support of this research by the American Heart Association, Arizona Affiliate, by the American Cancer Society, and by the University of Arizona Foundation and the Office of the Vice President for Research is gratefully acknowledged.

Registry No. 1, 99249-28-2; 2, 111970-30-0; 3, 125250-66-0; 4, 125250-67-1; 5, 111970-33-3; 6, 111970-32-2; 7, 111970-31-1; 8, 92803-20-8; (±)-9, 125353-72-2; 10, 117583-51-4; 11a, 99249-29-3; 11b, 99295-87-1; 12a, 111970-36-6; 12b, 112020-55-0; 13a, 125250-68-2; 13b, 125353-78-8; 14a, 125250-69-3; 14b, 125353-79-9; 15a, 111970-39-9; 15b, 112020-58-3; 16a, 111970-38-8; 16b, 112020-57-2; 17a, 111970-37-7; 17b, 112020-56-1; 18a, 111970-41-3; 18b, 112020-60-7; (±)-19a, 125355-34-2; (±)-19b, 125353-80-2; 20a, 117583-52-5; 20b, 117677-00-6; 21, 99249-30-6; 22, 117583-49-0; 23, 109908-38-5; 24, 125250-70-6; 25, 125250-71-7; 26, 99249-32-8; 27, 117583-53-6; 28a, 99249-31-7; 28b, 99295-88-2; 29a, 117583-50-3; 29b, 117676-99-0; 30a, 109908-39-6; 30b, 109958-06-7; 31a, 125250-72-8; 31b, 125353-81-3; 32a, 125250-73-9; 32b, 125353-82-4; 33a, 99249-34-0; 33b, 99295-89-3; 34a, 117583-54-7; 34b, 117677-01-7; 35, 125250-74-0; 36a, 125250-75-1; 36b, 125353-83-5; 37, 125250-76-2; 38, 125353-73-3; 39a, 125250-77-3; 39b, 125353-84-6; 40a, 125353-74-4; 40b, 125353-85-7; 41, 125250-78-4; 42a (R = CH_2OH), 125250-79-5; 42b (R = CH_2OH), 125353-86-8; 43, 50870-61-6; 44, 125250-80-8; 45, 125353-75-5; 46, 13351-28-5; 47, 125250-81-9; 48, 125250-82-0; 49, 125250-83-1; 50, 125250-84-2; 51, 85514-45-0; 52, 125250-85-3; 53, 125250-86-4; 54, 125250-87-5; 55a, 125250-88-6; 55b, 125353-87-9; 56, 125250-89-7; 57, 125250-90-0; dimethyl L-tartrate acetone ketal, 37031-29-1; (3*R*,4*R*)-2,5-dimethyl-2,3,4,5-hexanetetrol, 81706-69-6; (3*R*,4*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol acetone ketal, 125250-91-1; (3*R*,4*R*)-2,5-dimethoxy-2,5-dimethyl-3,4-hexanediol, 99267-98-8; 4-phenyl-1-butanol, 3360-41-6; 4-phenylbutyraldehyde, 18328-11-5; (*dl*)-1,8-diphenyl-4,5-octanediol, 125353-76-6; (*S*)-(+)-1,2-propanediol, 4254-15-3; ethyl cinnamate, 103-36-6; 2-carbethoxy-3,4-diphenylcyclopentanone, 125353-77-7; 1,5-pentanediol, 111-29-5; 1,5-pentanediol, mono(*tert*-butyldimethylsilyl) derivative, 83067-20-3; 1,5-pentanediol, mono(*tert*-butyldimethylsilyl) derivative, tosylate, 83084-58-6; 1,4-di-*O*-methyl-L-threitol, 50622-10-1; 1,4-bis-*O*-(*p*-biphenylmethyl)-L-threitol, 125250-92-2; 1,4-bis-*O*-(2-naphthylmethyl)-L-threitol, 125250-93-3; dimethyl L-tartrate, 608-68-4; (*R*,*R*)-2,3-butanediol, 24347-58-8; (*S*,*S*)-1,2-diphenyl-1,2-ethanediol, 2325-10-2; diisopropyl L-tartrate, 2217-15-4; 2-methyl-2-cyclopenten-1-one, 1120-73-6; 2-cyclohexen-1-one, 930-68-7; 1,4-di-*O*-benzyl-L-threitol, 2-bromo-2-cyclohexen-1-one ketal, 125250-94-4.

Supplementary Material Available: ^1H and/or ^{13}C NMR spectra of all new compounds (65 pages). Ordering information is given on any current masthead page.

Mechanistic Studies of Diastereoselective Cyclopropanation via Homochiral Ketals. 2. Studies with Conformationally Restricted 2-Cyclohexen-1-one Ketals

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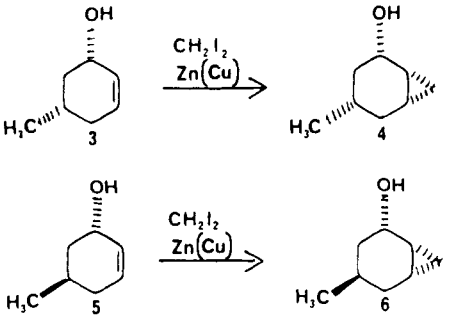
The effect of cyclohexene ring conformation on the diastereoselectivity observed for Simmons–Smith cyclopropanation of 2-cyclohexen-1-one ethylene ketals was examined by using (5*S*)-5-*tert*-butyl-2-cyclohexen-1-one 1,2-ethanediol, (2*R*,3*R*)-2,3-butanediol, and (2*S*,3*S*)-2,3-butanediol ketals. Reagent chelation by the pseudoequatorial dioxolane oxygen atom was shown to result in more effective methylene transfer. This regiochemical preference can either antagonize or reinforce diastereoselectivity due to steric hindrance of the dioxolane oxygen atoms from dissymmetric placement of methyl appendages on the dioxolane ring.

In the preceding article[1] a general mechanism was advanced that can account for the diastereoselectivity observed when common[2] 2-cycloalken-1-one ketals **1** are cyclopropanated using the Simmons–Smith reagent.[3] Preferential chelation of zinc by the least sterically hindered dioxolane oxygen atom proximal to the alkene effectively positions the reagent for diastereoselective methylene transfer (Figure 1). While this simplistic picture has predictive value, a wealth of mechanistic detail is absent. In particular, we wish to know, for 2-cyclohexen-1-one ethylene ketals, if a regiochemical preference for methylene delivery from reagent coordinated at either a pseudoequatorial or pseudoaxial dioxolane oxygen atom exists and also if this preference can be modified by the steric effects of suitably placed dioxolane appendages. This information should be useful in predictions of interactions of the Simmons–Smith reagent with conformationally constrained ene ketals.

