Table III. Rate Constants for Cyclohexyl Compounds in the Reverse Type Reactions

	k_0	solvent	ref
NH_2OH in basic conditions[a]	8×10^6 L mol^{-1} s^{-1}	H_2O	10
chromic acid oxidation[b]	3.5×10^{-3} L mol^{-1} s^{-1}	H_2O	19
decomposition of bisulfite addition compounds[c]	4.3×10^{-4} s^{-1}	H_2O	7

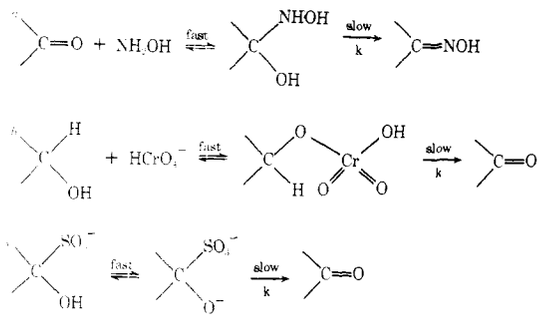

Table IV

ketones	slope A	intercept B	corr coeff	no. of points
cyclobutanone	0.80	−0.151	0.999	3[a]
cyclopentanone	1.06	0.165	0.999	3[a]
cycloheptanone	1.01	0.885	0.999	3[a]
cyclooctanone	1.00	1.157	0.998	3[a]
cyclononanone	1.00	0.40		2[b]

[a] NH_2OH in basic conditions,[10] chromic acid oxidation,[19] decomposition of bisulfite addition compounds.[7] [b] NH_2OH in basic conditions,[10] chromic acid oxidation.[19]

giving thus an apparent linear correlation.

Nevertheless, to a first approximation, $\log k/k_0 = B$ might be considered as a characteristic of the ketone and thus a function of the difference in internal energy between the ketone studied and cyclohexanone. However, if we plot B vs. f (ketone strain energy—cyclohexanone strain energy) we get a scatter diagram meaning that there is no evident correlation between ketone reactivity and the strain energy proposed by Allinger.[18]

The same type of relationship is also obtained in the inverse reaction to the addition reaction, still using cyclohexanone as reference (Table III). In Table IV, values of A and B are given for the decomposition of bisulfite addition compounds, chromic acid oxidation of secondary alcohols, and oximation in basic conditions where the reaction goes from the carbinolamine intermediate to the ketone.

The importance of such a relationship for the nucleophilic addition to carbonyl compounds is clear. Knowledge of the reactivity of one of the nucleophiles with an unknown ketone permits one to estimate the reactivity of this ketone with any of the other nucleophiles studied. Investigations are being performed to broaden the scale of ketones and nucleophiles and to gain further understanding into the factors which influence B.

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References and Notes

(1) P. Müller and J. C. Perlberger, *J. Am. Chem. Soc.*, **98**, 8407 (1976).
(2) J. C. Perlberger and P. Müller, *J. Am. Chem. Soc.*, **99**, 6316 (1977).
(3) C. Moreau, Thèse Docteur es Sciences Physiques, Montpellier (1972).
(4) P. Geneste and G. Lamaty, *Bull. Soc. Chim. Fr.*, **2**, 669 (1968).
(5) P. Geneste, G. Lamaty, C. Moreau, and J. P. Roque, *Tetrahedron Lett.*, 5011 (1970).
(6) G. Lamaty, A. Natat, A. Petitjean, J. P. Roque, P. Geneste, and B. Schlick, *Recl. Trav. Chim. Pays-Bas*, **95**, 54 (1976); G. Lamaty, A. Natat, A. Petitjean, and J. P. Roque, *ibid.*, **95**, 93 (1976).
(7) P. Geneste, G. Lamaty, and J. P. Roque, *Tetrahedron*, **27**, 5539 (1971).
(8) H. Brown and J. Muzzio, *J. Am. Chem. Soc.*, **88**, 2811 (1966).
(9) L. Fournier, G. Lamaty, A. Natat, and J. P. Roque, *Tetrahedron*, **31**, 1031 (1975).
(10) A. Finiels and P. Geneste, *Bull. Soc. Chim. Fr.*, in press.
(11) J. Jullien and G. Lamaty, *Tetrahedron Lett.*, 1023 (1964).
(12) P. Geneste, G. Lamaty, and B. Vidal, *Bull. Soc. Chim. Fr.*, **6**, 2027 (1969).
(13) B. Boyer, Thèse Docteur es Sciences Physiques, Montpellier (1978).
(14) C. D. Ritchie, *Acc. Chem. Res.*, **5**, 348 (1972).
(15) C. D. Ritchie, *J. Am. Chem. Soc.*, **97**, 1170 (1975).
(16) P. Geneste, G. Lamaty, and J. P. Roque, *Tetrahedron Lett.*, 5007 (1970).
(17) P. Geneste, G. Lamaty, and J. P. Roque, *Recl. Trav. Chim. Pays-Bas*, **91**, 188 (1972).
(18) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972).
(19) J. C. Richer and N. Thi Thanh Hao, *Can. J. Chem.*, **47**, 2479 (1969).

