in 15 mL of ethanol with 0.75 mL (0.9 mmol) of methyl acrylate and 2.5 mL of triethylamine for 3 h, cooling and concentrating to a solid residue, washing with ether, and concentrating to an oil. Chromatography on base-washed alumina ($CHCl_3$ eluant) gave **5** as a clear oil in 22% yield: ^1H NMR δ ($CDCl_3$) 3.54 (s, 3 H), 2.60 (t, 2 H), 2.35 (t, 2 H), 2.05 (s, 3 H); empirical formula determined by high-resolution mass spectroscopy.

VT NMR of **6** (^1H NMR δ ($CDCl_3$) 3.60 (t, NCH_2), 2.42 (t, $OCCH_2$), 2.15 (pent, CCH_2C)) was determined on a Bruker WP-270 in CH_2Cl_2. The AB pattern at δ 3.6 observed at low temperature when the δ 2.15 siganl was decoupled showed below coalescence at −90 °C (J_{AB} = 8.9 Hz, $\Delta\nu$ = 21.91 Hz), −86.8 (8.8, 22.7_3), −84.5 (8.7, 22.2_6) −79.0 (8.8, 24.4_3), −67.5 (8.6, 27.6_4), and coalescence was achieved at −48 °C, where $\Delta\nu$ was extrapolated to 32.3 Hz, leading to $\Delta G^{\ddagger}$(−48 °C) of 11.36 kcal/mol.

Photoelectron spectra were determined on a rebuilt[10] Varian IEE-15, ESR spectra on a Varian E-15, and cyclic voltammograms on Parr equipment.[10] Calculations were carried out on VAX 8600 and IBM PC-XT equipment.

Crystal Structure Data. Intensity data were measured with a Philips PW 1100 four-circle, computer-controlled diffractometer, using graphite-monochromated Mo Kα radiation (λ = 0.71069 Å). The crystal structures were solved either by MULTAN 80[33] or by SHELX 76[34] and refined by SHELX 76 with anisotropic vibrational parameters for O, N, and C atoms and isotropic parameters for H atoms. The scattering factors for O, N, and C atoms are from Cromer and Mann[35] and those for H from Stewart et al.[36]

6, $C_8H_{12}N_2O_2$; monoclinic $P2/n$ space group; a = 12.683 (6) Å, b = 5.282 (3) Å, c = 12.509 (6) Å, β = 92.48 (2)°; 1479 reflections measured, 1450 used in the refinement, R = 0.058, R_w = 0.079. There are two molecules in the asymmetric unit, each occupies a twofold-axis special position.

7, $C_6H_8N_2O_2$; monoclinic $P2_1/n$ space group; a = 10.722 (5) Å, b = 6.110 (3) Å, c = 10.321 (5) Å, β = 110.57 (2)°; 1291 reflections measured, 1153 used in the refinement, R = 0.050, R_w = 0.061.

Acknowledgment. We thank the National Science Foundation (Grants CHE-8025111, CHE-8415077, and CHE-8401836), the Technion VPR Fund, and the Lawrence Deutsch Research Fund for partial financial support of this work.

Registry No. 3, 3645-44-1; **4**, 6261-36-5; **5**, 18714-58-4; **6**, 60769-64-4; **7**, 19720-72-0; **7**$^+$, 109669-74-1; **8**, 3661-10-7; **8**$^+$, 109669-75-2; **9**, 72282-81-6; **9**$^+$, 84960-96-3.

Supplementary Material Available: Listing of atomic coordinates, anisotropic temperature factors, and bond lengths and angles for **6** and **7**, photoelectron spectra for **3–9**, MNDO and AM1 bond lengths and bond angles for comparison with Figures 3 and 4 for **6**, **7**, and **8**, and plots of NN twisting barriers for **6** and **6**$^{\cdot +}$ by MNDO and AM1 (17 pages). Ordering information is given on any current masthead page.

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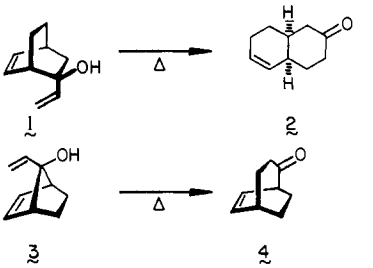
Anionic Rearrangements of *syn*- and *anti*-7-Cyclopentenyl-7-hydroxynorbornenes. The Case for Sequential Ring Cleavage and Intramolecular Michael Addition

Leo A. Paquette,* Francis Pierre, and Charles E. Cottrell[1]

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received February 23, 1987*

Abstract: Oxyanion formation within several *anti*-7-norbornenols is shown to foster rearrangement predominantly via formal antarafacial-retention [1,3]-sigmatropic bridgehead carbon migration. To a lesser extent, oxy-Cope bond reorganization takes place. Under the same conditions, the epimeric syn alcohols undergo exclusively the first of these processes, but with regiochemical and stereochemical characteristics identical with those observed in the first series. The favored mechanism for the [1,3]-shift pathway involves heterolysis of a norbornene bridgehead/apical bond, proper conformational alignment within the resulting 3-cyclohexenyl anion intermediate, and intramolecular Michael addition under kinetic (and thermodynamic) control. The presence of a 2-methyl group induces an avoidance to the positioning of this substituent at one of the allyl anion termini, for obvious energetic reasons. In contrast, the oxy-Cope process gives every indication of occurring concertedly in a boat transition state. The 2-methyl substituent, when present, directs rebonding to the second (unsubstituted) norbornenyl trigonal center in order to avoid generation of a quaternary carbon. Despite the concert with which [3,3]-sigmatropy takes place, it never is the dominant pathway, probably because of the somewhat distorted geometry required in the relevant transition states.

The rapid elaboration of polycyclic ketones with good stereochemical control is an important objective in organic synthesis. That 3-hydroxy-1,5-hexadienes can be made to undergo thermal oxy-Cope rearrangement with formation of such carbonyl compounds was first described by Berson and Jones in 1964.[2] In these reports, the conversion of **1** and **3** principally to **2** and **4**, respectively, was detailed. Both reactions were considered to proceed stepwise via diradical intermediates. Preferred operation



within **3** of the so-called "single-inversion" pathway was attributed to the less than ideal proximity of its diene termini. The geometric

(1) Campus Chemical Instrument Center.

(2) (a) Berson, J. A.; Jones, M., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 5017. (b) Berson. J. A.; Jones, M., Jr. *Ibid.* **1964**, *86*, 5019.

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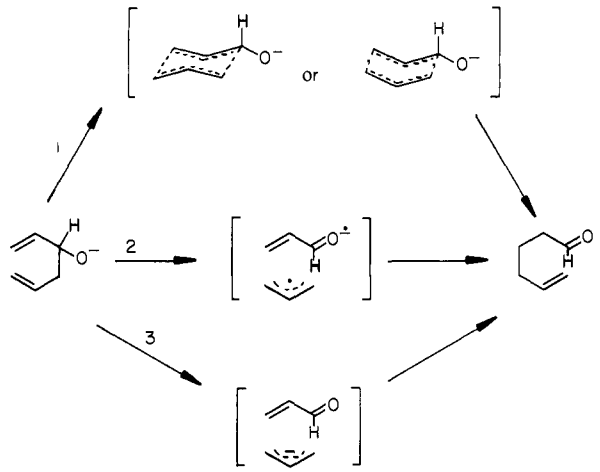
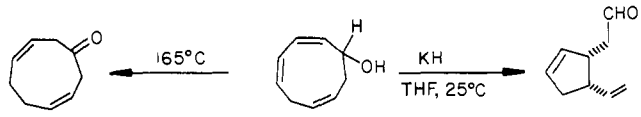


Figure 1. Some mechanistic extremes for the anionic oxy-Cope rearrangement.

constraints within **1** are less stringent.

Subsequently, Evans et al. demonstrated that the highly ionized potassium salts of **1** and select derivatives undergo the oxy-Cope process with substantial acceleration,[3] to an extent such that concerted [3,3]-sigmatropy (path 1, Figure 1) may emerge.[4] The question of mechanistic detail has been examined theoretically.[5] The recent Bartmess study makes the specific point that stepwise pathways 2 and 3 (Figure 1) can be expected to be comparable in energy, at least in the gas phase.[6]

So pronounced is the bond weakening resulting from "naked" alkoxide ion formation in these systems that otherwise symmetry-forbidden [1,3]-sigmatropic carbon migrations are seen to operate readily in certain cases.[7] Also, the normal predilection of *neutral* **5** for thermal [1,5]-hydrogen shift to **6** can be effectively overriden in favor of [3,3]-carbon sigmatropy (leading to **7**) upon conversion to the potassium salt.[8]



These intriguing observations suggest that there remains a great deal to learn concerning the manner in which various types of structural rearrangement are affected by oxyanionic substitution. Principally for this reason, we have undertaken a rather detailed analysis of the response to strongly ionizing conditions of molecules related to **3**. At issue is whether the C–C bond elongation available to the alkoxide[5] would provide to this class of compounds a lessening in structural rigidity adequate to permit operation of the oxy-Cope process. If so, to what extent? Should [1,3]-carbon migration (as **3** → **4**) continue to be favored, can stereocontrol be satisfactorily implemented? Also, if the symmetry in **3** is broken, e.g., by monosubstitution of the norbornene double bond, can reliable regiochemistry be attained in predictable fashion? Since complex polycyclic ketones can in principle be rapidly assembled by this protocol, the answers to these questions are crucial to our appreciation of their effective construction.

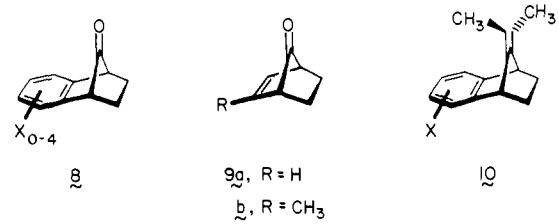
Table I. Relative Product Distributions from Alkenyllithium Additions to 7-Norbornenones **9a** and **9b**

7-norbornenone	lithium reagent	syn/anti ratio (**14**:**15**)	no. of runs[a]
9a	**11a**	1.36:1	1
9a	**12a**/**13a** (70:30)	1.76:1	3
9b	CH_2=CHLi	3.32:1	1
9b	**11a**	1.03:1	2
9b	**13a**	3.01:1	2

[a] The ratios provided for multiple runs constitute an average figure (error limits of ±10%).

