Medium-Ring γ-Epoxy Sulfones. Regio- and Stereochemistry of the Butyllithium-Promoted Transannular Epoxide Ring Opening

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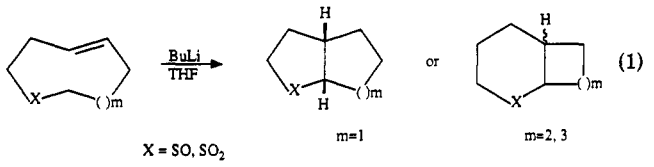
Cyclic 8- and 9-membered *E* and *Z* γ-epoxy sulfones yield bicyclic hydroxy sulfones stereospecifically upon treatment with BuLi in THF. The distribution of regioisomeric products markedly depends on the metalation mode, portionwise or at once. This suggests that the metal/proton exchange between the two positions α to the sulfone function is slow, relative to transannular cyclization, under conditions of complete metalation, but becomes fast in the presence of unmetalated sulfone (probably acting as a H^+-transfer agent). The product distribution also depends, though to a lesser extent, on temperature, perhaps in relation to changes in the aggregation of the organolithium intermediate. An unexpected phenomenon was observed with the 8-membered *Z* epoxy sulfone at −70 °C, where the time dependence of the transannular cyclization is consistent with an equilibrium being reached at $^2/_3$ conversion. However, at −40 °C or higher the reaction proceeds to completion without difficulty. A low-temperature metastable equilibrium is suggested involving some kind of aggregate of the lithio sulfone with the lithioalkoxide product.

Several reports have appeared on the transannular cyclization that takes place upon metalation of medium ring homoallylic sulfoxides and sulfones (eq 1):[1]



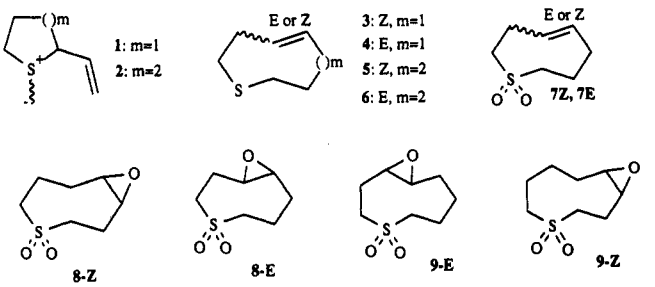
This unusual nucleophilic addition to an isolated double bond has a number of notable regio- and stereochemical features that make it an interesting case study of intramolecular reactivity: (1) it occurs with *E* but not with *Z* substrates; (2) it occurs rapidly only if a deficit of metalating agent is employed; (3) it is regiospecific with respect to the α-carbon (addition involving only the α-carbon farther from the double bond); (4) it is regiospecific also with respect to the double bond carbons; however, the direction of addition depends on the ring size (at C_4 in the 8-membered rings but at C_5 in both 9- and 10-membered rings); (5) the products formed may not be the thermodynamically more stable ones, i.e., the products are under kinetic control.

Epoxide ring openings by intramolecular nucleophilic (especially carbanionic) centers have been known for over 20 years[2] and, after Stork and co-workers' exploitation in synthesis,[3] have become a common methodology for the construction of functionalized alicyclic and heterocyclic systems.[4] Several reports have appeared focusing on the regiochemistry of ring opening in relation to various factors, such as the substitution pattern, the epoxide geometry, and the nature and mode of formation of the carbanionic moiety.[5] However, little attention has been paid to medium-sized monocyclic systems where the epoxide and carbanionic moieties are located transannularly and their interaction results in bicyclic systems.[6]

We have started such a study and in this paper give an account of the BuLi-promoted reaction of 8- and 9-membered *E* and *Z* γ-epoxy sulfones (**8-*E***, **8-*Z***, **9-*E***, and **9-*Z***) at low temperature and under conditions of full or partial metalation. The existence of two potential carbanionic centers (the α-SO_2 carbons) and the possibility of the H/Li exchange between them renders the regiochemistry problem an interestingly complicated one.

Results

Synthesis. The epoxy sulfones were prepared by exhaustive peracid oxidation of the corresponding alkene sulfides (**3–6**). These were generated by ring expansion



of cyclic 1-methyl-2-vinyl sulfonium salts (**1**, **2**) via 2,3-sigmatropic rearrangement of the methylides.[8] From the

(1) (a) Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Chem. Soc., Chem. Commun.* **1981**, 764–765; (b) *Ibid.* **1986**, 223–224; (c) *J. Org. Chem.* **1986**, *51*, 4880–4888; (d) *Ibid.* **1988**, *53*, 5689–5694. (e) Fava, A.; Bongini, A.; Cerè, V.; Paolucci, C.; Pollicino, S.; Sandri, E. *Pure Appl. Chem.* **1987**, *59*, 955–964.

(2) A number of references to earlier reports are collected under ref 1 of: Decesare, J. M.; Corbel, B.; Blount, J. F.; Durst, T. *Can. J. Chem.* **1981**, *59*, 1415–1424.

(3) (a) Stork, G.; Cama, L. D.; Coulson, D. R. *J. Am. Chem. Soc.* **1974**, *96*, 5268–5270. (b) Stork, G.; Cohen, J. F. *Ibid.* **1974**, *96*, 5270–5272.

(4) Reviews: (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323–2367. (b) Gorzynski Smith, J. *Synthesis* **1984**, 629–65.

(5) (a) Lallemand, J. Y.; Onanga, M. *Tetrahedron Lett.* **1975**, 585–588. (b) Durst, T.; Corbel, B. *J. Org. Chem.* **1976**, *41*, 3648–3650. (c) Gaoni, Y. *Tetrahedron Lett.* **1976**, 503–506. (d) Achini, R.; Oppolzer, W. *Ibid.* **1975**, 369–372. (e) Last, A. L.; Fretz, E. R.; Coates, R. M. *J. Org. Chem.* **1982**, *47*, 3211–3219. (f) Eisch, J. J.; Dua, S. K.; Behrooz, M. *Ibid.* **1985**, *50*, 3674–3676. (g) Cooke, M. P., Jr.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 3643–3646. (h) Babler, J. H. *J. Org. Chem.* **1987**, *52*, 4614–4616. (i) Babler, J. H.; Bauta, W. E. *Tetrahedron Lett.* **1984**, *25*, 4323–4324. (j) Benedetti, F.; Fabrissin, S.; Gianferrara, T.; Risaliti, A. *J. Chem. Soc., Chem. Commun.* **1987**, 406–407.

(6) However, a number of reports have appeared dealing with the electrophile-promoted intramolecular cyclization of medium-sized epoxy alkenes.[7]

(7) Shirama, H.; Hayano, K.; Arora, G. S.; Othsuka, T. *Chem. Lett.* **1982**, 1417–1418 and references cited therein.

(8) (a) Vedejs, E.; Hagen, J. P. *J. Am. Chem. Soc.* **1975**, *97*, 6878–6880. (b) Vedeja, E.; Arco, M. J.; Powell, P. D.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831–4837. (c) Cerè, V.; Pollicino, S.; Sandri, E.; Fava, A. *Ibid* **1978**, *43*, 4826–4831. (d) *J. Am. Chem. Soc.* **1978**, *100*, 1516–1520. (e) *J. Org. Chem.* **1979**, *44*, 4128–4135.

0022-3263/91/1956-4513$02.50/0

Table I. Product Distribution Resulting from Metalation of 8- and 9-Membered *E* and *Z* Epoxy Sulfones

run	substrate	C_n-Li[a] / C_2-Li	metalation method	temp (°C)	time (min)	conversion (%)	product distribution (%) from C_2-Li	product distribution (%) from C_n-Li
	8-*E*						**10**	**11**
1		9.0[c]	A	−70	30	44	92	8
2					120	60	80	20
3			B		(300)	88	100	0
4			A	−40	60	100	60	40
	9-*E*						**14**	**13**
5		>0.03[c]	A	−90	5	37	32	68
6				−70	30	84	64	36
7					120	100	70	30
8			B		(240)	100	20	80
9			A	−40	60	100	42	58
	8-*Z*						**12**	
10		1.9[c]	A	−90	5	3	100	
11		2.5		−70	10	18		
12					30	25		
13		2.4			40	32		
14		2.4			60	35		
15		1.7			120	49		
16		1.2			240	58		
17		1.0			480	64		
18			B		(300)	46		
19			A	−40	120	100		
	9-*Z*						**18** **19**	**17** **16**
20		2.6[c]	A	−70	10	35	22 11	46 21
21					900	87	11 16	49 24
22			*d*		300	90	3 0	72 25
23			A	−40	60	97	20 5	50 25
24					210	100	28 18	35 19
25			B		(300)	94	10 11	55 24

[a] Relative deuterium labeling at the positions of the unreacted epoxy sulfone resulting from MeOD quenching. [b] Mtehod A: 1.05–1.10 equiv of BuLi added at once. Method B: 3 × 0.3 equiv of BuLi added over a period of time (reported in parentheses in the time column). In the portionwise metalation experiments the conversion is relative to the metalating agent. [c] Approximate metalation fractions, C_n/C_2 (see ref 15): 8-*E*, 1.2; 9-*E*, 3; 8-*Z*, 1.8; 9-*Z*, 2.3. [d] Altogether 0.6 equiv of BuLI added at once; conversion relative to BuLi.

