Major product **18b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.24 (m, PhH), 5.7 (br s, C=CH), 3.49 (dd, J = 8.39, 5.49 Hz, COCH), 3.32 (dt, J = 8.7, 2.16 Hz, $COCHCH_2$), 3.23 (s, OCH_3), 2.79 (ddd, J = 16.17, 6.08, 1.98 Hz, $=CHCHH$), 2.63 (app d, J = 5.35 Hz, allylic CH), 2.46-1.39 (m, 7 H), 1.59 (s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.09, 177.56, 140.27, 132.14, 129.16, 128.52, 126.42, 119.81, 76.78, 48.5, 45.65, 42.14, 40.95, 31.81, 31.15, 24.02, 21.39, 20.31; IR ($CHCl_3$) 1710, 1500, 1450, 1390 cm^{-1}; high-resolution mass calcd for $C_{20}H_{24}NO_3$ (M^+ + H) 326.1756, found 326.1785.

X-ray Data. The crystals are triclinic, space group $P\bar{1}$, with a = 7.62 (4) Å, b = 9.37 (6) Å, c = 12.33 (3) Å, and ρ_{calc} = 1.28 g cm^{-3} for Z = 2 $C_{20}H_{23}NO_3$, M = 325.41. The intensity data were measured on a rotation anode diffractometer (Cu Kα radiation). The size of the crystal used for data collection was approximately 0.2 × 0.3 × 0.5 mm. A total of 2760 independent reflections were measured for $\theta < 60°$, of which 2333 were used for structure refinement ($I > 3.0\sigma I$). The structure was solved by a multisolution procedure (SDP software) and was refined by full-matrix least squares. In the final refinement, the hydrogen atoms were added and included in the structure factors but their parameters were not refined. The final discrepancy indices are R = 0.109 and R_w = 0.109 and 0.112 for 2333 observed reflections.

The other fraction was the minor adduct **17b** (115 mg, 18.6%), which was isolated along with a trace of NPM. Minor adduct **17b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.6-7.3 (m, PhH), 5.7 (br s, C=CH), 3.46 (dd, J = 8.97, 7.59 Hz, COCH), 3.32 (dt, J = 8.3, 3.44 Hz, $COCHCH_2$), 3.13 (s, OCH_3), 2.8 (m, 1 H), 2.56 (app d, J = 7.69 Hz, allylic CH), 2.5-1.4 (m, 7 H), 1.38 (s, CH_3); IR ($CHCl_3$) 1710, 1495, 1450, 1385 cm^{-1}; high-resolution mass calcd for $C_{20}H_{24}NO_3$ (M^+ + H) 326.1756, found 326.1686.

Reaction of 3-[(Trimethylsilyl)oxy]-3-methyl-1-vinylcyclohexene (7c) with *N*-Phenylmaleimide. A solution of silyl ether **7c** (123 mg, 0.59 mmol) and *N*-phenylmaleimide (102 mg, 0.59 mmol) in dry benzene (2 mL) was stirred for 5 days. The reaction mixture was concentrated, and the ^{1}H NMR showed the formation of two products. PLC separation (petroleum ether/EtOAc, 8:2) furnished two fractions. The major fraction was a mixture of adducts **17c** and **18c** (113 mg, 50%), which could not be further separated. The second fraction was the unreacted NPM (37 mg).

Hydrolysis of Silyl Adduct Mixture of 17c and 18c. To a methanolic solution (2 mL) of a silyl adduct mixture of **17c** and **18c** (113 mg, 0.29 mmol) was added a few drops of saturated oxalic acid solution, and the solution was stirred for 0.5 h. Solvent was removed, and the resulting mass was dried under vacuum. The crude mixture was separated by PLC (CH_2Cl_2/EtOAc, 9:1) to give lactone **19** (16.1 mg, 17.5%) and anti alcohol **18a** (68 mg, 74.1%).

Lactonization of 18a. A methanolic solution (1 mL) of the anti alcohol **18a** (27 mg, 0.08 mmol) with a few drops of saturated oxalic acid solution was kept under reflux for 72 h. Solvent was removed, and the crude mixture was purified by passing through a short column of Florisil and by eluting with EtOAc. Evaporation of solvent furnished a pasty mass, and ^{1}H NMR showed a mixture of products. The major product was identical with the tricyclic lactone **19**. The mixture was not further separated.

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Tandem Anionic [3,3] Sigmatropy and S_N' Displacement. New Synthetic Technology for the Construction of Hydroazulenone and Related Frameworks

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Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received April 27, 1990*

Abstract: Transmetalation of the 3-(trimethylstannyl)-2-norcarenes **9** and **28b** provides for the acquisition of optically pure bicyclic vinyllithium derivatives. These have been added to (±)-2-chlorocyclohexanone and the resultant *cis*-chlorohydrins have been exposed to excess vinylmagnesium bromide under conditions which promote pinacol rearrangement and allow for subsequent 1,2-addition to the newly liberated carbonyl group. Following analysis of the response of divinyl carbinols **12** and **13** to anionic oxy-Cope rearrangement, the title process has been examined for **31-34**. The precise conformational demands have been analyzed for each example. To some extent these are a function of the usual energetic advantages that accrue to chairlike conformations. However, other factors clearly contravene. These capabilities allow in turn for both syn and anti S_N' displacement of methoxide ion. The sequential operation of a [3,3] sigmatropic step and S_N' displacement is shown to be a powerful tool for rapid hydroazulenone construction.

Hydroazulenoid ring systems are structural units frequently encountered in naturally occurring substances such as the guaianolides and pseudoguaianolides.[2] Due to the high level of interest in these bioactive molecules[3] and the well-recognized problems associated with medium-ring construction, elaboration of these often richly functionalized target molecules has come to be regarded as a challenging and attractive synthetic undertaking. Achievements in the last 15 years have been truly impressive, culminating inter alia in total syntheses of bulnesol,[4] carpesiolin,[5] confertin,[6] cyclocolorenone,[7] damsin,[8] damsinic acid,[9] estafiatin,[10]

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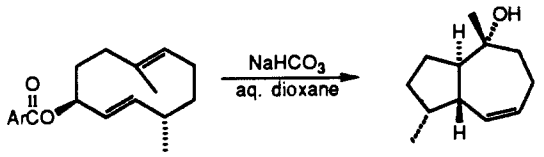
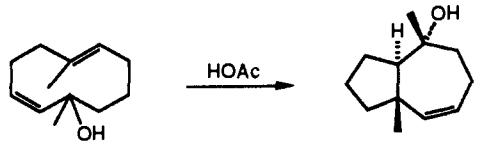
globulol,[11] guaiol,[12] hysterin,[13] kessanol,[14] and parthanin.[15] The strategies have been widely varied with only limited attention being paid to transannular cyclizations of 10-membered ring precursors. Notable exceptions include the solvolytic reactions applied to **1**[11] and **2**[16] and the base-promoted closure of **3**.[8a]



1



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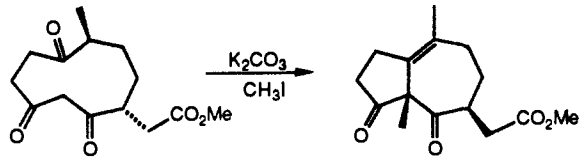
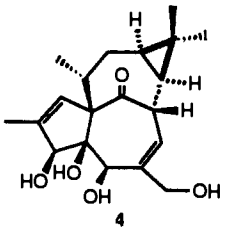


3

In connection with our program directed toward the total synthesis of tumor-promoter ingenol (**4**) esters,[17] diterpenes that feature a hydroazulenic substructure within a more elaborate tetracyclic framework, we set out to investigate the workability of a new, concise synthetic protocol for accessing structurally complex hydroazulenones. In this context, we were particularly



4

struck by the ease with which suitably constructed medium-ring enolate anions typified by **5** and **7** are capable of undergoing remarkably facile transannular displacement of methoxide ion, as exemplified by their conversion to **6** and **8**, respectively. The combination of this new bond-forming scheme and the well-recognized, though largely untapped, potential of oxy anionic [3,3]-sigmatropic rearrangements to transfer asymmetry in highly

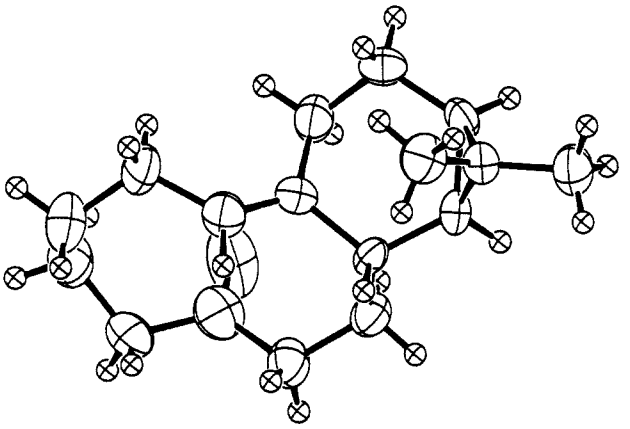
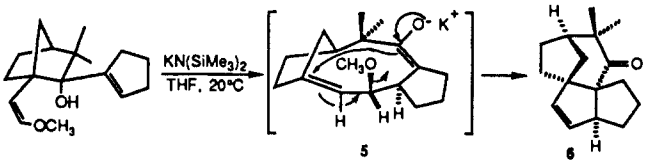
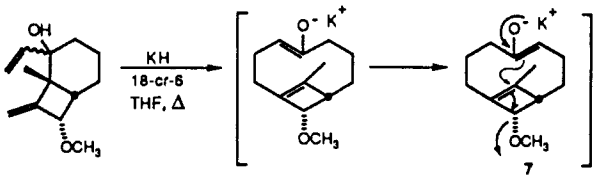
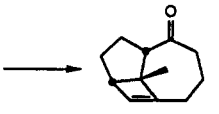


Figure 1. ORTEP drawing for **16**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an arbitrary radius.

controlled fashion[19-21] prompted investigation of the suitability of this tandem reaction sequence to the goals outlined above.[22]







Results

Assessment of the [3,3] Sigmatropic Component. The studies described herein were formulated to set the stage for ultimate arrival at **4**. The initial intent was to show workability in model systems as a prelude to demonstrating scope in the context of a total synthesis of one or more of the ingenanes. In either event, strong inducement existed for the opportunity to learn more about the reactivity of optically active 2-carenes[23] in the context of their participation in [3,3] sigmatropic reactions.

The problem was subdivided into its two obvious components. In the first, we sought to establish the serviceability of the anionic oxy-Cope rearrangement[24] under conditions where ensuing S_N' displacement is not at issue. Pertinent stereochemical features

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Scheme I

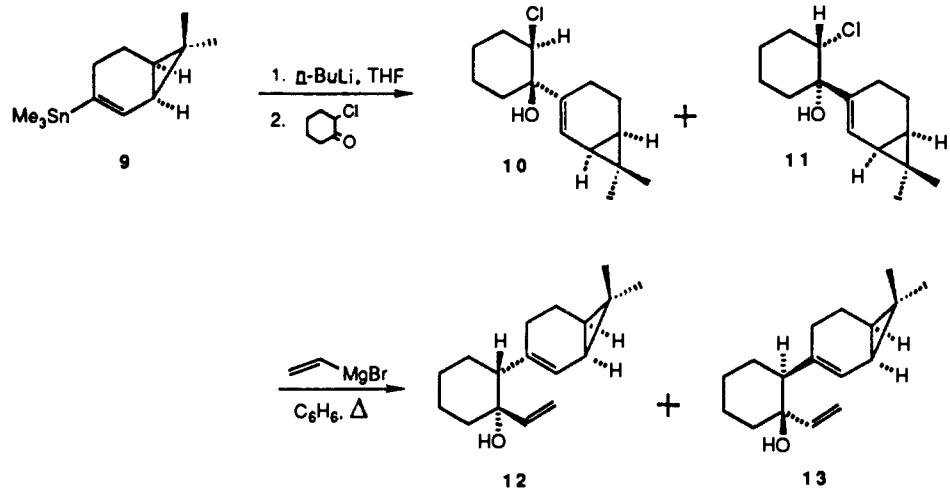

Table I. Crystallographic Details for **16**, **30**, and **33**

	16	**30**	**33**
formula	$C_{17}H_{26}O$	$C_{16}H_{25}ClO_2$	$C_{18}H_{28}O_2$
formula wt, amu	246.39	284.83	276.42
space group	$P2_12_12_1$	$P2_1$	$P6_5$(#170)
a, Å	10.891 (2)	9.639 (1)	10.202 (5)
b, Å	18.457 (2)	8.730 (1)	
c, Å	7.311 (2)	10.037 (2)	27.801 (9)
β, deg		107.86 (1)	
vol, Å^3	1470	804	2505.9
Z	4	2	6
density (calc), g/cm^3	1.11	1.18	1.10
crystal size, mm	0.88 × 0.38 × 0.46	0.23 × 0.31 × 0.50	0.10 × 0.28 × 0.55
radiation	Mo Kα with graphite monochromator	Mo Kα with graphite monochromator	Mo Kα with graphite monochromator
linear abs coeff, cm^{-1}	0.62	2.32	
temperature, °C	23	22	20
2θ limits	$4° \le 2\theta \le 55°$	$4° \le 2\theta \le 55°$	$\le 2\theta \le$
scan speed	4°/min in ω with a maximum of 4 scans/ref	8°/min in ω with a maximum of 4 scans/ref	
background time/scan time	0.5	0.5	
scan range	$(1.00 + 0.35(\tan\theta))°$ in ω	$(1.55 + 0.35(\tan\theta))°$ in ω	
data collected	$+h, +k, +l$	$+h, +k, \pm l$	$-h, +k, +l$
unique data	1973	1972	2776
unique data, with $F_o^2 > 0.5\sigma(F_o^2)$	1185	1223[c]	1084[d]
Final number of variables	1163	172	264
$R(F)$[a]	0.105	0.052	0.049
$R_w(F)$[b]	0.059	0.048	0.059
error in observation of unit weight, e	1.28	1.55	1.88
R (on F for $F_o^2 > 3\sigma(F_o^2)$)	0.045	0.043	0.049