Results

Stereochemical Course of Cycloalkenyllithium Additions to 7-Norbornenones. As a follow-up to the Bürgi–Duntz proposal concerning the favored trajectory of nucleophilic additions to carbonyl centers,[9] a considerable amount of attention has been paid to ketones **8** and **9a**. For **8**, the syn/anti stereoselectivity



gives indication of being fully controlled by the electronic characteristics of the pendant aromatic ring.[10,11] In many respects, the response is the reciprocal of that noted for electrophilic capture by 7-isopropylidenebenzonorbornenes **10**.[12]

The picture for **9a**, particularly with regard to organometallics, is less clear-cut.[13] Whereas Grignard[2,17,18] and *alkyl*lithium reagents.[19] give products resulting from bonding syn to the olefinic linkage in stereoselective or stereospecific fashion, vinyl-[20] and phenyllithiums[21] attack preferably from the seemingly more hindered direction.

Condensation of the functionalized cyclopentenyl systems **11a–13a** with **9a** and **9b**[22] was considered to offer the potential for ultimate resolution of the questions raised earlier. These vinyl organometallics were prepared by halogen–metal exchange of

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(13) Okada, Tomita, and Oda[11] have suggested that the origin of stereoselectivity for nucleophilic additions to 9a is probably also electronic in nature. This may well be true for those reactions involving diazomethane,[14] sodium borohydride,[15] and sulfonium[16] or sulfoxonium ylides.[17]

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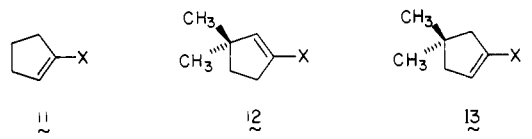
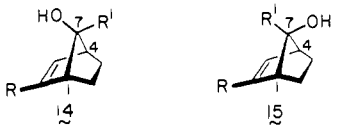


11 12 13

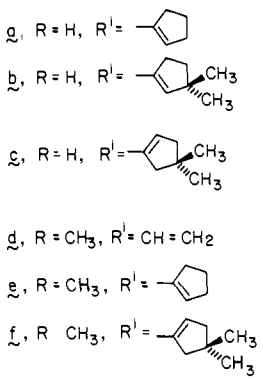
a, R = Li; b, R = Br

11b–13b with *tert*-butyllithium.[23] To obtain **11b**, cyclopentene was brominated[24] and subsequently dehydrobrominated[25] according to literature reports. Bromides **12b** and **13b** were obtained as a 70:30 mixture upon Shapiro degradation[26] of 3,3-dimethylcyclopentanone tosylhydrazone followed by in situ reaction with 1,2-dibromotetrafluoroethane.[27] Recourse to the trisylhydrazone[28] furnished **13b** exclusively.

Individual treatment of **9a** and **9b** with **11a–13a** at −78 °C in tetrahydrofuran solution led to complete ketone consumption. The syn alcohols **14**, cleanly separable from their anti counterparts **15** by medium-pressure silica gel chromatography, were less rapidly eluted. This phenomenon, which at first glance appears



14 15



a, R = H, R' = cyclopentenyl
b, R = H, R' = 3,3-dimethylcyclopentenyl
c, R = H, R' = 4,4-dimethylcyclopentenyl
d, R = CH_3, R' = $CH=CH_2$
e, R = CH_3, R' = cyclopentenyl
f, R = CH_3, R' = 3,3-dimethylcyclopentenyl

inconsistent with the availability of two opportunities within **14** for intramolecular hydrogen bonding, i.e., to either double bond, has been observed in other contexts.[29] The product ratios, which were determined by integration of the MPLC traces are compiled in Table I. It is significant that all of the condensations occur to a somewhat greater degree on the anti face of the carbonyl group in **9a** and **9b**. The presence of a 2-methyl substituent on the norbornenone exerts obvious steric consequences only when Grignard reagents are involved. Thus, Berson and Jones noted that **9a** reacts with vinylmagnesium bromide to give a 1:4 mixture of syn and anti alcohols.[2] The same Grignard reagent was found herein to exhibit considerably lower selectivity toward **9b** (syn/anti = 0.95:1). Strikingly, however, the highest level of discrimination presently observed involved vinyllithium (3.32:1 in favor of **14**).

Stereochemical definition of the isomeric 7-norbornenols was achieved by proper analysis of long-range shielding effects and by application of NOE techniques in particular to **14a** and **14e**. In both series, the less dominant epimer (e.g., **15a** and **15e**) possessing the shorter MPLC retention time exhibits chemical shifts for the exo-ethano protons (*exo*-H-5,6) that obscure those absorptions arising from the allylic hydrogens (H-10,12) on the

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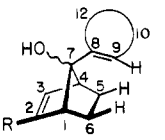
(29) For additional examples of this behavior as well as reversed observations, consult ref 19.

Table II. Selected ^{1}H NMR Data for **14** and **15** (300 MHz, C_6D_6 Solution)

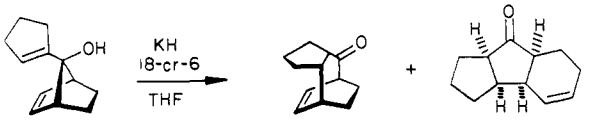


compd	chemical shift, ppm H-1	H-4	*exo*-H-5,6	H-9
	Syn Series			
14a		2.65–2.68	1.63–1.69	5.52–5.55
14b[a]		2.64–2.67	1.65–1.72	5.34
14c		2.64–2.67	1.65–1.72	5.42
14d	2.25	2.44–2.45	1.58–1.76	5.20, 5.72
14e	2.44–2.57	2.65–2.66	1.61–1985	5.54–5.57
14f	2.46	2.64	1.65–1.80	5.42–5.44
	Anti Series			
15a		2.50–2.53	2.18–2.30	5.33–5.36
15b		2.49–2.50	2.17–2.23	5.15
15c		2.49–2.50	2.17–2.23	5.22
15d	2.05–2.23	2.31–2.33	2.05–2.23	5.01, 5.25
15e	2.14–2.35	2.51–2.52	2.14–2.35	5.37–5.39
15f	2.05–2.32	2.48–2.50	2.05–2.32	5.26–5.27

[a] Spectrum recorded on a 70:30 mixture of **14b** and **14c**.

cyclopentenyl ring (see Table II). In contrast, the exo-ethano protons in the major alcohols are subject to shielding by the proximal cyclopentenyl double bond, are consequently shifted to higher field, and are well separated. When vinyl proton H-9 in **14a** and **14e** was doubly irradiated, the integrals due to *exo*-H-5,6 were enhanced (1.5–2.7%). These centers must therefore be reasonably close to each other. Also spectroscopically distinctive and stereochemically informative is the more deshielded nature of the bridgehead protons (H-1,4) in the syn alcohols. The universality of these trends is so obvious (Table II) as to facilitate greatly the classification of the remaining compounds.

Mechanistic Response to Oxyanion Generation in the *anti*-7-Norbornenol Series. The reaction of **15a** with iodine-pretreated[30] potassium hydride in tetrahydrofuran at room temperature for 30 min gave a mixture of two ketones in the relative ratio of 3:1.



15a 16 17

These products, individually obtained in pure form by MPLC on silica gel, were defined as **16** and **17**, respectively, on the basis of their spectral properties. In line with their cycloheptanone and cyclopentanone character, the infrared carbonyl absorptions were seen at 1693 and 1731 cm^{-1}. The 500-MHz ^{1}H NMR spectra of the ketones proved to be particularly distinctive. A combination of NOE and 2-D COSY experiments[31] (Figures 2 and 3) served to establish the complete profile of spin–spin interactions and proton connectivities. As a direct outgrowth of the proton sequencing and the magnitude of the *J* values, the stereochemical assignments shown could readily be deduced.

MM2 calculations show **16** to be approximately 1 kcal/mol more stable than **18**; consequently, kinetic and thermodynamic factors appear to operate synergistically in this instance. Ketone **17** obviously cannot be as stable as the cis,anti,cis alternative.[32] However, its three-dimensional structure is that demanded by

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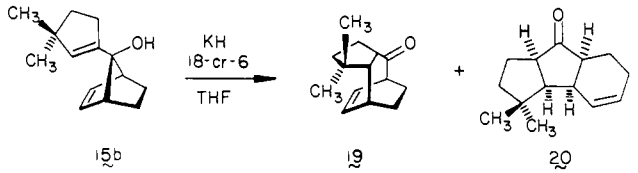
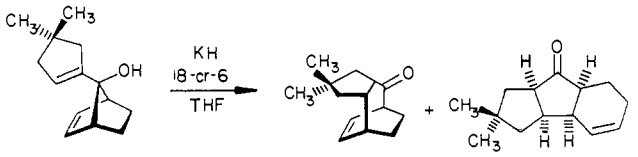
operation of the concerted anionic oxy-Cope rearrangement process.

18

Since the 70:30 mixture of alcohols **15b** and **15c** proved difficult to separate, oxyanion generation was performed directly. The four ketonic products were easily chromatographed apart and their specific origins were ultimately apparent. The trends proved similar to that observed earlier: **19/20** = 3.3; **21/22** = 2.3. Good

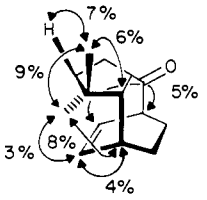


15b 19 20



15c 21 22

spectral correlations were also evident. NOE studies performed on **19** provided convincing confirmation of its syn stereochemistry. For example, double irradiation of the downfield olefinic proton induced integral enhancements in the signals due to the proximal bridgehead proton (4%) and the upfield methyl singlet (3%, see A). Also, the upfield olefinic proton produced an NOE effect

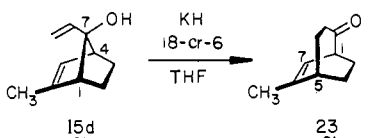


A

uniquely at its neighboring bridgehead proton (5%). Separate irradiation of the shielded methyl singlet caused at least four proximal hydrogen atoms to respond as detailed in A. The 2-D COSY spectrum of **21** (Figure 4) is similarly very informative of both structure and geometry.

