δ 24.0, 24.3, 28.5 (3 CH_2Br), 136.1, 138.7, 139.1, 139.3 (4 C_{ar}); MS (70 eV), m/z 1082.8 (M, $C_{22}H_{20}{}^{79}Br_6{}^{81}Br_4$, 3%), 342 (B, $C_8H_8{}^{81}Br^{79}Br_2$). Anal. Calcd for $C_{22}H_{20}Br_{10}$: C, 24.39; H, 1.86. Found: C, 24.65; H, 1.95.

Single-Crystal X-ray Structure of Biphenyl 3. A single crystal of the biphenyl **3** suitable for X-ray diffraction was prepared by slow evaporation of a toluene solution of **3**. Data were measured on a PW1100/20 Philips four-circle computer-controlled diffractometer. Mo Kα (λ = 0.71069 Å) radiation with a graphite crystal monochromator in the incident beam was used. Intensities were corrected for Lorentz, polarization, and absorption effects. Crystal data: formula, $C_{22}H_{20}Br_{10}$; M = 1083.4; space group, $P\bar{1}$; a = 12.037 (3); Å; b = 12.254 (3) Å; c = 12.020 (3) Å; α = 108.02 (4)°; β = 106.09 (4)°; γ = 108.51 (5)°; V = 1453.7 Å^3; Z = 2; ρ(calcd) = 2.48 g cm^{-3}; μ(Mo Kα) = 135.26 cm^{-1}; R = 0.077; R_w = 0.112.

Bromopentakis(bromomethyl)benzene (8). Pentamethylbenzene (1.32 g, 10 mmol), and 1.65 g of tetrabutylammonium bromide were dissolved in 250 mL of CCl_4. To the stirred solution was added 4 mL of bromine (12.4 g, 78 mmol). After the mixture was refluxed for 5 days, it was cooled, and the solid that precipitated was filtered and washed (EtOH). Recrystallization from chloroform gave 4.65 g (73%) of **8**: mp 245 °C; ^{1}H NMR ($CDCl_3$, room temperature) δ 4.67 (2 H), 4.74 (4 H), 4.81 (4 H); ^{13}C NMR ($CDCl_3$, room temperature) δ 24.1 (CH_2), 25.0 (CH_2), 29.8 (CH_2), 130.8 (C_{ar}), 136.9 (C_{ar}), 138.7 (C_{ar}); MS (70 eV), m/z 622 (M, $C_{11}H_{10}{}^{81}Br_3{}^{79}Br_3$, 4%), 141 (B). Anal. Calcd for $C_{11}H_{10}Br_6$: C, 21.25; H, 1.62. Found: C, 21.32; H, 1.71.

Decamethylbenzhydrol (7). The carbinol was prepared according to the literature procedure[18] and recrystallized from petroleum ether: mp 189 °C (lit. mp 190 °C); ^{1}H NMR ($CDCl_3$, room temperature) δ 1.83 (1 H, d, J = 4 Hz, OH), 2.19 (12 H, s, CH_3), 2.20 (12 H, s, CH_3), 2.25 (6 H, s, CH_3), 6.54 (1 H, d, J = 4 Hz, ArC*H*Ar).

When **7** was recrystallized from ethanol in the presence of acid, the ethyl ether of the carbinol was isolated: mp 160 °C; ^{1}H NMR ($CDCl_3$, room temperature) δ 1.20 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 2.14 (12 H, s, CH_3), 2.20 (12 H, s, CH_3), 2.25 (6 H, s, CH_3), 3.34 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 5.92 (1 H, s, ArC*H*Ar); MS (70 eV), m/z 352 (M, 4%), 175 (B, $C_6(CH_3)_5CHCH_3$). Anal. Calcd for $C_{25}H_{36}O$: C, 85.17; H, 10.29. Found: C, 85.06; H, 10.17.

Decamethylbenzophenone (6). Decamethylbenzhydrol (0.109 g, 0.34 mmol) and pyridinium dichromate (0.264 g, 0.7 mmol) were dissolved in 25 mL of dry CH_2Cl_2, and the mixture was stirred at room temperature for 24 h. Ether (125 mL) was added, and the solid that separated was filtered. Evaporation of the organic solvents resulted in a solid, which was recrystallized from $CHCl_3$/EtOH, yielding 0.056 g (50%) of **6**: mp 205 °C; ^{1}H NMR ($CDCl_3$, room temperature) δ 2.08 (CH_3, 12 H), 2.18 (CH_3, 12 H), 2.25 (CH_3, 6 H); ^{13}C NMR ($CDCl_3$, room temperature) δ 16.4 (CH_3), 17.2 (CH_3), 17.8 (CH_3), 131.6 (C_{ar}), 133.2 (C_{ar}), 136.9 (C_{ar}), 141.1 (C_{ar}), 205.2 (CO); MS (70 eV), m/z 322 (M, $C_{23}H_{30}O$, 41%), 307 (B, M − CH_3). Anal. Calcd for $C_{23}H_{30}O$: C, 85.66; H, 9.38. Found: C, 85.29; H, 9.25.

Attempted Synthesis of Decakis(bromomethyl)benzophenone (4). Decamethylbenzophenone (0.040 g, 0.12 mmol), tetrabutylammonium bromide (74.5 mg), and 0.12 mL of bromine (2.4 mmol) were dissolved in 5 mL of CCl_4, and the mixture was stirred at room temperature for 48 h. The mixture was treated with a saturated aqueous Na_2SO_3 solution, the phases were separated, and the organic phase was dried ($MgSO_4$) and evaporated, yielding 68 mg (0.11 mmol, 46%) of bromopentakis(bromomethyl)benzene (**8**).

Acknowledgment. We thank Professors Kurt Mislow and Yoel Sasson for helpful discussions and Dr. Shmuel Cohen for the X-ray structure determination. This work was supported by a grant of the United States–Israel Binational Science Foundation, to which we are grateful.

Supplementary Material Available: Tables of bond lengths and angles for **3** (2 pages). Ordering information is given on any current masthead page.

Stereochemical Course of the Base-Promoted Aldol Self-Coupling of Racemic 5-Norbornen-2-one and 2-Norbornanone

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The enolate anions of 5-norbornen-2-one and 2-norbornanone enter into self-coupling with their conjugate acids in a manner that exhibits diastereomeric discrimination. The major products obtained from aldol reactions conducted at low temperature are those where bonding has occurred preferentially to the ketone of like absolute configuration. Structural assignments rest on X-ray crystallographic analyses and chemical interconversions. When the reactions are effected at higher temperatures, dehydration also occurs spontaneously. All indicators point to adherence by these bicyclic systems to molecular recognition in these condensation reactions as well. The aldol products, which are stable to the conditions under which they are formed, have been evaluated for their inherent levels of total energy and strain energy by molecular mechanics methods. These data, when taken in conjunction with assumed reaction trajectories, suggest the possible causes that underlie this interesting selectivity.

