd, J = 12.0, 5.3, 2 H, CH_2OH), 2.56 (m, 1 H, CH$_3$C*H*C=O), 2.45 (m, 1 H), 2.39 (m, 1 H, C*H*C=O), 2.30 (m, 1 H), 2.21 (m, 1 H), 2.15 (m, 1 H), 1.80 (s, br, 1 H, O*H*), 1.59 (m, 1 H), 1.50 (m, 1 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 1.20 (m, 1 H), 1.03 (d, J = 6.7, 3 H, CH_3), 0.87 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 221.54 (*C*=O), 68.20 (*C*H$_2$OH), 42.42 (*C*HC=O), 41.64, 41.03 (CH$_3$*C*HC=O), 37.50, 35.14, 34.85, 30.11, 30.00 (*C*H$_3$), 26.18, 14.43 (*C*H$_3$); IR (CCl_4) 3640 (w, br), 3507 (w, br), 3395 (w), 2930 (s), 2872 (s), 1701 (s), 1462 (m), 1379 (m), 1354 (w), 1281 (w), 1244 (w), 1213 (w), 1172 (w), 1134 (w), 1115 (w), 1076 (w), 1049 (s), 995 (w), 916 (w), 884 (w); MS (70 eV) 196 (M^+, 26), 167 (11), 166 (94), 165 (16), 147 (15), 137 (10), 123 (18), 121 (16), 111 (11), 110 (100), 109 (28), 108 (26), 107 (75), 106 (19), 105 (23), 95 (69), 94 (24), 93 (60), 91 (28), 81 (56), 80 (17), 79 (54), 77 (22), 71 (12), 69 (18), 68 (11), 67 (46), 57 (10), 55 (48), 53 (25); R_f 0.15 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{12}H_{20}O_2$ (MW 196.29): C, 73.43; H, 10.27. Found: C, 73.35; H, 10.22.

(*R*,*S*)-(1*l*,3*x*,5*u*,7*u*)-3,7-Dimethyl-7-formylbicyclo[3.3.1]nonan-2-one (1). A solution of dry dimethyl sulfoxide (80 μL, 1.12 mmol) in 500 μL of CH_2Cl_2 was added to a magnetically stirred solution of oxalyl chloride (49 μL, 0.56 mmol) in 2 mL of CH_2Cl_2 at −78 °C. The resulting solution was stirred for 10 min, and then a solution of **15** (100 mg, 0.509 mmol) in 500 μL of CH_2Cl_2 was added. The cloudy solution was stirred for 30 min at −78 °C and then freshly distilled Et_3N (156 μL, 1.12 mmol) was added. The reaction mixture was stirred for 5 min at −78 °C and then was allowed to slowly warm to −25 °C and was immediately poured into pH 7 buffered water (10 mL) and extracted with Et_2O (3 × 15 mL). The organic extracts were combined, dried briefly ($MgSO_4$), and concentrated. During the oxidation, a cold-column chromatographic system was prepared by circulating cold (−40 °C or below) 2-propanol through a jacketed 10-mm column packed to a 15-cm height with Activity IV neutral alumina with use of a Neslab CC-100 II Cryocool immersion cooler and accompanying circulating pump. At least 3 h of cooling prior to circulation through the column is necessary to achieve temperatures of −40 °C or below. The crude keto aldehyde **1** was then placed onto the column and chromatographed on Activity IV neutral alumina with use of cold (−40 °C or below) column solvents under gradient conditions (hexane/EtOAc (15/1, 4/1, 1/1, 1 column volume each)) to afford 62 mg (62%) of **1** as a clear colorless oil. NMR samples of this compound were prepared by passing the $CDCl_3$ through basic alumina prior to use. The compound decomposed slowly at room temperature but could be stored at −15 °C under Ar atmosphere for up to 10 days without decomposition. The keto aldehyde decomposed upon attempted distillation and thus could not be further purified. Data for **1**: ^{1}H NMR (500 MHz, $CDCl_3$) 9.13 (s, 1 H, C*H*O), 2.57 (m, 1 H), 2.44 (m, 1 H, C*H*C=O), 2.39 (m, 1 H, CH$_3$C*H*C=O), 2.30 (m, 1 H), 2.23 (m, 2 H), 2.14 (m, 1 H), 1.55 (m, 1 H), 1.45 (dd, J = 4.8, 13.8, 1 H), 1.37 (dd, J = 4.3, 14.1, 1 H), 1.29 (dd, J = 11.1, 14.2, 1 H), 0.88 (s, 3 H, CH_3), 0.87 (d, J = 4.4, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 213.66 (*C*=O), 204.51 (*C*H=O), 45.23, 42.26 (*C*HC=O), 40.32 (CH$_3$*C*H=O), 38.44, 37.10, 31.50, 29.44, 26.13 (*C*H$_3$), 25.74, 13.35 (*C*H$_3$); IR (CCl_4) 2930 (s), 2872 (m), 2712 (w), 1709 (s), 1653 (w), 1456 (m), 1379 (w), 1248 (w), 1042 (w), 997 (w), 907 (w); MS (70 eV) 194 (M^+, 6), 166 (57), 124 (11), 123 (14), 111 (11), 110 (100), 109 (17), 108 (17), 107 (35), 105 (11), 95 (46), 94 (15), 93 (43), 91 (20), 81 (32), 79 (29), 77 (23), 67 (31), 55 (29); high-resolution MS for $C_{12}H_{18}O_2$ calcd 194.130 68, found 194.130 74; GC t_R = 13.04 min, 100 (5), 10, 200 (10), column C; HPLC t_R = 5.03 min (hexane/EtOAc (7/1)).

Preparation of (*R*,*S*)-(1*l*,3*u*,5*u*,7*u*,9*l*)-3,7-Dimethyl-9-hydroxyadamantan-2-one (3) and (*R*,*S*)-(1*l*,3*u*,5*u*,7*u*,9*u*)-3,7-Dimethyl-9-hydroxyadamantan-2-one (4). A solution of keto aldehyde **1** (45 mg, 0.24 mmol) in 500 μL of THF was added to a magnetically stirred solution of potassium *tert*-butoxide (34 mg, 0.30 mmol) in 500 μL of 2-methyl-2-propanol at room temperature. The resulting yellow solution was stirred for 30 min at room temperature and then was poured into 10 mL of brine and extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification by gradient radial chromatography (hexane/EtOAc 8/1 (90 mL), 6/1 (70 mL), 4/1 (150 mL)) afforded 10 mg (22%) of anti alcohol 4 as a clear colorless oil and 30 mg (66%) of syn alcohol **3** as a white crystalline solid.

Data from (*R*,*S*)-(1*l*,3*u*,5*u*,7*u*,9*l*)-3,7-dimethyl-9-hydroxyadamantan-2-one (**3**): mp 84–85 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.49 (d, J = 2.2, 1 H, C*H*OH), 2.49 (d, J = 2.6, 1 H, C*H*C=O), 2.18 (m, 1 H), 2.01 (m, 1 H), 1.95–1.85 (m, 4 H), 1.74 (m, 3 H), 1.51 (m, 1 H), 1.03 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 217.23 (*C*=O), 86.85 (*C*HOH), 51.80 (CHOH*C*C=O), 46.10 (*C*H-C=O), 43.46, 39.15, 38.60, 35.24, 28.27, 25.16 (*C*H$_3$), 18.94 (*C*H$_3$); IR (CCl_4) 3636 (w), 3489 (w, br), 2924 (s), 2857 (s), 1718 (s), 1466 (m), 1461 (m), 1453 (m), 1376 (m), 1346 (w), 1298 (w), 1259 (w), 1232 (w), 1166 (w), 1130 (w), 1099 (w), 1076 (m), 1064 (s), 1050 (m), 1037 (m), 1021 (w), 995 (w), 938 (m), 928 (w), 883 (w); MS (70 eV) 194 (M^+, 29), 166 (26), 120 (35), 110 (74), 109 (18), 108 (13), 107 (100), 105 (13), 95 (13), 93 (16), 91 (16), 79 (16), 77 (13), 67 (11), 55 (14), 53 (12), 41 (22); R_f 0.19 (hexane/EtOAc (4/1)); GC t_R = 23.41 min, 100 (5), 10, 200 (15), column C. Anal. Calcd for $C_{12}H_{18}O_2$ (MW 194.27): C, 74.19; H, 9.34. Found: C, 74.34; H, 9.12.