The Question of Regiochemical Control. As noted earlier, placement of a methyl substituent at C-2 of the norbornenyl framework breaks the symmetry of the molecule. In each compound of this general type, cleavage of either the C-1/C-7 or C-4/C-7 bond would perforce lead to different products. This doubling of both the [1,3]- and [3,3]-sigmatropic options provides a particularly stringent test of the consequences of a relatively small electronic and steric perturbation on achieving the four possible transition states. The results are particularly informative.

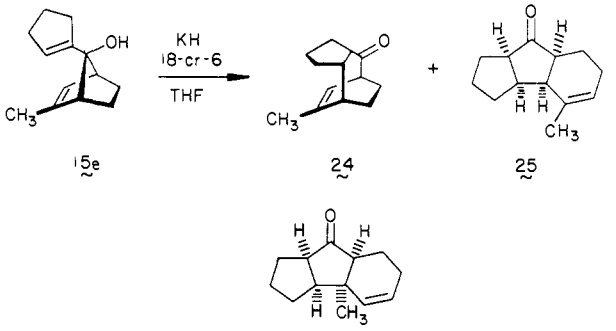
The simple vinyl example **15d** was examined initially. Despite access in theory by its potassium alkoxide to four reaction channels, anionic rearrangement in tetrahydrofuran at room temperature led to a *single* identifiable product, **23**. The relative positions



15d 23

of the methyl and carbonyl groups in the new compound were ascertained once again by NOE methods. While double irradiation of H-7 induced a 5.1% enhancement in the integral of the more downfield bridgehead proton H-1, comparable processing of the methyl absorption perturbed H-5 to the extent of 3.7%.

The cyclopentyl derivative **15e** proved somewhat more divergent in its reactivity under identical conditions. The two products, formed in a ratio of 2.5:1, were readily identified as **24** and **25** by spectral comparison. Distinctions between **25** and **26**, the second (nonoperative) oxy-Cope option, is particularly obvious.



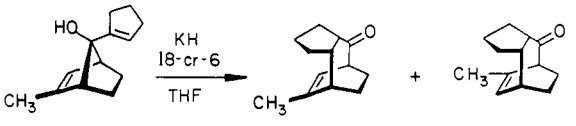
15e 24 25 26

Consequently, the intramolecular rearrangement leading to bicyclo[3.2.2]nonenyl ketones such as **23** and **24** as well as the [3.3] oxy-Cope process occur by preferential cleavage of the C-1/C-7 bond. This fact may be linked to a steric impedance for covalent bonding to the methyl-substituted carbon, an event that would generate a quaternary center (see below).

Products Arising from Anionic Rearrangement of the *syn*-7-Norbornenols. The obvious consequence of the C-7 stereochemistry present in **14** is to curtail any opportunity for *concerted* anionic oxy-Cope rearrangement (path 1, Figure 1), although either stepwise cleavage–recombination option (path 2 or 3) may still operate in principle.

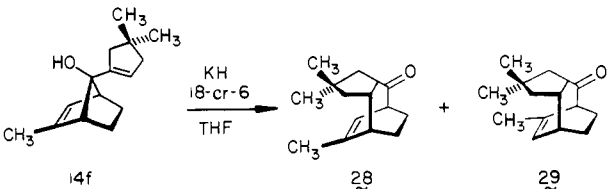
When **14a** was exposed to potassium hydride as before, isomerization exclusively to **16** was observed. In like fashion, **14b** and **14c** were transformed into **19** and **21**, respectively, without any evidence for the coproduction of **20** and **22**.

More striking was the response of **14e** to the same reaction conditions. While [1,3]-carbon sigmatropy still completely dominates, competition between cleavage of the two bridgehead/apical bonds happens now to be more competitive. The product mixture is dominated by the previously characterized ketone **24**; however, **27** is also formed (ratio 3.3:1).



14e 24 27

Where **14f** is concerned, the bias continues to be skewed toward heterolysis of the C-1/C-7 bond. In this instance, a 4.4:1 distribution of **28** and **29** was noted. Firm basis for the assignment of regio- and stereochemistry in this pair of carbonyl compounds emerged from NOE analysis of the ^{1}H NMR spectra.



14f 28 29

Discussion

Stepwise Nature of the [1,3]-Sigmatropic Migrations. In formal terms, the anionic rearrangements of anti alcohol **15a** and its syn counterpart **14a** to the common ketonic product **16** correspond to [1,3]-sigmatropic shifts. In both instances, structural reorganization necessarily takes place with retention in the migrating bridgehead carbon. The reactions also proceed with complete

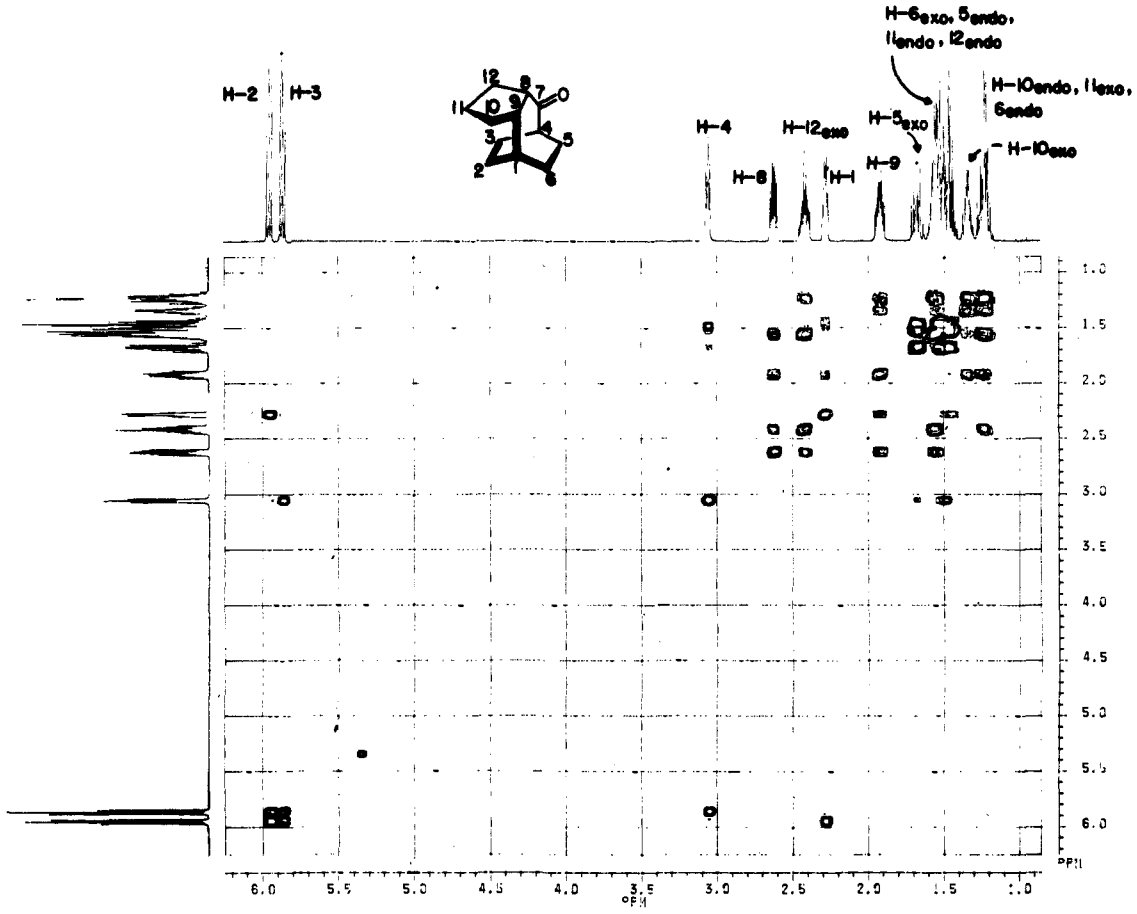
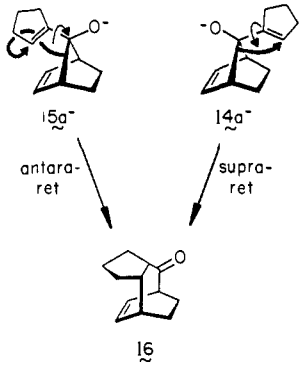
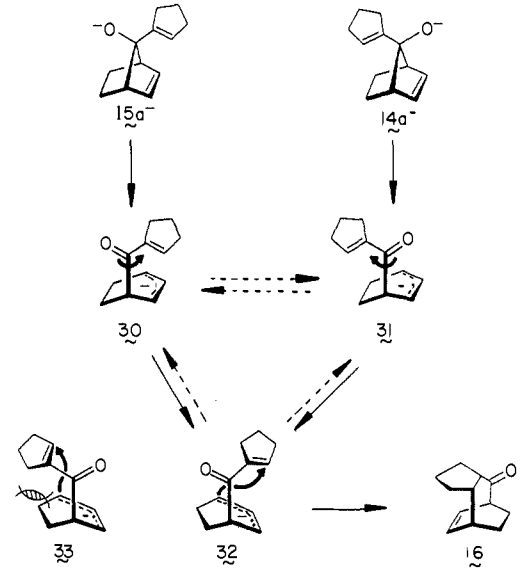


Figure 2. 2-D COSY spectrum of **16**.

Scheme I



Scheme II



stereospecificity at the cyclopentenyl carbon, the pathway from **14a** being entirely suprafacial and that from **15a** completely antarafacial (Scheme I). If the latter process were interpreted as the result of a concerted ($\sigma 2_s + \sigma 2_a$) reaction, the magnitude of the antarafacial stereospecificity (at least 97%) is seen to exceed that of any previously known example.[33] The exclusivity (within experimental error) of the suprafacial-retention behavior of **14a** is similarly astonishing.

Alternatively, these results appear more reconcilable with a fragmentation–recombination pathway, where the second stage is comprised of an intramolecular Michael addition of a cyclohexenyl anion to a conjugated cyclopentenyl ketone moiety (Scheme II).