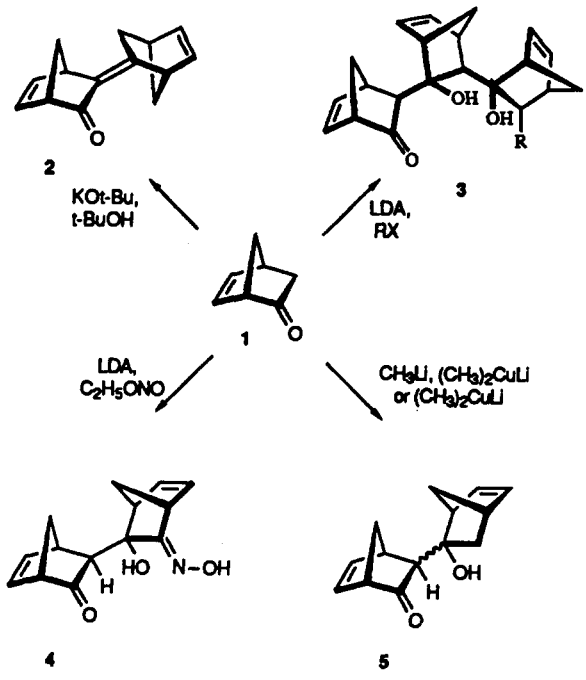
Molecular recognition need not be an exclusive feature of biochemical systems and should be observable in situations involving smaller molecules. The criterion need only be that a given reagent recognize a specific reaction partner in the presence of alternative compounds before the pair advance into C–C bond formation or some alternative reaction. A capacity for discrimination has been uncovered several times, often serendipitously, in the context of various studies involving the enolate ions of ketones possessing a bicyclo[2.2.1]heptene framework. Perhaps the earliest example to come to light is due to Cristol and Freeman,[2] who noted that heating (±)-5-norbornen-2-one (**1**) with a solution of potassium *tert*-butoxide in *tert*-butyl

(1) (a) Recipient of a National Need Fellowship sponsored by the U.S. Department of Education, 1989; Graduate Fellow of the ACS Division of Organic Chemistry sponsored by Eli Lilly Company, 1990. (b) Author to whom inquiries concerning the X-ray crystallographic analyses should be directed.

(2) Cristol, S. J.; Freeman, P. K. *J. Am. Chem. Soc.* **1962**, *83*, 4427.

0022-3263/91/1956-2449$02.50/0

Scheme I

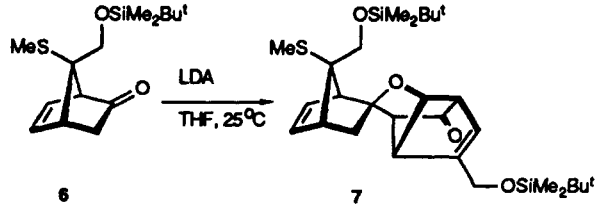


alcohol leads to a single bimolecular condensation product formulated by them as **2** (Scheme I). Should their structural assignment be correct, the implication is that those enolate anions prefer to couple with the ketone of like absolute configuration!

More recently, Grutzner and co-workers reported isolation of the single trimeric oligomer **3** from attempts to condense the lithium enolate of the same ketone with alkyl halides.[3] Note that all three of the bicyclo[2.2.1]heptenyl components in **3** originate from the 1*S* isomer. Since the starting material was racemic, an equivalent amount of the *R,R,R* diastereomer was produced concomitantly. Remarkably, however, none of the other possible stereochemical combinations was found.

The coupling of homochiral units also operates during the base-promoted oximation of **1** with ethyl nitrate. Once α-functionalization is initiated, an aldol reaction sets in to give **4**.[4] The same pattern emerges, viz., the enolate anion bonds only to that keto oxime having the identical enantiomeric configuration.

A somewhat more complex example is presented by **6**. In this instance, deprotonation at room temperature triggers dimerization with the ultimate ejection of CH_3S^-.[5] As before, the electrophilic partner that is recognized exclusively is of the same configuration (homochiral).



In light of these intriguing developments, we have been prompted to subject (±)-**1** and its dihydro derivative to aldol condensation under strictly controlled conditions and to identify the products of these reactions in unequivocal fashion. Arjona et al. have previously noted that exposure of **1** to organocuprates leads to a mixture of two products (**5**, 60% combined yield).[6] Since these organometallics are rather atypical promoters,[7] we have made recourse to more conventional bases. Single-crystal X-ray structure determinations now confirm that the selectivity is indeed skewed in the direction presented above.

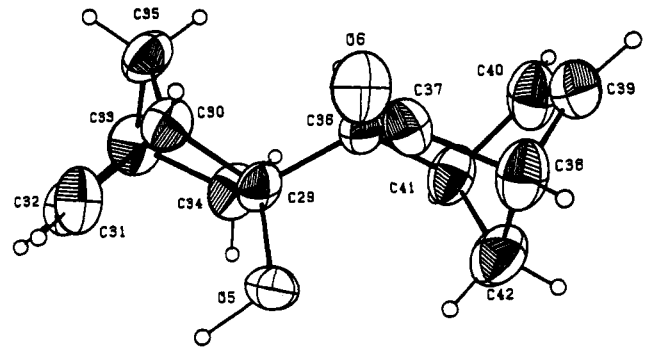


Figure 1. Computer-generated perspective drawing of the final X-ray model of **8**.

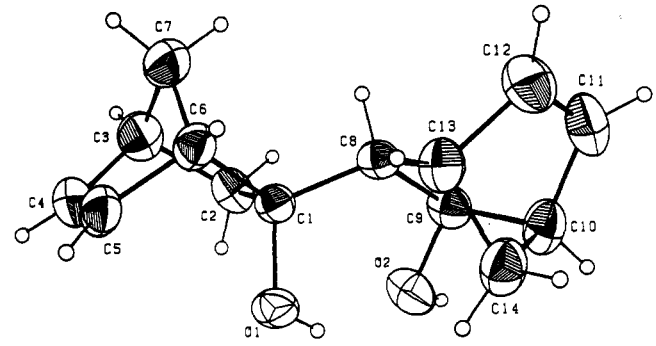


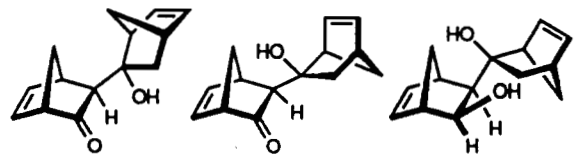
Figure 2. Computer-generated perspective drawing of the final X-ray model of **10**.