[a] $R(F) = \sum||F_o| - |F_c||/\sum|F_o|$. [b] $R_w(F) = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ with $w = 1/\sigma^2(F_o)$. [c] For $1\sigma(F_o^2)$. [d] For $5\sigma(F_o^2)$.

would thereby be clarified. Subsequently, the tandem process could be implemented with full knowledge of preferred transition state topographies.

Attention was therefore focused on transmetalating (−)-3-(trimethylstannyl)-2-norcarene (**9**) of established absolute configuration[23] with butyllithium[25] followed by condensation with (±)-2-chlorocyclohexanone.[26] The diastereomeric chlorohydrins **10** and **11**, obtained in a 1:1 ratio (Scheme I) proved not to be readily separated by chromatography. On the strength of subsequent findings, it was concluded that the stereochemical course of this condensation is controlled entirely by the neighboring chlorine such that nucleophilic attack occurs exclusively anti to this halogen atom.

Exposure of the **10**/**11** mixture to excess vinylmagnesium bromide served to promote pinacol rearrangement in the form of 1,2-migration of the 2-norcarenyl unit. The cyclohexanone carbonyl group so liberated is captured by a second equivalent of the organometallic. The divinyl carbinols **12** and **13** were produced in equivalent amounts and easily obtained in isomerically pure condition. By all indications, the level of steric control operating during the second step is again very good. No other diastereomers were detected.

Although the ^{1}H NMR spectra of carbinols **12** and **13** are distinctively different, these data were not useful in making a clear-cut distinction between the pair. Consequently, both dienes were independently subjected to anionic oxy-Cope rearrangement. In the case of **12**, the expectation was that the chairlike arrangement **14** would be adopted[27] so as to dispose both vinyl substituents equatorially (Scheme II). Electrocyclization along this pathway delivers the *trans,trans*-cyclodecadienolate **15**, protonation of which would generate tricyclic ketone **16**. At the experimental level, brief heating of **12** with potassium hexamethyldisilazide and 18-crown-6 in tetrahydrofuran solution resulted in smooth isomerization to a single enone. The high crystallinity of this product permitted structural confirmation to be accomplished by X-ray analysis (Table I). The ORTEP diagram in Figure 1 reveals the trans nature of the olefinic linkage and confirms that bonding to the norcarene occurred from the less

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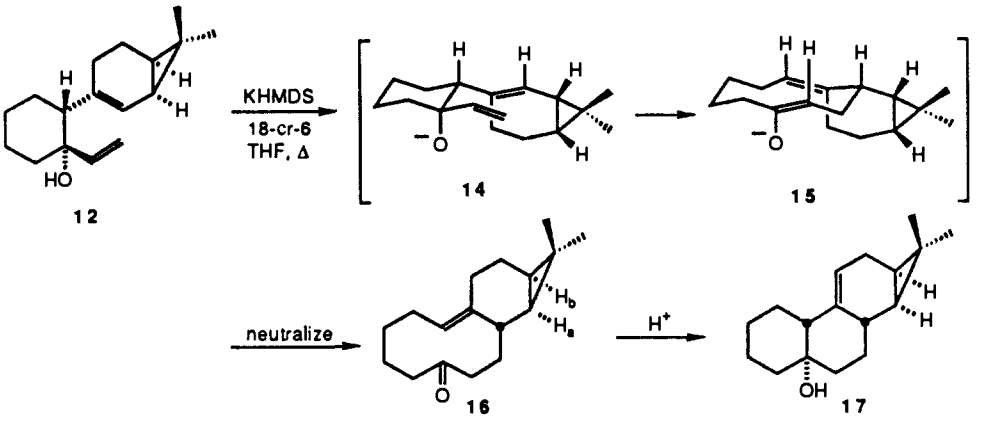
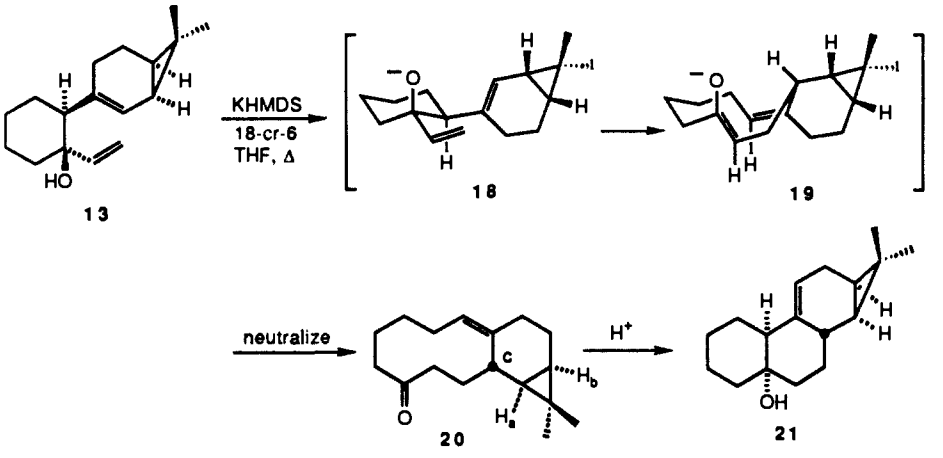
Scheme II



Scheme III



sterically congested direction anti to the *gem*-dimethyl-substituted cyclopropane ring.

The progenitor to **16** must therefore be **12**. Furthermore, the rearrangement trajectory via **14** and **15** produces the medium-ring ketone in a very specific conformation that the molecule seemingly maintains (see Figure 1). This spatial arrangement orients the carbonyl oxygen endo in rather close proximity to the double bond. This particular orientation makes available at least one kinetically accelerated process. Thus, exposure of **16** to silica gel results in rapid isomerization to **17**. The relative configurational assignment given to this tetracyclic alcohol is founded on the crystallographic data for **16** and supported by ^{1}H NMR data. That the absolute configurations of **16** and **17** are as shown is demanded by that present in **9**.

The anionic oxy-Cope rearrangement of **13** under similar conditions resulted in isomerization to **20**, presumably via boatlike **18** and **19** (Scheme III). The carbonyl stretching frequency of **20** (1700 cm^{-1}) differs only marginally from that of **16** (1705 cm^{-1}). The ^{13}C shifts of the carbonyl carbons in the two stereoisomers are more divergent, that for **20** (211.9 ppm) appearing downfield of that in **16** (206.8 ppm). The olefinic proton contained in **20** appears (in C_6D_6 solution) as a doublet of doublets centered at δ 4.85, signaling that its spatial orientation offers less opportunity for long-range interaction than that in **16** (ddd at δ 4.91).

Beyond this, the configuration of H_c in **20** could be ascertained as follows. Protons H_a and H_b in ketone **22** make their appearance below δ 0.9 and actually overlap with the methyl absorptions. Introduction of an α-methyl substituent as in **23** so perturbs the vicinal H_a that this proton experiences substantially greater shielding (δ 0.52) than H_b (δ 0.90; 2-D COSY experiments).[23]

The spectrum of **16**, whose structure has been corroborated crystallographically, displays an entirely similar pattern with H_a at δ 0.38 and H_b at δ 0.75. This effect persists in **20** (H_a at δ 0.47 and H_b at δ 0.67), although the $\Delta\delta$ gap is now somewhat less. Nevertheless, the strong spin interaction between protons H_a and H_c is also best accounted for in terms of a trans relationship.

While the modulation of spectral parameters seen for **20** is likely directly relatable to a difference in ground-state geometry, **20** remains entirely capable of facile transannular closure to **21** when treated with silica gel. Once again, the stereochemistry of the transannular cyclization product follows logically from the conformation of its enone precursor, where the carbonyl oxygen must be oriented syn to the vinylic proton in order to achieve proximity.

The preceding results hold fascination for several reasons. Firstly, the assembly of molecules such as **16**, **17**, **20**, and **21** stems

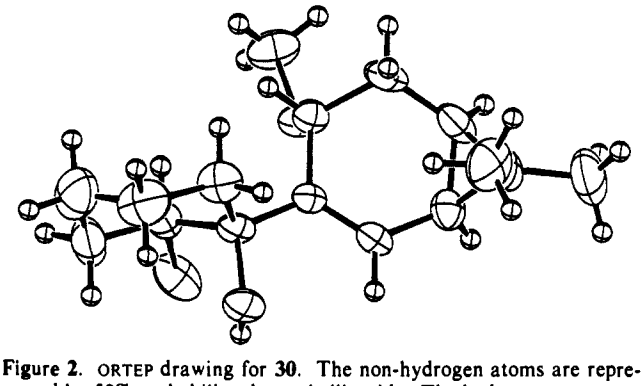
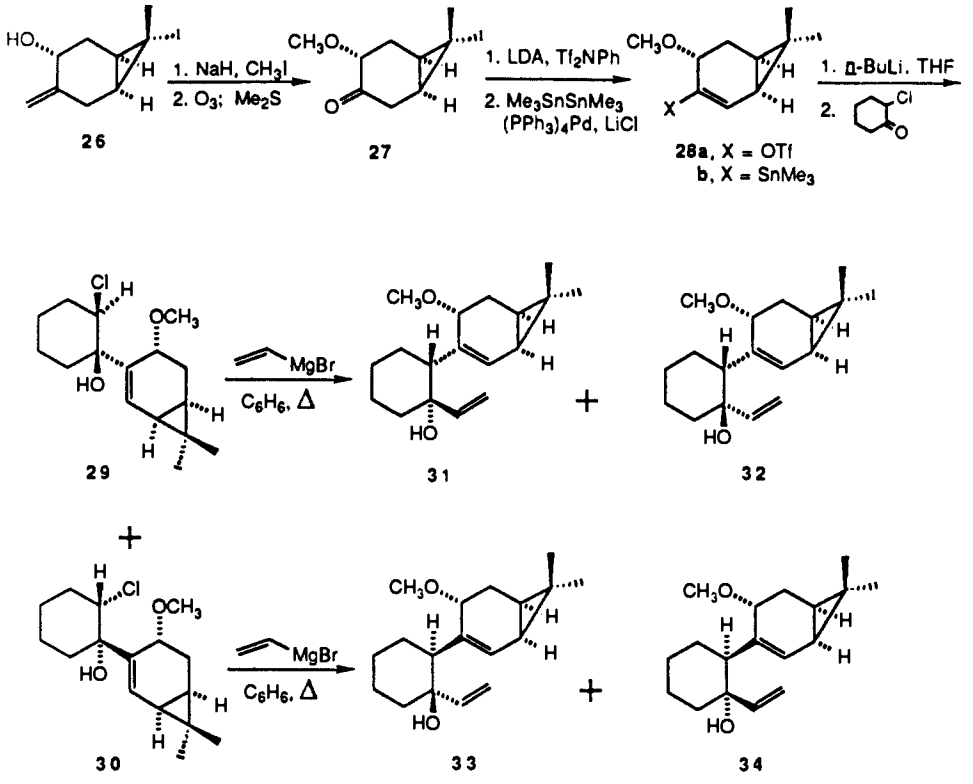
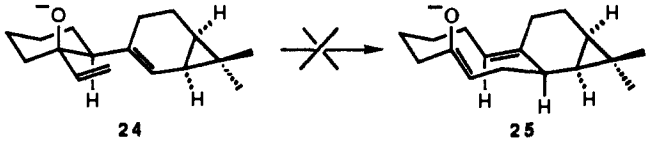


Figure 2. ORTEP drawing for **30**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an arbitrary radius.