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Epoxyannelation: New Reaction Path for Butadienylsulfonium Salts

Summary: Treatment of enolates from cyclic ketones and aldehydes with 1-butadienylsulfonium fluoborate yields the corresponding 1,3-cyclohexadiene 1-oxide.

Sir: Functionalized cyclohexane rings containing one or more epoxides include the prominent cytotoxic antibiotics crotopoxide[1a] and triptolide[1b] as well as the arene oxides.[1c] We wish to report a facile preparation of certain cyclohexadiene oxides, potential precursors for these biologically significant compounds.

The reaction of 1-butadienyldimethylsulfonium fluoborate (1) with certain ketone and aldehyde enolates affords dihydroarene oxides as the major product. The sequence depicted in Scheme I not only provides facile preparation of these oxides but also is one of the first examples of an intramolecular epoxidation with a sulfonium ylide where the sulfur is displaced from the molecule.[3,4]

Certain intramolecular Darzens condensations using chloroacrylates[5a] or 1,4-dichlorobutan-2-one[5b] with enolates also afford epoxides. The substituent patterns of these Darzens epoxides differ from the products reported here. This process has been termed epoxyannelation.[5b]

Scheme I

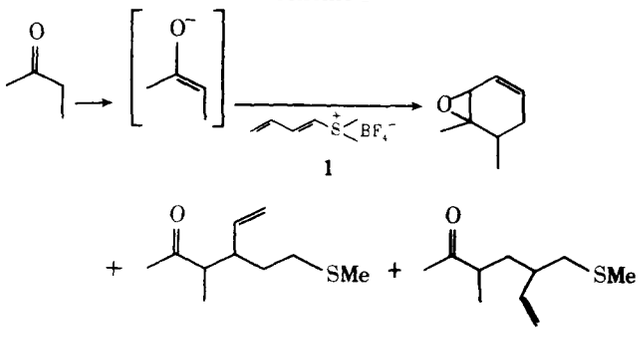
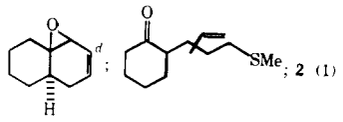
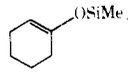
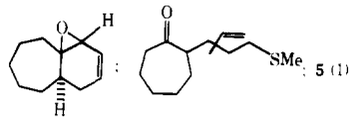
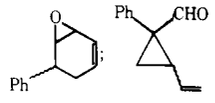
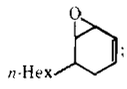
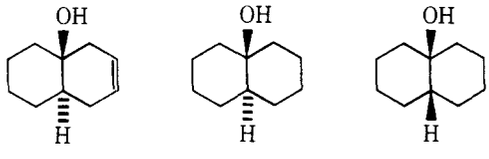