Results

Aldol Reactions. Deprotonation of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran, followed by the addition of a second equivalent of 5-norbornen-2-one at −78 °C, gave rise to two isomeric hydroxy ketones (**8** and **9**). The major component, present to the extent of 64% (HPLC analysis), crystallized directly from concentrated petroleum ether solutions of the mixture. The high quality of these crystals sufficed to allow the stereochemical features of **8** to be established unequivocally (Figure 1). Although the minor constituent **9** (36%) could be obtained in a pure state after medium-pressure chromatography on silica gel, X-ray quality crystals of this material could not be grown. For this reason, **9** was reduced with lithium aluminum hydride. Crystallographic examination of the major diol (Figure 2) provided requisite support for its definition as illustrated in **10**. As a consequence of the relative stereochemistry of the interconnective C–C bond in **9**, hydride reduction was forced to proceed predominantly from the endo direction to project the secondary hydroxyl exo.

At this juncture, we recognized that the "matched" exo,exo combination (**8**) is favored by almost 2:1 over the "mismatched" exo,exo option (**9**). When the same reaction

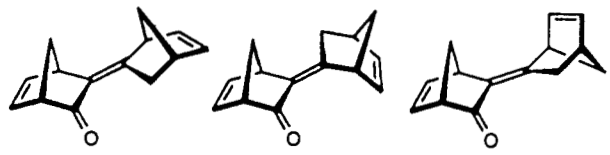
(3) Horner, J. H.; Vera, M.; Grutzner, J. B. *J. Org. Chem.* **1986**, *51*, 4212.
(4) Moorhoff, C. M.; Paquette, L. A. *J. Org. Chem.*, in press.
(5) Paquette, L. A.; Romine, J.; Barth, W.; Hsu, L.-Y. *Tetrahedron Lett.* **1985**, *26*, 567.
(6) Arjona, O.; Fernandez de la Pradilla, R.; Mallo, A.; Perez, S.; Plumet, J. *J. Org. Chem.* **1989**, *54*, 4158.
(7) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin, Inc.: Menlo Park, CA, 1972; Chapter 10.



8 9 10

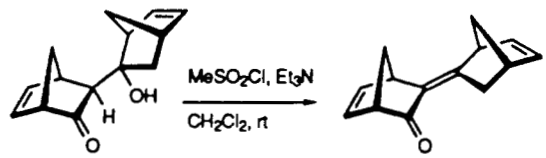
was carried out at 10-fold dilution or with varying equivalents of base, little change in the 8:9 ratio was noted. Periodic removal of aliquots from either aldol reaction indicated that the product distribution did not vary with time. In agreement with these findings, resubmission of pure samples of either aldol to the original reaction conditions did not result in equilibration.[8] Both isomers were recovered cleanly. Accordingly, 8 and 9 give every indication of being produced under kinetic control.

To dismiss explicitly any role possibly played by Li^+ during its involvement with the oxygen centers, 5-norbornen-2-one was also exposed for appropriate lengths of time to potassium and sodium hexamethyldisilazide as well as to potassium *tert*-butoxide. Reactions involving 0.5 equiv of NaHMDS or KHMDS in cold (−78 °C) THF for 4–5 h provided for isolation of the identical 68:32 mixture of 8 and 9. The parallel with LDA was therefore remarkably close. The KO*t*Bu-promoted condensation was effected in refluxing *tert*-butyl alcohol as earlier described.[2] In our hands, these conditions led to production of a mixture of 2 and 11–13 along with the 2- and 3-cyclo-



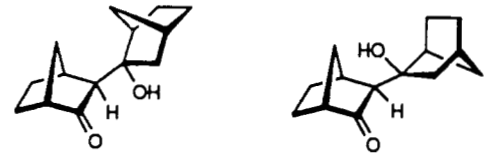
11 12 13

pentenylacetic acids.[9] No serious effort was made to separate the ketone isomers. However, the dehydration of 8 with methanesulfonyl chloride and triethylamine in dry CH_2Cl_2 at 0 °C afforded a heavily predominating conjugated enone. This isomerically pure oily substance displays ^{13}C signals that match those of a major component of the above mixture. Its ^1H NMR spectrum (Figure 3) shows no unusually deshielded bridgehead proton absorption as would be expected if the *Z* arrangement present in 2 had been produced.[10] Consequently, all indicators point to 11 as the resultant stereoisomer.[2] The similarity of the spectrum of 11 to that of the 18/19 pair (to be discussed later) is especially noteworthy.



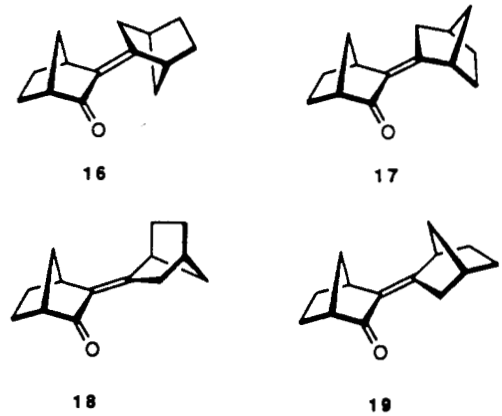
8 11

When racemic 2-norbornanone was treated with LDA in THF at room temperature, addition proceeded smoothly during 14 h to produce in 63% yield a mixture of two aldols. The ratio of 63:37 established by HPLC proved reproducible. The major hydroxy ketone could be isolated in a pure state by crystallization of the mixture followed by MPLC. The stereochemical features of 14 were convincingly established by hydrogenation of 8, which led cleanly to 14. Like treatment of 9 gave 15, identical in all aspects with the minor constituent of the aldol process.



14 15

When 2-norbornanone was treated with KHMDS or KH in THF at room temperature, rapid aldolization occurred with spontaneous elimination of water[11] to give a mixture of enones 16–19 (24:15:23:28, respectively) in 63% yield. By means of medium-pressure liquid chromatography, it proved possible to separate on a preparative scale a crystalline mixture of 16 and 17 from the oily 18/19 composite. A most distinguishing feature of the ^1H NMR



16 17 18 19

spectra of these pairs of ketones is the downfield position (δ 3.90) of the signal of area 1 seen for 16 and 17 (Figure 3). Molecular models of either diastereomer show clearly that the planarity about the double bond causes the allylic bridgehead proton of the nonoxygenated bicycloheptane to reside in close proximity and coplanar to the carbonyl oxygen where maximum deshielding is exerted.[10] In the case of 18 and 19, a pair of geminal methylene protons is also projected toward the oxygen. However, these are very much out-of-plane and subject to substantially less than the full impact of carbonyl anisotropy. This structural analysis applies as well to 11, with resultant spectral similarities to 18 and 19.

