Impact of Substituent Modifications on the Atropselectivity Characteristics of an Anionic Oxy-Cope Ring Expansion

Leo A. Paquette,* Keith D. Combrink, Steven W. Elmore,[1a] and Robin D. Rogers[1b]

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210, and Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115. *Received August 9, 1990*

Abstract: The phenomenon of atropisomerism is critically examined in the tricyclic *E*,syn,up enolates derived from anionic oxy-Cope rearrangement of 1-vinyl-2-cyclohexenyl-7,7-dimethyl-*exo*-norbornan-2-ols, as well as the ketones derived from their protonation and methylation. In all cases studied, the [3,3] sigmatropic shift proceeds with 100% stereoselectivity via the endo-chair transition-state option. The *E* and syn stereochemistry is established during chirality transfer at this stage. The "oxygen-up" conformation stems directly from the structural features inherent in the starting alcohols. In the unsubstituted example and with certain substitution patterns in the original cyclohexene ring, the *E*,syn,up enolates are seen to be thermodynamically unstable relative to their *E*,syn,down atropisomers, such that products result exclusively by electrophilic capture of the latter. By suitable substitution, the barrier to this preequilibrium can be sufficiently heightened so that products resulting from the *E*,syn,up species can be obtained. Kinetic studies involving several ketone congeners were carried out to show that the predescribed effects persist in neutral analogues as well. Epoxidation of the double bond in one example was shown to continue the trend. The global findings provide unusual insight into those factors that are most responsible for control of atropisomerism in a medium-ring setting.

Atropselective reactions are exceedingly rare.[2] This scarcity stems from the need of the product to possess molecular asymmetry as a consequence of restricted rotation, and this feature often needs to be specifically predesigned into a structure.[3] Also, it is mandatory that any candidate reaction eventuate in the formation of a heavy preponderance of one atropisomer, preferably a single discrete entity. The reaction conditions must therefore not be too forcing. Otherwise, energy might be made available to the system in an amount adequate to trigger competitive comformational isomerization. Reversion to the equilibrium mixture would, quite understandably, defeat the exclusivety that might otherwise have been achieved.

Since selectivity in all of its forms is a current, fashionable pursuit of organic chemistry, the recent discovery in this laboratory of the first example of an atropselective [3,3] sigmatropic shift[4] could not be allowed to pass without further scrutiny. The transformation in question involved the anionic oxy-Cope rearrangement of **1**. Treatment of **1** with potassium hexamethyldisilazide and 18-crown-6 in tetrahydrofuran *at room temperature* for 15 min followed by in situ methylation of the regiospecifically formed enolate resulted in the formation of **3** with 100% stereoselectivity. The very large accelerative rate effects associated with generation of the "naked" alkoxide of **1** allow for rapid conversion of the *E*,syn anion via the endo-chair transition-state **2**. Since there exists no need for thermal input, the reaction conditions can be considered to be near optimal for atropisomerism to surface if such is possible.

When **3** was independently heated in tetrahydrofuran at the reflux temperature, the ketone was gradually transformed into isomer **4**.[4] Evidently, the interconnective barrier associated with the onset of several necessary σ-bond rotations is capable of being surmounted under these conditions. If the energy-minimized structures of **3** and **4**[5] are examined closely (Figure 1), one is immediately struck by the rather significant degree to which these molecules differ in topography and nonbonded interactions. This awareness has prompted our inquiry into which of the specific pendant groups in **3** is singly most responsible for its kinetic stability. As a consequence, we have explored suitable structural modification of the bridgehead olefinic ketone core of this compound and report herein on a number of important observations made in the course of these studies.

Results

Kinetics of the Atropisomerization of 3. Estimation of the heats of formation and strain energies of **3** and **4** by MMX methods has suggested that **4** is approximately 4.3 kcal/mol more stable than **3**.[4] In order to improve upon our quantitative perception of this interconversion, we set out to achieve full kinetic characterization of the system. For this purpose, the thermal activation of **3** was performed on C_6D_6 solutions in the probe of a Bruker 300-MHz spectrometer at 338, 348, and 358 K. The percent composition of the two isomers was determined at regular time intervals by relative integration of the characteristic vinyl proton signal for each ketone. These are easily distinguished since an intense carbonyl shielding effect operates in **3** (δ 5.00 in C_6D_6;

* To whom correspondence should be addressed at The Ohio State University.

(1) (a) Chemistry Department Fellow, 1988-1989. (b) To whom inquiries concerning the X-ray crystallography should be directed at Northern Illinois University.

(2) (a) Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1983**, 657. (b) Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. (c) Although the present work is concerned mainly with atropselective *reactions*, atropisomerism has been known to occur in certain germacranolide natural products and in a few cases the isomers have been separated. For leading references, consult Marshall, J. A.; Lebreton, J.; DeHoff, B. S.; Jenson, T. M. *J. Org. Chem.* **1987**, *52*, 3883.

(3) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill, 1962; pp 156-178.

(4) Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.

(5) The global energy minima were calculated with the aid of MODEL (KS 2.93) in combination with its compansion program BAKMDL.

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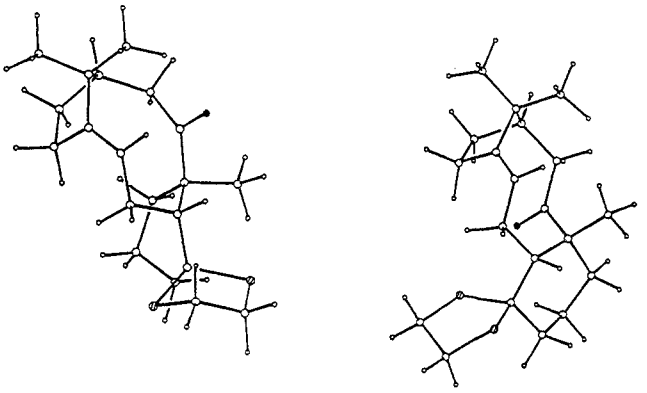
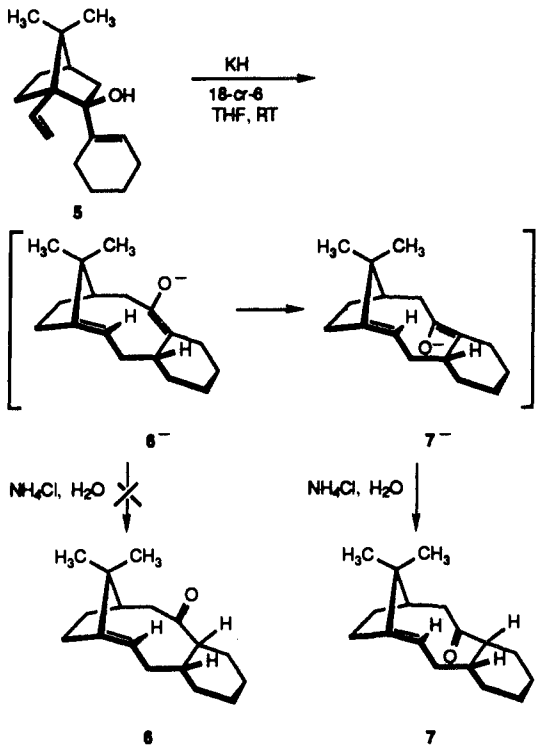


Figure 1. Energy-minimized conformations of atropisomers 3 (left) and 4 (right).

4.84 in $CDCl_3$). This is not possible in **4**, with expected consequences (δ 5.21 in C_6D_6; 5.25 in $CDCl_3$).

A nonlinear least-squares fit of the percent of **4** versus time provided optimized values of the equilibrium distribution (Figure 2). The resultant forward and reverse rate constants, determined by standard first-order kinetics based on ln ($\%\ 4_\infty - \%\ 4_t$) versus t, were determined at three temperatures and 10° intervals. From these data, the free energies of activation were found to be (for **3**) $\Delta G^{\ddagger}_{338}$ 26.3 kcal/mol and (for **4**) $\Delta G^{\ddagger}_{338}$ 27.2 kcal/mol with $K_{eq} = 3.63$.

One additional relevant observation was available from the original study.[4] A direct consequence of eliminating both the dithiolane function *and* angular methyl group (i.e., aqueous NH_4Cl quench of the anionic oxy-Cope rearrangement of **5**) was seen to be direct formation of that atropisomer in which the carbonyl oxygen is already "tucked under", viz., **7**. The vinyl proton of



7 (in $CDCl_3$ solution) appears as a nonshielded multiplet centered at δ 5.15. The stereochemical features of this ketone were further corroborated by X-ray crystallographic analysis of the derived epoxide.[6] However, it was not determined if the conformational isomerization occurred at the enolate stage or subsequent to protonation.

(6) We point out here that the product of DIBAH reduction of **7** is the α-alcohol and not the β-stereoisomer erroneously depicted in ref 4.

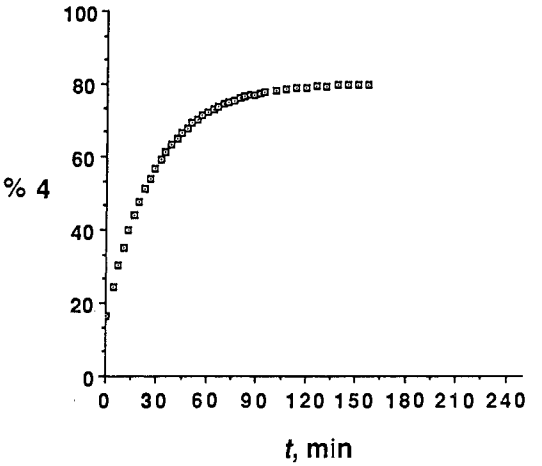
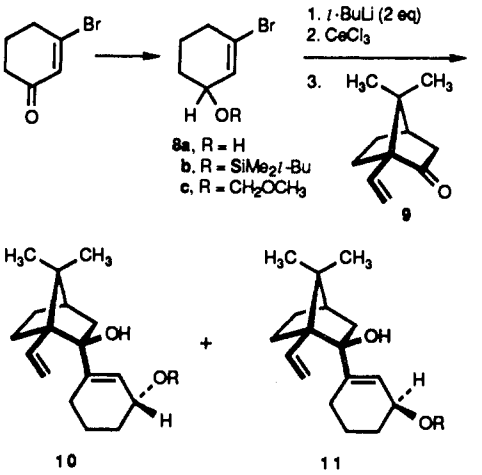


Figure 2. Plot of the appearance of **4** upon heating of **3** at 358 K in C_6D_6 solution as a function of time.

Scheme I



Whatever the case, this finding suggests that rather extensive excision of substituents in this fashion serves to lessen steric congestion considerably. Since 6^- represents the conformation in which the tricyclic product must initially make its appearance, the $6^- \rightarrow 7^-$ and/or $6 \rightarrow 7$ realignment is clearly facile at room temperature. Evidently, the two sites that have been modified in **6** relative to **3** are critical to attaining those elevated barriers conducive to the observation of atropselectivity. Consequently, controlled structural alterations at these positions augured well as being ideally suited to mechanistic clarification.