Analytical data from (*R*,*S*)-(1*l*,3*u*,5*u*,7*u*,9*u*)-3,7-dimethyl-9-hydroxyadamantan-2-one (**4**): bp 110 °C (0.10 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 3.15 (s, 1 H, C*H*OH), 2.55 (d, J = 2.9, 1 H, C*H*C=O), 2.14 (m, 1 H), 2.02–1.87 (m, 5 H), 1.67 (dd, J = 13.3, 2.7, 1 H), 1.52 (m, 1 H), 1.42 (m, 1 H), 1.34 (m, 1 H), 1.03 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 216.17 (*C*=O), 80.74 (*C*HOH), 52.17 (CHOH*C*C=O), 46.32 (*C*HC=O), 40.85, 39.15, 38.41, 35.74, 34.60, 27.91, 25.79 (*C*H$_3$), 18.37 (*C*H$_3$); IR (CCl_4) 3638 (w), 3524 (w), 3422 (w), 2928 (s), 2857 (s), 1717 (s), 1455 (m), 1375 (w), 1281 (w), 1248 (w), 1183 (w), 1132 (w), 1063 (m), 1049 (s), 1034 (m), 999 (s), 967 (w), 936 (w), 870 (w), 860 (w); MS (70 eV) 194 (M^+, 42), 166 (33), 123 (12), 120 (33), 110 (100), 109 (28), 108 (15), 107 (83), 106 (15), 105 (10), 95 (19), 94 (11), 93 (27), 91 (18), 81 (13), 79 (23), 77 (16), 67 (16), 55 (17), 53 (14); high-resolution MS for $C_{12}H_{18}O_2$ calcd 194.130 68, found 194.130 56; R_f 0.22 (hexane/EtOAc (4/1)); GC t_R = 22.84 min, 100 (5), 10, 200 (15), column C.

General Procedure for Cyclizations of 1. A magnetically stirred solution of **1** in dry THF (~0.01 M) was cooled to −55 °C (Cryocool CC-100 II), and then cyclododecane (0.5 equiv, as a solution in THF) and any additives were introduced. The appropriate base (1.1 equiv) was then added, and the reaction was stirred at −55 °C and monitored by withdrawing a small aliquot, quenching into a pH 7 buffer/Et_2O biphase, and injecting onto a cold (−10 °C) Excalibur alumina HPLC column. After the starting material was consumed as determined by HPLC, the reaction was quenched at −55 °C by addition of 100 μL of aqueous NH_4Cl, poured into 2 mL of water, and extracted with Et_2O (2 × 2 mL). The organic extracts were combined, dried ($MgSO_4$), and partially concentrated. Analysis of the product ratios was done by injection onto column C. Program: 100 (5), 10, 200 (10). Final ratios and yields were

calculated on the basis of independently obtained response factors relative to the cyclododecane internal standard: GC **1**, t_R = 13.04 min; **3**, t_R = 23.41 min; **4**, t_R = 22.84 min.

(1*l*,3*x*,5*u*,7*x*)-7-(Hydroxymethyl)bicyclo[3.3.1]nonan-3-ol (31). A magnetically stirred solution of **17** (3.0 g, 20.0 mmol) in 30 mL of THF was cooled to 0 °C, and a 1 M solution of BH_3·THF (30 mL, 30.0 mmol) was added dropwise over 10 min. The resulting mixture was stirred at room temperature for 90 min and then cooled to 0 °C and the excess BH_3·THF quenched by careful addition of water until the gas evolution ceased. A solution of 5 mL of 10% NaOH and 5 mL of 30% aqueous H_2O_2 solution was added, and the resulting biphasic solution was stirred rigorously at room temperature for 20 min and then at 50 °C for 15 min to ensure complete oxidation. The reaction mixture was cooled to room temperature, poured into brine (50 mL), and extracted with Et_2O (3 × 50 mL). The organic layers were combined, dried (K_2CO_3), and concentrated, and the residue was recrystallized from hot $CHCl_3$ to afford 2.17 g (64%) of **31** as a white crystalline solid. Data for **31**: mp 170–171 °C; ^{1}H NMR (300 MHz, DMSO-d_6) 3.92 (m, 1 H, C*H*OH), 3.12 (m, 2 H, CH_2OH), 1.96 (m, 2 H), 1.82–1.51 (m, 13 H), 1.02 (d, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) 67.44 (*C*H$_2$OH), 65.31 (*C*HOH), 40.04, 32.91, 29.61, 28.31, 23.78; IR (KBr pellet) 3300 (s, br), 2938 (s), 2915 (s), 2892 (s), 1460 (w), 1415 (w), 1370 (w), 1343 (w), 1311 (w), 1265 (w), 1240 (w), 1117 (m), 1080 (m), 1033 (s), 959 (m), 860 (w); MS (10 eV) 170 (M$^+$, 1), 152 (18), 134 (43), 122 (22), 121 (45), 119 (15), 105 (11), 95 (13), 94 (11), 93 (71), 92 (53), 91 (26), 81 (27), 80 (56), 79 (100), 78 (19), 77 (19), 67 (50), 56 (19), 55 (27), 54 (10), 53 (11), 43 (13). Anal. Calcd for $C_{10}H_{18}O_2$ (MW 170.25): C, 70.55; H, 10.65. Found: C, 70.49; H, 10.63.

(1*l*,3*x*,5*u*,7*x*)-7-[(*tert*-Butyldimethylsilyl)oxy]methylbicyclo[3.3.1]nonan-3-ol (18). A solution of *tert*-butyldimethylchlorosilane (6.80 g, 45.22 mmol) in 20 mL of dry DMF was added to a magnetically stirred solution of imidazole (6.16 g, 90.44 mmol), DMAP (500 mg, 4.11 mmol), and **31** (7.0 g, 41.11 mmol) in 120 mL of dry DMF at room temperature. The resulting clear, colorless solution was stirred at room temperature for 5 h and then heated to 45 °C overnight, during which time the color of the solution became yellow. The reaction mixture was then poured into 200 mL of water and extracted with Et_2O (3 × 200 mL). The organic extracts were washed sequentially with water (2 × 150 mL), combined, dried (K_2CO_3), and concentrated. Purification of the golden oil by column chromatography (hexane/EtOAc (10/1)) afforded 9.32 g (80%) of **18** as a white amorphous solid. Data for **18**: mp 83–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 4.09 (m, br, 1 H, C*H*OH), 3.41 (d, J = 4.8, 2 H, CH_2OSi), 2.13–2.08 (m, 2 H), 1.99–1.60 (m, 11 H), 1.12 (m, 1 H), 0.89 (s, 9 H, SiCCH_3), 0.04 (s, 6 H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 68.39 (*C*H$_2$OSi), 67.92 (*C*HOH), 40.55, 32.30, 29.78, 28.36, 26.07, 23.99, 18.52 (SiC*C*H$_3$), −5.29 (SiC*H*$_3$); IR (CCl_4) 3623 (w), 2928 (s), 2859 (s), 1472 (m), 1464 (m), 1387 (w), 1256 (s), 1125 (s), 1096 (s), 1061 (m), 1040 (m), 1005 (w), 963 (m), 939 (w); MS (70 eV) 284 (M$^+$, 1), 136 (11), 135 (100), 107 (17), 105 (18), 93 (42), 81 (15), 79 (31), 75 (47), 73 (16), 67 (39); R_f 0.38 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{16}H_{32}O_2Si$ (MW 284.52): C, 67.55; H, 11.33. Found: C, 67.67; H, 11.36.