Molecular Mechanics Calculations. The capture of uncharged 1 by its enolate ion can in principle lead to eight pairs of diastereomers. One representative enantiomer from all of these subsets except for the least likely endo,endo isomers, each in its lowest energy conformation, can be found in Table I. To arrive at these representations, preminimized structures were first produced with the MODEL KS 2.94 software package.[12] The resulting molecular graphs were subjected in turn to a multiconformer search using the Grid Search function within MODEL. A minimum of 73 conformers for each structure was included in this process. All spatial arrangements that fell within 5 kcal/mol of the global minimum were examined in MM2 for their total energy. The best candidate within each diastereomeric series was submitted to MMX

(8) The coaddition of HMPA also had no observable effect.
(9) (a) Gassman, P. G.; Zalar, F. V. *Tetrahedron Lett.* **1964**, 3031. (b) Paasivirta, J. *Ibid.* **1968**, 2867.
(10) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, 1969; pp 88–92.
(11) Contrast ref 2 and Garcia, M. A.; Sanchez, G. J. M.; Nunez, A. A. *An. Quim., Ser. C* **1981**, *77*, 209.
(12) Still, W. C., private communication.

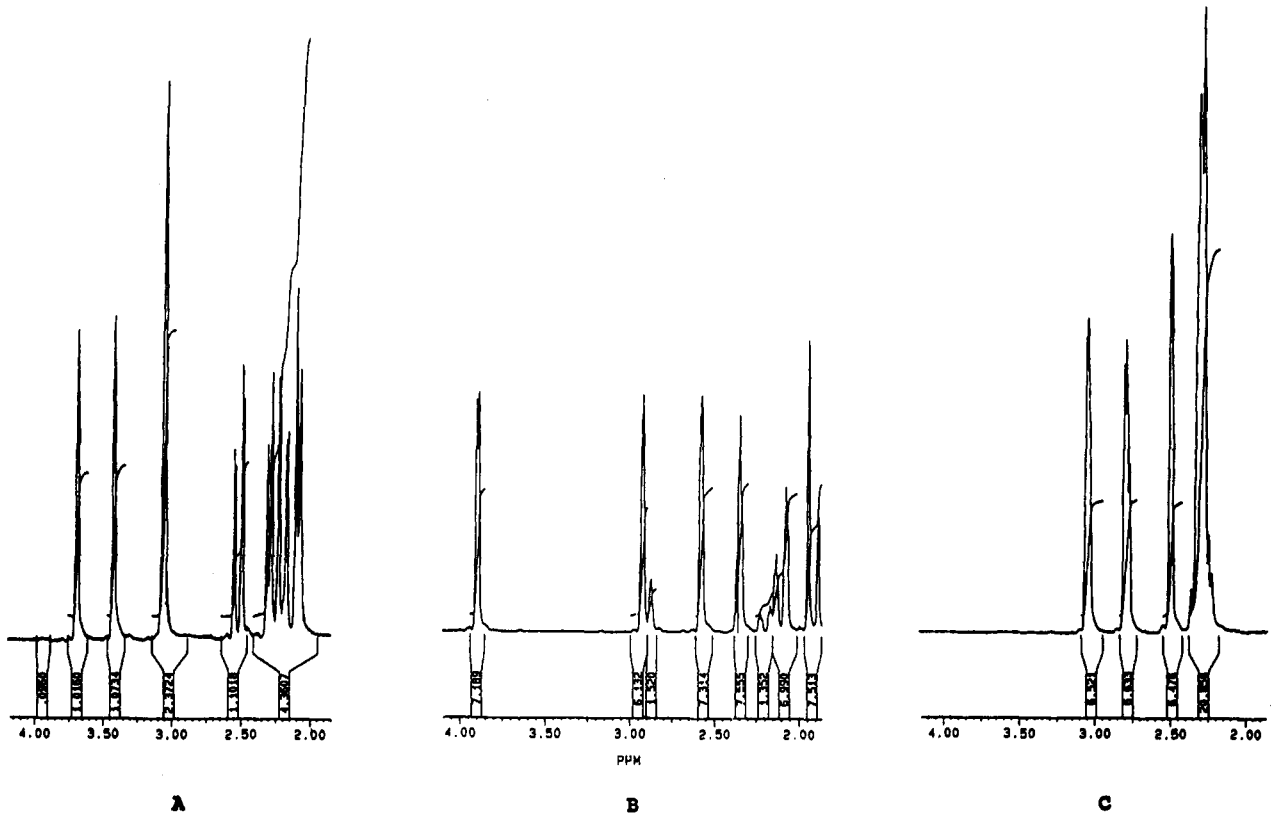


Figure 3. Partial 300-MHz ^1H NMR spectra (in $CDCl_3$) of 11 (A), 16/17 (B), and 18/19 (C) illustrating the dramatic effect of carbonyl anisotropy on the allylic bridgehead proton in 16/17.

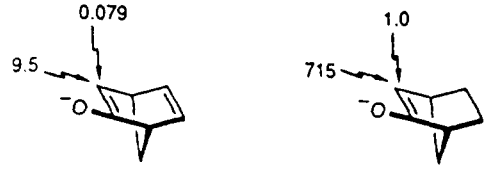


Figure 4. Relative exchange rates of exo and endo protons.

for final minimization and for acquisition of those refined total energy (E_t) and strain energy (E_s) values used in the tabulation. Hydrogen-bonding forces were incorporated in the calculations. Internal coordinates for the structures in Table I are available as supplementary material.

On this basis, the endo,exo isomers C (1*S*,1*S*; 1*R*,1*R*) and F (1*S*,1*R*; 1*R*,1*S*) are calculated to be lower in energy than the other structures. The total range of E_t and of E_s values is not large, reaching a maximum of 1.5 kcal/mol for ΔE_t and ΔE_s (see A and C). To the extent that these energy differences would be reflected in the corresponding diastereomeric transition states, irreversible attack by the enolate anion at the carbonyl group would lead to preferential formation of the corresponding aldol isomers. However, isomers C and F are not seen.

At least one major underlying reason for the absence of C and F is the overwhelming preference on the part of these bicyclic enolate anions to undergo exo attack. The relative base-catalyzed hydrogen–deuterium exchange rates for compound 1 and 2-norbornanone exemplify this pervasive trend (Figure 4).[13] These differences should be additionally skewed in the exo direction as the size of the electrophile is increased as in the present instance.