Synthesis and Coupling of Carbinol Derivatives. The readily available 3-bromo-2-cyclohexenone was subjected to Dibal-H reduction as previously described,[7] and the resultant racemic alcohol **8a** was transformed into ethers **8b** and **8c** by conventional means.[8,9] Unlike the two examples discussed above, the condensation of these vinyl bromides with optically pure **9** introduces the possibility of producing diastereomeric alcohols. Although the opportunity for kinetic resolution exists in principle,[10] the remoteness of the OR substituent from the seat of reaction makes it unlikely that heightened stereoselection would be seen.[11] Indeed, a 1:1 mixture of alcohols **10** and **11** was obtained in both series

(7) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.
(8) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
(9) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(10) Paquette, L. A.; DeRussy, D. T.; Cottrell, C. E. *J. Am. Chem. Soc.* **1988**, *110*, 890.
(11) (a) Paquette, L. A.; DeRussy, D. T.; Vandenheste, T.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 5562. (b) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291. (c) Paquette, L. A.; DeRussy, D. T.; Gallucci, J. C. *J. Org. Chem.* **1989**, *54*, 2278 and earlier references cited in these papers.

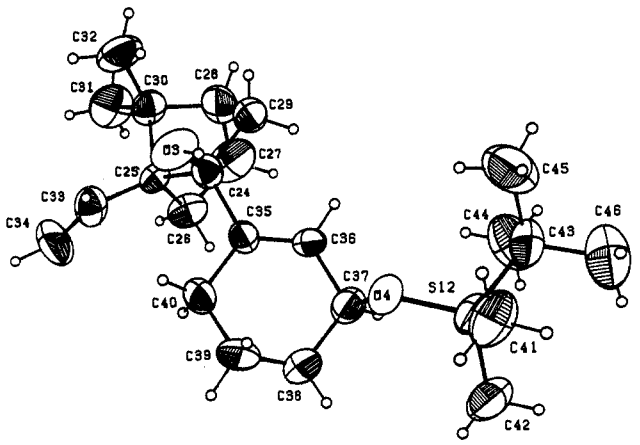
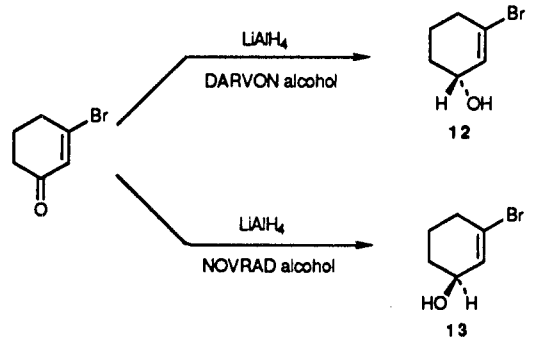


Figure 3. Computer-generated perspective drawing of the final X-ray model of **11b**.

Scheme II



following addition of the respective dichlorocerates[12] to **9** (Scheme I).

It proved possible to separate both sets of diastereomers chromatographically. Suitable definition of the absolute stereochemistry of silyl ethers **10b** and **11b** was accomplished by X-ray analysis of the nicely crystalline, less rapidly eluted norbornanol. Since **9** derives from (1*R*)-(+)-camphor[12] and the (*tert*-butyldimethylsilyl)oxy (O(TBS)) substituent in **11b** is spatially oriented as shown in Figure 3, the neighboring stereogenic center necessarily possesses the *S* configuration. The ^1H and ^{13}C NMR spectra of **10b** and **11b** are not adequately different to be stereochemically diagnostic. Consequently, when neither **10c** nor **11c** proved suitably crystalline for X-ray study, we turned to an alternative means for distinguishing these diastereoisomers.

Advantage was taken of the recognized ability of freshly prepared[13] DARVON alcohol–$LiAlH_4$ complex[14,15] to accomplish the enantioselective reduction of ketones.[14-17] In the presence of this reagent, 3-bromo-2-cyclohexenone was smoothly transformed into the dextrorotatory *R* alcohol **12** in 80% yield (Scheme II). The indicated absolute configurational assignment is based upon condensation with the acid chloride of (*S*)-(+)-O-methylmandelic acid[18] and ^1H NMR correlation of the diastereomeric esters according to Mosher[19] and Trost.[20-22] Integration of the olefinic region of these spectra indicated the reduction process to proceed with 50–60% enantiomeric excess (ee). The rotation of optically pure (*R*)-**12** was thereby calculated to be +40.9° in $CHCl_3$ (Figure 4).[23]

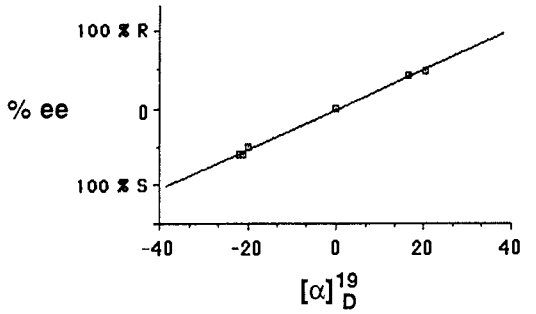
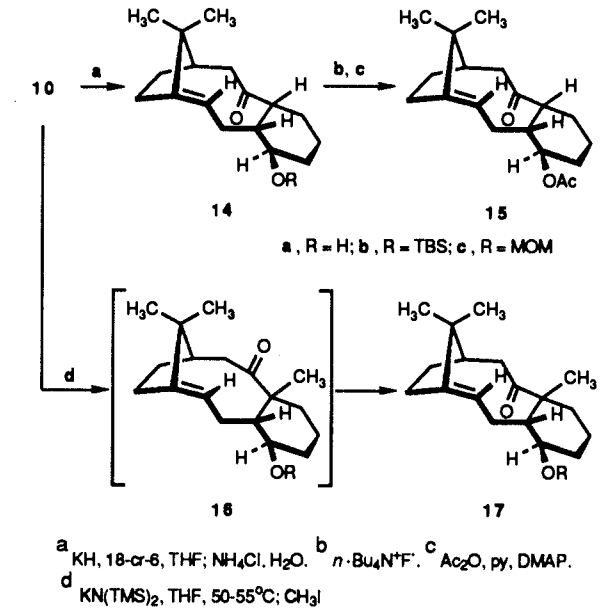


Figure 4. Plot of percent enantiomeric excess versus rotation for alcohols **12** and **13** ($CHCl_3$ solution).

Scheme III



Several decades ago, the remarkable observation was made that the DARVON alcohol–$LiAlH_4$ complex reverses its stereoselectivity toward ketones when aged.[13] In the present setting, the kinetic preference for formation of **12** did diminish when the reducing agent was allowed to stand, but the point was never reached where enantiomeric alcohol **13** became dominant. Furthermore, the actual level of stereoinduction varied considerably from run to run and was not predictable. For this reason, we made recourse to the NOVRAD alcohol–$LiAlH_4$ system.[24,25] When utilized under the original conditions described above, this reagent reproducibly gave rise to **13** (>75% yield, >50% ee).

These developments now allow for the convenient and selective preparation of **10b** and **10c** or **11b** or **11c** in enantiomerically

(12) Fischer, N.; Opitz, G. *Organic Syntheses*; Wiley: New York, 1973, Collect. Vol. V, p 877.
(13) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94*, 9254.
(14) DARVON alcohol is (+)-(2*S*,3*R*)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol: Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.
(15) Grandbois, E. R.; Howard, S. I.; Morrison, J. D. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1983; Vol. 2, pp 71–90.
(16) Marshall, J. A.; Robinson, E. D. *Tetrahedron Lett.* **1989**, *30*, 1055.
(17) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M.; Yarnell, T. M. *J. Am. Chem. Soc.* **1977**, *99*, 8341.
(18) Roy, B. L.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 651.
(19) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(20) (a) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 4929. (b) Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkoveck, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.
(21) Paquette, L. A.; Lau, C. J. *J. Org. Chem.* **1987**, *52*, 1634.
(22) (a) Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925. (b) Marshall, J. A.; Lebreton, J. *J. Org. Chem.* **1988**, *53*, 4108.
(23) Formation of the *O*-methylmandelate esters was found to proceed with a reproducible kinetic bias in this series. Thus, condensation with racemic **8a** produced a 1.5:1 mixture of esters favoring the *R*-alcohol. The data contained in Figure 3 following correction for this behavior are characterized by a correlation coefficient of 0.998.
(24) NOVRAD is DARVON spelled backwards to reflect the enantiomeric relationship of the two compounds; see: Deeter, J.; Frazier, J.; Staten, G.; Staszak, M.; Weigel, L. *Tetrahedron Lett.* **1990**, *31*, 7101.
(25) Pohland, A.; Sullivan, H. R. *J. Am. Chem. Soc.* **1955**, *77*, 3400.

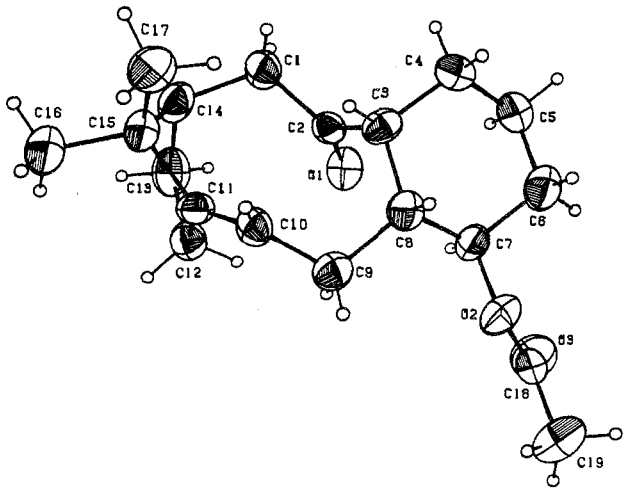


Figure 5. Computer-generated perspective drawing of the final X-ray model of **15**.

enriched fashion and for their ready identification in absolute stereochemical terms.

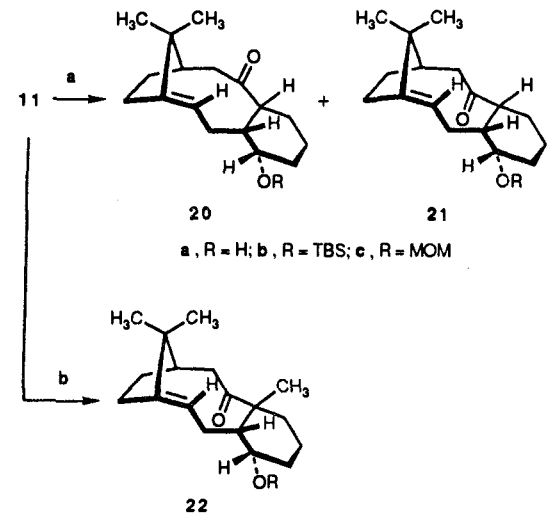
Studies Involving the *R*-Carbinol Derivatives. Analysis of the Anionic Oxy-Cope Trajectory and Atropisomeric Capacities. 1-Vinyl-2-alkenyl-7,7-dimethyl-*exo*-norbornan-2-ols exemplified by **1**, **5**, **10**, and **11** possess structural features that allow for the possible operation of four distinctively different transition states in the course of anionic [3,3] sigmatropic rearrangement.[4] We have previously established that **1** and **5** isomerize exclusively via their respective endo-chair activated complexes, of which **2** is representative. Since the magnitudes of the energy gaps separating the four stereoalignment options are not known, small structural changes in the starting material could bring about a crossover in kinetic preference. Were this scenario to develop, the several stereodiagnostic centers that are simultaneously established would, of course, be installed differently. Therefore, determination of product stereochemistry is a necessary prelude to any investigation of atropisomerization.