Several factors may contribute to facilitating the heterolytic opening in **14a**$^-$, **15a**$^-$, and their congeners. Certainly, the strain energy of norbornene (17–23 kcal/mol)[34] is relevant. The calculated decrease of the C–H bond strength in H–CH_2O^- relative to H–CH_2OH (16.5 kcal/mol)[5a] is substantial and closely comparable to the ca. 18 kcal/mol reduction in energy of activation observed in pertinent experiments.[3a,8a] The allyl anion resonance energy and the development of an α,β-unsaturated ketone chromophore can in principle lower the energetic demands still further

(33) (a) Berson, J. A. *Acc. Chem. Res.* **1968**, *1*, 152. (b) Berson, J. A. *Ibid.* **1972**, *5*, 406. (c) Berson, J. A.; Holder, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 2037. (d) Berson, J. A.; Dervan, P. B. *Ibid.* **1973**, *95*, 269 and more recent reports.

(34) (a) Turner, R. B.; Meador, W. R.; Winkler, R. E. *J. Am. Chem. Soc.* **1957**, *79*, 4116, 4122. (b) Hall, H. K.; Jr.; Smith, C. D.; Baldt, J. H. *Ibid.* **1973**, *95*, 3197.

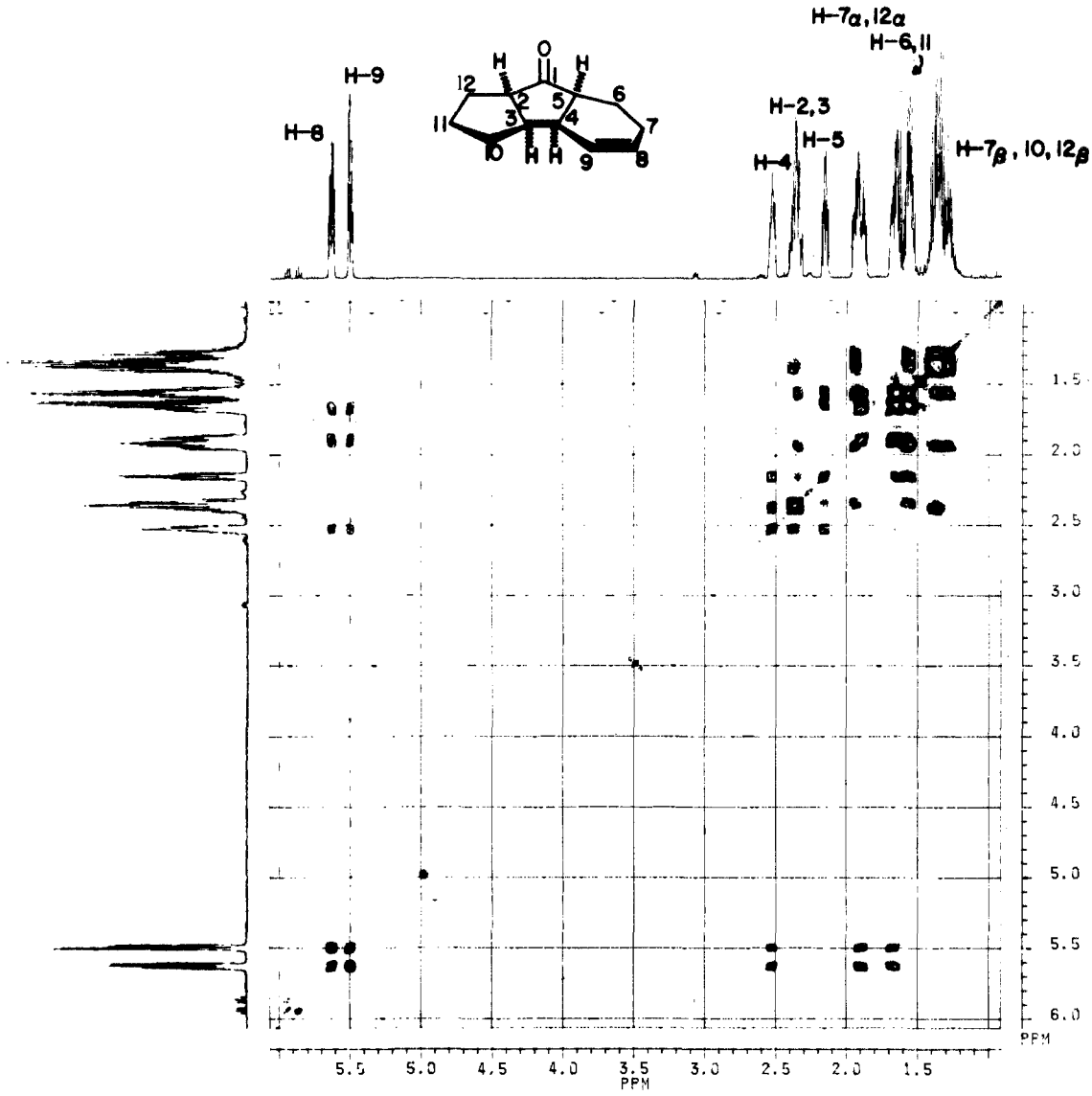


Figure 3. 2-D COSY spectrum of **17**.

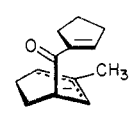
(see path 3, Figure 1). The weight of experimental evidence supports the working assumption that the sum of these enthalpic benefits is adequate to curtail the operation of any concerted [1,3]-carbon migration.

Another main point is that the [1,3]-shift is not set up geometrically with any kind of reasonable overlap to make possible a concerted migration.[7]

As shown in Scheme II, bond cleavage within the two 7-norbornenyloxy anions leads initially to the conformationally distinctive allyl anions **30** and **31**. Their conversion to **16** rather than **18** implicates their facile realignment to a geometry as in **32** prior to the final bonding event (solid arrows). While there is no information available on the reversibility of the conformational changes involving **30**, **31**, and **32** (dashed arrows), the product distribution permit, but do not require, it. What is clear, in view of our inability to detect any **17** in those reaction mixtures arising from **14a**, is that **14a**$^-$ does not interconvert with **15a**$^-$. Intermediates **30** and **31** must, therefore, not be capable of reclosure to 7-norbornenyloxy anions.

At this juncture, it is also important to consider why **18** is not seen. Our inspection of molecular models of allyl anion **33**, the conformational precursor to **18**, provided immediate indication of substantially higher levels of nonbonded strain in this species relative to **32**. As mentioned earlier, **16** has been shown by MM2 methods to be more stable than **18**. Evidently, the activation energies leading to **16** and **18** are sensitive to this ground-state thermodynamic imbalance, which must be adequately large to permit exclusive cyclization to **16**.

The mechanistic hypothesis illustrated in Scheme II nicely accommodates the regiochemical control exhibited by the 2-methyl-substituted *anti*-7-norbornenols. The strong predilection for cleavage of the C-1/C-7 bond is taken as an indication that the alkoxides within this stereochemical series are particularly sensitive to maintaining the methyl group on the central carbon of the allyl anion segment as in **34**, where electronic destabilization is held to a minimum. The alternative option **35** allows the methyl substituent full opportunity to exert its adverse electron-donating capability.



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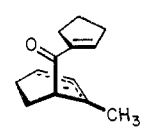


35

The syn alkoxides derived from **14a** and **14f** appear to be less responsive to this influence. Their product distributions, which continue to favor rearrangement via **34**, do reflect a proper response to the methyl effect. However, the competitive nature of those reactions proceeding via **35** may be construed as a signal that the possibly higher ground-state strain of these isomers causes bond scission to materialize earlier in the reaction profile, to pass through transition states that are less product-like, and consequently to be less capable of discrimination.

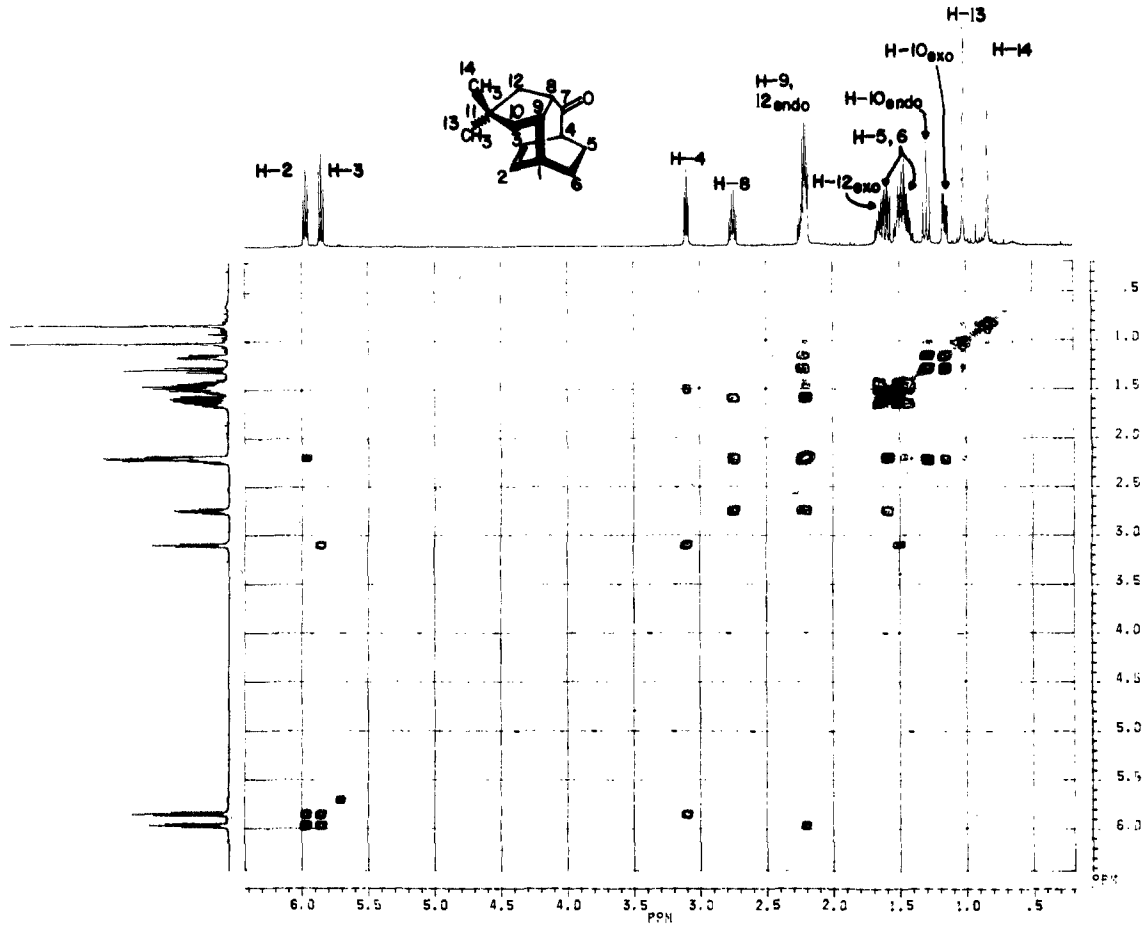
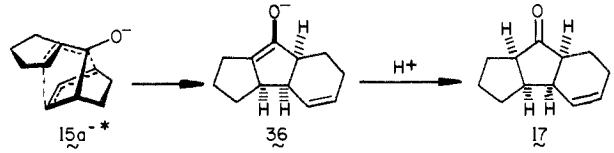
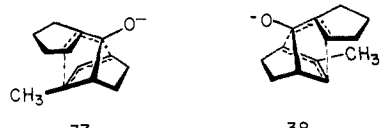


