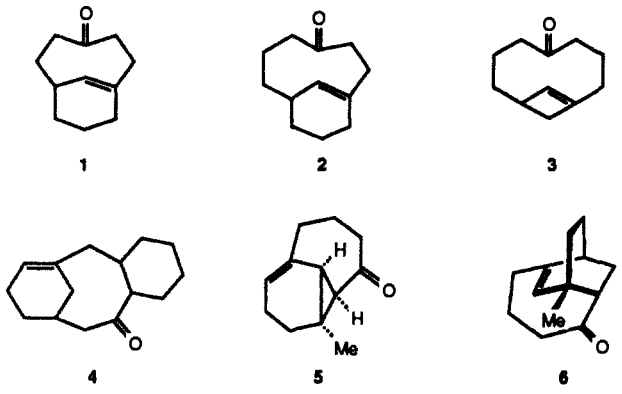
Boat/Chair Topographic Stereoselection during Anionic Oxy-Cope Rearrangement of 1-Alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols

Leo A. Paquette,* Christopher A. Teleha, Richard T. Taylor,[1] George D. Maynard,[2] Robin D. Rogers,[3a] Judith C. Gallucci,[3b] and James P. Springer[3c]

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, the Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115, and the Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey 07065.
Received April 12, 1989

Abstract: In order to examine which of four possible [3.3] sigmatropic transition states 1-alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols would adopt during oxy-Cope rearrangement of their potassium salts at room temperature, the functionalized norbornanones **15**, **19**, **20**, and **24–26** were prepared. Since those in the 3,3-dimethyl series are derived from (1*R*)-(−)-fenchone, they were available in optically pure form. Condensation of these ketones with cyclopentenyllithium (for the nonenolizable series) or cyclopentenyldichlorocerium(III) proceeded exclusively with C–C bond formation from the exo direction. In each example, oxy-Cope rearrangement took place efficiently, and structural assignments to the products were arrived at on the strength of extensive X-ray crystallographic data. In all but one instance, bridgehead olefinic ketones were formed. The major exception materialized because of unusual S_N' displacement of methoxide ion by the transannularly positioned enolate ion. The stereochemistries of these products are inextricably linked to the particular operational transition state. The results show clearly that exo-boat transition states are utilized as long as the sigmatropic change occurs readily, as it does except in one example. A slower reaction rate favors adoption of an exo-chair geometry. From the synthetic viewpoint, the stereochemical control elements elucidated herein point the way to the possible utilization of this methodology in elaboration of diverse oxacembranolides.

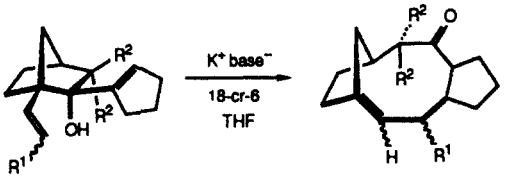
Particular advantages inherent to the anionic oxy-Cope rearrangement[4] include the following: (a) its customarily low reaction temperatures that are often tolerant of sensitive structural components; (b) its irreversibility characteristics;[5] and (c) its exceptional stereoselectivity,[6] which allows for ready construction of complex molecules with six or more stereogenic centers.[7] In recent years, several examples of this useful transformation have appeared that exemplify its potential for elaborating ketones carrying bridgehead double bonds. The findings of Kahn,[8] Levine,[9] Schreiber,[10] Martin,[11] Poupart,[12] and Snider[13] that describe the preparation of **1–6**, respectively, are noteworthy.



1 **2** **3** **4** **5** **6**

The high diastereoselectivity arises as a direct consequence of the highly ordered cyclic transition states of the oxy-Cope reactions. The preferred conformations are most often chairlike.[6,14,15] However, boat conformations are also energetically accessible and can in fact be required by specific structural features.[16]

The present effort deals with precise definition of the [3.3] sigmatropic pathway followed by 1-alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols (**7**) during their base-promoted isomerization to **8**. In these systems, four geometric arrangements can be attained that bring the terminal sp^2-hybridized carbon atoms into proximity. Two of these hypothetical transition states are chairlike, and two are of the boat type. Since each orientation generates a bridgehead olefinic product having diagnostic configuration at



7 **8**

R^1, the two ring fusion sites, and the double bond, experimental resolution of the mechanistic partitioning was considered feasible.

* Address correspondence to this author at The Ohio State University.

(1) On sabbatical leave during 1986–1987 from Miami University, Oxford, Ohio.

(2) Author to whom inquiries should be addressed (at OSU) regarding the computer calculations.

(3) Authors to whom inquiries should be directed concerning the X-ray crystallographic analyses: (a) Northern Illinois University for **34**, **44**, **50**, and **52**. (b) The Ohio State University for **37**, **40**, and **51**. (c) Merck Sharp and Dohme Laboratories for **29** and **32**.

(4) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.

(5) A critical factor in Cope equilibria is ring strain. While *cis*-1,2-divinylcyclopropanes and cyclobutanes undergo facile Cope rearrangement with ring enlargement [Brown, J. M.; Golding, B. T.; Stofko, J. J., Jr. *J. Chem. Soc., Chem. Commun.* **1973**, 319 and Vogel, E. *Liebigs Ann. Chem.* **1958**, *615*, 1], the position is totally reversed with 1,2-divinylcyclopentanes and cyclohexanes [Vogel, E.; Grimme, W.; Dinnē, E. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 739 and Wharton, P. S.; Johnson, D. W. *J. Org. Chem.* **1973**, *38*, 4117] because of the considerable strain in the medium-sized rings. The oxy-Cope process delivers an enol (or enolate anion) which rapidly tautomerizes to a carbonyl compound, is therefore usually irreversible, and has the ability to reverse the normal equilibria or to produce strained products [see, for example: Marvell, E. N.; Whalley, W. *Tetrahedron Lett.* **1970**, 509. Marvell, E. N.; Tao, T. *Tetrahedron Lett.* **1969**, 1341. Leriverend, P.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1970**, 1040].

(6) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: 1984; Vol. 3A, p 503. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Pergamon Press: in press.

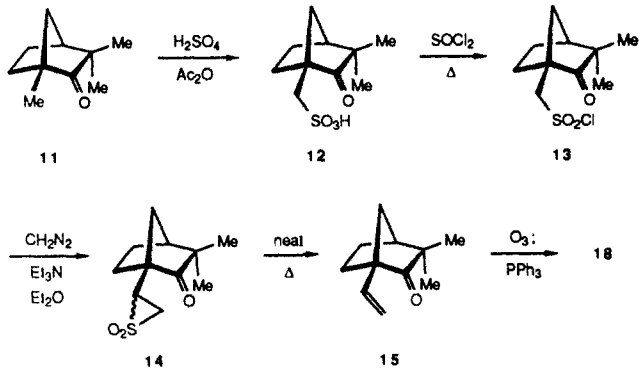
(7) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (c) Paquette, L. A.; Learn, K. S.; Romine, J. L. *Tetrahedron* **1987**, *43*, 4989. (d) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (e) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *Ibid.* **1988**, *110*, 890. (f) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, in press. (g) Paquette, L. A.; He, W.; Rogers, R. D. *Ibid.* **1989**, in press. (h) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

(8) Kahn, M. *Tetrahedron Lett.* **1980**, *21*, 4547.

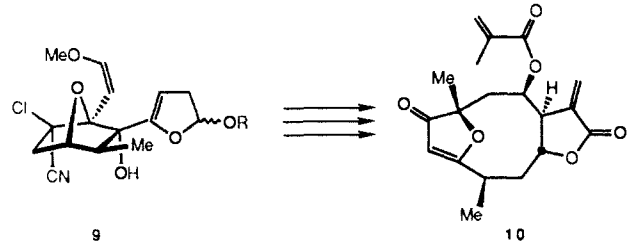
(9) Levine, S. G.; McDaniel, R. L., Jr. *J. Org. Chem.* **1981**, *46*, 2199.

0002-7863/90/1512-265$02.50/0

Scheme I



This investigation is intended to serve as a prototype of a synthetic pathway that might allow efficient synthetic access to such oxacembranolides as zexbrevin (**10**).[17]



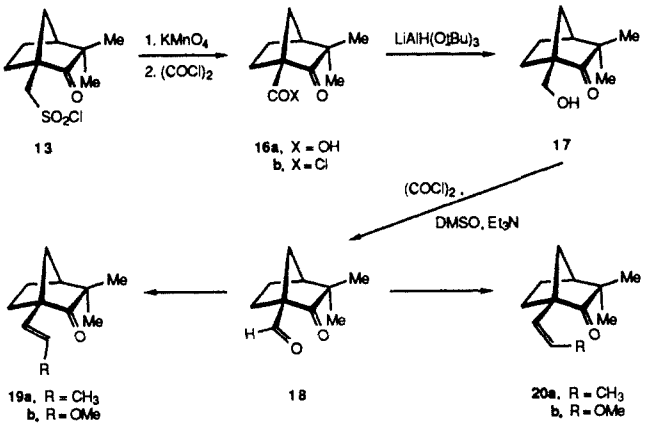
Results

Synthesis of the Functionalized Norbornanones. The zexbrevin model **9** derives from addition of a suitable vinyl anion to an *endo*-3-methyl-7-oxa-2-norbornanone. Though this heterocyclic system is not without its own difficult questions of functional group detail, it nevertheless provides the impetus for examination of two carboxylic analogues. At one extreme is the 3,3-dimethyl series; the other completely lacks methyl groups at C-3. The impact of the rather sizable steric crowding in the first instance on issues related to transition state selection during oxy-Cope rearrangement was obviously of specific interest.

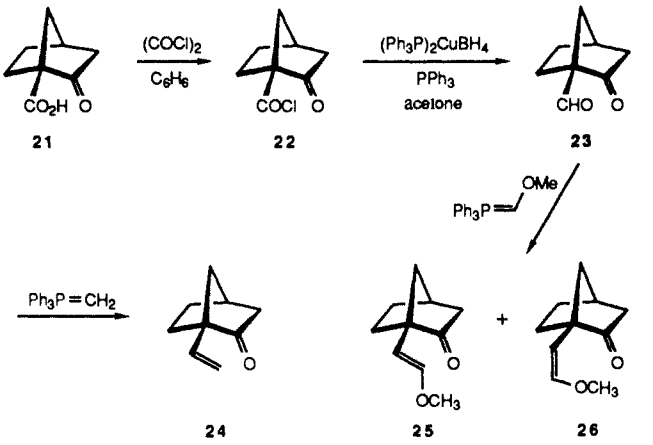
The synthesis of **15** began by exposing (1*R*)-(−)-fenchone (**11**) to acetic anhydride and sulfuric acid in accordance with precedent[18] (Scheme I). Following the conversion of **12** to **13**, dehydrochlorination of this sulfonyl chloride was performed in the presence of diazomethane[19] to afford episulfone **14**. Gentle heating of neat **14** at approximately 80 °C promoted the smooth loss of sulfur dioxide with formation of the desired **15**. The sequence from **11** proceeds in 20% overall yield to provide material exhibiting $[\alpha]_D^{23}$ −44.1°.

Arrival at the homologues **19** and **20** was initially predicated upon permanganate oxidation of **13** to provide the keto carboxylic acid **16a**.[18] Its derived acid chloride[20] underwent chemospecific reduction to **17** with lithium tri-*tert*-butoxyaluminum hydride.

Scheme II



Scheme III



Submission of **17** to Swern oxidation gave **18**, exposure of which to the appropriate Wittig reagent succeeded in delivering mixtures of **19** and **20**.

A more direct route to **18** involved direct ozonolysis of **15**.

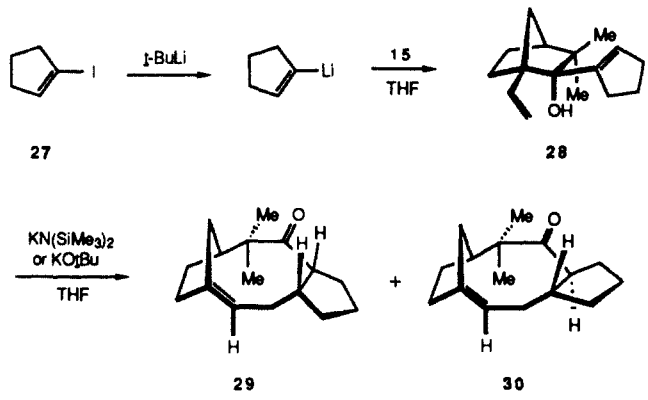
Brief examination of Warren's phosphine oxide anion chemistry[21] as a possible stereocontrolled route to **19b** and **20b** did not provide the desired stereoselectivity (1:1 mixtures were produced from the purified diastereomeric 1,2-adducts). Consequently, **18** was condensed with the requisite phosphorus ylides and the stereoisomeric products were straightforwardly separated in preparative quantities by elution chromatography on silica gel impregnated with 10% silver nitrate.[22]

Keto acid **21**, readily available in racemic form,[23] served as starting material for the desmethyl series. The most efficient means uncovered for transforming **21** into **24** involved conversion to the acid chloride **22** and its selective reduction with bis(triphenylphosphine)copper(I) borohydride[24] (Scheme III). Subsequent Wittig olefination cleanly furnished the highly volatile **24**. The enol ethers **25** and **26** were readily separated by conventional medium pressure liquid chromatography on silica gel.

Stereochemical Course of Anionic [3.3] Sigmatropy within the 3,3-Dimethyl Series. For the purpose of standardization, 1-lithiocyclopentene was added uniformly to all of the 2-norbornanones described above. This nucleophile was generated by reaction of 1-iodocyclopentene (**27**) with *tert*-butyllithium. Since **15**, **19**, and **20** are nonenolizable ketones, no special precautions had to be taken for obtaining the carbinols in good yield. The 1,2-additions invariably proceeded from the exo direction to give

(10) (a) Schreiber, S. L.; Santini, C. *Tetrahedron Lett.* **1981**, *22*, 4651. (b) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038. (c) Schreiber, S. L.; Hawley, R. C. *Tetrahedron Lett.* **1985**, *26*, 5971.
(11) Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3190.
(12) Paquette, L. A.; Poupart, M.-A. *Tetrahedron Lett.* **1988**, *29*, 273.
(13) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508.
(14) For a comprehensive review of the closely related aliphatic Claisen rearrangement, see: Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.
(15) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.
(16) For examples, consult: (a) Shea, K. J.; Phillips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156. (b) Kato, N.; Kataoka, H.; Ohbuchi, S.; Tanaka, S.; Takeshita, H. *J. Chem. Soc., Chem. Commun.* **1988**, 354. (c) See also ref 39.
(17) (a) Romo de Vivar, A.; Gurrero, C.; Diaz, E.; Ortega, A. *Tetrahedron* **1970**, *26*, 1657. (b) Baruah, N. C.; Sharma, L. P.; Madhusudanan, K. P.; Thyagarajan, G.; Herz, W.; Murri, R. *J. Org. Chem.* **1979**, *44*, 1831.
(18) Kuusinen, T.; Lampinen, M. *Suomenkemistehleti* **1958**, *31B*, 381.
(19) Fischer, N.; Opitz, G. *Organic Synthesis* 1973; Wiley: New York, Collect. Vol. V, p 877.
(20) Brown, F. C.; Morris, D. G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 125.
(21) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.
(22) Goering, H.; Closson, W. D.; Olson, A. C. *J. Am. Chem. Soc.* **1961**, *83*, 3507.
(23) (a) Boehme, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 2762. (b) Abeywickrema, R. S.; Della, E. W. *Org. Prep. Proc. Int.* **1980**, *12*, 357.
(24) Sorrell, T. N.; Pearlman, P. S. *J. Org. Chem.* **1980**, *45*, 3449.

stereochemically homogeneous products. Recourse was made to the dichlorocerate in the desmethyl series without affecting the strong preference for exo capture.