Following the treatment of **10b** with a small excess of potassium hydride in THF, heating at 50 °C for 1 h was necessary to achieve complete consumption of the alcohol. The coaddition of 18-crown-6 caused the isomerization to be complete in <30 min at room temperature. Either set of conditions led after an aqueous NH_4Cl quench to ketone **14b** as the sole product in good yield (Scheme III). The appearance of its proton at δ 5.12 (in $CDCl_3$) indicated it not to be in close proximity to the carbonyl group. Because this structural limitation could be minimally satisfied by two diastereomeric alternatives, further stereochemical details were sought. To accomplish this, **14b** was sequentially desilylated and acylated under mild conditions to give **15**, a superbly crystalline compound. Following X-ray analysis of the compound (Figure 5), two mechanistic issues were made apparent. Without doubt, **10b** also adopts an endo-chair transition state during the oxy-Cope process. In addition, the O(TBS) group was seen to be insufficient to maintain that original conformation where the enolate or carbonyl oxygen is projected in an upward direction. Much as in the case of **5**, therefore, the level of conformational control is adequate to permit the observation of discrete atropisomers at temperatures at or near ambient.

Ketone **14c**, as obtained from the comparable handling of **10c**, was likewise isolated as the thermodynamically favored conformer and showed no tendency to isomerize when heated.

To set the stage for a gradual increase in steric encumbrance, suitable introduction of an angular methyl group was next undertaken. Quite unexpectedly, the enolate anions produced by oxy-Cope rearrangement of **10b** and **10c** proved rather recalcitrant to reaction with various methylating agents. Following considerable experimentation, conditions were ultimately uncovered for achieving C-alkylation reproducibly. In no case did we find it possible to accomplish this step when KH and 18-crown-6 were used to promote [3,3] sigmatropy.[26] However, if either alcohol

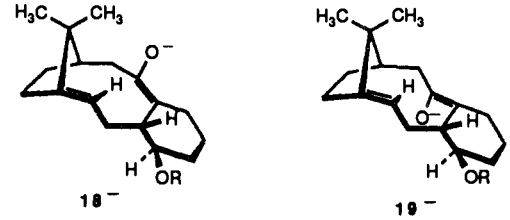
Scheme IV



[a] KH or KN(TMS)$_2$, 18-cr-6, THF; NH_4Cl, H_2O. [b] KH or KN(TMS)$_2$, 18-cr-6, THF; CH_3I

was briefly heated with potassium hexamethyldisilazide in THF at 50–55 °C, *not allowed to cool*, and exposed to excess methyl iodide at this temperature for 30 min, then **17b** and **17c** were obtained in yields exceeding the 60% level. Although this reaction temperature is somewhat more elevated than that usually employed, it would have initiated only early progress in the atropisomerization of **3**.

The spectral characteristics of **17b** and **17c**, including nuclear Overhauser effect (NOE) different experiments in the first instance, indicated that reactions had not stopped at **16** but proceeded beyond that point to deliver **17**. These data may be taken as a reflection of the inability of the triad consisting of the *E* double bond, angular methyl group, and β-OR substituent to hold the conformation present in **16**. Alternatively, it is entirely possible that **18**$^-$, the enolate anion through which these substrates must necessarily pass on the way to product, is thermodynamically unstable relative to **19**$^-$ and that **19**$^-$ is the species that experiences protonation and methylation. The experiments that follow shed considerable light on this major uncertainty.



Stereochemical Assessment of the *S*-Carbinol Series. Reversal in the Thermodynamic Bias of Two Enolate–Ketone Atropisomeric Equilibria. In continuation of our systematic investigation, **11b** and **11c** were treated with potassium hydride or potassium hexamethyldisilazide in tetrahydrofuran containing 18-crown-6 and ultimately quenched with aqueous ammonium chloride solution. Both derivatives were efficiently converted into a mixture of atropisomers **20** and **21**, the ratio of which when recorded immediately after isolation deviated little from 60:40 in the two examples (Scheme IV).' Quite unexpectedly, however, all of the bridgehead olefinic ketones in this series proved sensitive to silica gel chromatography. Purification was therefore carried out on Bio-Sil A. These conditions did not allow for the separation of **20b** from **21b** or of **20c** from **21c**.

(26) No methylation was observed with methyl iodide or methyl *p*-toluenesulfonate at ambient temperature. Dimethyl sulfate gave rise to O-methylated product. Recourse to methyl iodide in the presence of HMPA yielded an inseparable mixture of the product of O-methylation and at least two other unidentified compounds.

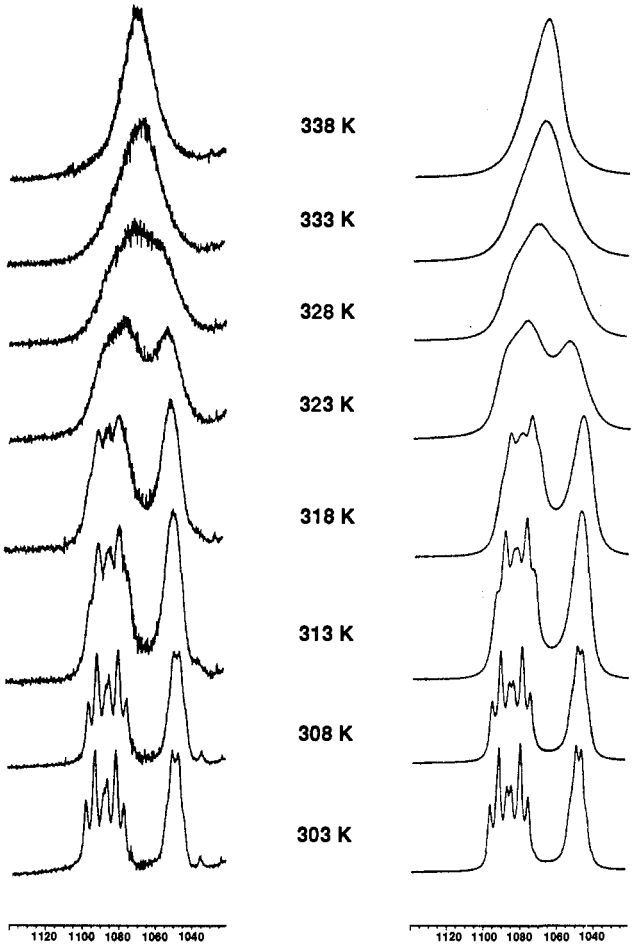


Figure 6. Experimental (left) and calculated (right) 300-MHz ^{1}H NMR spectra of the **20c**/**21c** equilibrium as a function of temperature in toluene-d_8 solution.

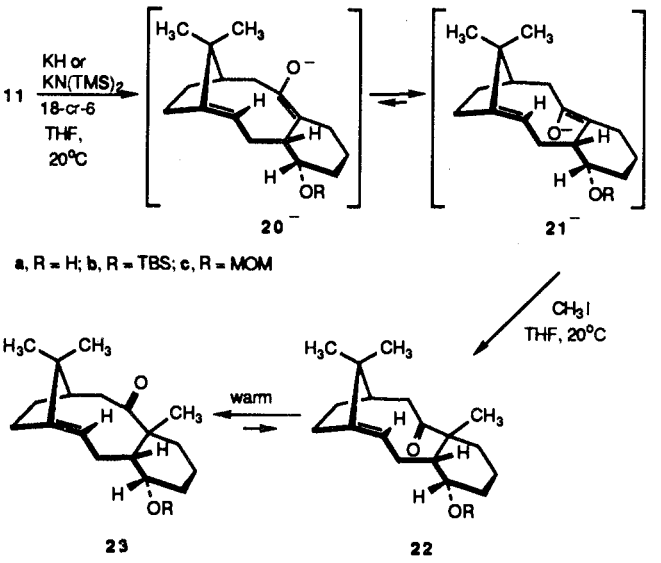
Table I. Rate Constants and Activation Parameters for the **20c** ↔ **21c** Equilibrium As Determined by Line-Shape Analysis

run	t, K	k_f	k_r
1	303	13.0	9.0
2	308	15.1	10.5
3	313	25.9	18.0
4	318	37.4	26.0
5	323	72.0	50.0
6	328	93.6	65.0
7	333	144	100.0
8	338	230	160.0
		k_1	k_r
E_A, kcal/mol		17.4	17.4
$\Delta H^{\ddagger}_{298}$, kcal/mol		16.8	16.8
$\Delta S^{\ddagger}_{298}$, kcal/mol		1.6	0.9
$\Delta G^{\ddagger}_{298}$, kcal/mol		16.3	16.5

However, since the interconversion of **20c** with **21c** was rapid on the NMR time scale, it proved possible to perform a definitive line-shape analysis. The temperature range studied was 303–338 K, and the solvent employed was toluene-d_8. Under these conditions, a K_{eq} of 1.44 favoring **20c** was observed. Representative experimental (300-MHz) data for **20c** (δ 3.62 at 303 K) and for **21c** (δ 3.49 at 303 K) are shown as a function of temperature on the left in Figure 6. The theoretical spectra illustrated on the right were calculated by means of a three-site exchange program written specifically for an ABCD system of the type present in these molecules.[27] Thereby accomplished was determination of the extent of line broadening due to rapid exchange for a particular rate constant. The first-order k's where matching occurred are compiled in Table I. The free energies of activation ($\Delta G^{\ddagger}_{338}$) associated with the forward and reverse reactions are 16.2 and 16.5 kcal/mol, respectively.

(27) We are grateful to Prof. Gideon Fraenkel and Dr. Jose Cabral for providing us with this program and to Dr. Cabral for providing instructions on its use in the present context.

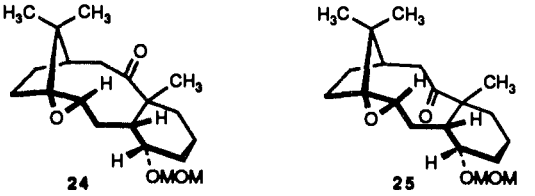
Scheme V



The rapidity with which **11b** and **11c** undergo anionic oxy-Cope rearrangement at room temperature provided us with the opportunity to see that condensation of the resulting enolate anions with methyl iodide was complete within 30 min at room temperature. *This behavior contrasts in a striking way with the considerably dampened reactivity of the R-enolates studied earlier.* Since only **22b** and **22c** were isolated from these reactions, the slower rates of formation of **17b** and **17c** can be attributed to the substantial steric interference brought on by the β-oriented OR group positioned in close proximity and syn to the entering CH_3 group.

