mass spectrum, m/z (relative intensity) 154 (M^+, 62), 136 (70), 111 (58), 74 (75), 59 (94), 31 (100). Analysis by GC on columns A and B indicated the alcohol derived from **25** was >99% of **63**.

Acknowledgment. We are grateful to Professor Bruce Rickborn (UCSB) and Professor Jack Crandall (Indiana University) for helpful discussions. The finnigan GC/MS instrument was purchased with a NIH shared instrument grant (No. GM 27583-01). High-resolution mass spectra were obtained at the Bioorganic, Biomedical Mass Spectrometry Resource (A. L. Burlingame, Director) supported by NIH Grant No. RR00719.

Registry No. **1**, 17094-21-2; **2** (X = Br), 83705-51-5; **3**, 83705-52-6; **4**, 77505-18-1; **5** (isomer 1), 77505-24-9; **5** (isomer 2), 77549-98-5; **6**, 10472-24-9; **7**, 83705-53-7; **8**, 77505-19-2; **9**, 77505-25-0; **10**, 10468-35-6; **11**, 41302-34-5; **12**, 83705-54-8; **13**, 77505-20-5; **14**, 77550-59-5; **15**, 696-98-0; **16**, 83705-55-9; **17**, 77505-21-6; **18** (isomer 1), 34459-06-8; **18** (isomer 2), 32432-88-5; **19**, 83705-56-0; **20**, 77505-22-7; **21** (isomer 1), 77549-99-6; **21** (isomer 2), 77610-39-0; **22**, 83705-57-1; **23**, 83705-58-2; **24**, 77505-23-8; **25**, 77550-66-4; **27**, 83705-60-6; **28**, 83705-61-7; **29**, 83705-62-8; **30**, 83705-63-9; **31**, 83705-64-0; **32**, 83705-65-1; **33**, 83705-66-2; **34**, 83705-67-3; **35**, 83705-68-4; **36**, 83705-70-8; **37**, 83705-71-9; **38**, 83705-72-0; **39**, 83705-73-1; **40** (X = I), 83705-74-2; **41**, 83705-75-3; **42**, 77510-84-0; **43**, 77505-26-1; **50** (X = I), 83705-76-4; **53** (X = I), 83705-77-5; **54**, 1072-72-6; **57**, 19550-45-9; **58**, 5402-29-9; **59**, 13366-91-1; **60**, 13366-92-2; **63**, 1654-87-1; *N,N*-dimethyl-4-oxopiperidinium iodide, 26822-37-7; sodium hydrogen sulfide, 16721-80-5; 4-hydroxy-4-methyltetrahydro-2(*H*)-thiapyran, 38447-82-4; 5,6-dihydro-4-methyl-2(*H*)-thiapyran, 39193-69-6; 6-bromohexanol, 4286-55-9; ethanethiol sodium salt, 811-51-8; 6-(ethylthio)-1-hexanol, 83705-78-6; 6-(ethylthio)-1-hexanol mesylate, 83705-79-7; 5-chloropentanol, 5259-98-3; 11-bromodecanol, 1611-56-9.

Epoxyannulation. 5. Reactions of 1-Butadienylsulfonium Salts

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Treatment of the lithium enolate from three aldehydes, cycloheptanone, and four unhindered cyclohexanones with (1,3-butadien-1-yl)dimethylsulfonium fluoborate (**1**) provides a 7-oxabicyclo[4.1.0]hept-4-ene stereoselectively in 30–58% yield. These epoxides are accompanied by 2-[2-[(methylthio)methyl]-3-butenyl] ketones. This alkylated ketone is the sole product from the enolates of three hindered cyclic ketones and three acyclic ketones. Five related sulfonium salts, **2**, **21**, **46**, **50**, and **63**, and the enolate from cyclohexanone gave these alkylated ketones accompanied by a 5–40% yield of the epoxyannulated product.

Recently we communicated that certain enolates combine with *S*-(1,3-butadien-1-yl)dimethylsulfonium fluoborate (**1**) to yield 7-oxabicyclo[4.1.0]hept-4-enes.[2] This specific reaction sequence illustrates the more general cyclization of oxo-ω-sulfonium ylides, a process called epoxyannulation. The use of **1** permits the entire epoxyannulation process to be completed in one pot.[3,4] In addition to the full details of our previous study, we are now reporting the reactions of additional enolates with **1** and the reactions of the enolate from cyclohexanone with sulfonium salts **2**, **21**, **46**, **50**, and **63** (Scheme I). *Sulfonium salts **1**, **2**, **46**, and **50** with enolates from unhindered cyclohexanones and cycloheptanones as well as from aldehydes provide epoxyannulation products in modest yet synthetically useful yields (Table I). This one-pot procedure using **1** is the most efficient preparation of these 7-oxabicyclo[4.1.0]hept-4-enes.*

The 7-oxabicyclo[4.1.0]heptene ring is a synthetic precursor for the major structural component of the cytotoxic antibiotics crotopoxide[5a] and triptolide[5b] as well as the arene oxides.[6] Our epoxyannulation protocol provides a single stereoisomer of this system containing functionalized carbons at four of the six atoms in a disposition complementing products from epoxides prepared by Birch reduction–epoxidation,[6] phosphonium ylide condensation–epoxidation,[7] or other epoxyannulation reactions[8] including Robinson annulations.[9]

Results

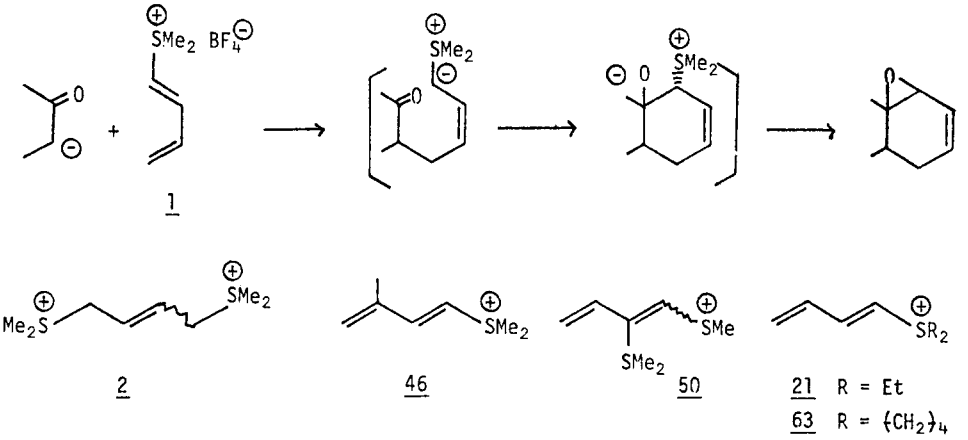
The reactions of fourteen enolates with sulfonium salts[10] **1**, **2**, **46**, and **50** are summarized in Table I. Unhindered cyclic ketone and aldehyde enolates with **1** in tetrahydrofuran (THF) provide 7-oxabicyclo[4.1.0]hept-4-enes in 30–60% yield, accompanied by a 10–20% yield of 2-[2-[(methylthio)methyl]-3-butenyl] ketones, such as **5**, and by the unreacted carbonyl compound. These butenyl ketones are the major products from acyclic ketone enolates and **1** as well as from all enolates with **2** in *t*-BuOH–THF solvent.