5-membered sulfonium ylide **1**, (*Z*)- and (*E*)-thiacyclooct-4-ene (**3** and **4**) are obtained as an 85/15 mixture.[8c] Their chromatographic separation turned out not to be feasible due to concomitant $E \rightarrow Z$ isomerization on the silica gel column. Since the separation of the epoxy sulfones mixture 8-*E* and 8-*Z* obtained by exhaustive oxidation also proved unsuccessful, it was found expedient to first oxidize the mixture of sulfides to an alkene sulfone mixture, 7-*E*–7-*Z*, which could be separated and eventually epoxidized.

Rearrangement of the 6-membered methylide **2** gave (*E*)-thiacyclonon-4-ene (**6**). The *Z* isomer **5**, which is not formed in any useful amount in the rearrangement, was obtained by photochemical isomerization of **6**.[9]

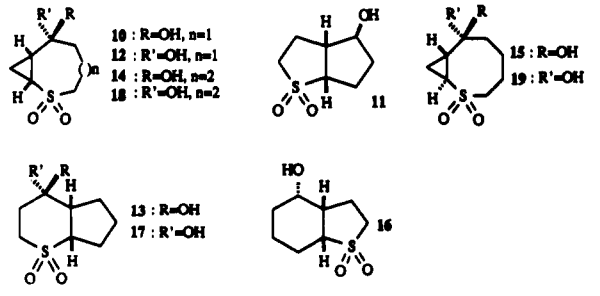
Metalation of Epoxy Sulfones. As shown in the following text, the product distribution depends on the temperature as well as on the mode of addition of the metalating agent. Essentially, two metalation methods were used. In the first (A in Table I), a 5–10% excess of BuLi was added at once to a vigorously stirred THF solution of the substrate cooled at −90 °C. The reaction vessel was then transferred to a thermostated bath for a specified length of time, quenched with methanolic HCl, and worked up. In the second method (B in Table I), a 5–10% deficit of BuLi was used, the metalating agent being added portionwise (normally 3 × 0.3 equiv) at specified time intervals. Other metalation modes are referred to specifically in Table I.

(9) In ref 8c we reported (*E*)-thiacyclonon-4-ene was formed along with a minor amount (ca. 4%, not isolated) of a compound that was tentatively identified as (*Z*)-thiacyclonon-4-ene on the basis of its ^{13}C shieldings. It now appears the assignment was incorrect. The minor component might have been a positional isomer.

Products. The structure of the products formed in the transannular cyclizations of the 8- and 9-membered *E* and *Z* epoxy sulfones are shown in the following text (compounds **10**–**19**). The product distributions obtained under various conditions of temperature, time, and metalation mode are reported in Table I.

For structural assignments, the following general criteria were applied:

(1) For compounds **10**, **12**, **14**, **15**, **18**, and **19** the presence of a cyclopropyl ring is evinced by the appearance in the ^{13}C NMR spectrum of a strongly shielded triplet (4–12 ppm) characterized by a $^1J_{CH}$ on the order of 160–170 Hz.



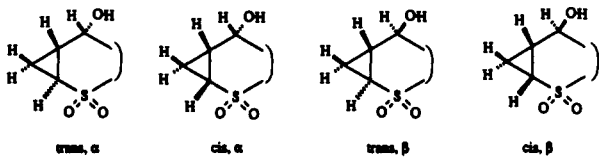
(2) The α or β configuration of the OH group was assigned on the basis of the stereochemistry of the starting epoxide, in turn related to the *Z* or *E* stereochemistry of the original double bond, assuming epoxide ring opening occurred with configurational inversion. However, for the bicyclic compounds containing a cyclopropyl moiety, two criteria for confirming the α- or β-OH structure could be applied. The first is based on the chemical shift of the proton geminal to OH: due to the cyclopropyl ring current this proton is expected to be strongly shielded in the β

Table II. Relevant ^{13}C and ^{1}H NMR Spectral Data of [n.1.0] Bicyclic Alcohols from Transannular Cyclization of Epoxy Sulfones

compd	$C_{8(9)}$	OCH[a]	J C_1H^b Hz	OH	ring junct
12	9.70	4.40	8.3, 8.3, 6.0		cis
10	12.60	3.52	8.3, 8.3, 5.0	β	cis
18	5.10	4.30	8.2, 8.2, 6.7		cis
14	7.60	4.00	8.2, 8.2, 5.7	β	cis
19	4.20	4.20	8.5, 5.5, 5.5		trans
15	7.10	3.30	8.5, 5.5, 5.5	β	trans

[a] Proton geminal to OH. [b] α bridgehead proton.

Chart I

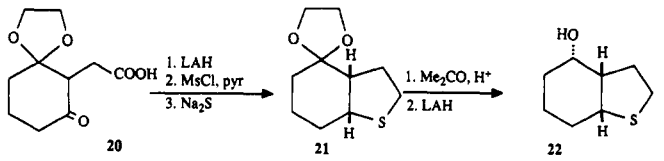


relative to the α series.[10] For the 10–12, 14–18, and 15–19 pairs the shieldings of the β members are 0.88, 0.30, and 0.90 ppm, respectively (Table II), confirming the assumed stereochemistry. The relatively small differential shielding observed for the 14–18 pair is due to the proton of 14 being much less shielded than in ought to be. An explanation for this behavior is suggested by the geometry of 14 as computed by molecular mechanics methods: the proton in question is compressed against the endo (or α) sulfone oxygen at a distance of only 2.40 Å, much shorter than the sum of the van der Waals radii. This steric compression may well cause a deshielding such as to largely offset the cyclopropyl ring current.[11] The second criterion is based on the differential ^{13}C shielding of the cyclopropyl methylene carbon (C_8 and C_9 in the [5.1.0] and [6.1.0] bicyclics, respectively). This carbon has a γ-gauche and γ-anti relationship with the hydroxyl oxygen in the α and β epimers, respectively, and is therefore expected to be more shielded in the former.[12] Applied to the 10–12, 14–18, and 15–19 α–β pairs (Table II), this criterion confirms the first member of each pair to be the β epimer.

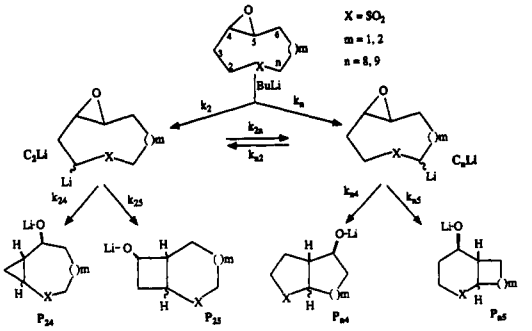
(3) For compounds featuring a cyclopropyl moiety, the cis or trans stereochemistry of the ring junction can be readily gauged from the vicinal couplings exhibited by either of the bridgehead hydrogens, based on the criterion that, for any given cyclopropyl ring system, cis vicinal couplings are always larger (8–12 Hz) than trans ones (5–8 Hz).[13,5e] Considering the HC_1SO_2 proton, which is coupled only to cyclopropyl protons and can be easily analyzed by homonuclear decoupling, it is immediately seen (Chart I) that it will feature two cis and one trans coupling in the cis isomers, but two trans and one cis coupling in the trans isomers. From the J values in Table II, compounds 10, 12, 14, and 18 are compatible with a cis and 15 and 19 with a trans ring junction.