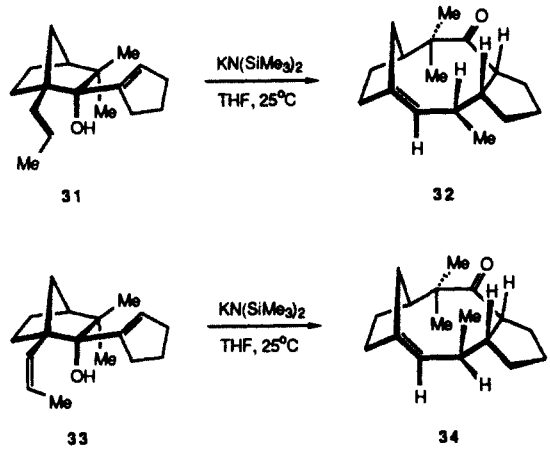


27 28 29 30

The availability of **28**[7h] set the stage for investigating the proclivity of its potassium salt for anionic [3.3] sigmatropy. When the oxy-Cope rearrangement was performed with potassium hexamethyldisilazide in tetrahydrofuran at room temperature, there was produced a mixture of two medium-ring unsaturated ketones, with **29** predominating heavily (>95%). If potassium *tert*-butoxide was used instead and the reaction mixture was refluxed for 2 h prior to workup, the product mixture became relatively enriched in **30** (33%).

The configurational assignments to **29** and **30** were not easy to make, since the two regions dense in stereochemical information are not contiguous. However, two lines of evidence leave little doubt about the correctness of our structural formulations: (1) X-ray crystallographic analysis of **29** showed its olefinic proton to be trans to the methano bridge. In addition, the ring juncture protons are fixed in a syn relationship to this same point of reference (Figure 1). (2) Independent treatment of **29** with potassium hydride and 18-crown-6 in tetrahydrofuran for 2 h resulted in partial isomerization to **30**. The latter must therefore be epimeric with **29** at its α-carbonyl site.

Like treatment of **31** and **33** with potassium hexamethyldisilazide gave the stereoisomeric ketones **32** and **34**, respectively.[25]



31 32 33 34

Similarities seen in the ^{1}H NMR spectra of **29** and **32** suggested that they may belong to the same stereochemical series. In particular, their α-carbonyl, olefinic, and syn-methano bridge protons exhibit closely comparable chemical shifts in $CDCl_3$ solution [**29**: δ 3.33 (t, J = 5.7 Hz), 5.19 (dd, J = 10.6, 6.2 Hz), and 2.75 (d, J = 12 Hz); **32**: δ 3.42 (t, J = 5.7 Hz), 4.90 (d, J = 9.8 Hz), and 2.72 (d, J = 12.1 Hz)]. The analogous protons in **34** differed substantially in their relative locations (see Experimental Section). It was not at all clear if these variations

(25) Reaction times longer than 7 h have on occasion (particularly with potassium *tert*-butoxide as base) resulted in formation of as much as 9% of the α-carbonyl epimer. These minor components were not characterized when they arose.

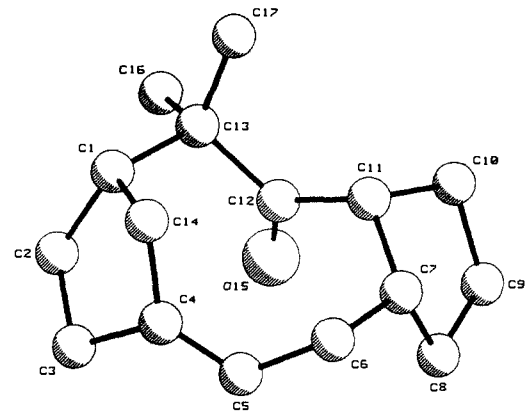


Figure 1. A computer-generated drawing of **29** derived from the X-ray coordinates with hydrogens omitted for clarity. The atom numbering is arbitrary.

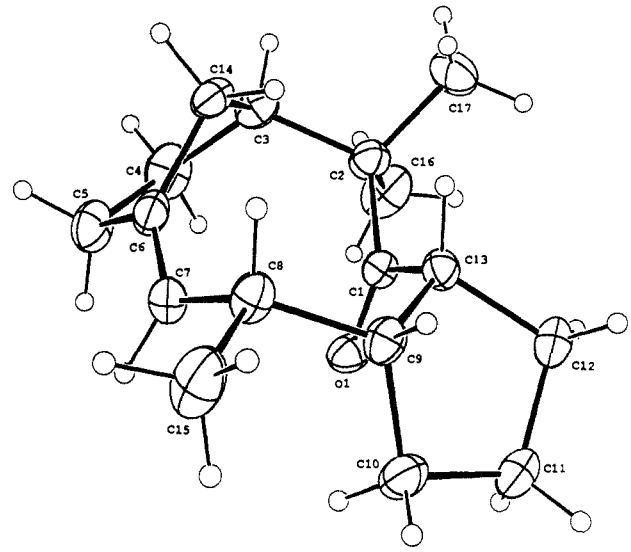


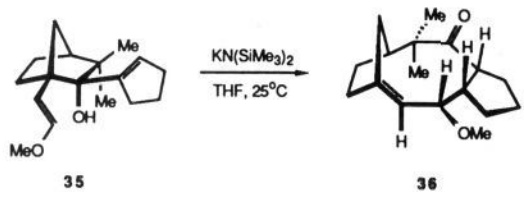
Figure 2. Perspective view of **32** showing the arbitrary atom numbering scheme. Atoms are represented by thermal ellipsoids at the 20% probability level except for the hydrogens which are drawn at an arbitrary size.

stemmed from a change in the transition state stereoalignment found more kinetically attractive by **33** or from adoption by **34** of a different ground-state conformation in order to accommodate better the steric demands of its secondary methyl group.

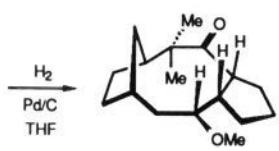
Therefore, both ketones were subjected to X-ray diffraction analysis. As can be seen for **32** (Figure 2), its general topography compares closely to that of **29**. Adoption of this spatial arrangement permits the third methyl group to reside quasi-equatorially. Consequently, this substituent is projected to the exterior of the molecule where it is not at all sterically encumbered.

Oxy-Cope rearrangement within **33** occurs a bit more slowly than in **31**, but follows the same exo-boat reaction profile (see below for definition) adopted by the other two *endo*-norbornan-2-ols. However, the quasi-axial orientation of the secondary methyl group demanded by this trajectory has nonbonded steric consequences that seek relief. Comparison of the conformations depicted in Figures 1 and 2 with the structural geometry of **34** shown in Figure 3 serves to demonstrate the deformation present in the latter. The considerable changes in diamagnetic shielding anticipated for the α-carbonyl, olefinic, and syn-methano bridge protons under these circumstances are in reasonable agreement with the spectral data.

Following admixture of alcohol **35** with a slight excess of potassium hexamethyldisilazide in tetrahydrofuran at room temperature, conversion to ketone **36** was complete after 5.5 h. Thus, once again, the anionic oxy-Cope rearrangement proceeded in an efficient, selective, and facile manner. The configurational status



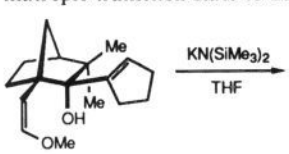
35 36



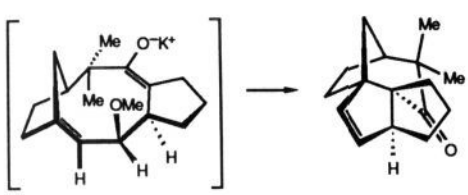
37

of the methoxyl group in **36** could not be confidently assigned on the basis of spectral comparisons with **29**, **32**, and **34** because of its appreciable long-range impact on chemical shifts. For instance, its α-carbonyl, olefinic, and syn-methano bridge protons are located at δ 3.08, 5.26, and 2.40, respectively. The coupling constants for the α-methoxy proton (δ 4.13) are clearly apparent (J = 8.7 and 2.3 Hz) but not especially useful for establishing relative configuration in the absence of information relating to the molecular conformation. Since **36** is an oily substance, its double bond was saturated to produce **37**, a crystalline compound well suited to X-ray analysis (Figure 4). From these data, we deduce that **31** and **35** respond with identical stereoselectivity to [3.3] sigmatropic rearrangement.

On this basis, a direct correspondence between **33** and **38** was also anticipated. Complete consumption of the cis vinyl ether required 4 days at room temperature. Again, a single product was formed. However, the ^{1}H NMR spectrum of the new ketone lacked the methoxyl group absorption, displayed two olefinic proton signals, and differed extensively in overall appearance from the general pattern seen for the other bridgehead olefinic ketones. Since this product crystallized as colorless, rectangular plates, it proved possible to determine that **40** was in actuality a tetracyclic diquinane by X-ray crystallographic means (Figure 5). As discussed elsewhere,[26] this remarkable transformation materializes as a consequence of adoption by **38** on an exo-chair [3.3] sigmatropic transition state to deliver **39** (note the significant dia-



38



39 40

stereomeric relationship to **34**), the subsequent intramolecular S_N' displacement of the properly stereoaligned methoxyl group by the transannular diposed enolate anion. The first step establishes the double bond geometry and three stereocenters. The internal cyclization subsequently proceeds along the trajectory that delivers a thermodynamically acceptable cis-fused diquinane moiety. Recognition that **33** and **38** do not isomerize in like manner is noteworthy.

Demonstration of Boat-like Transition State Preference within the Desmethyl Analogues. When the isomerization of **41**, as promoted by potassium hexamethyldisilazide, was carried out and the resulting two-component mixture was subjected to chromatography, the ketones **42** and **43** were isolated in pure condition. Their epimeric relationship was confirmed by independent equilibration, and the other configurational relationships were

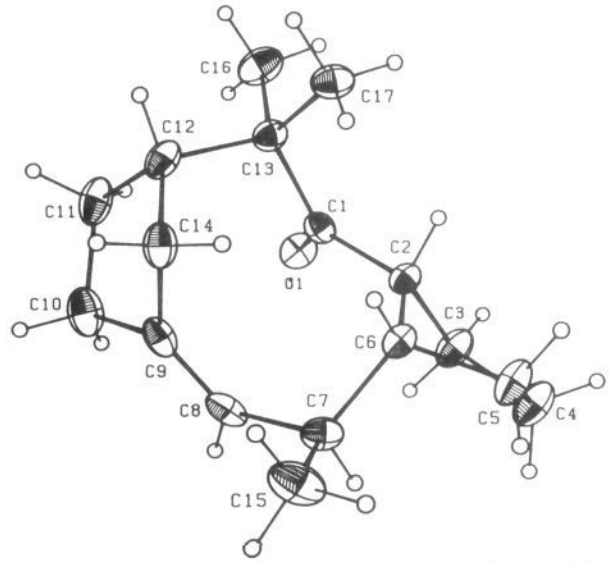


Figure 3. Computer-generated perspective drawing of **34** determined by X-ray analysis. The atom numbering is arbitrary.

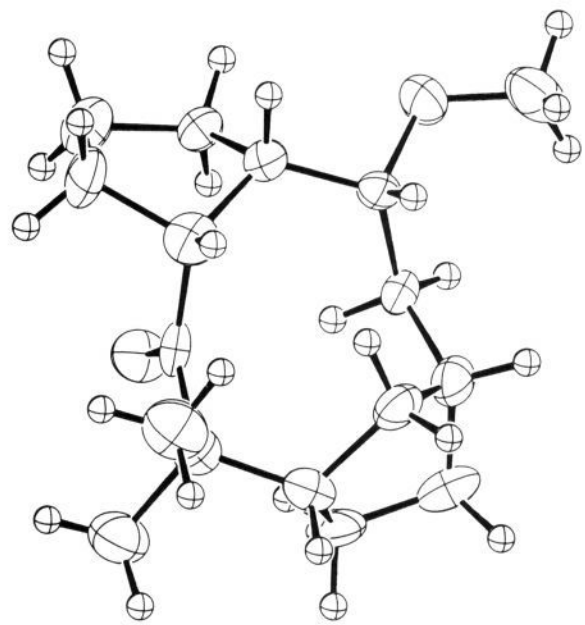


Figure 4. A computer-generated ORTEP drawing of **37** as derived from the X-ray coordinates. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids, and the hydrogen atoms are drawn with an artificial radius.

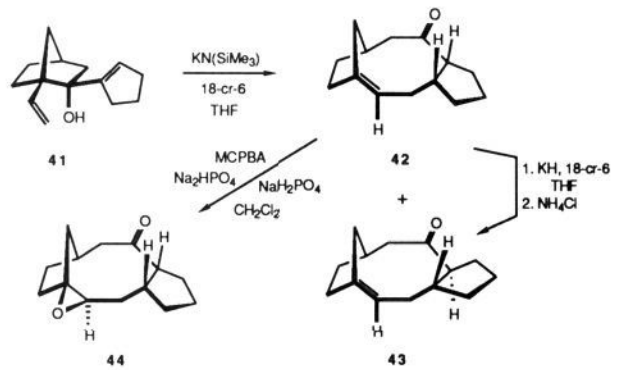
Table I. Products from Isomerization of **45** at 20 °C

run	reaction conditions	47a (%)	48a (%)	49 (%)	total yield (%)
1	KHMDS, 18-cr-6, THF, 30 min	40	40	*a*	81
2	KHMDS, 18-cr-6, THF, 1.5 h	34	33	3.4	71
3	KHMDS, 18-cr-6, THF, 3 h	50	41	3.7	95
4	KH, 18-cr-6, THF, 2 h	26	30	8.8	68

[a] Not determined.