Previously it was shown by Chan and Rickborn[4] that Simmons–Smith cyclopropanation of *cis*-5-methyl-2-cyclohexen-1-ol (**3**) gives exclusively **4** and is 3.3 times faster than cyclopropanation of the trans diastereomer **5**, which yields exclusively **6**. These results were rationalized



(1) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.*, previous article in this issue.

(2) Ring compounds have been classified into four categories, namely, small rings (three- and four-membered), common rings (five-, six-, and seven-membered), medium rings (eight- to 11-membered), and large rings (12-membered and larger). See: Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 189.

(3) For reviews of the Simmons–Smith reaction, see: (a) Furukawa, J.; Kawabata, N. In *Advances in Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic Press: New York, 1974; Vol. 12, Chapter 3. (b) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1–131.

(4) Chan, J. H.-H.; Rickborn, B. *J. Am. Chem. Soc.* **1968**, *90*, 6406–6411.

0022-3263/90/1955-2055$02.50/0

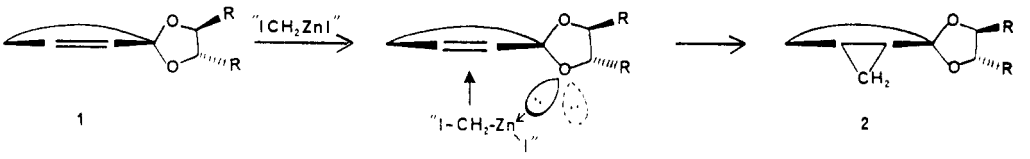


Figure 1.

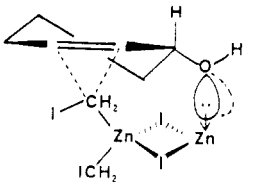
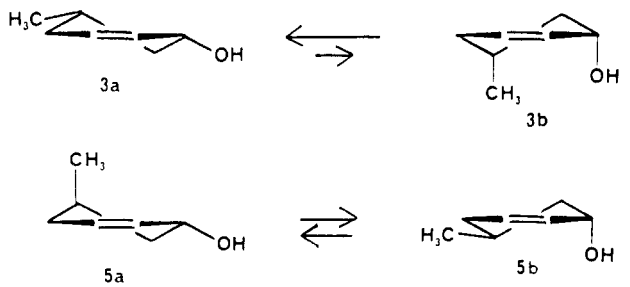


Figure 2.

by postulating that the species responsible for methylene transfer is a dimer, such as $(ICH_2)_2ZnI{\cdot}ZnI_2$ (Figure 2). The topographic requirements for centrosymmetric methylene transfer from such a reagent under chelation by an allylic oxygen atom would render conformers **3a** and **5a** more reactive than **3b** and **5b**, respectively. The increased ground-state energy difference between conformers **3a** and **3b** relative to conformers **5a** and **5b** due to differences in transannular steric strain might account for the observed ratio of rates assuming that the methyl at C-5 does not interfere directly with chelation or methylene transfer. This seems reasonable since for both **3** and **5** the stereochemistry of methylene transfer is completely controlled by the allylic oxygen atom.

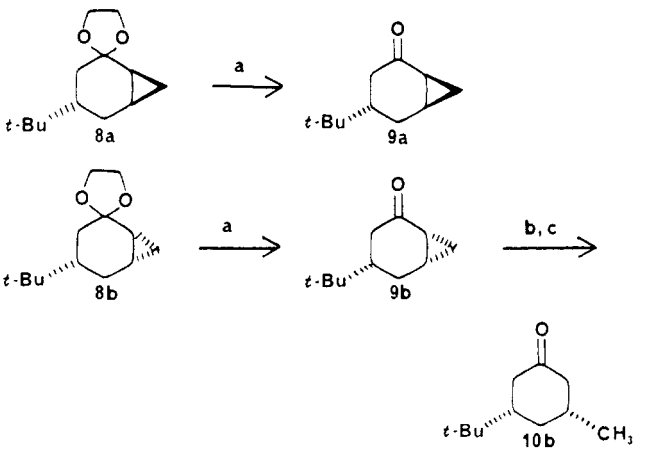


Studies of 2-cyclohexen-1-ols such as **3** and **5**, for which zincate formation is possible, are of uncertain relevance to 2-cyclohexen-1-one ethylene ketals such as **1**. For conformationally mobile ene ketals, either dioxolane oxygen atom can become pseudoequatorially disposed. However, for conformationally restricted systems there may be a regiochemical preference for methylene transfer from reagent chelated at one or the other dioxolane oxygen atom. Such a preference could interfere with the diastereoselectivity expected from the use of a C_2-symmetric homochiral diol auxiliary.[1] We examine these issues in the experiments outlined herein.

Results and Discussion

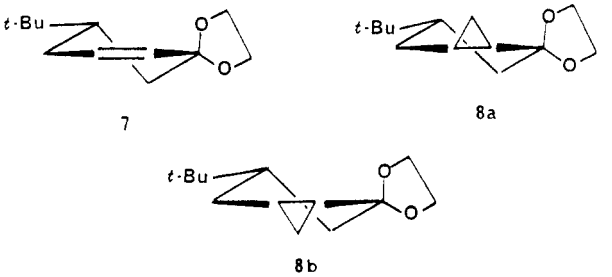
In order to determine, by means of an internal competition, whether a preference for methylene transfer from reagent coordinated at the pseudoequatorial or the pseudoaxial dioxolane oxygen atom exists, a conformationally restricted 2-cyclohexen-1-one ethylene ketal was required. One suitable compound was (5*S*)-5-*tert*-butyl-2-cyclohexen-1-one ethylene ketal (**7**).[5] From the observed ^1H NMR coupling constants (Figure 3), it seems reasonable to assume predominance of the half-chair conformer in which the *tert*-butyl group occupies a pseudoequatorial position. For this conformationally restricted system, the *pro-S* dioxolane oxygen atom is predominantly pseudoequatorially disposed, while the *pro-R* dioxolane oxygen atom is predominantly pseudoaxially disposed.

Scheme I[a]



[a] (a) Aqueous HCl, CH_3OH; (b) Li, NH_3(liq), *t*-BuOH, Et_2O; (c) PDC, CH_2Cl_2.

Treatment of ene ketal **7** with the Simmons–Smith reagent[6] gave, in 91% yield, a 1:3 mixture of diastereomeric cyclopropane ketals **8a** and **8b**. These diastereomers were



separated by column chromatography (α = 1.18) and characterized. Structures were assigned by conversion of **8b** to (3*S*,5*R*)-*cis*-3-*tert*-butyl-5-methylcyclohexanone (**10b**)[7,8] as outlined in Scheme I. Diastereomer **8a** was also hydrolyzed to cyclopropyl ketone **9a**.