When **22b** and **22c** were warmed in order to gain information on their inherent conformational stability, the very significant observations were made that conversion to **23b** and **23c** materialized and to a considerable degree (Scheme V). For example, heating **22b** to 40 °C in $CDCl_3$ for 31 h produced an 81.2:18.8 equilibrium distribution (K_{eq} = 4.3) of **23b** and **22b**. Kinetic analysis of this atropisomerization was performed on C_6D_6 solutions of **22c** in the probe of a Bruker 300-MHz NMR spectrometer at 313, 323, and 333 K. The two ketones are easily distinguished since shielding by the carbonyl group in **23c** (δ 4.85) cannot operate in **22c** (δ 5.16). The percent of **23c** versus time for each run provided forward and reverse rate constants that were assimilated into an Arrhenius plot. The free energies of activation ($\Delta G^{\ddagger}_{333}$) for **22c** and **23c** were thereby determined to be 24.4 and 25.1 kcal/mol, respectively (K_{eq} = 3.00). From these data, it can be discerned that **22c** (and **22b** by analogy) need be handled with reasonable care in order to avoid operation of those single-bond rotations that result in atropisomerization.

Added insight into the "carbonyl up" conformational character of **23c** was gained by means of epoxidation chemistry. Exposure of **23c** to MCPBA in the presence of phosphate buffer produced in 81% yield a 6:1 mixture of **24** and **25**. Recrystallization of



material of this quality from ether/hexane succeeded in providing pure **24** whose crystalline nature proved suitable for three-dimensional X-ray analysis. As seen in Figure 7, the carbonyl

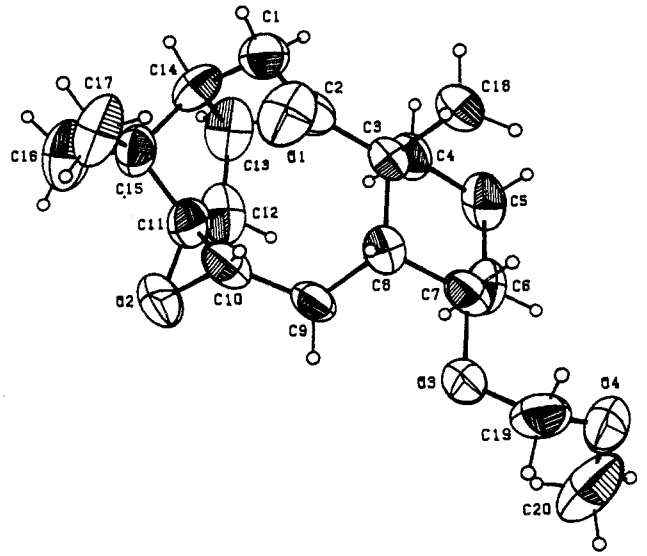


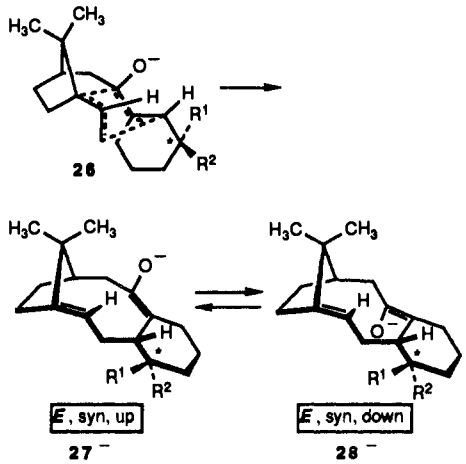
Figure 7. Computer-generated perspective drawing of the final X-ray model of **24**.

oxygen and angular methyl group in the thermodynamically favored isomer enjoy a synclinal relationship. Under identical conditions, **22c** was transformed into a 1:1.5 mixture of **24** and **25**. The latter epoxide could not be isolated free of **24**. In addition, heating a 1:1 mixture of these two atropisomers in refluxing tetrahydrofuran for 2 days caused **24** to dominate the equilibrium by a factor of 3.7:1.

Note that the atropisomeric bias favoring the "carbonyl up" conformer shown by **23** and **25** lies in that direction that is precisely opposite to the thermodynamic preference exhibited by **4**, **7**, and **17**.

Discussion

As the starting point for mechanistic discussion, we focus on the emergence of *E*,syn stereoisomeric products in every instance. On this basis, it is clear that all of the 1-vinyl-2-cyclohexenyl-7,7-dimethyl-*exo*-norbornan-2-ols examined undergo anionic oxy-Cope by way of the endo-chair transition state[4] represented by **26**.[4] This reaction trajectory is unique in its capacity for



transferring the requisite stereochemical characteristics to both the double bond and homoallylic ring junction site. The present data show in an impressive way that the degree of substitution at the asterisked carbon and its relative configuration impact prominently on the atropisomeric equilibrium defined by **27**$^-$ ⇄ **28**$^-$. The unsubstituted derivative **6**$^-$ provides a useful first calibration. Since no additional steric effects are introduced in this example, rotation about several peripheral single bonds can take place without serious impedance to arrive at the thermodynamically more stable *E*,syn,down conformer **7**$^-$. This ground-state preference is revealed upon simple protonation, the process giving **7** exclusively. When the [3,3] sigmatropic rearrangement of **5** was performed in an NMR tube (THF-d_8 as solvent) and subsequently quenched with NH_4Cl/D_2O at 0 °C, no vinyl proton signal appeared in the δ 5.0–4.5 region. Therefore, it appears unlikely that some modest amount of **6** is formed with post-isomerization to **7**.

An essentially identical reaction profile appears to be adopted by **10b** and **10c**. Under the conditions of the anionic oxy-Cope reaction, **18**$^-$ is produced first. Since the OR substituent resides on the open β face of enolate anion **18**$^-$, no unusual steric compression develops during the atropisomerization process that gives rise to **19**$^-$. Funneling of the system in this direction is consistent with the direct formation of **15** and **17**. Our failure to detect **16** is taken to mean that it probably is not formed. This conclusion is tantamount to claiming that the **18**$^-$/**19**$^-$ equilibrium is shifted heavily in the direction of **19**$^-$, such that **18**$^-$ does not find it possible to compete kinetically.

This need not always be so. In fact, the behavior of **11b** and **11c** is key to our understanding of how delicate the interplay of equilibrium and rate can become in this series. In these most compelling examples, the α orientation of the OR group introduces a new steric effect, a repulsion term stemming from congestion that develops in the interior of the molecule as it becomes "tucked inside" in **21**$^-$. Consequently, the energies corresponding to **20**$^-$ and **21**$^-$ are no longer as imbalanced as in the two preceding scenarios, since the latter is now destabilized to some degree. If the transition states for protonation come early in an exothermic process that conforms to the Hammond postulate,[28] then the 60:40 product distributions exhibited by **11b** and **11c** may well effect the equilibrium proportion of these enolate anions at room temperature. The increased energetic demands involved in methylation cause the associated transition states to be productlike. This turn of events provides the system with little choice but to react via **21**$^-$ to give **22**.

Kinetic studies dealing with the thermal isomerization of **3** to **4** have provided evidence that the rate achieved at 348 K compares closely to that realized by **22c** at a temperature some 25–30 °C cooler. Consequently, incorporation of the asterisked carbon in **27**$^-$ as C-2 of a spiro 1,3-dithiolane ring conveys enhanced rigidity to the framework of the first-formed *E*,syn,up conformer. As a result, the energetic demands of the methylation transition state can be met without prior atropisomerization of the system. Ketone **3** is therefore produced exclusively.

Analysis of the energy surfaces associated with protonation and alkylation of these tricyclic enolate anions based upon the thermochemical and kinetic characteristics of each isomer suggests that an unusual sensitivity to substitution at C* is at play. Advocacy of this central underlying controlling element takes its justification largely from the internal consistency of our observations and also from equilibration data acquired from examination of the netural ketone congeners. We have seen, for example, that the **3**/**4** equilibrium is heavily skewed in the *E*,syn,down direction at modest temperatures. An entirely comparable thermodynamic preference is exhibited by **7**, **14**, **15**, and **17**. On the other hand, the isomer pairs **20b**/**21b** and **20c**/**21c** are much more closely balanced in energy. In both cases, it was noted that the *E*,syn,up geometry is now preferred, a likely consequence of the α-oriented OR substituent. More complete is the crossover reflected in the **22**/**23** equilibrium where **23** is now substantially favored. The presence of an angular methyl group clearly serves to raise the barrier to atropisomeric interconversion. Epoxidation of the double bond continues this trend (**24** > **25**), thereby showing the oxirane ring to be capable of exerting conformational consequences comparable to those present in a double bond.

The findings reported herein provide unique insight into those factors that control atropisomerization in a medium-ring setting. Following stereocontrolled formation of *E*,syn,up enolates by oxyanion-promoted [3,3] sigmatropy, the stereoselectivity of protonation or alkylation is subsequently determined by the in-

(28) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

trinsic thermochemical stability of this atropisomer relative to the energetic demands of reaching the particular transition state. Whereas the *E*,syn,down geometry is often the more stable arrangement, this is not always so. Purposeful control is now entirely possible and genuinely feasible.

We hope to apply such knowledge with proper predetermination during more advanced, controlled functionalization of these molecules as demanded by a projected enantiospecific synthesis of taxane systems currently in progress.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and the ^{13}C NMR data obtained at either 75 or 20 MHz as indicated. Mass spectra were measured on a Kratos MS-30 instrument by Mr. Dick Weisenberger at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were performed under an inert atmosphere (nitrogen or argon) unless otherwise indicated. Solvents were reagent grade and dried prior to use.

1-Bromo-3-[(*tert*-butyldimethylsilyl)oxy]cyclohexene (8b). To a solution of **8a**[7] (3.24 g, 18 mmol) in dry, distilled DMF (30 mL) were added 1.88 g (28 mmol) of imidazole and 3.46 g (23 mmol) of *tert*-butyldimethylchlorosilane. The flask was purged with nitrogen, and the solution was stirred overnight at room temperature. Following dilution with ether (100 mL), the mixture was washed with water and brine prior to drying and concentration. The residual yellow oil was immediately purified by chromatography on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **8b** as a clear, colorless liquid (4.77 g, 89%); IR (neat, cm^{-1}) 3060–2790, 1640, 1470–1430, 1300–1220, 880–750, 740–720, 690–650; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (td, J = 3.4, 1.7 Hz, 1 H), 4.26–4.00 (m, 1 H), 2.46–2.33 (m, 2 H), 1.91–1.68 (m, 2 H), 1.67–1.50 (m, 2 H), 0.89 (s, 9 H), 0.073 (s, 3 H), 0.066 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.53, 125.32, 67.94, 35.06, 31.14, 25.82, 20.90, 18.16, −4.69; MS m/z (M^+) calcd 290.0701, obsd 290.0680. Anal. Calcd for $C_{12}H_{23}BrOSi$: C, 49.64; H, 7.99. Found: C, 49.62; H, 7.93.