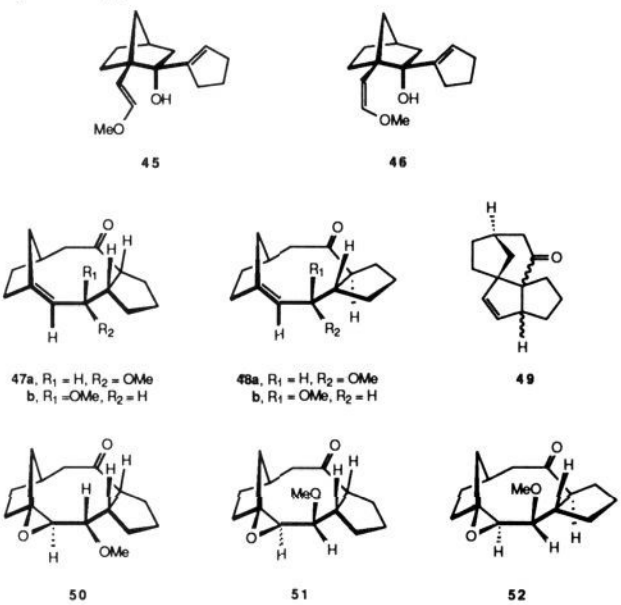
Table II. Products from Isomerization of **46** at 20 °C

run	reaction conditions	47b (%)	48b (%)	49 (%)	total yield (%)
1	KHMDS, 18-cr-6, THF, 1.5 h	32	11	17	60
2	KHMDS, 18-cr-6, THF, 2 h	35	20	25	80
3	KHMDS, 18-cr-6, THF, 2.5 h	38	14	30	82
4	KHMDS, 18-cr-6, THF, overnight	0	17	26	42
5	KH, 18-cr-6, THF, 2 h	31	0	8	39



corroborated by X-ray analysis of epoxide **44** (Figure 6).

The ring expansions of alcohols **45** and **46**, performed similarly, gave more complex product mixtures than heretofore because of the incursion of postsigmatropic epimerization and transannular cyclization. In both examples, the total yield of products was good (Tables I and II). Rather unexpected was the finding that the small amount of tetracyclic ketone **49** isolated from **45** was actually a 3:1 mixture of stereoisomers. It is noteworthy that **46** is transformed more efficiently into **49**, although with precisely the same 3:1 composition. Our attempts to elucidate the relative configuration of these inseparable stereoisomers by ^{1}H NMR spectroscopy were to no avail.



The trans enol ether **45** also gave rise to two bridgehead olefinic ketones (Table I). Since **47a** was partially converted into **48a** when treated with potassium hydride and 18-crown-6 in tetrahydrofuran, these molecules necessarily share the same methoxyl stereochemistry. In **47a**, the signals attributable to the vinyl, α-methoxyl, α-carbonyl, and syn-methano bridge protons appear (in C_6D_6) δ 5.27 (d, J = 9.2 Hz), 4.19 (dd, J = 9.2, 4.3 Hz), 2.61 (t, J = 5.8 Hz), and 2.25 (d, J = 12.5 Hz), respectively. While three of these chemical shifts correspond rather well with those observed for **36** (see Experimental Section), the crucial α-carbonyl proton absorption in the latter appears considerably downfield (δ 3.08; t, J = 5.1 Hz) to that in **47a**. We deemed this single lack of correspondence to warrant the epoxidation of **47a** for conversion to the more highly crystalline **50** in order to establish the stereochemical assignment crystallographically (Figure 7). With these data, there exists no doubt that **36** and **47a** are configurationally related.

When the anionic isomerization of **46** was allowed to proceed overnight (Table II, run 4), **47b** was absent as a product. For reasons discussed above, the enolate precursor to **47b** could cyclize to one isomer of **49**; however, no significant increase in the proportion of this ketone was seen. Evidently, degradation of one or more intermediates gradually sets in over time. Resubmission of **47b** to the reaction conditions merely returned it unchanged, suggesting that the kinetic enolate was being uniquely generated under these circumstances.

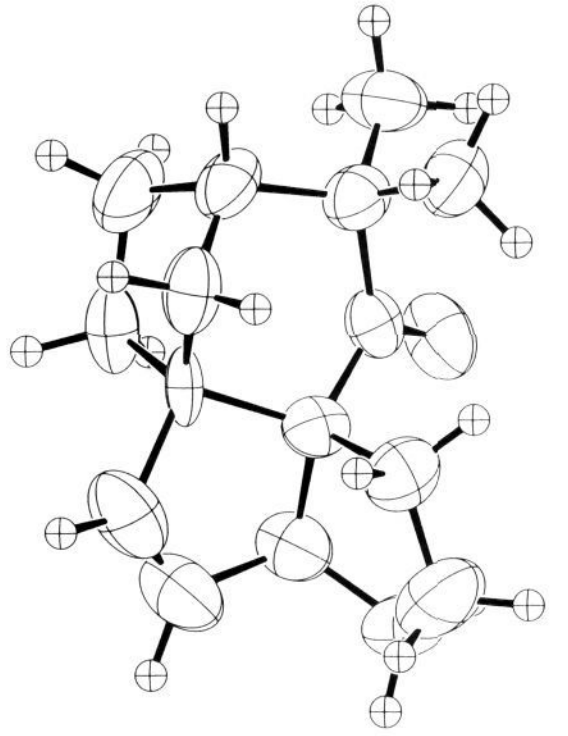


Figure 5. ORTEP drawing of **40** as derived from the X-ray coordinates. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids, and the hydrogen atoms are drawn with an artificial radius.

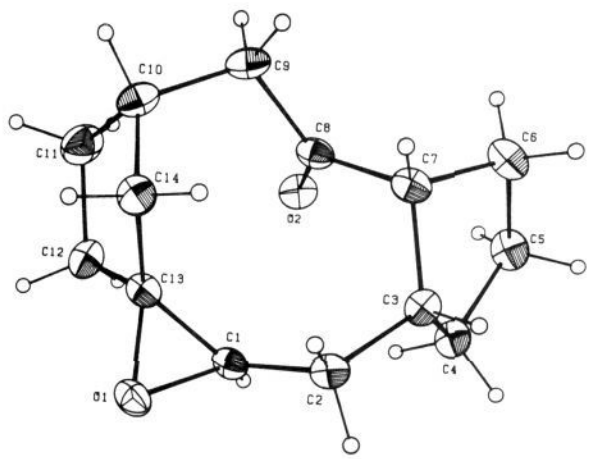


Figure 6. Computer-generated perspective drawing of **44** as determined by X-ray analysis. The atom numbering is arbitrary.

The olefin geometry in **47b** was tentatively assigned to be as in the other examples on the basis of its vinyl proton signal at δ 5.08. The 300 MHz ^{1}H NMR spectrum also exhibited a triplet (J = 4.8 Hz) for the α-methoxyl proton at δ 3.59 and an α-carbonyl proton doublet (J = 13.2 Hz, δ 3.12). Since these shifts did not closely parallel those observed for the expectedly most similar stereochemical analogue **34**, we were led to transform **47b** as well as **48b** into their nicely crystalline epoxides **51** and **52** for X-ray crystallographic analysis. The resultant findings (Figures 8 and 9) proved consistent with predominant passage via an exo-boat transition state during ring enlargement.

Mechanistic Analysis. The four anionic oxy-Cope transition states available to 1-alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ols are depicted in Scheme IV. Each can be characterized uniquely

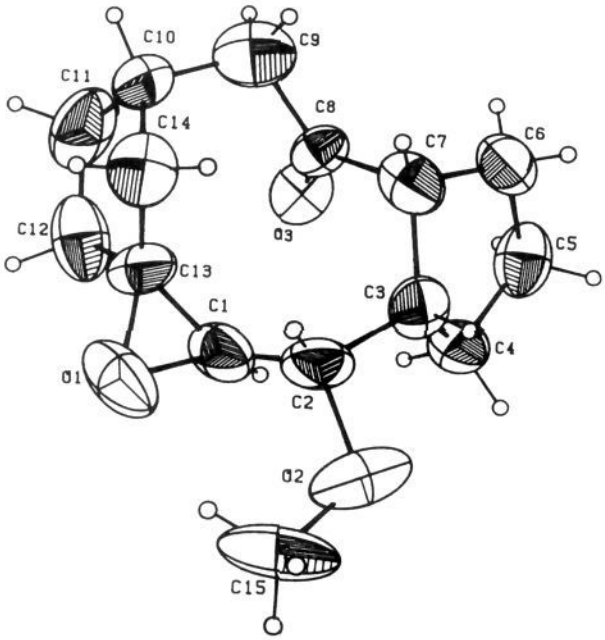


Figure 7. Computer-generated perspective drawing of **50** as determined by X-ray analysis. The atom numbering is arbitrary.

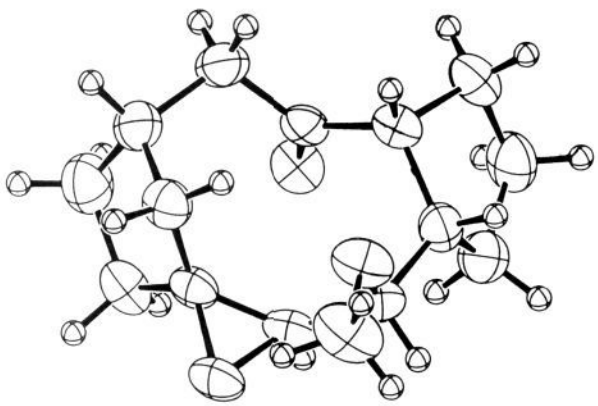


Figure 8. ORTEP drawing of molecule A of **51** as derived from the X-ray coordinates. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids, and the hydrogen atoms are drawn with an artificial radius.

by a combination of two descriptors. The first (exo or endo) defines the specific orientation of the bridgehead vinylic double bond relative to the norbornyl framework, while the second (chair or boat) connotes the specific geometry adopted by the pair of double bonds and the two interconnective tetrahedral carbons during the electrocyclic process proper.

Inspection of these options clearly reveals that endo alignment of the bridgehead vinyl group serves ultimately to lock the vinyl proton into an *E* olefin geometry. Exo vinyl orientation necessarily leads to the alternative *Z* olefin geometry. On the other hand, the relative stereochemistry of the cyclopentyl ring fusion site that is positioned β to the enolate anion center is inextricably linked to whether chair or boat topology is adopted. Here the analysis of potential product structure may be somewhat less than obvious. Whereas the endo-chair combination generates an enolate having *E*,syn stereochemistry, adoption of the exo-chair arrangement leads to the *Z*,anti product. The syn/anti dichotomy is mandated by the need of the cyclopentenyl double bond to align itself in a manner consistent with the particular orientation of the vinyl group such that the two π-bond termini are in adequate proximity for bonding. The boatlike transition states necessarily adhere to similar fundamental principles.

At this point, it was considered instructive to gain some appreciation of the strain energies associated with all eight structures

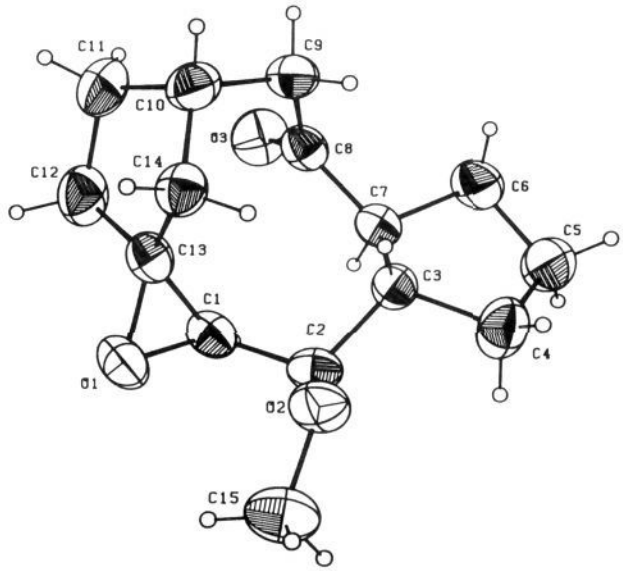
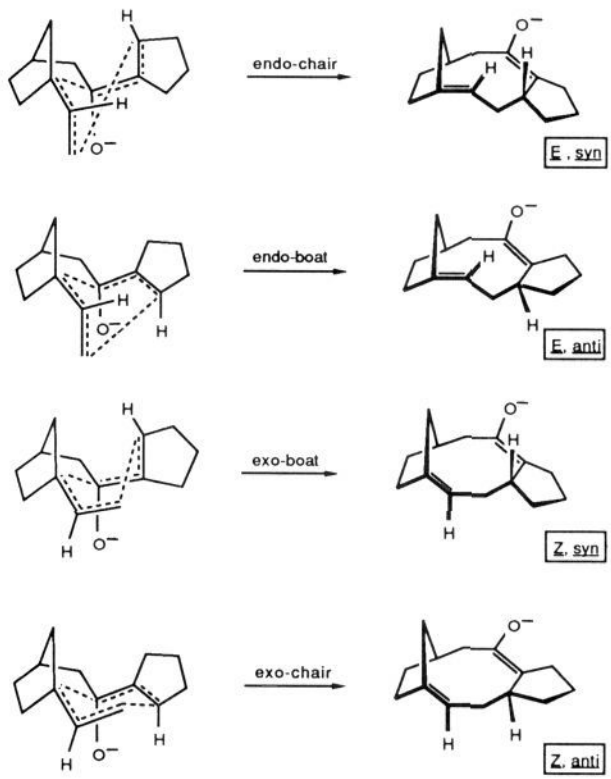


Figure 9. Computer-generated perspective drawing of **52** as determined by X-ray analysis. The atom numbering is arbitrary.

Scheme IV



of the type outlined in Scheme IV. Because calculations involving the transition states proved inconsistent, recourse was made instead to the global minimum energy ground-state conformations of **28**, **31**, **33**, and **38**. These were determined through initial use of MODEL (KS 2.93)[27] in combination with its companion program BAKMDL.[28] The MM2 energies derived from MODEL were calculated by using the alkoxide structures. When the preminimized structures were submitted to MMX for determination of the heats

(26) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331.

(27) We thank Professor W. C. Still (Columbia University) for making his program available for use.

(28) Professor K. Steliou (University of Montreal) is thanked for providing us with updates of this software package.

Table III. Calculated Strain Energies and Heats of Formation

alcohol	ground-state geometry	strain energy, kcal/mol	ΔH_f, kcal/mol	product enolate	strain energy, kcal/mol	ΔH_f, kcal/mol
28	endo-chair	36.1	−32.8	*E*, syn	64.0	−7.0
	endo-boat	38.3	−30.6	*E*, anti	64.0	−6.4
	exo-chair	38.2	−30.6	*Z*, syn	53.1	−17.2
	exo-boat	36.3	−32.6	*Z*, anti	55.2	−15.2
31	endo-chair	35.8	−40.6	*E*, syn	65.1	−19.3
	endo-boat	36.6	−39.8	*E*, anti	65.4	−12.2
	exo-chair	37.0	−39.4	*Z*, syn	54.0	−23.4
	exo-boat	35.4	−40.9	*Z*, anti	58.2	−19.3
33	endo-chair	38.0	−38.4	*E*, syn	68.7	−9.5
	endo-boat	39.5	−36.9	*E*, anti	65.2	−12.4
	exo-chair	40.8	−35.6	*Z*, syn	57.8	−19.8
	exo-boat	38.6	−37.8	*Z*, anti	55.0	−22.6
38	endo-chair	36.3	−71.0	*E*, syn	66.8	−41.1
	endo-boat	*a*	*a*	*E*, anti	63.9	−43.3
	exo-chair	37.9	−69.4	*Z*, syn	53.6	−53.6
	exo-boat	36.4	−7.40	*Z*, anti	52.9	−54.3

of formation and strain energy values, the program was observed not to function properly when alkoxides were involved. Consequently, it became necessary to replace $-O^-$ by $-OH$ for the MMX procedure. Although the actual MM2 energy values changed as a result, an ordering identical with that seen within MODEL was realized. The data are compiled in Table V.