Assuming that chelation does occur and does control the regiochemistry of the cyclopropanation, these results imply that while coordination leading to methylene transfer can occur at either dioxolane oxygen atom, coordination at the pseudoequatorially disposed *pro-S* dioxolane oxygen atom results in more efficient cyclopropanation. This result is consistent with the postulate by Chan and Rickborn that a flexible dimeric reagent is the active species.[4]

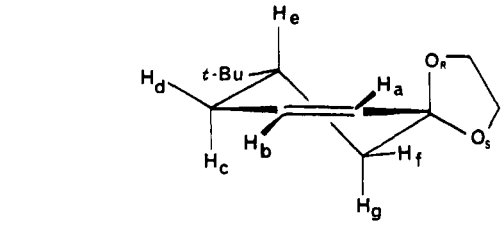
The interplay between the topographic preference for methylene transfer discussed above and the steric effects

(5) Optically active 5-*tert*-butyl-2-cyclohexen-1-one was required for experiments with homochiral diols. For characterization purposes, the *S* enantiomer was used throughout this work.

(6) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825–1826.

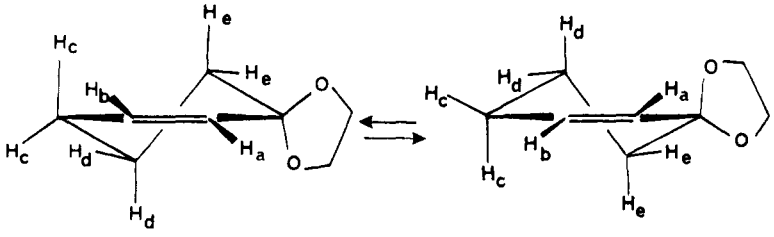
(7) Authentic samples of racemic **10a** and **10b** were prepared by adaptation of the method of Whitmore and Pedlow. See: Whitmore, F. C.; Pedlow, G. W. *J. Am. Chem. Soc.* **1941**, *63*, 758–760.

(8) Heathcock, C. H.; Germroth, T. C.; Graham, S. L. *J. Org. Chem.* **1979**, *44*, 4481–4487.



for 7:

	Chemical Shift, ppm	Coupling Constants, Hz
Ha	5.58	^{3}Jab = 10.0
Hb	5.96	^{3}Jbc = 2.5
Hc	1.79	^{3}Jbd = 5.6
Hd	2.10	^{2}Jcd = 17.5
He	1.65	^{3}Jce = 11.4
Hf	1.91	^{3}Jde = 2.5
Hg	1.44	^{3}Jef = 4.5
		^{3}Jeg = 12.8
		^{2}Jfg = 12.8
		^{4}Jac = 2.5

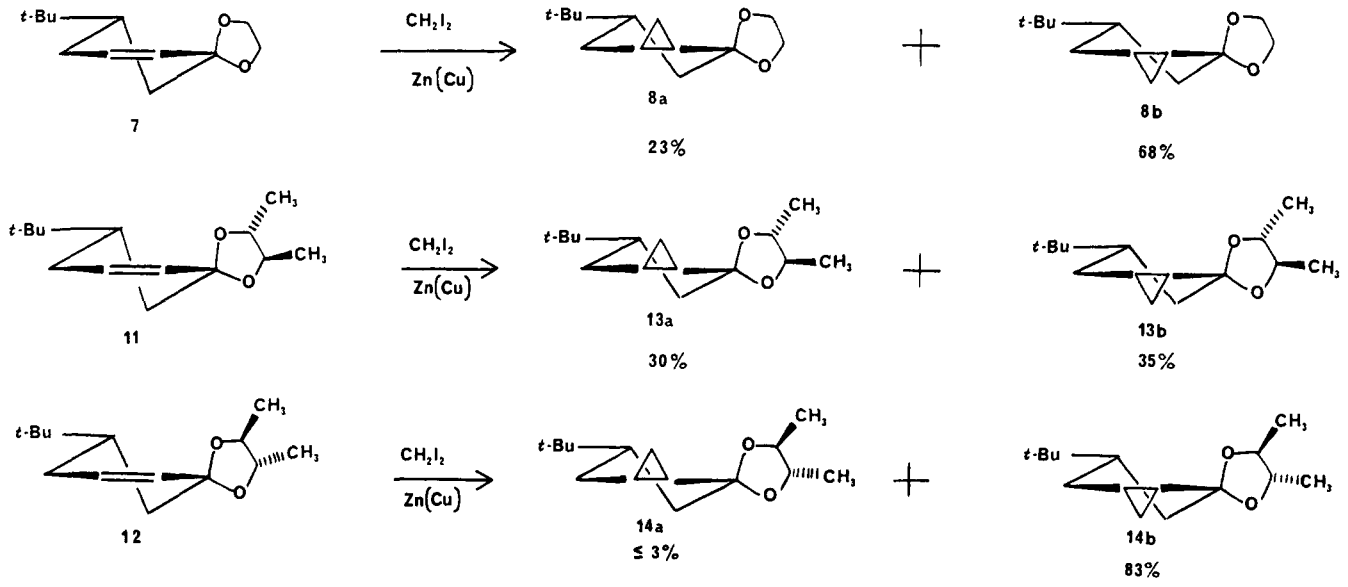


for 2-cyclohexen-1-one ethylene ketal:

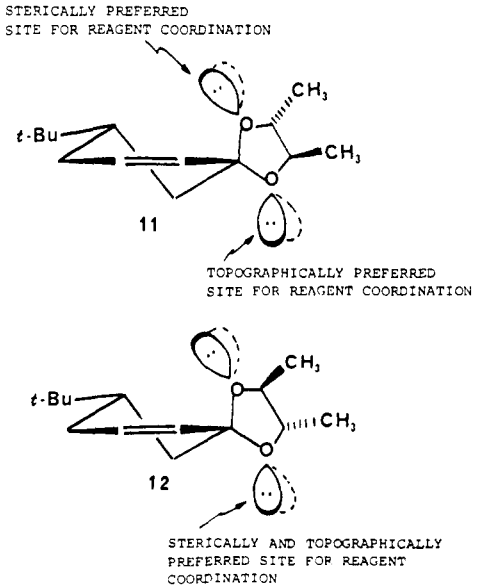
	Chemical Shift, ppm	Coupling Constants, Hz
Ha	5.58	^{3}Jab = 9.8
Hb	5.96	^{3}Jbc = 3.7
Hc	2.03	^{3}Jcd = 6.5
Hd	1.78	
He	1.78	^{4}Jac = 2.0

Figure 3.