The absence of exo,endo adducts B and E can be attributed to similar phenomena if the aldol reaction is kinetically controlled. Since these particular hydroxy ketones are the necessary end result of endo attack on the carbonyl group and such a trajectory is subject to considerable steric retardation,[14] this mode of assembly should also be subject to strong kinetic inhibition.

The above considerations form the basis for considering the exo,exo aldol products to be formed under kinetic control. This conclusion is supported experimentally by the stability of these hydroxy ketones to the reaction conditions. It now remains to rationalize why A is preferred kinetically to D. Molecular mechanics calculations do not show a meaningful difference between them.

Discussion

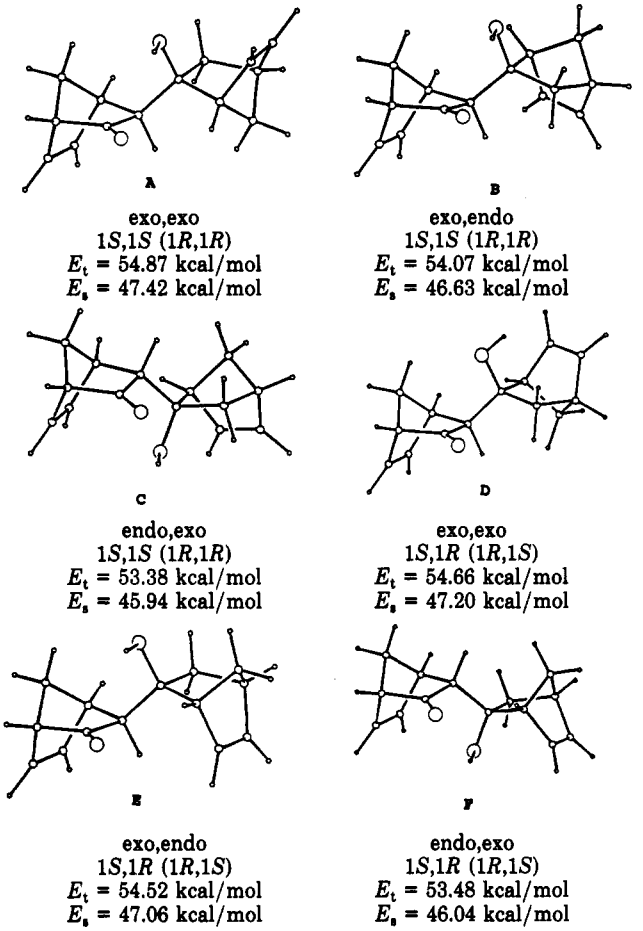
The capacity of norbornyl and norbornenyl enolates to combine in a diastereoselective manner with their neutral ketone counterparts has been demonstrated. That the aldol reaction between these racemic ketonic partners avails itself of the opportunity for C–C bond formation between homochiral molecules under a variety of conditions is clearly seen. Scheme I features a collection of additional transformations where the same trend persists. In part, the modest stereoselection arises by virtue of the complementary shape offered by these nucleophilic and electrophilic entities. The lesser steric demands associated with utilization of the exo surface in both components clearly provide a kinetic advantage to the formation of diastereoisomers related to A and D (Table I). However, the experimental facts are that coupling between reactants having the same absolute configuration (and therefore leading to A) is significantly preferred.

Grutzner has suggested that the cubic structure of the aggregated lithium enolate of 1 may provide the steric constraints necessary for stereoselection.[3] In the present study, sodium and potassium enolates which do not par-

(13) Tidwell, T. T. *J. Am. Chem. Soc.* **1970**, *92*, 1448.

(14) See, for example, Beckmann, S.; Metzger, R. *Chem. Ber.* **1956**, *98*, 2738.

Table I. Summary of Computationally Derived Minimized Energies for Six of the Possible Aldol Diastereomeric Pairs[a]



A	exo,exo	1S,1S (1R,1R)	E_t = 54.87 kcal/mol, E_s = 47.42 kcal/mol
B	exo,endo	1S,1S (1R,1R)	E_t = 54.07 kcal/mol, E_s = 46.63 kcal/mol
C	endo,exo	1S,1S (1R,1R)	E_t = 53.38 kcal/mol, E_s = 45.94 kcal/mol
D	exo,exo	1S,1R (1R,1S)	E_t = 54.66 kcal/mol, E_s = 47.20 kcal/mol
E	exo,endo	1S,1R (1R,1S)	E_t = 54.52 kcal/mol, E_s = 47.06 kcal/mol
F	endo,exo	1S,1R (1R,1S)	E_t = 53.48 kcal/mol, E_s = 46.04 kcal/mol

[a] The first pair of absolute stereochemical descriptors relate to the structure shown (left half designated first). The second pair define the enantiomer that is not shown.

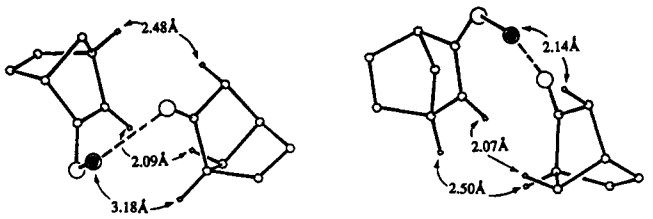


Figure 5. Simulated approaches to the "matched" (left) and "mismatched" (right) enantiomeric combinations (right) during aldol reaction of 1. The distance between the enolate and carbonyl carbons has been arbitrarily set at 2.59 ± 0.01 Å.

take of this high level aggregation were also examined, and no significant change in product distribution was noted. Accordingly, it becomes necessary to seek other sources of steric constraint more likely to operate in the rival transition state complexes.

The pair of drawings in Figure 5 are intended to serve as aids in visualizing the relative extent of steric compression that would accompany actual C–C bond formation. In both diagrams, the enolate carbon has been set at a distance of 2.59 ± 0.01 Å from the carbonyl carbon in MODEL KS 2.94. The hypothetical trajectories that are shown strive to incorporate the tenets of the Bürgi–Dunitz model for nucleophilic attack[15] as much as possible without incurring serious nonbonded steric interactions. At this point, a distinguishing feature is made clearly evident. The approach on the left, which would produce A[16] (as seen experimentally), features three close contacts of 2.09, 2.48, and 3.18 Å as illustrated (see the supplementary material for internal coordinates). Two of these distances are closely mirrored on the right (the precursor to D), but the third distance is more than 1 Å shorter! Without doubt, the compression will be even larger across this gap since the spatially demanding solvated metal ion forms one of the contact points. Based on this analysis, a possible cause resides in the fact that the *S,R* and *R,S* transition states are destabilized in this manner, such that their *S,S* and *R,R* counterparts are formed more rapidly. However, more precise definition of the actual transition states is needed to refine these concepts.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Model 1320 spectrometer. ^{1}H NMR were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 20 MHz as indicated. 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. All MPLC seprations 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. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