In the case of **38**, no conformer corresponding to the endo-boat orientation was found within 3 kcal of the global minimum and that value has therefore been omitted.

The global energy minima for each product were determined in like fashion (Table III). The MODEL and MMX values were both determined directly on the respective enolates, which were tagged specifically as π-systems in MMX. However, each π-system was not forced to be planar. No unusual complexities were uncovered.

Discussion

The exclusive formation from **28**, **31**, **32**, **35**, and **41** of *Z*,syn product requires that their bridgehead vinyl group be positioned exo with respect to the norbornyl frame of reference in the kinetically favored transition state that each adopts. In addition, the cyclopentenyl double bond must be oriented exo such that a boat geometry evolves during electronic reorganization. Comparable structural arrangements develop within **45** and **46** as [3.3] sigmatropy begins. However, the production of ketone **49** as a 3:1 mixture of isomers in both examples (Tables I and II) denotes that a small amount of stereochemical "leakage" away from the pure exo-boat pathway operates in these two systems.

The striking exception to the general trend is **38**. Although no medium-ring ketone could be isolated in this instance, the tetracyclic compound **40** that is formed efficiently possesses stereochemistry that provides firm evidence that the exo-chair transition state alternative is most favorable in this instance.

The exo-boat reaction trajectory profile that predominates conflicts with conventional expectation, since boatlike transition-state alignments are usually more elevated in their energy requirements than are those of the chair type.[29-33] Therefore, we have sought clues by examining the destabilizing nonbonded eclipsing interactions that the best possible geometries within the starting norbornanols must experience while proceeding to product. Of course, ground-state conformational preferences are not necessarily relevant to transition states (Curtin–Hammett principle). In the present instance, however, they do corroborate the results, and our inability to access transition-state energies computationally provides no useful, more accurate alternative.

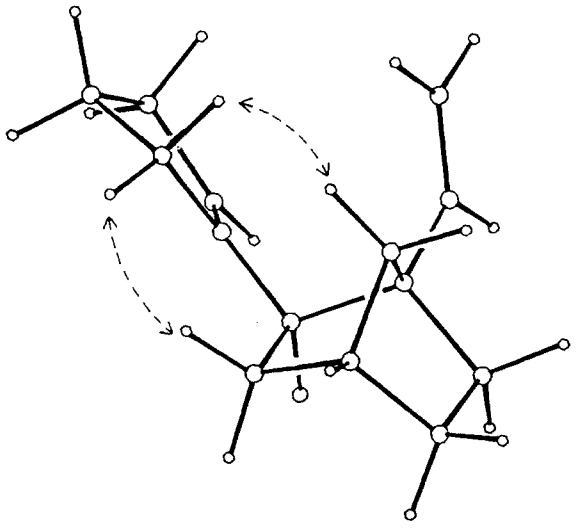


Figure 10. Exo-chair topology showing the pair of eclipsing interactions.

In all four examples documented in Table III, the *E*,syn and *E*,anti product consistently surface as being 7–14 kcal/mol more strained than either of the possible *Z* olefinic enolates. This increase in destabilization, which probably stems from enhanced angle strain and transannular congestion, may begin to surface in the precursor transition states and may be adequate to deter competitive rearrangement by these two routes.

Evidence has been obtained to suggest that the anionic oxy-Cope transition state often occurs early, or is reactant-like, especially when the [3.3] shift proceeds by way of a boatlike transition state.[32b] This behavior conforms to the dramatic decrease in adjacent bond strength arising from the presence of an oxy substituent[34-37] and the very marked rate enhancements that materialize.[4,38,39] The picture that emerges is one in which the exo-chair alignment must be disfavored relative to that present in the exo-boat. Under these circumstances, product conformational energies are less relevant than usual. In the present systems, attainment of the rotamer necessary to achieve isomerization by means of the exo-chair topology forces both C-5 methylene protons

(29) (a) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (b) Doering, W. von E.; Troise, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 5739.
(30) Goldstein, M. J.; Benzon, M. S. *J. Am. Chem. Soc.* **1972**, *94*, 7149.
(31) Gajewski, J. J. *Hydrocarbon Thermal Isomerization*; Academic Press: New York, 1981.
(32) (a) Gajewski, J. J.; Hoffman, L. K.; Shih, C. N. *J. Am. Chem. Soc.* **1974**, *96*, 3705. (b) Gajewski, J. J.; Jimenez, J. L. *Ibid.* **1986**, *108*, 468. (c) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198.
(33) Shea, K. J.; Philips, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 3156.
(34) (a) Evans, D. A.; Baillargeon, D. J. *Tetrahedron Lett.* **1978**, 3315, 3319. (b) Steigerwald, M. L.; Goddard, W. A., III; Evans, D. A. *J. Am. Chem. Soc.* **1979**, *101*, 1994.
(35) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877.
(36) Ahlgren, G. *Tetrahedron Lett.* **1979**, 915.
(37) Rozeboom, M. D.; Kiplinger, J. P.; Bartmess, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 1025.
(38) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3973.
(39) Paquette, L. A.; Crouse, C. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 4411.

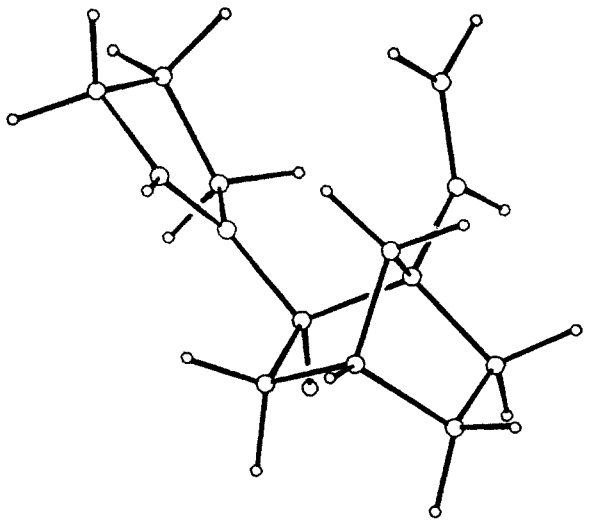


Figure 11. Exo-boat topology showing the staggered orientation of the vinyl proton.

of the cyclopentene ring to be rather awkwardly positioned; one virtually eclipses the syn-C-7 norbornyl proton, while the other is thrust into space closely proximate to that already occupied by the exo C-3 hydrogen (or methyl) of the norbornane (see Figure 10). The destabilization may be somewhat enhanced when the 1-substituent is *cis*-propenyl, for example, because of added steric crowding in this region of the molecule. In contrast, these untoward ground-state interactions are absent from the exo-boat ground states, since the vinyl proton of the cyclopentene is now nicely staggered between the same syn-C-7 and exo-C-3 substituents (Figure 11).[40] Thus, to the extent that the staggered arrangement is able to contribute to stabilization of the transition state, the exo-boat arrangement would be favored.

It remains to consider why **38** selects the exo-chair geometry during oxyanionic ring expansion, while its desmethyl congener **46** does so to a maximum of only 30% and **33** ignores this pathway altogether. Relevantly, the time required for **38** to isomerize completely at room temperature (4 days) is substantively longer than all other examples studied, including **46** (1 h) and **33** (1.5 h).[41] The *gem*-dialkyl effect that deters *convenient* access by **38**

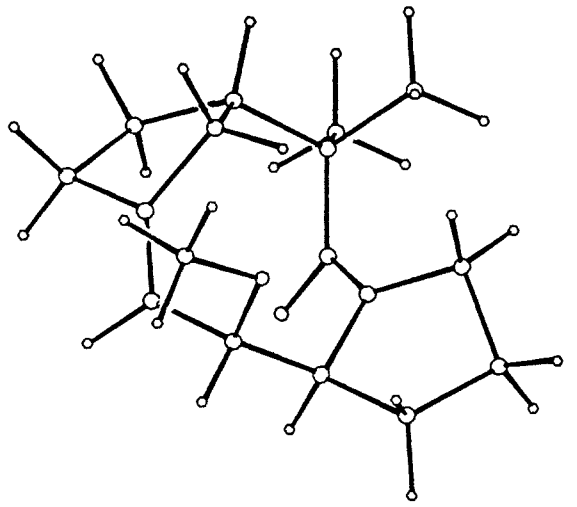


Figure 12. Energy-minimized conformation of enolate **39**.

to an activated complex has the net effect of forcing adoption of a later transition state than witnessed in the other systems. Gajewski and Jimenez have established that bond formation is significantly farther along (ca. 67%) in chairlike acyclic [3.3] shift transition states than in those having boatlike character (roughly 25%).[32b] Since **38** presumably adopts a late transition state with developed product-like features, [3.3] sigmatropy is made overall less energy-demanding by adopting the customarily more advantageous chair topology.

A striking consequence of the utilization of this pathway is the generation of enolate **39**, which has the minimum energy conformation shown in Figure 12. In this structure, the distance separating the β carbon of the enolate and the sp^2-hybridized bridgehead carbon is only 3.26 Å. Furthermore, the dihedral angle established by the allylic C–O bond and the neighboring olefinic proton is 136°. This combination of structural features lends itself to highly efficient transannular S_N' displacement of methoxide ion.

We consider the *gem*-dimethyl unit to be of primary relevance to the reactivity pattern and stereochemistry exhibited by **39**. This unit must be important since **45** and **46** are converted to **49** as a 3:1 mixture. In these cases, the initially formed enolates may tautomerize to regioisomeric enolates. Although unsubstituted, these may still be more important in this ring system. This tautomerization is impossible for **39**.

Summary

The involvement of exo-boat transition states in anionic oxy-Cope rearrangement of 1-alkenyl-2-cyclopentenyl-*endo*-norbornan-2-ol appears to be general as long as the sigmatropic change occurs readily. In the absence of overriding substituent influences, the exo-boat transition state is most free of destabilizing nonbonded interactions and other unfavorable structural characteristics. Adoption by these molecules of this particular reaction channel augurs well for the successful application of this protocol to the synthetic elaboration of diverse oxacembranolides typified by zexbrevin (**10**).

Our mechanistic analysis also suggests that exo-chair transition states are favored as rearrangement becomes slower and less readily accomplished. Apparently, in such circumstances, the customary difference in energy between the chair and boat transition states (ca. 6 kcal/mol)[32] is adequate to cause the more product-like activated complex to adopt the less energy-demanding chairlike arrangement. An added interesting facet of the isomerization of **38** is the ensuing high-yielding intramolecular S_N' displacement of methoxide by the enolate anion that operates to deliver diquinane **40**. The result is rapid and efficient construction

(40) The energy difference between the pair of conformers shown in Figures 10 and 11, as computed by means of the MODEL:MM2E procedure, is 1.5 kcal/mol.

(41) The effect of a 6-donor substituent on the rate of the Claisen rearrangement is to be accelerating: Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002 and pertinent references cited therein. A 6-methoxyl decelerates in the anionic Claisen rearrangement as well: Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

(42) The following library of crystallographic programs was used: SHELXS-86, Sheldrick, G. M. University of Gottingen, Gottingen, West Germany, 1986. PLUTO, W. Motherwell, D. S.; Clegg, W. University of Cambridge, Cambridge, England, 1978. SDP PLUS V1.1, Okaya, Y.; Frenz, B. A. B. A. Frenz and Associates, College Station, TX, 1984. SHELX76, Sheldrick, G. M. University of Cambridge, England, 1976.

(43) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham: England, 1969; Vol. 1.

(44) Sheldrick, G. M., 1985, SHELXS-86. *Crystallographic Computing*; 3 ed.; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: 1985; pp 175–189.

(45) The computer programs used in this analysis include the Enraf-Nonius *Structure Determination Package*. Version 3, Delft: The Netherlands, 1985; rewritten for a Sun Microsystems computer and several locally written or modified programs.

(46) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2B. (present distributor D. Reidel, Dordrecht).

(47) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.3.1. (present distributor D. Reidel, Dordrecht).

(48) TEXSAN, TEXRAY Structure Analysis Package, version 2.1; Molecular Structure Corporation: College Station, TX 1987.

(49) Gilmore, C. J. MITHRIL: A Computer Program for the Automatic Solution of Crystal Structures from X-ray Data; University of Glasgow; Scotland, 1983.

(50) Scattering factors for the carbon and oxygen atoms are from the *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 71 and 148. The scattering factor for the hydrogen atom is from the following: Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

of an intricate polycyclic system.

Experimental Section

(1*R*)-3,3-Dimethyl-1-vinyl-2-norbornanone (15). A magnetically stirred mixture of 40% sodium hydroxide solution (30 mL) and ether (100 mL) was cooled to 0 °C and treated portionwise with 11.25 g (129 mmol) of *N*-methyl-*N*-nitrosourea. The mixture was stirred until solid was no longer present, and the ether phase was carefully decanted into an ethereal solution (100 mL) of triethylamine (7.0 g, 69 mmol). A solution of **13**[18] (13.5 g, 55 mmol) in 100 mL of ether was added dropwise at 0 °C, and the reaction mixture was subsequently stirred at room temperature for 2 h and filtered. The filtrate was washed with 10% hydrochloric acid and water, dried, and evaporated to leave 10.3 g of impure **14** as an oil.

This oil was heated at 85 °C for 4 h, taken up in ether, and eluted through a short column of silica gel. The filtrate was carefully evaporated to give 3.5 g (38%) of **15** as a colorless oil, which was purified for analysis by preparative GC (7 ft × 0.25 in. 7% SE-30, 160 °C): IR (neat, cm^{-1}) 3080, 2965, 2870, 1738, 1640, 1465, 1385, 1110, 1000, 970, 930, 915; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (dd, J = 17.5, 10.9 Hz, 1 H), 5.17 (dd, J = 10.9, 1.6 Hz, 1 H), 5.13 (dd, J = 17.5, 1.6 Hz, 1 H), 2.19 (br s, 1 H), 1.91 (dd, J = 7.4, 2.5 Hz, 1 H), 1.90–1.65 (m, 4 H), 1.60–1.50 (m, 1 H), 1.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.18, 135.45, 115.28, 60.39, 47.65, 44.97, 39.44, 30.34, 24.36, 23.20, 21.51; MS m/z (M^+) calcd 164.1201, obsd 164.1192; $[\alpha]^{23}_D$ −44.1° (c 5.7, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O$: C, 80.43; H, 9.83. Found: C, 80.49; H, 9.83.