Scheme IV



from three building blocks. Since structural variations can presumably be easily implemented, the prospectus for broad scope is clearly present. In addition, the responses of **12** and **13** to [3,3] sigmatropy signal that the norcarene double bond prefers to engage in C–C bond formation from its sterically less encumbered α-face. This stereochemical feature is adopted by **13** at the expense of a boat arrangement (**18**); the alternative chair option **24** would entail electrocyclization syn to the cyclopropane. What is the



24 **25**

magnitude of the energy gap between these options? Should it be small, then minor substituent alterations could open up additional reaction channels. In the sequel, this possibility is affirmed.

Stereochemical Requirements of the Tandem Process. The stage was considered set for detailed scrutiny of the sequential anionic oxy-Cope–S_N' displacement transformation. (1*S*,6*R*)-4α-Methoxy-3-norcaranone (**27**), considered to be a logical precursor to the appropriate nucleophilic 2-carene derivative, was prepared by sequential O-methylation and ozonolysis of the conveniently accessible and optically pure allylic alcohol **26** (Scheme IV).[23] Treatment of **27** with lithium diisopropylamide and *N*-phenyltriflimide according to McMurry[28] resulted in totally regiocontrolled conversion into enol triflate **28a**. The latter was subjected to the action of hexamethylditin in the presence of lithium chloride and tetrakis(triphenylphosphine)palladium(0),[29] thereby providing the vinyl stannane **28b**.

Predictably, the lithiation of (−)-**28b** and subsequent 1,2-addition to (±)-2-chlorocyclohexanone was fully stereocontrolled, leading to a 1:1 mixture of **29** and **30**. Spectral information gleaned from the model studies (vide supra) was consistent with, but did not prove, the configurational assignments given to the diastereomeric chlorohydrins. To obtain that proof, **30** was subjected to X-ray crystallographic analysis (Table I). By this means, the absolute stereochemistry of both **29** and **30** (Figure 2) was made evident.

It was interesting to find that individual reaction of **29** and **30** with more than 2 equiv of vinylmagnesium bromide led in each instance to *two* divinyl carbinols. Notably, while the *trans*-**31** to *cis*-**32** ratio was approximately 2:1, *cis*-**34** was twice as prevalent as *trans*-**33**. This behavior contrasts in a striking way with that exhibited by **10** and **11**, each of which delivers exclusively, a trans divinyl carbinol (Scheme I). However, the methoxyl substituent in the ketones formed by pinacolization of **29** and **30** is seen to be propitiously placed for coordination to the incoming Grignard reagent, thereby possibly enabling intramolecular delivery of vinyl anion from the cis direction to compete effectively with trans attack from the sterically less encumbered carbonyl face.

All four stereoisomers could be obtained in a pure state by silica gel chromatography and characterized spectroscopically. Examination of the high-field ^{1}H NMR spectrum of **31** clearly indicated

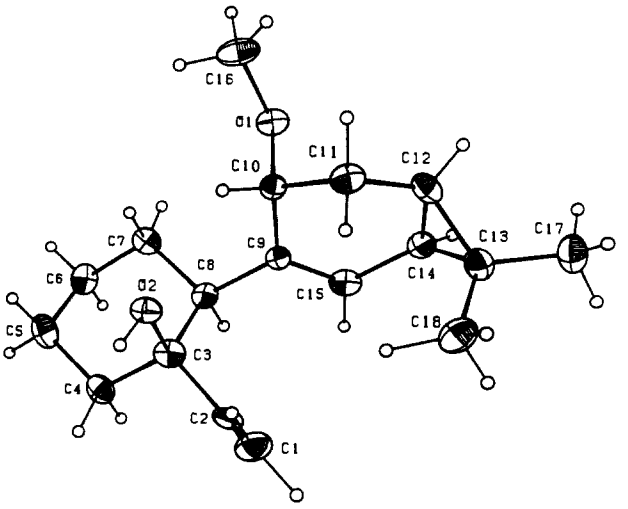
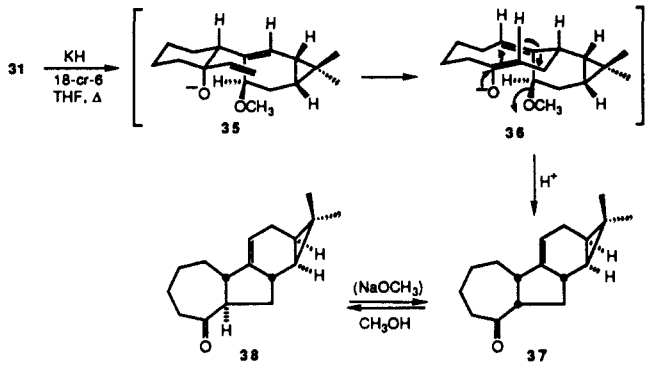


Figure 3. ORTEP drawing for **33**.

(28) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313.
(29) (a) Wulff, W. D.; Peterson, G. A.; Bauta, W. E.; Chan, K.-S.; Faron, K. L.; Gilbertson, S. R.; Kaesler, R. W.; Yang, D. C.; Murray, C. K. *J. Org. Chem.* **1986**, *51*, 277. (b) See also: Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

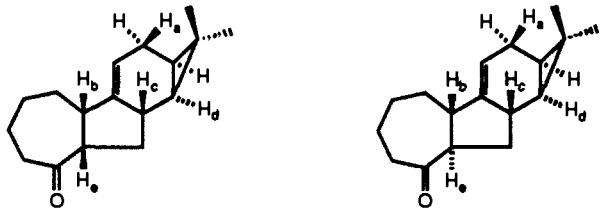
Scheme V



it to be structurally related to **12**. The status of trans isomer **33** was less clear and rigorous demonstration of its absolute configuration was achieved by a single-crystal X-ray determination (Table I, Figure 3). Compounds **32** and **34** are therefore the respective cis isomers. For reasons that will be made evident, only **31** and **33** possess the proper ensemble of desirable structural features. Accordingly, the sigmatropic response of their conjugate bases was examined first.

To the extent that **12** constitutes suitable precedent, **31** can be expected to undergo anionic oxy-Cope rearrangement via the chair arrangement **35** (Scheme V). Following electronic reorganization to generate **36**, an intermediate enolate is produced having olefinic centers separated by as little as 2.8 Å.[30] The heightened proximity in this *trans,trans*-cyclodecadiene is clearly conducive to *frontside* transannular S_N' displacement of methoxide ion since heating **31** with potassium hydride and 18-crown-6 in tetrahydrofuran resulted in the formation of **37**, a hydroazulenone capable of further equilibration with **38**. The actual distribution of **37** and **38** was a function of the work-up protocol. Quenching of the enolate with aqueous ammonium chloride caused cis isomer **37** to be twice as prevalent as **38**. When ethanol was introduced at −78 °C instead, a 1:1 isomer mixture was produced. Equilibration of either tetracyclic ketone in dilute methanolic sodium methoxide demonstrated **38** to be thermodynamically favored over **37** (ratio 2:1).

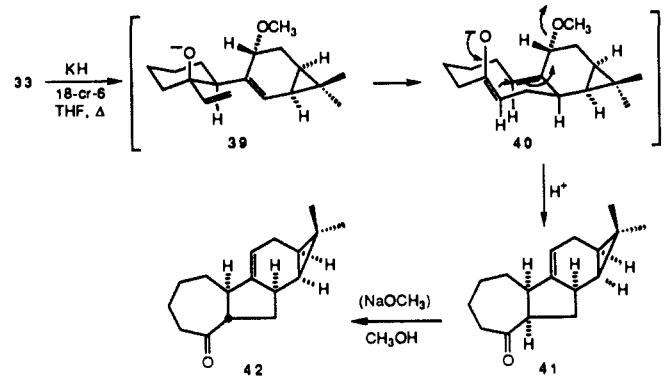
These isomeric ketones were examined by 2-D COSY NMR methods. Clearly revealed by this technique was the ring junction stereochemistry α to the carbonyl group and the β-orientation of the tertiary cyclopropylcarbinyl proton. Particularly definitive in both cases is the strong coupling operative between the protons labeled as H_a, H_b, and H_c in the illustrated formulas, and the lack of spin interaction between H_c and H_d due to their strictly enforced dihedral angle relationship of approximately 90–95°. The two isomers are most notably distinguished by the chemical shifts of H_e. In cis isomer **37**, this proton appears as a doublet of triplets



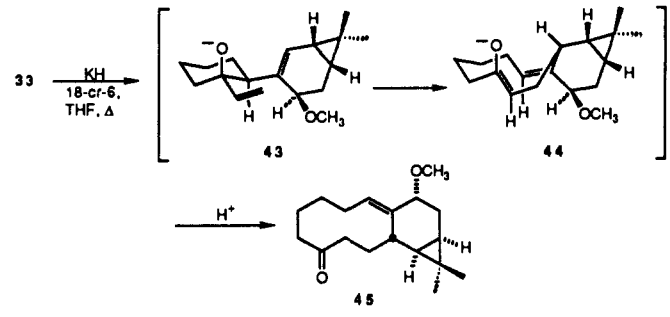
at δ 2.80 (J = 7.0, 10.8 Hz), a position *downfield* of that seen in trans isomer **38** (δ 2.54, dt, J = 3.9, 10.5 Hz). This prominent change is in full agreement with criteria earlier defined by others[31,32] for hydroazulenones.

Two different sets of five stereogenic centers are defined by analogous heating of the potassium alkoxide of **33**. In this instance, ketones **41** and **42** materialize, although not exclusively (see below). This result requires that **33** adopt conformation **39** (Scheme VI), a chair arrangement that can eventuate only in C–C bond formation syn to the cyclopropane subunit. One should recall that this process is completely shunned by **13** (Scheme III). Adoption of the stereoalignment found in **39**, a source of important mechanistic insight, is perhaps realized because of a steric deterrent to bonding from the α-face brought on by the presence of an allylic methoxyl group. Electrocyclization within **39** gives rise to a *trans,trans*-cyclodecadienolate structurally related to **36**. Access to **39** sets the stage for smooth transannular *backside* allylic ether displacement. Consequently, both stereochemical modes of S_N' displacement are capable of operation in these systems.[33]

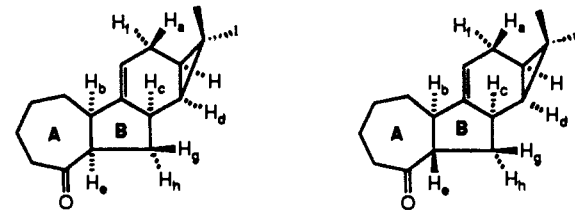
Scheme VI



Scheme VII



Stereochemical assignments to **41** and **42** are likewise founded on 2-D COSY measurements. Especially diagnostic of the α-disposition of H_b and H_c in these ketones is (a) the absence of their long-range coupling to H_a, a phenomenon that dominates the spectra of **37** and **38** and (b) the existence of intense spin interaction between H_c and H_d as well as H_h (see expanded formulas). A/B ring junction stereochemistry could not be



distinguished by comparison of the chemical shifts of H_e as before because this key absorption was seriously overlapped by other signals in **42**. For **41**, H_e could be ascertained to interact strongly with both H_b and H_h, the pattern proving consistent with its formulation as the cis isomer. A thermodynamic preference for the trans ring fusion was confirmed by base-catalyzed equilibration of a 1:1 mixture of **41** and **42**. Such treatment led to the exclusive recovery of **42**. This isomer proved inert to further chemical change under basic conditions.