Figure 4. 2-D COSY spectrum of **21**.

Timing of the Oxy-Cope Process. Were **15a**$^-$ and its homologues undergoing oxy-Cope rearrangement by fragmentation–recombination, i.e., pathway 3 of Figure 2, the option should also be available to **14a**$^-$ and the other epimerically related alkoxides. This cannot be, since unlike the situation in Scheme II, the particular stereochemistry of the starting material dictates whether [3,3]-sigmatropy operates or not. Consequently, no intermediate such as **30–33**, which is so constructed as not to carry specific indication of its stereochemical origin, can serve along this reaction channel. The conversion of **15a**$^-$ to enolate **36** and ultimately to **17** gives every indication of being a direct, concerted process.



15a$^-$* 36 17



37 38

Rearrangement by synchronous six-electron reorganization brings with it regiochemical criteria different from those encountered in Scheme II. Using **15e**$^-$ as our example, we see that the boat-like transition state reflected in **37**, where covalent bonding to the methyl-substituted carbon must operate, requires generation of a quaternary center. The more likely alternative, which does not suffer from a comparable buildup of steric compression, is **38**. This steric differentiation agrees fully with the observed formation of **25** to the total exclusion of **26**.

We conclude that the most plausible mechanisms for anionic rearrangement within **14** and **15** are a concerted [3,3]-sigmatropic pathway (available only to the anti alkoxides) that is sensitive to distal steric effects, and an indirect stepwise process where the eventual intramolecular Michael addition proceeds regio- and stereospecifically. Use of the anionic protocol seemingly does little to enhance operation of the concerted oxy-Cope reaction relative to indirect [1,3]-carbon sigmatropy. Certainly, both processes are accelerated, but to a roughly comparable degree.[35]

Experimental Section

2-Methylbicyclo[2.2.1]hept-2-en-7-one (9b). The following is a substantially modified version of the original Moss and Ho procedure.[22] A cold (−70 °C), magnetically stirred solution of 7,7-dimethoxy-1,2,3,4-tetrachlorobicyclo[2.2.1]hept-1-ene (67.25 g, 0.23 mol) in anhydrous ether (350 mL) was blanketed with nitrogen and treated dropwise during 2 h with ethereal methyllithium (168.5 mL of 1.5 M 0.236 mol). Stirring was maintained at this temperature for an additional 30 min, at 0 °C for 57 h, and at room temperature for 24 h. The reaction mixture was poured into water (1 L), and the aqueous phase was extracted with ether (3 × 250 mL). The combined ethereal solutions were washed sequentially with saturated ammonium chloride solution (2 × 200 mL) and brine (2 × 200 mL) prior to drying. Solvent removal left 62.2 g (99%) of 7,7-dimethoxy-2-methyl-1,3,4-trichlorobicyclo[2.2.1]hept-2-ene: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3 H), 3.53 (s, 3 H), 2.30–2.26 (m, 2 H), 1.85 (s, 3 H), 1.71–1.63 (m, 2 H); MS m/z (M^+ − Cl) calcd 235.0292, obsd 235.0280.

A solution of sodium (82.2 g, 3.57 mol, 15.9 equiv) in liquid ammonia (1.34 L) was prepared and maintained at −60 °C while the preceding trichloride (60.87 g, 0.22 mol) dissolved in anhydrous ethanol (365 :) and dry ether (500 mL) was added over 75 min. During the subsequeat 5-h period of stirring at −60 °C, a copious white precipitate formed.

(35) Although we have not examined the oxyanionic behavior of the parent vinyl-substituted anti alcohol thermolyzed earlier by Berson and Jones,[2] the response of **15d** to KH is largely analogous. Whereas the previously described thermal activation resulted in rearrangement predominantly (88%) by [1,3] carbon shift, **15d**$^-$ rearranges excusively via this pathway within the limits of our MPLC analysis. A preliminary study by us of the pyrolysis of **15a** revealed a similar close parallel in product distribution to that noted in the text.

Solid ammonium chloride was added in portions until discharge of the blue color occurred and the ammonia was allowed to evaporate. The remaining slurry was carefully poured into water and extracted with pentane (6 × 600 mL). The combined pentane phases were washed twice with brine (600 mL), dried, and evaporated. There was obtained 34.9 g (92.5%) of a pale yellow oil, which was used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.62–5.59 (m, 1 H), 3.17 (s, 3 H), 3.14 (s, 3 H), 2.68–2.66 (m, 1 H), 2.54–2.53 (m, 1 H), 1.76 (d, J = 1.66 Hz, 3 H), 1.81–1.73 (m, 2 H), 1.04–0.86 (m, 2 H).

A 35-g (0.208-mol) sample of the above intermediate and 55 mL of 5% aqueous sulfuric acid were vigorously stirred for 37 h and extracted with pentane (4 × 75 mL). The combined organic phases were washed with water (5 × 50 mL) and brine (2 × 50 mL) prior to drying. Solvent evaporation and distillation of the residue afforded 19.08 g (75%) of **9b** as a colorless liquid: bp 83–93 °C at 63 Torr; IR (neat, cm^{-1}) 1770; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.07–6.05 (m, 1 H) 2.74–2.72 (m, 1 H), 2.59–2.58 (m, 1 H), 1.99–1.87 (m, 2 H), 1.85 (d, J = 1.62 Hz, 3 H), 1.28–1.11 (m, 2 H).

3,3-Dimethylcyclopentanone. This procedure represents a substantial improvement over an earlier report.[36] To a cold (0 °C), mechanically stirred slurry of purified anhydrous cuprous iodide (108.2 g, 0.568 mol) in anhydrous ether (2.3 L) was added dropwise during 2 h 45 min an ethereal solution of methyllithium (815 mL of 1.4 M, 1.14 mol). After an additional hour of stirring, a solution of *freshly distilled* 3-methylcyclopentenone (45.56 g, 0.47 mol) in 460 mL of the same solvent was introduced in dropwise fashion during 5 h at 0 °C. After 2 h this temperature, the reaction mixture was transferred by suction into a pressure-equalizing dropping funnel from where it was slowly added dropwise into 1160 mL of saturated ammonium chloride solution whose pH had been adjusted to 8 by the addition of ammonia. After 1 h of vigorous stirring, the blue-colored aqueous phase was extracted with ether (3 × 400 mL), and the combined ethereal layers were washed with saturated ammonium chloride solution (2 × 400 mL) and brine (2 × 400 mL) prior to drying. The ether was removed by distillation at atmospheric pressure to leave a yellow-brown oil. Vacuum distillation of this residue afforded 33.8 g (63.6%) of the ketone, bp 75 °C (at 84 Torr).

3,3-Dimethylcyclopentanone Tosylhydrazone. A magnetically stirred solution of the ketone (6.0 g, 53.5 mmol) in methanol (30 mL) was treated with a slurry of tosylhydrazide (10.85 g, 56.5 mmol) in the same solvent (30 mL). The solution rapidly becomes clear and a short time later precipitation of the hydrazone occurs. The reaction mixture was stored at 0 °C overnight; the precipitate was collected on a filter, washed with cold methanol (3 × 10 mL), and dried (13.32 g, 88.9%). Recrystallization from methanol afforded colorless crystals: mp 176–177 °C (dec); IR (KBr, cm^{-1}) 3220, 2950, 1590, 1330, 1160, 815, 660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 7.9 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 2.48 (t, J = 7.6 Hz, 1.2 H), 2.42 (s, 3 H), 2.26 (t, J = 7.5 Hz, 0.8 H), 2.18 (s, 1.2 H), 2.00 (s, 0.8 H), 1.59 (t, J = 7.6 Hz, 1.2 H), 1.53 (t, J = 7.8 Hz, 0.8 H), 1.01 (s, 2.4 H), 0.96 (s, 3.6 H).

3,3-Dimethylcyclopentanone Trisylhydrazone. To a precooled (−10 °C), magnetically stirred suspension of finely ground 2,4,6-triisopropylbenzenesulfonylhydrazide (6.67 g, 22.35 mmol) in methanol (30 mL) was added 2.48 g (22.13 mmol) of freshly distilled 3,3-dimethylcyclopentanone, followed by 2.5 mL of concentrated hydrochloric acid. The resulting clear solution was stirred at −10 °C overnight and the precipitate that formed was separated by filtration, washed with cold (−10 °C) methanol, and dried at 100 °C in vacuo: 4.15 g (47.7%). Recrystallization from ether–petroleum ether gave white crystals: mp 151–152.5 °C; IR (KBr, cm^{-1}) 3225, 2950, 1595, 1325, 1165, 665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 2 H), 4,23 and 4.22 (overlapping heptets, J = 6.7 Hz, 2 H), 2.90 (heptet, J = 6.9 Hz, 1 H), 2.48 (t, J = 7.5 Hz, 0.8 H), 2.26 (t, J = 7.5 Hz, 1.2 H), 2.18 (s, 1.2 H), 2.00 (s, 0.8 H), 1.62 (t, J = 7.5 Hz, 1.2 H), 1.55 (t, J = 7.6 Hz, 0.8 H), 1.26 (d, J = 6.8 Hz, 10.8 H), 1.25 (d, J = 6.8 Hz, 7.2 H), 1.03 (s, 2.4 H), 0.97 (s, 3.6 H).