The identity of the epoxides was established by examination of their spectral properties. The NMR spectra of

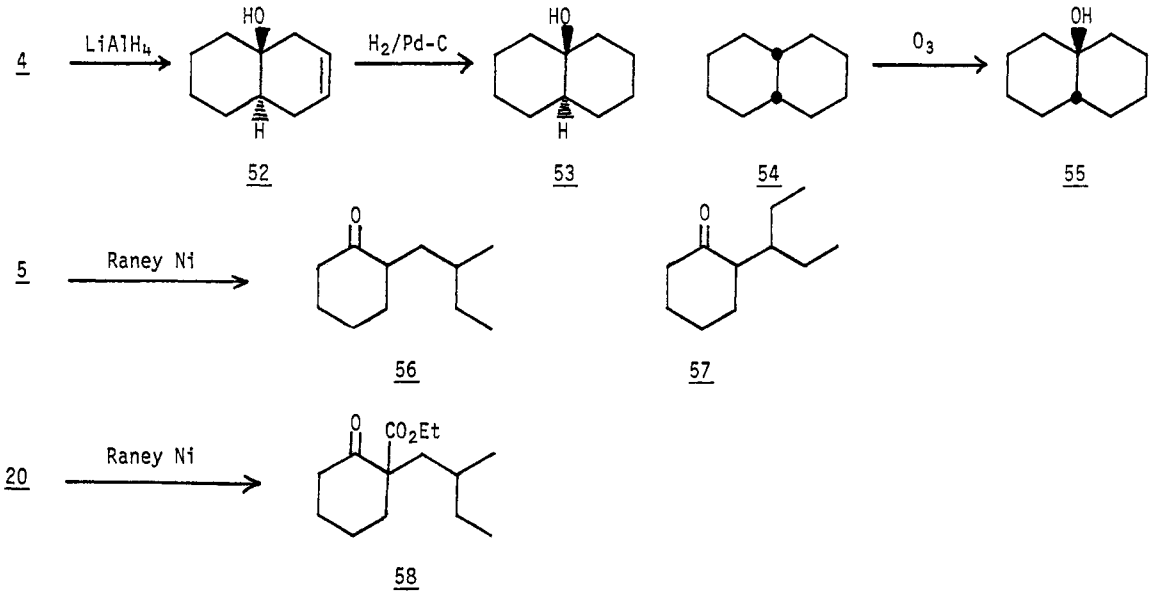
(1) Undergraduate Research Participant, 1978–1979.
(2) Garst, M. E. *J. Org. Chem.* **1979**, *44*, 1578–1580.
(3) (a) Garst, M. E.; Johnson, A. T. *Tetrahedron Lett.* **1980**, *21*, 4811–4814. (b) Garst, M. E.; McBride, W.; Johnson, A. T. *J. Org. Chem.*, previous paper in this issue. (c) Garst, M. E.; Frazier, J. D. *Heterocycles* **1981**, *16*, 17–19. (d) Garst, M. E.; Frazier, J. D. *J. Org. Chem.* **1982**, *47*, 3553.
(4) (a) Crandall, J. K.; Magaha, H. S.; Widener, R. K.; Tharp, G. A. *Tetrahedron Lett.* **1980**, *21*, 4807–4810. (b) Cazeau, P.; Muckenstrum, B. *Ibid.* **1977**, 1493–1494. (c) Newman, M. S.; Lee, L. F. *J. Org. Chem.* **1974**, *39*, 1446.
(5) (a) Ganem, B. *Tetrahedron*, **1978**, *34*, 3353–3383. (b) Lai, C. K.; Buckanin, R. S.; Chen, S. J.; Zimmerman, D. M. F.; Sher, F. T.; Berchtold, G. *J. Org. Chem.* **1982**, *47*, 2364–2369 and previous references. Garver, L. C.; van Tamelen, E. E.; *J. Am. Chem. Soc.* **1982**, *104*, 867–869 and previous references.
(6) Jerina, D. M.; Yagi, H.; Daly, J. W. *Heterocycles* **1973**, *1*, 267–326.
(7) (a) Fuchs, P. L. *Tetrahedron Lett.* **1974**, 4055–4058. (b) Büchi, G.; Pawlak, M. *J. Org. Chem.* **1975**, *40*, 100–102. (c) Büchi, G.; Wuest, H. *Helv. Chim. Acta* **1971**, *54*, 1767–1776. (d) Martin, S. F.; Garrison, P. J. *Tetrahedron Lett.* **1977**, 3875–3878. (e) Darling, S. D.; Muralidharan, F. N.; Muralidharan, V. B. *Ibid.* **1979**, 2757–2760, 2761–2762.
(8) (a) White, D. R. *J. Chem. Soc., Chem. Commun.* **1975**, 95–96. (b) McIntosh, J. M.; Khalil, H. *J. Org. Chem.* **1977**, *42*, 2123–2126. (c) Danishefsky, S.; Koppel, G. A. *J. Chem. Soc., Chem. Commun.* **1971**, 367.
(9) (a) Gawley, R. E. *Synthesis* **1976**, 777–794. (b) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31.
(10) (a) Braun, H.; Mayer, N.; Kresze, G. *Justus Leibigs Ann. Chem.* **1972**, *762*, 111–120. (b) Braun, H.; Mayer, N.; Strobl, G.; Kresze, G. *Ibid.* **1973**, 1317–1328. (c) Braun, H.; Huber, G.; Kresze, G. *Tetrahedron Lett.* **1973**, 4033–4036. (d) Braun, H.; Huber, G. *Ibid.* **1976**, 2121–2124.

0022-3263/83/1948-0016$01.50/0

Scheme I



Scheme II



the epoxides exhibited a multiplet at δ 2.0–3.2 and a two-proton olefin resonance at δ 5.9–6.0.[11] The mass spectra of these epoxides showed an appropriate parent ion and, frequently, intense ions corresponding to the expected mass losses of 2, 4, 16, and 18 m/z units.[12]

The stereochemistry of epoxide **4** was established by reduction to give alcohol **52**[13] (Scheme II). Hydrogenation of **52** by using palladium on carbon yielded decalinol **53**, contaminated with less than 1% of *cis*-decalinol **54**.[14] Lithium aluminum hydride reduction of either epoxide **31** or **35** gave a complex mixture of alcohols, suggesting carbonium ion rearrangements[15] and/or conjugate addition of hydride.[16] Subsequent olefin hydrogenation did not decrease this complexity. Epoxides **31** and **35** underwent rapid decomposition upon addition of europium shift reagents, which prevented the determination of the NMR coupling constants. We are certain that **31** and **35** contain greater than 90% of one isomer. In all other instances related epoxide isomers have separated cleanly on analytical gas chromatography (GC);[3,4] **31** and **35** appear as sharp GC peaks on three different columns. We assume that **31** and **35** are cis isomers by analogy with **4** and from mechanistic considerations (vide infra).

The identity of the side products such as **5** was more difficult to establish. The formation of either **5** or **61** can be rationalized (Scheme III).[10] Stereoelectronic factors in the rearrangements leading to **5** and/or **61** might favor one of the diasteriomers of **5** or of **61**. All of these alkylated ketones were isolated as mixtures containing at least two components. Standard spectroscopic techniques, including NMR measurements at 390 MHz with shift reagents and gas chromatography–mass spectrometry,[17] did not provide adequate data for unambiguous structural assignments. Since the constitution of this mixture was critical for definition of the overall mechanism, several experiments were designed to establish its composition.

A labeling experiment using sulfonium salt **46**, first prepared by Braun,[10] could solve the dilemma concerning **5**/**61** as well as provide additional information about sulfonium salt substituents on epoxyannulation. Salt

(11) For related spectral data see: Crandall, J. K.; Banks, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.* **1968**, *33*, 423–425.

(12) Budzikiewicz, H.; Djerassi, C.; Williams, D. G. "Mass Spectrometry of Organic Compounds"; Holden-Day: San Francisco, 1967; pp 449–465.

(13) Staroscik, J.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 738–740.

(14) Varkony, H.; Pass, S.; Mazur, Y. *J. Chem. Soc., Chem. Commun.* **1974**, 437–438.

(15) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, **1973**; pp 103–105.

(16) House, H. O. "Modern Synthetic Reactions"; W. A. Benjamin: Menlo Park, CA, 1973; pp 89–100.

(17) Bieman, K. "Mass Spectrometry: Organic Chemical Applications"; McGraw-Hill: New York, 1962; pp 144–145.