(4) Concerning products 13 and 17, their ring structure was established through dehydroxylation, via the Barton procedure,[14] to *cis*-2-thiabicyclo[4.3.0]nonane 2,2-dioxide identical with that prepared from authentic *cis*-2-thiabicyclo[4.3.0]nonane.[1c]

Scheme I



Scheme II



(5) Compound 16 was identified by comparison with a sample prepared through an independent synthesis starting from ethyl (1,3-dioxocyclohexyl)acetate (Scheme I). The mono ketal 20, obtained by acetalization of the dione, was reduced by LAH to the diol, which, by reaction with mesyl chloride, gave a mixture of epimeric dimesylates. This was reacted as such with sodium sulfide in ethanol to give the cis cyclic sulfide 21 in modest yield. Necessarily, 21 must have arisen from the trans dimesylate; apparently, the cis isomer resisted cyclization and was largely lost in the course of the reaction via elimination and intermolecular nucleophilic substitution in a manner analogous to that previously noted for a closely related system.[1c] The dioxolane sulfide 21 was deprotected and the resulting ketone reduced with LAH. As expected, the hydride reagent attacked the carbonyl carbon preferentially from the less hindered side yielding the endo alcohol 22 as the highly predominant epimer (endo:exo ≃ 20), which gave 16 by *m*-CPBA oxidation.

Discussion

The results of this study can be viewed in terms of the following mechanistic picture (Scheme II). Irreversible metalation of the epoxy sulfone substrate gives rise to two α-metalated regioisomers (C_2Li and C_nLi), which then react intramolecularly to form their respective hydroxy sulfone products. With the restriction that epoxide ring opening occurs exclusively with configurational inversion, a maximum of eight products can be formed, four diastereomeric pairs of regioisomers: cis and trans P_{24}, P_{25}, P_{n4}, and P_{n5} (Scheme II, depicting a *E* epoxide).

The nature of the products and their proportions depend on various factors: (i) the ratio in which C_2Li and C_nLi are formed, k_2/k_n; (ii) their individual reactivities toward transannular cyclization (k_{24}, k_{25}, k_{n4}, k_{n5}); (iii) their rate of equilibration, $k_{2n} + k_{n2}$, relative to the rates of transannular cyclization; (iv) the rate of cis/trans product epimerization (not considered in Scheme II) relative to their rate of formation.

The third point is crucial and appears to be largely responsible for the change of product distribution with changing the metalation mode (Table I). The case of metalated 9-*E* provides a clear illustration. Two products are formed, 13 and 14, arising from C_9Li and C_2Li, respectively. At −70 °C the 14/13 product ratio is 70:30 or 20:80 according to whether metalation was carried out at once or portionwise, respectively (Table I, runs 7 and 8). A behavior such as this is consistent with the following:

(10) Gassman, P. G.; Williams, E. A.; Williams, F. J. *J. Am. Chem. Soc.* **1971**, *93*, 5199–5208 and references cited therein.
(11) Jackman, L. M.; Sternell, S. *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd Ed.; Pergamon Press: Oxford, 1972; p 71–72.
(12) Wehrli, F. W.; Wirthlin, T. *Interpretation of C-13 NMR Spectra*; Heyden & Son: London, 1976; p 37 ff.
(13) Reference 11, p 286 ff.
(14) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574–1585.

(i) the two regioisomers, C_2Li and C_9Li do not interconvert substantially under conditions of full metalation while they do in the presence of unmetalated substrate; (ii) metalation of 9-*E* occurs preferentially at C_2; (iii) cyclization occurs faster from C_9Li than from C_2Li. The first is a reasonable hypothesis since the unmetalated substrate may well catalyze the interconversion of the α-metalated regioisomers via an intermolecular H/Li exchange mechanism:

$$LiC_2\text{–}SO_2\text{–}C_9H + HC_2\text{–}SO_2\text{–}C_9H^* \rightleftarrows {}^*HC_2\text{–}SO_2\text{–}C_9H + HC_2\text{–}SO_2\text{–}C_9Li$$

That at −70 °C under conditions of complete metalation the $C_2Li \rightleftarrows C_9Li$ interconversion is slow relative to cyclization is clearly evinced from runs 5 and 6 (Table I). In run 5, carried out at −90 °C for 5 min, the conversion was 37% (25% **13** and 12% **14**). MeOD quenching of the reaction mixture showed the unreacted epoxy sulfone was fully monodeuterated at C_2, while *no* deuterium was detectable (<3%) at C_9. Apparently, already after 5 min at −90 °C, all of the C_9Li regioisomer formed on metalation had reacted, while C_2Li, although formed preferentially by a factor of ~3, had reacted minimally. The evolution of products with time (runs 6 and 7) confirms transmetalation is indeed slow (relative to cyclization).

Although the other substrates display peculiarities of their own, all fit a picture similar to that just described. The differences in behavior arise from variations in the C_2/C_n metalation fractions (Table I, footnote c) and, more importantly, in the relative reactivity of the α-metalated regioisomers toward cyclization. Thus, C_2Li appears to be the more reactive regioisomer for both 8-membered substrates (unlike 9-*E*) so that the products arise from C_2Li entirely (8-*Z*) or very largely (8-*E*). On the other hand, for 9-*Z* products arise more comparably from either regioisomer.

In addition to the above factors, the temperature appears to play an important role. Although, as it could have been expected, the regioselectivity tends to decrease with increasing temperature (compare runs 4 and 9 with 1 and 6, respectively), the picture is not that simple. The most striking case is that of 8-*Z*: while at −40 °C the reaction goes to completion without problems (run 19), at −70 °C the reaction, after a rapid start, drastically slows down and seems to approach a limit of ca. 65–70% conversion. The circumstance that, under all conditions, only one product is formed, **10**, prompted us to study the reaction of 8-*Z* in greater detail. Thus, not only was the conversion of 8-*Z* to **10** followed more closely, but most of the runs were quenched with MeOD and the distribution of the D-label on the unreacted epoxy sulfone determined by quantitative ^{13}C NMR analysis (Table I). The zero-time distribution of the D-label indicates that metalation takes place more favorably at C_8 by a factor of ca. 2.2.[15] Since C_8Li is the non-product-forming regioisomer, the rate law expected is that of a species, C_8Li, that reversibly gives an intermediate, C_2Li, which irreversibly ($k_{P2} = 0$) is transformed to product, P (the O–Li derivative of **10**):

$$C_8Li \underset{k_{28}}{\overset{k_{82}}{\rightleftarrows}} C_2Li \underset{k_{P2}}{\overset{k_{2P}}{\rightleftarrows}} P \qquad (2)$$

Our kinetic data, admittedly very rough, do not support this mechanistic picture, but fit the rate law for a system tending toward an equilibrium state, one where the final product P reverts back ($k_{P2} > 0$) to some extent to the intermediate. Kinetic analysis of the data (runs 10–17, Table I) furnished the following values for the rate constants (10^{-4} s^{-1}) of eq 2: $k_{82} = 1.7$; $k_{28} = 1.6$; $k_{2P}P = 6.0$; $k_{P2} = 1.8$. The data of runs 8–15 are plotted in Figure 1 together with the curves calculated from the previous constants. From the previous values an overall equilibrium constant, $P/(C_8Li + C_2Li)$, of about 1.7 is deduced corresponding to 63% conversion. Our longest run (8 h, run 17) gave a 64% conversion, quite close to the calculated equilibrium value. Unfortunately, the time required to prove whether a steady equilibrium situation was actually reached is too long for the system to remain stable: there is evidence of material loss (3 and 6% after 4 and 8 h, respectively, probably due to reaction of the α-lithio sulfone with solvent. On the other hand, the obvious test for reversibility, checking whether *isolated* 10-Li does revert back to 8-*Z*, failed. In THF the lithio alkoxide from **10** immediately precipitated out as BuLi was added and remained intact after many hours at −70 °C, as well as at higher temperatures. It must be concluded that if an equilibrium was actually reached in the reaction of metalated 8-*Z* at −70 °C the product species involved was not simply the Li salt of **10** but some complex of it with the metalated sulfone (perhaps a 2:1 complex). At the present time, there is little more one can say except that, although the previous conclusions are largely speculative, the results are suggestive of "strange" phenomena occuring at low temperature. It may be pertinent in this context to note that while at −70 °C the reaction mixtures remain clear throughout, at −40 °C or higher they become progressively cloudy. A precipitate is eventually formed, more rapidly at the higher temperatures. While this may well be a purely physical phenomenon, the possibility cannot be discarded that if reflects an intimate interaction between the yet unreacted lithio sulfone and the lithioalkoxide product. Interactions of this type are well-known and have been extensively investigated, in particular by Seebach, Dunitz, and their groups,[16,17] and may be responsible of dramatic reactivity changes of the "carbanionic" moiety of the aggregate.[18]

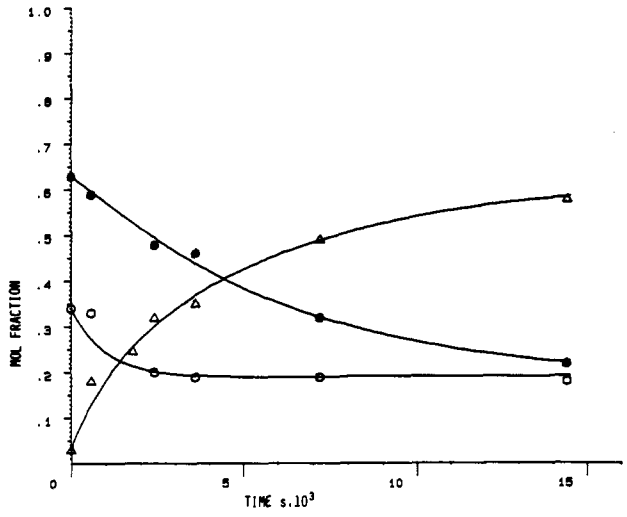


Figure 1. Kinetics of transannular cyclization of 8-*Z*: ●, C_8Li; ○, C_2Li; △, P (see text, eq 2).

