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NEW BRIDGEHEAD-SUBSTITUTED 1-(ARYLSULFONYL)BICYCLO[1.1.0]BUTANES AND SOME NOVEL ADDITION REACTIONS OF THE BICYCLIC SYSTEM

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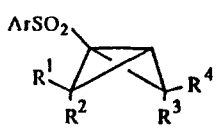
Summary. In view of planned syntheses of target cyclobutane derivatives, a series of new 3-substituted bicyclobutanes was prepared from sulfones **1-7**. Some novel addition reactions involving the central bond were then applied to several of the new compounds as well as to some previously described bicyclobutanes. These reactions include the additions of hydrazoic acid, of cyanocuprate reagents other than methyl reagents, and of phenylselenol, as well as single examples of addition of phenylselenyl azide and of lithium bromide. Several 3-allylated bicyclobutane derivatives were transformed into 1-(arylsulfonyl)bicyclo[2.1.1]hexanes by conversion to cyclobutanes, epoxidation and intramolecular base-induced cyclization.

1-(Arylsulfonyl)bicyclo[1.1.0] butanes (BCB's), readily obtainable from γ,δ-epoxysulfones,[1] are useful precursors of highly substituted, functionalized cyclobutanes.[2] Up to three additional groups can, indeed, be introduced into the cyclobutane ring by sequential substitution of the C3 bridgehead proton, addition of a nucleophile across the central bond, and substitution of the α-sulfonyl proton. This may then be followed by reductive elimination of the arylsulfonyl group.

In connection with the application of this methodology to the synthesis of yet other types of cyclobutane derivatives, such as cyclobutane amino acids[3] or bicyclo[2.1.1]hexanes, a series of new 3-substituted bicyclobutanes has been prepared. To some of these, and to other previously described BCB's, were then applied known or novel addition reactions involving the central bond. Some of these reactions were carried out with the target molecules in mind, others - in connection with the general scope of reactivity of the present system. The novel reactions, as applied to the bicyclic system, include azidation with tetramethylguanidinium azide (TMGA) or lithium azide, alkylation with cyanocuprate reagents, other than methyl reagents,[2] and selenylation with phenylselenol. Yet other addition reactions, including those of phenylselenyl azide, of lithium bromide, and of sodium cyanide, were also successful, but only single examples of these additions can be provided at the present time.

The starting materials for the new 3-substituted-BCB's were mainly sulfones **1**[1] and **2**[4] (see Experimental



1, $R^1=R^2=R^3=R^4=H$, Ar=Ph
2, $R^1=Me$, $R^2=R^3=R^4=H$, Ar=Ph
3, $R^1=R^2=Me$, $R^3=R^4=H$, Ar=Ph or *p*-tolyl
4, $R^1=R^3=Me$, $R^2=R^4=H$, Ar= *p*-tolyl
5, $R^1=R^4=Me$, $R^2=R^3=H$, Ar= *p*-tolyl
6, $R^1=Ph$, $R^2=R^3=R^4=H$, Ar=Ph
7, $R^1=i\text{-}Pr$, $R^2=R^3=R^4=H$, Ar=*p*-tolyl

Section for a modified procedure for the preparation of these compounds), with occasional use of sulfones **3-7**. Substitutions of the bridgehead hydrogen were carried out through the 3-lithium derivatives (3-Li-**n**), obtained by addition of butyllithium to a solution of the BCB in tetrahydrofuran (THF) at -78°C, and reaction with an electrophile.[2,5]

Tables I and III list the products derived from **1** and **2**, respectively. The ^{1}H NMR data of these products are given in Tables II and IV. Table V describes BCB's **4-6** and the products derived from them and from sulfones **3** and **7**.

The carboxyl derivatives **8**, **9**, **20** and **21** were prepared by reaction of the 3-Li derivatives with carbon dioxide. Quenching with water produced the acids. Quenching with excess methyl iodide, with addition of N-methyl-2-pyrrolidone (NMP) and warming to reflux, produced the methyl esters. In this way, the esters are obtained free of the by-products encountered in the reactions with chloroformate esters.[2]

The acid chlorides **11** and **23** were readily obtained from the acids by a short warming with thionyl chloride (75°C, 0.75 h), followed by evaporation of excess reagent and recrystallization. The crude chlorides could be used directly for the preparation of amides or esters. Amides were alternatively prepared from the acids by reaction with the amine in the presence of 1-methyl-2-chloropyridinium iodide[6] (**13**, **24**), or from the methyl ester by reaction with the corresponding lithium amide (**12**).

Alcohols **14** and **25** were obtained by reaction of the 3-Li derivatives with paraformaldehyde, while ethylene oxide was used in the preparation of alcohols **16** and **27**.

The allylated BCB's were obtained by reaction of the 3-Li derivatives with the corresponding allylic bromides.

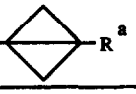
As mentioned above, a major target of this work has been the preparation of cyclobutane amino acids. The required introduction of nitrogen onto the cyclobutane ring could be realized by the known addition reaction of amines to the BCB system or, as was found to be more convenient, by the formal addition of hydrazoic acid. In both cases, the direction of addition was controlled by the sulfone group, the nucleophile adding at C3 regardless of the nature of the group already attached to this carbon. These additions as related to the carboxyl derivatives which are listed in Tables I and III will be described in detail separately.[7] The azidations related to a number of other BCB's are described in this paper.

A convenient method for the addition of hydrazoic acid to the BCB is that using TMGA[8] in NMP (or alternatively, in DMF). A separable mixture of trans and cis 3-azido-1-(arylsulfonyl)cyclobutane derivatives is obtained in high yield after a reaction time of 2 h at 85-90°C. Table VI describes the pairs of isomeric azides obtained from several, mostly 3-substituted, BCB's.

Lithium azide seems to be as effective an azidation reagent as TMGA, but until now has been applied to a more limited number of BCB's. Reactions were carried out in NMP at 60-80°C or at room temperature, yielding similar ratios of isomeric adducts to those obtained with TMGA. Thus, reaction with **1** was complete in 5 h at room temperature. The reaction with the 3-methyl derivative of **1** required, however, 40 h at room temperature for completion. Reactions with **8**, **9** or **13** at higher temperatures gave high yields of adducts.[7]

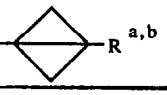
Trimethylsilyl azide reacted very slowly with several BCB's, but was useful in the case of ester **9** in providing the azido adducts without an accompanying solvolysis of the ester.[3,7]

Determination of the stereochemistry of the azide adducts is based on the established stereochemistry of addition of nucleophiles to the BCB's[4] and on the ^{1}H NMR of the adducts. In particular, the addition to **2**, possessing a 2-*exo*-methyl group, places the nucleophile trans to this methyl. If the reaction is carried out in the

Table I. Methods of Preparation, Yields and Melting Points of Bicyclobutanes 

Comp.	R	Preparation	Yield[b]	Mp°C[c]	Analysis[d] Calc.	C,H	Found	C,H
8	CO_2H	3-Li-**1**[e],CO_2[f]	94	178	55.47	$C_{11}H_{10}O_4S$ 4.23	55.40	4.20
9	CO_2Me	3-Li-**1**[e],CO_2,MeI[g]	83	117	57.14	$C_{12}H_{12}O_4S$ 4.80	57.25	4.83
10	CO_2Et	3-Li-**1**,$ClCO_2Et$[h]	63	56	58.65	$C_{13}H_{14}O_4S$ 5.30	58.64	5.38
11	COCl	**8**,$SOCl_2$	95	130		$C_{11}H_9ClO_3S$[i]		
12	$CONHCH_2Ph$	**9**,$PhCH_2NHLi$[j]	83	123	66.05	$C_{18}H_{17}NO_3S$ 5.23	66.22	5.25
13		**8**,piperidine[k]	79	126	62.94	$C_{16}H_{19}NO_3S$ 6.27	62.75	6.32
14	CH_2OH	3-Li-**1**,HCHO[l]	71	79	58.93	$C_{11}H_{12}O_3S$ 9.39	58.83	5.45
15	CH_2OTHP	**14**,DHP,PPTS[m]	86	74	62.33	$C_{16}H_{20}O_4S$ 6.54	62.15	6.66
16	CH_2CH_2OH	3-Li-**1**, ethylene oxide[n]	75	55	60.50	$C_{12}H_{14}O_3S$ 5.92	60.42	5.75
17	$CH_2CH_2OSO_2Me$	**16**,MsCl	95	67	49.37	$C_{13}H_{16}O_5S_2$ 5.10	49.55	5.17
18	$CH_2CH_2CH_2OH$	hydroboration[o]	80	68		$C_{13}H_{16}O_3S$[p]		
19	$CH_2CH{=}CHCH(CH_3)_2$	3-Li-**1**, $BrCH_2CH{=}CHCH(CH_3)_2$	85	-		$C_{16}H_{20}O_2S$[q]		

[a]All compounds showed IR absorption bands characteristic of the sulfone group around 1320 and 1150 cm^{-1}. [b]Yields refer to chromatographically and spectroscopically pure compounds. [c]The lower value of a one degree melting range is indicated. [d]Several compounds were analyzed also for sulfur or nitrogen, with found values consistent with the calculated ones. [e]3-Li-**1** refers to the lithiated species prepared from **1** and BuLi in THF at -78°C. [f]Solid CO_2 was added to 3-Li-**1** at -78°C and the mixture was allowed to warm to room temperature before work up. [g]To the reaction mixture obtained as described under footnote f, NM<P (ca. 1/5, v/v) and excess methyl iodide were added and the resultant mixture was refluxed for 2h before work up. [h]See reference 2 for the preparation of the corresponding *p*-tolyl derivative. [i]High resolution MS (HR-MS) m/e 221.0246 (37%, M^+-Cl); calc. for $C_{11}H_9O_3S$, 221.0273. [j]Lithiated benzylamine prepared from the amine and BuLi in THF at 0°C was transferred into a solution of **10** in THF, kept at 0°C. Amide **12** was also obtained from **8** via **11** and benzyl-amine in a similar yield. [k]Acid **8** was converted to the amide either, according to reference 6, or through the acid chloride, in similar yields. [l]Excess paraformaldehyde was added to 3-Li-**1** at -78°C and the reaction mixture was warmed to room temperature before work up. [m]Alcohol **14** was treated with dihydropyran and pyridimium tosylate according to Grieco *et al., J. Org. Chem.* **1977**, *42*, 3772. [n]BuLi was added to **1** and excess ethylene oxide in THF at -78°C and the solution was warmed slowly to 0°C before work up. The yield of **16** relative to unrecovered **1** was 87%. [o]The 3-allyl derivative of **1** (reference 2) was hydroborated with $BH_3{\cdot}Me_2S$ and oxidized to **18** according to standard procedures. [p]HR-MS m/e 111.0791 (22%, M^+-$PhSO_2$); calc. for $C_7H_{11}O$, 111.0810. [q]GC-MS (CI) m/e 277 (M^++1); *Mr* 276.