Table I. Epoxyannulation

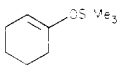
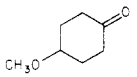
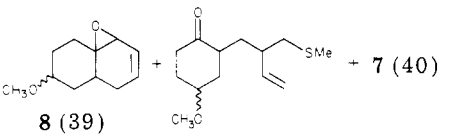
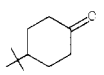
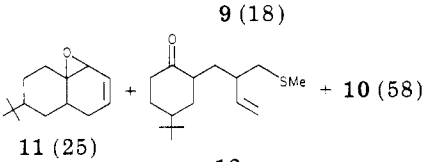
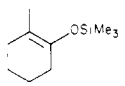
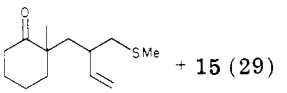
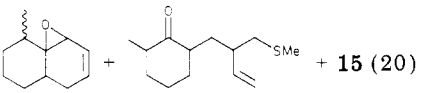
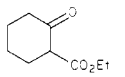
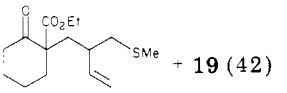
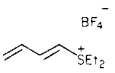
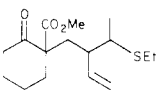
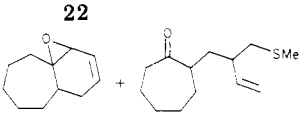
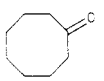
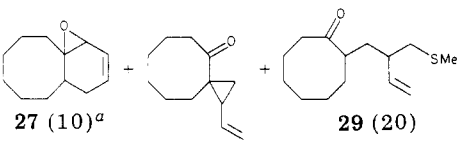
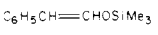
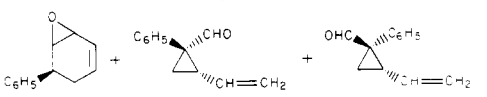
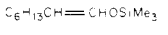
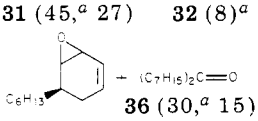
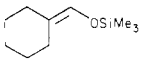
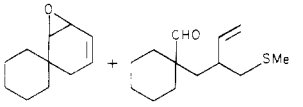
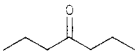
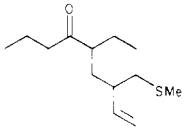
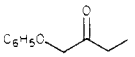
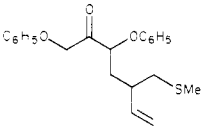
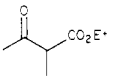
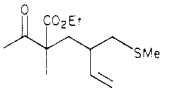
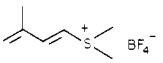
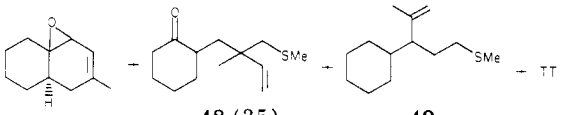
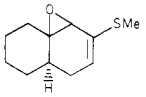
entry	enolate precursor	sulfonium salt (method of epoxyannulation)	products (% yield)[a]
I	 3	1 (A)	4 (58) + 5 (23) + 3 (20)
II	 6	1 (A)	4 (55) + 5 (21) + 3 (19)
III	3	2 (C)	4 (20) + 5 (65)
IV	 7	1 (A)	 8 (39) + 9 (18) + 7 (40)
V	 10	1 (A)	 11 (25) + 12 + 10 (58)
VI	 13	1 (B)	 14 (65) + 15 (29)
VII	 15	2 (C)	14 (80) + 15 (18)
VIII	 16 (B)	1 (A)	 17 (<5) 18 (65) + 15 (20)
IX	 19 (A)	1 (A)	 20 (50) + 19 (42)
X	19	2 (C)	20 (85)
XI	19	 21 (C)	 22
XII	 23 (A)	1 (A)	 24 (52) 25 (20) + 19
XIII	 26	1 (A)	 27 (10)[a] 28 (10)[a] 29 (20)
XIV	 30	1 (B)	 31 (45,[a] 27) 32 (8)[a] 33 (16)[a]
XV	 34	1 (B)	 35 (40,[a] 29) 36 (30,[a] 15)

Table I (*Continued*)

entry	enolate precursor	sulfonium salt (method of epoxyannulation)	products (% yield)[a]
XVI	 37	1 (B)	 38 (48) 39 (31)
XVII	 40	1 (A)	 41 (55)
XVIII		2 (C)	41 (85)
XIX	 42	1 (A)	 43 (42)
XX	 44	2 (C)	 45 (74)
XXI	3	 46 (A)	 47 (5) 48 (35) 49
XXII	3	50 (A)	 51 (15)

[a] All yields are isolated yields unless specifically noted by the superscript *a*. These yields were obtained from GC and NMR data.

1,4-addition and rearrangement with **46** would afford **48** while 1,2-addition would give **49** (Table I, entry XXI). Proton NMR spectra of this product mixture would exhibit quaternary and/or vinyl methyls. Salt **46** and the enolate from cyclohexanone provided only trace amounts of the expected epoxide **47**, accompanied by **48** and 2-methylcyclohexanone. Thus salt **46** yields a product mixture significantly different from that of **1**.

To clearly establish the structure of **5**, we treated the mixture of isomers with Raney nickel to afford **56**.[18] Compound **56** was then prepared by alkylation of the pyrrolidine enamine of cyclohexanone with 2-methylbutyl bromide. Compound **56** had the same constitution when prepared by either route. The composition of **20** was determined in an analogous fashion. The Raney nickel reduction product **58** was identical with an independently prepared sample.

The identities of **32**, **33**, and **36** were apparent from the NMR spectral data. The mixture of compounds **32** and **33** contained cyclopropane and aldehyde moieties as judged from NMR spectra exhibiting upfield multiplets (0.3–1.5 ppm) and two sharp singlets at 9.50 and 9.55 ppm, the latter in a 2:1 ratio. The presence of aldehydes was further supported by the IR adsorptions of 2750 and 1710 cm^{-1} in the IR spectrum. Reexamination of the NMR spectrum of **32** and **33** after storage for several days at −30 °C indicated that the minor isomer (**32**) had decomposed. Repurification afforded **33** which could easily be assigned the trans structure. A europium shift study of **33** at 220 MHz indicated that two nonolefin hydrogens moved downfield by the same relative amounts with increasing increments of shift reagent. This behavior is expected for **33** which has two cyclopropane hydrogens cis to the basic aldehyde carbonyl. Ketone **36** was identified by comparison with a commercial sample.

The experiments summarized in Table II were designed to maximize the yield of **4**. The sulfonium salt structure, the enolate cation, the solvent, and the temperature affected the ratio of **4** to **5**. *S*-(1,3-Butadien-1-yl)diethylsulfonium fluoborate (**21**)[10] and *S*-(1,3-butadien-1-yl)-tetrahydrothiophenyl fluoborate (**63**)[10] were prepared to provide an ylide with sulfur appendages of higher acidity than the methyl groups of **1**. Both **62** and **63** failed to yield **4** but afforded complex mixtures in which compounds analogous to **5** appeared to be present. The use of softer cations such as copper or cadmium did increase the **4** to **5** ratio but decreased the yield of **4** by affording numerous additional products. Protic solvents such as *tert*-butyl alcohol favored **5**. In fact, when bis salt **2**, the precursor to **1**, and an enolate generated in *t*-BuOH–THF were used, products such as **5** were formed exclusively in most instances. A temperature study using the enolate from either **3** or **40** indicated that the reaction was very slow below −50

(18) We are grateful to Mr. Keith Munson and Mr. Thomas Arrhenius for gifts of Raney nickel.