Table I. Synthesis of Dihydroarene Oxides

example	enolate precursor	method of enolate formation[a]	products[b] (relative amounts)[c]	isolated yield of oxirane, %
I	 2	A	 3 (3); 4 (1)	58[d]
II		B	3(3); 4 (1); 2 (1)	
III	 5	A	 6 (2); (1)	52[d]
IV	PhCH=CHOSiMe$_3$	B	 8 (4); 9 (1)	27[e]
V	*n*HexCH=CHOSiMe$_3$	B	 ; $(C_7H_{15})_2CO$ (1)[f] 10 (2)	29[e]

[a] For A we used LDA/THF at −78 °C. For B we used MeLi/THF at 0 °C. [b] All new compounds characterized by IR, NMR, and mass spectra with exact mass measurement on the parent ion. [c] Determined by GC and NMR integration. Compounds indicated account for >90% of the material recovered. This amount was always >90% based upon enolate precursor. [d] Purified by column chromatography on Florisil followed by evaporative distillation. [e] For convenience, purified by preparative GC followed by bulb-to-bulb distillation. Material balance was only about 50% owing to inefficient collection. [f] The origin of this product is unexplained.

The structures of the products in Table I have been assigned on the basis of spectral characterization and chemical reactivity. For example, all of the dihydroarene oxides exhibit NMR spectra containing a two-proton multiplet at δ 5.8–6.0 and an additional multiplet at δ 2.8–3.2.[6] To establish the trans stereochemistry of structure **3**, two reductions were completed. Treatment of **3** with lithium aluminum hydride[6] yielded alcohol **11** in 82% yield, identical with an authentic sample.[7] Hydrogenation of **11** with 10% palladium on carbon afforded alcohol **12**. Alcohol **12** was the same as the minor

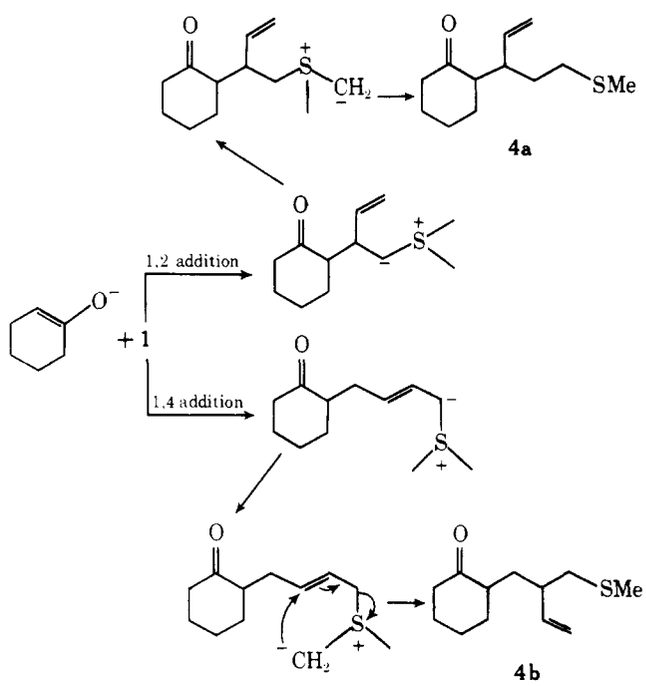


11 **12** **13**

isomer from ozonolysis of *cis*-decalin and contained less than 1% of *cis*-decalinol (**13**).[8] We thus assume **6** is also exclusively the trans isomer. Although the stereochemistry of **8** and **10** has not yet been established, these compounds are probably a mixture of cis–trans isomers. These stereochemical observations are comparable to those of the intramolecular Darzens condensation.[5]

The identity of the side product(s) **4** has been more difficult to define. The spectra (IR, NMR, and mass) clearly suggest two possible structural isomers. Unfortunately, analytical gas chromatography shows at least two very closely related species to be present as yet preparatively unseparable. From a mechanistic viewpoint, either **4a** or **4b** seems logical (Scheme II). Careful GC–mass spectrometry indicates both GC peaks