(1*l*,3*x*,5*u*,7*x*)-7-[(*tert*-Butyldimethylsilyl)oxy]methyl-3-(methanesulfonyl)bicyclo[3.3.1]nonane (32). A magnetically stirred solution of **18** (9.32 g, 32.76 mmol) in 100 mL of CH_2Cl_2 was cooled to 0 °C and triethylamine (6.85 mL, 49.14 mmol) was added rapidly. A solution of methanesulfonyl chloride (3.04 mL, 39.31 mmol) in 20 mL of CH_2Cl_2 was then added dropwise over a period of 5 min, and the resulting cloudy white solution was stirred at 0 °C for 1 h. The reaction mixture was then poured into brine (200 mL) and extracted with Et_2O (3 × 250 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated *at room temperature* to afford 11.90 g (100%) of **32** as a thick light yellow oil. Compound **32** was usually used without further purification; however, an analytical sample of **32** was obtained by silica gel column chromatography (hexane/EtOAc (5/1)). Data for **32**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.06 (m, 1 H, C*H*OSO$_2$CH$_3$), 3.39 (d, J = 6.6, 2 H, CH_2OSi), 2.98 (s, 3 H, SO$_2$CH_3), 2.18–1.76 (m, 10 H), 1.35 (dt, J = 12.3, 2.2, 2 H), 1.11 (m, 1 H), 0.88 (s, 9 H, SiCCH_3), 0.03 (s, 6 H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 79.45 (*C*HOSO$_2$CH$_3$), 69.56 (*C*H$_2$OSi), 38.77 (SO$_2$*C*H$_3$), 38.29, 32.42, 29.16, 27.83, 26.06, 23.34, 18.48 (SiC*C*H$_3$), −5.26 (SiC*H*$_3$); IR (CCl_4) 2932 (s), 2857 (s), 1472 (m), 1464 (m), 1426 (w), 1343 (s), 1256 (s), 1177 (s), 1128 (s), 1113 (m), 1092 (s), 1061 (m), 1007 (w), 970 (m), 907 (s), 858 (s), 837 (s); MS (70 eV) 153 (16), 135 (43), 93 (18), 80 (16), 79 (21), 75 (100), 67 (14), no M$^+$; R_f 0.30 (hexane/EtOAc (4/1)).

(*R*,*S*)-(1*l*,5*l*,7*x*)-7-[[(*tert*-Butyldimethylsilyl)oxy]methyl]bicyclo[3.3.1]non-2-ene (19). A solution of crude mesylate **32** (11.80 g, 32.54 mmol) in 35 mL of THF was added dropwise over 15 min to a solution of potassium *tert*-butoxide (9.10 g, 81.36 mmol) in 100 mL of THF. The resulting golden, viscous solution was stirred at room temperature for 2 h, poured into 150 mL of water, and extracted with Et_2O (3 × 150 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification of the yellow oil by column chromatography (hexane/EtOAc (30/1)) afforded 7.95 g (92%) of **19** as a clear, colorless oil. An analytical sample of **19** was obtained by Kugelrohr distillation. Data for **19**: bp 70 °C (0.10 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 5.84 (m, 1 H, CH$_2$CH=C*H*), 5.54 (m, 1H, CH$_2$C*H*=CH), 3.48 (d, J = 7.1, 2 H, CH_2OSi), 2.27 (m, 2 H), 2.12 (m, 1 H), 1.91 (m, 1 H), 1.84–1.73 (m, 4 H), 1.59 (m, 1 H), 1.47 (m, 1 H), 1.31 (m, 2 H), 0.88 (s, 9 H, SiCCH_3), 0.02 (s, 6 H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 134.99 (CH$_2$CH=*C*H), 125.84 (CH$_2$*C*H=CH), 68.36 (*C*H$_2$OSi), 34.08, 33.23, 31.58, 30.23, 28.90, 27.61, 26.05 (SiC*C*H$_3$), 25.21, 18.43 (SiC*C*H$_3$), −5.18 (SiC*H*$_3$); IR (CCl_4) 3019 (w), 2928 (s), 2857 (s), 1644 (w), 1472 (m), 1462 (m), 1441 (w), 1389 (w), 1362 (w), 1256 (s), 1188 (w), 1121 (m), 1090 (s), 1007 (w), 939 (w), 874 (m), 839 (s); MS (70 eV) 209 (28), 135 (18), 75 (100), 73 (10), no M$^+$; R_f 0.75 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{16}H_{30}OSi$ (MW 266.51): C, 72.11; H, 11.35. Found: C, 71.93; H, 11.25.