Scheme III

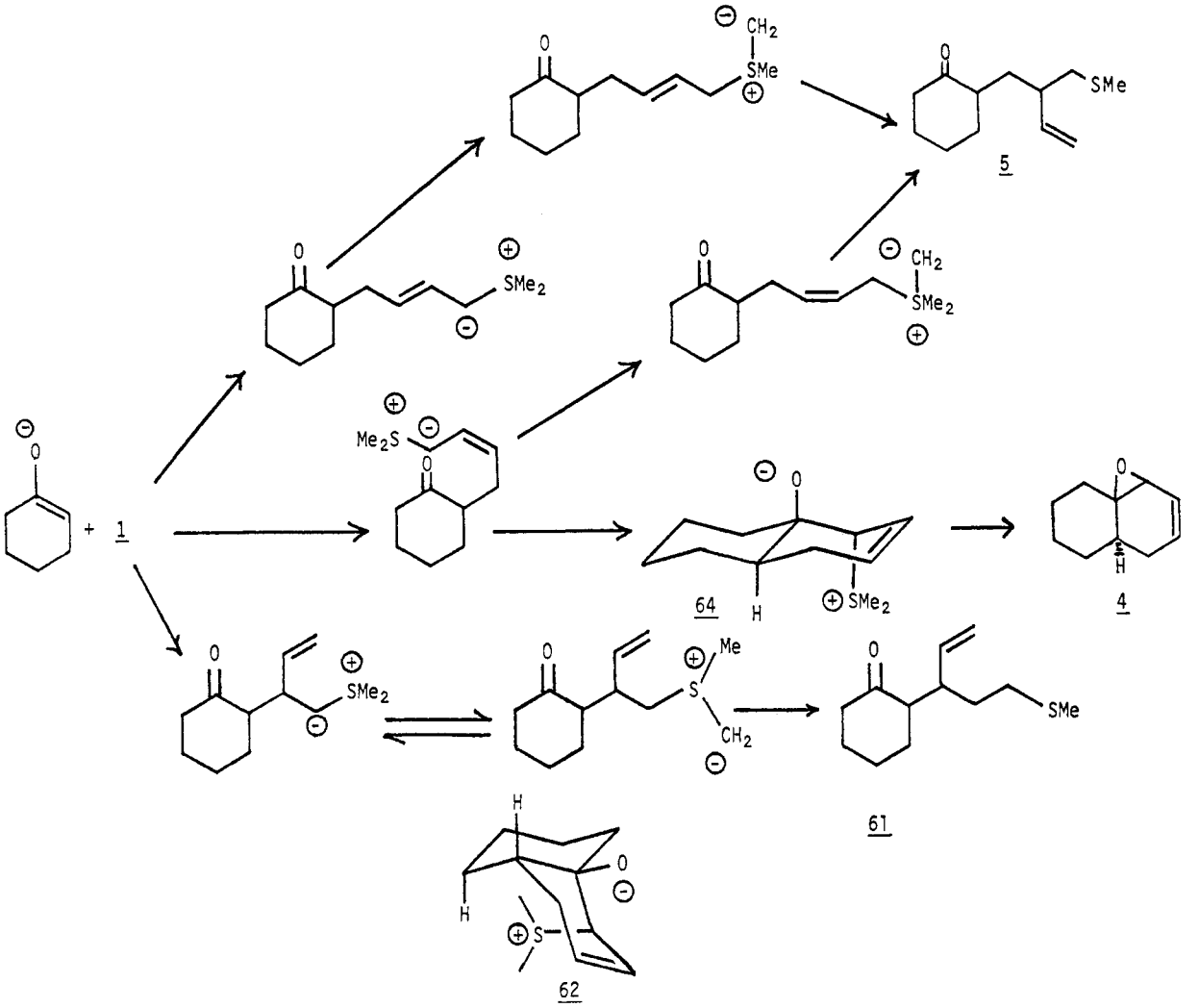


Table II

entry	enolate precursor	conditions with 1	product ratio 4	5	other
1	3	*t*-BuOK/*t*-BuOH	1	4	
2	3	LDA/0 °C	2	1	
3	3	LDA/CuBr-SMe_2/−78 °C	1	tr	10 other major
4	3	LDA/$CdCl_2$/−78 °C	~3	1	other products
5	3	LDA/−78 °C	~3	1	
6	6	MeLi/THF/−78 °C	3	1	
7	6	MeLi/THF/−78 °C	~2	1	
8	6	MeLi/**2**/THF/−78 °C	~1	5	
9	3	2LDA/**2**/THF/−78 °C	1	1	
10	3	LDA/**62**/THF/−78 °C		1	other products
11	3	LDA/**63**/THF/−78 °C		1	other products

°C and moderately rapid between −30 °C and 0 °C, without any marked change in product ratio. Elevated temperatures favored **5**.

In addition to the variations for the use of **1** described in the Experimental Section, one other procedure should be mentioned. A suspension of salt **2** in THF at −78 °C can be treated with 1 equiv of lithium diisopropyl amide followed, in 15–20 min, by the ketone enolate. On utilization of this technique, **3** provided **4** and **5** in a 1:1 ratio. For the casual user of epoxyannulation with readily available enolates, this protocol may be the procedure of choice. Salt **2** is much easier to prepare than salt **1**.

To test heteroatom substituents in epoxyannulation, we prepared salt **50** from **59**. We had previously reported the efficient formation of 1,2-bis(methylthio)-1,3-butadiene (**59**) from 1,4-bis(methylthio)-3-butyne.[19] Salt **50** could be generated and underwent epoxyannulation with cyclohexanone to afford a modest 20% yield of **51**, amid numerous other products including 2-methylcyclohexanone.

Discussion

Epoxyannulation was anticipated from reaction of enolates and **1**. Analogous phosphonium salts had been shown to provide 1,3-cyclohexadienes.[6] Braun and coworkers[10a-c] had demonstrated that **1** underwent addition of alkoxides to generate ylides which could be trapped in

(19) Garst, M. E.; Arrhenius, P. A. *Synth. Commun.* **1981**, *11*, 481–487.

situ by aromatic aldehydes. Braun's sequence required nonenolizable carbonyls since the alkoxide nucleophile and carbonyl electrophile were added simultaneously.

Our initial expectations were fulfilled. Certain enolates do yield epoxides when the enolate is generated in an irreversible fashion. Epoxyannulation requires the successful completion of a complex series of events. The enolate must add to the salt in a 1,4-mode to generate a cisoid allylic ylide. Equatorial addition of the ylide to the carbonyl is required to give a *trans*-betaine which can collapse to the observed product. This process occurs when the carbonyl carbon is unhindered and electrophilic (aldehydes) or unhindered and conformationally accessible (cyclic ketones). In other cases this intermediate allylic ylide undergoes an internal acid–base reaction followed by a [3,2] rearrangement. This latter process is well precedented. La Rochelle, Trost, and Krespy[20] found that the ylide from *S*-(3,3-dimethyl-3-propenyl)dimethylsulfonium fluoborate rearranged to 2,2-dimethyl-3-buten-1-yl methyl thioether when generated at −78 °C and immediately treated with benzaldehyde. Furthermore, base treatment of certain β-hydroxy sulfonium salts has been reported to yield these rearranged products in competition with epoxide formation.[21] The requirements for epoxyannulation could be simplified by invoking a [4 + 2] cycloaddition between **1** and the enolate followed by isomerization, closure, etc. to yield the epoxide. Attempted cycloadditions of **1** with **6** or enamines were unsuccessful. The latter compounds demethylated **1**.[22,23]

The stereochemistry of the oxirane is set by the stereochemistry of the betaine. Betaine **64** arises from equatorial addition to the cyclohexanone as observed with ylides which add reversibly,[24] with diphenylsulfonium allylide,[20] and as observed in a related, kinetically controlled aldol reaction.[25] Introduction of an angular methyl into **64** (Scheme III and Table I, entry VI) produces a 1,3-diaxial sulfonium salt–methyl interaction in the betaine. This interaction makes betaine formation and collapse less favorable than ylide rearrangement. The betaine leading to the trans isomers of **31** or of **35** by "equatorial addition" also forces a 1,3-diaxial interaction between the sulfonium salt and the appendage group, which is avoided in the betaine leading to *cis*-**31** or *cis*-**35**. The stereochemistry assigned to **31** and **35** predominated in a related reaction.[3a,b] Betaine **62** resulting from axial attack has a costly sulfonium salt–hydrogen interaction.[26]

Generalizations about the reactivity of **1** in epoxyannulation can be based upon the entries in Table I. The enolates from aldehydes **30**, **34**, and **37** afforded epoxyannulated compounds as the major products. Unhindered, cyclic ketone enolates with rigid geometry (**3**, **7**, **10**, and **23**) also undergo epoxyannulation. Hindering the carbonyl (**13**, **16**, and **19**) or increasing conformational mobility of the enolate (**26**, **40**, **42**, and **44**) provides higher yields of rearranged products at the expense of epoxyannulation. Again, the betaine **64** suggests a rationale for this generalization. Any substituent will add a 1,3-diaxial interaction which may disfavor formation of the desired betaine or promote reverse reaction of the betaine. Either of these reactions would encourage the ylide rearrangement. Floppy cyclic ketones or acyclic ketones may not be fixed in the appropriate conformation for ylide addition and are less electrophilic than smaller cyclic ketones or aldehydes. To increase the carbonyl electrophilicity, we prepared compound **42** and treated it with **1**. Although the equilibrium for hydration of **42** is at least 10 times that of **40**,[27] **42** still gave only rearranged products.