Table II. ^{1}H NMR Spectra of Bicyclobutanes 

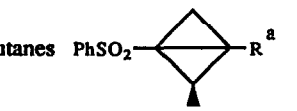
Comp	Two *endo* protons	Two *exo* protons[c]	Side chain R
8	1.71	3.01	6.92 (br s, OH)
9	1.64	3.00	3.77 (s, Me)
10	1.64	3.02	1.30 (t, 3), 4.25(q, 2)
11	1.86	3.16	
12	1.57	2.87	4.53(d,*J*=5.8, CH_2NH), 5.65(br, NH)
13	[~1.6]	2.86	1.63(br, 6 heteroring-H+2 endo-H), 3.58(br, 4 heteroring-H)
14	1.43	2.65	2.70(t,OH), 4.44(d,*J*=7.1, CH_2OH; s after addition of D_2O)
15	1.46	2.52	1.5-1.8(m,6), 3.3-4.05(m,2), 4.36(ABq,*J*=12.2, 2), 4.78(br s,1)
16	1.32	2.38	1.94(OH), 2.50(t,*J*=6.1,2), 3.93(t,*J*=6.1,2)
17	1.38	2.40	2.70(t,*J*=6.3,2),3.05(s,Me), 4.51(t, *J*=6.3,2)
18	1.28	2.33	1.92(br,CH_2+OH,3), 2.33(m,2), 3.75(t,*J*=6.2,2)
19	1.29	2.33	1.00(d,*J*=6.7, two Me), 2.33(m,1), 2.9(br,2), 5.6(br,2)

[a]See Table I. [b]Spectra were taken in $CDCl_3$. Chemical shifts are given in δ values. Multiplicities, coupling constants (Hz), proton assignments, and/or relative integrations are given in parentheses. The aromatic protons appear as a three-proton and a two-proton multiplet in the δ7.5-8.0 region and are not indicated in the table. [c]The two *endo*-H and two *exo*-H appeared as singlets in all cases.

absence of a proton source, subsequent protonation also places the sulfone group trans to this methyl.[2,4] The chemical shift of the 2-methyl doublet then falls in the range of δ 0.8 to 1.05. A cis-1,2 relationship, which may result from kinetic protonation by the medium during addition, shifts the methyl doublet by ca. 0.5 ppm to a lower field.

Assignment of a cis-S,N or a trans-S,N configuration to isomers **39** is then straightforward. The configurations of isomers **38** is determined by comparison of the spectra to those of **39**. Similar patterns and shifts of the ring methylenes in the two first-eluted isomers I and in the two isomers II are clearly observed. A trans-S,N configuration is therefore assigned to isomer **38-I**.

In general, it has been observed that in all amine and azide adducts of the BCB's, a trans-S,N relationship was associated with disparate chemical shifts of the equatorial and axial ring protons, while an equal or almost equal shift of all ring protons was associated with a cis-S,N relationship. This was later corroborated by an X-ray structure determination of an amino acid derivative.[3]

Table III. Methods of Preparation, Yields and Melting Points of Bicyclobutanes 

Comp.	R	Preparation	Yield[b]	Mp°C[c]	Analysis[d] Calc.	C,H	Found	C,H
20	CO_2H	3-Li-2,CO_2[b]	86	179		$C_{13}H_{14}O_4S$		
					56.69	5.55	56.52	5.70
21	CO_2Me	3-Li-2[e],CO_2,MeI[c]	86	76		$C_{12}H_{12}O_4S$		
					58.65	5.30	58.45	5.32
22	CO_2Et	3-Li-2,$ClCO_2Et$[d]	70	--		$C_{14}H_{16}O_4S$[e]		
23	COCl	20,$SOCl_2$	95	82		$C_{12}H_{11}ClO_3S$[f]		
24	CON⟨⟩	20,piperidine[g]	66	124		$C_{17}H_{21}NO_3S$		
					63.94	6.63	63.85	6.56
25	CH_2OH	3-Li-2,HCHO[h]	76	--		$C_{12}H_{14}O_3S$[i]		
26	CH_2OTHP[j]	25,DHP,PPTS[k]	49	70-80[j]		$C_{17}H_{22}O_4S$		
					63.34	6.88	63.06	6.69
27	CH_2CH_2OH	3-Li-2, ethylene oxide[l]	44	--		$C_{13}H_{16}O_3S$[m]		
28	$CH_2CH=CH_2$	3-Li-2, $BrCH_2CH=CH_2$	75	--		$C_{14}H_{16}O_2S$[n]		
29	$CH_2CH=C(CH_3)_2$	3-Li-2, $BrCH_2CH=C(CH_3)_2$	70	--		$C_{16}H_{20}O_2S$[o]		

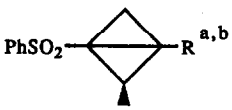
[a]See footnotes a-d, Table I. [b]See footnote f, Table I. [c]See footnote g, Table I. [d]See reference 2 for the method of preparation. [e]GC-MS (CI) m/e 281 (M^++1); *Mr* 280. [f]HR-MS m/e 235.0358 (20%, M^+-Cl); calc. $C_{12}H_{11}O_3S$, 235.0429. [g]See footnote k, Table I. [h]See footnote l, Table I. [i]GC-MS (CI) m/e 239 (M^++1); *Mr* 238. [j]Compound **26** was obtained as a mixture of two diastereomers, the one displaying an ABq for the side-chain CH_2 and the other, a singlet (see Table IV). [k]See footnote m, Table I. [l]Ethylene oxide was added to 3-Li-2 at 0°C and the reaction was worked up after 15 minutes. The yield relative to unrecovered **2** was of 79%. [m]GC-MS (CI) m/e 253 (M^++1); *Mr* 252. [n]GC-MS (CI) m/e 249 (M^++1); *Mr* 248. [o]HR-MS m/e 276.1159 (10%, M^+); calc. 276.1174.

All azido derivatives obtained from the BCB's may be viewed as precursors of primary amines, attached in most cases, to a quaternary carbon.[9] Some examples may be provided by the reductions of several azides to α-amino cyclobutanecarboxylic acid derivatives.[3,7] Other examples include the catalytic hydrogenation of **41**-II and of **44**, the amines being isolated as the amides **45** and **46**. Also, hydrogenation of **38**-I or II with 5% Pd/C in acetic acid-acetic anhydride provided the trans or cis acetamides **47** in 94% yield.

Reduction of **38** with zinc in a similar medium (2 h, 130°C) furnished a large proportion of **48** (26% yield) besides **47** (35% yield).

Acetic acid itself reacted with **1**with formation of **49**, an electropilic-addition product,[5] formed in about 50% yield (4 h at 60°C or several days at room temperature; about 30% of **1** was recovered). It was identical to the acylation product of the corresponding alcohol, known to be of a trans configuration.[1]

Several other addition reactions of the BCB's have been explored on a limited number of substrates or just on the basic sulfone **1**.

Table IV. ^{1}H NMR spectra of Bicyclobutanes 

Compound	2-Me and 2-*endo*-H[c]	4-*endo*-H, 4*exo*-H	Side chain R
20	1.6-1.9	1.39(d) 2.85(d) *J*=1.6	6.0 (OH)
21	1.6-1.9	1.34(d) 2.84(d) *J*=1.4	3.79 (s, Me)
22	1.6-1.9	1.34(s) 2.84(s)	1.31 (t, Me), 4.26 (q, 2)
23	1.64(d, Me) 1.95(q, 1)	1.65(d) 3.12(d) *J*=1.9	
24	[1.5-1.85]	1.28(s) 2.62(s)	1.5-1.85 (br, 10), 3.59 (br, 4)
25	1.4-1.7	1.13(s) 2.47(s)	1.75 (OH), 4.45 (d, 2; s after addition of D_2O)
26	[1.4-2.0]	1.24(s) 2.39(s)	1.4-2.0 (m, 10), 3.3-4.0 (m, 2), 4.16 and 4.59 (ABq, *J*=11.9, 2)[d], 4.38 (s, 2)[d], 4.76 (br, 1)
27	1.3-1.6	1.05(s) 2.23(s)	2.1 (OH), 2.40 (m, 2), 3.85 (t, 2)
28	1.3-1.6	1.07(s) 2.20(s)	2.94 (m, 2), 5.05-5.35 (m, 2), 5.75-6.75 (m, 1)
29	1.3-1.6	1.02(s) 2.19(s)	1.68 (s) and 1.75 (s, two Me), 2.88 (t, 2), 5.25 (br t, 1)

[a]See Table III. [b]See footnote b, Table II. [c]The 2-*exo*-methyl and the 2-*endo*-H have similar chemical shifts and usually form a non-first order AB_3 spectrum. [d]See footnote j, Table III.

Phenyl selenyl azide, reported recently to add to carbon-carbon double bonds,[10] reacts readily with **1** to provide one adduct isomer (**50**), of undetermined configuration, in about 50% yield, besides cis and trans **51**, formed in about 20% yield. The reaction was carried out in NMP, the reagent being preformed by warming phenyl selenyl chloride with sodium azide in the solvent before addition of **1**. The formation of adducts **38** by addition of sodium azide to **1** was thus avoided. When the three components were mixed together from the start,[10] products **38** were, indeed, produced alongside with **50** and **51** in up to 35% yield.

The structure of **51** was confirmed by addition of phenylselenol to **1** in benzene. Trans and cis **51**, readily separable by chromatography, were obtained in about equal amounts and in a total 72% yield.