(*R*,*S*)-(1*l*,2*l*,3*u*,5*l*,7*x*)-2,3-Epoxy-7-[[(*tert*-butyldimethylsilyl)oxy]methyl]bicyclo[3.3.1]nonane (20). A magnetically stirred suspension of *m*-chloroperoxybenzoic acid (6.20 g, 35.98 mmol) and $NaHCO_3$ (3.45 g, 41.12 mmol) in 130 mL of CH_2Cl_2 was cooled to 0 °C, and then a solution of **19** (6.85 g, 25.70 mmol) in 20 mL of CH_2Cl_2 was added dropwise over 5 min. The resulting mixture was stirred at room temperature for 1 h, poured into 200 mL of 2 N aqueous $Na_2S_2O_3$ solution, and extracted with Et_2O (3 × 200 mL). The Et_2O layers were washed in series with saturated aqueous Na_2CO_3 solution (1 × 200 mL), dried (K_2CO_3), and concentrated, and the residue was distilled to afford 7.07 g (98%) of **20** as a clear, colorless oil. An analytical sample of **20** was obtained by gradient silica gel column chromatography (hexane/EtOAc: 15/1, 7/1, 2/1, 1 column volume each). Data for **20**: bp 130 °C (0.60 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 3.52 (d, J = 6.9, 2 H, CH_2OSi), 3.11 (t, J = 4.5, 1 H, CH$_2$C*H*O), 3.00 (s, br, 1 H, CHC*H*O), 2.30 (m, 1 H, C*H*CHO), 2.03 (dd, J = 15.6, 6.9, 1 H, CH_2CHO), 1.94–1.80 (m, 3 H), 1.73 (m, 2 H, CH_2CHO), 1.63 (m, 1 H), 1.50 (m, 1 H), 1.25 (m, 2 H), 0.89 (s, 9 H, SiCCH_3), 0.39 (s, 6 H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) 67.74 (*C*H$_2$OSi), 57.40 (CH*C*HO), 51.80 (CH$_2$*C*HO), 33.52, 32.90, 31.05, 27.90, 27.06, 25.99 (SiC*C*H$_3$), 24.57, 22.91, 18.35 (SiC), −5.23 (SiC*H*$_3$); IR (CCl_4) 2930 (s), 2857 (s), 1472 (m), 1462 (m), 1445 (w), 1426 (w), 1389 (w), 1362 (w), 1256 (s), 1109 (m), 1094 (s), 1082 (s), 1007 (w), 963 (w), 939 (w), 882 (w), 862 (m), 837 (s); MS (70 eV) 282 (M$^+$, 1), 225 (20), 133 (24), 105 (37), 93 (12), 91 (48), 89 (12), 79 (21), 75 (100), 73 (28), 67 (13), 59 (14), 55 (23); R_f 0.25 (hexane/EtOAc (15/1)). Anal. Calcd for $C_{16}H_{30}O_2Si$ (MW 282.51): C, 68.03; H, 10.70. Found: C, 67.98; H, 10.64.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*x*)-7-[[(*tert*-Butyldimethylsilyl)oxy]methyl]bicyclo[3.3.1]nonan-2-ol (33). Lithium triethylborohydride (1.0 M in THF, 23.36 mL, 23.36 mmol) was added dropwise over 10 min to a solution of **20** (3.00 g, 10.62 mmol) in 40 mL of THF at room temperature. The resulting solution was heated to 45 °C for 4 h and then cooled to room temperature. The excess reagent was quenched by careful addition of water, and then 10 mL of a 1/1 mixture of 10% aqueous NaOH solution and 30% aqueous H_2O_2 solution was added and the resulting biphasic solution stirred vigorously at room temperature for 20 min. The reaction mixture was then poured into saturated aqueous Na_2CO_3 solution (60 mL) and extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated, and the residue was distilled to afford 2.17 g (72%) of **33** as a white solid. An analytical sample was obtained by silica gel column chromatography (hexane/EtOAc (4/1)). Data for **33**: mp 77–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.67 (s, br, 1 H, C*H*OH), 3.40 (m, 2 H, CH_2OSi), 2.02–1.76 (m, 9 H), 1.59 (s, 1 H), 1.52 (m, 1 H), 1.43 (m, 1 H), 1.35 (m, 1 H), 1.21 (m, 1 H), 0.89 (s, 9 H, SiCCH_3), 0.04 (s, 6 H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 71.94 (*C*HOH), 68.52 (*C*H$_2$OSi), 32.90, 32.60, 28.57, 28.31, 27.85, 25.99 (SiC*C*H$_3$), 24.67, 22.91, 22.19, 18.37 (SiC), −5.33 (SiC*H*$_3$); IR (CCl_4) 3629 (w), 3513 (w), 2930 (s), 2857 (s), 1475 (w), 1464 (w), 1387 (w), 1362 (w), 1252 (m), 1127 (m), 1098 (m), 1073 (m), 1048 (w), 1007 (w), 970 (w), 943 (w), 893 (w), 837 (s); MS (70 eV) 135 (100), 107 (23), 105 (46), 93 (47), 91 (11), 81 (18), 79 (34), 75 (65), 73 (19), 67 (43), 55 (11), no M$^+$; R_f 0.25 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{16}H_{32}O_2Si$ (MW 284.53): C, 67.54; H, 11.33. Found: C, 67.5; H, 11.33.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*x*)-2-(Benzoyloxy)-7-[[(*tert*-butyldimethylsilyl)oxy]methyl]bicyclo[3.3.1]nonane (21). A magnetically stirred solution of **33** (1.00 g, 3.51 mmol) in 30 mL of Et_2O was cooled to −5 °C, and 2.50 mL of *n*-butyllithium (1.55 M in hexane, 3.87 mmol) was added dropwise. The resulting solution was stirred for 5 min, and then a solution of benzoyl chloride (530 μL, 4.57 mmol) in 3 mL of Et_2O was added dropwise. The reaction was allowed to warm to room temperature and stirred 30 min and then poured into water (50 mL) and extracted with

Et_2O (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Purification by gradient column chromatography (hexane/EtOAc: 100/1, 30/1, 1 column volume each; 10/1, 3 column volumes) afforded 1.30 g (95%) of **21** as a clear, colorless oil. An analytical sample of **21** was obtained by Kugelrohr distillation. Data for **21**: bp 170 °C (0.35 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 8.07 (dd, J = 5.6, 1.0, 2 H, *H*Ar), 7.55 (dd, J = 6.8, 1.2, 1 H, *H*Ar), 7.44 (dd, J = 7.9, 1.0, 2 H, *H*Ar), 4.97 (s, br, 1 H, C*H*OBzl), 3.44 (m, 2 H, CH_2OSi), 2.24 (m, 1 H), 2.10 (m, 2 H), 2.02–1.79 (m, 5 H), 1.71–1.61 (m, 3 H), 1.34 (m, 1 H), 1.02 (m, 1 H), 0.91 (s, 9 H, SiCCH_3), 0.05 (s, 6 H, SiCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 165.91 (*C*=O), 132.68 (*C*Ar), 131.44 (*C*Ar), 129.54 (*C*Ar), 128.31 (*C*Ar), 74.99 (*C*HOBzl), 68.26 (*C*H_2OSi), 32.68, 29.62, 28.68, 28.63, 27.76, 25.99, 24.46, 23.21, 20.43, 18.40, −5.32 (Si*C*H_3); IR (CCl_4) 2932 (s), 2859 (s), 1717 (s), 1603 (w), 1586 (w), 1464 (m), 1451 (m), 1387 (w), 1362 (w), 1345 (w), 1314 (m), 1273 (s), 1208 (w), 1177 (m), 1119 (s), 1098 (s), 1071 (s), 1046 (m), 1005 (w), 951 (w), 911 (m), 837 (s); MS (70 eV) 180 (13), 179 (90), 136 (11), 135 (100), 105 (31), 93 (20), 79 (17), 77 (17), 75 (23), 73 (15), 67 (17), no M$^+$; R_f 0.37 (hexane/EtOAc (10/1)). Anal. Calcd for $C_{23}H_{36}O_3Si$ (MW 388.62): C, 71.08; H, 9.34. Found: C, 71.01; H, 9.29.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*x*)-2-(Benzoyloxy)-7-(hydroxymethyl)bicyclo[3.3.1]nonane (34). A solution of tetrabutylammonium fluoride in THF (34.0 mL, 1.0 M, 34.0 mmol) was added to a magnetically stirred solution of **21** (12.00 g, 30.88 mmol) in 150 mL of THF at room temperature. The resulting solution was stirred for 8 h and then poured into 150 mL of brine and extracted with Et_2O (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc (2/1)) afforded 7.95 g (94%) of **34** as a clear, colorless, extremely viscous oil. An analytical sample of **34** was obtained by Kugelrohr distillation. Data for **34**: bp 185 °C (0.30 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 8.06 (dd, J = 5.6, 1.0, 2 H, *H*Ar), 7.55 (m, 1 H, *H*Ar), 7.44 (dd, J = 7.9, 1.0, 2 H, *H*Ar), 4.97 (d, J = 2.8, 1 H, C*H*OBzl), 3.50 (s, 2 H, CH_2OH), 2.28 (m, 1 H), 2.17 (m, 1 H), 2.09–1.81 (m, 6 H), 1.73–1.62 (m, 3 H), 1.52 (s, 1 H), 1.35 (m, 1 H), 1.00 (dt, J = 13.2, 2.9, 1 H), 0.88 (dt, J = 13.2, 2.6, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 165.96 (*C*=O), 132.73 (*C*Ar), 131.01 (*C*Ar), 129.49 (*C*Ar), 128.31 (*C*Ar), 74.80 (*C*HOBzl), 68.29 (*C*H_2OH), 32.68, 29.51, 28.55, 27.70, 24.33, 23.09, 20.39; IR (CCl_4) 3640 (w), 3530 (w, br), 2938 (s), 2861 (m), 1717 (s), 1603 (w), 1462 (m), 1451 (m), 1345 (w), 1312 (m), 1271 (s), 1208 (w), 1177 (m), 1119 (s), 1098 (s), 1071 (m), 1026 (s), 988 (w), 959 (w), 916 (w); MS (70 eV) 152 (11), 134 (15), 108 (12), 106 (12), 105 (100), 96 (20), 95 (35), 93 (23), 92 (15), 91 (16), 81 (12), 79 (33), 77 (73), 67 (16), 55 (12), 51 (16), 41 (22, no M$^+$); R_f 0.22 (hexane/EtOAc (2/1)); GC t_R = 17.06 min, 250 isothermal, column D. Anal. Calcd for $C_{17}H_{22}O_3$ (MW 274.36): C, 74.42; H, 8.08. Found: C, 74.43; H, 8.09.