All of the products discussed thus far can be rationalized by enolate 1,4-addition to **1**, followed by processes depicted in Scheme II. Compounds **32**, **33**, and **36** cannot be rationalized by this mechanism. Cyclopropanes, such as **32** and **33** were detected by Braun[10d] from **1** and β-dicarbonyl compounds with two acidic hydrogens. Apparently, the acidifying effect of the phenyl group permits the acid–base reaction necessary for the generation of **32** and **33**. Ketone **36** was always generated during epoxyannulation with **34** and **1**. We subsequently demonstrated that **36** was slowly formed from **34**, presumably by a sequential aldol reaction, an internal redox process, and deformylation.[28] This sequence is far too slow to account for the large amount of **36** produced, unless the epoxyannulation reagents catalyze this reaction.

To test the effect of sulfonium salt functional groups, we examined salts **46** and **50**. Salt **46** mainly rearranged to give product **48**; salt **50** produced a complex mixture containing 20% of the epoxyannulated product. We anticipated that **50** was a reasonable model for other substituted dienyl sulfonium salts. A substituent at the 2-position blocks nucleophilic addition to that site without altering the stability/reactivity of the allylic ylide by resonance. Salts **46** and **50** provided 2-methylcyclohexanone, indicating them to be more prone to S-demethylation than **1**. Dienyl salt instability may account for the lower yields of epoxyannulation. Although **50** is a useful epoxyannulating agent which produces a functionalized cyclohexane, the yield is modest, and the sequence is technically demanding.

Epoxyannulation with 1-butadienyl sulfonium salts affords cyclohexadiene oxides from aldehyde and unhindered, cyclic ketone enolates. These unique products should be particularly valuable in the synthesis of certain arene oxides.

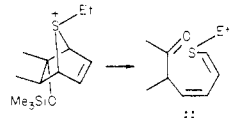
Experimental Section

General Methods. Infrared spectra (IR) were recorded on

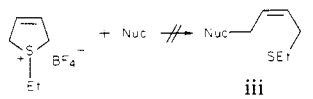
(20) LaRochelle, R. W.; Trost, B. M.; Krepski, L. *J. Org. Chem.* **1971**, *36*, 1126–1136.

(21) Kano, S.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **1978**, 4125–4126.

(22) The [4 + 2] cycloaddition of a silyl enol ether with an *S*-ethylthiophonium fluoborate followed by elimination, etc. (i to ii) is an attractive alternative to epoxyannulation thwarted by the lack of reactivity of the thiophonium salts (Heldeweg, R. F.; Hogeveen, H. *Tetrahedron Lett.* **1974**, 75–78).



(23) Treatment of *S*-ethyl-2,5-dihydrothiophenonium fluoborate (Birch, S. F.; McAllan, D. T. *J. Chem. Soc.* **1951**, 3411–3416) with nucleophiles to give iii was thwarted by elimination, affording only 1,3-butadien-1-yl ethyl thioether.



(24) Trost, B. M.; Melvin, L. S. "Sulfur Ylides"; Academic Press: New York, 1975; pp 34–42, 67–68, 128–131.

(25) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501–2505.

(26) The enolate from cyclohexenone would avoid these interactions. Although spectral data of the crude products from this enolate suggest epoxyannulation has occurred, attempted purification resulted in substantial decomposition.

(27) The hydration constant for 1,3-dichloroacetone is 10^3 times that of an acetone. 1,3-Dialkoxyacetone should be comparable. Bell, R. B. *Adv. Phys. Org. Chem.* **1966**, 4, 1–29. We prepared four 2-substituted 5-oxa-1,3-dioxanes. Unfortunately the enolates from these compounds decomposed at −78 °C in less than 30 min.

(28) Garst, M. E. *Synth. Commun.* **1980**, *10*, 863–866.

a Beckman IR 18 AX spectrophotometer; bands yielding structural information are reported in reciprocal centimeters with using polystyrene calibration. Nuclear magnetic resonance spectra (NMR) were recorded on a Varian EM 390 at 35 °C in deuteriochloroform, and peak positions are reported in parts per million from tetramethylsilane as an internal standard with a multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s) designation. Low-resolution mass spectra were obtained from an LKB 9000 or from a Finnigan 4021 GCMDS system at a 70- or 16–20-eV ionizing voltage. The sample was introduced by GC. Percentages relative to the most abundant fragment are given in parentheses. High resolution spectra were obtained at the California Institute of Technology Analytical Facility or the Biomedical Mass Spectrometry Resource, Berkeley. The sample was introduced by direct probe. All compounds exhibited identical low- and high-resolution spectra.

GC analysis was performed on a Varian 3700 gas chromatograph with an FID detector; preparative GC was carried out on a Hewlett-Packard 5700 gas chromatograph with a TC detector. Both instruments were outfitted with a 6 ft × 0.25 in. glass column containing the following: (A) 3% HI EFFIC 8BP on 100/120 Chromosorb (Applied Science); (B) 3% OV-255 on 100/120 Chromosorb (Applied Science); (C) 3% DEXIL 300 on 100/20 Supelcoport (Supelco, Inc.); (D) 3% SE-30 on 100/120 Supelcoport (Supelco, Inc.).

The term "standard workup" means that the organic layer was washed with brine, dried over Na_2SO_4, and filtered and the solvent removed on a rotary evaporatory at aspirator pressure. The term "base wash" means the organic layer was washed with saturated aqueous Na_2CO_3.

Reagents and Solvents. Tetrahydrofuran (THF) was distilled from sodium–benzophenone[29] immediately prior to use. Hexane was washed with sulfuric acid and distilled from calcium hydride. Dimethyl sulfoxide (Me_2SO) was distilled from calcium hydride at reduced pressure. All amines were distilled from barium oxide and stored over molecular sieves under nitrogen. All organolithium reagents were purchased from Alfa Ventron. All other reagents and solvents were purchased from Aldrich Chemical and Mallinckrodt Chemical, respectively, and were used as received after determining the purity by usual spectroscopic methods. All reactions were magnetically stirred under a nitrogen atmosphere.

Silyl enol ethers **6**, **16**, **30**, **34**, and **37** were prepared according to House[30] and ether **13** by the method of Rubottom.[31] Ketone **42** was prepared from epichlorohydrin by established procedures.[32]

(Butadien-1-yl)dimethylsulfonium Fluoborate (1). The procedure of Braun[10] was modified. 1,4-Bis(dimethylsulfonium) dichloride **2** was prepared from butadiene dichloride and dimethyl sulfide in Me_2SO. This bis salt was collected and repeatedly crushed and washed with ether to remove the Me_2SO. A mechanically stirred solution of this salt (248 g, 1 mol) in 800 mL of methanol was prepared at 0 °C and treated with 110 g (1 mol) of sodium fluoborate. A white precipitate remained. A solution of sodium methoxide prepared from 50 g of sodium in 1 L of methanol was added as rapidly as possible (5–15 min), keeping the internal temperature below 10 °C. The addition was continued until pH 8 (indicator paper) was obtained. This usually required 500–550 mL of methanolic base. The resulting greenish yellow solution containing a white precipitate was stirred at 0 °C for 40 min and then treated with fluoroboric acid (40%) dropwise until the pH reached 3–4 (indicator paper). The solution was filtered, and the solids were washed with 100 mL of methanol. The precipitate was mainly sodium salts but occasionally contained the bissulfonium salt (NMR) which could be recycled. The filtrate was concentrated on a rotary evaporator with a water bath at 20 °C. The final traces of methanol were removed under high vacuum to leave a solid which was suspended in CH_2Cl_2 (1 L) and filtered. The solids were washed with CH_2Cl_2 (3 × 100 mL). The pooled CH_2Cl_2 layers were filtered through sodium sulfate and concentrated below 30 °C to leave 87.7 g (43%) of yellowish **1** which was sufficiently pure for reactions. This salt could be stored for months at 0 °C without substantial decomposition.