(15) On the basis of the assumption that transmetalation is negligible in the earliest reaction stage. To the extent that this is a good approximation the product distribution can be combined with the actual C_nLi/C_2Li ratio (as measured by the D-label distribution) to give the zero-time distribution of the α-metalated regioisomers.

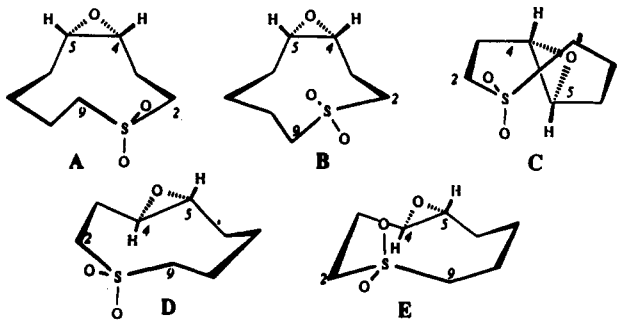
(16) A fascinating account of the structure and reactivity of organolithium aggregates is given by: Seebach, D. *Angew Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.

(17) The structure of lithium derivatives of organosulfur compounds is reviewed by: Boche, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *29*, 277–297.

(18) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805–1810. (b) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *Ibid.* **1985**, *107*, 1810–1815.

The analytical complexities arising from competitive formation of four products, 16–19, from 9-*Z* discouraged detailed investigations such as that carried out for 8-*Z*. 9-*Z* is peculiar in so far as attack of C_9Li occurs at both epoxidic carbons. The product ratio, 16/17 ≃ 0.45, is independent of conditions, consistent with irreversible partitioning of C_9Li between the two regioisomeric courses. In contrast, the product ratio from C_2Li, 18/19, is highly variable. However, 18 and 19 are not regioisomers, but epimers at C_1, and their distribution may not be the kinetic one but be the result of base-catalyzed epimerization of 18. The proportion of 19, the trans epimer, is in fact larger in the longer runs (compare runs 20 and 23 with 21 and 24, respectively). Why would 18 isomerize under the reaction conditions, while 16 and 17, which also have a cis ring junction and are formed concurrently, remain stable is accountable for in terms of the high kinetic acidity of the α bridgehead proton of 18, bound, as it is, to a cyclopropyl ring. For cyclopropyl isopropyl sulfone the kinetic acidity of the cyclopropyl proton is over 200 times greater than that of the isopropyl proton.[19] If a similar factor applies to the present case, it is understandable that 16 and 17 may not epimerize appreciably while 18 does.

Concerning the ring junction, our cyclizations with perhaps the one exception just discussed, are cis stereospecific, independent of the relative stability of the cis or trans product epimers.[20] For kinetically controlled



products, the stereochemistry is determined by the relative orientation of the transannular fragments centered around the reacting sites, the carbanionic and the epoxidic carbons. Consider conformation A, which is representative of a family of conformations of compound 9-*Z* (see supplementary material). (Epoxy sulfones and their lithio derivatives will be assumed to have essentially the same ring conformations.) With respect to the transannular cyclization of the C_9-metalated regioisomer, the relevant fragments are S–C_9–C_8 on one side and C_4–C_5–C_6 or C_5–C_4–C_3 on the other. It can be appreciated on inspection that bond formation between C_9 and C_4 or C_5 will result in a cis junction in either case. The result is similar for the reaction of the C_2-metalated regioisomer where the relevant fragments are S–C_2–C_3 and C_3–C_4–C_5. According to our molecular mechanics calculations, there is at least one conformation of 9-*Z*, B, of slightly greater energy than A, whose geometry suggests the opposite stereochemical outcome for what concerns cyclizations from C_9. Apparently, cyclization leading to [4.3.0] bicyclic products does not appreciably occur from this conformer type. This is reasonable since not only are the distances of C_9 from C_4 and C_5 considerably greater than in A (3.6 against 3.2 Å) but stereoelectronics are also unfavorable: the C_9–C_5–O and C_9–C_4–O angles are appreciably smaller in B than in A (120° against 131°). This type of analysis equally applies to 8-*Z*.

Coming to the *E* epoxy sulfones, a cis [3.3.0] product is expected from a conformation (C) of 8-*E* derived from the "twist" structure of its alkene sulfide precursor,[22] similar to that of *E* cyclooctene.[23] For 9-*E*, however, the picture is different. From molecular mechanics calculations, two conformers, D and E, appear to be substantially populated (~15 and 85%, respectively). It can be seen immediately that attachment of C_9 to C_4 or C_5 would lead to cis or, respectively, trans junction in the case of conformer D, while the opposite stereochemical outcome would result in the case of E. That only one product is formed, 14, cis joined, indicates that of the four courses available for transannular cyclization of C_9Li only one is actually followed, that involving attack to C_5 from the D conformer. A clue as to why this course is preferred can perhaps be found in the conformers geometries. In D the angles of approach C_9–C_5–O and C_9–C_4–O are 138° and 129°, respectively, while the C_9–C_5 and C_9–C_4 distances are 3.12 and 3.32 Å, respectively. In E the angles are C_9–C_5–O, 128°, C_9–C_4–O, 136°, and the distances are C_9–C_4, 3.21 Å, and C_9–C_5, 3.33 Å. To the extent that the rate of an intramolecular nucleophilic reaction will be faster the shorter the distance between the reacting centers and the smaller the deviation from 180° alignment, the previous values indicate the more favorable course to be that where C_9 attacks C_5 from conformer D. It is remarkable that no product is formed resulting from bond formation C_9 to C_4 (from conformer E) in spite of the not too unfavorable geometry and of the circumstance that the corresponding product (*cis*-7-thia-2β-hydroxybicyclo[4.3.0]nonane 7,7-dioxide) is calculated to be more stable than 14, the product that is actually formed, by some 4 kcal/mol. Apparently, the reaction occurs entirely via conformer D, via rapid D ⇄ E equilibrium, even though E may be the more populated conformer.

Experimental Section

General Data. Unless otherwise specified, ^1H NMR spectra were recorded at 200 MHz. ^{13}C NMR spectra were obtained at 20 or 50.3 MHz. Single-frequency off-resonance spectra were obtained by irradiation at δ~4 in the proton spectrum. Proton and ^{13}C NMR shifts, unless otherwise specified, refer to $CDCl_3$ solvent. The ^{13}C spectral assignments are based on the following: (i) off-resonance decoupling; (ii) shielding effects of substituents, in particular oxygenated ones; (iii) regiospecific deuterium labeling; (iv) deuterium isotope shifts experienced by β carbons. Where two or more ^{13}C assignments are given in parentheses, they are interchangeable. For the quantitative ^{13}C NMR analysis, a pulse delay of 6 s was found to be adequate. The ^1H spectral assignments of bicyclic compounds containing a cyclopropyl moiety (10, 12, 14, 15, 18, and 19) were secured by means of two-dimensional ^{13}C–^1H chemical shift correlation. Geometries and relative energies of molecules to which reference is made throughout the paper were computed by molecular mechanics using the MMX force field.[24] Solvents were obtained dry as follows: CH_2Cl_2 and toluene

(19) Kirmse, W.; Mrotzeck, U. *J. Chem. Soc., Chem. Commun.* **1987**, 709–710.

(20) For [5.1.0] and [3.3.0] bicyclic hydrocarbons the cis are known to be more stable than the trans forms by several kcal/mol.[21] This is most likely the case of our corresponding hydroxy sulfones (10, 12, and 11). Indeed these compounds remained intact on treatment with base under conditions (see Experimental Section compound 16) where all the other bicyclic hydroxy sulfone products did isomerize, at least to some extent.[22]

(21) Wiberg, K. B.; Lupton, E. C., Jr.; Wasserman, D. J.; de Meijere, A.; Kass, S. R. *J. Am. Chem. Soc.* **1984**, *106*, 1740–1744.