Aldolization of 1 by Lithium Diisopropylamide. A solution of *n*-butyllithium in hexanes (1.7 mL, 2.55 mmol) was added via syringe to a solution of dry diisopropylamine (288 mg, 2.85 mmol) in dry THF (3 mL) at −78 °C. This mixture was brought to room temperature, stirred for 15 min, recooled to −78 °C, and treated with a solution of 5-norbornan-2-one (1) (250 mg, 2.31 mmol) in dry THF (1 mL). Stirring was maintained for 30 min at −78 °C and for 5 min at 0 °C. Upon being recooled to −78 °C, the reaction mixture was treated with a second 250-mg portion of 1. After 60 min, the solution was brought to room temperature, quenched with saturated brine (30 mL), and extracted with ether (2 × 30 mL). The combined organic phases were dried and evaporated, and the residue was chromatographed on silica gel (elution with ether–petroleum ether, 3:7). This process returned 55 mg (11%) of unconsumed 1 and provided 370 mg (74%) of a 64:36 mixture of 8 and 9 (analytical HPLC analysis). Crystallization of the mixture from petroleum ether gave pure 8. Submission of the mother liquor to MPLC (silica gel, elution with ether–petroleum ether, 1:4) furnished pure 9 as the more polar component.

For 8: colorless crystals; mp 122–123 °C; IR ($CHCl_3$, cm^{-1}) 3570, 3060, 3000, 2980, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (dd, *J* = 2.7, 5.3 Hz, 1 H), 6.44 (dd, *J* = 3.0, 5.6 Hz, 1 H), 6.20 (dd, *J* = 3.3, 5.3 Hz, 1 H), 6.13 (dd, *J* = 3.2, 5.6 Hz, 1 H), 3.70 (m, 1 H), 3.22 (s, 1 H), 2.96 (s, 1 H), 2.84 (d, *J* = 5.5 Hz, 1 H), 2.83 (s, 1 H), 2.03 (d, *J* = 2.9 Hz, 1 H), 1.94 (dd, *J* = 3.8, 12.6 Hz, 2 H), 1.62–1.58 (m, 1 H), 1.43 (s, 1 H), 1.41 (d, *J* = 10.1 Hz, 1 H), 1.17 (dd, *J* = 3.5, 12.6 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 215.27, 145.02, 140.66, 133.09, 132.92, 82.24, 55.99, 51.52, 50.14, 48.71, 47.57, 44.32, 43.54, 42.59; MS *m/z* (M^+) calcd 216.1150, obsd 216.1151.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.72; H, 7.42.

For 9: colorless crystals; mp 55–58 °C; IR ($CHCl_3$, cm^{-1}) 3580, 3060, 3000, 2950, 2920, 2850, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (dd, *J* = 5.6, 3.1 Hz, 1 H), 6.46 (dd, *J* = 5.7, 3.1 Hz, 1 H), 6.23 (dd, *J* = 5.6, 3.1 Hz, 1 H), 6.13 (dd, *J* = 5.7, 3.1 Hz, 1 H), 3.33 (br s, 1 H), 2.97 (m, 2 H), 2.89 (s, 1 H), 2.75 (d, *J* = 9.0 Hz, 1 H), 2.56 (dd, *J* = 13.2, 3.7 Hz, 1 H), 2.19 (d, *J* = 3.1 Hz, 1 H),

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(16) Note should be taken of the considerable conformational similarity of A and D relative to the models depicted in Figure 4.

2.00 (dm, J = 9.0 Hz, 1 H), 1.64 (s, 1 H), 1.54 (dm, J = 9.0 Hz, 1 H), 1.42 (d, J = 9.0 Hz, 1 H), 1.09 (dd, J = 13.2, 3.6 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 216.52, 145.04, 140.79, 135.51, 132.44, 81.83, 55.74, 51.99, 51.16, 48.85, 47.62, 44.00, 43.74, 43.16; MS m/z (M^+) calcd 216.1150, obsd 216.1166.

Aldolization of 1 with Sodium Hexamethyldisilazide. A solution of 1 (200 mg, 1.85 mmol) in dry THF (1 mL) was added to a solution of NaHMDS in toluene (1 mL of 1.0 M, 1.00 mmol), cooled to −78 °C, and stirred for 5 h. Brine (20 mL) and 1 M HCl (3 mL) were added to the cold reaction mixture, which was brought to room temperature and extracted with ether (3 × 20 mL). Drying and solvent evaporation left a residue, analysis of which by analytical HPLC indicated 8 and 9 to be present in a ratio of 68:32.

The exact same procedure was performed in parallel with KHMDS. HPLC analysis indicated the 8:9 ratio to again be 68:32.

Self-Condensation of 1 Promoted by Potassium *tert*-Butoxide. A solution of 1 (1.00 g, 9.24 mmol) in dry *tert*-butyl alcohol (0.5 mL) was added to a freshly prepared solution of potassium *tert*-butoxide in *tert*-butyl alcohol (from 360 mg of K in 8 mL of *t*-BuOH). The reaction mixture was refluxed for 9.5 h and stirred for an additional 15 h at room temperature. Ice and brine were added, and the products were extracted into ether (3 × 20 mL). The combined ethereal phases were dried and evaporated to leave a brown residue (410 mg), column chromatography of which on silica gel (elution with ether–hexanes, 1:9) gave a mixture of 2 and 11–13 (135 mg). Acidification of the aqueous phase and extraction with CH_2Cl_2 (3 × 20 mL), followed by drying and evaporation gave a 1:1 mixture of 2- and 3-cyclopentenylacetic acid (430 mg, 37%), as determined by ^{1}H and ^{13}C NMR analysis and direct comparison.[9]