Scheme II



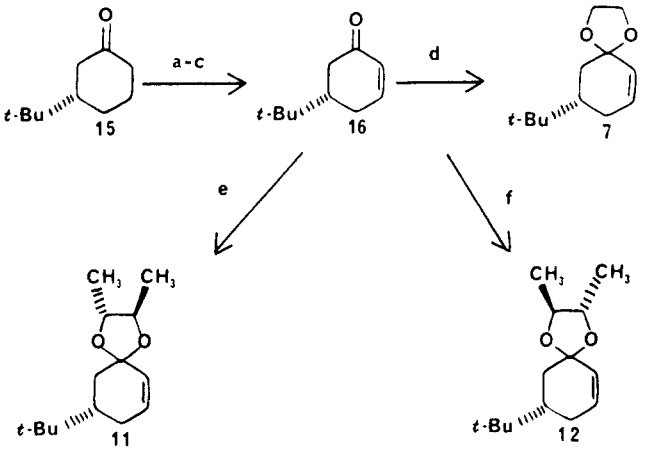
of dissymmetrically positioned dioxolane methyl appendages was examined by using homochiral 2,3-butanediol ketals **11** and **12**. For (2*R*,3*R*)-2,3-butanediol ketal **11**, the regiochemical preference for chelation of the reagent by the pseudoequatorial dioxolane oxygen atom should be opposed by the steric hindrance to chelation due to the dioxolane methyl appendage proximal to the alkene.[1] For (2*S*,3*S*)-2,3-butanediol ketal **12**, the regiochemical preference for chelation by the pseudoequatorial dioxolane oxygen atom should be reinforced by steric hindrance to chelation of the reagent by the pseudoaxial dioxolane oxygen atom.[1]



Treatment of ene ketal **11** with the Simmons–Smith reagent produced, in 65% yield, a 1:1 mixture of cyclopropane ketals **13a** and **13b**, whereas similar treatment of ene ketal **12** gave cyclopropane ketal **14b** in 83% yield with no evidence for formation of **14a** (Scheme II). Diastereomers **13a** and **13b** were separated by column chromatography (α = 1.62) and were characterized. Structures were assigned by hydrolysis of **13a** and **13b** to norcaranones **9a** and **9b**, respectively. Cyclopropane ketal **14b** was characterized and subsequently hydrolyzed to **9b**.

The above results confirm that for at least some conformationally constrained 2-cycloalken-1-one ethylene ketals a regiochemical bias exists for methylene transfer that results from preferential coordination of the Simmons–Smith reagent at the pseudoequatorially disposed dioxolane oxygen atom. This preference is presumably due

Scheme III[a]



[a] (a) LDA, THF, −78 °C; (b) PhSeBr; (c) H_2O_2; (d) $TMSOCH_2CH_2OTMS$, TMS-OTf, CH_2Cl_2; (e) (2*R*,3*R*)-2,3-butanediol bis(trimethylsilyl ether), TMS-OTf, CH_2Cl_2; (f) (2*S*,3*S*)-2,3-butanediol bis(trimethylsilyl ether), TMS-OTf, CH_2Cl_2.

to the topographic requirements for methylene transfer imposed by the nature of the active reagent. This regiochemical preference can be modified by steric hindrance to reagent chelation due to dissymmetrically positioned dioxolane appendages. Where these effects act in concert, high diastereoselectivities can be expected. Where these effects act in opposition, attenuated diastereoselectivities will result.

Syntheses of Ene Ketals 7, 11, and 12. The syntheses of ene ketals **7**, **11**, and **12** are outlined in Scheme III. Racemic 3-*tert*-butylcyclohexanone (**15**)[7] was resolved by the method of Adolphen et al.[9] Deprotonation of the *S* enantiomer with LDA at −78 °C, followed by addition of benzeneselenenyl bromide and treatment of the crude α-phenyl selenide with aqueous hydrogen peroxide[10] gave enone **16** in 44% yield.[11] Ketalization by the method of Noyori[12] using the bis(trimethylsilyl ethers) **17**–**19** of ethylene glycol, (2*R*,3*R*)-2,3-butanediol, and (2*S*,3*S*)-2,3-butanediol produced ene ketals **7**, **11**, and **12** in 44, 72, and 66% yields, respectively.

Experimental Section

Benzene was distilled from calcium hydride and diethyl ether was distilled from phosphorus pentoxide or sodium benzophenone ketyl under an inert atmosphere. Dimethyl sulfoxide was distilled from calcium hydride under reduced pressure and stored over 3Å molecular sieves. Zinc–copper couple was prepared according to the method of Shank and Shechter[6] immediately before use. The purity of all title compounds was judged to be ≥95% by ^1H and ^{13}C NMR spectral determinations. Proton magnetic resonance spectra were recorded at 250 MHz on a Bruker WM-250 spectrometer. Chemical shifts are reported in parts per million (ppm) from tetramethylsilane. Carbon-13 magnetic resonance spectra were recorded at 62.9 MHz on Bruker WM-250 or AM-250 NMR spectrometers. Chemical shifts are reported in parts per million (ppm) from the center line of the chloroform-*d* triplet (77.0). Mass spectral determinations were performed at the Midwest Center for Mass Spectrometry, an NSF Regional Instrumentation Facility (Grant CHE-0211164). Elemental analyses were performed by Desert Analytics, Tucson, AZ. Infrared spectra were recorded on a Perkin-Elmer Model 983 infrared spectrophotometer. Optical rotations were measured at 589 nm on a Rudolph Research Autopol 3 polarimeter. CD spectra were recorded on a Cary Model 60 CD/ORD spectrometer. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70–230 mesh ASTM).

(*S*)-5-*tert*-Butyl-2-cyclohexen-1-one (16).[10,11] A three-necked flask equipped with a stir bar, pressure-equalized addition funnel, and two septum caps was flame-dried under vacuum and cooled under argon. The flask was cooled to −78 °C and charged with dry THF (10 mL), diisopropylamine (0.45 mL, 3.20 mmol), and *n*-BuLi (1.85 mL, 1.6 M in hexanes). A solution of (3*S*)-3-*tert*-butylcyclohexanone[9] (380 mg, 2.46 mmol) in dry THF (1.0 mL) was added dropwise via syringe. After stirring for 15 min at −78 °C, a solution of diphenyl diselenide (0.46 g, 1.48 mmol) in dry THF (1.0 mL) was placed in the addition funnel. Bromine (236 mg, 1.48 mmol) was added to the solution in the addition funnel dropwise via syringe, with agitation of the funnel to dissolve any phenylselenium tribromide that may have formed. Decolorization of the deep maroon benzeneselenenyl bromide solution occurred as it was rapidly added in one portion to the reaction mixture. The cold reaction mixture was then poured into a mixture of 0.5 M HCl (25 mL) and 50% ether/pentane (20 mL). The bright yellow organic phase was separated and washed successively with water, saturated sodium bicarbonate, and saturated sodium chloride, then dried over anhydrous sodium sulfate, and concentrated, giving the crude α-phenyl selenide, which was immediately oxidized as follows.