1-Bromo-3,3-dimethylcyclopentene (12b) and 1-Bromo-4,4-dimethylcyclopentene (13b). A. Shapiro Degradation of the Tosylhydrazone with Methyllithium and Cyanogen Bromide Quench. A suspension of 3,3-dimethylcyclopentanone tosylhydrazone (5.0 g, 17.8 mmol) in anhydrous *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was cooled to −55 °C and, while being stirred, was treated dropwise with ethereal methyllithium (51.5 mL of 1.4 M, 72.1 mmol) during 30 min. The reaction mixture was maintained at −72 °C for an additional hour and allowed to warm to room temperature where it was maintained for 4 h. The flask was cooled to −78 °C and a solution of cyanogen bromide (7.5 g, 71.5 mmol) in 12 mL of anhydrous tetrahydrofuran was added dropwise. Stirring was continued at −78 °C for another hour, at which point 150 mL of saturated sodium bicarbonate solution was introduced. The product was extracted into petroleum ether (1 × 100 mL; 3 × 50 mL), and the combined organic phases were washed with water (10 × 50 mL) and brine 2 × 50 mL) prior to drying. Concentration left a brown oil (1.4 g), which was doubly distilled in a Kugelrohr apparatus to give 640 mg (20.5%) of a 70:30 mixture of **12b** and **13b** as a pale yellow oil.

For **12b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (t, J = 1.8 Hz, 1 H), 2.42 (dt, J = 7.3, 1.8 Hz, 2 H), 1.42 (t, J = 7.3 Hz, 2 H), 0.82 (s, 6 H).

For **13b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.52 (quintet, J = 2.2 Hz, 1 H), 2.21 (q, J = 2.2 Hz, 2 H), 1.77 (br d, J = 2.3 Hz, 2 H), 0.83 (s, 6 H); MS (on mixture m/z (M$^+$) calcd. 174.0044, obsd 174.0048.

B. Quench with 1,2-Dibromotetrafluoroethane. The vinyllithium reagent was prepared from the tosylhydrazone (20.0 g, 71.4 mmol) in anhydrous TMEDA (300 mL) and ethereal methyllithium (206 mL of 1.4 M, 288 mmol) in the predescribed manner. With the reaction mixture at −78 °C, 1,2-dibromotetrafluoroethane (74.4 g, 286 mmol) was introduced rapidly and stirring was continued at this temperature for 2 h prior to the addition of water (600 mL). The corresponding workup furnished 4.28 g (34.2%) of a 72:28 mixture of **12b** and **13b** following Kugelrohr distillation.

The pot residue (1.29 g) was chromatographed on neutral alumina (hexane elution) to give a colorless liquid which partially crystallized in a freezer. The low-melting crystals were constituted of an 80:20 mixture of **12b** and **13b**.

C. Starting from the Trisylhydrazone. A cold (−55 °C), magnetically stirred slurry of the trisylhydrazone (13.05 g, 33.24 mmol) in anhydrous TMEDA (100 mL) was treated during 30 min with 50 mL of 1.4 M ethereal methyllithium (70 mmol). The reaction mixture was stirred at −70 °C for 1 h at room temperature for 2.75 h before being recooled to −70 °C, where 1,2-dibromotetrafluoroethane (9.5 g, 36.56 mmol) was added rapidly. Processing from this point was performed in the predescribed manner to give 1.49 g (25.6%) of **13b**.

Prototypical Condensation Reaction. A magnetically stirred solution of the 70:30 mixture of **12b** and **13b** (4.88 g, 27.9 mmol) in anhydrous tetrahydrofuran was blanketed withnitrogen, cooled to −78 °C, and treated dropwise during 25 min with a solution of *tert*-butyllithium in pentane (49.3 mL of 1.13 M, 55.7 mmol). After the reaction mixture had been stirred at −78 °C for 45 min, 23.6 mL of a 1.165 M stock solution of **9a** in dry tetrahydrofurn (27.5 mmol) was introduced dropwise over 25 min. Reaction was allowed to proceed for 45 min before saturated ammonium chloride solution (255 mL) was added and the product was extracted into ether. The combined organic layers were washed with saturated ammonium chloride solution (220 mL) and brine (2 × 220 mL) before drying. Solvent evaporation left 6.95 g of a yellow oil, which was separated into its components by MPLC on silica gel (elution with 93:7 petroleum ether–ethyl acetate). The integrals of the three peaks were used to ascertain the product composition.

Fraction 1: 60 mg of 7-*tert*-butylnorbornen-7-*anti*-ol;[19] IR (neat, cm^{-1}) 3502, 2970, 2874, 1482, 1466, 1369, 1269, 1130, 1066, 1004, 724; ^{1}H NMR (300 MHz, C_6D_6) δ 5.64–5.63 (m, 2 H), 2.32–2.31 (m, 2 H), 2.03–1.98 (m, 2 H), 0.94 (s, 9 H), 0.90–0.86 (m, 2 H).

Fraction 2: 1.62 g (28.9%) of a 70:30 mixture of **15b** and **15c**; IR (neat, cm^{-1}) 3640–3140, 2930, 1445, 1350, 1255, 1110, 1040, 846, 702; ^{1}H NMR (300 MHz, C_6D_6) δ 5.83–5.80 (m, 1 H) 5.22 (quintet, J = 2 Hz, 1 H), 5.15 (t, J = 1.81 Hz, 1 H), 2.50–2.49 (m, 1 H), 2.32 (dt, J = 7.16, 1.77 Hz, 1 H), 2.23–2.17 (m, 1 H), 2.10–2.04 (m, 4 H), 1.60 (t, J = 7.17 Hz, 1 H), 1.08–1.01 (m, 3 H), 1.02 (s, 1.8 H), 1.01 (s, 4.2 H).

Fraction 3: 2.69 g (47.9%) of a 64:36 mixture of **14b** and **14c**; IR (neat, cm^{-1}) 3600–3160, 2930, 1450, 1356, 1155, 1130, 1044, 855, 718; ^{1}H NMR (300 MHz, C_6D_6) δ 5.86–5.83 (m, 1 H), 5.42 (quintet, J = 2.0 Hz, 1 H), 5.34 (t, J = 1.85 Hz, 1 H), 2.67–2.64 (m, 1 H), 2.49 (dt, J = 7.19, 1.82 Hz, 1 H), 2.28 (q, J = 2.0 Hz, 1 H), 2.44–2.12 (br s, 1 H), 2.09 (q, J = 2.2 Hz, 2 H), 1.72–1.65 (m, 2 H), 1.65 (t, J = 7.23 Hz, 1 H), 1.07 (s, 2.2 H), 1.02 (s, 3.8 H), 0.80–0.7o (m, 2 H).

Similar condensation of **11b** (0.85 g, 5.78 mmol) with **9a** (5.53 mmol) afforded 45.7 mg of *tert*-butylated anti alcohol, 158 mg (16.2% of **15a**, and 191 mg (19.6%) of **14a**.

For **14a**: IR (neat, cm^{-1}) 3600–3160, 1370, 1053; ^{1}H NMR (300 MHz, C_6D_6) δ 5.84–5.83 (m, 2 H), 5.55–5.52 (m, 1 H), 2.68–2.65 (m, 2 H), 2.50–2.42 (m, 2 H) 2.32 (s, 1H), 2.28–2.21 (m, 2 H), 1.83–1.73 (m, 2 H), 1.69–1.63 (m, 2 H), 0.78–0.74 (m, 2 H); MS m/z (M$^+$) calcd 176.1201, obsd 176.1195.

For **15a**: IR (neat, cm^{-1}) 3620–3140, 2938, 1260, 1112, 1050, 709; ^{1}H NMR (300 MHz, C_6D_6) δ 5.83–5.82 (m, 2 H), 5.36–5.33 (m, 1 H), 2.53–2.50 (m, 2 H), 2.30–2.18 (m, 6 H), 1.77–1.69 (m, 2 H), 1.20–1.06 (br s, 1 H), 1.07–1.02 (m, 2 H); MS m/z (M$^+$) calcd. 176.1201, obsd 176.1201.

Analogous condensation of vinyl bromide (4.50 g, 42.1 mmol) with **9b** (41.1 mmol) afforded the syn-7-*tert*-butyl-7-anti alcohol, as well as **15d** and **14d** in a 3.32:1 ratio.

(36) Pines, H.; Pavlik, F. J.; Ipatieff, V. N. *J. Am. Chem. Soc.* **1951**, *73*, 5738.

For the *tert*-butylated product: IR (neat, cm^{-1}) 3624, 3500, 2964, 2909, 2874, 1482, 1468, 1445, 1368, 1064, 1003, 812, 792; ^1H NMR (300 MHz, $CDCl_3$) δ 5.42–5.41 (m, 1 H), 2.46–2.44 (m, 1 H), 2.27–2.25 (m, 1 H), 2.04–1.88 (m, 2 H), 1.68 (d, J = 1.55 Hz, 3 H), 1.51 (s, 1 H), 0.96 (s, 9 H), 1.02–0.85 (m, 2 H); MS m/z (M^+) calcd 180.1514, obsd 180.1514.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.06; H, 11.28.

For **14d**: IR (neat, cm^{-1}) 3620–3180, 2960, 1440, 1418, 1330, 1198, 1130, 1070, 990, 925, 802; ^1H NMR (300 MHz, C_6D_6) δ 6.00 (dd, J = 17.1, 10.8 Hz, 1 H), 5.72 (dd, J = 17.1, 2.5 Hz, 1 H), 5.36–5.35 (m, 1 H), 5.20 (dd, J = 10.8, 2.5 Hz, 1 H), 2.52 (br s, 1 H), 2.45–2.44 (m, 1 H), 2.25 (d, J = 3.5 Hz, 1 H), 1.76–1.58 (m, 2 H), 1.49 (d, J = 1.6 Hz, 3 H), 0.93–0.85 (m, 1 H), 0.78–0.76 (m, 1 H); MS m/z (M^+) calcd 150.1045, 150.1040.