(*R*,*S*)-(1*l*,2*u*,5*u*,7[70*x*:30*x*])-2-(Benzoyloxy)-7-formylbicyclo[3.3.1]nonane (35). A solution of dry dimethyl sulfoxide (4.84 mL, 68.16 mmol) in 30 mL of CH_2Cl_2 was added dropwise over 5 min to a magnetically stirred solution of oxalyl chloride (2.97 mL, 34.08 mmol) in 120 mL of CH_2Cl_2 at −78 °C; gas evolution was observed during the addition. The resulting solution was stirred for 10 min, and then a solution of **34** (8.50 g, 30.98 mmol) in 30 mL of CH_2Cl_2 was added dropwise over 5 min. The resulting cloudy solution was stirred 30 min at −78 °C, and then freshly distilled Et_3N (17.30 mL, 123.92 mmol) was added dropwise over 5 min. The reaction mixture was stirred 5 min at −78 °C and then was allowed to slowly warm to room temperature and stirred 30 min. The solution was then poured into 150 mL of water and extracted with Et_2O (3 × 150 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Purification by gradient silica gel column chromatography (hexane/EtOAc: (4/1, 2 column volumes; 2/1, 1 column volume) afforded 6.29 g (75%) of **35** as a clear colorless oil along with 1.75 g (21%) of recovered **34** as a clear, light yellow oil. An analytical sample of **35** was obtained by Kugelrohr distillation. Data for **35**: bp 175 °C (0.50 Torr); ^{1}H NMR (500 MHz, $CDCl_3$) 9.71 (s, 0.3 H), 9.52 (s, 0.7 H), 8.06 (d, J = 7.1, 2 H), 7.56 (m, 1 H), 7.44 (m, 2 H), 5.22 (s, br, 0.7 H), 5.03 (s, br, 0.3 H), 2.88 (m, 0.7 H), 2.58 (m, 0.3 H), 2.26–1.37 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) 204.66, 203.76, 165.52, 132.74, 130.71, 129.39, 128.22, 73.91, 73.75, 44.74, 43.19, 37.41, 34.07, 33.49, 31.39, 30.15, 29.10, 28.18, 27.63, 27.29, 27.22, 27.08, 26.76, 26.58, 26.14, 25.73, 24.34, 24.25, 24.09, 21.02; IR (CCl_4) 3067 (w), 2932 (s), 2861 (m), 2811 (w), 2710 (w), 1721 (s), 1603 (w), 1586 (w), 1491 (w), 1453 (s), 1348 (m), 1314 (s), 1271 (s), 1198 (m), 1177 (s), 1156 (m), 1115 (s), 1096 (s), 1070 (s), 1026 (s), 1015 (m), 992 (m), 909 (s); MS (70 eV) 150 (48), 122 (16), 121 (13), 106 (12), 105 (100), 94 (11), 93 (18), 92 (14), 80 (12), 79 (20), 77 (48), 41 (12), no M$^+$; R_f 0.50 (hexane/EtOAc (2/1)). Anal. Calcd for $C_{17}H_{20}O_3$ (MW 272.35): C, 74.97; H, 7.40. Found: C, 74.48; H, 7.39.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*u*)-2-(Benzoyloxy)-7-formyl-7-methylbicyclo[3.3.1]nonane (22). A solution of **35** (1.71 g, 6.28 mmol) in 10 mL of THF was added dropwise over 3 min to a magnetically stirred solution of potassium *tert*-butoxide (846 mg, 7.53 mmol) in 50 mL of 2-methyl-2-propanol at room temperature. The resulting clear yellow solution was stirred 5 min, and then a solution of methyl iodide (782 μL, 12.56 mmol) in 3 mL of THF was added dropwise over 1 min. The resulting milky yellow solution was stirred 35 min at room temperature and then poured into 80 mL of brine and extracted with Et_2O (3 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated. Purification of the thick golden liquid by gradient silica gel column chromatography (hexane/EtOAc: 10/1, 2 column volumes: 7/1, 4/1, 1 column volume each) afforded 1.41 g (78%) of **22** as a white solid. An analytical sample of **22** was obtained by recrystallization from warm hexane. Data for **22**: mp 82–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 9.59 (s, 1 H), 8.04 (dd, J = 7.2, 1.3, 2 H), 7.55 (m, 1 H), 7.43 (m, 2 H), 5.09 (s, br, 1 H), 2.38 (d, J = 15.2, 2 H), 2.18 (m, 1 H), 2.06 (m, 2 H), 1.88 (m, 1 H), 1.70–1.42 (m, 6 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 206.71, 165.65, 132.77, 130.94, 129.51, 128.32, 73.85, 43.89, 37.08, 34.68, 31.43, 29.76, 27.99, 26.60, 26.18, 23.86; IR (CCl_4) 2930 (m), 2861 (w), 2689 (w), 1719 (s), 1453 (m), 1346 (w), 1314 (w), 1273 (s), 1177 (w), 1115 (s), 1096 (m), 1071 (w), 1026 (w), 1007 (w), 949 (w), 912 (w), 855 (w); MS (70 eV) 164 (16), 136 (32), 135 (17), 107 (100), 106 (11), 105 (100), 93 (33), 80 (11), 79 (19), 77 (47), 41 (15), no M$^+$; R_f 0.30 (hexane/EtOAc (4/1)); GC t_R = 15.04 min, 250 isothermal, column D. Anal. Calcd for $C_{18}H_{22}O_3$ (MW 286.38): C, 75.50; H, 7.74. Found: C, 75.33; H, 7.78.