(22) The epimerization experiments were not followed as a function of time. Thus, the observed cis/trans ratios (see the Experimental Section at the pertinent cis isomer) may not correspond to equilibrium values.

(23) Calderoni, C.; Cerè, V.; Pollicino, S.; Sandri, S.; Fava, A. *J. Org. Chem.* **1980**, *45*, 2641–2649.

(24) Purchased from Serena Software, P.O. Box 3076, Bloomington, IN 47402-3076.

were refluxed over and distilled from CaH_2; THF was distilled from benzophenone ketyl. Melting points are uncorrected. The trivial α and β notations are used to indicate the hydroxy group in the bicyclic compounds to be on the opposite or on the same side, respectively, of the H atom at the nearest bridgehead.

(*Z*)-Thiacyclonon-4-ene (5). A solution of (*E*)-thiacyclonon-4-ene[9] in hexane (0.7 g in 60 mL) under N_2 was irradiated (125-W high-pressure quartz mercury vapor lamp) without stirring, the $E \rightarrow Z$ conversion being monitored by GLC. A maximum Z/E ratio of ~50 was reached in 5 h at rt. The residue after solvent evaporation was distilled, bp 60 °C (1 mm), to give the title compound (0.62 g, 90%) containing ~2% of the *E* isomer. ^1H NMR: δ 5.60 (m, 2 H; resolved by irradiation at δ 2.60 into an AB quartet, $\Delta\nu$ = 18.4 Hz, J = 10.7 Hz, *cis*-HC=CH); 2.55 (m, 8 H); 1.68 (m, 4 H). ^{13}C NMR: δ 132.5; 129.0 (C_4, C_5); 30.7; 30.6; 29.0; 26.6; 26.1; 25.8. Anal. Calcd for $C_8H_{14}S$: C, 67.54; H, 9.92; S, 22.53. Found: C, 67.68; H, 10.01; S, 22.31.

(*E*)- and (*Z*)-Thiacyclooct-4-ene 1,1-Dioxide (7-*E* and 7-*Z*). The 85/15 mixture of sulfides **3** and **4** (4.5 g, 35 mmol) obtained by ring expansion of sulfonium ylide **18c** was partially separated by selective extraction with 20% aqueous $AgNO_3$.[1c] The enriched 80/20 E/Z sulfide mixture (0.7 g, 5.5 mmol) was oxidized with 85% *m*-CPBA in CH_2Cl_2 (2.23 g, 2 equiv in 30 mL) for 5 h at rt. After the mixture was cooled to 0 °C, *m*-chlorobenzoic acid was filtered off and the filtrate washed sequentially with 10% Na_2CO_3 and H_2O and dried over $CaSO_4$. The CH_2Cl_2 layer was evaporated to give a mixture of alkene sulfones that could be separated by flash chromatography (silica, ethyl ether/MeOH = 100/3). The more slowly eluted material was 7-*E*; crystallized from hexane/benzene (0.34 g, 60%), mp 95–96 °C.[25] ^1H NMR (100 MHz): δ 5.72 (m, 2 H, olefinic H's); 3.51 and 3.12 (m's, 2 H each, CH_2SCH_2); 2.32 (m, 6 H). Anal. Calcd for $C_7H_{12}SO_2$: C, 52.47; H, 7.55; S, 20.01. Found: C, 52.64; H, 7.61; S, 19.96. The ^{13}C NMR spectrum was identical with that previously reported.[26] The material eluted first was 7-*Z* (100 mg, 71%), identical with that previously reported.[26]

(*E*)-4,5-Epoxy-1-thiacyclooctane 1,1-Dioxide (8-*E*). To a CH_2Cl_2 solution of alkene sulfone 7-*E* (1.6 g, 10 mmol in 70 mL) was added 85% *m*-CPBA (2.23 g, 11 equiv) and the mixture stirred for 1 h at 40 °C. Workup as for 7-*E* above gave 8-*E*; crystallized from hexane/benzee (1.6 g, 90%), mp 118–119 °C. ^{13}C NMR (CD_3OD): δ 59.7; 57.4 (C_4, C_5); 59.3 (C_8); 56.1 (C_2); 30.9 (C_6); 29.0 (C_3); 22.8 (C_7). ^1H NMR (60 MHz): δ 3.40 (m, 4 H, CH_2SCH_2); 2.83 (m, 2 H, HCOCH); 2.03 (m, 5 H); 1.03 (m, 1 H). Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 48.09; H, 6.91; S, 18.12.

(*Z*)-4,5-Epoxy-1-thiacyclooctane 1,1-Dioxide (8-*Z*). Sulfide **3**[8c] (1.30 g, 10 mmol) dissolved in CH_2Cl_2 (200 mL) was treated portionwise with 85% *m*-CPBA (6.42 g, 32 equiv) at 0 °C under stirring. After the mildly exothermic reaction had subsided, the temperature was allowed to raise to 25 °C, with stirring being continued for 6 h. Workup as for 7-*E* gave (crystallized from hexane/benzene) 1.3 g (80%) of the title compound, mp 148–149 °C. ^{13}C NMR: δ 54.1; 53.4 (C_4, C_5); 53.8 (C_8); 52.3 (C_2); 23.5 (C_6); 21.7 (C_3); 19.5 (C_7). ^1H NMR (60 MHz): δ 3.22 (6 H, m, CH_2SCH_2 and HCOCH); 1.90 (m, 6 H). Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.53; H, 6.95; S, 18.27.

(*E*)- (9-*E*) and (*Z*)-4,5-epoxy-1-thiacyclononane 1,1-dioxide (9-*Z*) were prepared from sulfides **5** and **6**, respectively, by the procedure described previously for 8-*Z*. 9-*E*: crystallized from hexane/benzene (90%)/mp 81–82 °C. ^{13}C NMR: δ 58.8; 58.2 (C_4, C_5); 56.7 (C_9); 52.5 (C_2); 30.7 (C_6); 25.6 (C_3); 22.7; 20.2 (C_7, C_8). ^1H NMR (60 MHz): δ 3.24 (m, 4 H, CH_2SCH_2); 2.79 (m, 2 H, HCOCH); 2.60–0.60 (m's, 8 H overall). Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.62; H, 7.61; S, 16.96.

(9-*Z*): crystallized from hexane/benzene 90%, mp 120–121 °C. ^{13}C NMR: δ 56.2; 55.7 (C_4, C_5); 48.7 (C_9); 48.3 (C_2); 23.3; 22.3; 20.2; 19.1 (C_3, C_6, C_7, C_8). ^1H NMR (60 MHz): δ 3.03 (m, 6 H, CH_2SCH_2 and HCOCH); 1.80 (m, 8 H). Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.65; H, 7.48; S, 16.79.

Transannular Cyclization of Epoxy Sulfones. To minimize local heat effects in the full metalation experiments (method A, Table I), the required epoxy sulfone (1 mmol) dissolved in THF (10 mL) was cooled at a temperature 20 °C lower than that selected for reaction before adding BuLi (1.05 mmol, 1.65 M in hexane) and transferred to a thermostated bath (±2 °C) for a specified length of time. (In spite of these precautions, the zero-time reaction percent turned out to be quite variable.) No precooling was done in the experiments effected under portionwise metalation (Method B, Table I). The reaction mixture was quenched with MeOH and neutralized with methanolic HCl (to avoid possible MeOLi-catalyzed product epimerization). The residue after solvent evaporation was extracted with CH_2Cl_2 and the dried extract evaporated. This material was analyzed by GLC and ^{13}C NMR spectroscopy. The distribution of products from the four epoxy sulfones investigated here are reported in Table I.

Experiments were also performed where the reaction mixture was quenched with MeOD and the unreacted epoxy sulfone was analyzed by quantitative ^{13}C NMR spectroscopy. The extent of deuteration at the α positions, assumed to represent the degree of metalation, was evaluated from the integrated intensities of the signals of the carbons β to the sulfone function. These resonances are split in two signals separated by 0.1 ppm whose relative intensity (high field vs low field) reflects the relative deuteration of the adjacent α carbon. The thus obtained deuteration ratios agree qualitatively with those that can be derived from the intensity decrease of the carbon resonances themselves. Although the latter are not amenable to accurate measurement, due to superposition of the CH singlet to the CD triplet, their intensities are nevertheless useful for telling which α and β carbons are which. The product distributions obtained from all the epoxy sulfone substrates under various temperature and metalation conditions are collected in Table I.