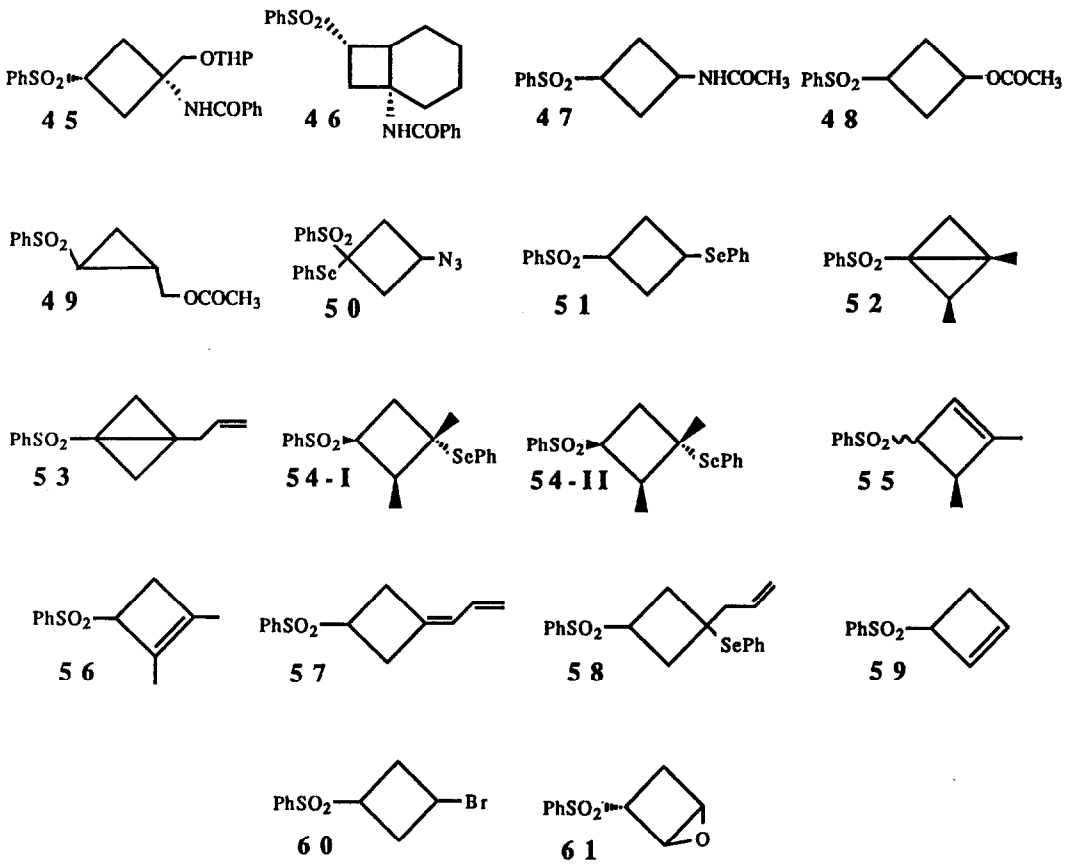
Phenylselenol was also added to **52** and **53**. Isomers **54-I** and **II**, obtained from **52**, could be separated by chromatography. Their oxidation with hydrogen peroxide in THF furnished a mixture of the cyclobutene derivatives **55** (cis- and trans-1,2 isomers, not separated) and **56** in a total 66% yield.

The reaction of phenylselenol with **53** in benzene (80°C, 20 h) furnished mainly diene **57** (38% yield), besides a small amount of one adduct isomer **58** (16%).

Another addition reaction which was applied to **1** was that of lithium bromide. Reaction in NMP at 100°C for 24h provided the elimination product **59** and bromide **60** in about 60 and 20% yield, respectively. Epoxidation of **59** produced one epoxide isomer, probably trans (**61**), isolated in 60-65% yield.

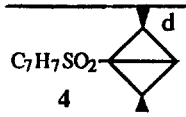
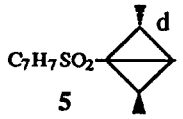
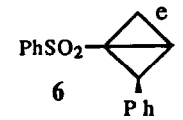
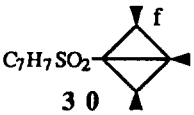
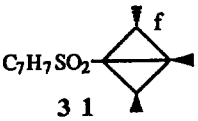
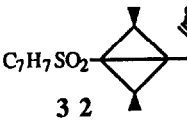
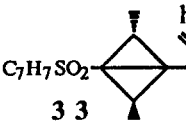
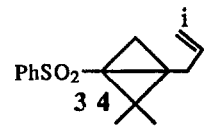
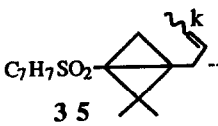
An example of addition of sodium cyanide (to **53**) is given in Table VIII.

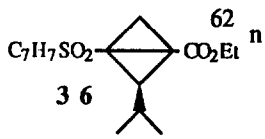
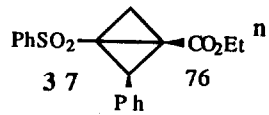
Additions of organocopper reagents to **1** or **2** have been shown to provide 3-alkyl cyclobutane derivatives in good yields. Methylcopper reagents were shown to add even to 3-substituted derivatives of **1** or **2**, leading to a quaternary carbon at position 3.[2] In order to check the generality of this addition, a number of higher order cyanocuprate reagents were reacted with a few 3-substituted BCB's. The results, as summarized in Table VII, indicate that the reaction is of a wide scope. The use of 2-*exo*-methyl derivatives as substrates assured that only one adduct isomer be formed. The moderate yields are probably mainly due to unoptimized reaction conditions.



As mentioned above, several of the 3-substituted compounds described in Tables I, III and V have been prepared with the idea of converting them, into bicyclic systems. The cyclization was planned to proceed by conversion of a 3-allyl-bicyclobutane into a cyclobutane by addition across the central bond, to be followed by epoxidation and intramolecular ring formation. The sequence of reactions is depicted in Scheme I for the simplest, unsubstituted 3-allyl-BCB, where R represents a general nucleophile added to the system. An *Exo*-mode[11] of opening of the oxirane ring by the α-sulfonyl carbanion would lead to a bicyclo[2.1.1]hexane ring system, while an *Endo*-mode would lead to a bicyclo[3.1.1]heptane system. Since no bond distortion is required for a six-membered ring formation from ε-epoxide,[5,12] it was hoped that the *Endo*-mode would prevail in the

Table V. Melting Points and ^{1}H NMR Spectra of Miscellaneous Bicyclobutanes[a,b]

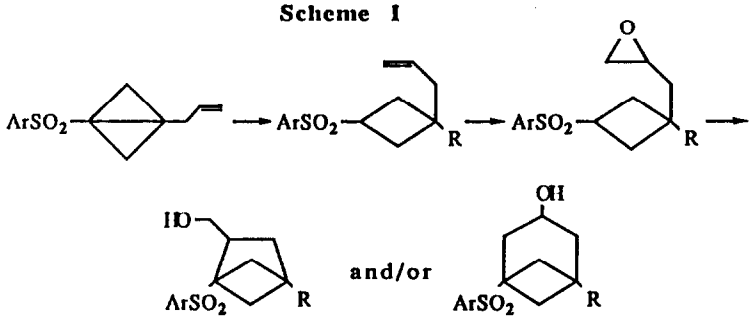
Compound	Mp°C	^{1}H NMR[c]			Analysis			
		endo-H or Me	*exo*-H or Me	Side chain	Calc.	C,H	Found	C,H
 4	112	1.35 (s) (two Me + two endo-H)		2.34 (s, arom. Me), 2.59 (s, 1, C3-H)	$C_{13}H_{14}O_2S$ 66.66	6.02	66.57	6.05
 5	77	0.88 (d, *J*= 6.0, Me) ~2.4 (m,1)	1.43 (d, *J*= 5.9, Me) 3.0 (m,1)	2.43 (s, arom. Me), ~2.4 (m, 1, C3-H)	$C_{13}H_{14}O_2S$ 66.66	6.02	66.43	6.12
 6	53	1.25 (br s,1) 2.42 (d, *J*= 3.8,1)	2.60 (br s,1)	3.25 (m, 1), 7.25 (s, Ph)	$C_{16}H_{14}O_2S$ 70.58	5.92	70.97	5.73
 30	64	1.1-1.4 (m) (two Me + two endo-H)		1.70 (s, Me), 2.42 (s, arom. Me)	$C_{14}H_{16}O_2S$ 67.73	6.50	67.97	6.62
 31	67	0.85 (d, *J*= 6.0, Me) 2.17(q,C2-H)	1.41 (d, *J*= 6.0, Me) 2.88(q,C4-H)	1.76 (s, Me), 2.43 (s, arom. Me)	$C_{14}H_{16}O_2S$ 67.73	6.50	67.85	6.55
 32	68	1.33 (s) (two Me + two endo-H) 5.0-5.25 (m, 2), 5.7-6.1 (m, 1)		2.43 (s, arom. Me), 2.87 (d, *J*=5.8, 2),	$C_{16}H_{20}O_2S$ 69.55	7.30	69.73	7.36
 33	73	0.88 (d, *J*= 6.0, Me) 2.21 (m, 1)	1.41 (d, *J*= 6.1, Me) [2,86]	2.43 (s, arom. Me), 2.86 (m,3), 5.0-5.25 (m,2), 5.7-6.2(m,1)	$C_{16}H_{20}O_2S$ 69.55	7.30	69.44	7.35
 34	--	0.93 (s, Me) 1.80 (s, 1)	1.50 (s, Me) 2.32 (s, 1)	2.91 (br t, 2), 4.9-5.2 (m, 2), 5.7-6.1 (m, 1)	$C_{15}H_{18}O_2S$[j]			
 35	--	0.90 (s, Me)[l] [~1.8, 1] (m, 2), 5.46-5.58 (m, 2)	1.48 (s,Me) 2.29 (d, 1)	1.69 (br, Me), 2.43 (s, arom. Me), 2.74-2.88	$C_{17}H_{22}O_2S$[m]			

	62	1.25 (d, *J*= 1.2, C4-H) [~1.3, C2-H] 2.44 (s, arom. Me), 4.25 (q, *J*=7.1, 2)	2.71 (d, *J*= 1.2, C4-H)	1.05 (d, *J*=6.4, Me), 1.11 (d, *J*=6.4, Me), 1.30 (t, *J*=7.1, Me),	$C_{17}H_{22}O_4S$ 63.34 6.88	63.22 6.73
	76	1.39 (s, 1) 2.63 (s, 1)	2.88 (s, 1)	1.29 (t, Me), 4.30 (q, 2), 7.2-7.8 (m, 10)	$C_{19}H_{18}O_4S$ 66.66 5.30	66.52 5.43

[a]See footnotes a-d, Table I; C_7H_7 stands for *p*-tolyl. [b]The methods of preparation, according to known procedures or to those encountered in Tables I and III, are indicated in footnotes. [c]See footnote b, Table II.