Scheme II



to have similar yet not identical mass spectra, implying a mixture of **4a** and **4b**. Preliminary labeling experiments with substituted sulfonium salts support this conclusion.[9]

Typically, the enolate (2 mmol) generated in tetrahydrofuran (THF, 5 mL) by cleavage of the silyl enol ether with methyllithium or by treatment of the carbonyl component with lithium diisopropylamide is added to a rapidly stirred

suspension of 1[10] (2.1 mmol) in 50 mL of THF at −78 °C under nitrogen. After stirring at −78 °C for 12 h, the yellow solution is partitioned between brine and pentane. The aqueous layer is washed with pentane, and the pooled organic layers are concentrated after drying over Na_2SO_4. The oily residue was purified in the manner described in Table I. From 0.440 g of cyclohexanone, 0.395 g (58%) of pure **3**, 0.086 g (18%) of **4**, and 0.071 g (16%) of cyclohexanone were obtained.

The entries in Table I imply some limitations of this sequence. The reaction works well for aldehydes as illustrated by examples IV and V. The isolated yields of dihydroarene oxides from aldehydes are low owing to mechanical losses during purification. With certain cyclic ketones the selectivity is also good. Acyclic ketones have failed, as yet, to undergo epoxyannelation, providing only products analogous to **4**.[11] To further define the limitations of this process we have examined the substituent effects of the cyclohexanone enolate structure upon the course of this reaction. The methyl cyclohexanone enolate generated from cleavage of 1-(trimethylsilyloxy)-2-methylcyclohexene yields only products similar to 4. The kinetic enolate from 2-methylcyclohexanone affords some of the desired dihydroarene oxide accompanied by products such as 4 derived from both the kinetic enolate and from the isomeric, methyl-substituted enolate. Clearly enolate equilibration competes favorably with oxirane formation. Finally, as expected, 4-substituted cyclohexanones (methoxy or *tert*-butyl) behave as the parent ketone to provide epoxides in comparable isolated yields (see Table I, ref a, b, d). Thus, this sequence transforms aldehyde and nonhindered, cyclic ketone enolates into dihydroarene oxides in about 50% yield. Both structures of types **3** and **4** are novel products from vinyl[11] or butadienylsulfonium[2] salts.

Although we have examined this reaction in detail, we will defer most comments about the mechanism until a full paper. We observe products arising from ~90% 1,4 addition of enolates to 1. The product distribution depends upon temperature and solvent. For example, treatment of **2** as described above at 0 °C rather than −78 °C affords a **3** to **4** ratio of 1.5:1, while use of *tert*-butyl alcohol/*tert*-butoxide as the solvent/base at ambient temperature provides a **3** to **4** ratio of 1:4.

The dihydroarene oxides formed in this process are not available by the other common methods, including intramolecular Darzens condensations,[5] aromatic reduction followed by epoxidation,[1c] or cycloaddition–epoxidation.[1c] We believe this sequence will find application in several syntheses and are continuing our studies of **1**, **3**, and related species.

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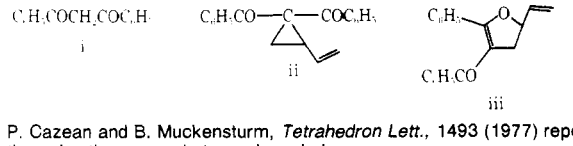
References and Notes

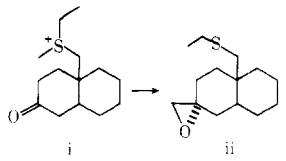
(1) (a) B. Ganem, *Tetrahedron*, **34**, 3353 (1978); (b) F. T. Sher and G. A. Berchtold, *J. Org. Chem.*, **42**, 2569 (1977); (c) D. M. Jerina, H. Yagi and J. W. Daly, *Heterocyles*, **1**, 267 (1973).

(2) H. Braun and G. Huber, *Tetrahedron Lett.*, 2121 (1976). Among the reactions noted by Braun is the conversion of i into ii and iii.



(3) P. Cazean and B. Muckensturm, *Tetrahedron Lett.*, 1493 (1977) reports the only other example to our knowledge.