It is significant that **33** does not isomerize completely via **39** and **40**, but also utilizes that reaction channel involving **43** and

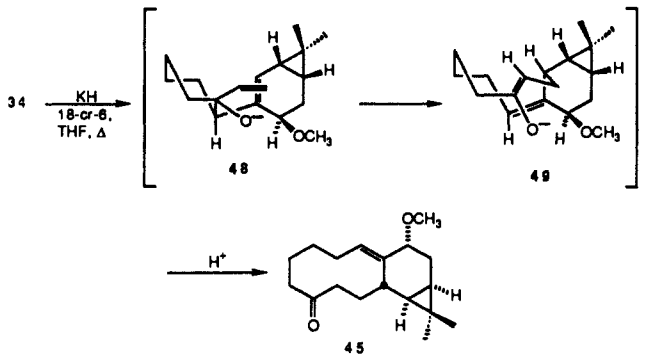
(30) Evaluation of the trans 1,5-enols of cis- and trans-cyclodecen-5-one by means of the MODEL program with complete energy minimization gave the following transannular gaps for potential cyclization: trans,trans isomer, 2.86 Å; cis,trans isomer, 3.20 Å.

(31) Weller, T.; Seebach, D.; Davis, R. E.; Laird, B. B. *Helv. Chim. Acta* **1981**, *64*, 736.

(32) Sworin, M.; Lin, K.-C. *J. Am. Chem. Soc.* **1989**, *111*, 1815.

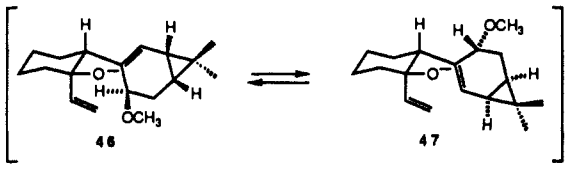
(33) (a) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (b) Overton, K. H. *Chem. Soc. Rev.* **1979**, *8*, 447. (c) Cane, D. E. *Tetrahedron* **1980**, *36*, 1109.

Scheme VIII



44 to an approximately equal extent (Scheme VII). Its structural relationship to **12** is thereby made apparent. Since **44** is a *cis,trans*-decadienolate, a distance of approximately 3.2 Å separates the reactive trigonal centers. As a consequence, transannular closure with expulsion of methoxide ion does not operate. Protonation ultimately delivers tricyclic enone **45**.

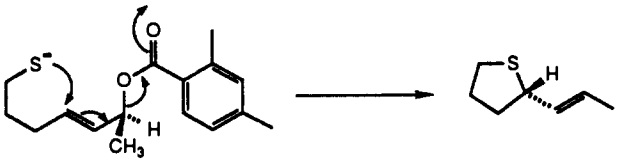
Attempts to achieve anionic oxy-Cope rearrangement in divinyl carbinol **32** were not successful. This is because the topography intrinsic to this isomer is not sterically conducive to [3,3] sigmatropy. As is evident in conformation **46**, the two π-termini are not at all in adequate proximity for bonding. The chair alternative **47** poses a different dilemma. Here the combination of diminished accessibility to the syn face of the norcarene double bond *and* steric screening of the solvated alkoxide substituent is apparently not easily surmounted.



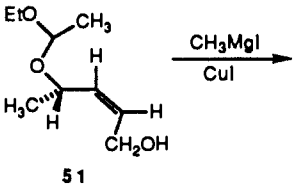
In contrast, initial ring expansion within **34** can proceed forward via a chairlike transition-state geometry, viz. **48**, like that found in **43** (Scheme VIII). Following isomerization and arrival at **49**, the cis, trans arrangement offers no option for transannular bonding because of those distance factors discussed earlier.[30] Consequently, protonation again delivered **45**.

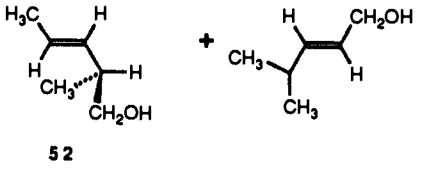
Discussion

Stereochemical Bias in the S_N' Process. Detailed understanding of how bonds are made or broken is of fundamental importance to mechanistic and synthetic chemists. As a consequence, the 1956 publication by Stork and White,[34] which concluded that a syn relationship exists between the entering and departing groups in S_N2' reactions, was accepted for more than two decades because of its practical appeal and synthetic potential. Bordwell later pointed out that satisfactory kinetic proof for concerted S_N2' behavior is exceedingly difficult to acquire.[35] Nonetheless, the extent of bond making and bond breaking operative at the transition state can in no way invalidate any inherent bias for a stereochemical preference.[36,37] Despite numerous early qualitative theoretical treatments in support of a syn preference,[38] these conclusions have not withstood the test of time. It is now apparent that the entire spectrum spanned by the syn and anti extremes can be expected, with the result in any specific instance being dependent on the nature of the entering and leaving groups, solvent, and counter ion.[33,39,40] The intramolecular S_N variant **50** offers useful insight. Despite the absence of any obvious steric bias to either stereochemical reaction channel, cyclization proceeds exclusively anti with an *E*:*Z* ratio of 93:7.[41]

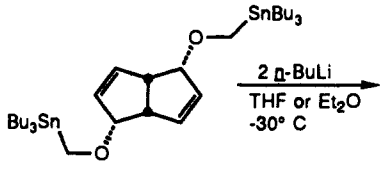


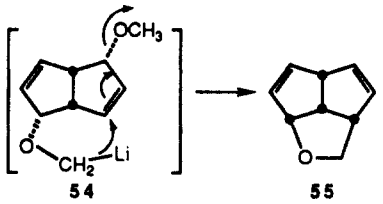
Although allylic halides and esters are often subject to bimolecular nucleophilic substitution with allylic rearrangement, the range of substrates has only recently been extended to include allylic ethers. Reasonable reactivity has been noted toward Grignard reagents admixed with 10–20% CuX[42] or with $TiCl_4$.[43] In order to delineate stereochemistry, **51** was treated with 10 mol percent of CH_3MgI–CuI; γ attack was favored (80%) and **52** was formed with an anti preference greater than 95%.[44]





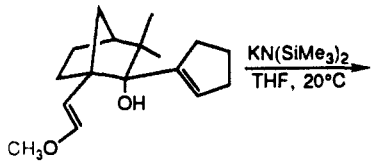
The earliest known example of a transition-metal-free S_N' ether displacement is an intramolecular process discovered by Farnum and Monego.[45] Following dimetalation, **53** is initially converted to **54** by proton abstraction from solvent, thereby setting the stage for ring closure and arrival at **55**. More recent developments in this area[18] are cited in the introduction.

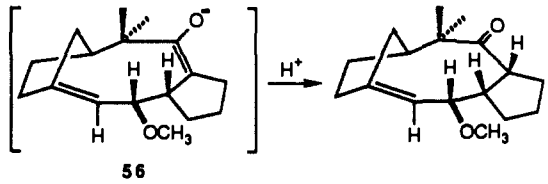




(34) Stork, G.; White, W. N. *J. Am. Chem. Soc.* **1956**, *78*, 4609.
(35) Bordwell, F. G. *Acc. Chem. Res.* **1970**, *3*, 281.
(36) de la Mare, P. B.; Vernon, C. A. *J. Chem. Soc. B* **1971**, 1700.
(37) Yates, R. L.; Epiotis, N. D.; Bernardi, F. *J. Am. Chem. Soc.* **1975**, *97*, 6615.
(38) (a) Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2018. (b) Drenth, W. *Rec. Trav. Chem. Pays-Bays* **1967**, *86*, 318. (c) Mathieu, J. *Bull. Soc. Chim. Fr.* **1973**, 807. (d) Mathieu, J.; Rassat, A. *Tetrahedron* **1974**, *30*, 1753. (e) Liotta, C. L. *Tetrahedron Lett.* **1975**, *523*, 1660. (f) Toromanoff, M. E. *Compt. Rend.* **1977**, *284C*, 113.
(39) (a) Dobbie, A. A.; Overton, K. H. *J. Chem. Soc. Chem. Commun.* **1977**, 722. (b) Oritani, T.; Overton, K. H. *Ibid.* **1978**, 454. (c) Magid, R. M.; Fruchey, O. S. *J. Am. Chem. Soc.* **1977**, *99*, 8368; **1979**, *101*, 2107.
(40) Stork, G.; Kraft, I. *J. Am. Chem. Soc.* **1977**, *99*, 3850; 8373.
(41) Stork, G.; Kraft, I. *J. Am. Chem. Soc.* **1977**, *99*, 3851.
(42) (a) Normant, J. *Pure Appl. Chem.* **1978**, *50*, 709. (b) Claesson, A.; Tamnefors, I.; Olsson, L.-I. *Tetrahedron Lett.* **1975**, 1509. (c) Claesson, A.; Sahlberg, C. *Ibid.* **1978**, 5049. (d) Claesson, A.; Sahlberg, C. *J. Organometal. Chem.* **1979**, *170*, 355. (e) Normant, J. F.; Commercon, A.; Gendreau, Y.; Bourgain, M.; Villieras, J. *Bull Soc. Chim. Fr.* **1979**, II-309. (f) Gendreau, Y.; Normant, J. F. *Ibid.* **1979**, II-305.
(43) Mukaiyama, T.; Ishikawa, H. *Chem. Lett.* **1974**, 1077.
(44) Claesson, A.; Olsson, L. I. *J. Chem. Soc. Chem. Commun.* **1978**, 621.
(45) Farnum, D. G.; Monego, T. *Tetrahedron Lett.* **1983**, *24*, 1361.

In view of the essentially nonexistent reactivity of alkoxy groups toward conventional S_N2 displacement, it is legitimate to inquire why they play a serviceable role in S_N' processes. Proper stereoalignment of the C–OCH_3 bond with the flanking π-orbital is, of course, essential to onset of any bond formation. Comparison of the inertness of **56** to the high reactivity of **5** illustrates that failure to meet this minimum geometry requirement inhibits S_N' behavior.[18]





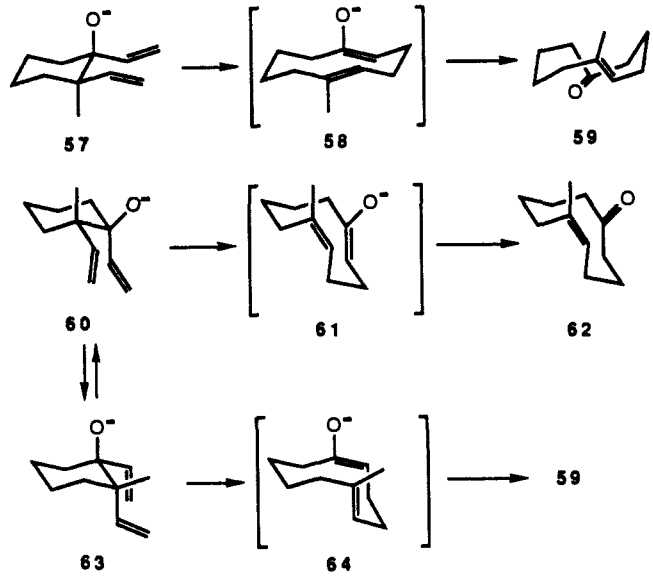
56

Once suitable spatial orientation of the alkoxy group is realized, onset of the S_N' process is very likely facilitated by the length of the C–O bond being broken. As the extensive crystallographic compilations by Kirby have shown, axial ether oxygens in cyclic acetals are effectively more electronegative than their equatorial counterparts.[46] The onset of $n \rightarrow \sigma^*_{C-OR}$ interaction is reflected in strikingly longer bond lengths in the axial isomers. Since phenomenologically related orbital overlap can operate within the allylic ethers that adopt antiplanar conformations, comparable lengthening of the critical C–O bond can be anticipated. Heterolytic cleavage of this bond is thereby facilitated. *Moreover, we have now shown that syn and anti pathways are both capable of efficient operation.*

Stereochemical Requirements for Ring Expansion. 1,3-Divinyl derivatives of cyclopentanes and larger rings are capable of Cope rearrangement, customarily adopting a chair transition state during the sigmatropic event. Equilibria usually favor the monocyclic ring expanded isomer.[19] In the oxy-Cope variant of these processes, tautomerism within the enol product can be relied upon to shift an equilibrium that may otherwise be unfavorable. When performed anionically, the activation energy for the same reaction is often dramatically lowered, such that structural isomerization can be realized at very modest temperatures.[47] The advantages offered by sharply decreased demands for thermal input are, of course, highly utilitarian in the context of natural products synthesis.[24] Additionally, mechanistic nuances gain greater visibility. The alkoxide pair **57** and **60** studied by Clive and co-workers[27] nicely illustrate this point (Scheme IX). Whereas **57** isomerizes exclusively via **58** to provide > 99% of **59**, isomer **60** gives only 3% of **62** (via **61**). Instead, conformational inversion to provide **63** precedes the preferred isomerization route via **64**. The finding that **60** also produces largely **59** signals that *both compounds prefer utilization of those chair transition states that carry axial alkoxide substituents* (as in **57** and **63**). Is **60** inherently disadvantagd because of its *equatorial* electron-rich substituent, or is the *Z* double bond geometry in **62** (and **61**) responsible?