1-Bromo-3-(methoxymethoxy)cyclohexene (8c). To a solution of **8a** (5.5 g, 31.1 mmol) in CH_2Cl_2 (15 mL) was added diisopropylethylamine (27 mL, 155 mmol). The reaction mixture was cooled in ice as chloromethyl methyl ether (7.1 mL, 93 mmol) was introduced, and the solution was stirred overnight at room temperature and poured into water (100 mL). The aqueous phase was extracted with ether, and the combined organic layers were dried and concentrated. The residue was rapidly eluted through a short column of silica gel (elution with 10% ethyl acetate in hexanes) and distilled to give 5.9 g (86%) of **8c** as a colorless oil: bp 70–72 °C (0.35 Torr); IR (neat, cm^{-1}) 2915, 2865, 1639, 1430, 1350, 1320, 1140, 1089, 1025, 910; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (dt, J = 2, 4 Hz, 1 H), 4.64 (s, 2 H), 4.08–4.00 (m, 1 H), 3.34 (s, 3 H), 2.48–2.20 (m, 2 H), 1.90–1.52 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.51, 127.07, 95.05, 71.81, 55.18, 35.12, 27.80, 20.57; MS, the molecular peak was observed, but was too transient for high-resolution measurement. Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93. Found: C, 43.47; H, 5.91.

Reduction of 3-Bromo-2-cyclohexenone with the DARVON Alcohol–$LiAlH_4$ Complex. Under nitrogen, a solution of DARVON alcohol (42.6 g, 150 mol), $[\alpha]^{20}_D$ +8.0° (c 2.02, EtOH) in anhydrous ether (250 mL) was added to a solution of $LiAlH_4$ (62.8 mL of 1.0 M in ether, 62.8 mmol) at −40 °C over 10 min. To the insoluble complex was immediately added during 2 min a solution of the bromo ketone (5.7 mL, 57.1 mmol) in anhydrous ether (100 mL). The reaction flask was stored at −78 °C overnight. After 16 h, saturated aqueous sodium sulfate solution (20 mL) was carefully introduced, the mixture was filtered, and the solid filter cake was washed with hot THF (300 mL). The aqueous layer was extracted with ether, and the combined organic solutions were washed with 0.1 N HCl (10 × 50 mL) and 0.5 N HCl (10 × 50 mL), dried, and concentrated. The residue was purified by silica gel chromatography (elution with 15% ethyl acetate in petroleum ether) to give **12** (8.06 g, 80%) as a clear oil, $[\alpha]^{19}_D$ +22.2° (c 1.0, $CHCl_3$) of 55% ee.

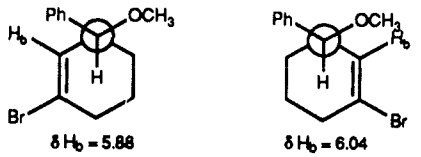
Reduction of 3-Bromo-2-cyclohexenone with the NOVRAD Alcohol–$LiAlH_4$ Complex. A 10.0-g (57.1-mmol) sample of the bromo ketone was comparably reduced with 42.6 g (150 mmol) of NOVRAD alcohol, $[\alpha]^{20}_D$ −7.88° (c 3.55, EtOH) and $LiAlH_4$ (62.8 mL of 1.0 M, 62.8 mmol) in ether (250 mL) at −40 °C and then at −78 °C. The identical workup afforded 7.70 g (76%) of **13** as a colorless oil, $[\alpha]^{19}_D$ −22.0° (c 2.08, $CHCl_3$) of 55% ee.

Mosher Ester Correlations. Oxalyl chloride (0.4 mL, 4.58 mmol) was added to (*S*)-(+)-α-methoxyphenylacetic acid (100.8 mg, 0.606 mmol), and the mixture was stirred for 2 h. The excess oxalyl chloride was removed in vacuo, and benzene (1 mL) was added. A solution containing racemic 3-bromo-2-cyclohexen-1-ol (93 mg, 0.525 mmol) and pyridine (0.2 mL) in benzene (1 mL) was introduced, and the mixture was stirred for 30 min before being poured into water (20 mL). The aqueous layer was extracted with ether. The combined organic phases were washed with 0.1 N HCl and brine, dried, and evaporated. ^1H NMR analysis of the unpurified product showed a 1.5:1 mixture of the *S,R*- and *S,S*-esters to be present.

Following this procedure, a sample of alcohol exhibiting $[\alpha]^{19}_D$ +20.5° (c 2.48, $CHCl_3$) gave in 85% yield a 4:1 mixture of esters with the *S,R*-distereomer predominating. In the same way, an alcohol sample characterized by $[\alpha]^{19}_D$ +16.6° (c 1.45, $CHCl_3$) gave in 78% yield a 2.75:1 ester mixture.

Other results: (a) $[\alpha]^{19}_D$ −20.2° (c 1.8, $CHCl_3$) gave in 81% yield a 3.1:1 (corrected for established kinetic bias) mixture of esters rich in the *S,S* form. (b) $[\alpha]^{19}_D$ −22.0° (c 1.7, $CHCl_3$) afforded in 71% yield a 3.9:1 (corrected for kinetic bias) mixture of esters having the *S,S* form as the major constituent.

The configurational assignments follow from the Newman projections shown:



Addition of Racemic 8b to (1*S*)-2-Oxo-7,7-dimethyl-7-vinylbicyclo[2.2.1]heptane (9). A 6.85-g (18.4-mmol) sample of $CeCl_3 \cdot 7H_2O$ was dried by heating at 140 °C (0.1 Torr) overnight. The cooled dry solid was covered with 30 mL of dry THF, and the slurry was magnetically stirred under nitrogen for 3 h. Meanwhile, a solution of (±)-**8b** (4.0 g, 13.8 mmol) in 25 mL of anhydrous THF was cooled to −78 °C and treated dropwise via syringe with a solution of *tert*-butyllithium in pentane (16.8 mL of 1.7 M, 28.5 mmol) with vigorous stirring. This dark green solution was stirred at this temperature for 30 min.

To ensure dryness, the $CeCl_3$ slurry was titrated to a persistent orange at room temperature with *tert*-butyllithium. Following this, the slurry was cooled to −78 °C and the vinyllithium solution was introduced via cannula. The dark reaction mixture was stirred for 45 min prior to the addition of **9** (1.52 g, 9.2 mmol) dissolved in 20 mL of THF. A color change to green occurred after 5 min and to orange after an additional 30 min. Following a total of 2 h of stirring, the cold bath was removed and 5 mL of saturated aqueous NH_4Cl was introduced. The quenched reaction mixture was diluted with ethyl acetate, filtered through Celite, washed with brine, and dried. Solvent evaporation left a yellow oil that was purified by chromatography on TLC mesh silica gel (elution with 2% ethyl acetate in petroleum ether). There were isolated in order of elution 1.005 g (29%) of **10b** and 1.035 g (30%) of **11b**.

For 10b: colorless oil; IR ($CHCl_3$, cm^{-1}) 3000–2900, 2880, 2850, 1100–1060, 1050, 830; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (dd, J = 11.1, 17.8 Hz, 1 H), 5.72 (t, J = 1.2 Hz, 1 H), 5.20 (dd, J = 2.0, 11.1 Hz, 1 H) 4.99 (dd, J = 2.1, 7.8 Hz, 1 H), 4.26–4.24 (m, 1 H), 2.14–1.91 (m, 3 H), 1.85–1.60 (series of m, 5 H), 1.50–1.35 (m, 3 H), 1.21 (s, 3 H), 1.30–0.93 (series of m, 3 H), 0.87 (s, 9 H), 0.76 (s, 3 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.67, 137.35, 126.41, 115.43, 84.80, 67.47, 58.82, 53.40, 45.67, 42.01, 32.08, 26.43, 26.21, 25.87, 25.48, 21.64, 21.01, 20.32, 18.21, −4.28, −4.55; MS m/z (M^+) calcd 376.2797, obsd 376.2789; $[\alpha]^{20}_D$ −26.5° (c 3.46, $CHCl_3$).

For 11b: colorless crystals, mp 90–92 °C (from ethyl acetate–hexane); IR ($CHCl_3$, cm^{-1}) 3000–2900, 2880, 2850, 1100–1060, 1050, 830; ^1H NMR (300 MHz, $CDCl_3$) δ 6.15 (dd, J = 11.1, 17.8 Hz, 1 H), 5.61 (s, 1 H), 5.07 (dd, J = 1.9, 11.1 Hz, 1 H), 4.89 (dd, J = 1.9, 17.8 Hz, 1 H), 4.15 (d, J = 2.4 Hz, 1 H), 2.15–1.51 (series of m, 8 H), 1.50–1.30 (m, 3 H), 1.09 (s, 3 H), 1.20–0.83 (series of m, 3 H), 0.78 (s, 9 H), 0.63 (s, 3 H), −0.03 (s, 3 H), −0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.26, 137.71, 125.77, 114.92, 84.79, 67.50, 58.55, 51.25, 45.75, 42.30, 32.20, 26.22, 26.07, 25.96, 25.47, 21.66, 21.03, 20.15, 18.24, −4.48, −4.59; MS m/z (M^+) calcd 376.2797, obsed 376.2789; $[\alpha]^{21}_D$ −56.9° (c 2.0, $CHCl_3$).

X-ray Data Collection Structure Determination and Refinement for 11b.[29-31] A transparent single crystal of **11b** was mounted on a pin and

(29) Sheldrick, G. M. SHELX76, a system of computer programs for X-ray structure determination as locally modified, University of Cambridge, England, 1976.

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

transferred to a goniometer. The space group was determined to be $P2_12_12_1$ from the systematic absences. A summary of data collection parameters is given in Table II (see supplementary material).

Least-squares refinement with isotropic thermal parameters led to $R = 0.121$. High thermal motion was noted in molecule 1 for one of the Si–Me groups and for the methyl group of Si-1's *tert*-butyl group. It was not possible to refine a disorder model for these atoms. The high B-(equiv) parameter probably does reflect thermal motion rather than static disorder.

The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 Å^2. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C–H = 0.95 Å, B = 5.5 Å^2). The remaining hydrogen atoms were located from a difference Fourier map and included with fixed contributions (B = 5.5 Å^2). Refinement of non-hydrogen atoms with anisotropic temperature factors led to the final values of $R = 0.054$ and $R_w = 0.066$. The final values of the positional parameters are given in the supplementary material.

Addition of Optically Active 8c to 9. A. The *R*-Enriched Bromide. $CeCl_3 \cdot 7H_2O$ (4.16 g, 11.2 mmol) was dried under vacuum (1–1.5 Torr) at 145 °C for 3–5 h. The flask was cooled, and dry nitrogen was introduced. The white powder was covered with anhydrous THF (40 mL) and the solution stirred for 2 h. The slurry was cooled to −78 °C and treated with *tert*-butyllithium in pentane until a pale orange persisted (0.9 mL of 1.7 M).