[d]Sulfones **4** and **5** were obtained as a separable mixture from $C_7H_7SO_2CH_2CH(CH_3)\overset{O}{\frown}CH\text{-}CHCH_3$ in a total 51% yield according to the general procedure (reference 1). [e]Sulfone **6** was prepared in 53% yield from $PhSO_2CH_2CH_2\overset{O}{\frown}CH\text{-}CH\text{-}Ph$ (reference 1). [f]Compounds **30** and **31** were obtained as a separable mixture from a mixture of lithiated **4** and **5** and MeI in a total 81% yield. [g]Obtained from 3-Li-**4** and allylbromide in 82% yield. [h]Obtained from 3-Li-**5** and allyl bromide in 75% yield. [i]Obtained from 3-Li-**3** (prepared at 0°C) and allyl bromide in 85% yield. [j]GC-MS (CI) m/e 263 (M^++1); *Mr* 262. [k]Obtained from 3-Li-**3** (prepared at 0°C) and crotyl bromide in 58% yield. [l]Satellite methyl singlets, due probably to a cis isomer, are observed at δ 0.89 and 1.51. [m]GC-MS (CI) m/e 291 (M^++1); *Mr* 290. [n]See reference 2 for the method of preparation.

Scheme I

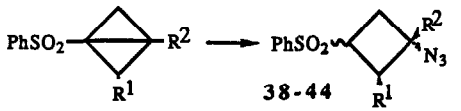


present case, particularly with ω-unsubstituted epoxides.

Table VIII describes the allylcyclobutanes which have been prepared, their mode of formation and the epoxides derived from them. The first epoxides prepared were the isomeric epoxides **73** (see below) which could have led to the formation of the pinane skeleton. Treatment of these with BuLi in THF led, however, to the exclusive formation of bicyclo[2.1.1]hexane products. Similar results were obtained with all other epoxides listed in Table VIII.

The bicyclic products are described in Table IX. Several of these have an isoprenoid skeleton, but of types which are apparently not found in nature (isomers **80-82**, isomers **83-84**, isomers **88-89** and compound **90**). The number of bicyclo[2.1.1]hexane monoterpenes isolated until now from natural sources seems to be very limited. One example is that of the 1-vinyl-5,5-dimethyl derivative, first obtained photochemically from

Table VI. Cyclobutyl Azide Derivatives Obtained by Addition of TMGA to Various Bicyclobutanes.[a,b]



38-44

Starting Material		Product (Isomer ratio)[c]	Yield, %	mp, °C	^{1}H NMR	Formula	High Resolution-MS[d] m/e (%)
1	38	R^1=R^2=H (1.1)	96	I[e] 67	I, 2.15-2.45 (m,2), 2.70-3.05 (m,2), 3.78 (m,1), 4.30 (m,1)	$C_{10}H_{11}N_3O_2S$	I 68.0442 (36)
				II[e] --	II, 2.56 (t, *J*~8, 4), 3.49 (pent, *J*~8, 1), 3.79 (pent, *J*~8, 1)		II 68.0480 (75) calc.for C_4H_6N, 68.0500
2	39	R^1=Me, R^2=H (1.6)	96	I --	I, 1.48 (d, *J*=7.1, Me), 1.9-3.0 (m,3), 3.90 (dt, J_1=9.4, J_2=3.2, 1), 4.13 (q, *J*~8.3, 1)	$C_{11}H_{13}N_3O_2S$	I 82.0680 (76)
				II --	II, 1.03 (d, *J*=6.5, Me), 2.43 (t, *J*~7.4, 2), 2.6-3.5 (m, 2)		II 82.0617 (77) calc.for C_5H_8N, 82.0656
R^1=H, R^2=Me	40	R^1=H, R^2=Me	89	I --	I, 1.52 (s, Me), 2.18-2.78 (m, 4), 3.86 (pent, 1)	$C_{11}H_{13}N_3O_2S$	I 82.0721 (100)
				II --	II, 1.40 (s, Me), 2.05-2.35 (m, 2), 2.6-2.9 (m, 2), 3.5 (pent, 1)		II 82.0718 (94) calc. for C_5H_8N, 82.0656
15	41	R^1=H, R^2=CH_2OTHP (0.25)	85[e]	I 63	I. 1.65 (br, 6), 2.14-2.86 (m, 4), 3.5-4.1 (m, 5), 4.68 (br s, 1)	$C_{16}H_{21}N_3O_4S$[f]	I 80.0478 (25) calc. for C_5H_6N, 80.0500
				II 69	II, 1.60 (br, 6), 2.1-2.9 (m, 4), 3.31-3.86 (m, 5), 4.61 (br s, 1)		II[f]
16	42	R^1=H R^2=CH_2CH_2OMs[g] (0.25)	80	I --	I, 2.23 (t, *J*=6.1, 2), 2.4-2.8 (m, 4), 3.03 (s, Me), 3.92 (pent, 1), 4.32 (t, *J*=6.1, 2)	$C_{13}H_{17}N_3O_5S_2$	I 190.0578 (3) (M^+-$PhSO_2$)

				II	102	II, 2.04 (t, J=6.4, 2), 2.4-2.9 (m, 4), 2.98 (s, Me), 3.62 (pent, 1), 4.28 (t, J=6.4, 2)		II	190.0474 (14) calc. for $C_7H_{12}NO_3S$. 190.0538
48	**43**	R^1=H R^2=$CH_2CH{=}CH_2$ (0.2)	91	I	--	I, 2.1-2.9 (m, 6), 3.89 (pent, 1), 5.1-6.0 (m, 3)	$C_{13}H_{15}N_3O_2S$	I	108.0856 (54)
				II	--	II, 2.1-2.9 (m, 6), 3.51 (pent, 1) 5.0-6.0 (m, 3)		II	108.0838 (61) calc. for $C_7H_{10}N$, 108.0813
R^1,R^2=$(CH_2)_4$	**44**	R^1,R^2=$(CH_2)_4$ (0.25)	94	I	61	I, 1.0-3.0 (m, 11), 3.95 (q, J~7.7, 1)	$C_{14}H_{17}N_3O_2S$	I	122.0972 (40)
				II	83	II, 1.0-3.0 (m, 11), 3.32 (dd, 1, J_1=7.0, J_2=7.4)		II[h]	122.0964 (79) calc. for $C_8H_{12}N$, 122.0970

[a]The bicyclobutane was warmed in NMP (1 mL/mmol) at 85-90°C with 1.1-1.2 molar excess of TMGA of 2h. Extractive work up with water and ether, followed by chromatography of the residue from the ether extract furnished the two isomeric azides. [b]Footnotes a-d of Table I also apply to this table. All azides showed a strong IR absorption band in the range of 2100-2115 cm^{-1}. [c]The isomer ratio is that of the trans-S,N isomer (isomer I) to the cis-S,N isomer (isomer II). [d]HR-MS analyses of the azides usually showed prominent peaks of fragments obtained by loss of $PhSO_2$ radical of a nitrogen molecule. [e]The reaction time was 4h. [f]C,H,N-analysis; found, isomer I: C,54.55; H, 6.05; N, 11.88; isomer II: C, 54.95; H, 5.95; N, 11.93. Calc. for both isomers: C, 54.70; H, 6.02; N, 11.96%. [g]The crude addition product of alcohol **16** was mesylated (MsCl, Et_3N, CH_2Cl_2, 0°C) and then chromatographed. [h]C,N,H analysis, found: C, 57.46; H, 5.69; N, 14.25. Calc.: C, 57.72; H, 5.88; N, 14.42%.

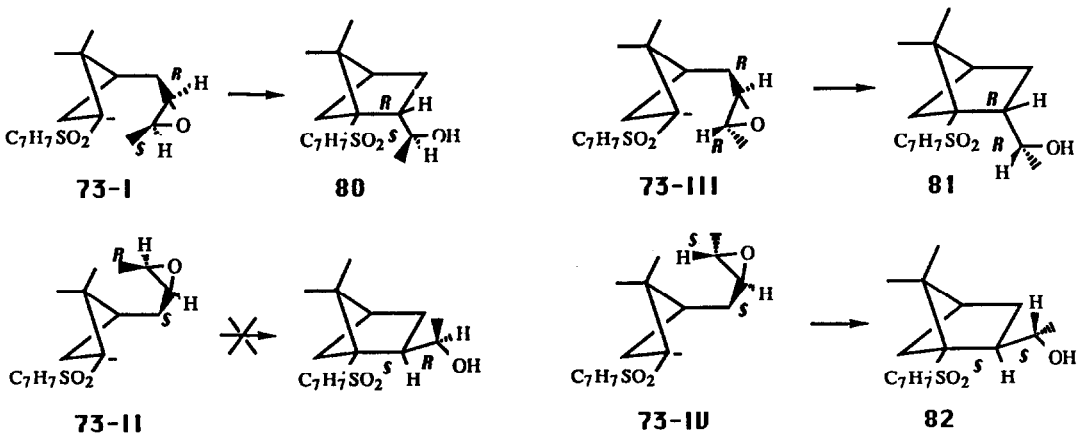
myrcene[13] and then isolated from a natural source.[14] Another example is that of the 1,5,5-trimethyl-6-carboxaldehyde derivative again first obtained photochemically and only later isolated from natural verbena oil.[15]

The formation of three isomeric bicyclohexanes from epoxides **73** and of pairs of isomers from other epoxides of Table VIII raised the question of their stereochemistry. With that the appearance of extremely shielded methyl signals (up to δ 0.26) in the ^{1}H NMR spectra of several derivatives was also associated.

The case of epoxides **73** was complicated by the presence of cis and trans olefin precursors (**67**), the cis isomer probably originating from the secondary allylic bromide present in the commercial crotyl bromide used in the preparation of **35**. Two pairs of diastereomeric epoxides **73** are thus obtained from **67**, notwithstanding the relative geometry of the sulfone which is assumed to be cancelled out by anion formation. The four epoxides can then furnish four different isomeric bicyclohexanes, the geometry of each product isomer being dictated by the prerequisite condition of a colinear backside attack of the epoxide by the anion (Figure I). Molecular models, and Figure I, show that the cis-epoxide **73-II** cannot be oriented so as to assume a reacting geometry becuase of severe steric congestion of two methyl groups. Indeed, one pure epoxide isomer was recovered from the reaction mixture, besides the three product isomers. Of these, the first eluted one was the least abundant (10% yield) and was assumed to derive from the cis-epoxide **73-I** and to have, therefore, structure **80**. This was then confirmed by X-ray crystallographic analysis (Figure II).[16,17]

In this configuration, the hydroxymethyl side chain, which is trans to the endo methyl, forces the aryl sulfone to rotate so as to bring the aromatic ring to eclipse this methyl. A hydrogen bond between the hydroxyl hydrogen and one of the sulfur oxygens, helps to maintain such a configuration. As a result, the ^{1}H NMR signal

Figure 1[a]

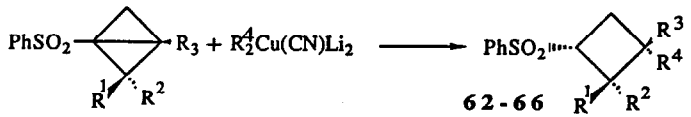


[a] Only one enantiomer is drawn, for clarity reasons, for each racemic diastereomer of starting material or product.

of this methyl appears at δ 0.3.