(1,3-Butadien-1-yl)diethylsulfonium fluorobrate (**21**), (1,3-butadien-1-yl)tetrahydrothiophenium fluoborate (**63**), and (3-methyl-1,3-butadien-1-yl)dimethylsulfonium fluoborate (**46**) were prepared by the method of Braun.[10]

General Reaction with Enolates. Procedure A. A suspension of 3 mmol of salt **1** in 100 mL of anhydrous THF was treated with 1–2 g of Linde 4A molecular sieves, stirred under N_2 at room temperature for 15–30 min, cooled to −78 °C, and treated with a solution of the ketone enolate (2.5 mmol) in 5–10 mL of dry THF. The enolate was transferred via canula under N_2 pressure. This enolate had been prepared by the addition of the ketone (2.5 mmol) in 2 mL of THF to a solution of *n*-butyllithium (2.6 mmol) and diisopropylamine (2.6 mmol) in 4 mL of THF at 0 °C. The resulting enolate–sulfonium salt suspension was stirred at −78 °C for 3 h, allowed to gradually warm to room temperature, and allowed to stand for 12 h. The suspension was filtered through Celite and washed with ether. The pooled organics were subjected to the standard workup. Chromatography of the crude product on 15 g of Florisil afforded the products. Elution with 1% ether–pentane provided the epoxide and with ether provided the ketonic products. These ketones were separated by evaporative distillation.

Procedure B. This method differs from procedure A only in the method of enolate generation. The trimethylsilyl enol ether (2.5 mmol) in 6 mL of THF was treated with *n*-butyllithium (2.6 mmol) at 0 °C. This solution was stirred until only ketone could be detected by GC.

Procedure C. A suspension of salt **2** (3 mmol), ketone (3 mmol), and potassium *tert*-butoxide (7 mmol) in 15 mL each of *tert*-butyl alcohol and of THF was stirred for 12 h. Completion of the standard workup by using ether–brine afforded a crude product which was purified as before.

Other reaction conditions that were attempted to improve the yield of oxirane from cyclohexanone are listed in Table II. Entries 5 and 6 represent the optimal procedures employed for epoxyannulation.

(1α,2α,7β)-2-Oxabicyclo[5.4.0.0^{1,3}]undec-4-ene (4). Procedure A: 58% yield; IR 935, 910, 880, 855 cm^{-1}; NMR δ 1.2–2.4 (m, 11), 3.05 (t, $J \approx 3$ Hz, 1), 5.85 (br s, 2); mass spectrum, *m/z* (relative intensity) 150 (M^+, 10), 148 (2), 144 (4), 132 (57), and 104 (base, 100); HRMS, *m/z* 150.104 ($C_{10}H_{14}O$ requires 150.105).

Procedure B gave a 55% yield, and procedure C gave a 20% yield.

2-[2-[(Methylthio)methyl]-3-butenyl]cyclohexanone (5). Procedure A: 23% yield; IR 1720 cm^{-1}; NMR δ 1.1–2.6 (m, 14), 2.1 (s, 3), 5.1 (m, 2), 5.5 (m, 1); NMR (CCl_4 + Eu(fod)$_3$) δ 2.30 and 2.55 (s, methyl); mass spectrum (gc peak 1, 70 eV), *m/z* (relative intensity) 214 (M + 2, 1.3), 2.1 (M + 1, 5.3), 212 (M, 25.5), 111 (100), 61 (59); mass spectrum (gc peak 2, 70 eV), *m/z* (relative intensity) 214 (M^+ + 2, 4.9), 213 (M^+ + 1, 9.7), 212 (M^+, 27.5), 111 (100), 61 (82); HRMS, *m/z* 212.121 ($C_{12}H_{20}OS$ requires 212.130).

Procedure B gave a 21% yield, and procedure C gave a 65% yield.

(1α,2α,7β)-9-Methoxy-2-oxabicyclo[5.4.0.0^{1,3}]undec-4-ene (8). Procedure A: 39% yield; IR 1080, 910, 860 cm^{-1}; NMR δ 1.0–2.5 (m, 9), 3.05 (t, J = 3 Hz, 1), 3.30 (s, 3), 3.60 (br t, J = 3 Hz, 1), 5.85 (m, 2); mass spectrum, *m/z* (relative intensity) 180 (M^+, 5), 178 (1), 162 (12), 148 (8), 147 (5), 131 (12), 130 (100), 129 (15), 115 (12), 104 (57); HRMS, *m/z* 180.114 ($C_{11}H_{16}O$ requires 180.115).

4-Methoxy-2-[2-[(methylthio)methyl]-3-butenyl]cyclohexanone (9). Procedure A: 18% yield; IR 1720 cm^{-1}; NMR δ 1.0–2.4 (m, 12), 1.05 and 2.10 (2 s, 3), 3.40 (s, 3), 3.60 (br t, 1), 5.10 (m, 2), 5.50 (m, 1); mass spectrum, *m/z* (relative intensity) 244 (M^+ + 2, 0.2), 243 (0.6), 242 (4), 210 (25), 120 (100); HRMS, *m/z* 242.133 ($C_{13}H_{22}O_2S$ requires 242.134).

(1α,3α,7β,9α)-9-*tert*-Butyl-2-oxabicyclo[5.4.0.0^{1,3}]undec-4-ene (11). Procedure A: 25% yield; NMR δ 0.9 (s, 9), 1.4–2.4 (m, 10), 3.05 (t, J = 3 Hz, 1), 5.85 (m, 2); HRMS, *m/z* 206.168 ($C_{14}H_{22}O$ requires 206.167).

4-*tert*-Butyl-2-[2-[(methylthio)methyl]-3-butenyl]cyclohexanone (12). Procedure B: 10% yield; NMR δ 0.9 (s, 9),

(29) Seyferth, D.; Spohn, R. J. *J. Am. Chem. Soc.* **1969**, *91*, 3037–3044.
(30) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324–2336.
(31) Rubottom, H. M.; Mott, R. C.; Krueger, D. S. *Synth. Commun.* **1977**, *7*, 327–332.
(32) Piantadosi, C.; Hall, I. H.; Wyrich, S. D.; Ishaq, K. S. *J. Med. Chem.* **1979**, *19*, 223–231.

1.4–2.4 (m, 13), 2.10 (s, 3), 5.0 (m, 2), 5.4 (m, 1); HRMS, m/z 268.186 ($C_{16}H_{28}SO$ requires 268.186).

4-*tert*-Butylcyclohexanone was recovered in 58% yield.

2-Methyl-3-[2-[(methylthio)methyl]-3-butenyl]cyclohexanone (14). Procedure B: 65% yield; IR 1700 cm^{-1}; NMR δ 1.0 (s, 3), 1.4–2.5 (m, 13), 2.05 (s, 3), 5.0 (m, 2), 5.5 (m, 1); mass spectrum, m/z 266 (M^+), 212, 198 183, 55 (base); HRMS, m/z 266.141 ($C_{13}H_{22}OS$ requires 226.139).

Procedure C gave an 80% yield.

11-Methyl-2-oxabicyclo[5.4.0.0^{1,3}]undec-4-ene (17). Procedure A: 5% yield; NMR δ 0.85 (d, J = 6 Hz, 3), 1.4–2.4 (m, 10), 3.15 (t, J = 3 Hz, 1), 5.85 (m, 2); mass spectrum, m/z 164 (M^+).

6-Methyl-2-[2-[(Methylthio)methyl]-3-butenyl]cyclohexanone (18) and 14. Procedure A: 65% yield; NMR δ 0.85 (d, J = 6 Hz), 1.00 (s), 2.0 (s), 1.4–2.4 (m), 5.0 (m), 5.4 (m); GC/MS (70 eV) for peak 1, m/z 226 (M^+); GC/MS for peak 2 identical with that for **14** above.