To a well-stirred solution of the selenide in dry CH_2Cl_2 (8.0 mL) containing pyridine (0.4 mL) was cautiously added a solution of 30% H_2O_2 (726 mg, 6.4 mmol) in water (0.655 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature, stirred for an additional 15 min, and poured into a mixture of CH_2Cl_2 (12 mL) and saturated sodium bicarbonate (15 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were washed successively with 10% HCl and saturated sodium chloride solutions, then dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography gave the crude enone product **16**. Column chromatography on silica gel 60 (50 g) eluted with 5% EtOAc/hexanes gave the enone **16** as an orange oil: R_f 0.32 (20% EtOAc/hexanes); $[\alpha]^{23}_D$ +14.32° (*c* 0.81, CCl_4) [lit.[11] $[\alpha]^{20}_D$ +5.02° (*c* 0.0566, CCl_4), ≈20% ee]; yield 166 mg, 1.09 mmol, 44%; ^1H NMR ($CDCl_3$) δ 0.89–0.95 (9, s), 1.79–1.92 (1, m), 2.03–2.21 (2, m), 2.36–2.59 (2, m), 5.99–6.07 (1, m), 6.99–7.08 (1, m); ^{13}C NMR ($CDCl_3$) δ 26.9 (CH_3), 27.4 (CH_2) 32.2 (C), 39.9 (CH_2), 45.2 (CH), 129.1 (CH), 150.7 (CH), 200.9 (C).

General Procedure for the Preparation of Bis(trimethylsilyl ethers). A flask equipped with a stir bar and a pressure-equalized addition funnel was flame-dried under vacuum and cooled under argon. The flask was charged with diol (1 equiv) and CH_2Cl_2 (5.0 mL/mmol diol) and cooled to 5 °C in an ice–water bath. Following the addition of triethylamine (3 equiv) and chlorotrimethylsilane (2.5 equiv) dropwise via the addition funnel, a cloudy precipitate formed. The resulting mixture was stirred and gradually warmed to room temperature. Progress of the reaction was monitored by TLC. The pink reaction mixture was filtered and the precipitate washed with anhydrous diethyl ether several times until no more precipitate formed in the flask. After concentration, the crude product was purified by column chromatography on silica gel 60 eluted with 20% EtOAc/hexanes.

Ethylene glycol bis(trimethylsilyl ether) (17): R_f 0.63 (20% EtOAc/hexanes); yield 52%.

(2*R*,3*R*)-2,3-Butanediol bis(trimethylsilyl ether) (18): R_f 0.67 (20% EtOAc/hexanes); yield 96%.

(2*S*,3*S*)-2,3-Butanediol bis(trimethylsilyl ether) (19): R_f 0.67 (20% EtOAc/hexanes); yield 83%.

General Procedure for Ketalizations.[12] To a dry flask under argon at −60 °C (dry ice/2-propanol bath) were added dry CH_2Cl_2 (3 mL/mmol ketone), trimethylsilyl triflate (3 mol %), and a solution of the bis(trimethylsilyl ether) (1.5 equiv) in dry CH_2Cl_2 (3 mL/mmol ketone). After several minutes, a solution of enone (1 equiv) in dry CH_2Cl_2 (3 mL/mmol ketone) was added dropwise via syringe. A thin layer chromatogram was taken every 5 °C as the reaction was allowed to warm gradually from −60 °C. The reaction was maintained at the coldest temperature at which the

(9) Adolphen, G.; Eisenbraun, E. J.; Keen, G. W.; Flanagan, P. W. K. *Org. Prep. Proc. Int.* **1970**, *2*, 93–100.
(10) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434–5447.
(11) Gorthey, L. A.; Vairamani, M.; Djerassi, C. *J. Org. Chem.* **1985**, *50*, 4173–4182.
(12) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.

ketalization proceeded smoothly. When complete, the reaction was quenched by the addition of pyridine (0.5 mL/mmol ketone). Concentration of the reaction mixture and column chromatography afforded the pure ketal.

(*S*)-5-*tert*-Butyl-2-cyclohexen-1-one Ethylene Ketal (7). Column chromatography of the crude product on silica gel 60 eluted with 5% EtOAc/hexanes gave the ketal as a white solid: R_f 0.22 (10% EtOAc/hexanes); $[\alpha]^{24}_D$ +66.32° (*c* 0.775, $CHCl_3$); yield 44%; IR ($CHCl_3$) cm^{-1} 3030, 3025, 3017, 3013, 3011, 2961, 2885, 2834, 1654, 1476, 1469, 1439, 1427, 1394, 1365, 1293, 1271, 1240, 1154, 1119, 1089, 1064, 1030, 999, 973, 946, 931, 919, 897, 849, 803, 783, 667; ^1H NMR ($CDCl_3$) δ 0.81–0.87 (9, s), 1.35–1.45 (1, m), 1.52–1.90 (3, m), 2.01–2.14 (1, m), 3.82–4.02 (4, m), 5.50–5.58 (1, m), 5.87–5.97 (1, m); ^{13}C NMR ($CDCl_3$) δ 26.6 (CH_2), 27.0 (CH_3), 31.9 (C), 34.9 (CH_2), 42.4 (CH), 64.2 (CH_2), 64.5 (CH_2), 107.3 (C), 126.8 (CH), 132.6 (CH); mass spectrum (70 eV) *m/z* (rel intensity) 196 (0.6), 181 (4), 155 (1), 140 (1), 139 (13), 137 (2), 121 (2), 114 (1), 113 (14), 112 (4), 100 (7), 99 (3), 96 (3), 95 (9), 94 (1), 93 (3), 91 (3), 86 (2), 81 (1), 80 (2), 79 (3), 78 (3), 77 (7), 73 (3), 69 (100), 68 (25), 67 (16), 57 (14), 55 (5), 53 (4); exact mass calcd for $C_{12}H_{20}O_2$ 196.1464, obsd 196.1470.