Of the two other isomers, the second eluted (33% yield) shows a methyl singlet at δ 0.62 and is therefore assigned structure **81**. Furthermore, oxidation of **80** and **81** with bichromate supported on silica gel[18] furnished the same ketone **93**, while a different ketone was obtained from the third isomer. This third isomer (29% yield)

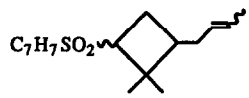
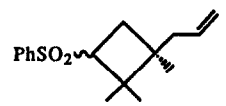
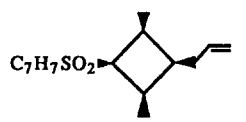
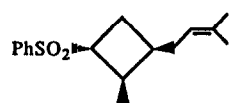
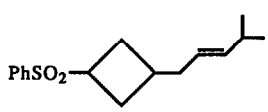
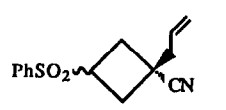
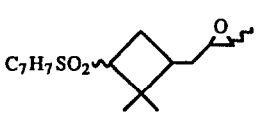
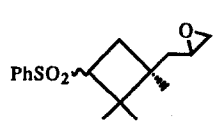
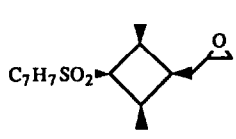
Table VII. Reaction Conditions, Yields and Physical Properties of Cyanocuprate Addition Products of Some Bicyclobutyl Sulfones[a]

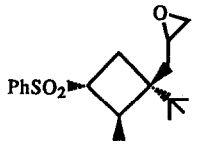
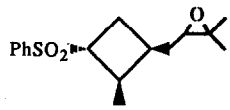
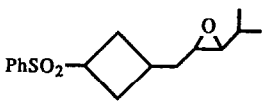
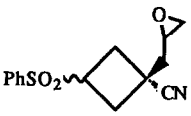


	Product	Starting Material	Reaction Conditions[b]	Yield %	mp, °C	^{1}H NM	Formula
62	R^1=R^3=Me, R^2=H R^4=n-Bu	**47**	2;20h, r.t.	71	--	0.77, 0.85, 0.88, 0.95 (superimposed Me peaks, 9), 1.53-2.66(m,3), 3.19(q,*J* ~7,1)	$C_{16}H_{24}O_2S$[c]
63	R^1=R^3=Me, R^2=H R^4=t-Bu	**47**	1.5;0.25h, O°C 0.5h, r.t.	50	--	0.81(s, t-Bu), 0.85(d,Me), 1,00(s,Me), 1.51 and 2.36 [dq,AB(X),J_{AB}=11.1, J_{AX}=8.9, J_{BX}=7.9,2], 2.8-3.4(m,2).	$C_{16}H_{24}O_2S$[d]
64	R^1=R^3=Me, R^2=H R^4=Ph	**47**	2; 3h, r.t.	40	101	1.05(d,*J*=6.8,Me), 1.31(s,Me), 2.15 and 2.71[dq,AB(X),J_{AB}=11.1,J_{AX}=9.5, J_{BX}=7.9], 3.13-3.54(m,2).	$C_{18}H_{20}O_2S$[e]
65	R^1=Me, R^2=H R^3=CH_2·CH=CH_2, R^4=t-Bu	**28**	2; -78→O°C slow warming[f]	47	57	0.85(s,t-Bu), 0.90(d,Me), 1.85(dd, B part of ABX spectrum, J_{AB}=12.0, J_{BX}=7.9,2) 2.28(d+dd,3), 2.95-3.3(m,2), 4.9-5.2 (m,2), 5.7-6.2(m,1).	$C_{18}H_{26}O_2S$[g]
66[h]	R^1=R^2=R^4=Me R^3=CH_2CH=CH_2	**34**	3; 5h, r.t.	48[i]	--	[h]0.98, 1.01, 1.06, 1.44, 1.49 (Me signals, 9), 1.6-2.5(m,4), 3.2-3.55(m,1), 4.8-5.15 (m,2), 5.35-5.95(m,1).	$C_{16}H_{22}O_2S$[j]

[a]See footnotes a-d, Table I. [b]The cuprate reagents were prepared in ether at 0°C from two equivalents of R^4Li and one equivalent of CuCN. After dissolution, the sulfone was added either as a solid or in ether solution (see also references 2,4). Numbers in the column indicate the relative molar ratio of cuprate to sulfone, the reaction time, and the temperature (r.t. is room temperature). [c]GC-MS (CI) m/e 281(M^++1); *Mr* 280. [d]GC-MS (CI) m/e 281 (84.2%, M^++1), 139 (100%, M^++1-$PhSO_2H$); *Mr* 280. [e]Anal. calc.: C,71.98; H,6.71. Found: C, 71.86; H, 6.80%. [f]The cuprate reagent was prepared at -78°C. [g]Anal. calc.: C,70.56; H,8.55. Found: C,70.42; H,8.43%. [h]Mixture of cis and trans isomers. [i]The yield relative to unrecovered **34** was of 72%. [j]GC-MS (CI) m/e 279(M^++1), *Mr* 278.

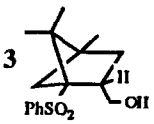
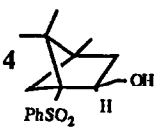
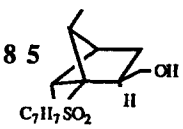
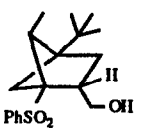
Table VIII. 1-(Arylsulfonyl)-3-allylcyclobutane Derivatives and Their Epoxidation Products, Precursors of Bicyclo[2.1.1]hexanes[a,b]

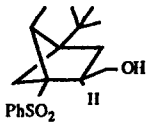
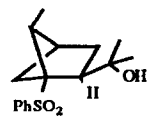
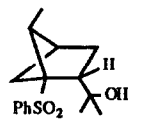
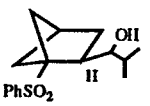
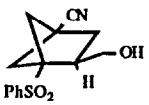
	Product	Preparation	Yield,%	^{1}H NMR
67[c]		35, LAH[d]	75	[e]1.05-1.62 (numerous Me signals due to several isomers),~2.0(m,4), 2.43(s,Me), 3.2(m,1), 5.3(m,2), 7.3 and 7.7(4).
68[f]		34, $Me_2Cu(CN)Li_2$[g]	53[h]	[e]0.98-1.49 (five Me signals due to two isomers), 1.6-2.5(m,4), 3.2-3.55(m,1), 4.8-5.15 and 5.35-5.95(m,3), 7.5-8.0(5).
69[i]		32, LAH[d,i]	90	0.88(d,*J*=6.2, two Me), 2.15(br t,2), 2.44(s,Me), 2.4-3.0(m,4), 4.9-5.1 and 5.4-6.0(m,3), 7.32 and 7.76(4).
70[j]		29, LAH[d]	71	0.91(d,*J*=6.9,Me), 1.58(Me),1.66(Me), 1.7-2.5(m,4), 3.00(m,1), 3.31(m,1), 4.95 (br t, 1), 7.5-8.0 (5).
71[f]		19, LAH[d]	95	0.94(d,*J*=6.6,two Me), 1.6-2.7(m,8), 3.65(m,1), 5.30(m,2), 7.5-8.0 (5).
72[k]		53, NaCN		1.8-3.2(m,6), 3.6-4.2(m,1), 5.0-5.8(m,3), 7.5-8.0(5).
73[l]		67[b], MCPBA	86	[e]1.13-1.37 (numerous Me signals) 1.5-2.3(m,5), 2.43(s,Me), 2.65-3.1 (m,2),3.29(m,1), 7.32 and 7.72 (4).
74[m]		68, MCPBA	96	[e]1.05-1.47 (six Me signals due to two isomers), 1.5-2.9(m,7), 3.4(br t,1) 7.5-8.0 (5).
75[n]		69, MCPBA	94	0.89(br d,two Me), 1.65(m,2), 2.44 (s,Me), 2.4-3.1(m,7), 7.32 and 7.76 (4).

76[o]		69[p], MCPBA	90	Isomer I: 0.90(s, three Me, and d,*J*= 6.6,Me), 1.65-3.45(m,9), 7.5-8.0(5). Isomer II: 0.90(s, three Me), 0.94 (d,*J*= 6.7,Me), 1.61-3.40(m,9),7.5-8.0(5).
77[q]		70, MCPBA	95	[e]0.92(d,*J*=6.8) and 0.96(d,*J*=6.8; C2-Me of two isomers,3), 1.24(s) and 1.27(s, two Me), 1.4-2.1(m,4), 2.61 (m,2), 3.05 (m,1), 3.35(m,1), 7.5-8.0 (5).
78[q]		71, MCPBA	95	[e]0.88,0.95,1.02(partly superimposed Me doublets), 1.1-2.8(m,10), 3.65 (m,1), 7.5-8.0(5).
79[r]		72, MCPBA	40	Isomer I: 1.8-2.3(m,2), 2.5-3.1(m,7), 4.04(pent,1), 7.5-8.0(5). Isomer II: 1.6-3.3(m,9), 3.85(pent,1), 7.5-8.0(5).