While a quantitative assessment of these questions in structurally unbiased systems is ongoing,[48] we viewed as entirely plausible the possibility that the stereochemical outcome of such

Scheme IX



reactions may be subject to a certain amount of alternative control. For example, the trans alcohols **13**, **31**, and **33** are so constructed that one of their vinyl units provides for concurrent analysis of π-facial selectivity. Relevantly, the norcarene double bond is not equally accessible from its two surfaces. The energetic advantage of engaging this π-linkage in C–C bond formation from the less sterically congested direction is certain to impact on the global [3,3] sigmatropic transition-state costs.

Our results disclose that **13** and **31** both isomerize via pathways wherein the alkoxide substituent is oriented axially and the norcarene double bond is captured anti to the cyclopropane ring (see **18** and **35**). There the similarity stops, since **18** leads to a *cis,trans*-dienolate, **19**, and **35** is precursor to the *trans,trans*-cyclodecadiene **36**. Despite the geometry differences in these intermediates, neither pathway appears to be kinetically disadvantaged.

More striking yet is the influence of the added methoxyl substituent in **33**. Since **13** and **33** are stereochemically related, one might expect a comparable sigmatropic response following conversion to their potassium salts. Indeed, **33** does find it possible to isomerize to **45** via **43** and **44**, but this pathway is not dominant. This system displays an equivalent preference for rearrangement via **39** and **40** from which the S_N' process occurs. As before, **39** also carries an axial alkoxide. However, adoption of this geometry requires syn bonding to the norcarene double bond!

The fate of **34** is reasonably explained in terms of the involvement of **48**. This conformational arrangement is similar to that in **35** and **43** from the norcarene perspective. However, the alkoxide has an equatorial disposition in **48**. Nonetheless, [3,3] sigmatropy does materialize. In contrast, chair conformer **47**, which likewise carries an equatorial C–O substituent, is totally unreactive. In this example, the need to approach syn to the cyclopropane ring is a serious deterrent.

The distinctions made above, in particular the ability of substituents to exert substantial control on the eventual course of events, reflect the considerable amount of additional incisive work that is required before the precise role of pendant groups can be defined. In this connection, we have not commented on the possibility that the S_N' step eventuating in loss of the methoxyl group may proceed via allyl radical pair intermediates.[32,35] This is purposeful, since we have no evidence whatsoever that heterolytic character develops at the temperature of refluxing tetrahydrofuran. What is clear is that the formal S_N' displacement of methoxide by enolate anions proceeds with good efficiency in a manner that can establish at least five stereogenic centers concurrently. For this reasons, the process must be regarded as an exceptionally powerful tool for the rapid elaboration of polycyclic molecules.

The Ingenol Connection. In suitable cases, the anionic oxy-Cope rearrangement of *trans*-1,2-divinylcyclohexanols is seen to result

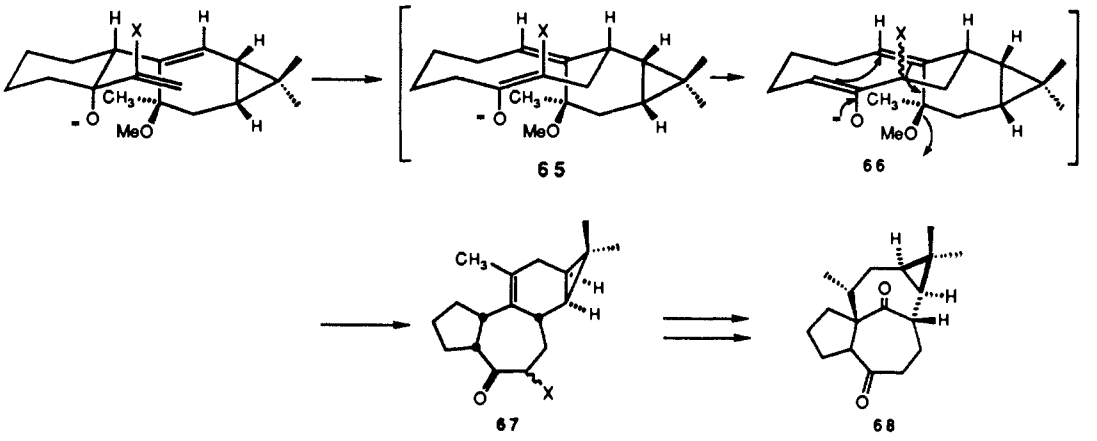
(46) (a) Jones, P. G.; Kirby, A. J. *J. Chem. Soc., Chem. Commun.* **1979**, 288. (b) Allen, F. H.; Kirby, A. J. *J. Am. Chem. Soc.* **1984**, *106*, 6197. (c) Briggs, A. J.; Glenn, R.; Jones, P. G.; Kirby, A. J.; Ramaswany, P. *Ibid.* **1984**, *106*, 6200. (d) Jones, P. G.; Kirby, A. J. *Ibid.* **1984**, *106*, 6207.

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

(48) Maynard, G. D. Unpublished results.

(49) Examples of enolate exchange in the absence of a stimulatory group X are well known. See: ref 18, 20b, and 20d, as well as (a) Oplinger, J. A.; Paquette, L. A. *Tetrahedron Lett.* **1987**, *28*, 5441. (b) Paquette, L. A.; Oplinger, J. A. *Tetrahedron* **1984**, *45*, 107. (c) Paquette, L. A.; DeRussy, D. T.; Pegg, N. A.; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.

Scheme X



in direct conversion to perhydroazulenones. As matters stand currently, products such as **37**, **38**, **41**, and **42** contain a seven-membered A ring and a five-membered B ring. One adaptation of this technology to the synthesis of ingenol (**4**) requires that the A/B ring sizes be reversed. In order to assess whether this fact can be accomplished directly, studies are in progress to determine if enolate exchange[18] (i.e., **65** → **66** in Scheme X) can be driven by a suitable X group such that the S_N' reaction will occur uniquely via the transposed intermediate. The transannular dimensions in **66** appear commensurate with the chemistry planned. Should bonding in this manner prove feasible and deliver **67**, subsequent stereocontrolled Wagner–Meerwein shift of one C–C bond would guarantee rapid access to a tetracyclic molecule (**68**) possessing the appropriate inside, outside bridge stereochemistry.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrophotometer. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. ^{1}H NMR were recorded at 300 MHz and the ^{13}C NMR spectra at either 75 or 20 MHz as indicated. 2-D COSY spectra were recorded on a Bruker 500 MHz spectrometer by Dr. Charles Cottrell of The Ohio State University Chemical Instrument Center. Mass spectra were recorded on a Kratos MS-30 instrument by Mr. Dick Weisenberger at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The preparative GC work made use of a Varian Series 2700 unit. All MPLC separations were conducted on Merck Lobar columns (Lichroprep Si-60) with the help of a Fluid Metering INC pump and a Waters Associates Model R403 differential refractometer detector. All reactions were performed under an inert atmosphere (dry nitrogen or argon). The organic extracts of crude products were dried over anhydrous magnesium or sodium sulfate. Solvents were reagent grade and dried prior to use.

Condensation of 9 with (±)-2-Chlorocyclohexanone. A solution of *n*-butyllithium in hexanes (1.75 mL of 1.4 M, 2.46 mmol) was added to a cold (−78 °C), magnetically stirred solution of **9** (350 mg, 1.23 mmol) in 10 mL of anhydrous tetrahydrofuran and stirred at that temperature for 50 min. A solution of 2-chlorocyclohexanone (341 mg, 2.58 mmol) in tetrahydrofuran (5 mL) was introduced, and after 10 min the cooling bath was removed and stirring was continued for 1 h at room temperature. The reaction mixture was poured into a cold (0 °C), saturated ammonium chloride solution and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 1% ethyl acetate in petroleum ether) afforded 106 mg (34%) of a 1:1 mixture of **10** and **11** as a colorless oil: IR (neat, cm^{-1}) 3560, 3480, 2990, 2930, 2860, 1640, 1445, 1370, 1340, 1325, 1285, 1230, 1200, 1170, 1140, 1125, 1105, 1065, 1030, 990, 980, 970, 945, 885, 870, 845, 810, 740; ^{1}H NMR (300 MHz, C_6D_6) δ 6.12 (dd, J = 3.1, 6.1 Hz, 0.5 H), 6.01 (dd, J = 2.2, 3.9 Hz, 0.5 H), 3.87–3.77 (m, 1 H), and multiplets to higher field; MS m/z calcd 254.1437, obsd 254.1430.

Vinylmagnesium Bromide Induced Pinacol Rearrangement of 10/11. A solution of vinylmagnesium bromide in tetrahydrofuran (0.75 mL of 0.92 M, 0.688 mmol) was added to a solution of the 1:1 chlorohydrin mixture (70 mg, 0.28 mmol) in dry benzene (8 mL) at 0–5 °C and stirred for 10 min. The reaction mixture was heated at 75 °C in a preheated oil bath for 10 min, cooled to 0 °C, quenched with saturated ammonium chloride solution, and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 1% ethyl acetate in petroleum ether) provided 21 mg of **12** and 25 mg of **13** (total yield of 68%).

For **12**: colorless oil; IR (neat, cm^{-1}) 3545, 3085, 2995, 2975, 2925, 2855, 1640, 1450, 1405, 1375, 1355, 1285, 1165, 1000, 980, 925; ^{1}H NMR (300 MHz, C_6D_6) δ 5.75 (dd, J = 1.2, 10.6 Hz, 1 H), 5.69 (br s, 1 H), 5.26 (dd, J = 1.2, 17.1 Hz, 1 H), 4.88 (dd, J = 1.2, 10.6 Hz, 1 H), 2.10–0.70 (series of m, 15 H), 1.00 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.36, 140.94, 121.79, 110.66, 73.13, 53.71, 38.56, 29.30, 28.62, 27.49, 26.67, 24.11, 23.57, 22.00, 21.62, 18.68, 15.79; MS m/z (M^+) calcd 246.1984, obsd 246.1963; $[\alpha]^{20}_D$ −21° (c 1.38, C_6H_6). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.84; H, 10.63.

For **13**: colorless oil; IR (neat, cm^{-1}) 3545, 3085, 2985, 2925, 2865, 1640, 1450, 1415, 1375, 1355, 1285, 1250, 1175, 1140, 1075, 1055, 995, 975, 920, 820; ^{1}H NMR (300 MHz, C_6D_6) δ 5.75 (dd, J = 10.6, 17.2 Hz, 1 H), 5.62 (d, J = 4.3 Hz, 1 H), 5.20 (dd, J = 1.6, 17.2 Hz, 1 H), 4.90 (dd, J = 1.6, 10.6 Hz, 1 H); 2.20–0.75 (series of m, 15 H), 1.04 (s, 3 H), 0.94 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.18, 140.46, 122.02, 110.37. 73.46, 53.89, 38.75, 28.88, 28.82, 27.39, 26.68, 24.35, 23.32, 22.83, 21.64, 18.69, 15.91; MS m/z (M^+) calcd 246.1984, obsd 246.2003; $[\alpha^{20}_D$ +59° (c 0.88, C_6H_6). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.92; H, 10.63.

Anionic Oxy-Cope Rearrangement of 12. A solution of potassium hexamethyldisilazide in toluene (0.63 mL of 0.5 M, 0.317 mmol) was added to a solution of **12** (26.0 mg, 0.106 mmol) and 18-crown-6 (83.6 mg, 0.317 mmol) in 8 mL of anhydrous tetrahydrofuran. After being heated at reflux under nitrogen for 1 h, the reaction mixture was cooled to −78 °C, quenched with ethanol (2 mL), stirred for 10 min at −78 °C, and poured into water. The product was extracted into ether and the combined ethereal phases were washed with water and brine, dried, and evaporated. Chromatography of the residue on Florisil (elution with 2% ethyl acetate in petroleum ether) gave **16** (20 mg, 77%) as a colorless solid, mp 118–119 °C (from petroleum ether); IR (CCl_4, cm^{-1}) 2925, 2885, 2855, 1705, 1445, 1425, 1375, 1360, 1260, 1215, 1180, 1130, 1100, 1020, 960, 905, 860; ^{1}H NMR (300 MHz, C_6D_6) δ 4.91 (ddd, J = 0.8, 1.4, 4.0 Hz, 1 H), 2.69 (dq, J = 1.9, 12.3 Hz, 1 H), 2.29–1.80 (m, 8 H), 1.70–0.90 (series of m, 8 H), 1.03 (s, 3 H), 1.02 (s, 3 H), 0.75 (dt, J = 4.0, 9.5 Hz, 1 H), 0.38 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.79, 144.27 123.80, 44.63, 43.89, 42.93, 34.41, 29.38, 29.22, 28.64, 28.07, 23.32, 23.15, 21.33, 20.27, 18.40, 15.28; MS m/z (M^+) calcd 246.1984, obsd 246.2002; $[\alpha]^{20}_D$ + 54° (c 1.13, C_6H_6).