(4) Several instances of the i to ii path have been reported: see R. S. Matthews and T. E. Meteyer, *Synth. Comm.*, **2**, 399 (1972); *Chem. Commun.*, 1576 (1971), and see ref 7.



(5) (a) D. R. White, *J. Chem. Soc., Chem. Commun.*, 95 (1975); J. M. McIntosh and H. Khalil, *J. Org. Chem.*, **42**, 2123 (1977); (b) S. Danishefsky and G. A. Koppel, *Chem. Commun.*, 367 (1971).

(6) J. K. Crandall, D. B. Banks, R. A. Colyer, R. J. Watkins, and J. P. Arrington, *J. Org. Chem.*, **33**, 423 (1968).

(7) J. Staroscik and R. B. Rickborn, *J. Org. Chem.*, **37**, 738 (1978).

(8) Prepared by the method of H. Varkony, S. Pass, and Y. Mazur, *J. Chem. Soc., Chem. Commun.*, 437 (1974).

(9) M. E. Garst and P. Arrhenius, work in progress.

(10) In our hands, the fluoborate salt is more stable than the corresponding bromide or chloride and appears to be somewhat more soluble in THF. Several modifications of butadienylsulfonium salt structure have failed to increase the amount of **3** formed.

(11) A different set of products has been observed with vinylsulfonium salts: K. Takai, H. Takahashi, Y. Ohshiro, and T. Agawa, *J. Chem. Soc., Chem. Commun.*, 675 (1977); K. Takai and T. Agawa, *J. Org. Chem.*, **42**, 3303 (1977).

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Stereoselective Synthesis of 7-Thia-16-oxa-14β-estrones

Summary: An efficient and stereoselective synthesis of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),9(11)-estratetraen-17-one was achieved by an application of the Diels–Alder reaction between 7-methoxy-4-vinylthiaisochromene with citraconic anhydride, followed by reduction of the Diels–Alder adduct with $NaBH_4$.

Sir: Although much attention has been devoted to the synthesis of heterocyclic steroids[1] in view of their biological interests, there are few works on the synthesis of thia steroids.[2] An interest in a synthesis of thia estrogens led us to the preparation of 3-methoxy-7-thia-16-oxa-14β-1,3,5(10),-9(11)-estratetraen-17-one (**12**) in order to obtain physiological active steroidal derivatives. A short synthesis of 7-thia-16-oxa-14β-estrone analogues was realized by an application of the Diels–Alder reaction of 7-methoxy-4-vinylthiaisochromene. Herein we wish to report the results of our studies.

First, we explored the Vilsmeier reaction of 7-methoxythiaisochromene (**1**)[3] with dimethylformamide–phosphoryl chloride at 60 °C for 2 h to yield 4-formyl-7-methoxythiaisochromene (**2**),[4,5] mp 75–76 °C, in 90% yield. The Wittig reaction of **2** with methylenetriphenylphosphorane derived from methyltriphenylphosphonium bromide[6] by treatment with *n*-BuLi in THF at room temperature gave 7-methoxy-4-vinylthiaisochromene (**3**)[5] in 90% yield. The Diels–Alder reaction of this sulfur-substituted 1,3-diene was extended for formation of C and D rings of a steroidal system. Treatment of **3** with maleic anhydride in benzene at 60 °C for 5 h yielded the adduct (**4**), mp 202–205 °C (acetone), in 65% yield. Characteristic structural data for **4** are given below: ^1H NMR (acetone-d_6) δ 2.34–3.10 (4 H, m), 3.57 (1 H, d, J = 14 Hz), 3.76 (3 H, s), 3.91 (1 H, d, J = 14 Hz), 4.22 (1 H, d, J = 3 Hz), 6.36–6.56 (1 H, m), 6.72–6.88 (2 H, m), 7.43 (1 H, d, J = 8 Hz); mass spectrum 302 (M^+). Doublet signals at δ 4.22 ($J_{8,14}$ = 3

0022-3263/79/1944-1580$01.00/0