(1*R*)-3,3-Dimethyl-2-oxonorbornane-1-carboxaldehyde (18). A. By Reduction–Oxidation of 16b. A solution of **16a**[18] (14.0 g, 76.9 mmol) in benzene (100 mL) was treated with oxalyl chloride (9.78 g, 77.0 mmol), and stirring was continued overnight with exclusion of moisture. The solvent was evaporated to leave a semicrystalline material that was directly reduced.

A solution of lithium tri-*tert*-butoxyaluminum hydride (154 mmol) in anhydrous ether (250 mL) was cooled to −78 °C, and the acid chloride in 100 mL of anhydrous ether was added dropwise with vigorous stirring. After 2 h, saturated ammonium chloride solution was introduced, followed by 6 N hydrochloric acid to solubilize the aluminum salts. The product was extracted into ether (4 × 150 mL), and the combined ethereal solutions were dried and evaporated. The *tert*-butyl alcohol was removed by maintaining the resulting sample at 0.1 Torr overnight. Final purification was accomplished by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether). There was isolated 9.4 g (73%) of **17** whose IR and ^1H NMR spectra were identical with those reported earlier.[20]

A flame-dried, 500-mL, three-necked flask was charged with oxalyl chloride (7.11 g, 56 mmol) and dichloromethane (50 mL). This solution was cooled to −78 °C under nitrogen and treated dropwise with dimethyl sulfoxide (13.2 g, 169 mmol) in the same solvent (30 mL). Stirring was maintained at −78 °C for 30 min, at which point a solution of **17** (9.4 g, 56 mmol) in 25 mL of dichloromethane was added dropwise. Sixty minutes later, triethylamine (25 mL) was slowly introduced, and the reaction mixture was allowed to warm to room temperature. After 45 min, water (250 mL) was added, and the separated aqueous phase was extracted with dichloromethane (100 mL). The combined organic layers were washed with 100 mL of 20% hydrochloric acid, dried, and carefully concentrated. The residue was purified by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) to give **18** (87%) as a colorless oil that crystallizes when cooled: IR ($CHCl_3$, cm^{-1}) 3015, 2975, 2930, 2885, 1737, 1715, 1465, 1388, 1215, 750, 665; ^1H NMR (300 MHz, $CDCl_3$) δ 9.99 (s, 1 H), 2.39 (dd, J = 11.7, 3.7 Hz, 1 H), 2.32 (br s, 1 H), 2.25 (dd, J = 10.7, 2.0 Hz, 1 H), 2.0–1.55 (m, 4 H), 1.13 (s, 3 H), 1.10 (s, 3 H); MS m/z (M^+) calcd 166.0994, obsd 166.0978.

B. Ozonolysis of 15. A solution of **15** (6.38 g, 38.9 mmol) in dichloromethane (70 mL) was ozonolyzed at −78 °C and reduced at this temperature with triphenylphosphine (11.22 g, 42.8 mmol). The reaction mixture was allowed to warm slowly to room temperature overnight, evaporated under reduced pressure, and triturated with ether–petroleum ether (1:4) to allow removal of the phosphine oxide by filtration. The filtrate was concentrated, rapidly eluted through a plug of silica gel (20% ether in petroleum ether), and concentrated. There was isolated 6.41 g (99%) of **18**, which was used without further purification.

(1*R*)-3,3-Dimethyl-1-(2-propenyl)-2-norbornanone (19a and 20a). A cold (0 °C), magnetically stirred slurry of ethyltriphenylphosphonium iodide (2.77 g, 6.62 mmol) in anhydrous ether (45 mL) was treated dropwise with *n*-butyllithium (4.27 mL of 1.55 M in hexane, 6.62 mmol). The reddish-orange ylide solution was allowed to warm to room temperature during 20 min, recooled to −78 °C, and treated via cannula with a solution of **18** (1.0 g, 6.0 mmol) in ether (45 mL). The color was immediately discharged, and the reaction mixture was warmed to room temperature and quenched with water (50 mL). After 30 min of stirring, the layers were separated, the aqueous phase was extracted with ether (4 × 100 mL), and the organic extracts were combined, washed with water (4 × 100 mL) and brine (2 × 100 mL), dried, and concentrated. The resulting suspension was triturated with 20% ether in petroleum ether and filtered to remove phosphine oxide. The filtrate was concentrated, and the trituration was repeated. MPLC purification of the yellow oil (silica gel, elution with 2% ethyl acetate in petroleum ether) afforded 309 mg (29%) of a mixture of **19a** and **20a**.

These isomers were separated by chromatography on silver nitrate (10%) impregnated silica gel.[22] Trans isomer **19a** eluted with 10% ether in petroleum ether, whereas the cis isomer **20a** was obtained upon elution with ether.

For **19a**: colorless oil; IR ($CHCl_3$, cm^{-1}) 2960, 2915, 2875, 1735, 1450, 1415, 1385, 1105, 1050, 1022, 973, 928, 913; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (dd, J = 15.8, 1.1 Hz, 1 H), 5.48 (dq, J = 15.7, 6.2 Hz, 1 H), 2.07 (br s, 1 H), 1.87 (dt, J = 8.8, 1.8 Hz, 1 H), 1.8–1.65 (m, 3 H), 1.63 (dd, J = 6.3, 1.5 Hz, 3 H), 1.55 (dd, J = 10.5, 1.9 Hz, 1 H), 1.42 (m, 1 H), 0.95 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 221.28, 128.24, 126.16, 59.78, 47.77, 45.09, 40.08, 30.89, 24.56, 23.35, 21.68, 18.29; MS m/z (M^+) calcd 178.1358, obsd 178.1356; $[\alpha]^{20}_D$ −42.7° (c 0.6, $CHCl_3$). Anal. Calcd for $C_{12}H_{18}O$: C, 80.84; H, 10.18. Found: C, 80.67; H, 10.26.

For **20a**: colorless oil; IR ($CHCl_3$, cm^{-1}) 2968, 2929, 1731, 1459; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (dq, J = 11.5, 6.8 Hz, 1 H), 5.56 (dd, J = 11.6, 1.2 Hz, 1 H), 2.18 (br s, 1 H), 2.13 (dt, J = 12.7, 1.8 Hz, 1 H), 1.85–1.75 (m, 5 H), 1.63 (dd, J = 6.6, 1.2 Hz, 3 H), 1.07 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 219.86, 127.74, 126.33, 58.07, 47.01, 45.09, 40.28, 31.66, 24.16, 23.33, 21.58, 14.69; MS m/z (M^+) calcd 178.1357, obsd 178.1335; $[\alpha]^{23}_D$ −23.2° (c 2.16, $CHCl_3$).

(1*R*)-3,3-Dimethyl-1-(2-methoxyethenyl)-2-norbornanone (19b and 20b). A cold (−78 °C), magnetically stirred slurry of (methoxymethyl)triphenylphosphonium bromide (14.67 g, 43.0 mmol) in dry ether (135 mL) was treated dropwise with *n*-butyllithium (26.8 mL of 1.6 M in hexane, 42.8 mmol). The reaction mixture was allowed to warm to 0 °C, stirred at that temperature for 30 min, and recooled to −78 °C, at which point a solution of **18** (9.41 g, 39.0 mmol) in cold (−78 °C) ether was introduced via cannula during 20 min. The resulting slurry was allowed to warm to room temperature overnight and filtered. The filtrate was washed with water (100 mL) and brine (3 × 100 mL), dried, filtered, and concentrated. Chromatography of the residual oil on silica gel (elution with 5% ethyl acetate in petroleum ether) provided 2.2 g (29%) of a yellow oil, ^1H NMR analysis of which showed it to be a 1:1 mixture of *E* and *Z* isomers.

A 1.0-g portion of this material was applied to a column of 10% silver nitrate on silica gel. Initial elution with 50% ether in petroleum ether gave **19b** (389 mg). Subsequent elution with ether furnished **20b** (289 mg).

For **19a**: colorless oil: IR (neat, cm^{-1}) 3060, 2970, 2830, 1735, 1655, 1470, 1385, 1330, 1280, 1225, 1140, 1020, 940; ^1H NMR (300 MHz, $CDCl_3$) δ 6.44 (d, J = 13.1 Hz, 1 H), 5.00 (d, J = 13.1 Hz, 1 H), 3.55 (s, 3 H), 2.18 (br s, 1 H), 1.95 (d, J = 8.6 Hz, 1 H), 1.90–1.45 (m, 5 H), 1.05 (s, 6 H); MS m/z (M^+) calcd 194.1307, obsd 194.1306. Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.20; H, 9.33. Found: C, 74.12; H, 9.39.

For **20b**: colorless oil; IR (neat, cm^{-1}) 3040, 2970, 2825, 1735, 1665, 1460, 1400, 1385, 1360, 1280, 1100, 1020, 970; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, J = 6.6 Hz, 1 H), 4.61 (d, J = 6.6 Hz, 1 H), 3.56 (s, 3 H), 2.17–2.06 (m, 2 H), 2.0–1.85 (m, 2 H), 1.80–1.65 (m, 2 H), 1.65–1.45 (m, 1 H), 1.050 (s, 3 H), 1.046 (s, 3 H); MS m/z (M^+) calcd 194.1307, obsd 194.1297.

2-Oxonorbornane-1-carbonyl Chloride (22). A mixture of **21** (1.004 g, 6.5 mmol), benzene (10 mL), oxalyl chloride (0.75 mL, 8.5 mmol), and dimethylformamide (1 microdrop) was stirred in the absence of moisture for 3 h at room temperature and concentrated on a rotary evaporator. The resulting brown oil was immediately subjected to bulb-to-bulb distillation. There was isolated 0.988 g (88%) of **22**, bp 115–118 °C at 0.2 Torr, as a pale yellow pungent oil: IR (neat, cm^{-1}) 2965, 2915, 2885, 1790, 1742, 1452, 1407, 1299, 1264, 1194, 1168, 1065, 1000, 856, 780, 700; ^1H NMR (300 MHz, $CDCl_3$) δ 2.67 (br s, 1 H), 2.34–2.19 (m, 2 H), 2.17–1.87 (m, 4 H), 1.54 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.96, 171.92, 72.47, 44.68, 42.19, 33.94, 27.89, 27.42; MS m/z (M^+) calcd 172.0291, obsd 172.0311.

2-Oxonorbornane-1-carboxaldehyde (23). A stirred slurry of bis(triphenylphosphine)copper borohydride (36.7 g, 0.061 mol) and triphenylphosphine (32.0 g, 0.122 mol) in acetone (150 mL) was cooled in an ice bath while a solution of **22** (9.98 g, 0.058 mol) in acetone (30 mL) was introduced in dropwise fashion. The reaction mixture was allowed to stir at room temperature for 1.5 h, filtered, and concentrated under reduced pressure. After overnight refrigeration, the impure product was slurried with pentane (80 mL) and decanted. This procedure was re-

peated four times, and the combined pentane layers were evaporated to give **23**, which was used directly in the next step. A small amount was purified by preparative GC (5% SE-30 on Chromosorb W, 130 °C, 1.5 m): colorless oil; IR ($CHCl_3$, cm^{-1}) 2980, 1760, 1720, 1400, 1300, 1047; ^1H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1 H), 2.76 (br s, 1 H), 2.28 (dd, J = 20.0, 3.0 Hz, 1 H), 2.00 (m, 3 H), 1.80 (m, 2 H), 1.59 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.54, 200.57, 67.91, 45.78, 39.49, 34.80, 27.76, 26.09; MS m/z (M^+) calcd 138.0681, obsd 138.0709. Anal. Calcd for $C_8H_{10}O_2$: C, 69.53; H, 7.30. Found: C, 69.16; H, 7.42.

1-Vinyl-2-norbornanone (24). (NOTE: The product formed in this reaction is quite volatile. Special attention must be paid to those solvents used for the reaction proper and for the chromatographic purification. Solvent evaporation was invariably performed at atmospheric pressure.)

A 500-mL, round-bottomed flask was charged with methyltriphenylphosphonium bromide (24.9 g, 0.070 mol) and heated at 110 °C and 0.2 Torr for several hours to achieve drying. Following return to room temperature, dry ether (150 mL) was added, the stirred slurry was cooled to 0 °C, and *n*-butyllithium (46.7 mL of 1.49 M in hexane, 0.070 mol) was introduced via syringe during 15 min. The ylide was allowed to form for 1 h before use. A cold (−78 °C) solution of unpurified **23** (from reduction of 0.07 mol of **22**) in anhydrous ether (150 mL) was treated with the ylide as transferred through a wide-bore cannula. A white precipitate formed immediately; the addition was continued until the yellow color of excess ylide persisted for 20 min. The reaction was allowed to warm to room temperature overnight and filtered. The filter cake was triturated with 100 mL of petroleum ether, and the combined filtrates were washed with water (3 × 75 mL), dilute sodium bicarbonate solution (2 × 75 mL), and brine (2 × 75 mL) prior to drying and solvent removal. The residual yellow oil was applied to a column of TLC mesh silica gel (elution with 10% ether in petroleum ether), the eluate was refrigerated to induce precipitation of residual triphenylphosphine, and the concentrate was purified by preparative GC (5% SE-30 on Chromosorb W, 170 °C, 11 ft × 0.25 in.) on an as-need basis: colorless oil; IR ($CHCl_3$, cm^{-1}) 2965, 2865, 1735, 1640, 1454, 1408, 1175, 1000, 914; ^1H NMR (300 MHz, $CDCl_3$) δ 6.13 (dd, J = 17.5, 10.9 Hz, 1 H), 5.20 (br t, J = 15 Hz, 2 H), 2.63 (br s, 1 H), 2.19 (dt, J = 20.6, 2.8 Hz, 1 H), 2.15–2.00 (m, 3 H), 1.75–1.50 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 216.21, 134.89, 115.95, 60.33, 45.90, 42.20, 34.14, 30.01, 28.46; MS m/z (M^+) calcd 136.0888, obsd 136.0895. Anal. Calcd for $C_9H_{12}O$: C, 79.36; H, 8.89. Found: C, 79.24; H, 8.88.

1-(2-Methoxyethenyl)-2-norbornanone (25 and 26). A 5.05-g (0.0293 mol) sample of **22** was reduced to the keto aldehyde with use of $(Ph_3P)_2CuBH_4$ as described earlier. The unpurified **23** was dissolved in anhydrous ether (150 mL) and tetrahydrofuran (50 mL), cooled to −78 °C, and treated with the ylide derived from (methoxymethyl)triphenylphosphonium bromide (15.07 g, 0.0439 mol) in the predescribed manner. Following the usual workup, the product was initially purified by rapid passage through a column of silica gel (elution with 8% ethyl acetate in petroleum ether): 0.91 g of a 1:1 mixture of **25** and **26** was obtained (^1H NMR analysis). The isomers were separated by MPLC (silica gel, elution with 6.5% ethyl acetate in petroleum ether). The less polar isomer was **26** (0.41 g) and the more polar was **25** (0.38 g). The respective isolated yields (based on **22**) are 8.4 and 7.7%, respectively.