(*S*)-5-*tert*-Butyl-2-cyclohexen-1-one (2*R*,3*R*)-2,3-Butanediol Ketal (11). Column chromatography of the crude product on silica gel 60 eluted with 5% EtOAc/hexanes gave the ketal as a yellow oil: R_f 0.50 (20% EtOAc/hexanes); $[\alpha]^{24}_D$ +44.26° (*c* 3.92, $CHCl_3$); yield 72%; IR ($CHCl_3$) cm^{-1} 3032, 3009, 2965, 2869, 1652, 1476, 1466, 1453, 1441, 1387, 1377, 1365, 1295, 1271, 1241, 1194, 1179, 1111, 1086, 1009, 978, 933, 918, 839; ^1H NMR ($CDCl_3$) δ 0.83–0.90 (9, s), 1.22–1.31 (6, dd, *J* = 5.8 Hz), 1.40–2.36 (5, m), 3.61–3.81 (2, m), 5.59–5.69 (1, m), 5.90–5.98 (1, m); ^{13}C NMR ($CDCl_3$) δ 17.2 (CH_3), 17.4 (CH_3), 26.6 (CH_2), 26.9 (CH_3), 31.9 (C), 36.9 (CH_2), 41.9 (CH), 78.4 (CH), 78.7 (CH), 106.4 (C), 128.6 (CH), 132.3 (CH).

(*S*)-5-*tert*-Butyl-2-cyclohexen-1-one (2*S*,3*S*)-2,3-Butanediol Ketal (12). Column chromatography of the crude product on silica gel 60 eluted with 5% EtOAc/hexanes gave the ketal as a pale yellow oil: R_f 0.47 (20% EtOAc/hexanes); $[\alpha]^{21}_D$ +47.71° (*c* 2.12, $CHCl_3$); yield 66%; IR ($CHCl_3$) cm^{-1} 3028, 3018, 3007, 2963, 2870, 1654, 1468, 1453, 1440, 1387, 1365, 1292, 1270, 1240, 1194, 1179, 1158, 1113, 1085, 1010, 976, 931, 918, 894, 838, 668; ^1H NMR ($CDCl_3$) δ 0.83–0.90 (9, s), 1.22–1.30 (6, dd, *J* = 1.4 Hz), 1.40–1.52 (1, m), 1.60–1.93 (3, m), 2.03–2.18 (1, m), 3.52–3.74 (2, m), 5.52–5.62 (1, m), 5.88–5.98 (1, m); ^{13}C NMR ($CDCl_3$) δ 16.5 (CH_3), 16.6 (CH_3), 26.5 (CH_2), 27.0 (CH_3), 31.9 (C), 36.3 (CH_2), 42.4 (CH), 77.5 (CH), 78.0 (CH), 106.3 (C), 128.1 (CH), 131.8 (CH); mass spectrum (70 eV) *m/z* (rel intensity) 224 (0.7), 209 (3), 167 (8), 141 (9), 140 (100), 137 (2), 123 (8), 114 (4), 111 (1), 109 (1), 96 (2), 95 (14), 86 (3), 80 (6), 68 (45), 67 (7), 57 (15), 55 (12); exact mass calcd for $C_{14}H_{24}O_2$ 224.1777, obsd 224.1779.

General Procedure for Cyclopropanations.[1,6] A flask equipped with a stir bar and coiled condenser was flame-dried under vacuum and cooled under argon. To the flask were added anhydrous K_2CO_3 (10 equiv), Zn–Cu couple (20 equiv), a small iodine crystal, diethyl ether (freshly distilled from P_2O_5, 7 mL/mmol olefin), and CH_2I_2 (10 equiv). The mixture was heated to reflux in an oil bath. When the slurry had darkened to charcoal black, a solution of the olefin (1 equiv) in dry diethyl ether (7 mL/mmol olefin) was added via syringe and refluxing was continued. Progress of the reaction was monitored by TLC. The reaction was quenched by the dropwise addition of saturated K_2CO_3 solution (1.4 mL/mmol olefin) at 0 °C. The mixture was stirred at room temperature for 1 h and then filtered, and the precipitate was washed well with diethyl ether. The organic phase was washed successively with saturated ammonium chloride, saturated sodium bicarbonate, and saturated sodium chloride solutions, dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via column chromatography.

(1*S*,4*S*,6*R*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one Ethylene Ketal (8a) and (1*R*,4*S*,6*S*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one Ethylene Ketal (8b). Column chromatography of the crude products on silica gel 60 eluted with 5% EtOAc/hexanes gave the separate diastereomers **8a** and **8b** in a 1:3 ratio.

The less polar diastereomer **8a** was obtained as a yellow oil: R_f 0.47 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ +45.0° (*c* 1.00, $CHCl_3$); yield 23%; IR ($CHCl_3$) cm^{-1} 3015, 3013, 3009, 2961, 2882, 1469, 1394, 1366, 1278, 1239, 1129, 1095, 1085, 1064, 1041, 1000, 957, 942, 885, 825; ^1H NMR ($CDCl_3$) δ 0.35–0.57 (2, m), 0.75–0.81 (9, s), 0.90–1.22 (4, m), 1.32–1.48 (1, m), 1.60–1.69 (1, m), 1.83–1.94 (1, m), 3.86–4.03 (4, m); ^{13}C NMR ($CDCl_3$) δ 5.2 (CH_2), 12.3 (CH), 19.0 (CH), 23.9 (CH_2), 27.1 (CH_3), 31.8 (C), 35.9 (CH_2), 36.9 (CH), 63.6 (CH_2), 63.9 (CH_2), 109.1 (C).

The predominant more polar diastereomer **8b** was obtained as a yellow oil: R_f 0.40 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ −29.14° (*c* 3.15, $CHCl_3$); yield 68%; IR ($CHCl_3$) cm^{-1} 3022, 3013, 3011, 2959, 2868, 1468, 1393, 1365, 1343, 1286, 1240, 1192, 1140, 1120, 1084, 1073, 1032, 1003, 978, 946, 895, 852, 799, 699; ^1H NMR ($CDCl_3$) δ 0.04–0.13 (1, q, *J* = 5.2 Hz), 0.65–0.79 (10, m), 0.80–1.57 (6, m), 1.86–2.02 (1, m), 3.87–4.04 (4, m); ^{13}C NMR ($CDCl_3$) δ 11.2 (CH_2), 11.9 (CH), 18.2 (CH), 23.9 (CH_2), 27.0 (CH_3), 31.3 (CH_2), 31.8 (C), 43.6 (CH), 64.2 (CH_2), 64.4 (CH_2), 111.5 (C); mass spectrum (70 eV) *m/z* (rel intensity) 210 (2), 195 (2), 155 (3), 154 (7), 153 (69), 141 (1), 127 (2), 126 (16), 125 (7), 123 (5), 113 (2), 112 (9), 109 (5), 99 (100), 95 (4), 91 (5), 86 (5), 81 (12), 79 (7), 69 (13), 67 (10), 57 (26), 55 (19); exact mass calcd for $C_{13}H_{22}O_2$ 210.1620, obsd 210.1621.