(*R*,*S*)-(1*l*,5*u*,7*u*)-7-(Hydroxymethyl)-7-methylbicyclo[3.3.1]nonan-2-one (23). A magnetically stirred solution of **22** (1.26 g, 4.40 mmol) in 10 mL of Et_2O was treated with 15 mL of a 5% methanolic NaOH solution at room temperature, and the resulting homogeneous solution was stirred 9 h at room temperature, during which time a flocculent white solid gradually appeared in the solution. The reaction mixture was poured into 40 mL of brine and extracted with EtOAc (3 × 60 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification of the residue by gradient silica gel column chromatography (hexane/EtOAc: 2/1, 1/1, 2 column volumes each) afforded 753 mg (95%) of **23** as a clear thick oil that later solidified. An analytical sample of **23** was obtained by Kugelrohr distillation of the solid. Data for **23**: bp 115 °C (0.40 Torr); mp 65–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.17 (dd, J = 8.1, 5.0, 2 H), 2.54–2.38 (m, 3 H), 2.30 (m, 2 H), 2.15 (m, 1 H), 2.03 (m, 1 H), 1.67 (m, 2 H), 1.60 (m, 2 H), 1.47 (dd, J = 14.5, 5.3, 1 H), 1.32 (dd, J = 14.1, 5.3, 1 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 220.15, 68.77, 42.63, 41.03, 37.42, 37.29, 34.91, 29.94, 29.46, 25.73, 25.02; IR (CCl_4) 3463 (w, br), 2926 (s), 1707 (s), 1462 (m), 1418 (w), 1375 (w), 1350 (w), 1296 (w), 1281 (w), 1221 (w), 1112 (m), 1051 (s), 1036 (s), 1015 (w), 992 (w), 947 (w); MS (70 eV) 182 (M$^+$, 7), 152 (30), 151 (16), 133 (19), 110 (17), 109 (22), 108 (20), 107 (62), 106 (13), 105 (28), 97 (10), 96 (100), 95 (30), 94 (23), 93 (39), 91 (31), 83 (11), 81 (50), 80 (12), 79 (52), 77 (23), 69 (10), 68 (12), 67 (58), 65 (10), 57 (11), 55 (42), 53 (27), 43 (20), 41 (67), 39 (36); R_f 0.15 (hexane/EtOAc (2/1)); GC t_R = 9.66 min, 130 (5), 10, 250 (10), column D. Anal. Calcd for $C_{11}H_{18}O_2$ (MW 182.26): C, 72.49; H, 9.95. Found: C, 72.49; H, 9.96.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*u*)-2-(Benzoyloxy)-7-methyl-7-ethenylbicyclo[3.3.1]nonane (36). A magnetically stirred suspension of methyltriphenylphosphonium bromide (2.99 g, 8.38 mmol) in 60 mL of THF was cooled to −78 °C, and then 5.35 mL of *n*-butyllithium (1.50 M in hexane, 8.03 mmol) was added dropwise. The resulting orange solution was then allowed to warm to room temperature to ensure complete formation of the ylide, recooled to −78 °C, and a solution of **22** (2.00 g, 6.98 mmol) in 8 mL of THF was added dropwise. The resulting solution was allowed to warm to room temperature, stirred 20 min, poured into water (100 mL), and extracted with pentane (3 × 100 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc (15/1)) afforded 1.82 g (92%) of **36** as a white solid. An analytical sample of **36** was obtained by Kugelrohr distillation of the solid. Data for **36**: bp 155 °C (0.30 Torr); mp 75–76 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 8.06 (m, 2 H), 7.55 (m, 1 H), 7.44 (m, 2 H), 5.94 (dd, J = 17.6, 10.7, 1 H), 5.05 (s, 1 H), 4.98 (m, 2 H), 2.33 (m, 1 H), 2.17 (m, 1 H), 2.07 (m, 1 H), 1.94 (m, 1 H), 1.86 (m, 1 H), 1.81–1.73 (m, 4 H), 1.64 (m, 2 H), 1.44 (m, 1 H), 1.11 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 165.89, 152.30, 132.68, 131.21, 129.53, 128.30, 109.41, 75.18, 40.50, 38.33, 35.82, 33.82, 31.67, 27.94, 26.29, 23.09; IR (CCl_4) 2928 (m), 2863 (w), 1717 (s), 1451 (w), 1348 (w), 1314 (w), 1269 (s), 1177 (w), 1117 (m), 1071 (w), 1026 (w), 1003 (w), 984 (w), 909 (w); MS (70 eV) 162 (30), 119 (12), 106 (18), 105 (100), 94 (18), 93 (14), 92 (20), 91 (12), 79 (20), 77 (37), 41 (12), no M$^+$; R_f 0.63 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{19}H_{24}O_2$ (MW 284.40): C, 80.24; H, 8.51. Found: C, 80.15; H, 8.54.

(*R*,*S*)-(1*l*,2*u*,5*u*,7*u*)-2-Hydroxy-7-methyl-7-ethenylbicyclo[3.3.1]no-

nane (24). A magnetically stirred solution of 36 (1.82 g, 6.40 mmol) in 15 mL of Et_2O was treated with 20 mL of a 5% methanolic NaOH solution at room temperature, and the resulting homogeneous solution was stirred for 19 h at room temperature, during which time a flocculent white solid gradually appeared in the solution. The reaction mixture was poured into 60 mL of brine and extracted with Et_2O (3 × 80 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc (4/1)) afforded 1.10 g (96%) of 24 as a white crystalline solid. An analytical sample of 24 was obtained by Kugelrohr distillation of the solid. Data for 24: bp 150 °C (2.0 Torr); mp 60–61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 5.87 (dd, J = 17.6, 10.7, 1 H), 4.90 (dd, J = 17.6, 10.7, 2 H), 3.72 (s, 1 H), 2.16 (m, 1 H), 1.97 (m, 1 H), 1.91 (m, 1 H), 1.79 (m, 2 H), 1.65 (m, 3 H), 1.56 (m, 3 H), 1.38 (m, 1 H), 1.28 (m, 1 H), 1.09 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 152.59, 108.83, 71.92, 39.97, 38.47, 35.15, 34.32, 33.88, 27.62, 26.20, 25.29, 24.67; IR (CCl_4) 3626 (m), 3083 (w), 2926 (s), 2863 (s), 1634 (w), 1453 (m), 1231 (w), 1087 (w), 1046 (w), 1003 (m), 945 (m), 907 (m); MS (70 eV) 180 (M^+, 2), 123 (13), 109 (26), 108 (30), 105 (14), 97 (17), 96 (100), 95 (25), 94 (13), 93 (28), 92 (12), 91 (27), 83 (15), 81 (30), 80 (13), 79 (49), 77 (20), 70 (12), 69 (14), 68 (19), 67 (40), 57 (15), 55 (41), 53 (25), 41 (14), 39 (67); R_f 0.33 (hexane/EtOAc (4/1)). Anal. Calcd for $C_{12}H_{20}O$ (MW 180.29): C, 79.94; H, 11.18. Found: C, 79.98; H, 11.13.

(*R*,*S*)-(1*l*,5*u*,7*u*)-7-Methyl-7-ethenylbicyclo[3.3.1]nonan-2-one (25). A solution of dimethyl sulfide (941 μL, 12.81 mmol) in 5 mL of toluene was added dropwise to a magnetically stirred solution of *N*-chlorosuccinimiade (1.22 g, 9.15 mmol) in 35 mL of toluene at 0 °C. The resulting suspension was cooled to −25 °C (CCl_4/CO_2), and a solution of alcohol 24 (1.10 g, 6.10 mmol) in 5 mL of toluene was added dropwise over 3 min. The reaction mixture was stirred for 2 h at −25 °C, and then a solution of Et_3N (1.28 mL, 9.15 mmol) in 3 mL of toluene was added dropwise. The solution was allowed to warm to room temperature and stirred for 10 min. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 60 mL). The organic extracts were combined, dried (K_2CO_3), and concentrated. Purification of the residue by silica gel column chromatography (hexane/EtOAc (4/1)) afforded 982 mg (90%) of 25 as a white solid. An analytical sample was obtained by Kugelrohr sublimation of the solid. Data for 25: mp 66–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 5.73 (dd, J = 17.8, 11.0, 1 H), 4.96 (dd, J = 17.8, 10.9, 2 H), 2.47 (s, br, 1 H), 2.34–2.25 (m, 4 H), 2.03 (m, 1 H), 1.90 (m, 2 H), 1.84 (m, 1 H), 1.62 (m, 2 H), 1.50 (dd, J = 14.0, 5.1, 1 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 218.65, 146.98, 112.80, 44.53, 43.62, 39.92, 36.63, 35.30, 35.21, 30.00, 25.56, 23.43; IR (CCl_4) 3087 (w), 2921 (s), 2867 (s), 1709 (s), 1639 (m), 1456 (s), 1410 (m), 1375 (w), 1347 (m), 1279 (w), 1231 (m), 1181 (w), 1121 (m), 1094 (w), 1069 (w), 1038 (w), 1015 (m), 1001 (m), 914 (s); MS (70 eV) 178 (M^+, 55), 135 (16), 121 (15), 120 (15), 119 (14), 109 (16), 108 (17), 107 (36), 106 (23), 105 (17), 96 (100), 95 (29), 94 (33), 93 (77), 92 (24), 91 (35), 83 (13), 82 (10), 81 (36), 80 (22), 79 (63), 77 (30), 69 (10), 68 (28), 67 (56), 66 (10), 65 (13), 55 (44), 54 (11), 53 (36), 43 (16), 41 (82), 40 (11), 39 (48); R_f 0.33 (hexane/EtOAc (6/1)). Anal. Calcd for $C_{12}H_{18}O$ (MW 178.27): C, 80.85; H, 10.18. Found: C, 80.89; H, 10.16.