For **15d**: IR (neat, cm^{-1}) 3640–3120, 2960, 1626, 1439, 1264, 1116, 1000, 916, 800; ^1H NMR (300 MHz, C_6D_6) δ 6.35 (dd, J = 17.5, 10.7 Hz, 1 H), 5.42–5.41 (m, 1 H), 5.25 (dd, J = 17.5, 2.3 Hz, 1 H), 5.01 (dd, J = 10.7, 1.6 Hz, 1 H), 2.33–2.31 (m, 1 H), 2.23–2.05 (m, 3 H), 1.53 (d, J = 1.4 Hz, 3 H), 1.28 (s, 1 H), 1.13–1.06 (m, 1 H), 1.00–0.93 (m, 1 H); MS m/z (M^+) calcd 150.1045, obsd 150.1046.

Comparable condensation of **11b** (0.65 g, 4.42 mmol) with **9b** (4.26 mmol) gave rise to *tert*-butyl anti alcohol (1.6 mg), **15e** (52.3 mg, 6.4%), and **14e** (56.5 mg, 7%).

For **14e**: IR (neat, cm^{-1} 3600–3080, 2950, 1439, 1370, 1120, 1050; ^1H NMR (300 MHz, C_6D_6) δ 5.57–5.54 (m, 1 H), 5.42–5.41 (m, 1 H), 2.66–2.65 (m, 1 H), 2.57–2.44 (m, 3 H), 2.62–2.42 (br s, 1 H), 2.30–2.23 (m, 2 H), 1.85–1.61 (m, 4 H), 1.57 (d, J = 1.6 Hz, 3 H), 0.94–0.84 (m, 1 H), 0.78–0.72 (m, 1 H); MS m/z (M^+) calcd 190.1358, obsd 190.1360.

For **15e**: IR (neat, cm^{-1}) 3620–3080, 2950, 1435, 1110, 1050; ^1H NMR (300 MHz, C_6D_6) δ 5.42 (s, 1 H), 5.39–5.37 (m, 1 H), 2.52–2.51 (m, 1 H), 2.35–2.14 (series of m, 7 H), 1.78–1.68 (m, 2 H), 1.57 (d, J = 1.2 Hz, 3 H), 1.20–1.13 (m, 1 H), 1.07 –0.99 (m, 2 H); MS m/z (M^+) calcd 190.1358, obsd 190.1358.

The final condensation, which involved reaction of **13b** (0.57 g, 3.25 mmol) with 310 mmol of **9b**, furnished 0.7 mg of *tert*-butylated product, 21.5 mg (6.5%) of **15f**, and 104.3 mg (14.3%) of **14f**.

For **14f**: IR (neat, cm^{-1}) 3600–3180, 2950, 1456, 1435, 1155, 1120, 1046; ^1H NMR (300 MHz, C_6C_6) δ 5.45–5.44 (m, 1 H), 5.44–5.42 (m, 1 H), 2.64 (br s, 1 H), 2.4 (d, J = 3.3 Hz, 1 H), 2.39 (br s, 1 H), 2.34–2.31 (m, 2 H), 2.13–2.11 (m, 2 H), 1.80–1.65 (m, 2 H), 1.57 (d, J = 1.5 Hz, 3 H), 1.09 (s, 3 H), 1.08 (s, 3 H), 0.95–0.85 (m, 1 H), 0.79–0.72 (m, 1 H); MS m/z (M^+) calcd 218.1671, obsd 218.1684.

For **15f**: IR (neat, cm^{-1}) 3620–3160, 2945, 1455, 1432, 1358, 1260, 1170, 1043, 1033, 985, 800; ^1H NMR (300 MHz, C_6D_6) δ 5.45–5.43 (m, 1 H), 5.27–5.26 (m, 1 H), 2.50–2.48 (m, 1 H), 2.32–2.05 (series of m, 7 H), 1.58 (d, J = 1.6 Hz, 3 H), 1.22–1.14 (m, 1 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 1.08–1.03 (m, 1 H); MS m/z (M^+) calcd 218.1671, obsd 218.1665.

Oxyanionic Rearrangements. Prototypical Procedure.[37] **Response of 15b and 15c.** A 25% suspension of potassium hydride in mineral oil (5.13 g, 32 mmol) was washed with dry pentane (3 × 4 mL) and then suspended in 21 mL of anhydrous tetrahydrofuran. This magnetically stirred suspension was treated dropwise with a 0.5 M solution of iodine in the same solvent until the orange iodine color persisted for at least 5 min. A solution of 18-crown-6 (8.13 g, 30.8 mmol) dissolved in 17 mL of anhydrous tetrahydrofuran was admixed with a tetrahydrofuran solution (6 mL) containing 1.26 g (6.16 mmol) of the **15b**/**15c** (70:30) mixture and introduced into the reaction flask in one portion. A modestly exothermic reaction ensued. After 30 min, the contents were cooled to −78 °C and treated with absolute ethanol (17 mL) in one portion. The resulting slurry was poured into petroleum ether (60 mL) and saturated ammonium chloride solution (60 mL) and thoroughly shaken. The organic phase was removed and the aqueous layer was extracted with petroleum ether (60 mL). The combined organic solutions were washed with brine (60 mL), dried, and evaporated to leave 1.31 g of an orange oil, which was subjected to MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether). Three fractions were collected (total 839 mg, 66% yield):

Fraction 1: 1.1 mg (42.7%) of **21**; IR (neat, cm^{-1}) 3043, 2941, 2867, 1690, 1465, 1446, 1367, 860, 730, 685; ^1H NMR (300 MHz, C_6D_6) δ 5.97 (t, J = 8.0 Hz, 1 H), 5.85 (t, J = 8.2 Hz, 1 H), 3.09 (t, J = 6.7 Hz, 1 H), 2.77–2.69 (m, 1 H), 2.27–2.15 (m, 3 H), 1.66–1.42 (series of m, 5 H), 1.32–1.24 (m, 1 H), 1.18–1.12 (m, 1 H), 1.02 (s, 3 H), 0.83 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.85, 136.95, 126.38, 51.52, 49.08, 46.90, 46.04, 43.97, 37.35, 35.80, 29.54, 28.22, 26.13, 21.92; MS m/z (M^+) calcd 204.1514, obsd 204.1516.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.44; H, 9.88.

Fraction 2: 142 mg (16.1%) of **20**; IR (neat, cm^{-1}) 3041, 2956, 1733, 1468, 1390, 1371, 1312, 1266, 1129, 1049, 1026, 920, 668; ^1H NMR (300 MHz, C_6D_6) δ 5.83 (br d, J = 10.5 Hz, 1 H), 5.56–5.52 (m, 1 H), 2.53–2.44 (m, 2 H), 2.20–1.97 (m, 3 H), 1.94–1.82 (m, 2 H), 1.75–1.39 (m, 4 H), 1.21–1.13 (m, 1 H), 1.02 (s, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 221.83, 129.51, 127.75, 56.67, 51.11, 50.02, 42.38, 38.82, 37.56, 32.13, 26.26, 22.84, 21.14, 19.21; MS m/z)(M^+) calcd 204.1515, obsd 204.1522.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.32; H, 9.85.

Fraction 3: 536 mg of a mixture comprised of **19** (87%) and **22** (13%). The spectral data for **19** are given below. For **22**: IR (neat, cm^{-1}) 1731; ^1H NMR (300 MHz, C_6D_6) δ 5.69–5.64 (m, 1 H), 5.54–5.48 (m, 1 H), 0.91 (s, 3 H), 0.76 (s, 3 H).

Rearrangement of **15** (146 mg) in this manner produced 145 mg of crude product, chromatography of which as before afforded 62 mg (42.6%) of **16** and 21 mg (14.2%) of **17**.

For **16**: IR (neat, cm^{-1}) 3042, 2945, 2870, 1693, 1468, 1448, 1160, 1113, 820, 735, 690; ^1H NMR (300 MHz, C_6D_6) δ 5.94 (t, J = 8.1 Hz, 1 H), 5.86 (t, J = 8.1 Hz, 1 H), 3.07 (t, J = 6.4 Hz, 1 H), 2.65–2.57 (m, 1 H), 2.49–2.40 (m, 1 H), 2.26–2.25 (m, 1 H), 1.94–1.83 (m, 1 H), 1.70–1.19 (series of m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.58, 136.84, 126.53, 51.91, 49.47, 48.81, 35.46, 30.69, 27.63, 25.66, 24.71, 22.03; MS m/z (M^+) calcd 176.1201, obsd 176.1211.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77, H, 9.15. Found: C, 81.61; H, 9.49.

For **17**: IR (neat, cm^{-1}) 3026, 2946, 2871, 1731, 1450, 1135, 655; ^1H NMR (300 MHz, C_6D_6) δ 5.65–5.59 (m, 1 H), 5.52–5.46 (m, 1 H), 2.51–2.48 (m, 1 H), 2.38–2.32 (m, 2 H), 2.15 (dt, J = 11.7, 4.3 Hz, 1 H), 1.99–1.85 (m, 2 H), 1.70–1.51 (m, 4 H), 1.50–1.24 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 223.32, 128.22, 127.34, 53.40, 47.26, 44.28, 36.46, 28.97, 28.64, 26.39, 22.59, 21.50; MS m/z (M^+) calcd 176.1201, obsd 176.1192.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.75; H, 9.20.

The reaction involving **15d** (150 mg, 1 mmol) ultimately gave 55 mg (36.3%) of pure **23** as the only chromatographically observable product: IR (neat, cm^{-1}) 2924, 2864, 1704, 1454, 1381, 1252, 1186, 1146, 1066, 859; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, J = 7.6 Hz, 1 H), 3.00–2.96 (m, 1 H), 2.63–2.41 (m, 3 H), 1.81 (d, J = 1.7 Hz, 3 H), 1.95–1.75 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 210.13, 145.51, 120.06, 49.16, 39.09, 36.88, 29.96, 24.51, 23.72, 22.17; MS m/z (M^+) calcd 150.1044, obsd 150.1013.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96,; H, 9.39. Found: C, 79.77; H, 9.42.