***cis*-2-Thiabicyclo[5.1.0]octan-6β-ol 2,2-Dioxide (10).** Method B, run 3, 0.14 g, 79%, mp 121–122 °C (benzene). ^1H NMR (acetone-d_6): δ 3.52 (m, 1 H, C_6H); 3.30 and 3.10 (m's, 1 H each, C_3H_2); 3.05 (m, 1 H, OH); 2.60 (ddd, J = 8.3, 8.3, 5.0 Hz, 1 H, C_1H); 2.05–1.65 (m, 4 H, C_5H_2 and C_4H_2); 1.40 (m, 3 H, C_8H_2 and C_7H). ^{13}C NMR: δ 72.2 (C_6); 55.4 (C_3); 36.2 (C_5); 33.3 (C_1); 23.5 (C_7); 20.8 (C_4); 12.6 (C_8). Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 48.10; H, 6.91; S, 18.06.

By use of method A (Table I, run 1) a second product was formed, **11**, along with **10**, whose ^{13}C NMR spectral properties, compared to those of the parent ring sulfone,[28] indicate the ***cis*-2-thiabicyclo[3.3.0]octan-6β-ol 1,1-dioxide** structure. ^{13}C **NMR:** δ 78.8 (C_6); 62.8 (C_1); 52.0 (C_3); 51.4 (C_5); 34.5 (C_7); 25.1; 24.9 (C_4 and C_8). Due to its minute amount, the product could not be separated and no further confirmatory structural evidence was obtained for this compound.

***cis*-2-Thiabicyclo[5.1.0]octan-6α-ol 2,2-dioxide (12),** from run 19, mp 96–97 °C (benzene), 0.16 g, 91%. ^1H NMR (acetone-d_6): δ 4.40 (m, 1 H, C_6H); 3.50 and 3.20 (m's, 1 H each, C_3H_2); 2.95 (s, 1 H, OH); 2.65 (ddd, J = 8.3, 8.3, 6.0 Hz, 1 H, C_1H); 2.2–1.6 (m, superimposed to the solvent resonance). (In $CDCl_3$: δ 2.3–1.3 (m, 6 H); 1.38 (m, 1 H).) ^{13}C NMR: δ 66.7 (C_6); 57.0 (C_3); 37.0 (C_1); 33.0 (C_5); 22.4 (C_7); 16.1 (C_4); 9.7 (C_8). Anal. Calcd for $C_7H_{12}SO_3$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.22; H, 6.91; S, 17.98.

Alcohol **12** was converted into its epimer alcohol **10** by configurational inversion of the hydroxylic functionality via the Mitsonobu procedure.[29] To a THF solution of **12** (0.4 g, 2.27 mmol, in 30 mL) was added PPh_3 (1.19 g, 4.54 mmol) followed by PhCOOH (0.553 g, 4.54 mmol) and, after cooling to 10 °C, by DEAD (0.79 g, 4.54 mmol in 5 mL of THF). The mixture was stirred for 15 h at rt, and after concentration in vacuo, the residue was subjected to flash chromatography (silica gel, ethyl ether/methanol = 100/3). The material eluted last was the benzoic ester

(25) This material has been previously reported,[26] though in impure form due to the oxidation procedure (aqueous $NaIO_4$) inducing concomitant E–Z isomerization.

(26) Cerè, V.; Guenzi, A.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* **1980**, *45*, 261–264.

(27) Reference 12, p 107 ff.

(28) Obtained by oxidation of authentic sulfoxide.[1c] The ^{13}C NMR spectrum of *cis*-2-thiabicyclo[3.3.0]octane 2,2-dioxide is: δ 62.5 (C_1); 50.1 (C_3); 42.0 (C_6); 27.3 (C_8); 25.6 (two signals, C_4 and C_7).

(29) (a) Mitsonobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427–34. (b) Mitsonobu, O. *Synthesis* **1981**, 1–28.

(30) Stetter, H.; Dierichs, W. *Chem. Ber.* **1952**, *85*, 61–72.

of **10** (0.54 g, 85%, mp 163–164 °C, hexane/benzene), which, after saponification (KOH, THF/MeOH/H_2O; room temperature, 4 h) and crystallization, gave pure **10** (0.245 g, 72%). The benzoate had the following ^{13}C NMR spectrum: δ 165.0 (C=O); 132.8; 129.8; 129.3; 128.1 (Ph ring C's); 75.1 (C_6); 55.5 (C_3); 34.0; 33.6 (C_1, C_5); 21.5; 21.0 (C_4, C_7); 13.5 (C_8).

***cis*-2-Thiabicyclo[4.3.0]nonan-5β-ol 2,2-Dioxide (13) and Trimethylsilyl Ether (13a).** The 4:1 mixture of **13** and **14** from run 8 (Table I; (1 g, 5.3 mmol) was flash chromatographed (silica gel, ethyl acetate/ethyl ether = 100/40) to give **13** (0.60 g, 75%, first eluted material) as a viscous oil. ^{13}C NMR: δ 64.1 (C_5); 60.2 (C_1); 49.5 (C_6); 44.8 (C_3); 28.0; 26.7; 23.2; 21.5 (C_4, C_7, C_8, C_9). ^1H NMR: δ 3.78 (br s, 1 H, HCO); 3.50 (s, 1 H, OH); 3.32 (m, 2 H) and 2.80 (m, 1 H, H_2CSCH); 2.50–1.50 (m, 9 H). The alcohol was converted to the *O*-trimethylsilyl derivative **13a**, mp 51–52 °C (hexane). ^{13}C NMR: δ 65.1 (C_5); 60.1 (C_1); 45.1 (C_3); 28.3; 26.6; 22.9; 22.1 (C_4, C_7, C_8, C_9; –0.2 ($SiMe_3$). ^1H NMR: δ 3.90 (m, 1 H, HCO); 3.42 (m, 2 H) and 2.82 (m, 1 H, H_2CSCH); (m, 3 H); 2.08–1.60 (m, 6 H); 0.10 (s, 9 H, $SiMe_3$). The structure of product **13** was confirmed by transforming it into the known 2-thiabicyclo[4.3.0]nonane 1,1-dioxide by deoxygenation via the Barton-McCombie procedure (see the following text).

***cis*-2-Thiabicyclo[6.1.0]nonan-7β-ol 2,2-Dioxide (14).** The 7:3 mixture of **14** and **13** from run 7 (1 g, 5.3 mmol) was chromatographed as in the previous text to give **14** as the second eluted material (0.45 g, 64%), mp 119–120 °C (hexane). ^1H NMR (acetone-d_6): δ 4.00 (m, 1 H, C_7H); 3.35 (m, 1 H, C_3H); 3.10–2.90 (m, 2 H overall, C_3H and OH); 2.72 (ddd, J = 8.2, 8.2, 5.7 Hz, 1 H, C_1H); 2.20–1.30 (m's superimposed on solvent resonance). (In $CDCl_3$: δ 2.10–1.75 (m, 3 H); 1.65–1.20 (m, 6 H).) ^{13}C NMR: 67.1 (C_7); 57.2 C_3); 36.0 C_6); 35.8 (C_1); 24.6 (C_8); 23.2 (C_4); 20.3 (C_5); 7.6 (C_9). Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 51.01; H, 7.56; S, 17.02.

***trans*-2-Thiabicyclo[6.1.0]nonan-7β-ol 1,1-Dioxide (15).** Compound **14** (0.475 g, 2.5 mmol) in THF (45 mL) was treated with BuLi 1.5 M in hexane (2.25 mL, 3.4 mmol). The cloudy mixture was let to stand 4 h at 40 °C and quenched with aqueous HCl. The residue after solvent evaporation was a 60/40 cis/trans epimeric mixture, which was twice chromatographed (silica gel, ethyl ether/metanol = 100/6); the more slowly eluted material was twice crystallized (benzene) to give **15** (70 mg, 37%), mp 112–113 °C. ^1H NMR (acetone-d_6): δ 3.42–3.12 (m, 3 H overall, C_7H and C_3H_2); 3.08 (d, J = 6.5 Hz, 1 H, OH); 2.55 (ddd, J = 8.5, 5.5, 5.5 Hz, C_1H); 2.45–2.10 (m superimposed on solvent resonance); 1.95–1.55 (m, 3 H); 1.55, 1.20 (m's, 1 H each, C_9H_2). ^{13}C NMR: δ 74.4 (C_7); 58.0 (C_3); 38.8 (C_6); 32.6 (C_1); 26.3 (C_8); 24.2; 24.2 (C_4, C_5); 7.1 (C_9).