A solution of **8c** (2.0 g, 9.0 mmol, R:S = 4:1) in dry THF (30 mL) cooled to −78 °C was treated with *tert*-butyllithium (10.6 mL of 1.7 M in pentane, 18.2 mmol) and stirred for 45 min. The resulting vinyllithium was transferred via cannula to the $CeCl_3$ slurry also at −78 °C. This mixture was stirred for 5 h, at which point a solution of **9** (640 mg, 4.0 mmol) was introduced. The reaction mixture was stirred overnight at −78 °C and worked up in the predescribed manner. Chromatography on TLC-grade silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 399 mg (33%) of **10c** and 51 mg (4%) of **11c** (as a 4:1 mixture with **10c**), in addition to 191 mg (30%) of unreacted **9**.

B. The *S*-Enriched Bromide. Recourse to the identical reaction conditions, but now involving **8c** (R:S = 1:3), gave 76 mg (6%) of **10c** (as a 3:1 mixture with **11c**) and 279 mg (23%) of **11c**.

For 10c: colorless oil; IR ($CHCl_3$, cm^{-1}) 3688, 2992, 2941, 2884, 1450, 1386, 1367, 1325, 1290, 1149, 1099, 1038, 918; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (dd, J = 11.1, 17.8 Hz, 1 H), 5.77 (m, 1 H), 5.10 (dd, J = 2.0, 11.1 Hz, 1 H), 4.93 (dd, J = 2.0, 17.8 Hz, 1 H), 4.61 (dd, J = 6.9, 12.6 Hz, 2 H), 4.05–4.04 (m, 1 H), 3.28 (s, 3 H), 2.11–1.49 (m, 13 H), 1.13 (s, 3 H), 1.11–1.01 (m, 1 H), 0.68 (s, 3 H); ^{13}C NMR (75 MHz) δ 145.66, 137.39, 122.47, 114.83, 94.85, 84.50, 72.00, 58.28, 54.87, 51.15, 45.45, 41.94, 28.83, 26.17, 26.05, 25.23, 21.49, 20.84, 19.91; MS m/z (M$^+$) calcd 306.2195, obsd 306.2217; $[\alpha]^{19}_D$ +26.6° (c 1.13, $CHCl_3$).

For 11c: colorless oil; IR ($CHCl_3$, cm^{-1}) 3688, 2992, 2942, 2882, 1626, 1450, 1387, 1367, 1290, 1148, 1099, 1037, 918; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (dd, J = 11.1, 17.8 Hz, 1 H), 5.80 (m, 1 H), 5.13 (dd, J = 2.0, 11.0 Hz, 1 H), 4.96 (dd, J = 2.0, 17.8 Hz, 1 H), 4.65 (dd, J = 6.8, 13.1 Hz, 2 H), 4.12–4.10 (m, 1 H), 3.34 (s, 3 H), 2.27–1.47 (series of m, 13 H), 1.17 (s, 3 H), 1.14–0.81 (m, 1 H), 0.71 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.48, 137.50, 121.64, 114.57, 94.79, 84.59, 71.03, 58.22, 55.04, 51.10, 45.54, 41.94, 28.55, 26.15, 25.99, 25.17, 21.48, 20.85, 19.36; MS m/z (M$^+$) calcd 306.2195, obsd 306.2217; $[\alpha]^{19}_D$ −71.1° (c 0.51, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.48; H, 9.87.

Anionic Oxy-Cope Rearrangement of 10b. A. With Protonation. KH (24 mg, 0.60 mmol) was suspended in dry THF (5 mL) and treated dropwise with a solution of **10b** (45 mg, 0.12 mmol) in the same solvent (10 mL) while being stirred. The resulting yellow mixture was warmed to 50 °C and maintained at that temperature for 1 h, at which time reaction was complete (TLC analysis). The mixture was cooled to 25 °C and treated with saturated aqueous NH_4Cl solution. The separated organic phase was washed with 0.4 N HCl and brine, dried, and concentrated. Chromatographic purification (silica gel, elution with 4% ethyl acetate in hexane) gave **14b** (41 mg, 87%) as a colorless oil; IR ($CHCl_3$, cm^{-1}) 2940, 1720, 1680, 1450, 1375, 1250, 1220, 1085, 1020; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 12.7 Hz, 1 H), 4.05 (dt, J = 4.7, 10.2 Hz, 1 H), 3.08 (s, 1 H), 2.59 (d, J = 11.3 Hz, 1 H), 2.50–2.42 (m, 1 H), 2.18–2.06 (m, 1 H), 2.01–1.79 (m, 7 H), 1.73–1.63 (m, 2 H), 1.57–1.46 (m, 1 H), 1.41–1.31 (m, 3 H), 1.26 (s, 3 H), 1.11 (s, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.18, 146.30, 122.91, 74.08, 51.84, 51.57, 48.58, 45.32, 42.71, 36.15, 29.42, 26.65, 25.92, 25.06, 24.16, 22.45, 22.14, 19.82, 18.03, −3.89, −4.53; MS m/z (M$^+$) calcd 376.2798, obsd 376.2792; $[\alpha]^{20}_D$ −84.7° (c 0.91, $CHCl_3$).

B. With Methylation. A nitrogen-blanketed, magnetically stirred solution of **10b** (125 mg, 0.33 mmol) in dry THF (15 mL) was heated to 60 °C and treated via syringe with KHMDS (3.32 mL of 0.5 M in toluene, 1.66 mmol). TLC analysis showed reaction to be complete at once. Freshly distilled methyl iodide (0.21 mL, 3.32 mmol) was introduced, and the resulting white suspension was stirred at 60 °C for 1 h. The cooled reaction mixture was quenched with saturated aqueous NH_4Cl solution and diluted further with ether. The separated aqueous phase was extracted with ether, and the combined organic solutions were washed with water and brine prior to drying and solvent evaporation. Silica gel chromatography of the residue (elution with 2% ethyl acetate in petroleum ether) afforded 95 mg (74%) of **17b** and 22 mg (18%) of **14b**.

For 17b: colorless crystals, mp 94–96 °C (from ether); IR ($CHCl_3$, cm^{-1}) 2960, 2925, 1660, 1460, 1250, 1100–1000, 870, 840; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (m, 1 H), 3.91 (ddd, J = 4.8, 9.4, 10.8 Hz, 1 H), 3.48 (d, J = 7.0 Hz, 1 H), 2.56 (m, 1 H), 2.25 (m, 1 H), 2.10–1.70 (series of m, 6 H), 1.70–1.45 (series of m, 4 H), 1.45–0.95 (series of m, 3 H), 1.42 (s, 3 H), 1.24 (s, 3 H), 1.12 (s, 3 H), 0.88 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.47, 147.05, 121.59, 77.28, 56.99, 51.60, 51.18, 45.17, 39.12, 36.17, 35.08, 31.80, 30.90, 25.96, 25.81, 24.58, 22.05, 20.96, 19.92, 14.04, −3.71, −4.52; MS m/z (M$^+$) calcd 390.2954, obsd 390.2940; $[\alpha]^{25}_D$ −111.6° (c 1.25, $CHCl_3$). Anal. Calcd for $C_{24}H_{42}O_2Si$: C, 73.78; H, 10.84. Found: C, 73.75; H, 10.85.

Desilylation of 14b. A solution of **14b** (197 mg, 0.52 mmol) and tetra-*n*-butylammonium fluoride (3.2 mL of 1 M in THF) in dry tetrahydrofuran (10 mL) was heated overnight at the reflux temperature. The cooled reaction mixture was diluted with ether and washed with water and brine. Drying and concentration gave a yellow oil, purification of which by silica gel chromatography (elution with 30% ethyl acetate in petroleum ether) gave **14a** (128 mg, 93%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3610, 3000, 2990, 2960, 2935, 1660, 1465, 1450, 1385, 1335, 1265, 1220, 1050, 1045, 1020, 900; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14–5.10 (m, 1 H), 4.07 (dt, J = 4.5, 10.6 Hz, 1 H), 3.08 (t, J = 5.2 Hz, 1 H), 2.58 (d, J = 11.8 Hm, 1 H), 2.54–2.47 (m, 1 H), 2.36 (t, J = 7.5 Hz, 1 H), 2.15–1.75 (series of m, 7), 1.75–1.45 (m, 3 H), 1.45–1.00 (series of m, 3 H), 1.24 (s, 3 H), 1.09 (s, 3 H), 0.88 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.12, 146.58, 122.37, 73.24, 51.78, 51.27, 48.34, 45.31, 42.64, 35.57, 28.70, 26.59, 24.97, 24.09, 22.34, 22.08, 19.74; MS m/z (M$^+$) calcd 262.1933, obsd 262.1983; $[\alpha]^{21}_D$ −96.1° (c 1.7, $CHCl_3$).

Acetylation of 14a. A solution of **14a** (106 mg, 0.40 mmol) in dry THF (10 mL) was blanketed with nitrogen and treated sequentially with 4-(dimethylamino)pyridine (5 mg), pyridine (0.196 mL, 2.43 mmol) and acetic anhydride (0.190 mL, 2.02 mmol). The reaction mixture was stirred at 25 °C for 1 h, diluted with ether, and poured into a separatory funnel. Washing with water, 1 N HCl, saturated $NaHCO_3$ solution, and brine was followed by drying and concentration. Recrystallization of the residue from ether gave **15** as clear cubic crystals (120 mg, 98%): mp 136–138 °C; IR ($CHCl_3$, cm^{-1}) 2940, 1720, 1680, 1375, 1250, 1220, 1085, 1020; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (dt, J = 10.6, 4.7 Hz, 1 H), 5.10–5.06 (m, 1 H), 3.13 (s, 1 H), 2.58 (d, J = 11.0 Hz, 1 H), 2.35–2.28 (m, 1 H), 2.17–1.84 (m, 9 H), 2.01 (s, 3 H), 1.77–1.72 (m, 1 H), 1.61 (d, J = 9.8 Hz, 1 H), 1.48–1.31 (m, 3 H), 1.26 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.17, 170.45, 147.22, 121.59, 76.42, 51.76, 51.08, 45.39, 45.11, 42.51, 31.89, 28.37, 26.40, 25.01, 24.18, 22.34, 22.10, 19.43; MS m/z (M$^+$) calcd 304.2038, obsd 304.2062; $[\alpha]^{21}_D$ −105.0° (c 1.5, $CHCl_3$).

X-ray Data Collection. Structure Determination and Refinement for 15.[29-31] A transparent single crystal of **15** was mounted on a pin and transferred to the goniometer. The space group was determined to be the acentric $P2_12_12_1$ from the systematic absences. A summary of data collection parameters is given in Table II (see supplemenary material).

Least-squares refinement with isotropic thermal parameters led to $R = 0.112$. The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 Å^2. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C–H = 0.95 Å, B = 5.5 Å^2). Refinement of non-hydrogen atoms with anisotropic temperature factors led to the final values of $R = 0.044$ and $R_w = 0.064$. The final values of the positional parameters are given in the supplementary material.