(1*S*,4*S*,6*R*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one (2*R*,3*R*)-2,3-Butanediol Ketal (13a) and (1*R*,4*S*,6*S*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one (2*R*,3*R*)-2,3-Butanediol Ketal (13b). Column chromatography of the crude products on silica gel 60 eluted with 5% EtOAc/hexanes gave separable diastereomers **13a** and **13b** in a 1:1 ratio.

The less polar diastereomer **13a** was obtained as an oil contaminated with approximately 14% of (*S*)-5-*tert*-butyl-3-cyclohexen-1-one (2*R*,3*R*)-2,3-butanediol ketal: R_f 0.42 (10% EtOAc/hexanes); yield (corrected) 30%; ^1H NMR ($CDCl_3$) δ 0.40–0.58 (2, m), 0.78–0.85 (9, s), 0.98–1.55 (11, m), 1.66–1.73 (1, m), 1.83–1.95 (1, m), 3.58–3.85 (2, m); ^{13}C NMR ($CDCl_3$) δ 5.1 (CH_2), 12.6 (CH), 17.0 (CH_3), 17.7 (CH_3), 20.7 (CH), 23.6 (CH_2), 27.0 (CH_3), 31.8 (C), 36.7 (CH), 37.5 (CH_2), 77.9 (CH), 78.3 (CH), 108.3 (C).

The more polar diastereomer **13b** was obtained as an oil: R_f 0.26 (10% EtOAc/hexanes); $[\alpha]^{23}_D$ −35.26° (*c* 1.27, $CHCl_3$); yield 35%; IR ($CHCl_3$) cm^{-1} 3005, 2963, 2868, 1730, 1454, 1383, 1365, 1290, 1241, 1141, 1116, 1091, 980, 953, 915, 892, 819, 698; ^1H NMR ($CDCl_3$) δ 0.11–0.21 (1, m), 0.74–1.38 (20, m), 1.45–1.67 (2, m), 1.91–2.08 (1, m), 3.67–3.80 (2, m); ^{13}C NMR ($CDCl_3$) δ 11.3 (CH_2), 11.7 (CH), 16.9 (CH_3), 17.3 (CH_3), 19.6 (CH), 23.8 (CH_2), 26.9 (CH_3), 31.9 (C), 33.0 (CH_2), 43.0 (CH), 77.8 (CH), 78.5 (CH), 110.6 (C).

(1*R*,4*S*,6*S*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one (2*S*,3*S*)-2,3-Butanediol Ketal (14b). Column chromatography of the crude product on silica gel 60 eluted with 5% EtOAc/hexanes gave a single diastereomer as an oil (limit of detection 30:1 by ^{13}C NMR): R_f 0.47 (20% EtOAc/hexanes); $[\alpha]^{20}_D$ −27.54° (*c* 2.11, $CHCl_3$); yield 83%; IR ($CHCl_3$) cm^{-1} 3665, 3070, 3005, 2961, 2868, 2456, 1462, 1394, 1380, 1365, 1341, 1325, 1287, 1269, 1241, 1197, 1175, 1143, 1117, 1090, 1054, 1028, 1015, 1002, 981, 950, 915, 893, 851, 819, 802, 700; ^1H NMR ($CDCl_3$) δ 0.10–0.19 (1, m), 0.66–0.89 (10, m), 0.89–1.60 (12, m), 1.91–2.10 (1, m), 3.55–3.81 (2, m); ^{13}C NMR ($CDCl_3$) δ 11.1 (CH_2), 11.9 (CH), 16.7 (CH_3), 16.8 (CH_3), 19.6 (CH), 23.7 (CH_2), 26.8 (CH_3), 31.6 (C), 32.5 (CH_2), 43.3 (CH), 77.7 (CH), 77.9 (CH), 110.3 (C); mass spectrum (70 eV) *m/z* (rel intensity) 238 (4), 223 (5), 183 (3), 182 (12), 181 (100), 154 (7), 153 (5), 149 (2), 137 (10), 128 (6), 127 (80), 123 (2), 114 (5), 111 (3), 110 (2), 109 (16), 107 (5), 97 (6), 95 (6), 93 (9), 91 (5), 81 (31), 69 (23), 57 (40), 55 (36); exact mass calcd for $C_{15}H_{26}O_2$ 238.1934, obsd 238.1934.

General Procedure for Ketal Hydrolyses. The ketal was dissolved in methanol (2 mL/mmol ketal) and 10% aqueous HCl (0.2 mL/mmol ketal) was added. The resulting solution was stirred at room temperature and progress of the reaction was monitored by TLC. When complete, saturated sodium bicarbonate solution (40 mL/mmol) was poured into the reaction mixture, which was then extracted several times with diethyl ether. The combined ether layers were dried over anhydrous magnesium sulfate, filtered, concentrated, and purified via column chromatography.

(1*S*,4*S*,6*R*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one (9a). Column chromatography of the crude product from **8a** on silica gel 60 eluted with 10% EtOAc/hexanes gave the product **9a** as a colorless oil: R_f 0.15 (10% EtOAc/hexanes); $[\alpha]^{24}_D$

-117.49° (c 1.32, $CHCl_3$); yield 68%; IR ($CHCl_3$) cm^{-1} 3663, 3455, 3078, 3013, 2962, 2868, 1679, 1556, 1537, 1476, 1469, 1457, 1395, 1367, 1335, 1276, 1237, 1184, 1163, 1115, 1086, 1067, 1024, 982, 953, 931, 861, 846, 804, 699; ^1H NMR ($CDCl_3$) δ 0.70–0.83 (10, m), 1.14–1.40 (2, m), 1.53–1.83 (4, m), 2.04–2.20 (2, m); ^{13}C NMR ($CDCl_3$) δ 19.1 (CH_2), 19.4 (CH), 24.8 (CH_2), 25.0 (CH), 26.8 (CH_3), 32.4 (C), 38.2 (CH_2), 50.2 (CH), 211.7 (C); mass spectrum (70 eV) m/z (rel intensity) 166 (3), 149 (2), 137 (3), 129 (2), 125 (1), 123 (3), 111 (6), 110 (47), 109 (11), 107 (4), 105 (2), 99 (2), 98 (2), 97 (8), 95 (26), 81 (26), 69 (38), 67 (15), 61 (37), 57 (100), 55 (28); exact mass calcd for $C_{11}H_{18}O$ 166.1358, obsd 166.1365.