For **25**: colorless oil; IR (neat, cm^{-1}) 2953, 2875, 1733, 1649, 1220, 1169; ^1H NMR (300 MHz, $CDCl_3$) δ 6.45 (d, J = 13.1 Hz, 1 H), 5.00 (d, J = 13.1 Hz, 1 H), 3.56 (s, 3 H), 2.61 (m, 1 H), 2.15 (m, 1 H), 2.08–1.82 (m, 3 H), 1.78–1.50 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.67, 148.05, 99.14, 56.34, 55.52, 45.59, 42.94, 33.83, 31.16, 28.38; MS m/z (M^+) calcd 166.0994, obsd 166.0985.

For **26**: colorless oil; IR (neat, cm^{-1}) 2980, 2904, 1741, 1666, 1458, 1406, 1286, 1181, 1108, 1064, 974 741; ^1H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, J = 6.6 Hz, 1 H), 4.60 (d, J = 6.6 Hz, 1 H), 3.56 (s, 3 H), 2.55 (m, 1 H), 2.12 (dt, J = 19.0, 2.1 Hz, 1 H), 2.0–1.80 (m, 4 H), 1.60–1.45 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.48, 148.36, 101.25, 59.72, 56.11, 45.12, 42.60, 34.30, 30.42, 28.27; MS m/z (M^+) calcd 166.0994, obsd 166.0985. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.49. Found: C, 72.31; H, 8.55.

Anionic Oxy-Cope Rearrangement of 28. To a solution of potassium *tert*-butoxide (1.1 g, 9.8 mmol) in anhydrous tetrahydrofuran (10 mL) was added **28**[7h] (284 mg, 1.2 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at room temperature for 17 h and heated at reflux for 2 h. Following return to 20 °C, the contents were poured onto ice (25 g). The separated aqueous layer was extracted with ether (4 × 20 mL), and the combined organic phases were washed with brine (2 × 25 mL), dried, and concentrated. The residue was subjected to chromatography on silica gel (TLC grade) with use of 7% ethyl acetate in petroleum ether as eluent. Following collection of the colorless highly crystalline **29** (100 mg, 35%), ketone **30** was isolated as a colorless oil that slowly crystallized (76 mg, 28%). The sample of **29**, mp 117–118 °C, was identical with that reported earlier.[7h]

For **30**: mp 49–51 °C (no recrystallization); IR ($CHCl_3$, cm^{-1}) 2960, 2880, 1680, 1468, 1458, 1395, 1374, 1343, 1310, 1225, 1170, 1088, 1051, 1041, 1000, 872, 672; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26–5.20 (m, 1 H), 2.62 (ddd, J = 10.8, 10.7, 7.3 Hz, 1 H), 2.46–1.02 (series of m, 16 H), 1.09 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 220.55, 145.40, 116.27, 52.49, 51.77, 45.31, 42.09, 34.59, 32.50, 30.28, 30.27, 28.36, 27.81, 26.55, 22.70, 21.42; MS m/z (M^+) calcd 232.1827, obsd 232.1846; $[\alpha]^{20}_D$ +19.7° (c 1.01, $CHCl_3$).

Epimerization of 29. A flame-dried, 10-mL, round-bottomed flask was charged with potassium hydride (25% oil dispersion, 11 mg, 0.067 mmol), and the oil was removed by washing with pentane (3 × 1 mL). The oil-free potassium hydride was suspended in anhydrous tetrahydrofuran (0.5 mL), and a solution of **29** (13 mg, 0.056 mmol) and 18-crown-6 (17.7 mg, 0.967 mol) in the same solvent (1 mL) was introduced at room temperature. The reaction mixture was stirred for 2 h, quenched with saturated ammonium chloride solution (2 mL), and transferred to a separatory funnel containing more NH_4Cl solution (10 mL) and petroleum ether (2 × 10 mL). The aqueous fraction was extracted with petroleum ether (2 × 10 mL), and the combined organic phases were washed with brine (2 × 10 mL), dried, and evaporated. Direct ^1H NMR analysis of the residual oil showed **29** and **30** to be present in a 2:1 ratio.

Alcohol 31. A cold (−78 °C), magnetically stirred solution of 1-iodocyclopentene (111 mg, 0.573 mmol, purified by passage through neutral alumina) in anhydrous tetrahedrofuran (2 mL) was treated dropwise with *tert*-butyllithium (0.34 mL of 1.7 M in pentane, 0.573 mmol) and allowed to stir for 30 min. A solution of **19a** (34 mg, 0.191 mmol) in dry tetrahydrofuran (4 mL) was introduced at −78 °C, and warming to room temperature was immediately allowed to occur. Saturated ammonium chloride solution (10 mL) was added, the separated aqueous phase was extracted with ether (4 × 5 mL), and the combined organic solutions were washed with brine (2 × 5 mL), dried, and concentrated. MPLC purification of the residue (silica gel, elution with 5% ether in petroleum ether) afforded 27.2 mg of **31** as a colorless oil and 9 mg of recovered **19a**. The yield based on this level of recovery was 79%: IR (neat, cm^{-1}) 3580, 3493, 2920, 2870, 1470, 1385, 1365, 1320, 1299, 1041, 967, 800; ^1H NMR (300 MHz, C_6D_6) δ 5.67 (dd, J = 15.7, 1.5 Hz, 1 H), 5.56 (quintet, J = 2.1 Hz, 1 H), 5.37 (dq, J = 15.7, 6.3 Hz, 1 H), 2.43 (tt, J = 9.8, 2.5 Hz, 1 H), 2.33 (m, 2 H), 2.20 (m, 2 H), 1.95 (dq, J = 10.3, 2.1 Hz, 1 H), 1.84–1.61 (m, 4 H), 1.59 (dd, J = 6.3, 1.6 Hz, 3 H), 1.40 (m, 2 H), 1.22 (m, 2 H), 1.08 (s, 3 H), 0.92 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.47, 134.42, 126.61, 122.65, 83.41, 58.85, 49.34, 45.46, 39.02, 36.08, 32.15, 31.67, 28.57, 25.01, 24.39, 22.47, 18.43; MS m/z (M^+) calcd 246.1984, obsd 246.1999; $[\alpha]^{21}_D$ +8.3° (c 1.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.87; H, 10.78.

Anionic Oxy-Cope Rearrangement of 31. To a flame-dried, 10-mL, round-bottomed flask was added **31** (27.2 mg, 0.11 mmol), 18-crown-6 (32.1 mg, 0.12 mmol), and dry tetrahydrofuran (2 mL). With stirring at room temperature, a solution of potassium hexamethyldisilazide (0.24 mL of 0.5 M in toluene, 0.12 mmol) was introduced dropwise. Stirring was continued for an additional 10 min before the predescribed workup was implemented. MPLC of the residual oil (silica gel, elution with 2% ethyl acetate in petroleum ether) furnished **32** (22.7 mg, 83%) as a colorless crystalline solid, mp 121–122 °C (from ethanol): IR ($CHCl_3$, cm^{-1}) 2960, 2865, 1677, 1450, 1375, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 4.90 (d, J = 9.8 Hz, 1 H), 3.42 (t, J = 5.7 Hz, 1 H), 2.85 (septet, J = 3.3 Hz, 1 H), 2.72 (d, J = 12.1 Hz, 1 H), 2.11–1.75 (m, 9 H), 1.71–1.57 (m, 3 H), 1.35 (s, 3 H), 1.02 (d, J = 6.9 Hz, 1 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 222.46, 141.13, 125.35, 56.14, 49.55, 48.45, 48.22, 33.81, 31.64 (2 C), 31.17, 27.87, 25.24, 23.27, 22.28, 22.20, 20.31; MS m/z (M^+) calcd 246.1984, obsd 246.1976; $[\alpha]^{23}_D$ +12.7° (c 1.7, $CDCl_3$). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.54; H, 10.66.

Alcohol 33. A 337 mg (1.736 mmol) sample of **27** was converted to its lithium derivative (1.0 mL of 1.7 M *tert*-butyllithium in pentane, 1.736 mmol) and condensed with **20a** (103 mg, 0.579 mmol) as described above. Following the usual workup, the residue was purified by MPLC on silica gel (elution with 5% ether in petroleum ether) to give 112 mg (79%) of **33** as a faintly yellow oil: IR (neat, cm^{-1}) 3505, 2925, 2865, 1465, 1388, 1367, 1300, 1045, 965, 800; ^1H NMR (300 MHz, C_6D_6) δ 5.58 (t, J = 1.8 Hz, 1 H), 5.46 (d, J = 12.7 Hz, 1 H), 5.34 (dq, J = 11.9, 6.9 Hz, 1 H), 2.45 (dt, J = 8.1, 2.2 Hz, 1 H), 2.40–2.15 (m, 4 H), 2.05 (dd, J = 10.7, 2.1 Hz, 1 H), 1.77–1.68 (m, 6 H), 1.66 (dd, J = 6.8, 1.3 Hz, 3 H), 1.37 (dd, J = 7.5, 1.9 Hz, 2 H), 1.07 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.67, 133.05, 126.25, 122.35, 84.27, 58.42, 49.83, 44.26, 39.94, 35.77, 32.16, 30.63, 28.52, 24.72, 24.33, 22.46, 14.53; MS m/z (M^+) calcd 246.1983, obsd 246.1985; $[\alpha]^{23}_D$ +23.5° (c 1.88, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.83; H, 10.60.

Anionic Oxy-Cope Rearrangement of 33. A solution of **33** (21 mg,

0.085 mmol) and 18-crown-6 (24.8 mg, 0.094 mmol) in dry tetrahydrofuran was treated with 0.0939 mmol of potassium hexamethyldisilazide at room temperature. The complete consumption of starting material required 1.5 h. The usual workup was followed by MPLC on silica gel (elution with 2.2% ethyl acetate in petroleum ether) to give 13 mg (62%) of **34** and 2 mg (9.5%) of the α-carbonyl epimer.

For **34**: colorless crystals, mp 134–135 °C; IR ($CHCl_3$, cm^{-1}) 2960, 1670, 1450; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (d, J = 8, 9 Hz, 1 H), 2.85 (m, 1 H), 2.81 (d, J = 12.5 Hz, 1 H), 2.68 (quintet, J = 4.7 Hz, 1 H), 2.2 (m, 2 H), 1.94 (m, 5 H), 1.8–1.55 (m, 6 H), 1.39 (s, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.24, 143.12, 127.35, 56.09, 50.96, 50.05, 49.92, 33.93, 33.40, 32.31, 31.79, 26.50, 26.29, 25.40, 22.51, 21.36, 19.09; MS m/z (M^+) calcd 246.1984, obsd 246.2031; $[\alpha]^{20}_D$ +54.2° (c 0.24, $CHCl_3$).

Alcohol 35. From 591 mg (3.05 mmol) of **27**, 1.8 mL of 1.7 M *tert*-butyllithium in pentane (3.05 mmol), and 197 mg (1.02 mmol) of **19b** that were reacted in the predescribed manner, MPLC on silica gel (elution with 4% ethyl acetate in petroleum ether) afforded 218 mg (86%) of **35**: IR (neat, cm^{-1}) 3500, 3060, 2930, 1650, 1465, 1390, 1365, 1220, 1160, 1050, 940; ^1H NMR (300 MHz, C_6D_6) δ 6.37 (d, J = 13 Hz, 1 H), 5.59 (quintet, J = 1.9 Hz, 1 H), 4.99 (d, J = 13 Hz, 1 H), 3.18 (s, 3 H), 2.40 (m, 2 H), 2.30 (m, 1 H), 2.20 (m, 2 H), 1.94 (dd, J = 4.2, 2.2 Hz, 1 H), 1.85–1.60 (m, 4 H), 1.40 (tt, J = 12.4, 4.6 Hz, 1 H), 1.35–1.15 (m, 4 H), 1.07 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 149.59, 147.05, 126.69, 105.69, 83.88, 55.82, 55.31, 49.29, 45.24, 39.49, 36.21, 32.07, 31.82, 28.69, 25.07, 24.54, 22.54; MS m/z (M^+) calcd 262.1932, obsd 262.1927; $[\alpha]^{23}_D$ –6.9° (c 1.3, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O$: C, 77.81; H, 9.99. Found: C, 77.76; H, 10.10.

Anionic Oxy-Cope Rearrangement of 36. A solution of **36** (72.3 mg, 0.276 mmol) and potassium hexamethyldisilazide (0.6 mL of 0.5 M in toluene, 0.304 mmol) in anhydrous tetrahydrofuran (5 mL) was stirred at room temperature for 5.5 h and worked up as before. Purification by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) afforded 63.6 mg (88%) of **36** as colorless crystals, mp 63–64.5 °C (from ethanol): IR ($CHCl_3$, cm^{-1}) 3117, 1680, 1107, 1086; ^1H NMR (300 MHz, C_6D_6) δ 5.26 (d, J = 8.2 Hz, 1 H), 4.13 (dd, J = 8.7, 3.2 Hz, 1 H), 3.24 (s, 3 H), 3.08 (t, J = 5.1 Hz, 1 H), 2.45–2.15 (m, 3 H), 2.15–1.95 (m, 4 H), 1.80 (m, 1 H), 1.65–1.4 (m, 6 H), 1.03 (s, 3 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 219.70, 144.38, 122.60, 79.33, 56.30, 54.05, 49.40, 47.89, 46.67, 32.19, 31.89, 31.25, 27.58, 25.60, 23.56, 23.16, 22.72; MS m/z (M^+) calcd 262.1932, obsd 262.1914; $[\alpha]^{23}_D$ –8.8° (c 6.5, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.80; H, 10.01.

Hydrogenation of 36. A solution of **36** (11.7 mg, 0.045 mmol) in tetrahydrofuran (2 mL) was admixed with 10 mg of 10% palladium on carbon and magnetically stirred overnight under 40 psi of hydrogen. The catalyst was separated by filtration through Celite, the filtrate was concentrated, and the solid residue was purified by MPLC (silica gel, elution with 5% ethyl acetate in petroleum ether) to give **37** (13.0 mg, 100%) as colorless crystals, mp 103–105 °C (from methanol): IR ($CHCl_3$, cm^{-1}) 2945, 2870, 1678, 1458, 1093, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 3.43 (br t, 2 H), 3.29 (s, 3 H), 2.41 (m, 1 H), 2.02 (quintet, J = 6.3 Hz, 1 H), 1.95 (m, 2 H), 1.77 (br dd, J = 17, 2 Hz, 2 H), 1.71 (m, 3 H), 1.64 (m, 4 H), 1.48 (m, 2 H), 1.36 (s, 3 H), 1.25 (m, 2 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 221.89, 80.77, 56.29, 51.72, 51.03, 48.16, 47.12, 38.95, 33.19, 32.49, 30.76, 30.14, 26.79, 25.30, 24.85, 22.81, 21.73; MS m/z (M^+) calcd 265.2089, obsd 264.2099; $[\alpha]^{23}_D$ +34.9° (c 0.7, $CHCl_3$).