Separation of Products from Metalation of 9-*Z*. Since metalation methods A and B favor the formation of the **18–19** and the **16–17** pair, respectively (runs 24 and 25), in order to facilitate product isolation, separation was performed on mixtures arising from both metalation modes. The two pairs were quantitatively separated by flash chromatography (silica gel, AcOEt/ethyl ether = 100/40), with the **18–19** pair being eluted first. Successful separation of **16** from **17** could be achieved only after transformation in their *O*-trimethylsilyl derivatives **16a** and **17a** (see the following text).

***cis*-7-Thiabicyclo[4.3.0]nonan-2α-ol 1,1-Dioxide (16) and Trimethylsilyl Ether (16a).** A 1:2 mixture of **16** and **17** (0.75 g, 3.95 mmol) was first crystallized (benzene; 0.68 g, 3.56 mmol, 91%) and then silylated (THF, 27 mL; Me_3SiCl, 0.62 g, 5.7 mmol; Et_3N, 0.65 g, 6.48 mmol; 4 h, rt) to give 0.93 g (99%) of silyl ethers **16a** and **17a**. Flash chromatographic separation (Florisil, ethyl ether/light petroleum ether = 1/1) of the silyl ethers gave as the first eluted material **16a**, mp 83–84 °C (0.20 g, 65%; hexane). ^{13}C NMR: δ 69.5; 60.2; 50.3; 41.1; 29.2; 21.9; 21.4; 18.9; 0.01. ^1H NMR (60 MHz): δ 3.93 (m, 1 H, HCO); 2.90 (m, 4 H, $HCSCH_2$ and C_1H); 1.70 (m, 12 H); 0.1 (s, 9 H, CH_3's). Cleavage of **16a** (3% HCl in MeOH) gave quantitatively **16**, mp 122–123 °C (0.11 g, 79%; benzene). ^{13}C NMR: δ 68.7 (C_2); 59.9 (C_6); 50.2 (C_8); 40.2 (C_1); 28.4 (C_3); 21.3; 21.1; 18.7 (C_4, C_5, C_9). ^1H NMR: δ 4.03 (m, 1 H, HCO); 3.34–2.77 (m, 4 H); 2.35–1.70 (m, 6 H); 1.40 (m, 3 H). Anal. Calcd for $C_8H_{14}SO_3$; C, 50.50; H, 7.42; S, 16.85. Found: C, 50.06; H, 7.29; S, 17.97.

In order to confirm the structure, compound **16** was also prepared by an independent route starting from ethyl (1,3-dioxocyclohexyl)acetate.[30] This dione (14 g, 71 mmol), ethylene glycol (4.8 g, 75 mmol), and *p*-toluenesulfonic acid (0.35 g) in 0.8 L of benzene were refluxed in a Dean-Stark apparatus for 5 h. The cooled solution was added with 5 g of $NaHCO_3$ and evaporated. The residue was taken up with H_2O and extracted with ether. The residue after ether evaporation was flash chromatographed (silica gel, ethyl ether) to give, in order, the mono- and the diketal. The monoketal, **20** (6.2 g, 36%), was a liquid, bp 95–96 °C (1 mm). ^{13}C NMR: δ 206.3 (carbonyl); 172.9 (carboxyl); 111.3 (quaternary C); 65.1, 65.3 (dioxolane CH_2's); 60.4; 56.1; 40.1; 34.1; 27.4; 19.9; 14.1 (CH_3). ^1H NMR (60 MHz): δ 4.10 (q, OCH_2CH_3) and 3.90 (s, OCH_2CH_2O, 6 H overall); 3.30 (t, 1 H, CH); 2.40 (m, 4 H, CH_2COOEt and CH_2C=O); 1.85 (m, 4 H); 1.20 (t, 3 H, CH_3). The diketal (4.9 g, 25%) was a viscous oil. ^{13}C NMR: δ 173.6, 110.1, 65.2, 64.0, 48.6, 33.6, 28.4, 19.1, 14.1. From the aqueous layer, after acidification and ether extraction, 4 g were recovered of the starting dione.

$LiAlH_4$ reduction of monoketal **20** gave the corresponding diol, **2-(2-hydroxyethyl)-3-oxocyclohexanol ethylene ketal** as a ~1:1 mixture of diastereoisomers. ^{13}C NMR: δ 110.9; 110.8 (C_1); 72.1; 69.3 (C_3); 64.6; 64.4; 64.1; 63.8; 61.9; 61.0 (OCH_2CH_2O and CH_2OH); 50.8; 45.5 (C_2); 33.4; 33.2; 32.8; 31.0; 29.3; 27.2; 19.3; 18.2. No separation was attempted, and the mixture (6.2 g, 30.7 mmol) dissolved in CH_2Cl_2 (200 mL) with added triethylamine (9.4 g, 93 mmol) was reacted with methanesulfonyl chloride (8.9 g, 78 mmol). After 2 h at rt the reaction mixture was extracted with water. The CH_2Cl_2 layer was dried and evaporated to give 11.0 g (100%) of a ~1:1 mixture of diastereomeric dimesylates. ^{13}C NMR: δ 109.8; 109.7 (C_1); 82.6; 80.1 (C_3); 69.7; 69.1 (CH_2OMs): 64.6; 64.4; 64.1; 64.0 (OCH_2CH_2O); 46.1; 43.3 (C_2); 38.6; 38.2 (CH_3SO_3); 33.1; 32.0; 30.4; 27.4; 25.5; 24.4; 18.9; 18.4. ^1H NMR (60 MHz): δ 4.40 (m, 3 H, CH_2OMs and CHOMs); 3.95 (m, 4 H, OCH_2CH_2O); 2.98 and 3.01 (s's, 6 H overall, O_2SCH_3's); 2.35–0.85 (m, 9 H). This mixture was reacted as such with Na_2S as previously described for *cis*-2-thiabicyclo[4.3.0]nonane.[1c] The crude (4.6 g) was purified by flash chromatography (silica, light petroleum ether/ethyl ether 2/1) to give 1.2 g (20%) of ***cis*-7-thiabicyclo[4.3.0]nonan-2-one ethylene ketal (21).** ^{13}C NMR: δ 110.3, 64.4, 64.0, 52.7, 45.9, 32.3, 30.3, 29.4, 28.9, 23.0. Deprotection of **21** (1% H_2SO_4, acetone 90 mL, reflux, 1 h) gave the corresponding ketone **23** (0.93 g, 100%), bp 114 °C (2 mm). ^{13}C NMR: δ 209.5; 55.8; 49.7; 40.6; 30.7; 29.9; 27.7; 22.2. As expected, hydride reduction ($LiAlH_4$ 0.131 g, 3.45 mmol in 15 mL THF, 2 h, reflux) occurred highly diastereoselectively (~20:1) from the less hindered side yielding ***cis*-7-thiabicyclo[4.3.0]nonan-2α-ol (22)** as the major product, which was obtained pure (0.82 g, 86%) by crystallization (hexane), mp 91–92 °C. ^{13}C NMR: δ 71.1 (C_2); 50.4 (C_1); 46.3 (C_6); 31.9 (C_3); 29.7 (C_8); 26.3 (C_5); 26.3 (C_9); 22.9 (C_4). Eventually, oxidation of **23** with *m*-CPBA gave sulfone **16**.

Treatment of **16** (0.095 g, 0.5 mmol) with *t*-BuOK/THF (0.08 g, 0.75 mmol, in 10 mL, 4 h, 70 °C) gave rise to a 1:2 mixture of **16** and its trans epimer. The latter was not isolated; however, its ^{13}C NMR spectrum (δ 66.6 (C_2); 58.2 (C_1); 50.5 (C_8); 43.8 (C_6); 32.0 (C_3); 22.7; 22.0; 17.9 (C_4, C_5, C_8)) is thoroughly compatible with the assigned stereochemistry.