Ethyl 1-[2-[(Methylthio)methyl]-3-butenyl]-2-oxocyclohexanecarboxylate (20). Procedure A: 50% yield; IR 1720 (br) cm^{-1}; NMR δ 1.3 (t, 3), 1.4–2.2 (m, 8), 2.05 (br s, 3), 2.2–2.6 (m, 5), 4.1 (br q, 2), 4.9 (m, 2), 5.5 (m, 1); mass spectrum, m/z 284 (M^+), 278, 173, 59 (base); HRMS, m/z 284.145 ($C_{15}H_{24}O_3S$ requires 284.145).

Procedure C gave an 85 yield.

Ethyl 1-[2-Vinyl-3-(ethylthio)butenyl]-2-oxocyclohexanecarboxylate (22). Procedure C was used with diethyl (1,3-butadien-1-yl)sulfonium fluoborate (**21**); IR 1720 (br) cm^{-1}; NMR δ 1.2 (m, 9), 1.4–2.8 (m, 14), 4.2 (m, 2), 5.0 (m, 2), 5.3 (m, 1); mass spectrum, m/z 310 (M^+), 308, 283, 224, 170, 149, 119, 117, 87 (base), 74, 69; HRMS, m/z 310.150 ($C_{17}H_{26}O_3S$ requires 310.160).

(1α,3α,7β)-2-Oxabicyclo[5.5.0.0^{1,3}]dodec-4-ene (24). Procedure A: 52% yield; IR 870, 830 cm^{-1}; NMR δ 1.4–2.0 (m, 13), 2.75 (t, J = 3 Hz, 1), 5.70 (m, 2), mass spectrum, m/z (relative intensity) 164 (M^+, 10), 156 (base) 131, 118, 117, 104; HRMS, m/z 164.121 ($C_{11}H_{16}O$ requires 164.120).

2-[2-[(Methylthio)methyl]-3-butenyl]cycloheptanone (25). Procedure A: 25% yield; IR 1700 cm^{-1}; NMR δ 1.0–2.4 (m, 16), 2.1 (br s, 3), 5.1 (m, 2), 5.5 (m, 1); mass spectrum, m/z (relative intensity) 228 (M^+ + 2, 2), 227 (M^+ + 2, 4), 226 (M^+, 26), 61 (base, 100); HRMS, m/z 226.141 ($C_{13}H_{22}OS$ requires 226.139).

Compounds 26–29 (Entry XIII, Table I). Procedure A: five products each in 10% yield as determined by GC on column A; NMR (partial) δ 0.65 (dd, J = 4, 7.5 Hz, 1), 0.85 (dd, J = 4, 12 Hz, 1), 2.70 (t, $J \approx$ 3 Hz, 1), 5.85 (br s, 1); GC/MS (70 eV) for GC peaks 1–3, m/z 178 (M^+) for each peak.

Product **29** was isolated by column chromatography on Florisil (ether): 19% yield; NMR δ 1.0–2.0 (m, 12), 2.1 (s, 3), 2.0–2.5 (m, 6), 5.0 (m, 2), 5.3 (m, 1); GC/MS (70 eV), m/z 240 (M^+) for both GC peaks.

(1α,3α,7α)-7-Phenyl-3-oxabicyclo[4.1.0]hept-4-ene (31). This compound was isolated by preparative GC (col B). Procedure B: isolated in 27% yield, crude yield 45%; homogeneous on GC columns A, C, D; IR 1650, 1600, 1560, 1500, 980 cm^{-1}; NMR δ 2.10 (m, 1), 2.30–3.10 (m, 2), 3.50 (m, 1), 3.75 (m, 1), 6.00 (m, 2), 7.30 (m, 5); mass spectrum, m/z 172 (M^+), 170, 154, 129, 128, 118, 92, 91; HRMS, m/z 172.089 ($C_{12}H_{12}O$ requires 172.089).

Addition of $Eu(fod)_2$ shift reagent catalyzed decomposition.

(*E*)- and (*Z*)-1-Phenyl-2-vinylcyclopropane-1-carboxaldehyde (32 and 33). Procedure B: isolated in 25% yield, crude yield ca. 25%; IR 3040, 2940, 2840, 2750, 1710 cm^{-1}; NMR δ 1.60 (dd, J = 4, 7.2 Hz, 1), 1.80 (m, 0.5), 2.00 (dd, J = 4, 10 Hz, 1), 2.40 (m, 1.5), 2.75 (m, 0.5), 5.10 (m, 3), 5.90 (m, 1.5), 7.30 (br s, 7.5), 9.50 (s, 1), 9.55 (s, 0.5); mass spectrum, m/z 172 (M^+), 143, 129, 128, 115, 105, 103; HRMS, m/z 172.090 ($C_{12}H_{12}O$ requires 172.089).

After being allowed to stand for 30 days at −30 °C, the minor isomer decomposed. Evaporative distillation yielded pure **33**: NMR δ 1.60, 2.00, 2.40, 5.10, 5.90, 7.30, 9.50 ppm. A $Eu(fod)_2$ shift study using 10, 20, 30, 40, and 60 mol % of $Eu(fod)_2$ showed that the δ 2.0 and 2.4 peaks moved downfield most rapidly and by the same relative amount.

The remaining 30% of the crude product was unidentified.

(1α,3α,7α)-7-*n*-Hexyl-2-oxabicyclo[4.1.0]hept-4-ene (35). These samples were isolated by using preparative GC (column B). Procedure B: isolated in 29% yield, crude yield about 40%; homogeneous on GC columns A, C, D; NMR δ 0.9 (br t, 3), 1.0–1.8 (m, 10), 1.8–295 (m, 3), 3.0 (m, 2), 5.8 (m, 2); mass spectrum, m/z 180 (M^+), 178, 162, 127, 131, 129, 127, 96 (base); HRMS, m/z 180.154 ($C_{12}H_{20}O$ required 180.151).

8-Pentadecanone (36). Procedure B: isolated in 15% yield, crude yield about 30%; identical IR, NMR, MS, and HRMS data with those of a commercial sample.

The remaining 30% of the crude product was not identified.

7,7-Pentamethylene-2-oxabicyclo[4.1.0]hept-4-ene (38). Procedure B: 48% yield; NMR δ 1.0–2.2 (m, 12), 3.2 (br m, 2), 5.8 (m, 2); mass spectrum, m/z 164, 146, 136, 113, 95, 87, 69 (base); HRMS m/z 164.122 ($C_{11}H_{16}O$ requires 164.120).

1-[2-[(Methylthio)methyl]-3-butenyl]cyclohexane-1-carboxaldehyde (39). Procedure B: 31% yield; NMR δ 1.0–2.0 (m), 2.0 (s), 2.1–2.4 (m), 5.0 (m), 5.4 (m); mass spectrum, m/z 266 (M^+), 197, 183, 102, 91, 77, 71 (base); HRMS, m/z 226.142 ($C_{13}H_{22}OS$ requires 226.130).

5-Ethyl-3-[(methylthio)methyl]-1-nonen-6-one (41). Procedure A: 55% yield; IR 1710 cm^{-1}; NMR δ 0.9 (t, $J \sim$ 9 Hz, 6), 1.2–1.8 (m, 6), 2.05 (br s, 3), 2.5 (m, 6), 5.1 (m, 2), 5.6 (m, 1); mass spectrum, m/z 228 (M^+), 213, 199, 185, 183, 157, 119, 117, 71, 61 (base), 55; HRMS, m/z 228.156 ($C_{13}H_{24}OS$ requires 228.155).

Procedure C gave 85% yield. In all instances starting ketone accounted for the remaining material. With use of procedure A at −20 °C, <10% of a compound having the formula of $C_{11}H_{18}O$ was detected by GC/MS. The NMR spectrum of the crude material *did not* indicate the presence of epoxides or cyclopropanes.

3-[(Methylthio)methyl]-5,7-diphenoxy-1-hepten-6-one (43). Procedure A: 42% yield; NMR δ 1.4 (m, 2), 2.1 (s, 3), 2.5 (m, 3), 4.1 (m, 3), 5.0 (m, 2), 5.4 (m, 1), 7.0 (m, 10); mass spectrum, m/z 358 (M^+).