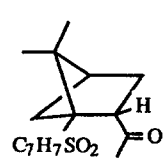
[a]See footnotes a,b,d of Table I. [b]Epoxidations were carried out with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at room temperature (see reference 1). [c]Obtained as a mixture of cis and trans double bond isomers, and probably also as 1,3-cis or trans isomers; GC-MS (CI) m/e 293 (M^++1); $C_{17}H_{24}O_2S$, *Mr* 292. [d]See reference 2. [e]Spectrum of a mixture of isomers. [f]Obtained as a mixture of cis and trans isomers; GC-MS(CI) m/e 279 (M^++1); $C_{16}H_{22}O_2S$, *Mr* 278. [g]A threefold excess of the cuprate in ether was used, 1.5h, 0°C (see references 2,4). [h]The yield relative to unrecovered 34 was 72%. [i]One isomer was obtained, mp 83-84°C (pentane); analysis: found C,69.15; H, 7.95. Calc. for $C_{16}H_{22}O_2S$: C,69.04; H,7.97%. [j]One isomer was obtained, GC-MS (CI) m/e 279 (M^++1); $C_{16}H_{22}O_2S$, *Mr* 278. [k]Obtained as a mixture of cis and trans isomers by reaction of the bicyclobutane with excess NaCN (4:1) in NMP at 70°C for one hour, and used directly for epoxidation. [l]Mixture of isomers. One single epoxide isomer was recovered from base treatment; HR-MS m/e 153.1328 (M^+-$C_7H_7SO_2$); calc. for $C_{10}H_{17}O$, 153.1279; ^1H NMR δ 1.17 (s, Me), 1.27(d, *J*=5.5, Me), 1.37(s,Me), 1.5-1.7(m, 3), 2.0-2.2 (m,2) 2.43(s,Me), 2.7-3.3(m,3), 7.32 and 7.73 (4). [m]Mixture of two isomers, HR-MS m/e 153.1371 (M^+-$PhSO_2$); calc. for $C_{10}H_{17}O$, 153·1279. [n]One isomer, mp 103-104°C (hexane); analysis found: C, 69.15; H, 7.95. Calc. for $C_{16}H_{22}O_3S$: C,65.29; H,7.53%. [o]The two diastere-omeric epoxides could be partly separated by chromatography. Isomer I, mp. 71-72°C (ether-hexane); analysis, found: C 67.22, H, 8.02%. Isomer II, mp. 108-109°C (ether-hexane); analysis, found: C 67.15, H, 8.09%. Calc. for $C_{18}H_{26}O_3S$: C,67.06; H,8.13%. [p]See Table VII. [q]Mixture of two diastereomers, GC-MS(CI) m/e 295 (M^++1); $C_{16}H_{22}O_2S$, *Mr* 294. [r]The cis and trans isomers could be separated by chromatography. Isomer II, mp. 86-87°C (CH_2Cl_2-hexane); analysis found C,60.37; H, 5.40; N, 5.11. Calc. for $C_{14}H_{15}NO_3S$: C,60.65; H,5.45; N,5.05%. Isomer I, obtained as a liquid, was analyzed by MS but did not show, like Isomer I, any recognizable fragments. Both isomers yielded, however, the same bicyclohexane product (Table IX).

Table IX. Preparation, Yields and Physical Properties of some 1-(Arylsulfonyl)bicyclo[2.1.1]hexanes[a,b]

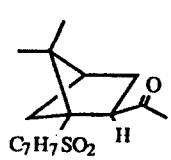
Product	Epoxide Precursor[c]	Yield %	mp, °C	^{1}H NMR	Analysis Formula	calculated found C %	H %
80	**73**	87[d]	119	(270 MHz) 0.30(s,Me), 1.28 (d,*J*=6.5,Me), 1.30(s,Me), 1.36 (m,1), 1.65 (d,*J*=8.0,1), 1.94 (br t,1), 2.04(br,1), 2.45(s,Me), 2.74 (m,1), 4.06(m,1), 5.40(s,1,OH), 7.36 and 8.00 (4)	$C_{17}H_{24}O_3S$	66.21 66.30	7.84 7.77
81	**73**		109	(270 MHz) 0.62(s,Me), 1.13(s, Me), 1.19 (d,*J*=6.5,Me), 1.79(m, 2), 2.03(s,1), 2.16(br,1), 2.30(d, *J*=7.2,1), 2.46(s,Me), 2.52(br,1), 2.84(d,*J*=4.1,1,OH), 4.67(m,1), 7.35 and 7.76 (4)	$C_{17}H_{24}O_3S$	66.21 66.22	7.84 7.80
82	**73**		105	(270 MHz) 1.19(s,Me), 1.27(s, Me), 1.29 (d,*J*=6.6,Me), 1.42(d, *J*=7.0,1), 1.77(m,1), 2.14(br,2), 2.29(m,1), 2.39(d,*J*=4.0,1,OH), 2.45(s,Me), 2.50(m,1), 7.34 and 7.75 (4)	$C_{17}H_{24}O_3S$	66.21 66.32	7.84 7.85
83 	**74**	71[e]	---	0.26(s,Me), 0.91(s,Me), 1.17(s, Me), 1.28 (br,1), 1.5-2.5(m,2), 2.35-2.8(m,2), 3.4-4.2[m,AB(X) dq after addition of D_2O,J_{AB}=12.5, J_{AX}=8.4, J_{BX}=3.4, 2), 7.5-7.7(m, 3), 8.0-8.1 (m,2)	$C_{16}H_{22}O_3S$[f]		
84 	**74**		76	0.93(s,Me), 1.06(s,Me), 1.27(s, Me), 1.5-2.5(m,5), 2.5-2.8(br,1, O*H*), 3.5-4.5[m,2; AB(X) dq after addition of D_2O, J_{AB}=11.8, J_{AX}= 6.9, J_{BX}=5.3], 7.5-8.0 (5).	$C_{16}H_{22}O_3S$	65.29 65.15	7.53 7.66
85 	**75**	34	108	0.63(d,*J*=6.4,Me), 1.06(d,*J*=6.8, Me), 1.0-2.3(m,5), 2.46(s,Me), 2.55(m,1), 3.5(br,1,O*H*), 3.70 and 4.13, [AB(X) dq after addition of D_2O, J_{AB}=11.8, J_{AX}=8.3, J_{BX}=4.2,2], 7.36 and 7.84 (4)	$C_{16}H_{22}O_3S$	65.29 65.42	7.53 7.63
86 	**76**	66[e]	---	0.59(d,*J*=6.5,Me), 0.77(s,t-Bu), 1.2-2.1(m,5), 2.6(br,1), 3.5-4.1(m,3, 2 after addition of D_2O), 7.5-8.0(5)	$C_{18}H_{26}O_3S$[g]		

87		76		---	0.81(s,t-Bu), 1.16(d,*J*=7.0,Me), 1.0-2.5(m,6), 3.5-4.3[m,3; AB(X) dq after addition of D_2O, J_{AB}=12.2, J_{AX}=8.3, J_{BX}=5.2, 2] 7.5-8.0(5)	$C_{18}H_{26}O_3S$[h]		
88		77	60[e]	88	1.14(d,*J*=6.8,Me), 1.33(s,Me), 1.59(s,Me), 1.2-2.1(m,5), 2.22 (br s,1), 2.69(t,*J*=7.7,1), 3.51 (br s,1,O*H*), 7.5-8.0 (5)	$C_{16}H_{22}O_3S$	65.29 65.35	7.53 7.47
89		77		94	0.59(d,*J*=6.4,Me), 1.34(s,Me), 1.42(s,Me), 1.3-2.0(m,5), 2.18 (br s,1), 2.55(br dd,1), 3.90 (br s,1,O*H*), 7.5-8.1 (5)	$C_{16}H_{22}O_3S$	65.29 65.24	7.53 7.45
90		78	58	95	0.84(d,*J*=6.6,Me), 1.05(d,*J*= 6.4,Me), 1.1-2.0(m,6), 2.1-2.5(m,3), 2.57(d,*J*=4.6,1,O*H*), 3.9(m,1; dd after addition of D_2O), 7.5-8.0 (5)	$C_{16}H_{22}O_3S$	65.29 65.17	7.53 7.45
91		79	53	118	1.6-2.0(m,2), 2.1-2.6(m,5), 2.8 (br,1,O*H*), 3.8(m,2), 7.5-8.0 (5)	$C_{14}H_{15}O_3S$	60.65 60.53	5.45[i] 5.32
92[j]			67	69	[k]1.33(dd,J_1=4.1, J_2=1.9,2), 1.79(s,4), 2.03(br s,2), 2.57 (br s,1), 7.5-8.0 (5)	$C_{12}H_{14}O_2S$	64.85 64.51	6.35 6.30

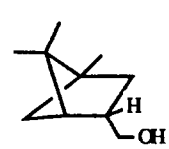
[a]See footnotes a-d, Table I. The shifts of the aromatic protons are given in this table. [b]All reactions were carried out by treatment of the epoxide precursors with 1.1-1.2 equivalents of BuLi in THF at 0°C. The progress of the reaction was checked by TLC. Purification and isomer separation were done by chromatography. Isomeric products are presented by order of elution from the chromatography column. [c]See Table VIII. [d]Combined yield of isomers **80-82**. [e]Combined yield of the two isomers. [f]GC-MS (CI) m/e 295 (M^++1); *Mr* 294. [g]HR-MS m/e 181.1625 (54.6%, M^+-$PhSO_2$), 163.1502 (20.4%, 181-H_2O), 57.0766 (100%, t-Bu); calc. for $C_{12}H_{21}O$, 181.1592. [h]HR-MS m/e 163.1455 (8.7%, M^+-H_2O-$PhSO_2$), 57.0699 (100%, t-Bu); calc. for $C_{12}H_{19}$, 163.1487. [i]N, calc. 5.05, found 5.19%. [j]Prepared by $LiAlH_4$ reduction of 27, mesylation, and treatment of the mesylate with BuLi in THF at 0°C. [k]Double irradiation experiments at 270 MHz show the endo protons at δ1.33 to be coupled with the exo protons (δ 2.03). The four protons of the ehtylene bridge (δ 1.79) are slightly coupled with the bridgehead proton (δ 2.57); when the former are irradiated, the latter appears as a sharp triplet due to a small coupling with the exo protons.



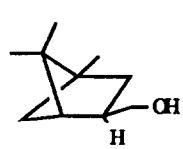
93



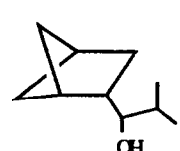
94



95



96



97

should then have structure **82** and the derived ketone - structure **94**.

The appearance of a high-field methyl signal allows the assignment of a trans hydroxymethyl-endo-methyl geometry to isomers **83**, **86** and **89**. In sulfone **85**, which has by construction two endo methyls, one appears at a relatively high field (δ 0.63) and the other at an expected position (δ 1.06).

A number of the bicyclic sulfones have been reduced with sodium in ethanol-THF (**83** and **84**) or with lithium in ethylanine (**90**) to yield the isoprenoid alcohols **95-97** in high yields. The chemical shifts of the three methyls in **95** are now very similar to those in **96**.