X-ray Crystallographic Analysis of 16. Crystals of **16** are clear, colorless rectangular plates. Examination of the diffraction pattern on a Rigaku AFC5 diffractometer indicated an orthorhombic crystal system with systematic absences: $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$, and $00l$, $l = 2n + 1$, which uniquely determine the space group as $P2_12_12_1$. The unit cell is based on a symmetry restricted least-squares fit of the diffractometer setting angles for 25 reflections in the 2θ range 18 to 24° with Mo Kα radiation.

Intensities were measured by the $\omega - 2\theta$ scan method. The intensities of six standard reflections, which were measured after every 150 reflections, decreased slowly during the course of data collection. The overall average change in intensity was 3% and the data set was corrected for this small amount of crystal decomposition. All calculations were done with the TEXSAN package of crystallographic programs.[50]

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

The structure was solved with the direct methods program MITHRIL,[51] with 13 out of the 18 non-hydrogen atoms located on the electron density map. The remainder of the atoms were located by standard Fourier methods. The correct enantiomer was chosen on the basis of the known stereochemistry of the two asymmetric carbon atoms of the fused cyclopropane ring. After the model reached the anisotropic refinement stage, hydrogen atoms were included as fixed contributions in their calculated positions with the assumptions C–H = 0.95 Å and $B_H = C_{C(iso)} + 1.0$ Å^2. The final refinement cycle used 1185 intensities with $F_o^2 > 0.5\sigma(F_o^2)$ and 163 variables and resulted in agreement indices of $R = 0.105$ an $R_w = 0.059$.

The final difference electron density map contains maximum and minimum peak heights of 0.30 and −0.34 e/Å^3. Scattering factors were obtained from the usual sources.[52] A structure factor calculation for the 673 reflections with $F_o^2 > 3\sigma(F_o^2)$ yields an R value of 0.045.

Transannular Cyclization of 16. Chromatography of **16** on silica gel resulted in quantitative conversion to **17**. The same result was achieved by stirring **16** with silica gel in ether for 1.5 h: IR (CCl_4, cm^{-1}) 3565, 2985, 2930, 2855, 2825, 1445, 1435, 1375, 1325, 1295, 1250, 1205, 1175, 1150, 1140, 1090, 970, 955, 905; ^{1}H NMR (300 MHz, C_6D_6) δ 5.08 (t, J = 3.5 Hz, 1 H), 2.33–2.22 (m, 1 H), 2.00–1.90 (m, 1 H), 1.88–1.08 (m, 15 H), 1.03 (s, 3 H), 0.87 (s, 3 H), 0.62 (t, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 139.37, 118.73, 71.13, 49.75, 40.64, 38.96, 34.12, 32.50, 28.70, 26.52, 26.32, 24.25, 21.77, 21.47, 17.71, 16.91, 13.85; MS m/z (M^+) calcd 246.1983, obsd 246.1964; $[\alpha]^{20}_D$ −43° (c 1.67, C_6H_6).

Anionic Oxy-Cope Rearrangement of 13. A solution of potassium hexamethyldisilazide in toluene (0.68 mL of 0.5 M, 0.342 mmol) was added to a solution of **13** (28 mg, 0.114 mmol) and 18-crown-6 (90.2 mg, 0.342 mmol) in 10 mL of anhydrous tetrahydrofuran. Following heating of the reaction mixture at reflux for 1.5 h, ketone **20** was isolated as described above (20 mg, 71%): colorless oil; IR (CH_2Cl_2, cm^{-1}) 2985, 2935, 2860, 1700, 1450, 1450, 1435, 1410, 1375, 1370, 1215, 1205, 1190, 1130, 1120, 1010, 995, 975, 935, 870, 845; ^{1}H NMR (300 MHz, C_6D_6) δ 4.85 (dd, J = 2.9, 12.4 Hz, 1 H), 3.0 (dd, J = 5.1, 11.6 Hz, 1 H), 2.62–2.50 (m, 1 H), 2.40–0.80 (series of m, 15 H), 0.93 (s, 3 H), 0.92 (s, 3 H), 0.67 (dt, J = 3.6, 9.2 Hz, 1 H), 0.47 (d, J = 9.0 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.90, 141.54, 125.47, 45.36, 34.50, 30.89, 29.98 (2C), 29.36, 28.99, 28.40, 24.72, 23.62, 22.89, 19.61, 18.10, 14.77; MS m/z (M^+) calcd 246.1983, obsd 246.1972; $[\alpha]^{20}_D$ +95° (c 1.63, C_6H_6). Anal. Calcd for $C_{17}H_{26}O$: C, 82.86; H, 10.64. Found: C, 82.70; H, 10.60.

Transannular Cyclization of 20. Tricyclic enone **20** was transformed quantitatively into **21** by elution (ether) through silica gel; colorless oil; IR (CH_2Cl_2, cm^{-1}) 3550, 2995, 2975, 2925, 2855, 2845, 2825, 1465, 1450, 1435, 1375, 1340, 1320, 1220, 1200, 1175, 1130, 1095, 945, 915, 865, 830; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.38 (dd, J = 3.5, 5.1 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.16–1.17 (series of m, 16 H), 1.02 (s, 3 H), 0.77 (s, 3 H), 0.67 (t, J = 8.6 Hz, 1 H), 0.35 (d, J = 8.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 139.66, 121.40, 71.84, 55.65, 40.12, 32.18, 31.87, 29.88, 28.70, 27.73, 26.53, 25.31, 24.23, 21.18, 17.83, 16.80, 13.74; MS m/z (M^+) calcd 246.1983, obsd 246.1991; $[\alpha]^{20}_D$ +0.87° (c 5.09, C_6H_6).

(−)-(1*S*,6*R*)-4α-Methoxy-β-carene. To a suspension of sodium hydride (640 mg of 97% purity, 25.8 mmol) in 10 mL of dry tetrahydrofuran was added dropwise a solution of alcohol **26**, $[\alpha]^{20}_D$ −119.8° (c 2.47, $CHCl_3$), (2.61 g, 17.2 mmol) in 10 mL of the same solvent. After 1 h of stirring, methyl iodide (2.33 mL, 37.8 mmol) was introduced and the reaction mixture was stirred overnight, quenched with saturated ammonium chloride solution (20 mL), and extracted with ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 3% ethyl acetate in petroleum ether) provided 2.57 g (90%) of the methyl ether as a colorless oil: bp 80–90 °C (20 Torr); IR (neat, cm^{-1}) 3070, 2990, 2930, 2900, 2870, 2820, 1645, 1450, 1430, 1375, 1325, 1285, 1200, 1155, 1100, 1070, 1030, 990, 950, 850; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73 (s, 1 H), 4.66 (s, 1 H), 3.35 (t, J = 2.9 Hz, 1 H), 3.05 (s, 3 H), 2.47–2.37 (m, 1 H), 2.22–2.12 (m, 2 H), 1.39–1.30 (m, 1 H), 0.84 (s, 3 H), 0.75 (s, 3 H), 0.85–0.51 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 146.72, 111.23, 79.85, 55.23, 28.64, 27.41, 25.09, 20.98, 18.23, 15.93, 14.21; MS m/z (M^+) calcd 166.1357, obsd 166.1364; $[\alpha]^{20}_D$ −66° (c 1.55, $CHCl_3$). Anal. Calcd for $C_1{}^H{}_{18}O$: C, 79.45; H, 10.92. Found: C, 79.45; H, 10.98.

(+)-(1*S*,6*R*)-4α-Methoxy-3-norcaranone (27). A stream of ozone in oxygen was bubbled through a solution of the above compound (3.11 g, 18.7 mmol) in a mixture of methanol (20 mL) and dichloromethane (4 mL) at −78 °C for about 40 min until a blue color persisted. Dimethyl sulfide (8 mL) was introduced at this temperature and stirring was maintained for 1 h at −78 °C and then at room temperature for 2 h. Following the removal of solvent, the residue was taken up in ether (250 mL), washed with brine, and dried. Evaporation and silica gel chromatography (elution with 5% ethyl acetate in petroleum ether) afforded 2.01 g (66%) of **27** as a colorless oil: bp 155–165 °C (20 Torr); IR (neat, cm^{-1}) 3300, 2985, 2960, 2940, 2880, 2820, 1714, 1450, 1405, 1374, 1320, 1240, 1190, 1150, 1095, 1058, 1020, 1000, 975, 910, 832, 760; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 3 H), 3.25 (t, J = 3.4 Hz, 1 H), 2.75 (dd, J = 8.9, 17.5 Hz, 1 H), 2.58–2.48 (m, 1 H), 2.30 (d, J = 17.5 Hz, 1 H), 1.82–1.74 (m, 1 H), 1.28–1.22 (m, 1 H), 1.04 (s, 3 H), 0.89 (s, 3 H), 0.83–0.79 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.48, 81.01, 57.17, 34.25, 27.98, 27.91, 24.09, 19.35, 15.74, 14.63; MS m/z (calcd 168.1151, obsd 168.1180; $[\alpha]^{20}_D$ +5.0° (c 1.53, $CHCl_3$). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.40; H, 9.55.

(+)-(1*S*,6*R*)-4α-Methoxy-3-[[(trifluoromethyl)sulfonyl]oxy]-2-norcarene (28a). A solution of **27** (1.008 g, 6.00 mmol) in 10 mL of dry tetrahydrofuran (10 mL) was added to a cold (−78 °C) solution of lithium diisopropylamide (from 4.41 mL of 1.5 M *n*-butyllithium and 0.924 mL of diisopropylamine in 20 mL of tetrahydrofuran). After 1 h of stirring, *N*-phenyltriflimide (2.253 g, 6.30 mmol) in 10 mL of the same solvent was introduced. The reaction mixture was then stirred at −78 °C for 10 min and at 0 °C for 3 h. Following solvent evaporation, the residue was filtered through a short silica gel column (elution with 1% ethyl acetate in petroleum ether) and purified further by MPLC (silica gel, same solvent system). There was isolated 950 mg (53%) of **28a** as a colorless liquid: IR (neat, cm^{-1}) 2980, 2920, 2820, 1665, 1450, 1415, 1240, 1205, 1140, 1090, 1050, 1000, 975, 890, 875, 830, 810; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (d, J = 4.2 Hz, 1 H), 3.64 (dd, J = 3.4, 5.5 Hz, 1 H), 3.39 (s, 3 H), 2.45–2.20 (m, 1 H), 2.10–2.00 (m, 1 H), 1.35–1.20 (m, 1 H), 1.13 (s, 3 H), 1.08–0.98 (m, 1 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 149.52, 122.05, 118.48, 72.84, 56.49, 27.36, 26.46, 23.34, 17.88, 14.51; MS m/z (M^+) calcd 300.0643, obsd 300.0677; $[\alpha]^{20}_D$ +112° (c 2.82, hexane).

(−)-(1*S*,6*R*)-4α-Methoxy-3-(trimethylstannyl)-2-norcarene (28b). A mixture of **28a** (237 mg, 0.790 mmol), hexamethylditin (230 mg, 0.702 mmol), lithium chloride (210 mg, 4.95 mmol), and tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.014 mmol) in 15 mL of dry tetrahydrofuran was placed in a 50-mL flask, deoxygenated by passing argon through for 30 min, and heated with stirring at 60 °C for 18 h. The insoluble solids were separated by filtration and rinsed with ether. The combined organic filtrates were washed with water (2 × 30 mL) and brine (2 × 30 mL), dried, and evaporated. Chromatography of the residue on Florisil (elution with petroleum ether) furnished 200 mg (80%) of **28b** as a colorless liquid: bp 85–87 °C (0.3 Torr); IR (neat, cm^{-1}) 2970, 2930, 2900, 2800, 1600, 1460, 1440, 1370, 1350, 1185, 1120, 1105, 1090, 1070, 1020, 970, 870, 835, 765; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (dd, J = 2.2, 5.2 Hz, 1 H), 3.45 (dt, J = 2.2, 5.9 Hz, 1 H), 3.34 (s, 3 H), 2.45–2.25 (m, 1 H), 1.55–1.40 (m, 1 H), 1.25–1.10 (m, 1 H), 1.09 (s, 3 H), 0.95–0.55 (m, 1 H), 0.87 (s, 3 H), 0.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.01, 135.70, 77.27, 56.59, 29.13, 25.19, 23.96 (2 C), 21.76, 16.57, −6.42; MS m/z ($M^+ - SnMe_3$) calcd 151.1123, obsd 151.1168; $[\alpha]^{20}_D$ −9° (c 1.70, hexane). Anal. Calcd for $C_{13}H_{24}OSn$: C, 49.54; H, 7.62. Found: C, 49.69; H, 7.71.