Ethyl 5-[(Methylthio)methyl]-3-methyl-2-oxo-6-heptene-3-carboxylate (45). Procedure C: 74% yield; IR 1720 cm^{-1}; NMR δ 1.4 (s, 3), 2.05 (s, 3), 2.15 (s, 3), 1.4–2.5 (m, 5), 2.6 (s, 3), 4.8–5.6 (m, 3); mass spectrum, m/z 246 (M^+ + 2, 1.3), 245 (M^+ + 1, 3), 244 (M^+, 24), 201 (43), 123 (57), 61 (100).

Entry XXII, Table I (15, 47–49). Procedure A with salt **46**: IR 1710 cm^{-1}; NMR (partial) δ 1.0 (s), 1.05 (d, J = 8 Hz), 1.32 (s), 2.09 (s), 5.0 (m, 2), 5.7 (m, 1); GC/MS in order of elution from column A; (1) (20% yield) m/z 112 (M^+), 98, 55 (base); (2) (5% yield) m/z 164 (M^+ and base), 149, 146; (3) (5% yield) m/z 164 (M^+), 149 (base); (4) (35% yield) m/z 226 (M^+), 211, 175, (base), 137; (5) m/z (relative intensity) 226 (M^+), 211 (small), 208, 137 (base).

5-(Methylthio)-2-oxabicyclo[5.4.0.0^{1,3}]undec-4-ene (51). A solution of 0.073 g (5×10^{-4} mol) of **59** in 0.3 mL of nitromethane at 0 °C was treated with 0.073 g (5×10^{-4} mol) of trimethyloxonium fluoborate in 0.2 mL of nitromethane. After 1 h at 0 °C the solvent was removed at 0.25 mm and less than 20 °C. Toluene (2 × 1 mL) was added to assist in removal of the last traces of nitromethane.

A suspension of freshly prepared salt **50** (0.413 g, 1.5×10^{-1} mol) in 30 mL of THF was treated according to procedure A with cyclohexanone. Processing of this mixture as usual followed by preparative GC afforded 0.044 g (15%) of **51**: NMR δ 1.1–2.0 (m, 11), 2.3 (s, 3), 3.05 (d, $J \approx$ 3 Hz, 1), 5.5 (m, 1); mass spectrum, m/z 196 (M^+ and base), 178, 153, 131, 91, 79; HRMS, m/z 196.095 ($C_{11}H_{16}OS$ requires 196.092). GC/MS of the crude reaction mixture indicated ca. 15% of **15** to be present.

1-Hydroxybicyclo[4.4.0]decanes 52, 53, and 55. A solution of 0.20 g of **4** in THF was treated with excess lithium aluminum hydride. After 5 h at room temperature, this solution was treated with a saturated sodium sulfate paste and processed to leave 0.19 g of alcohol **52** which exhibited IR, NMR, MS, and GC characteristics identical with those of an authentic sample provided by Professor B. Rickborn.[13]

Treatment of 0.050 g of **52** with 0.01 g of 10% Pd/C in 5 mL of ethyl acetate under 1 atm of hydrogen for 12 h followed by filtration and evaporation yielded 0.045 g of (1aα,6aβ)-1a-hydroxydecahydronaphthalene: mass spectrum, m/z relative intensity) 154 (M^+, 62), 136 (50), 111 (base, 100), 98 (50), 84 (40), 49 (50). (1aα,6aβ)-1a-hydroxydecahydronaphthalene (**55**) was prepared by the method of Mazur:[14] mass spectrum, m/z 154 (M^+, 30), 136 (70), 111 (66), 74 (75), 59 (94), 31 (base, 100).

Ethyl 1-(2-Methylbutyl)-2-oxocyclohexane-1-carboxylate (58). Treatment of 0.030 g of **20** with excess of active Raney nickel in 5 mL of refluxing ethanol for 6 h followed by filtration and evaporation of the ethanol left 0.015 g of oily **58**: 63% yield; IR 1740, 1720 cm^{-1}; NMR δ 0.9 (t, 3), 1.1–2.5 (m, 18, 3.0–3.4 (m, 3), 4.1 (dq, 2); mass spectrum, m/e 242 (M^+), 170, 124, 95, 81; HRMS, m/e 242.188 ($C_{14}H_{26}O_3$ requires 242.188).

An authentic sample of **58** was prepared by generation of the sodium enolate of **19** by using NaH in THF and treatment with 2-methyl-1-bromobutane. This product was identical in all respects with **58**.

2-(2-Methylbutyl)cyclohexanone (56). A solution of 3.51 g (2×10^{-2} mol) of 1-pyrrolidinylcyclohexene with 3.5 g (2×10^{-2} mol) of 1-bromo-2-methylbutane in 20 mL of dioxane was heated at reflux for 20 h. The mixture was diluted with 10 mL of 3 N HCl and stirred for 1 h. The usual workup afforded 1.95 g of oil from which an analytical sample of **56** was obtained by preparative GC (column C): IR 1710 cm^{-1}; NMR δ 1.0 (d, $J \approx 8$ Hz, 3), 1.1 (d, $J \approx 8$ Hz, 3), 1.4–2.5 (m, 14); mass spectrum, m/z (relative intensity) 168 (M^+, 5), 98 (base, 100).

A solution of 0.050 g of **5** in 5 mL of ethanol was treated with about 0.1 g of activated Raney nickel and heated at reflux for 3 h. Filtration and evaporation left 0.035 g of a mixture containing ca. 45% of **56**, identical with the **56** above by GC (columns A, C, D). None of the remaining compounds in this mixture were **57** (GC/MS).

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Natural Ferric Ionophores: Total Synthesis of Schizokinen, Schizokinen A, and Arthrobactin

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The synthesis of the microbial iron chelators schizokinen (**1**) and arthrobactin (**2**) are described. *O*-Benzyl-*N*-(carbobenzyloxy)hydroxylamine (**7**) was subjected to triphenylphosphine/diethyl azodicarboxylate mediated alkylation with alcohol amine **10** to give the N-alkylated product **13**, which was converted to the protected 1-amino-3-(acetylhydroxyamino)propane **4a** by hydrogenation in the presence of acetic anhydride. Several citric acid derivatives were prepared which were activated at both terminal carboxyl groups and protected at the internal carboxyl groups. 1-Amino-3-[(benzyloxy)amino]propane *p*-toluenesulfonic acid double salt (**19**) was coupled to citric acid derivative **28c** to give protected schizokinen **29c**, which was deprotected in two steps to yield schizokinen (**1**). The 1-amino-5-(acetylhydroxyamino)pentane derivative **4b** was deprotected and coupled with citric acid derivative **28a** to give **31**, which was deprotected in two steps to yield arthrobactin (**2**). Preliminary attempts to synthesize schizokinen resulted in formation of succinimide **26**. Reductive debenzylation of **26** provided **33** which was shown to be identical with schizokinen A.

Iron is an essential element for all life forms. Although iron is one of the most abundant elements, the extreme insolubility of ferric ion at neutral and alkaline pH places severe restrictions on its metabolism. Iron absorption from the diet is physiologically controlled, but the body has no regulatory mechanism for eliminating a toxic excess introduced by accidental overdose or by multiple transfusions. Cooley's anemia and its transfusional treatment provide an example of the difficulty of correcting deficient iron metabolism. According to the World Health Organization, the group of diseases called the thalassemias, of which Cooley's anemia is the most severe, is the largest health problem in the world for single-locus genetic diseases. Extensive iron overload induced by the multiple transfusions during treatment of Cooley's anemia causes deposition of the metal in the heart, liver, endocrine glands, and other organs. The ultimate result is organ malfunction and early death.[1]

In principle, iron overload can be treated by administration of an iron-chelating agent to promote remobilization and excretion of the deposited iron. Perhaps the best models for iron chelation are provided by microbial systems which have envolved highly specific and efficient iron-sequenstering agents.[2] These siderophores primarily utilize either hydroxamic acids[3] or catechols[4] for the che-

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