(*R*,*S*)-(1*l*,5*u*,7*u*)-7-Formyl-7-methylbicyclo[3.3.1]nonan-2-one (2). A solution of 25 (70 mg, 0.393 mmol) in 7 mL of CH_2Cl_2 was cooled to −78 °C and purged for 30 min with O_2, which was introduced via a gas diffusion bubbler. Ozone (Welsbach Corp. ozonator with the voltage set to 85 V and oxygen pressure at 7.5 psi) was then bubbled in at a rate of ~1 mmol/min until the solution turned blue. The solution was then purged with O_2 until it became colorless, and trimethyl phosphite (370 μL, 3.14 mmol) was added. The reaction was warmed to room temperature and stirred for 21 h. The mixture was again cooled to −78 °C and purged with O_2 for 30 min. Ozone was again bubbled into the solution until a blue color persisted, and then the solution was purged with O_2 until it became colorless. The solvent was then removed in vacuo and the residue dissolved in cold (−45 °C or below) hexane/EtOAc (4/1). During the second ozonolysis, a cold-column chromatographic system was prepared by circulating cold (−40 °C or below) 2-propanol through a jacketed 10-mm column packed with 15 cm of Activity V neutral alumina with use of a Neslab CC-100 II Cryocool immersion cooler and accompanying circulating pump. At least 3 h of cooling prior to circulation through the column is necessary to achieve temperature of −40 °C or below. The crude keto aldehyde 2 was then placed onto the column and eluted with use of cold (−40 °C or below) solvents under gradient conditions (hexane/EtOAc: 4/1, 2/1, 1 column volume each) to afford 54 mg (76%) of 2 as a semisolid. NMR samples of this compound were prepared by passing the $CDCl_3$ through basic alumina prior to use. The compound decomposed slowly at room temperature but could be stored at −15 °C under a static Ar atmosphere for up to 5 days without decomposition. The compound decomposed upon attempted distillation and thus could not be further purified. Data for 2: ^{1}H NMR (500 MHz, $CDCl_3$) 9.31 (s, 1 H), 2.47 (m, 2 H), 2.29 (m, 3 H), 2.07 (m, 2 H), 1.96 (m, 1 H), 1.66 (m, 2 H), 1.50 (m, 2 H), 0.93 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 216.65, 204.63, 45.00, 43.12, 38.67, 36.09, 29.73, 26.53, 25.12, 23.91; IR (CCl_4) 2926 (s), 2869 (m), 2707 (w), 1730 (s), 1711 (s), 1458 (m), 1119 (w), 1090 (w), 1069 (w), 910 (w); GC t_R = 16.49 min, 100 (5), 20, 200 (15), column C.

(*R*,*S*)-(1*l*,5*l*,7*u*,9*l*)-9-Hydroxy-7-methyladamantan-2-one (5) and (*R*,*S*)-(1*l*,5*l*,7*u*,9*u*)-9-Hydroxy-7-methyladamantan-2-one (6). A solution of 2 (60 mg, 0.33 mmol) in 1 mL of THF was added to a magnetically stirred solution of potassium *tert*-butoxide (45 mg, 0.40 mmol) in 3 mL of THF at room temperature. The resulting orange-yellow solution was stirred for 15 min at room temperature and then poured into 10 mL of brine and extracted with Et_2O (3 × 15 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification of the residue by gradient silica gel column chromatography (hexane/EtOAc: 10/1, 1 column volume; 4/1, 3/1, 2/1, 2 column volumes each) afforded 10 mg (17%) of anti alcohol 6 as a clear colorless oil that later solidified and 39 mg (65%) of syn alcohol 5 as a white crystalline solid. Analytical samples of both 5 and 6 were obtained by Kugelrohr sublimation.

Data for (*R*,*S*)-(1*l*,5*l*,7*u*,9*l*)-9-hydroxy-7-methyladamantan-2-one (5): mp 189–191 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.83 (d, J = 2.3, 1 H), 2.59 (s, br, 1 H), 2.47 (s, br, 1 H), 2.33 (d, J = 2.6, 1 H), 2.26 (d, J = 12.8, 1 H), 2.07–1.91 (m, 5 H), 1.76 (m, 1 H), 1.69 (m, 1 H), 1.54 (m, 1 H), 0.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 217.59, 81.91, 54.18, 46.26, 42.94, 39.20, 38.35, 38.09, 34.73, 27.56, 24.92; IR (CCl_4) 3621 (w), 3416 (m, br), 2926 (s), 2861 (m), 1719 (s), 1692 (m), 1453 (m), 1374 (w), 1300 (w), 1275 (w), 1242 (w), 1225 (w), 1173 (w), 1090 (w), 1071 (s), 1055 (w), 972 (w), 932 (w); MS (70 eV) 180 (M^+, 30), 162 (18), 152 (28), 107 (14), 106 (44), 105 (10), 96 (100), 95 (38), 94 (27), 93 (71), 92 (15), 91 (24), 81 (11), 79 (28), 77 (17), 67 (19), 55 (15), 53 (12), 43 (14), 41 (32), 39 (19); high-resolution MS for $C_{11}H_{16}O_2$ calcd 180.115 05; found 180.115 14; R_f 0.20 (hexane/EtOAc (3/1)); GC t_R = 23.50 min, 100 (5), 20, 200 (15), column C. Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.24; H, 9.03.

Data for (*R*,*S*)-(1*l*,5*l*,7*u*,9*u*)-9-hydroxy-7-methyladamantan-2-one (6): mp 174–175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.54 (s, 1 H), 2.63 (s, br, 1 H), 2.53 (s, br, 1 H), 2.37 (m, 1 H), 2.06 (m, 1 H), 2.00–1.88 (m, 4 H), 1.76 (d, J = 4.3, 1 H), 1.71 (m, 1 H), 1.52 (m, 1 H), 1.37 (m, 1 H), 0.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) 215.38, 76.30, 53.77, 46.56, 40.82, 38.28, 36.35, 34.09, 32.12, 27.20, 25.43; IR (CCl_4) 3631 (w), 3453 (w, br), 2928 (s), 2859 (m), 1717 (s), 1692 (m), 1455 (m), 1374 (w), 1300 (w), 1345 (w), 1281 (w), 1266 (m), 1242 (w), 1088 (m), 1065 (m), 1040 (m), 1019 (w), 980 (w), 936 (w), 909 (w), 878 (w); MS (70 eV) 180 (M^+, 43), 162 (15), 152 (18), 110 (13), 107 (11), 106 (31), 105 (11), 96 (100), 95 (37), 94 (27), 93 (63), 92 (17), 91 (26), 81 (14), 79 (30), 77 (18), 67 (22), 57 (11), 55 (18), 53 (15), 43 (17), 41 (35), 39 (23); high-resolution MS for $C_{11}H_{16}O_2$ calcd 180.115 05, found 180.114 52. R_f 0.24 (hexane/EtOAc (3/1)); GC t_R = 22.90 min, 100 (5), 20, 200 (15), column C.

General Procedure for Cyclizations of 2. A magnetically stirred solution of 2 in the appropriate dry solvent (~0.01 M) was cooled to −78 °C, and then any additives required were added in their appropriate amounts. In the reactions using Kryptofix 222, the appropriate amount of this compound was added to the *base* at room temperature prior to the addition of the base to the reaction. The appropriate base (1.1 equiv) was then added, and the reaction was stirred at −78 °C for 30–60 min. Cyclododecane (0.5 equiv, as a solution in THF or CH_2Cl_2) was added, and the reaction was quenched at −78 °C by addition of 100 μL of a 1/1 mixture of pH 7 buffer/MeOH and was allowed to warm to room temperature. The reaction mixture was dried ($MgSO_4$), was filtered through a pipette of silica gel with hexane/EtOAc (1/1) as the eluent, and was partially concentrated. Analysis of the product ratios was done by injection onto column C (program: 100 (5), 20, 200 °C (15)). Final ratios and yields were calculated on the basis of independently obtained response factors relative to the cyclododecane internal standard.