Anionic Oxy-Cope Rearrangement of 10c. A. With Protonation. A flame-dried flask was charged with KH (620 mg, 4.65 mmol) and washed with petroleum ether (3 × 50 mL). The solid reagent was covered with

(31) Sheldrick, G. M. SHELX. In *Crystallographic Computing 3*; Sheldrick, G. M., Kruger, C., Goddard, R., Eds.; Oxford University Press: Cambridge, 1985; pp 175–189.

dry THF (8 mL), treated with 18-crown-6 (1.23 g, 4.65 mmol), and stirred for 20 min. A solution of **10c** (285 mg, 0.93 mmol) in the same solvent (5 mL) was introduced. After the solution was stirred for 10 min at room temperature, isomerization was complete (TLC analysis). Methanol (1 mL) was cautiously added, and when the evolution of hydrogen had ceased, the reaction mixture was poured into saturated NH_4Cl solution. The separated aqueous phase was extracted with ether, and the combined organic solutions were dried and concentrated. The residual clear oil (244 mg, 86%) was pure **14c**: IR ($CHCl_3$, cm^{-1}) 2986, 2940, 1682, 1468, 1448, 1387, 1271, 1151, 1121, 1099, 1086, 1077, 1041, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 5.04 (dd, J = 2.9, 12.8 Hz, 1 H), 4.60 (dd, J = 6.6, 24.7 Hz, 2 H), 3.89 (dt, J = 4.7, 10.5 Hz, 1 H), 3.28 (s, 3 H), 3.03 (t, J = 4.8 Hz, 1 H), 2.51 (d, J = 11.7 Hz, 1 H), 2.47–2.40 (m, 1 H), 2.10–2.00 (m, 2 H), 1.94–1.81 (m, 5 H), 1.80–1.61 (m, 2 H), 1.66 (d, J = 8.9 Hz, 1 H), 1.38–1.23 (m, 3 H), 1.18 (s, 3 H), 1.03 (s, 3 H), 1.08–1.01 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.57, 146.44, 122.38, 95.63, 79.86, 55.23, 51.72, 51.19, 46.31, 45.23, 42.46, 32.74, 28.94, 26.42, 24.90, 24.03, 22.26, 21.99, 19.46; MS m/z (M^+) calcd 306.2195, obsd 306.2200; $[\alpha]^{19}_D$ −105.4° (c 0.36, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.61; H, 9.92.

B. With Methylation. A solution of KHMDS (0.9 mL of 0.5 M in toluene, 0.45 mmol) in dry tetrahydrofuran (15 mL) was heated to 50–55 °C under nitrogen and treated with a solution of **10c** (27.8 mg, 0.09 mmol) in THF (5 mL). The mixture was stirred for 30 min, at which point freshly distilled methyl iodide (50 μL, 0.8 mmol) was added. The cloudy reaction mixture was stirred at 50–55 °C for 30 min and at room temperature for 1 h before being poured into saturated $NaHCO_3$ solution. The separated aqueous phase was extracted with ether, and the combined organic solutions were dried and concentrated. The residue was purified by silica gel chromatography (elution with 10% ethyl acetate in hexanes) to give 18 mg (62%) of **17c** as a clear, colorless oil: IR (neat, cm^{-1}) 2920, 1660, 1465, 1448, 1335, 1267, 1215, 1150, 1100, 1046, 920, 735; ^1H NMR (300 MHz, $CDCl_3$) δ 5.46 (dd, J = 3.5, 12.7 Hz, 1 H), 4.70 (dd, J = 6.7, 30.6 Hz, 2 H), 3.84 (ddd, J = 4.5, 10.3, 10.3 Hz, 1 H), 3.36 (s, 3 H), 2.63 (d, J = 12.8 Hz, 1 H), 2.60–2.50 (m, 1 H), 2.3–1.8 (m, 7 H), 1.7–1.5 (m, 4 H), 1.44 (s, 3 H), 1.24 (s, 3 H), 1.12 (s, 3 H), 1.5–1.1 (series of m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.06, 147.41, 121.18, 95.80, 83.40, 55.55, 54.59, 51.31, 51.12, 45.19, 39.06, 36.04, 31.94, 31.78, 30.48, 25.78, 24.57, 21.99, 20.91, 19.72; MS m/z (M^+) calcd 320.2351, obsd 320.2353; $[\alpha]^{19}_D$ −129.6° (c 0.68, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.05; H, 10.05.

Anionic Oxy-Cope Rearrangement of 11b. A. With Protonation. A magnetically stirred solution of **11b** (60 mg, 0.159 mmol) and 18-crown-6 (253 mg, 0.957 mmol) in dry THF (10 mL) was blanketed with nitrogen and treated with KHMDS in toluene (1.59 mL of 0.5 M, 0.80 mmol). After 30 min at room temperature, TLC analysis indicated complete disappearance of starting material. Saturated NH_4Cl solution was added, the layers were separated, and the organic phase was washed with water and brine. The original aqueous phase was extracted with ether, and the combined organic portions were dried and concentrated to give a yellow solid. Silicic acid (Bio-Sil A) chromatographic purification (elution with 2% ether in petroleum ether) afforded 43 mg (72%) of a colorless solid, mp 96–99 °C, that proved to be a 60:40 mixture of atropisomers **20b** and **21b**: IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2950, 1705, 1650, 1460, 1360, 1255, 1095, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (d, J = 13.1 Hz, 1 H), 4.85 (m, 1 H), 3.80 (m, 2 H), 2.80 (br m, 2 H), 2.65–2.35 (series of m, 4 H), 2.35–2.08 (series of m, 6 H), 2.05–1.90 (m, 4 H), 1.90–1.63 (series of m, 7 H), 1.60–1.40 (m, 7 H), 1.40–0.75 (series of m, 4 H), 1.25 (s, 6 H), 1.07 (s, 3 H), 1.01 (s, 3 H), 0.88 (s, 18 H), 0.70 (s, 3 H), 0.07 (s, 3 H), 0.05 (s, 6 H); MS m/z (M^+) calcd 376.2797, obsd 376.2784.

B. With Methylation. A solution of **11b** (60 mg, 0.159 mmol) and 18-crown-6 (253 mg, 0.957 mmol) in dry THF (10 ml) was blanketed with nitrogen and treated with KHMDS (2.74 mL of 0.5 M, 1.37 mmol) followed 20 min later by methyl iodide. The resulting white suspension was stirred at room temperature for 30 min, quenched with saturated NH_4Cl solution, and processed as in A. Chromatography on Bio-Sil A, with elution involved 3% ether in petroleum ether, provided **22b** (43 mg, 69%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2960, 2940, 2860, 1675, 1460, 1250, 1090, 880, 840; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (d, J = 9.3 Hz, 1 H), 3.88 (m, 1 H), 2.55 (d, J = 13.8 Hz, 1 H), 2.49 (m, 1 H), 2.39 (m, 1 H), 1.95–1.20 (series of m, 11 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 1.11 (s, 3 H), 0.92 (s, 9 H), 0.95–0.80 (m, 2 H), 0.09 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.79, 143.50, 124.34, 70.00, 56.21, 53.91, 48.71, 45.92, 33.97, 30.60, 28.66, 25.82, 24.56, 24.30, 24.06, 23.65, 21.60, 21.44, 19.36, 18.10, −4.47, −4.75; MS m/z (M^+) calcd 390.2954, obsd 390.2934; $[\alpha]^{20}_D$ −6.7° (c 2.7, $CHCl_3$). Anal. Calcd for $C_{24}H_{42}O_2Si$: C, 73.79; H, 10.85. Found: C, 73.43; H, 10.80.

Anionic Oxy-Cope Rearrangement of 11c. A. With Protonation. To a magnetically stirred slurry of KH (340 mg of a 30% slurry in mineral oil, 3.2 mmol) in dry THF (5 mL) was added 18-crown-6 (850 mg, 3.2 mmol). After 5 min, a solution of **11c** (196 mg, 0.64 mmol) in the same solvent (5 mL) was introduced, and the mixture was stirred for 24 h under a nitrogen atmosphere. Following the careful addition of methanol (1 mL), the reaction mixture was poured into saturated NH_4Cl solution (20 mL). The usual workup gave a residue that was purified by chromatography on Bio-Sil A (elution with 5% ethyl acetate in petroleum ether). There was isolated 157 mg (80%) of a colorless oil that was an inseparable 1.3:1 mixture of **20c** and **21c**: IR ($CHCl_3$, cm^{-1}) 2990–2870, 1693, 1653, 1468, 1338, 1390, 1160, 1150, 1106, 1041, 947, 916; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (d, J = 12.5 Hz, 1 H), 4.77 (dd, J = 3.2, 11.6 Hz, 1 H), 4.55–4.51 (m, 4 H), 3.70–3.60 (m, 4 H), 3.35 (s, 3 H), 3.30 (s, 3 H), 3.10–2.82 (m, 2 H), 2.62–2.40 (series of m, 4 H), 2.35–2.05 (m, 6 H), 2.00–1.72 (series of m, 8 H), 1.72–1.4 (series of m, 10 H), 1.18 (s, 8 H), 1.14–1.04 (m, 2 H), 1.04 (s, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.42, 210.38, 147.43, 145.32, 123.07, 121.33, 95.66, 94.28, 77.07, 73.09, 55.39, 55.21, 53.58, 51.93, 49.17, 49.01, 48.71, 46.55, 46.25, 45.25, 43.80, 42.99, 30.53, 28.35, 27.19, 27.09, 27.02, 25.70, 25.00, 24.41, 24.24, 23.85, 23.36, 22.55, 22.12, 18.65, 15.30 (1 C coincident or not seen); MS m/z (M^+) calcd 306.2195, obsd 306.2208; $[\alpha]^{21}_D$ −116° (c 0.48, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.60; H, 10.02.

B. With Methylation. A 30% mineral oil slurry of KH (692 mg, 4.55 mmol) was washed well with petroleum ether (3 × 20 mL) and then covered with dry THF (10 mL). 18-Crown-6 (1.2 g, 4.55 mmol) was introduced, and the mixture was stirred for 10 min prior to the addition of **11c** (279 mg, 0.91 mmol) in THF (5 mL). After 30 min, freshly distilled methyl iodide (1.0 mL, 16.1 mmol) was subjected via syringe and a thick white precipitate was formed immediately. Stirring was maintained for 30 min, and the mixture was poured into saturated $NaHCO_3$ solution. The organic phase resulting from the usual workup was dried, concentrated in the absence of heat, and chromatographed on Bio-Sil A (elution with 10% ether in petroleum ether). There was obtained 256 mg (88%) of **22c** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 2995–2865, 1680, 1478, 1450, 1154, 1107, 1042, 952, 918; ^1H NMR (300 MHz, $CDCl_3$) δ 5.02 (dd, J = 2.5, 11.1 Hz, 1 H), 4.68 (s, 2 H), 3.43 (m, 1 H), 3.38 (s, 3 H), 2.6–2.5 (m, 2 H), 2.3–2.25 (m, 1 H), 2.00–1.50 (series of m, 10 H), 1.50–1.20 (m, 3 H), 1.06 (s, 3 H), 0.98 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.30, 143.87, 123.67, 95.17, 75.61, 55.32, 53.59, 53.38, 48.58, 45.86, 33.91, 28.91, 27.50, 24.59, 24.49, 23.97, 23.71, 21.58, 21.35, 19.21; MS m/z (M^+) calcd 320.2351, obsd 320.2346; $[\alpha]^{19}_D$ +11.6° (c 0.49, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 75.07; H, 10.13.