Hydride Reduction of 9. A solution of 9 (50 mg, 0.231 mmol) in dry ether (3 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (43 mg, 1.13 mmol) in the same solvent (3 mL) at −78 °C. After 90 min, brine (4 drops) was introduced cautiously, and the mixture warmed to room temperature, filtered through Celite, and concentrated. There was isolated a 7:3 mixture of 10 and its epimer (42 mg, 83%). MPLC on silica gel (elution with ether–petroleum ether, 1:1) afforded pure 10 as colorless crystals: mp 142 °C (after sublimation); IR ($CHCl_3$, cm^{-1}) 3560, 3460, 3060, 2980, 2870; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J = 5.5, 2.9 Hz, 1 H), 6.32 (dd, J = 5.8, 3.0 Hz, 1 H), 6.17 (dd, J = 5.5, 3.0 Hz, 1 H), 6.04 (dd, J = 5.8, 3.0 Hz, 1 H), 4.03 (dd, J = 8.2, 7.1 Hz, 1 H), 3.60 (d, J = 8.5 Hz, 1 H), 3.07 (s, 1 H), 2.94 (s, 1 H), 2.89 (s, 1 H), 2.74 (s, 1 H), 2.15 (d, J = 9.0 Hz, 1 H), 2.13 (d, J = 1.5 Hz, 1 H), 2.05 (dd, J = 13.0, 3.7 Hz, 1 H), 1.86 (d, J = 6.9 Hz, 1 H), 1.57 (dm, J = 8.8 Hz, 1 H), 1.49 (dm, J = 8.8 Hz, 1 H), 1.35 (dd, J = 13.0, 3.6 Hz, 1 H), 0.88 (dd, J = 6.7, 6.7 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 142.60, 140.97, 134.74, 132.74, 82.62, 74.42, 51.72, 51.55, 50.32, 49.15, 45.16, 44.65, 43.87, 43.12; MS m/z (M^+) calcd 218.1307, obsd 218.1319.

For the endo,endo diol isomer: white crystals, mp 113–115 °C after sublimation; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.58 (dd, J = 5.6, 3.2 Hz, 1 H), 6.48 (dd, J = 5.7, 3.0 Hz, 1 H), 6.17 (m, 2 H), 4.49 (dd, J = 3.7, 3.7 Hz, 1 H), 2.90 (br s, 2 H), 2.83 (s, 2 H), 2.28 (dd, J = 12.5, 3.6 Hz, 1 H), 2.01 (d, J = 8.2 Hz, 1 H), 1.57–1.39 (m, 5 H), 1.24 (dd, J = 3.3, 3.3 Hz, 1 H), 1.10 (dd, J = 12.6, 3.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 142.36, 140.98, 133.26, 132.69, 81.70, 75.45, 58.83, 51.42, 49.30, 48.06, 46.07, 45.74, 43.76, 42.89; MS m/z (M^+) calcd 218.1307, obsd 218.1319.

Dehydration of 8. Methanesulfonyl chloride (0.25 mL, 3.17 mmol) was introduced via syringe to a solution of 8 (135 mg, 0.624 mmol) and triethylamine (361 mg, 3.57 mmol) in cold (0 °C), dry dichloromethane (3 mL). The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 4 h. Water (30 mL) was added, and the product was extracted into ether (3 × 10 mL), dried, and concentrated. MPLC on silica gel gave 11 (45 mg, 36%) as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3060, 3015, 2990, 2970, 2860, 1720, 1660, 1630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (dd, J = 5.5, 2.9 Hz, 1 H), 6.22 (dd, J = 5.5, 3.3 Hz, 1 H), 6.19 (dd, J = 5.5, 3.0 Hz, 1 H), 5.91 (dd, J = 5.5, 3.1 Hz, 1 H), 3.69 (s, 1 H), 3.42 (dd, J = 3.0, 1.5 Hz, 1 H), 3.05 (m, 2 H), 2.51 (dd, J = 16.7, 3.4 Hz, 1 H), 2.29 (d, J = 8.7 Hz, 1 H), 2.19 (dd, J = 16.7, 3.5 Hz, 1 H), 2.09 (dm, J = 9.3 Hz, 1 H), 1.64 (d pent, J = 8.3, 1.7 Hz, 1 H), 1.40 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 207.36, 147.32, 142.92, 139.11, 133.90, 131.73, 126.12, 56.45, 52.71, 50.57, 48.26, 45.87, 41.81, 33.75; MS m/z (M^+) calcd 198.1045, obsd 198.1039.

Aldolization of 2-Norbornanone by Lithium Diisopropylamide. A solution of LDA (from 3.60 mmol of *n*-butyllithium and 4.28 mmol of diisopropylamine) was treated with two 320-mg (2.91-mmol) portions of 2-norbornanone as described above for the reaction of 1. The slower reaction rate was compensated for by stirring the mixture at room temperature for 14 h. The crude mixture showed the ratio of 14 to 15 to be 63:37 (392 mg, 63%) as determined by HPLC analysis. Recrystallization of this residue from petroleum ether–chloroform (10:1) gave pure 14. MPLC of the mother liquor furnished pure 15.

For 14: colorless crystals; mp 131–132 °C; IR ($CHCl_3$, cm^{-1}) 3570, 3450, 2960, 2880, 1735; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.98 (dm, J = 3 Hz, 1 H), 2.70 (m, 1 H), 2.53 (dm, J = 3.2 Hz, 1 H), 2.35 (d of pent, J = 10.2, 2.0 Hz, 1 H), 2.19 (m, 1 H), 1.85–1.70 (m, 4 H), 1.60–1.50 (m, 3 H), 1.50–1.25 (m, 5 H), 1.60 (d, J = 11.3 Hz, 1 H), 1.33 (dd, J = 11.8, 3.6 Hz, 1 H), 1.21 (dd, J = 13.0, 3.4 Hz, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 219.03, 81.25, 60.96, 50.08, 45.69, 45.56, 38.40, 36.96 (2 C), 35.88, 29.44, 28.02, 23.71, 21.98; MS m/z (M^+) calcd 220.1463, obsd 220.1457.

For 15: colorless solid; mp 83–84 °C (after sublimation); IR ($CDCl_3$, cm^{-1}) 3480, 2980, 2960, 2940, 2880, 1730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 (br s, 1 H), 2.65 (d, J = 1.6 Hz, 1 H), 2.53 (m, 1 H), 2.20–2.08 (m, 4 H), 2.05 (d, J = 3.4 Hz, 1 H), 2.03–1.94 (m, 1 H), 1.88–1.75 (m, 2 H), 1.60–1.50 (m, 3 H), 1.48–1.40 (m, 1 H), 1.37–1.23 (m, 4 H), 1.14 (dd, J = 13.3, 3.4 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 221.46, 81.36, 61.56, 49.48, 46.30, 45.71, 38.77, 38.71, 37.04, 35.63, 29.91, 28.39, 23.61, 22.91; MS m/z (M^+) calcd 220.1463, obsd 220.1457.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 76.33; H, 9.15. Found: C, 76.32; H, 9.18.

Hydrogenation Experiments. A. Reduction of 8. A solution of 8 (280 mg, 1.30 mmol) in ethyl acetate (10 mL) containing 5% Pd–C catalyst (20 mg) was hydrogenated at atmospheric pressure over a period of 20 h. Filtration of the reaction mixture through Celite, washing with ethyl acetate, and concentration gave 284 mg (100% of 11, identical in all respects with the aldol described above.