Condensation of 28b with (±)-2-Chlorocyclohexanone. A solution of **28b** (200 mg, 0.635 mmol) in 10 mL of anhydrous tetrahydrofuran was added slowly to a cold (−78 °C), magnetically stirred solution of *n*-butyllithium (0.54 mL of 1.4 M, 0.762 mmol) in the same solvent (10 mL) and stirred for 10 min. A cold (−78 °C) solution of 2-chlorocyclohexanone (101 mg, 0.762 mmol) in 5 mL of tetrahydrofuran was added next, and the reaction mixture was allowed to warm to room temperature, stirred for 30 min, and quenched at 0 °C with saturated ammonium chloride solution. The products were extracted into ether, and the combined organic phases were washed with brine (3 × 30 mL), dried, and evaporated. Chromatography of the residue on silica gel (elution with 5% ethyl acetate in petroleum ether) gave 40 mg of less polar **29** and 41 mg of more polar **30** (combined yield of 45%).

For **29**: colorless oil; IR (neat, cm^{-1}) 3560, 3460, 3000, 2940, 2870, 2820, 1650, 1460, 1450, 1380, 1355, 1290, 1275, 1200, 1135, 1085, 1020, 985, 855, 820, 750; ^{1}H NMR (300 MHz, C_6D_6) δ 6.00 (d, J = 3.5 Hz, 1 H), 3.97 (dd, J = 4.5, 11.7 Hz, 1 H), 3.53 (dd, J = 2.9, 4.2 Hz, 1 H), 3.13 (s, 3 H), 2.35 (d, J = 1.8 Hz, 1 H), 2.27–1.97 (m, 2 H), 1.90–1.56 (m, 3 H), 1.50–1.02 (m, 5 H), 1.00–0.60 (m, 2 H), 1.00 (s, 3 H), 0.90 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.14, 125.19, 76.09, 70.89, 66.23, 54.70, 38.22, 32.83, 27.85, 26.45, 23.96 (2 C), 23.22, 20.97, 18.40,

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

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

15.32; MS m/z (M^+) calcd 284.1543, obsd 284.1482; $[\alpha]^{20}_D$ +30° (c 1.49, CH_2Cl_2).

For **30**: colorless solid; mp 63–64 °C; IR (CH_2Cl_2, cm^{-1}) 3540, 2960, 2930, 2860, 2820, 1545, 1440, 1415, 1270, 1250, 1190, 1150, 1075, 980, 900, 890; ^1H NMR (300 MHz, C_6D_6) δ 5.80 (d, J = 3.4 Hz, 1 H), 3.91–3.85 (m, 2 H), 3.17 (s, 3 H), 2.36 (d, J = 1.8 Hz, 1 H), 2.25–2.00 (m, 3 H), 1.90–1.60 (m, 4 H), 1.55–1.10 (m, 6 H), 1.10–0.75 (m, 1 H), 1.00 (s, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 144.21, 125.02, 75.58, 70.95, 68.71, 54.63, 38.65, 33.26, 27.86, 26.40, 24.07, 23.83, 23.17, 20.89, 18.40, 15.19; MS m/z ($M^+ - OCH_3$) calcd 255.1330, obsd 255.1374; $[\alpha]^{20}_D$ +65° (c 1.18, CH_2Cl_2).

X-ray Crystallographic Analysis of 30. Crystals of **30** are clear, colorless rectangular rods. Upon exposure to X-rays, one crystal became cloudy and its diffraction profiles were noted to be significantly broadened with decreasing intensities. With this in mind, a second crystal was sealed inside a capillary tube for data collection. Examination of the diffraction pattern on a Rigaku ARC5 diffractometer indicated that the crystal system is monoclinic with systematic absences $0k0$, $k = 2n + 1$. Since the crystal is expected to contain a single enantiomer and a reasonable density is obtained with two molecules in the unit cell, the space group is assumed to be $P2_1$. At room temperature, the cell constants a = 9.629 (1) Å, b = 8.730 (1) Å, c = 10.037 (2) Å, and β = 107.86 (1)° are based on a least-squares fit of the diffractometer setting angles for 25 reflections in the 2θ range of 29–30° with Mo Kα radiation.

Intensities were measured by the $\omega - 2\theta$ scan method. During the course of data collection there was an interruption of power to the generator. Upon firing up of the X-ray tube and resumption of data collection, the structure factor values obtained for the set of six standard reflection were, on average, 81% of their original values. Prior to this point, the standards appeared to be stable. Because of observations noted above with the first crystal, this crystal was most likely decomposing as a result of X-ray exposure. This sudden decrease in intensities was accounted for by including two scale factors in the least-squares refinements. All calculations were done with the TEXSAN package of crystallographic programs.[50]

The position of the chlorine atom was located on a Patterson map and was used as a phasing model in DIRD<<iF.[51] Most of the atoms appeared on the resulting electron density map and the remainder of the atoms were then located by standard Fourier techniques. The correct enantiomer was chosen on the basis of the known chemistry which generated this molecule. After the anisotropic stage of refinement had been reached, hydrogen atoms were located on a difference electron density map and were then included in the model as fixed contributions in calculated positions with the assumptions C–H = 0.98 Å and B_H = 1.2Beq(C). The hydrogen atoms bonded to the methyl carbon atoms were idealized to sp^3 geometry. The hydrogen atom bonded to oxygen was included in the model at its position as located on a difference electron density map. The final refinement cycle for the 1223 intensities with $F_o^2 > 1\sigma(F_o^2)$ and the 172 variables resulted in agreement indices of R = 0.052 and R_w = 0.048. The final difference electron density map contains maximum and minimum peak heights of 0.21 and −0.22 e/Å^3. Scattering factors were obtained from the usual sources.[52] There is an intermolecular hydrogen bond between O(1) and O(2), where the O(1)···O(2) distance is 2.944 (5) Å.

Vinylmagnesium Bromide Induced Pinacol Rearrangement of 29. A solution of vinylmagnesium bromide in dry tetrahydrofuran (3.62 mL of 0.90 M, 3.26 mmol) was added to a solution of **29** (310 mg, 1.09 mmol) in 20 mL of anhydrous benzene at 0–5 °C. The mixture was stirred at 0 °C for 10 min, heated at 75 °C in a preheated oil bath for 15 min, quenched with saturated ammonium chloride solution at 0 °C, and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated. MPLC purification of the residue (silica gel, elution with 8% ethyl acetate in petroleum ether) furnished 85 mg of **31** and 45 mg of **32** in a total yield of 43%.

For **31**: colorless oil; IR (neat, cm^{-1}) 3560, 3400, 3010, 2980, 2940, 2870, 1640, 1450, 1410, 1375, 1200, 1185, 1130, 1075, 995, 980, 920, 830; ^1H NMR (300 MHz, C_6D_6) δ 5.87 (dd, J = 10.6, 17.2 Hz, 1 H), 5.59 (d, J = 3.5 Hz, 1 H), 5.41 (dd, J = 1.8, 17.2 Hz, 1 H), 5.01 (dd, J = 1.8, 10.6 Hz, 1 H), 3.58 (dd, J = 2.8, 4.7 Hz, 1 H), 3.54 (s, 1 H), 3.09 (s, 3 H), 2.15–1.71 (m, 5 H), 1.52–1.08 (m, 6 H), 0.98–0.86 (m, 1 H), 0.95 (s, 3 H), 0.80 (s, 3 H), 0.72–0.64 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.88, 139.53, 128.77, 111.08, 73.34, 71.59, 54.31, 53.61, 38.83, 27.70, 27.20, 26.77, 23.91, 23.61, 22.57 (2 C), 21.91, 18.42; MS m/z (M^+) calcd 276.2090, obsd 276.2120; $[\alpha]^{20}_D$ +42° (c 1.49, C_6H_6).

For **32**: colorless solid; mp 89–90 °C (from petroleum ether); IR (CCl_4, cm^{-1}) 3540, 3480, 3010, 2950, 2870, 2820, 1640, 1450, 1405, 1380, 1360, 1200, 1135, 1080, 100, 985, 930; ^1H NMR (300 MHz, C_6D_6) δ 5.78 (d, J = 3.5 Hz, 1 H), 5.65 (dd, J = 10.0, 17.0 Hz, 1 H), 5.52 (dd, J = 2.6, 17.0 Hz, 1 H), 5.06 (dd, J = 2.6, 10.1 Hz, 1 H), 3.72 (dd, J = 2.4, 4.5 Hz, 1 H), 3.08 (s, 3 H), 2.97 (s, 1 H), 2.28–2.11 (m, 2 H), 1.80–1.39 (m, 7 H), 1.36–1.27 (m, 1 H), 1.18–1.09 (m, 1 H), 1.04–1.00 (m, 1 H), 0.99 (s, 3 H), 0.82 (s, 3 H), 0.78–0.70 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 143.77, 141.59, 125.22, 112.02, 79.54, 71.02, 54.63, 45.24, 27.87, 27.78, 27.10, 26.95, 24.14, 23.23, 22.81, 17.93, 15.15; MS m/z ($M^+ - H_2O$) calcd 258.1983, obsd 258.2007; $[\alpha]^{20}_D$ +159° (c 1.24, C_6H_6). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.20; H, 10.22. Found: C, 78.10; H, 10.18.

Vinylmagnesium Bromide Induced Pinacol Rearrangement of 30. Reaction of **30** (449 mg, 1.57 mmol) with vinylmagnesium bromide (5.25 mL of 0.90 M, 4.72 mmol) in the predescribed manner provided after MPLC purification (silica gel, elution with 8% ethyl acetate in petroleum ether) 106 mg of **33** and 250 mg of **34** for a composite yield of 82%.

For **33**: colorless crystals; mp 94–95 °C (from petroleum ether); IR (CCl_4, cm^{-1}) 3600, 3430, 3000, 2980, 2940, 2865, 2820, 1635, 1460, 1450, 1410, 1375, 1195, 1170, 1130, 1085, 995, 970, 920; ^1H NMR (300 MHz, C_6D_6) δ 5.84 (dd, J = 10.6, 17.2 Hz, 1 H), 5.70 (d, J = 3.7 Hz, 1 H), 5.23 (dd, J = 1.9, 17.2 Hz, 1 H), 4.95 (dd, J = 1.9, 10.6, Hz, 1 H), 3.81 (t, J = 3.9 Hz, 1 H), 3.19 (s, 3 H), 2.1–1.9 (m, 4 H), 1.8–1.5 (m, 5 H), 1.5–1.2 (m, 3 H), 1.02 (s, 3 H), 0.93 (s, 3 H), 1.2–0.75 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.51, 141.33, 127.14, 110.59, 74.54, 73.62, 55.15, 53.82, 40.22, 28.36, 28.16, 26.80, 24.14, 23.62, 22.99, 21.71, 18.99, 15.83; MS m/z ($M^+ - CH_3OH$) calcd 244.1827, obsd 244.1806; $[\alpha]^{20}_D$ +96° (c 1.73, C_6H_6).

For **34**: colorless oil; IR (neat, cm^{-1}) 3580, 3405, 3000, 2980, 2940, 2870, 2820, 1635, 1460, 1450, 1400, 1375, 1335, 1200, 1170, 1130, 1120, 1085, 1070, 1000, 980, 965, 925, 850; ^1H NMR (300 MHz, C_6D_6) δ 6.24 (dd, J = 10.8, 18.0 Hz, 1 H), 5.65 (dd, J = 2.4, 17.0 Hz, 1 H), 5.50 (d, J = 3.2 Hz, 1 H), 5.20 (dd, J = 2.4, 10.8 Hz, 1 H), 4.57 (s, 1 H), 3.20 (t, J = 2.9 Hz, 1 H), 3.06 (s, 3 H), 2.2–2.0 (m, 3 H), 2.0–0.80 (series of m, 10 H), 0.97 (s, 3 H), 0.81 (s, 3 H), 0.80–0.60 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 141.08, 140.14, 128.14, 113.87, 77.42, 74.42, 57.36, 56.25, 41.42, 29.74, 27.71, 27.10, 23.95, 23.90, 22.91, 22.83, 17.96, 15.02; MS m/z (M^+) calcd 276.2089, obsd 276.2108.