Thermal Atropisomerization of 22b. A solution of **22b** (40 mg, 0.102 mmol) in 1 mL of $CDCl_3$ contained in an NMR tube was heated at 40 °C in an oil bath for 31 h. After this time, the equilibrium distribution was 81.2% of **23b** and 18.8% of **22b** as determined by integration of their respective vinyl proton absorptions. The solvent was evaporated and the residue was chromatographed on Bio-Sil A (elution with 3% ether in petroleum ether) to give 29 mg (73%) of **23b** as a colorless solid: IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2860, 1650, 1465, 1255, 1090, 1010, 890, 870, 840; ^1H NMR (300 mHz, $CDCl_3$) δ 4.83 (m, 1 H), 4.07 (m, 1 H), 2.70–2.07 (series of m, 6 H), 2.01 (m, 1 H), 1.88–1.47 (series of m, 7 H), 1.46–0.80 (m, 2 H), 1.35 (s, 3 H), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.88 (s, 9 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.74, 144.34, 125.24, 69.16, 52.15, 51.65, 48.62, 46.84, 46.75, 29.28, 29.02, 26.23, 25.94, 25.85, 25.52, 24.09, 23.76, 20.35, 18.73, 18.10, −4.64, −4.78; MS m/z (M^+) calcd 390.2954, obsd 390.2934; $[\alpha]^{20}_D$ −109.6° (c 2.3, $CHCl_3$).

Thermal Atropisomerization of 22c. A solution of ketone **22c** (123 mg, 0.38 mmol) in toluene (5 mL) was heated at the reflux temperature for 6 h, cooled, and evaporated in vacuo. The residue was chromatographed on Bio-Sil A (elution with 10% ether in petroleum ether) to give 40 mg (33%) of **23c**, 17 mg (14%) of recovered **22c**, and 5 mg (4%) of an unidentified compound.

For 23c: colorless oil; IR ($CHCl_3$, cm^{-1}) 3004–2968, 1655, 1472, 1447, 1390, 1376, 1242–1208, 1152, 1125, 1103, 1038, 916; ^1H NMR (300 MHz, $CDCl_3$) δ 4.81 (dd, J = 4.1, 12.1 Hz, 1 H), 4.65 (dd, J = 6.7, 21.4 Hz, 2 H), 3.98 (dt, J = 10.9, 5.0 Hz, 1 H), 3.36 (s, 3 H), 2.69–2.60 (m, 2 H), 2.56–2.39 (m, 2 H), 2.35–2.18 (m, 4 H), 2.00 (t, J = 7.2 Hz, 1 H), 1.83–1.52 (m, 6 H), 1.39 (d, J = 11 Hz, 1 H), 1.34 (s, 3 H), 1.08 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.36, 144.56, 124.77, 94.43, 73.51, 55.30, 51.42, 49.07, 48.57, 46.74, 28.94, 26.29, 26.26, 25.90, 25.54, 24.27, 23.82, 20.24, 18.67 (1 C not observed); MS m/z (M^+) calcd 320.2351, obsd 320.2346; $[\alpha]^{19}_D$ −207.6° (c 0.64, $CHCl_3$).

Expoxidation of 23c. To a magnetically stirred solution of **23c** (79 mg, 0.247 mmol) in dichloromethane (3 mL) containing monobasic sodium phosphate monohydrate (62.7 mg, 0.454 mmol) and anhydrous dibasic sodium phosphate (110 mg, 0.410 mmol) was added portionwise

59.3 mg (0.344 mmol) of 85% *m*-chloroperbenzoic acid at 0 °C. After 10 min, the reaction mixture was warmed to room temperature, stirred for 3 h, and washed in turn with saturated $NaHSO_3$ solution, saturated $NaHCO_3$ solution, and brine. Following drying and solvent evaporation, the residue was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to give 67 mg (81%) of **24** as colorless prisms: mp 87-88 °C (from ether-hexanes); IR ($CHCl_3$, cm^{-1}) 2942, 1665, 1460, 1443, 1149, 1128, 1102, 1038; ^1H NMR (300 MHz, $CDCl_3$) δ 4.65 (dd, J = 6.7, 16.5 Hz, 2 H), 4.05-3.95 (m, 1 H), 3.36 (s, 3 H), 2.75-2.65 (m, 2 H), 2.65-2.60 (m, 2 H), 2.30-2.15 (m, 3 H), 2.10-1.85 (m, 3 H), 1.80-1.60 (m, 4 H), 1.60-1.45 (m, 4 H), 1.2-1.14 (m, 1 H), 1.06 (s, 6 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.85, 94.54, 72.99, 70.96, 61.44, 55.36, 51.64, 47.62, 45.43, 43.94, 42.16, 22.53, 26.28, 26.20, 25.63, 24.87, 23.98, 23.22, 19.98, 16.24; MS m/z (M^+) calcd 336.2300, obsd 336.2316; $[\alpha]^{20}_D$ -88.7° (c 0.56, $CHCl_3$).

X-ray Data Collection Structure Determination and Refinement for 24.[29-31] A transparent single crystal of **24** was mounted on a pin and transferred to the goniometer. The space group was determined to be acentric $P2_12_12_1$ from the systematic absences. A summary of data collection parameters is given in Table II (see supplementary material).

Least-squares refinement with isotropic thermal parameters led to R = 0.166. The geometrically constrained hydrogen atoms were placed in calculated positions 0.95 Å from the bonded carbon atom and allowed to ride on that atom with B fixed at 5.5 Å^2. The methyl hydrogen atoms were included as a rigid group with rotational freedom at the bonded carbon atom (C-H = 0.95 Å, B = 5.5 Å^2). High thermal motion was noted for the terminal methoxy group. However, disorder of this group could not be resolved. Refinement of non-hydrogen atoms with anisotropic temperature factors led to the final values of R = 0.081 and R_w = 0.082. The final values of the positional parameters are given in the supplementary material.

Epoxidation of 22c. A 280-mg (0.247-mmol) sample of **22c** was reacted with *m*-chloroperbenzoic acid (326 mg of 85%, 1.60 mmol) in phosphate-buffered dichloromethane (10 mL) as described previously. Chromatographic purification of the residue (silica gel, elution with 20% ethyl acetate in petroleum ether) afforded 166 mg (56%) of a 1:1.5 mixture of **24** and **25** as a colorless oil.

For 25: IR ($CHCl_3$, cm^{-1}) 2937, 2893, 1686, 1467, 1447, 1389, 1374, 1347, 1330, 1152, 1131, 1103, 1047, 957; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (s, 2 H), 3.80 (dt, J = 12.0, 4.1 Hz, 1 H), 3.37 (s, 3 H), 2.86 (dd, J = 1.5, 10.6 Hz, 1 H), 2.79 (d, J = 14.4 Hz, 1 H), 2.70-2.55 (m, 2 H), 2.55-2.49 (m, 2 H), 2.35-2.10 (m, 3 H), 2.10-1.85 (m, 3 H), 1.85-1.25 (m, 6 H), 1.04 (s, 3 H), 1.01 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.82, 95.31, 75.21, 70.89, 70.05, 62.25, 55.50, 54.76, 45.93, 44.89, 41.46, 32.14, 27.74, 27.39, 24.00, 23.09, 22.99, 21.47, 19.51, 19.30.

Kinetic Studies Involving 1 and 22b. Freshly chromatographed samples of **1** and **22b** (ca. 20 mg) were dissolved in C_6D_6 (1.2 mL) and placed in NMR tubes. A Bruker AM 300 NMR instrument equipped with automated acquisition programming was used for all of the kinetic studies. Percent composition of the two components in each case was determined at regular time intervals by relative integration of their vinyl proton absorptions. A minimum of 10-15 spectra were recorded for each kinetic run.

A nonlinear last-squares fit of the percent new atropisomer (B) versus time provided optimized values for the equilibrium distributions. Next, a linear least-squares fit of ln (% B_∞ - % B_t) versus time gave the overall rate constant k as the negative slope. These data, when taken in combination with K_{eq} provided the rate constants and activation energies for the forward and reverse reactions. Lastly, the kinetic data recorded at several temperatures made possible the construction of an Arrhenius plot from which the pertinent activation parameters could be extracted.

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Supplementary Material Available: Tables of X-ray crystal data, bond distances and angles, final fractional coordinates, and thermal parameters, as well as additional ORTEP diagrams for **11b**, **15**, and **24** (18 pages). Ordering information is given on any current masthead page.

Structural Effects on the Rates of Formation and the Stability of Enols of Cyclic Benzyl Ketones

Sherif Eldin, Ralph M. Pollack,* and Dale L. Whalen*

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228-5398.
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Abstract: The acid dissociation constants (K_a^K), the keto-enol equilibrium constants (K_E), and the rate constants for enolization of the cyclic benzyl ketones 2-indanone (**1a**), 2-tetralone (3,4-dihydro-2(1*H*)-naphthalenone, **1b**) and 2-benzosuberone (3,4-benzo-3-cyclohepten-1-one, **1c**) were measured in aqueous solution at 25 °C. The rate constants for ketonization of the enols and the acid dissociation constants (K_a^E) for the corresponding enols were also determined. The presence of a conjugating phenyl group provides sufficient stabilization of the negative charge to enable these ketones to ionize in the pH range. pK_a^K values were determined from the rate constants for ionization of the ketones and for ketonization of the enolate ions. These values were confirmed by spectral titration. The acidity of the ketones decreases with increasing size; pK_a^K values are 12.2 (**1a**), 12.9 (**1b**), and 14.9 (**1c**). Similarly, the acid dissociation constants of the enols decrease with increasing ring size; pK_a^E's are 8.3 (**2a**), 9.2 (**2b**), and 10.0 (**2c**). Equilibrium constants for enolization also vary with ring size; pK_E values are 3.8 (**1a**), 3.6 (**1b**), and 4.9 (**1c**).

A knowledge of the factors that control the rates and equilibria of proton transfers is fundamental for an understanding of reactivity in organic chemistry.[1] Particularly important is the effect of structure on the acidity of carbon acids. These acids cover an enormous range from the strongly acidic 1,2,3,4,5-pentacyanocyclopentadiene (pK_a -11)[2] to simple alkanes with pK_a's of ca. 55-70.[1] Although investigations leading to extensive tabulations of acidities of carbon acids in nonaqueous media have been carried out by several groups, notably those of Bordwell[3] and Streitwieser,[4]

(1) For an excellent recent monograph, see: Stewart, R. *The Proton: Applications to Organic Chemistry*; Academic Press: New York, 1985.

(2) Webster, O. W. *J. Am. Chem. Soc.* **1966**, *88*, 3046.

(3) For recent reviews, see: (a) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. (b) Taft, R. W.; Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 463.

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