B. Reduction of 9. Comparable processing of a 35-mg (0.162-mmol) sample of 9 in ethyl acetate (5 mL) gave after workup 34 mg (97%) of 12, the IR, ^{1}H NMR, and ^{13}C NMR of which were identical with those reported above for this material.

Self-Condensation of 2-Norbornanone Promoted by Potassium Hexamethyldisilazide. A solution of 2-norbornanone (750 mg, 6.81 mmol) in dry THF (5 mL) was added during 5 min to a cold (−78 °C), magnetically stirred solution of KHMDS in toluene (13.6 mL of 0.5 M, 6.8 mmol) and THF (10 mL). The reaction mixture was stirred for 10 min at 0 °C, recooled to −78 °C, and treated with a second 750-mg portion of the ketone dissolved in THF (5 mL). This solution was stirred at −78 °C for 60 min and at room temperature for 3.5 h before being processed in the predescribed manner. Bulb-to-bulb distillation of the residue at 65 °C and 0.1 Torr gave 865 mg (63%) of a mixture of 16–19. MPLC on silica gel (elution with ether–petroleum ether, 1:9) gave two fractions in a 39:61 ratio. The first was a crystalline mixture of 16/17 (62:38 by ^{1}H NMR analysis): mp 76 °C; IR ($CHCl_3$, cm^{-1}) 2960, 2920, 2880, 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (d, J = 4 Hz, 1 H), 2.93 (d, J = 0.4 Hz, 1 H), 2.77 (m, 1 H), 2.35 (s, 1 H), 2.11 (dm, J = 17.5 Hz, 1 H), 1.92 (d, J = 17.6 Hz, 1 H), 1.77–1.09 (series of m, 12 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm (major component, 83% of total) 206.43, 154.70, 130.99, 50.64, 41.31, 40.39, 39.69, 38.58, 37.23, 35.15, 28.59, 27.70, 27.60, 24.09; MS m/z (M^+) calcd 202.1388, obsd 202.1357.

The second fraction, consisting of a mixture of 18 and 19 (28:72 by ^{1}H NMR analysis), was a colorless oil: IR ($CHCl_3$, cm^{-1}) 2960, 2930, 2910, 2880, 1710, 1660; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.06 (s, 1 H), 2.80 (m, 1 H), 2.50 (s, 1 H), 2.31–2.25 (m, 3 H), 1.76–1.07 (seris of m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.00, 154.01, 130.18, 50.19, 42.95, 40.65, 39.20, 38.97, 38.07, 35.95, 28.01, 27.90, 27.37, 23.63; MS m/z (M^+) calcd 202.1388, obsd 202.1357.

The use of potassium hydride led to the same result, although the product mixture was less pure.

Acknowledgment. We thank the National Institutes of Health (Grant CA-12115) for financial support.

Supplementary Material Available: 300-MHz NMR spectra of **9**, **10**, and its endo,endo-epimer, and **14**; experimental for the X-ray structure determinations; and tables of crystal data, intensity data collection, structure refinement, final positional parameters, anisotropic thermal parameters, bond lengths, and bond angles for **8** and **10**; internal coordinates for **A–F** (Table I); and the pair of structures of Figure 5 (31 pages). Ordering information is given on any current masthead page.

Regio- and Stereoselective Oxidation of Unsaturated Bicyclo[2.2.2]octanones with Selenium Dioxide

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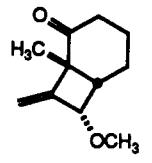
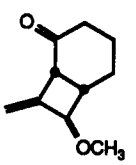
The selenium dioxide oxidation of several unsaturated bicyclo[2.2.2]octanones has been examined in connection with the projected utility of properly functionalized products in tandem oxyanionic Cope rearrangement–S_N' transformations. The oxidations studied proved to be regioselective, with attack in the olefinic sector of each molecule occurring to the exclusion of chemical reaction α to the carbonyl. Stereoselectivity was also often encountered, with steric factors appearing to contribute heavily to establishing the particular configuration of the newly introduced stereogenic center.

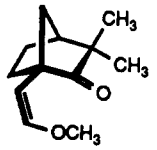
Earlier disclosures from this laboratory have demonstrated the feasibility of tandem anionic oxy-Cope rearrangement–S_N' allylic ether displacement as a powerful tool for multiple C–C bond construction with rapid elaboration of complex polycyclic frameworks.[1,2] The structural features essential to those alcohols that can undergo this reaction cascade can be assembled in two ways. In the first, represented by **1–3**, the alkoxy group is present in the electrophilic ketone precursor.[1] Alternatively, the ultimate leaving group can reside in the vinyl anion segment as exemplified by **4**.[2]



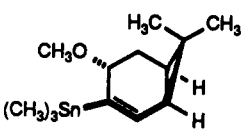
1



2



3



4

The serviceability of this new methodology rests to a degree upon ready access to precursor molecules of the type **1–4**. Compounds from the classes represented by **3** and **4** are readily prepared[3,4] and present no obvious availability problems. In contrast, **1** and **2** constitute small, multiply functionalized molecules of a category that has been accorded little past attention. The need for a β,γ-unsaturated ketone subunit where the double bond also forms part of an allyl ether moiety should be capable of elaboration from several diverse directions. In the case of **1** and **2**, recourse was made to the [2 + 2] photocycloaddition of methoxyallene to a 2-cyclohexenone.[5]

In the present paper, we describe a series of observations made in conjunction with an examination of the oxidation of several selected unsaturated bicyclo[2.2.2]octanones with selenium dioxide. Our goal was to gain insight into the reliability of an approach wherein an allylic oxygen was incorporated into systems in which the carbonyl group and double bond are already present. Should the regiochemistry and stereoselectivity of these oxidations proceed at acceptable levels, future implementation of this strategy would hold promise and be attractive.

Results and Discussion

As a consequence of its unique position as an oxidant, selenium dioxide has received considerable attention and several detailed reviews of its chemistry are available.[6-10] Stemming from this past work are several general reactivity patterns associated with alkene oxidation. The trends are seen to vary widely, depending on whether the olefin is cyclic or acyclic and, more critically, on the level of substitution about the double bond. Virtually without exception, the molecules studied have not also carried a ketone carbonyl, a functional group recognized in its own right to be prone to oxidation by SeO_2.

One need therefore inquire into several issues. One concern that arises immediately deals with relative reactivities at carbonyl and olefinic sites. Is there a suitably wide reactivity differential? Is allylic rearrangement a potential complication? If allylic alcohols are formed, is the oxidation regio- and/or stereoselective? Are the allylic alcohols prone to ready rearrangement and/or facile dehydration?

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