X-ray Crystallographic Analysis of 33,[53–55] A transparent single crystal of **33** was mounted on a pin and transferred to the goniometer. The crystal was cooled to −150 °C during data collection by use of a stream of cold nitrogen gas. The space group was determined to be acentric $P6_5$ (or $P6_1$) from the systematic absences. Successful refinement of the correct absolute configuration (determined spectroscopically) was carried out in $P6_5$. A summary of data collection parameters is given in Table I.

Least-squares refinement with isotropic thermal parameters led to R = 0.958. The B hydrogen atoms were located from a difference Fourier map and isotropically refined. Refinement of non-hydrogen atoms with anisotropic temperature factors led to the final values of R = 0.049 and R_w = 0.059. The final values of the positional parameters are provided in the supplementary material.

Anionic Oxy-Cope Rearrangement of 31. A. Acidic Workup. To a suspension of potassium hydride (140 mg of 24% in oil, 0.826 mmol) and 18-crown-6 (219 mg, 0.827 mmol) in dry tetrahydrofuran (10 mL) was added a solution of **31** (45.8 mg, 0.165 mmol) in the same solvent (5 mL). The reaction mixture was stirred at room temperature for 45 min and at reflux for 2 h, cooled to −78 °C, and quenched with saturated ammonium chloride solution (3 mL). The resultant mixture was poured into 20% ammonium chloride solution (15 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with water and brine, dried, and evaporated. MPLC purification (silica gel, elution with 2% ethyl acetate in petroleum ether) gave 19.9 mg (47%) of **37** and 9.6 mg (24%) of **38**, both as colorless oils.

For **37**: IR (neat, cm^{-1}) 3005, 2930, 2860, 2835, 1705, 1450, 1380, 1240, 1225, 1170, 1150, 1140, 1120, 1000, 950; ^1H NMR (500 MHz, C_6D_6) δ (dd, J = 2.3, 5.1 Hz, 1 H), 2.80 (dt, J = 7.0, 10.8 Hz, 1 H), 2.34–2.28 (m, 2 H), 2.26–2.20 (m, 1 H), 2.12–2.03 (m, 2 H), 1.93–1.88 (m, 1 H), 1.85–1.78 (m, 2 H), 1.73–1.69 (m, 1 H), 1.56–1.46 (m, 2 H), 1.37–1.27 (m, 1 H), 1.23–1.14 (m, 1 H), 1.03 (s, 3 H), 0.96–0.88 (m, 1 H), 0.79 (s, 3 H), 1.66 (d, J = 9.0 Hz, 1 H), 0.56 (t, J = 8.3 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.29, 144.36, 115.55, 53.45, 43.10, 41.54, 33.81, 32.37, 29.61, 27.88, 27.80, 24.62, 23.03, 20.84, 17.70, 16.41, 14.65; MS m/z (M^+) calcd 244.1827, obsd 244.1818; $[\alpha]^{20}_D$ −57° (c 0.44, $CHCl_3$).

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(54) *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 72, 99, 149. (Present distributor: Kluwer Academic Publishers, Dordrect).

(55) Sheldrick, G. M. SHELXS. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goodard, R., Eds.; Oxford University Press: Oxford 1985; pp 175–189.

For **38**: colorless oil; IR (neat, cm^{-1}) 3000, 2930, 2865, 2835, 1705, 1450, 1410, 1380, 1360, 1245, 1225, 1170, 1155, 1140, 1120, 1000, 950, 870; ^1H NMR (500 MHz, C_6D_6) δ 5.08 (dd, J = 2.4, 4.9 Hz, 1 H), 3.10 (ddd, J = 3.9, 9.9, 12.8 Hz, 1 H), 2.54 (dt, J = 3.9, 10.5 Hz, 1 H), 2.33–2.24 (m, 2 H), 2.14 (ddd, J = 3.4, 12.5, 18.6 Hz, 1 H), 1.99–1.95 (m, 1 H), 1.94–1.84 (m, 2 H), 1.79 (br t, J = 10.7 Hz, 1 H), 1.70–1.66 (m, 1 H), 1.40–1.25 (m, 2 H), 1.25–1.15 (m, 1 H), 1.04 (s, 3 H), 1.01–0.90 (m, 2 H), 0.75 (s, 3 H), 0.61–0.56 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 210.16, 145.37, 112.89, 54.43, 46.33, 43.18, 32.19, 32.02, 30.92, 29.20, 27.99, 23.77, 23.52, 20.56, 17.61, 16.51, 14.37; MS m/z (M^+) calcd 244.1827, obsd 244.1812; $[\alpha]^{20}_D$ −49° (c 0.72, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O$: C, 83.54; H, 9.91. Found: C, 83.63; H, 9.93.

B. Ethanolic Workup. A mixture of **31** (40 mg, 0.145 mmol), potassium hydride (19 mg of 24% in oil, 0.47 mmol), 18-crown-6 (115 mg, 0.47 mmol), and anhydrous tetrahydrofuran was stirred at room temperature for 45 min, refluxed under argon for 2 h, and cooled to −78 °C. Ethanol (1.0 mL) was introduced and the resulting solution was poured into water (10 mL) and extracted with ether. The combined organic phases were washed with water and brine, dried, and evaporated. MPLC purification (silica gel, elution with 5% ethyl acetate in petroleum ether) gave 14.2 mg of a mixture of **37** and **38** (40% combined yield) and returned 14.7 mg of starting alcohol (37% recovery). Further MPLC separation (2% ethyl acetate in petroleum ether) provided equal amounts of **37** and **38**.

C. Equilibration Study. A solution of **31** (5 mg) in 1 mL of methanol was treated with 0.5 mL of 0.044 M methanolic sodium methoxide and stirred at room temperature for 1.5 h. The reaction mixture was cooled to 0 °C, quenched with saturated ammonium chloride solution, and extracted with ether. The combined organic layers were washed with brine, dried, and evaporated to leave 4.7 mg (94%) of a 2:1 mixture of **37** and **38**.

Anionic Oxy-Cope Rearrangement of 33. A. Acidic Workup. To a suspension of potassium hydride (157 mg of 24% in oil, 0.935 mmol, washed with dry petroleum ether) and 18-crown-6 (247 mg, 0.935 mmol) in dry tetrahydrofuran (10 mL) was added a solution of **33** (51.8 mg, 0.187 mmol) in the same solvent (5 mL) at room temperature. The reaction mixture was stirred for 30 min, refluxed for 5 h, cooled to −78 °C, and quenched with saturated ammonium chloride solution (2 mL). This mixture was poured into 20% ammonium chloride solution (15 mL) and extracted with ether (3 × 50 mL). The combined organic layers were washed with water and brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 2% ethyl acetate in petroleum ether) afforded 15.8 mg (35%) of **42** as a colorless solid and 18.4 mg (36%) of **45** as a colorless oil.

For **42**: mp 71–72 °C (from ether); IR (mull, cm^{-1}) 2950, 2910, 2850, 1705, 1460, 1375, 1195, 1160, 1135, 1000, 960; ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (t, J = 2.0 Hz, 1 H), 2.92 (br s, 1 H), 2.86 (dt, J = 4.1, 9.8 Hz, 1 H), 2.65 (dt, J = 4.0, 14.2 Hz, 1 H), 2.51–2.42 (m, 2 H), 2.31–2.27 (m, 1 H), 2.18–2.13 (m, 1 H), 2.02–1.98 (m, 1 H), 1.74–1.65 (m, 1 H), 1.58–1.38 (m, 5 H), 1.03 (s, 3 H), 1.00–0.92 (m, 1 H), 0.95 (s, 3 H), 0.80 (t, J = 6.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.25, 138.92, 119.29, 53.27, 47.28, 45.51, 36.42, 32.78, 29.74, 28.85, 28.72, 25.63, 25.47, 22.40, 19.84, 18.19, 15.70; MS m/z (M^+) calcd 244.1827, obsd 244.1811; $[\alpha]^{20}_D$ −18° (c 0.46, $CHCl_3$).

B. Ethanolic Workup. A mixture of **33** (60 mg, 0.218 mmol) potassium hydride (26 mg, 24% in oil, 0.652 mmol) and 18-crown-6 (160 mg, 0.652 mmol) in dry tetrahydrofuran (15 mL) was stirred at room temperature for 30 min and refluxed under argon for 5 h. After the solution was cooled to −78 °C, ethanol (2.0 mL) was introduced and the mixture was subsequently poured into water, extracted with ether, and processed as above. There was isolated 12.4 mg (24%) of **42**, 4.4 mg (8%) of **41**, and 14 mg (23%) of **45**.

For **41**: colorless oil; IR ($CHCl_3$, cm^{-1}) 2980, 2940, 2860, 2820, 1690, 1450, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (br s, 1 H), 2.95 (dd, J = 4.0, 7.6 Hz, 1 H), 2.84–2.75 (m, 1 H), 2.66–1.20 (series of m, 14 H), 1.04 (s, 3 H), 0.95 (s, 3 H), 0.74 (t, J = 7.9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.43, 137.02, 124.62, 54.07, 51.54, 42.30, 32.34, 32.14, 29.39, 28.69, 28.55, 27.26, 25.57, 23.16, 21.87, 18.96, 16.66; MS m/z (M^+) calcd 244.1824, obsd 244.1827; $[\alpha]^{20}_D$ −55° (c 0.42, $CHCl_3$).

C. Equilibration Study. A solution of ketones **41** and **42** (4.4 mg, 1:1 ratio) in tetrahydrofuran (1.0 ratio) in tetrahydrofuran (1.0 mL) was treated with 1.5 mL of 0.1 M sodium methoxide in methanol, stirred for 1.5 h at room temperature, diluted with water (5 mL), and extracted with ether. The combined organic extracts were washed with brine, dried, and evaporated to leave 3.6 mg of a white solid consisting exclusively of **42** (300 MHz, ^1H NMR analysis).

Anionic Oxy-Cope Rearrangement of 34. A mixture of potassium hydride (265 mg of 24% in oil, freshly rinsed with dry petroleum ether, 1.58 mmol) 18-crown-6 (418 mg, 1.58 mmol), and **34** (146 mg, 0.53 mmol) in 12 mL of anhydrous tetrahydrofuran was stirred at room temperature until hydrogen evolution ceased, refluxed for 2 h under argon, and cooled to −78 °C. Following the addition of ethanol (1 mL), the reaction mixture was stirred at −78 °C for 10 min, poured into water, and extracted with ether. The combined organic phases were washed with water and brine, dried, and evaporated. Chromatographic purification of the residue on Florisil (elution with 5% ethyl acetate in petroleum ether) furnished 98 mg (67%) of **45** as a colorless oil: IR (neat, cm^{-1}) 2980, 2920, 2865, 2820, 1705, 1450, 1410, 1375, 1220, 1205, 1195, 1140, 1120, 1095, 1005, 980, 845, 800; ^1H NMR (300 MHz, C_6D_6) δ 4.95 (dd, J = 3.4, 12.3 Hz, 1 H), 3.24 (t, J = 2.7 Hz, 1 H), 3.11 (s, 3 H), 3.03–2.88 (m, 2 H), 2.49–2.38 (m, 2 H), 2.38–2.15 (m, 1 H), 2.10–1.90 (m, 3 H), 1.90–1.00 (series of m, 7 H), 0.95 (s, 3 H), 0.95–0.65 (m, 2 H), 0.79 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 212.36, 140.21, 129.41, 84.08, 55.76, 45.41, 34.87, 30.31, 28.94 (2 C), 28.84, 28.71, 27.69, 25.02, 23.88, 17.69, 16.53, 14.43; MS m/z (M^+) calcd 276.2089, obsd 276.2085; $[\alpha]^{20}_D$ +12° (c 1.27, C_6H_6). Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.20; H, 10.22. Found: C, 78.28; H, 10.23.

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Supplementary Material Available: Figures illustrating the labeling schemes for **16** and **30**, tables of final positional and thermal parameters, bond lengths, bond angles, and torsion angles for **16** and **30**, and tables of final fractional coordinates, thermal parameters, and bond distances and angles for **36** (16 pages). Ordering information is given on any current masthead page.