Procedure for Calculation of Relative Response Factors. Stock solutions of known molarity of cyclododecane, syn diastereomers 3 and 5, and anti diastereomers 4 and 6 were prepared by dissolving known amounts of each in separate volumetric flasks and diluting to the mark with THF. A portion of each of the solutions containing the diastereomeric aldol adducts was then separately mixed with an *equimolar* amount of the cyclododecane stock solution. The resulting solutions were then injected onto GC column C, and the area of the aldol adduct peak was divided by the area of the cyclododecane peak. The injections were repeated in triplicate and averaged to give a response factor relative to cyclododecane. The entire procedure was repeated twice more and the numbers obtained averaged to give the final relative response factors.

(*R*,*S*)-(1*l*,3*x*,5*u*,7*u*,1′*x*)-3-(1-Hydroxypropyl)-7-methyl-7-ethenyl-

bicyclo[3.3.1]nonan-2-one (26). Triethylamine (17 μL, 0.12 mmol) was added to a magnetically stirred solution of dibutylboron triflate (31 μL, 0.12 mmol) in 2 mL of dry Et_2O. The solution was cooled to −78 °C, and a solution of **25** (20 mg, 0.11 mmol) in 200 mL of Et_2O was added. The formation of a white precipitate was noted upon completion of the addition. The resulting solution was stirred for 30 min, and then propionaldehyde (10 μL, 0.134 mmol) was added. The reaction was stirred for 30 min at −78 °C, warmed to room temperature and stirred for 30 min, poured into water (5 mL), and extracted with Et_2O (3 × 10 mL). The organic extracts were concentrated, and the residue was dissolved in 1 mL of MeOH. This solution was then treated with 200 μL of 30% aqueous H_2O_2 solution and stirred for 15 min at room temperature. The reaction was poured into water (5 mL) and extracted with Et_2O (3 × 10 mL). The organic layers were combined, dried (K_2CO_3), and concentrated. Purification by silica gel gradient column chromatography (hexane/EtOAc: 7/1, 4/1, 2/1, 1 column volume each) afforded 19 mg (66%) of **26** as a clear colorless oil. Data for **26**: ^1H NMR (200 MHz, $CDCl_3$) 5.82 (m, 1 H), 5.01 (m, 2 H), 4.21 (m, 1 H), 3.59 (m, 1 H), 2.88 (m, 1 H), 2.54 (s, br, 1 H), 2.25-1.21 (m, 11 H), 0.97 (s, 3 H), 0.87 (t, 3 H).

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Syntheses and Properties of Soluble Carceplexes[1,2]

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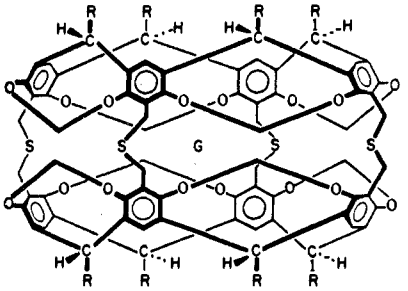
Abstract: The syntheses and characterizations of three soluble carceplexes (**1**·G, where G is guest) are reported. Carcerands are noncollapsible molecular cells whose interiors are large enough to contain molecules or ions (guests) and whose closed surfaces contain pores too small for guest molecules to enter or depart from their interiors without making or breaking covalent bonds. A carceplex is composed of a carcerand containing at least one guest (prisoner) molecule in its interior. The carceplexes reported here differ only in their guest structures. Their shell is shaped like a U.S. football, to which are attached around each of their small ends four phenylethyl groups for solubilization. The carceplexes were made by shell-closing two identical bowl-shaped cavitands (**2**), each containing on their rims four phenolic hydroxyls. The reaction was $2(ArOH)_4 + 4CH_2BrCl + 4Cs_2CO_3 \rightarrow (ArOCH_2OAr)_4 + 4CsBr + 4CsCl + 4CO_2 + 4H_2O$, in which eight covalent bonds were formed. In each synthesis, one molecule of solvent was encapsulated in remarkably good yield, leading to **1**·$(CH_3)_2SO$ (61%), **1**·$(CH_3)_2NCOCH_3$ (54%), and **1**·$(CH_3)_2NCHO$ (49%). The reaction, when run in $CH_2(CH_2CH_2)_2NCHO$, a solvent too large to be encapsulated, gave only polymers, indicating that the shell closures must be templated by the molecule that is ultimately incarcerated. A shell closure run in equimolar $(CH_3)_2NCOCH_3$-$(CH_3)_2NCHO$ gave a 27% yield of a mixture of **1**·$(CH_3)_2NCOCH_3$ and **1**·$(CH_3)_2NCHO$ (ratio 5.3), the mixture being separated chromatographically. Each carceplex's desorption chemical ionization mass spectra (DCI MS) gave substantial $M^+ + 1$ peaks. The ^1H and ^{13}C NMR spectra of each carceplex were taken, and all protons were assigned. All guest protons were moved upfield from their normal resonances by 1-4 ppm. Incarcerated $(CH_3)_2NCHO$ rotates about the host's short equatorial and long polar axes rapidly on the ^1H NMR time scale, even at −38 °C ($CDCl_3$); rotation of incarcerated $(CH_3)_2NCOCH_3$ about the host's long axis is fast, but about the short axes is slow, even at 175 °C ($C_6D_5NO_2$); incarcerated $(CH_3)_2SO$ rotations about all axes are fast above 2 °C, but slow about the short axes below 2 °C ($CDCl_3$). The rates of rotation about the C-N bond of amide guests vary with phase changes ($C_6D_5NO_2$ solvent when needed) as follows: for $(CH_3)_2NCHO$, vacuum > *interior phase* > solution; for $(CH_3)_2NCOCH_3$, vacuum > solution > *interior phase*. The crystal structures of **1**·$(CH_3)_2NCOCH_3$ and **5** correspond to those expected from scale molecular model examination.

Carcerands are closed-surface, globe-shaped compounds with enforced hollow interiors large enough to incarcerate simple organic compounds, inorganic ions, or both. Carceplexes are carcerands whose interiors are occupied by prisoner molecules or ions that cannot escape their molecular cells without breaking covalent bonds between the atoms that block their escape. We reported the syntheses of the first carceplexes[3a,b] (Ia) as inseparable, insoluble mixtures whose components possessed the same shell, but differed as to their prisoner molecules and ions (guests or G). The guests were identified by FAB MS, elemental analyses, and ^1H NMR spectra to be $(CH_3)_2NCHO$, $(CH_2)_4O$, Cs^+, argon, and $ClCF_2CF_2Cl$,[3] each of which was present in the medium used for shell closure of the two cavitands in the synthesis. The insolubility of these carceplexes prevented their isolation, characterization, and study as single chemical entities.



Ia, R = CH_3; **Ib**, R = $CH_2CH_2C_6H_5$; **Ic**, R = $(CH_2)_4CH_3$

The present and a companion study[4] were undertaken to overcome this limitation by appending eight long and conformationally mobile hydrocarbon groups to the carceplexes arranged in two groups of four around the arctic and antarctic circles of

(1) (a) We warmly thank the National Science Foundation for Grant CHE 88 02800, which supported this work. (b) Host-Guest Complexation. 56.

(2) Some of these results were previously communicated. Sherman, J. C.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 4527-4528.

(3) (a) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Kalleymeyn, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 2575-2576; (b) Cram, D. J.; Karbach, S.; Kim, Y. H.; Baczynskyj, L.; Marti, K.; Sampson, R. M.; Kalleymeyn, G. W. *Ibid.* **1988**, *110*, 2554-2560.

(4) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Chem. Soc. Chem. Commun.* **1990**, 1403-1405.

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