Exposure of **15e** (107 mg, 0.56 mmol) to potassium hydride in the predescribed manner gave two products in 55.8% combined yield after chromatographic purification.

For **24**: 43 mg (40%); IR (neat, cm^{-1}) 2946, 2878, 1696, 1468, 1450, 1147, 1114, 865; ^1H NMR (300 MHz, C_6D_6) δ 5.56 (d, J = 8.0 Hz, 1 H)8 3.11–3.07 (m, 1 H), 2.62–2.48 (m, 2 H), 2.04 (m, 1 H), 1.89–1.79 (m, 1 H), 1.50 (d, J = 1.6 Hz, 3 H), 1.70–1.38 (m, 6 H) 1.35–1.12 (m, 2 H), 1.10–0.96 (7, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.12, 144.80, 119.27, 51.21, 49.74, 48.82, 40.72, 30.20, 25.74, 25.56, 24.17, 23.98, 21.89; MS m/x (M^+) calcd 190.1357, obsd 190.1356.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.91; H, 9.47.

For **25**: 17 mg (15.8%); IR (neat, cm^{-1}) 2951, 2876, 1731, 1449, 1382, 1339, 1216, 1075, 946; ^1H NMR (300 MHz, C_6D_6) δ 5.41–5.40 (m, 1 H), 2.39–2.27 (m, 3 H), 2.16–2.04 (m, 2 H), 1.92–1.83 (m, 1 H), 1.78–1.71 (m, 2 H), 1.56 (d, J = 1.3 Hz, 3 H), 1.68–1.49 (m, 1 H), 1.47–0.97 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 225.70, 133.35, 122.86, 54.50, 46.35, 43.42, 40.57, 29.36, 28.26, 26.28, 24.35, 23.02, 21.82; MS m/z (M^+) calcd 190.1357, obsd 190.1350.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.15; H, 9.43.

Base-promoted isomerization of **14a** (173 mg, 0.98 mmol) according to the above procedure gave rise after chromatography to **16** (34 mg, 19.5%) as the only product in evidence. The spectral properties of this compound were identical with those described earlier.

The reaction involving the 64:36 mixture of **14b** and **14c** (613 mg, 3.0 mmol) and potassium hydride was carried out in the predescribed man-

(37) Mention needs to be made of the low *isolated* yields often cited in this section. In large part, the amounts of material obtained following chromatography are diminished because of the quite high volatility of the products and the purely mechanical losses that accrue during solvent removal. It is for this reason that all product distributions were determined chromatographically prior to or concurrent with workup of the reaction mixtures. Consequently, the purified yields should not be construed as indicators of the inefficiency of the anionic rearrangement.

ner. On chromatography, there was isolated 75 mg (34.2%) of **21** and 164 mg (41.8%) of **19**.

For **19**: IR (neat, cm^{-1}) 3048, 2950, 2870, 1691, 1465, 1391, 1370, 1164, 856, 715; ^1H NMR (300 MHz, C_6D_6) δ 5.92 (t, J = 8.2 Hz, 1 H), 5.75 (t, J = 8.3 Hz, 1 H), 3.14 (t, J = 7.0 Hz, 1 H), 2.77-2.68 (m, 1 H), 2.45-2.27 (m, 2 H), 1.58 (dd, J = 11.2, 3.4 Hz, 1 H), 1.72-1.37 (m, 5 H), 1.30-1.23 (m, 1 H), 1.08-0.98 (m, 1 H), 0.84 (s, 3 H), 0.67 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 208.28, 137.47, 124.89, 59.10, 51.33, 48.57, 42.53, 39.88, 32.89, 28.59, 27.63, 25.08, 24.11, 22.22; MS m/z (M^+) calcd 204.1514, obsd 204.1520.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.38; H, 9.87.

Exposure of **14e** (90 mg, 0.47 mmol) to the identical reaction conditions furnished after chromatographic separation the pair of ketones **27** (7 mg, 7.3%) and **24** (22 mg, 24.3%).

For **27**: IR (neat, cm^{-1}) 2940, 2867, 1690, 1446, 1159, 875, 841; ^1H NMR (300 MHz, C_6D_6) δ 5.64 (d, J = 7.6 Hz, 1 H), 2.89 (d, J = 5.9 Hz, 1 H), 2.64-2.48 (m, 2 H), 2.26-2.22 (m, 1 H), 1.96-1.89 (m, 1 H), 1.70 (d, J = 1.6 Hz, 3 H), 1.75-1.17 (series of m, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.12, 134.89, 129.24, 54.36, 51.65, 51.43, 35.40, 30.61, 27.18, 25.86, 24.77, 21.98, 21.71.

The reaction involving **14f** (232 mg, 1.06 mmol) resulted in the formation of **29** (11 mg, 4.8%) and **28** (49 mg, 21.3%).

For **28**: IR (neat, cm^{-1}) 2944, 2870, 1693, 1464, 1446, 1366, 1140, 869; ^1H NMR (300 MHz, C_6D_6) δ 5.57 (d, J = 7.9 Hz, 1 H), 3.11 (dd, J = 7.8, 5.3 Hz, 1 H), 2.75-2.67 (m, 1 H), 2.37 (dd, J = 13.6, 5.4 Hz, 1 H), 2.29-2.18 (m, 1 H), 1.99 (m, 1 H), 1.52 (d, J = 1.6 Hz, 3 H), 1.66-1.40 (m, 5 H), 1.16-1.12 (m, 2 H), 1.04 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.47, 145.03, 119.10, 51.27, 48.97, 47.32, 45.49, 41.88, 40.99, 36.71, 29.88, 28.80, 26.03, 24.40, 21.70; MS m/z (M^+) calcd 218.1670, obsd 218.1697.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.15. Found: C, 82.37; 10.06.

For **29**: IR (neat, cm^{-1}) 2942, 2866, 1688, 1463, 1443, 1365, 843; ^1H NMR (300 MHz, C_6D_6) δ 5.68 (dd, J = 7.5, 1.5 Hz, 1 H), 2.92 (d, J = 6.0 Hz, 1 H), 2.76-2.70 (m, 1 H), 2.31-2.18 (m, 3 H), 1.770 (d, J = 1.6 Hz, 3 H), 1.72-1.65 (m, 1 H), 1.60-1.41 (m, 4 H), 1.39-1.30 (m, 1 H), 1.19-1.12 (m, 1 H), 1.03 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 207.39, 134.52, 129.34, 54.50, 51.20, 48.64, 45.88, 43.45, 37.36, 35.65, 29.63, 28.34, 26.34, 21.72 (2C); MS m/z (M^+) calcd 218.1670, obsd 218.1681.

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Surface-Specific Cleavage of a Cationic Carbonate-Functionalized Vesicular Surfactant

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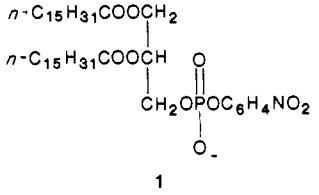
Abstract: The cationic, *p*-nitrophenyl carbonate functionalized 1,2-dipalmitoylglyceryl surfactant **2** was synthesized. Vesicles created at pH 3.9 from this surfactant gave rapid partial *p*-nitrophenol release at pH 7.9, attributed to site-specific hydrolysis of exovesicular *p*-nitrophenyl carbonate moieties. Endovesicular *p*-nitrophenyl carbonates are cleaved ~700 times more slowly under these conditions, probably because they are protected by the maintenance of a pH gradient across the outer vesicle bilayer.

The ubiquity of morphological and functional asymmetry between the two halves of bilayer biological membranes[2] has stimulated attempts to create *synthetic* vesicular (liposomal) membranes that are chemically differentiated at their exovesicular and endovesicular surfaces.[3] Although glyceryl diester lipids are major constituents of biological membranes,[4] very little has been done in the way of generating exo/endo-differentiated, synthetic glyceryl diester vesicles.

Recently, we reported that anionic vesicles created from the *p*-nitrophenyl phosphate derivative of 1,2-dipalmitoylglycerol (**1**) could be specifically cleaved at their exovesicular surfaces by hydroxide ions at pH 11.8.[5] The endovesicular *p*-nitrophenyl



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phosphate moieties became accessible only after "damaging" the vesicles with the cationic, single-chain surfactant cetyltrimethylammonium chloride (CTACl). Exo/endo surface specificity was attributed to the inability of hydroxide ions to cross the vesicular bilayers, a suggestion supported by the finding that vesicle-entrapped riboflavin (at pH 5.5) was not deprotonated by bulk aqueous hydroxide ion at pH 11.8, although this reaction, and the attendant loss of riboflavin fluorescence, occurred immediately upon the addition of CTACl.[5]

Despite the novel, locus-specific chemistry observed with vesicular **1**, there remained the suspicion that it constituted somewhat of a special case even among liposomes, which, as a class, are known to maintain a variety of chemical gradients.[6] Thus, the *p*-nitrophenyl phosphate scissile groups present in vesicular **1** ensure that the initial cleavage of *p*-nitrophenoxide (PNPO) from the monoanionic disubstituted phosphate will leave behind a less reactive, dianionic monoalkylphosphate ester and that these residual phosphatidic acid dianionic surfactants will form particularly stable vesicles.

In order to generalize the hydrolytic procedure for the creation of surface-differentiated glyceryl diester vesicles, we have now prepared a cationic, nonphospholipid, diester, reactive carbonate surfactant, **2**. Vesicles of **2**, created at pH 4, support surface-specific exovesicular cleavage of $PNPO^-$ by bulk aqueous hydroxide ions at pH 8. The resulting vesicles should carry "choline" hydroxyl at their exovesicular surfaces but retain *p*-nitrophenyl carbonate functionalities at their endovesicular surfaces. The new results are particularly interesting in contrast to the inability of vesicles created from the analogously functionalized dihexadecylmethylammonium surfactant, **3**, to support surface-specific

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