Alcohol 38. A 426-mg (2.20 mmol) sample of **27** was converted to its lithium derivative (4.4 mmol) and condensed with **20b** (142 mg, 0.73 mmol) in the usual way. Purification by silica gel chromatography (elution with 5% ethyl acetate in petroleum ether) furnished 144 mg (75%) of **38** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3360, 2980, 2930, 2840, 1650, 1450, 1380, 1270, 1115, 1080, 955; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 6.6 Hz, 1 H), 5.55 (br s, I H), 4.57 (d, J = 6.6 Hz, 1 H), 3.50 (s, 1 H), 3.38 (s, 3 H), 2.30 (m, 3 H), 2.23 (m, 2 H), 2.01 (dd, J = 10.2. 2.0 Hz, 1 H), 1.80–1.57 (m, 4 H), 1.33 (tt, J = 12.5, 4.7 Hz, 1 H), 1.25 (d, J = 9.2 Hz, 1 H), 1.09 (dt, J = 12.4, 4.2 Hz, 1 H), 0.94 (s, 3 H), 0.84 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 150.18, 144.80, 125.24, 111.38, 83.10, 58.87, 56.63, 49.39, 45.67, 41.70, 36.23, 32.27, 30.63, 28.78, 24.97, 24.51, 22.59; MS m/z (M^+) calcd 262.1932, obsd 262.1952; $[\alpha]^{23}_D$ –5.6° (c 2.84, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.99. Found: C, 77.73; H, 10.02.

Rearrangement–S_N' Displacement within 38. A solution of **38** (76.1 mg, 0.29 mmol) in dry tetrahydrofuran (6 mL) was treated dropwise with potassium hexamethyldisilazide (0.64 mL of 0.5 M in toluene, 0.32 mmol) and stirred at room temperature for 4 days under an atmosphere of nitrogen. Following the usual workup, purification was achieved by MPLC (silica gel, elution with 4% ethyl acetate in petroleum ether) to give 34.0 mg (51%) of **40** as colorless crystals, mp 80–80.5 °C (from ethanol): IR ($CHCl_3$, cm^{-1}) 2925, 2868, 1692, 1470, 1460, 1448, 1387, 1230; ^1H NMR (300 MHz, C_6D_6) δ 5.49 (dd, J = 5.8, 2.0 Hz, 1 H), 5.18 (dd, J = 5.8, 1.5 Hz, 1 H), 3.33 (d, J = 6.4 Hz, 1 H), 2.15 (d, J = 11.9 Hz, 1 H), 2.05 (m, 1 H), 1.85 (m, 1 H), 1.74 (t, J = 4.6 Hz, 1 H), 1.35 (m, 5 H), 1.18 (quintet, J = 5.1 Hz, 1 H), 1.11 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 217.55, 136.07, 134.16, 72.06, 59.42, 51.87, 49.49, 48.96, 34.62, 34.25, 33.47, 30.34, 28.99, 25.40, 25.30, 24.45; MS m/z (M^+) calcd 230.1670, obsd 230.1665; $[\alpha]^{23}_D$ +71.3° (c 3.6, $CHCl_3$).

Alcohol 41. Cerium trichloride heptahydrate (526 mg, 1.41 mmol) was placed in a 50-mL, three-necked flask fitted with a magnetic stirring bar and heated at 150 °C and 0.05 Torr for 2 h. After cooling to room temperature, dry tetrahydrofuran (15 mL) was added, and the slurry was stirred overnight at 20 °C. In a separate flask, a solution of **27** (270 mg, 1.41 mmol) in the same solvent (4 mL) was cooled to –78 °C and treated dropwise with *tert*-butyllithium (1.65 mL of 1.7 M in pentane, 2.82 mmol). After 30 min of stirring at this temperature, the vinyl anion solution was transferred via cannula to the precooled (–78 °C) cerium trichloride slurry. The vinyl cerate was allowed to form during 2 h at –78 °C, at which point a freshly purified (preparative GC) sample of **24** (120 mg, 0.88 mmol) in anhydrous tetrahydrofuran (14 mL) was slowly added. After 2 h, methanol (58 μL, 1.41 mmol) was introduced via syringe, followed 30 min later with a preformed solution of 1-lithiocyclopentene (1.44 mmol). After 2 h had elapsed, this process was repeated, and the reaction mixture was then allowed to warm *slowly* to room temperature overnight. Once recooled to 0 °C, saturated ammonium chloride solution (10 mL) was added, and the separated aqueous phase was extracted with ether (4 × 30 mL). The combined organic layers were washed with brine, dried, and concentrated in vacuo. The residue was purified by MPLC on silica gel (elution with 10% ether in petroleum ether) to give **41** (136 mg, 76%) as a colorless oil: IR (CCl_4, cm^{-1}) 3608, 3590, 3080, 2945, 2865, 2845, 1635, 1449, 1418, 1272, 1085, 1042, 1010, 960, 915, 780, 685; ^1H NMR (300 MHz, C_6D_6) δ 6.03 (dd, J = 17.4, 10.7 Hz, 1 H), 5.38 (t, J = 1.8 Hz, 1 H), 5.00 (dd, J = 17.4, 2.0 Hz, 1 H), 4.96 (dd, J = 10.7, 2.0 Hz, 1 H), 2.41 (m, 1 H), 2.35–2.15 (m, 5 H), 2.22 (dd, J = 5.0, 2.7 Hz, 2 H), 1.82–1.67 (m, 3 H), 1.63 (m, 1 H), 1.45 (m, 1 H), 1.36–1.23 (m, 3 H); ^{13}C NMR (20 MHz, C_6D_6) ppm 151.31, 140.05, 125.04, 113.24, 81.19, 58.93, 47.47, 42.08, 36.47, 34.12, 32.53, 30.04, 28.92, 24.44; MS m/z (M^+) calcd 204.1514, obsd 204.1515. Anal. Calcd for $C_{14}H_{20}O$: C, 82.29; H, 9.87. Found: C, 82.14; H, 9.85.

Anionic Oxy-Cope Rearrangement of 41. A solution of **41** (15.3 mg, 0.075 mmol) and 18-crown-6 (24 mg, 0.090 mmol) in tetrahydrofuran (2 mL) was stirred at room temperature, while a solution of potassium hexamethyldisilazide (0.18 mL of 0.5 M in toluene, 0.090 mmol) was added dropwise. The reaction mixture was stirred for 1 h, quenched with saturated ammonium chloride solution (5 mL), and worked up as before. MPLC purification of the residual oil (silica gel, elution with 12% ether in petroleumether) gave 4.0 mg (26%) of **42** and 6.0 mg (40%) of **43**.

For **42**: mp 59–60 °C; IR ($CHCl_3$, cm^{-1}) 2940, 2872, 1683, 1455, 1155, 1045; ^1H NMR (300 MHz, $CDCl_3$) δ 5.24 (br t, J = 8.1 Hz, 1 H), 2.87 (dd, J = 9.7, 5.5 Hz, 1 H), 2.69 (m, 1 H), 2.64 (d, J = 16.4 Hz, 1 H), 2.63 (m, 1 H), 2.49 (m, 2 H), 2.16 (m, 1 H), 2.11–1.90 (m, 6 H), 1.90–1.80 (m, 2 H), 1.72–1.50 (m, 4 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 218.49, 144.03, 121,25, 56.52, 50.51, 48.29, 36.05, 33.82, 30.85, 29.26, 28.93, 28.54, 27.23, 22.07; MS m/z (M^+) calcd 204.1514, obsd 204.1497. Anal. Calcd for $C_{14}H_{20}O$: C, 82.29; H, 9.87. Found: C, 81.87; H, 9.86.

For **43**: amorphous solid; IR ($CHCl_3$, cm^{-1}) 2930, 2855, 1675, 1451, 1440; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (dd, J = 8.3, 6.5 Hz, 1 H), 2.77 (m, 1 H), 2.60 (dd, J = 11.3, 4.0 Hz, 2 H), 2.49 (br d, J = 12.5 Hz, 2 H), 2.31 (m, 1 H), 2.12 (br d, J = 9.7 Hz, 2 H), 2.09–1.87 (m, 4 H), 1.83–1.64 (m, 4 H), 1.50 (m, 1 H), 1.25 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.29, 145.19, 124.32, 61.55, 45.88, 42.35, 36.85, 36.29, 33.99, 31.26, 30.39, 29.40, 26.60, 24.50; MS m/z (M^+) calcd 204.1514, obsd 204.1516.

Epimerization of 42. A solution of **42** (10 mg, 0.049 mmol) and 18-crown-6 (15.5 mg, 0.059 mmol) in dry tetrahydrofuran (1 mL) was added to a magnetically stirred slurry of potassium hydride (10 mg of 25% oil dispersion prewashed with pentane, 0.059 mmol) in the same solvent (0.5 mL). After 2 h at room temperature, saturated ammonium chloride solution was introduced, and the product was partitioned between ether (10 mL) and additional NH_4Cl solution (10 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 5 mL). The combined organic solutions were washed with brine (2 × 5 mL), dried, and concentrated in vacuo. Analysis of the residue by 300 MHz ^1H NMR spectroscopy showed the ratio of **42**:**43** to be 2:1 by integration of their respective olefinic signals at δ 5.25 and 5.35.

Epoxidation of 42. A cold (0 °C), magnetically stirred mixture of **43**

(26.5 mg, 0.13 mmol), monobasic sodium phosphate hydrate (20 mg, 0.21 mmol), dibasic sodium phosphate (25 mg, 0.21 mmol), and methylene chloride (2 mL) was treated with *m*-chloroperbenzoic acid (27 mg, 0.16 mmol) in one portion. After 1 h, an additional 27 mg of MCPBA was added, and stirring was maintained for an additional 60 min. Following quenching with saturated sodium thiosulfate solution (5 mL), the reaction mixture was poured into water (5 mL) and ether (5 mL), and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic solutions were washed with sodium bicarbonate solution (2 × 10 mL) and brine (2 × 10 mL), dried, and evaporated. The residue was purified by chromatography on TLC grade silica gel (elution with 35% ethyl acetate in petroleum ether) to give 28 mg (98%) of **44** as colorless crystals, mp 44–45 °C (from hexane): IR ($CHCl_3$, cm^{-1}) 3010, 2975, 2950, 2877, 1691, 1453, 1380, 1370, 1309, 1240–1210, 1131, 1103, 1050, 895; ^1H NMR (300 MHz, $CDCl_3$) δ 3.05 (m, 1 H), 2.79 (m, 2 H), 2.56 (m, 1 H), 2.30 (m, 2 H), 2.18 (dt, J = 11.9, 3.6 Hz, 2 H), 2.13–1.97 (m, 4 H), 1.95–1.73 (m, 3 H), 1.73–1.48 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 219.81, 69.22, 64.00, 55.86, 49.61, 44.25, 36.55, 32.57, 30.65, 30.17, 29.61, 28.98, 27.31, 22.96; MS m/z (M^+) calcd 220.1463, obsd 220.1478.

Alcohol 45. 1-Iodocyclopentene (367 mg, 1.93 mmol) was treated with *tert*-butyllithium (2.3 mL of 1.7 M in pentane, 3.86 mmol) at −78 °C in tetrahydrofuran (4 mL) and transferred via cannula to a slurry of dried cerium trichloride (1.932 mmol) in the same solvent (10 mL). The vinyl cerate was allowed to form for 40 min before a solution of **25** (200 mg, 1.20 mmol) in dry tetrahydrofuran (4 mL) was introduced dropwise. Stirring was continued at −78 °C for 2 h before methanol (80 μL) was added, followed 30 min later by an additional 1.93 mmol of freshly prepared 1-lithiocyclopentene. This process was repeated 2 h later, and the reaction mixture was allowed to warm slowly to room temperature overnight. Following application of the predescribed workup and MPLC purification (silica gel, elution with 6.5% ethyl acetate in petroleum ether), there was obtained 129.5 mg (46%) of **45** as a colorless oil: IR (CCl_4, cm^{-1}) 3615, 2950, 2857, 2843, 1650, 1453, 1310, 1215, 1170, 1134, 1095, 943, 742; ^1H NMR (300 MHz, C_6D_6) δ 6.32 (d, J = 12.9 Hz, 1 H), 5.36 (t, J = 1.9 Hz, 1 H), 4.92 (d, J = 12.9 Hz, 1 H), 3.18 (s, 3 H), 2.37–2.21 (m, 5 H), 2.07 (m, 2 H), 1.81–1.59 (m, 5 H), 1.49 (m, 1 H), 1.37–1.15 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 151.93, 146.97, 124.96, 103.81, 81.34, 55.23, 55.04, 47.32, 42.89, 36.25, 34.22, 32.62, 30.26, 29.39, 24.61; MS m/z (M^+) calcd 234.1620, obsd 234.1608. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.93; H, 9.48.

Alcohol 46. Reaction of **26** (200 mg, 1.20 mmol) with 1-lithiocyclopentene and anhydrous cerium trichloride in a manner entirely comparable to that described above afforded 66 mg (62%) of **46** (92% based on recovered **26**) as a colorless oil: IR (CCl_4, cm^{-1}) 3513, 2948, 2868, 2848, 1658, 1453, 1278, 1263, 1108, 1098, 1030, 963; ^1H NMR (300 MHz, C_6D_6) δ 5.72 (br s, 1 H), 5.42 (d, J = 6.5 Hz, 1 H), 4.53 (d, J = 6.5 Hz, 1 H), 3.38 (br s, 1 H), 2.87 (s, 3 H), 2.82 (m, 1 H), 2.44 (m, 2 H), 2.31 (m, 2 H), 2.08 (br s, 1 H), 2.00–1.79 (m, 4 H), 1.68 (m, 3 H), 1.43 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 152.37, 146.39, 123.25, 108.90, 81.37, 58.98, 55.21, 46.78, 45.17, 36.82, 34.20, 32.42, 30.78, 29.87, 24.67; MS m/z ($M^+ - H_2O$) calcd 216.1514, obsd 216.1465. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.90; H, 9.59.

Anionic Oxy-Cope Rearrangement of 45. A solution of **45** (75 mg, 0.43 mmol) and 18-crown-6 (137 mg, 0.52 mmol) in anhydrous tetrahydrofuran (5 mL) was treated at room temperature with potassium hexamethyldisilazide (1.0 mL of 0.5 M in toluene, 0.50 mmol). Isomerization was judged to be complete (TLC analysis) after 30 min. The usual workup provided a residue that was purified by MPLC on silica gel (elution with 6.5% ethyl acetate in petroleum ether). There was isolated 3 mg (3%) of **49** as a 3:1 isomeric mixture, 18.9 mg (25%) of **47a**, and 21.1 mg (28%) of **48a** in addition to a mixed fraction of **47a** and **48a** (11.3 mg). The overall yield was 71%.