***cis*-2-Thiabicyclo[4.3.0]nonan-5α-ol 2,2-Dioxide (17) and Trimethylsilyl Ether (17a).** The second eluted material in the chromatographic separation from **16a** was the silyl ether **17a** (0.51 g, 82%) mp 82–83 °C; crystallized from hexane (0.31 g, 60%). ^{13}C NMR: δ 67.8, 63.6, 46.3, 43.7, 30.2, 26.9, 26.7, 22.2, –0.04. ^1H NMR (60 MHz): δ 3.90 (m, 1 H, HCO); 3.25 (m, 2 H); 2.80 (m, 1 H); 2.45 (m, 1 H); 1.90 (m, 8 H); 0.10 (s, 9 H, $SiMe_3$). Desilylation of **17a** (3% HCl in MeOH) gave **17**, mp 107–108 °C (0.20 g, 90% (benzene/hexane). ^{13}C NMR: δ 67.0 (C_5); 63.0 (C_1); 46.4 (C_6); 45.7 (C_3); 29.0 (C_4); 25.5; 25.1 (C_7, C_9); 22.3 (C_8). ^1H NMR: δ 4.10 (m, 1 H, HCO); 3.27 (m, 2 H) and 2.90 (m, 1 H, CH_2SCH); 2.30 (m, 4 H); 2.15–1.60 (m, 5 H). Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.23; H, 7.64; S, 16.84. The nature of the ring system and the stereochemistry of the ring junction was confirmed by subjecting **17** to deoxygenation[14] affording *cis*-2-thiabicyclo[4.3.0]nonane 2,2-dioxide identical with authentic material (see the following text).

Treatment of **17** with *t*-BuOK (for conditions see **16**) gave a ~35/65 mixture of **17** and a second component. Although this material was not isolated, its ^{13}C NMR spectrum is consistent with the ***trans*-2-thiabicyclo[4.3.0]nonan-5α-ol 2,2-dioxide**

structure: 66.6 (C_2); 58.2 (C_6); 50.5 (C_8); 43.8 (C_1); 32.0 (C_3); 22.7; 22.1 (C_4, C_5); 17.9 (C_9).

***cis*-2-Thiabicyclo[6.1.0]nonan-7α-ol 2,2-Dioxide (18).** A ~3:2 mixture of **18** and **19** (0.70 g) was chromatographed (silica gel, ethyl ether/methanol = 100/6) to give 0.30 g (75%) of **18** as the slower eluting component; crystallized from hexane/benzene (0.18 g, 60%), mp 108-109 °C. ^{13}C NMR: δ 66.3 (C_7); 55.0 (C_3); 36.4 (C_6); 34.3 (C_1); 25.5 (C_8); 23.4 (C_4); 18.1 (C_5); 5.1 (C_9). ^1H NMR (acetone-d_6): δ 4.36 (m, 1 H, C_7H); 3.40-3.10 (m, 2 H, C_3H_2); 2.85 (s, 1 H, OH); 2.50 (ddd, J = 8.2, 8.2, 6.7 Hz, 1 H, C_1H); 2.20-1.50 (m, 8 H); 1.30 (m, 1 H). Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 51.00; H, 7.51; S, 16.97.

***trans*-2-Thiabicyclo[6.1.0]nonan-7α-ol 2,2-Dioxide (19).** Mp 168-169 °C (0.16 g, 67%, benzene). ^{13}C NMR: δ 63.4 (C_7); 57.9 (C_3); 38.8 (C_6); 27.6 (C_1); 25.1, 25.0 (C_4, C_8); 20.9 (C_5); 4.2 (C_9). ^1H NMR (acetone-d_6): δ 4.20 (m, 1 H, C_7H); 3.30; 3.00 (m's, 1 H each, C_3H_2); 2.55 (ddd, J = 8.5, 5.2, 5.2 Hz, 1 H, C_1H); 2.40-1.50 (m, 8 H); 1.15; 1.05 (m's, 1 H each, C_9H_2). In $CDCl_3$, the latter multiplets resonate at δ 1.40 and 1.10 and, in the presence of a praseodymium shift reagent [Pr(hfc)$_3$], the 1.10 resonance is shifted upfield more strongly than the 1.40 multiplet. On this basis the corresponding H's (at C_9) can be assigned to the α and β side, respectively. Anal. Calcd for $C_8H_{14}SO_3$: C, 50.50; H, 7.42; S, 16.85. Found: C, 50.02; H, 7.53; S, 17.03.

***trans*-2-Thiabicyclo[4.3.0]nonan-5β-ol 2,2-Dioxide (24).** Base treatment of **13** (0.40 g, 2.1 mmol, for conditions see **16**) yielded a 80/20 trans/cis epimer mixture from which the title compound was separated by chromatography (silica gel, ethyl ether/methanol = 100/6) as the slower eluting component, mp 139-140 °C (benzene; 0.22 g, 70%). ^{13}C NMR: δ 72.5 (C_5); 62.2 (C_1); 50.9 (C_6); 50.4 (C_3); 32.9 (C_4); 29.0 (C_7); 21.7; 20.5 (C_8, C_9). ^1H NMR: δ 3.62 (m, 1 H, HCO); 3.08 (s, OH); 3.03 (m, 1 H); 2.78 (m, 1 H); 2.34-1.96 (m, 7 H); 1.79 (m, 2 H); 1.40 (m, 1 H).

Deoxygenation of alcohols 13 and 17 was performed by way of the Barton-McCombie procedure via the *S*-methyl dithiocarbonate ester derivatives.[14] ***cis*-2-Thiabicyclo[4.3.0]nonan-5β-ol 2,2-Dioxide Xanthate Ester.** Mp 140-141 °C (EtOH). ^{13}C NMR: δ 215.8; 76.5; 60.6; 46.9; 45.7; 26.6; 25.1; 23.2; 21.9; 19.1. ***cis*-2-Thiabicyclo[4.3.0]nonan-5α-ol 2,2-Dioxide Xanthate Ester.** Mp 129-130 °C (MeOH). ^{13}C NMR: δ 215.9; 77.7; 62.7; 45.6; 43.8; 25.5; 25.4; 22.1; 19.0.

Each of the above xanthates (0.40 g, 1.5 mmol) was reacted with tributylstannane (0.65 g, 2.25 mmol, toluene, 12 mL, AIBN, reflux, 7 h) to give after solvent evaporation and flash chromatography (silica gel, ethyl ether/petroleum ether = 2/1) ***cis*-2-thiabicyclo[4.3.0]nonane 2,2-dioxide** (0.20 g, 77%) identical with the sulfone obtained by *m*-CPBA oxidation of authentic *cis*-2-thiabicyclo[4.3.0]nonane,[1c] mp 72 °C (hexane/benzene). ^{13}C NMR: δ 63.2 (C_1); 48.0 (C_3); 40.7 (C_6); 29.7 (C_5); 24.6 (C_7): 23.7 (C_9); 21.4, 21.0 (C_4, C_8).

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Supplementary Material Available: MMX force fields, minimized geometries, and strain energies of conformations A-E (5 pages). Ordering information is given on any current masthead page.

Cyclization of Epoxyneocembrene Derivatives to Secotrinervitanes[1]

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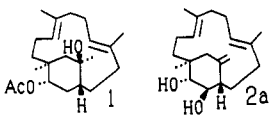
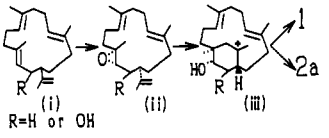
Four stereoisomers of epoxyneocembrene derivatives **5-8** were treated with BF_3·OEt_2 as potential model reactions for the proposed biogenesis of secotrinervitane-type diterpenoids (Scheme I). Two of them (**5** and **6**) afforded secotrinervitane derivatives, while the remaining isomers **7** and **8** gave no cyclization products (Table I). The natural product, secotrinervitene-2β,3α-diol (**2a**) was synthesized from **5** in *dl*-form.

When disturbed, soldiers of the naste termite (Nasititermitinae) are known to eject from their frontal gland a viscous defensive secretion. Recently, several diterpenoids have been isolated from the secretion and identified as 3α-acetoxy-15β-hydroxy-7,16-secotrinervita-7,11-diene (**1**) and its analogue **2a**, respectively. The former (**1**) was isolated by J. C. Braekman from *Nasutitermes princeps* soldiers collected in Papua, New Guinea,[2] while the latter (**2a**) was characterized by G. D. Prestwich as a secretion component of *Longipedtermes longipes* soldiers in Malaysia.[3]



These natural products belong to the secotrinervitane class of diterpenoids, which are structurally unique by virtue of their bicyclic IN-OUT ring system. X-ray crystallographic analysis of both compounds has unequivocally revealed that the termini of the macrocyclic ring are disposed on the cyclohexane ring with 1,4-trans diequatorial orientation. The cyclohexane ring possesses the chair conformation in the crystalline state. The secotrinervitane class is believed to arise biogenetically from epoxyneocembrene (ii, R = H or OH). The carbon skeleton (iii) of the secotrinervitane class is generated by cyclization at the isopropenyl group onto the epoxide ring to the bridging cyclohexane ring as shown in Scheme I. The parent hydrocarbon, neocembrene (i, R = H) is well-known as a termite trail pheromone[4] used by the workers of a Nastitermes species.

Scheme I



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