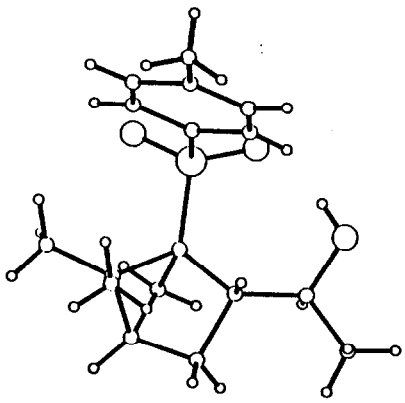


Figure II. Molecular structure of **80**. The distance between the hydroxyl hydrogen and the closest sulfur oxygen is 2.722Å. The distance between the plane of the aromatic ring and the endo-methyl carbon is approximately 3.43Å.

Experimental Section

General Procedures. Melting points were taken on a Fisher-Johns apparatus and were not corrected. FT-IR spectra were measured in chloroform with a Mattson Cygnus Spectrophotometer. Proton NMR spectra were measured with a Varian FT-80A spectrometer. Combined gas-chromatographic - mass spectral analysis (GC-MS) were performed with a Finnigan automated spectrometer. High resolution mass spectra (HR-MS) were measured with a Varian MAT 731 instrument.

A general description of standard procedures for reactions carried out with BuLi in THF, for epoxidation reactions, or for chromatographic separations is given in the experimental sections of references 1 and 4.

Preparation of 1: A slight modification of the general procedure,[1] especially as applied to the preparation of **1**, consists of adding 0.85 equiv of BuLi on the second addition instead of one full equivalent. This prevents a possible fast polymerization and lowering of the yield towards the end of the addition.

The procedure for the preparation of **1** is now as follows. To an ice-cooled solution of the starting epoxide [4-(phenylsulfonyl)-1,2-epoxybutane] in THF, a solution of BuLi in hexane (1.06 equiv) is added quite rapidly. This is followed after five minutes by the addition of methanesulfonyl chloride (neat, 1 equiv; 1 mmol=0.078 ml) and after another five minutes, by rapid dropwise addition of 0.85 equiv of BuLi. The reaction is worked up after 2-3 more minutes by addition of aqueous ammonium chloride, evaporation of most of the THF under reduced pressure, and partition between water and ether. The crude product is chromatographed on ten times its weight of silica gel (elution: hexane - dichloromethane - ethyl acetate, 10:8:1). Solid **1**, obtained by evaporation of the solvent and trituration with cold hexane in 55-60% yield, is pure for most further uses.

Sulfone **2** is similarly prepared in 70% yield (elution with hexane - ether, 7:3).

*Reduction of **41-II***: The cis-S,N isomer of azide **41** (2.4g) was stirred in ethyl acetate (50 mL) with 5% Pd/C catalyst (0.3g) under hydrogen, at atmospheric pressure and room temperature, for 20 h. After filtration of the catalyst, the solvent was evaporated and the residue taken in benzene (50 mL) and shaken at 0°C with 1N NaOH (8 mL) and benzoyl chloride (0.9 mL). Amide **45** was isolated in 94% yield (2.76g), mp 132-133°C (benzene-hexane); NMR δ 1.56 (br,6), 2.4-3.0 (m,4), 3.3-4.0 (m,5), 4.54 (br s, 1), 6.58 (s, 1, NH), 7.5-8.0 (m,10). Anal. Found: C, 64.74; H, 6.30; N, 3.32. Calc. for $C_{23}H_{27}NO_5S$: C, 64.32; H, 6.34; N, 3.26%.

*Reduction of **44-II***: The cis-S,N isomer of **44** (0.12g) was stirred in ethanol (3 mL) with PtO_2 catalyst (14 mg) under hydrogen, at atmospheric pressure and room temperature for 1h. The crude amine, obtained after filtration and evaporation of the solvent, was benzoylated with benzoyl chloride (0.06 mL) in pyridine (1 mL) for 20 h. The crude amide, obtained by extractive work up with CH_2Cl_2, was filtered over a plug of silica gel with ethyl acetate-hexane. Amide **46** was obtained in 79% yield (0.12g), mp 168-169°C (benzene-hexane); NMR δ1.1-1.7 (br,8), 2.50 (m,2), 3.1 (m,1), 3.47 (m,1), 6.37 (s, 1, NH), 7.3-7.9 (m,10). Anal. Found: C, 69.19; H, 6.31; N, 3.52. Calc. for $C_{21}H_{23}NO_3S$: C, 68.28; H, 6.28; N, 3.79%.

*Reductions of **38-I and II***: The trans isomer **38-I** (0.6g) was stirred in acetic acid (12 mL) and acetic anhydride (4 mL) with 5% Pd/C catalyst (0.135g) under hydrogen, at atmospheric pressure and room temperature for 4 h. The solid residue (0.62g) obtained after filtration of the catalyst and evaporation of the solvents, was pure by NMR. It was dissolved in warm CH_2Cl_2 and precipitated with ether, yielding 0.6g (94%) of trans-**47**, mp 151-152°C (CH_2Cl_2-hexane); NMR δ 1.92 (s,Me), 2.1-2.5 (m,2), 2.6-3.0 (m,2), 3.81 (m,1),4.40 (pent, 1), 7.5-8.0 (5); IR ($CHCl_3$) 1673, 1308, 1151 cm^{-1}. HR-MS m/e 112.0805 (100%, M-$PhSO_2$), 70.0663 (100%); Calc. for $C_6H_{10}NO$, 112.0848; C_4H_8N, 70.0656.

The cis isomer **38-II** was likewise reduced to yield cis-**47** in a similar yield. Mp 129-130°C NMR δ 1.94 (s,Me), 2.3-2.8 (m,4), 3.55 (pent, 1), 4.47 (m,1; pent after addition of D_2O), 6.5 (br d, 1, NH), 7.5-8.0 (5); IR ($CHCl_3$) 1666, 1309, 1150 cm^{-1}. HR-MS m/e 112.0784 (100%), 70.0664 (100%). Anal. Found C, 56.60; H, 5.76; N,5.40. Calc. for $C_{12}H_{15}NO_3S$: C, 56.91; H, 5.97; N, 5.53%.

Chemical reduction of **38-II** (0.75g) was carried out by warming it in acetic acid (11 mL) and acetic anhydride (16 mL), with added zinc powder (3.5g) for 2h at 100-130°C. The mixture was filtered while still warm and the solvents were evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried and re-evaporated to dryness. Trituration with ether-hexane, filtration and recrystallization from CH_2Cl_2-hexane yielded cis-**47** (285 mg, 35% yield). The mother liquors of trituration and crystallization were combined and evaporated to yield a residual liquid (420 mg), the NMR of which corresponded to a mixture of cis and trans **48**. Chromatography on silica gel (15g; elution hexane - CH_2Cl_2 - AcOEt, 5:5:1) provided an unseparated mixture of isomers **48** (0.21g, 26%), with an NMR spectrum very similar to that of the starting mixture before chromatography. NMR δ 2.02 s and 2.03 s (Me), 2.2-3.0 (m,4), 3.44 (pent, 1), 4.87 (pent, 1) with satellite multiplets at 3.8 and 4.2, 7.5-8.0 (5). GC-MS (two peaks) m/e 255 (100%, M^++1), 195 (29%, M^++1-CH_3COOH); $C_{12}H_{14}O_4S$, *Mr* 254.

The free amine derived from **38-I** was obtained by catalytic hydrogenations (PtO_2, EtOH). Its NMR spectrum was recorded [δ 1.78 (s, NH_2) 1.9-2.2 (m, 2), 2.6-2.9 (m, 2), 3.55-3.85 (m, 2), 7.5-8.0 (5)] before being acetylated to yield trans-**47**.

Addition of acetic acid to 1: A solution of **1** (0.2g) in acetic acid (1 mL) was warmed at 60°C for 4 h. A white precipitate formed in the reaction flask was insoluble upon work up with dichloromethane-water and was filtered off. The residue from the organic phase (0.18g) showed the presence of **1** and product only (^{1}H NMR). Chromatography on silica gel (6g; hexane-dichloromethane-ethylacetate 6:6:1) separated, recovered **1** (60 mg) from **49** (120 mg; 46% yield). NMR δ 1.03-1.22 (m,1), 1.50-1.75 (m,1), 1.85 (s, Me), 1.97-2.10 (m,1), 2.39-2.61 (m,1), 3.78 and 4.13 (d ABq, J_{AB}=10.7, J_{AX}=5.6, J_{BX}=7.6, 2), 7.5-8.0 (5); GC-MS (CI) m/e 255 (M^++1), $C_{12}H_{14}O_4S$, *Mr* 254. The product was identical to the acetylation product of trans-1-hydroxymethyl-2-(phenylsulfonyl)cyclopropane.[1]

Addition of phenylselenyl azide to 1: A mixture of phenylselenyl chloride (0.4g, 2.1 mmol) and sodium azide (0.13g, 2 mmol) was stirred and warmed in NMP (2 mL) at 60°C for 0.5 h. Sulfone **1** (0.35g, 1.8 mmol) was then added to the flask and the resultant solution was warmed at 85°C for 0.5 h. Extractive workup with water and ether provided 0.7g of a crude product that was chromatographed on silica gel (20g). Elution with hexane - ether (7:3) first furnished **50** (0.33g, 46% yield), NMR δ 2.15-2.65 (m,2), 2.85-3.35 (m,2), 4.07 (pent, 1) 7.1-8.1 (m,10); HR-MS m/e 66.0274 (8.4%, M^+-$PhSO_2$-N_2-PhSeH; Calc for C_4H_4N 66.0314). This was followed by the separated **51** isomers (50 and 85 mg, 21% yield), identical with the addition products of **1** and phenylselenol.

Addition of phenylselenol to 1: A solution of **1** (0.23g, 1.2 mmol) and phenylselenol (0.17g, 1.1 mmol) in benzene (3 mL) was warmed at 60°C for 1h. Extractive work up with ether and aq. sodium carbonate, followed by chromatography on silica gel (15g; hexane - ether 3:2) separated trans- and cis-**51** (120 and 133 mg, 72% yield).

Trans-**51**, NMR δ 2.1-2.5 (m,2), 2.85-3.25 (m,2), 3.65-4.25 (m,2), 7.1-8.0 (m,10). HR-MS m/e 53.0379 (100%; M^+ - $PhSO_2$ - PhSeH); calc. for C_4H_5, 53.0392.

Cis-**51**, NMR δ 2.63 (br t, 4), 3.70 (two, partly superimposed pent, 2), 7.1-7.9 (m,10). HR-MS m/e 53.0390 (10%).

Addition of phenylselenol to 52: A solution of **52** (170 mg, 0.77 mmol) and excess phenylselenol (350 mg, 2.2 mmol), with added AIBN (10 mg), was warmed at 80°C for 20 h. Work up and chromatography as above separated **54-I** (52 mg) from **54-II** (82 mg), with intermediate mixed fractions (41 mg; total yield 60%).