For **49**: IR ($CHCl_3$, cm^{-1}) 3005, 2945, 2865, 1690, 1452, 1422, 1355, 1335, 1220, 815; ^1H NMR (300 MHz, C_6D_6) δ 5.37 and 5.35 (m, 1 H), 5.26 and 5.20 (m, 1 H), 3.49 (br m, 1 H), 3.42 (d, J = 7.7 Hz, 1 H), 2.38 (d, J = 3.5 Hz) and 2.32 (d, J = 6.7 Hz) (1 H total), 2.15–1.85 (m, 2 H), 1.85–1.65 (m, 3 H), 1.65–1.35 (m, 3 H), 1.35–1.10 (m, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.00, 210.12, 135.34, 134.77, 134.50, 134.44, 72.99, 68.88, 60.61, 58.67, 54.15, 48.42, 47.69, 46.17, 43.40, 39.72, 36.05, 35.28, 34.99, 33.39, 32.40, 31.95, 31.47, 31.27, 30.12, 29.10, 25.76, 25.16; MS m/z (M^+) calcd 202.1358, obsd 202.1333. Anal. Calcd for $C_{14}H_{18}O$: C, 83.11; H, 8.97. Found: C, 82.81; H, 9.06.

For **47a**: colorless crystals, mp 78.5–79 °C; IR ($CHCl_3$, cm^{-1}) 3005, 2973, 2945, 2873, 1687, 1450, 1105, 1081; ^1H NMR (300 MHz, C_6D_6) δ 5.27 (d, J = 9.2 Hz, 1 H), 4.19 (dd, J = 9.2, 4.3 Hz, 1 H), 3.21 (s, 3 H), 2.61 (t, J = 5.8 Hz, 1 H), 2.36 (m, 1 H), 2.25 (d, J = 12.5 Hz, 1 H), 2.18 (m, 2 H), 2.15–1.87 (m, 6 H), 1.78 (dd, J = 9.1, 4.0 Hz, 2 H), 1.69–1.50 (m, 3 H), 1.42 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 217.31, 145.01, 123.78, 79.15, 56.33, 54.87, 54.29, 35.09, 34.27 (2 C), 31.66, 31.14, 27.57, 23.25, 22.82; MS m/z (M^+) calcd 234.1620, obsd 234.1664. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.82; H, 9.48.

For **48a**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3004, 2942, 2874, 1675, 1449, 1108, 1090; ^1H NMR (300 MHz, C_6D_6) δ 5.32 (dd, J = 4.7, 1.1 Hz, 1 H), 3.92 (m, 1 H), 3.11 (s, 3 H), 2.75 (m, 1 H), 2.66 (m, 1 H), 2.21 (m, 2 H), 2.05 (m, 5 H), 1.74 (dd, J = 11.4, 4.9 Hz, 1 H), 1.62 (m, 7 H), 1.25 (br q, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.11, 143.27, 130.51, 77.63, 57.65, 56.72, 50.45, 42.16, 36.92, 36.07, 29.70, 26.73, 26.16, 25.04; MS m/z (M^+) calcd 234.1619, obsd 234.1594. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.86; H, 9.47.

Epoxidation of 47a. An 18.1-mg (0.077 mmol) sample of **47a** was subjected to phosphate-buffered epoxidation in the predescribed manner. Following flash chromatography on silica gel (elution with 20% ethyl acetate in petroleum ether), there was obtained 15.6 mg (81%) of **50** as a colorless, crystalline solid, mp 78–80 °C (from ethanol): IR ($CHCl_3$, cm^{-1}) 3002, 2947, 2867, 1692, 1465, 1446, 1376, 1220, 1125, 1107, 1087, 1080, 1046; ^1H NMR (300 MHz, C_6D_6) δ 3.50 (s, 3 H), 3.11 (dd, J = 8.7, 4.1 Hz, 1 H), 2.98 (d, J = 8.7 Hz, 1 H), 2.49 (t, J = 5.6 Hz, 1 H), 2.16 (m, 2 H), 2.10–1.83 (m, 4 H), 1.83–1.72 (m, 4 H), 1.64 (m, 1 H), 1.60–1.40 (m, 2 H), 1.40–1.30 (m, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 217.64, 80.93, 66.10 (2 C), 58.12, 53.41, 50.80, 50.01, 36.77, 33.46, 31.02, 30.14, 27.98, 24.82, 22.42; MS m/z (M^+) calcd 250.1569, obsd 250.1588.

Anionic Oxy-Cope Rearrangement of 46. A solution of **46** (60.7 mg, 0.260 mmol) and 18-crown-6 (82 mg, 0.311 mmol) in anhydrous tetrahydrofuran (5 mL) was treated with potassium hexamethyldisilazide (0.62 mL of 0.5 M in toluene, 0.311 mmol) and stirred for 1 h, at which point an additional 0.1 mmol of base was added. Forty minutes later, the usual workup was initiated. The crude product was purified by MPLC on silica gel (elution with 6.5% ethyl acetate in petroleum ether). There was obtained 14.7 mg (25%) of **49** as a 3:1 isomeric mixture, 21.3 mg (35%) of **47b**, and 12.4 mg (20%) of **48b**.

For **47b**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3303, 2923, 2865, 1685, 1447, 1092; ^1H NMR (300 MHz, C_6D_6) δ 5.08 (d, J = 5.3 Hz, 1 H), 3.59 (t, J = 4.8 Hz, 1 H), 3.16 (s, 3 H), 3.12 (d, J = 13.2 Hz, 1 H), 2.64 (m, 1 H), 2.58 (m, 1 H), 2.30 (dd, J = 10.8, 5.1 Hz, 1 H), 2.11 (m, 4 H), 2.02–1.79 (m, 4 H), 1.69–1.50 (m, 5 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 214.92, 146.68, 122.15, 80.63, 56.24, 55.04, 54.05, 50.43, 36.21, 35.55, 32.22, 29.03, 28.62, 27.03, 21.38; MS m/z (M^+) calcd 234.1620, obsd 234.1657. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.84; H, 9.53.

For **48b**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3000, 2965, 2937, 2867, 2817, 1677, 1467, 1450, 1439, 1357, 1274, 1225, 1137, 1097, 1059; ^1H NMR (300 MHz, C_6D_6) δ 5.28 (d, J = 6.3 Hz, 1 H), 3.24 (dd, J = 8.7, 6.5 Hz, 1 H), 3.18 (s, 3 H), 2.83 (d, J = 13.2 Hz, 1 H), 2.77 (m, 1 H), 2.35–2.20 (m, 4 H), 2.11 (m, 3 H), 1.83 (dd, J = 13.0, 6.2 Hz, 1 H), 1.71 (dd, J = 11.3, 5.3 Hz, 1 H), 1.63 (m, 2 H), 1.48 (m, 2 H), 1.21 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.72, 149.42, 125.64, 83.07, 60.13, 56.39, 51.53, 41.82, 37.31, 36.81, 32.65, 30.93, 29.58, 25.57, 24.65; MS m/z ($M^+ - C_5H_9$) calcd 165.0915, obsd 165.0968. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.87; H, 9.47. Found: C, 76.82; H, 9.53.

Epoxidation of 47b. A 15.1-mg (0.065 mmol) sample of **47b** was subjected to phosphate-buffered peracid oxidation as before. Purification was achieved by flash chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) to give **51** in quantitative yield: colorless crystals, mp 60–61.5 °C (from ether); IR ($CHCl_3$, cm^{-1}) 2955, 2968, 2925, 2865, 1685, 1447, 1385, 1225, 1185, 1105, 1045; ^1H NMR (500 MHz, C_6D_6) δ 3.60 (dd, J = 3.9, 2.7 Hz, 1 H), 3.35 (s, 3 H), 2.90 (dt, J = 5.7, 2.1 Hz, 1 H), 2.71 (d, J = 2.4 Hz, 1 H), 2.54 (d, J = 12.9 Hz, 1 H), 2.36 (dd, J = 11.4, 4.9 Hz, 1 H), 2.19 (m, 1 H), 2.11 (m, 2 H), 2.03 (m, 2 H), 1.96 (m, 1 H), 1.88 (m, 2 H), 1.73 (m, 2 H), 1.57–1.47 (m, 2 H), 1.47–1.37 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 217.93, 78.67, 68.72, 66.46, 59.97, 52.80, 51.47, 49.73, 37.47, 34.08, 30.95, 30.25, 27.86, 27.59, 22.37; MS m/z (M^+) calcd 250.1563, obsd 250.1569.

Epoxidation of 48b. Reaction of **48b** (18 mg, 0.077 mmol) with excess *m*-chloroperbenzoic acid under phosphate-buffered conditions as detailed earlier afforded 15.3 mg (80%) of **52** following flash chromatography (silica gel, elution with 20% ethyl acetate in petroleum ether): colorless crystals, mp 90–92 °C (from ether); IR ($CHCl_3$, cm^{-1}) 3007, 2967, 2947, 2877, 1687, 1512, 1430, 1209, 1118, 1102, 943, 670; ^1H NMR (300 MHz, C_6D_6) δ 3.39 (s, 3 H), 3.04 (dd, J = 8.1, 4.7 Hz, 1 H), 2.56 (d, J = 4.7 Hz, 1 H), 2.29–2.18 (m, 4 H), 2.08 (m, 2 H), 1.91 (m, 2 H), 1.87–1.54 (m, 5 H), 1.36 (m, 2 H), 1.18–1.03 (m, 2 H): MS m/z (M^+) calcd 250.1569, obsd 250.1566.

Acknowledgment. We are grateful to the National Institutes of Health for their financial support by means of Grant CA-12115 and to Susan Reid and Richard G. Ball for their help with selected

crystallographic solutions and refinements. G.D.M. is the recipient of a Department of Education-sponsored National Need Fellowship.

Supplementary Material Available: X-ray experimental details, tables of crystallographic data for all compounds, tables of atomic positional and thermal parameters, bond distances and angles, and torsional angles (in selected compounds), and numbering schemes for **37**, **40**, and **51A–C** (74 pages). Ordering information is given on any current masthead page.

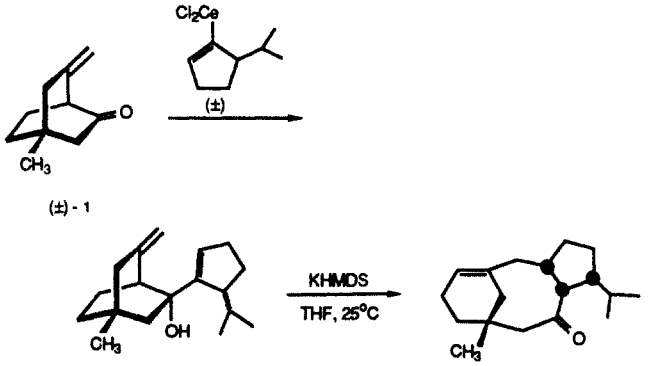
[3.3] Sigmatropy within 1-Vinyl-2-alkenyl-7,7-dimethyl-*exo*-norbornan-2-ols. The First Atropselective Oxyanionic Cope Rearrangement

Leo A. Paquette,* Neil A. Pegg, Dana Toops,[1] George D. Maynard, and Robin D. Rogers[2]

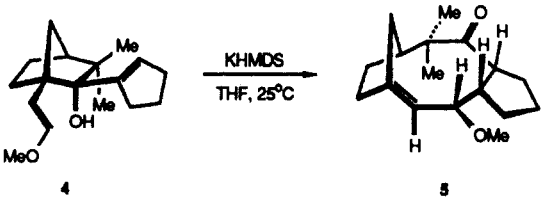
Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and the Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115. *Received April 12, 1989*

Abstract: The anionic oxy-Cope rearrangement of several title compounds is shown to occur rapidly at room temperature exclusively via the respective endo-chair transition states. These reactions occur with complete stereoinduction to generate stereochemically homogeneous bridgehead olefinic ketones and therefore offer especially stringent probes of transition-state topographical stereoselection. Evidence is provided to show that these conversions are remarkably atropselective as well. The illustrative example selected for study was **17**, its α-methyl group serving as a utilitarian ^{1}H NMR probe of structural homogeneity and conformation. This ketone is the product of a tandem [3.3] sigmatropic shift-methylation sequence. On being heated in tetrahydrofuran for several days, **17** is completely transformed into its more thermodynamically favored conformational isomer **18**. These results are nicely accommodated by molecular mechanics calculations. The stereochemical course of the oxy-Cope rearrangements is compared to the pathways followed by structurally related *exo*-norbornan-2-ols and allied molecules.

The anionic oxy-Cope rearrangement has emerged as an important transformation in organic synthesis.[3] When preceded by condensation of a chiral vinyl organometallic to a chiral β,γ-unsaturated ketone, the two-step conversion (e.g., **1** → **3**)[4] constitutes a carbonyl regenerative scheme that proceeds with considerable structural embellishment.[5] The emerging relationship of the carbinol center in **2** relative to those of dissymmetric elements preexisting in the pair of starting reagents falls under the category of diastereomeric differentiation.[5] While recent studies have focused on the molecular recognition aspects of the 1,2-carbonyl addition,[5,6] almost no attention has been paid to those structural features that might divert the ensuing [3.3] sigmatropic shift away from the transition-state chair topology that usually enjoys a kinetic advantage.[3,7,8]



It has been found, however, that the potassium salts of alcohols exemplified by **4** isomerize at room temperature to provide products of type **5**.[9] The stereodiagnostic centers in **5** clearly attest to exclusive adoption of an exo-boat geometry during Cope rearrangement, despite the availability of two chairlike transition-state options.



To investigate systematically the degree of control that norbornane frameworks might be capable of exerting on such sig-

* Address correspondence to this author at The Ohio State University.

(1) Undergraduate research participant, 1986–1987.
(2) Author to whom inquiries relating to the X-ray crystallographic analyses should be directed at Northern Illinois University.
(3) (a) Hill, R. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, 1984; Vol. 3A, p 503. (b) Hill, R. K. In *Comprehensive Organic Synthesis*; Pergamon Press; in press.
(4) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, in press.
(5) Paquette, L. A. In *Organic Synthesis*: Modern Trends; Chizhov, O., Ed.; Blackwell Scientific Publications: 1988; pp 1–12.
(6) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31. (c) Paquette, L. A.; Learn, K. S.; Romine, J. L. *Tetrahedron* **1987**, *43*, 4989. (d) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879. (e) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *Ibid.* **1988**, *110*, 890. (f) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, in press. (g) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.
(7) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.
(8) (a) Gajewski, J. J.; Jimenez, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 468. (b) Gajewski, J. J.; Benner, C. W.; Hawkins, C. M. *J. Org. Chem.* **1987**, *52*, 5198.
(9) Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P., preceding paper in this issue.

0002-7863/90/1512-277$02.50/0