(1*R*,4*S*,6*S*)-4-(1,1-Dimethylethyl)bicyclo[4.1.0]heptan-2-one (9b). Column chromatography of the crude product from **8b** on silica gel 60 eluted with 7% EtOAc/hexanes gave the product **9b** as a colorless oil: R_f 0.13 (10% EtOAc/hexanes); $[\alpha]^{23}_D$ -52.18° (c 0.55 $CHCl_3$): yield 79%; IR ($CHCl_3$) cm^{-1} 3663, 3017, 3011, 2963, 2869, 1671, 1557, 1537, 1476, 1469, 1445, 1396, 1367, 1351, 1308, 1282, 1236, 1182, 1128, 1094, 1057, 1023, 1000, 972, 921, 847, 827, 666; ^1H NMR ($CDCl_3$) δ 0.75–0.85 (9, s), 0.93–1.08 (1, m), 1.16–1.24 (1, q, J = 5.0 Hz), 1.33–1.87 (5, m), 2.02–2.11 (1, m), 2.23–2.36 (1, m); ^{13}C NMR ($CDCl_3$) δ 9.5 (CH_2), 16.9 (CH), 22.1 (CH_2), 25.3 (CH), 27.0 (CH_3), 32.1 (C), 37.3 (CH), 39.0 (CH_2), 210.5 (C).

Preparation of (3*S*,5*R*)-*cis*-3-*tert*-Butyl-5-methylcyclohexanone (10b). To a well-stirred solution of Li metal (45 mg, 6.49 mmol) in liquid ammonia (10 mL) at -78 °C was added a solution of *t*-BuOH (0.003 mL) and ketone **9b** (21 mg, 0.126 mmol) in ether (3 mL). The cold bath was removed and the mixture allowed to reflux (-33 °C). Progress of the reaction was monitored by TLC. After 30 min, the reaction was quenched with solid NH_4Cl (1 g), diluted with ether (20 mL), and warmed to room temperature, and the ammonia was allowed to evaporate. The mixture was filtered and concentrated, leaving an oil.

To a well-stirred solution of the above oil in CH_2Cl_2 (5 mL) at room temperature was added pyridinium dichromate (71 mg, 0.189 mmol). After 1 h, the mixture was diluted with ether and filtered through a short plug of silica gel. After concentration, the crude product was purified via column chromatography on silica gel 60 (40 g) eluted with 10% EtOAc/hexanes: yield of **10b** 7.5 mg, 0.0446 mmol, 36%; ^1H NMR ($CDCl_3$) δ 0.84–0.92 (9, s), 1.03–1.07 (3, d, J = 6.0 Hz), 1.0–2.48 (8, m).

Authentic *trans*- and *cis*-3-*tert*-Butyl-5-methylcyclohexanones (10a and 10b).[8] These compounds were prepared as described for **7** by substituting 5-methyl-2-cyclohexen-1-one for 2-cyclohexen-1-one. Column chromatography of the crude mixture of cis and trans products on silica gel 60 (100 g) eluted with 10% EtOAc/hexanes gave analytical samples of the separated products.

The less polar product **10b** was the cis isomer: R_f 0.45 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 0.87–0.91 (9, s), 1.03–1.06 (3, d, J = 6.0 Hz), 1.0–2.38 (8, m); ^{13}C NMR ($CDCl_3$) δ 22.6 (CH_3), 27.2 (CH_3), 32.6 (C), 33.2 (CH), 35.1 (CH_2), 42.8 (CH_2), 48.0 (CH), 49.6 (CH_2), 212.8 (C).

The more polar and major product **10a** was the trans isomer: R_f 0.42 (20% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 0.87–0.91 (9, s), 0.94–0.98 (3, d, J = 7.5 Hz), 1.58–1.81 (3, m), 1.99–2.18 (2, m), 2.33–2.51 (3, m) [lit.[8] ^1H NMR (CCl_4) δ 0.92 (9 H, s), 0.96 (3 H, d, J = 6 Hz)]; ^{13}C NMR ($CDCl_3$) δ 19.2 (CH_3), 27.0 (CH_3), 29.4 (CH), 31.7 (CH_2), 32.3 (C), 42.8 (CH), 43.1 (CH_2), 47.3 (CH_2), 213.2 (C).

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Registry No. **7**, 125413-68-5; **8a**, 125413-70-9; **8b**, 125473-20-3; **9a**, 125413-72-1; **9b**, 125413-73-2; (±)-**10a**, 125413-75-4; (±)-**10b**, 125413-74-3; **11**, 125413-69-6; **12**, 125514-91-2; **13a**, 125413-71-0; **13b**, 125473-21-4; **14b**, 125473-22-5; **16**, 97590-69-7; **17**, 7381-30-8; **18**, 125473-19-0; **19**, 108813-04-3; CH_2I_2, 75-11-6; (3*S*)-3-*tert*-butylcyclohexanone, 57287-85-1; ethylene glycol, 107-21-1; (2*R*,3*R*)-2,3-butanediol, 24347-58-8; (2*S*,3*S*)-2,3-butanediol, 19132-06-0; (±)-5-methyl-2-cyclohexen-1-one, 54352-35-1.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra of all new compounds (26 pages). Ordering information is given on any current masthead page.

Reactive Annulenones: A Comparative Study

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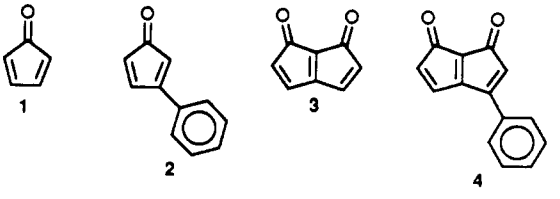
Two new and hitherto elusive annulenones, 3-phenylcyclopentadienone and bicyclo[3.3.0]octa-1(5),3,6-triene-2,8-dione, are reported. Their lifetimes and reactivities have been studied in comparison with those of the related annulenones cyclopentadienone and 4-phenylbicyclo[3.3.0]octa-1(5),3,6-triene-2,8-dione. The influence of structure and substituents on the stabilities of these species has thereby been established.

As part of our ongoing studies of highly reactive mono- and bicyclic annulenones, we decided to carry out a comparative experimental study of both the stabilities and Diels–Alder reactivities of unstable ketones **1**–**4** (Chart I). The parent compound cyclopentadienone (**1**) has been extensively studied in our research group.[1,2] In the course of these studies, we demonstrated the existence of this ketone as a monomeric free species in solution as well as its ability to perform as a diene as well as a dienophile in Diels–Alder processes. The lifetime of this intermediate was determined as well by using the polyphasic dynamic reactor (PDR), devised by us for this purpose.[2]

Chart I



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