54-I, NMR δ 1.37 (d, *J*=8.0, Me), 1.60 (s, Me), 2.2-2.75 (m,2), 3.07 (m,1), 3.90 (q,1), 7.1-7.9 (m,10). HR-MS m/e 81.0728 (100%; M^+ - $PhSO_2$ - PhSeH); calc. for C_6H_9, 81.0705.

54-II, NMR δ 0.80 (d, *J*=7.2, Me), 1.41 (s, Me), 2.01 (dd, BX part of ABX dq, J_{AB}=12, J_{BX}=8, 1), 2.4-3.5 (m,3), 7.1-7.9 (m,10). HR-MS m/e 81.0752 (100%; M^+ - $PhSO_2$ - PhSeH).

Cyclobutenes 55 and 56: A mixture of isomers **54** (113 mg) was warmed intermittantly in THF (3 mL) and 0.5 mL 30% hydrogen peroxide at 50°C for 10 minutes. Addition of saturated sodium chloride and extraction with ether, followed by chromatography on silica gel (7g; hexane - ether 7:3) provided **55** and **56**.

Sulfone **55** was constituted mainly of the trans-isomer (methyl doublet at δ 1.01) but also contained the cis-isomer, and was not free of some **56** (GC-MS showed a ratio of ca. 12:5:2, respectively). NMR δ 1.01 (d, *J*=6.4, Me), 1.65 (br, Me), ca. 2.7 (m,1), 3.3 (m,1), 4.86 (br s,1) 7.5 (5). GC-MS (CI) m/e 223 (M^++1) for all three peaks; $C_{12}H_{14}O_2S$, *Mr* 222.

Sulfone **56**, NMR δ 1.65 (br s, two Me), 2.49 (br s,2), 4.05 (br s,1) 7.5-8.0 (5). GC-MS (CI) m/e 223.

Addition of phenylselenol to 53: The reaction was carried out under the same conditions as for **52**, but with an insufficient amount of phenylselenol (0.15g, 0.96 mmol for 0.3g, 1.3 mmol of **53**). Work up and chromatography as above separated recovered **53** (130 mg, 43%) from the addition product **58** (45 mg, identified by NMR only) and the elimination product **57** (65 mg, 16 and 38% yield, respectively, relatively to unrecovered **53**).

Product **58**, NMR δ 1.17 (d, *J*=6.3, 2), 1.8-2.8 (m,4), 3.8 (pent,1), 4.9-5.2 and 5.5-6.0 (m,3), 7.1-7.9 (m, 10).

Product **57**, NMR δ 2.67-2.83 (m,4), 4.15 (br s,1) 4.94 (br d, 1), 5.11 (d, *J*=1.1,1), 5.5-5.8 (m,2), 7.5-8.0 (5). GC-MS (CI) m/e 235; $C_{13}H_{14}O_2S$, *Mr* 234.

Addition of lithium bromide to 1: Sulfone **1** (0.69g, 3.6 mmol) was warmed in NMP (7 mL) with excess lithium bromide (2g, 23 mmol) at 100°C for 22h. Partition between ether and water, and chromatography on silica gel (50g; hexane - dichloromethane-ethyl acetate 8:8:1) separated bromide **60** (0.20g, 20%) from **59** (0.39g, 57%).

Product **59**, NMR δ 2.80 (d, *J*~2.9, 2), 4.32 (t, *J*~2.9, 1), 5.94 (d, *J*=2.8, 1), 6.35 (d, *J*=2.8, 1), 7.5-8.0 (5). HR-MS m/e 194.0359 (1.9%, M^+); calc. for $C_{10}H_{10}O_2S$, 194.0401.

Product **60**, mp 138-139°C (CH_2Cl_2-hexane). NMR δ 2.5-3.1 (m,4), 3.65 (pent, 1), 4.30 (pent, 1), 7.5-8.0 (5). Anal. Found: C, 43.94; H, 4.14; Br, 29.38. Calc. for $C_{10}H_{11}BrO_2S$: C, 43.65; H, 4.03; Br, 29.04%.

Epoxidation of **59** with *m*-chloroperbenzoic acid in dichloromethane (10 days, room temperature) furnished recovered **59** (25-30%) and **61** (60-65% yield). Epoxide **61**, mp 64-65°C (ether-hexane); NMR δ 2.15 (ddd) and 2.77 (dd, ABX_2, J_{AB}=12.7, $J_{AX}{}^1$=3.5, $J_{AX}{}^2$ ~0, $J_{BX}{}^1$=5.5, $J_{BX}{}^2$=2.2, C4-H_2), 3.52 (narrow m, C1-H), 4.02 (br s) and 4.13 (t, *J*=2.2, C2-H and C3-H), 7.5-8.0 (5). HR-MS m/e 68.0218 (2.9%, M^+-$PhSO_2H$); calc. for C_4H_4O, 68.0262. Anal. found: C, 57.32; H, 4.76. Calc. for $C_{10}H_{10}O_3S$: C, 57.14; H, 4.80%.

Ketones 93 and 94: Alcohols **80**, **81** and **82** were oxidized separately in ether with silica-supported sodium bichromate, as described,[13] and purified by passage on silica gel. Alcohols **80** and **81** yielded the same ketone (**93**), alcohol **82** yielded ketone **94**.

Ketone **93**, mp 86-87°C (hexane); NMR δ 0.88 (s, Me), 1.18 (s, Me), 1.65-2.3 (m, 5), 2.35 (s,Me), 2.44 (s, Me), 3.45 (m, 1), 7.33 and 7.74 (4); IR ($CHCl_3$) 1714, 1300, 1289, 1147 cm^{-1}. Anal. Found: C, 66.62; H, 7.29. Calc. for $C_{17}H_{22}O_3S$: C, 66.65; H, 7.24%.

Ketone **94**, mp 113-114°C (hexane); NMR δ 0.82 (s, Me), 1.38 (s, Me), 1.45-1.7 (m, 2), 2.13 (br, 3), 2.20 (s,Me) 2.43 (s, Me), 3.20 (m, 1), 7.31 and 7.78 (4); IR ($CHCl_3$) 1721, 1301, 1288, 1145 cm^{-1}. Anal. Found: C, 66.76; H, 7.19. Calc. for $C_{17}H_{22}O_3S$: C, 66.65; H, 7.24%.

Alcohols 95 and 96: To a solution of alcohol **83** (548 mg, 1.86 mmol) in THF (10 mL) and ethanol (1 mL), cooled to 5-10°C, small pieces of sodium (0.3g) were added and the mixture was stirred for 1.5 h. The solution was decanted from excess sodium, evaporated to dryness, taken with sat. NaCl solution, slightly acidified with 1N HCl and extracted with ether. Drying of the ether solution ($MgSO_4$) and evaporation of the ether gave **95** (235 mg, 82% yield), pure by NMR and not further purified. NMR δ 0.73 (s, Me), 0.91 (s,Me), 1.11 (s,Me), 1.5-2.5 (m,5), 1.54 (br s, OH), 3.63 (d, *J*=7.5,2); IR ($CHCl_3$) 3424, 2873-3000 br, 1462, 1376, 1368, 1010, 995 cm^{-1}. GC-MS (EI) m/e 139 (1.75%, M^+-CH_3), 123 (21.2%, M^+-CH_2OH), 111 (13.9%), 93 (24.4%), 81 (91.3%), 55 (100%).

995 cm^{-1}. GC-MS (EI) m/e 139 (1.75%, M^+-CH_3), 123 (21.2%, M^+-CH_2OH), 111 (13.9%), 93 (24.4%), 81 (91.3%), 55 (100%).

Alcohol **96** was similarly obtained from **84**. NMR δ 0.78 (s, Me), 0.93 (s,Me), 1.10 (s, Me), 1.2-2.2 (m,5), 1.5 (br, OH), 3.81 (d, *J*=7.0,2); IR ($CHCl_3$) 3388, 2878-3006 br, 1467, 1387, 1376, 1368,1315, 1286, 1219, 1213, 1147, 1043, 1027, 997 cm^{-1}. GC-MS (EI) m/e 139 (1.4%), 123 (21.4%), 111 (14.4%), 93 (23.6%), 81 (100%) 55 (94.9%).

Alcohol 97: Sulfone **90** (0.39 g) was dissolved in ethylamine (7 mL) at 0°C and excess lithium (ca. 0.1g) cut into small pieces was added to the solution. The mixture was stirred for 1.5 h, turning green to dark green. Solid ammonium chloride was added to the reaction mixture and the amine was evaporated. The residue was taken with saturated NaCl solution and extracted with ether, providing **97** (190 mg, 93% yield), pure by NMR and not further purified. NMR δ 0.94 (d, *J*=6.3, Me), 1.05 (d, *J*=6.3, Me), 1.1-2.5 (m,8), 2.36 (s, OH), 2.70 (br s, 1), 3.1-3.6 (m,1), 4.35 (dd,1). GC-MS (CI) m/e 155 (M^++1); $C_{10}H_{18}O$, *Mr* 154.

Preparation of 92: Alcohol **16** was reduced with lithium aluminium hydride in THF according to the general procedure described.[2] The crude cyclobutane product (1.75g) was obtained as a mixture of cis and trans isomers. NMR δ 1.5-2.8 (m,5), 3.4-3.8 (m,3), 7.5-8.0 (m,5). It was treated in dichloromethane (20 mL) at 0°C with triethylamine (1 mL) and mesyl chloride (0.6 mL) for 0.5 h. Extractive work up and chromatography on silica gel (20g; hexane - CH_2Cl_2 - ether 2:2:3) provided a mixture of cis and trans 1-(2-mesyloxy)ethyl-3-(phenyl-sulfonyl)cyclobutane (2.0g, 86% yield). NMR δ 1.8-2.7 (m,7), 2.98 (s,Me), 3.65 (m,1), 4.18 (two partly superimposed t,2), 7.5-8.0 (5). HR-MS m/e 177.0597 (11.1%, M^+ - $PhSO_2$), 81.0720 (100%, M^+ - $PhSO_2$ - CH_3SO_3H); calc. for $C_7H_{13}O_3S$: 177.0585; for C_6H_9: 81.0704.

The mixture of mesylates (1.5g) was treated in THF (40 mL) at 0°C with 1.2 molar equiv of BuLi and was then warmed to room temperature. Work up after 20 h, followed by chromatography (silica gel, 20g; hexane - ether 4:1) provided **92** (see Table IX).

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