Stereoselectivity of the .alpha.-sulfenylation of 4-phenylbutyrolactone. Configurational and conformational analyses by proton NMR spectroscopy

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Table III. Kinetic Data for the Reaction of *o*-1 with MnO_2/THF at 45 °C

run	$[o\text{-}1]_0$, M	quantity of MnO_2[a]	k_1[b]	κ[c,d]	$(k_2 + k_2')$[b,f]	K[c,g]	(k_2/k_2')[c,i]	k_2[b,h]	(k_2')[b,h]
14	0.040	0.13	2.2	0.10 (0.09)	0.22	2.6	1.6	0.135	0.084
15	0.026	0.15		0.08 (0.05)		2.7	1.4		
16	0.090	0.15		0.07 (0.07)		2.8	1.2		
av				0.08 ± 0.02		2.7 ± 0.1	1.4 ± 0.2		

[a] Expressed in (moles of MnO_2 added/L of original reaction mixture). [b] Rate constants k_1, k_2, and k_2' are in units of 10^{-4} M^{-1} s^{-1}. [c] Error limits are standard deviations. [d] Values in parentheses calculated with the method in ref 11. [e] Mean of a point-by-point κ. [f] Calculated from $k_2 + k_2' = \kappa k_1$. [g] Mean of a point-by-point K (=[5]/[*o*-2]). [h] Calculated from $k_2 + k_2'$ and k_2/k_2'. [i] Mean of a point-by-point k_2/k_2' (=[*o*-3]K/[6]).

Table IV. Bond Dissociation Energies of Benzylic C–H Bonds from Extended Hückel Calculations

compd	BDE, eV	compd	BDE, eV
o-1	4.33	*m*-2	5.31
o-2	4.94	*p*-1	5.31
5	5.98	*p*-2	5.02
m-1	5.18		

withdrawn every 2–6 h, filtered, diluted with water, and analyzed by HPLC (or filtered, evaporated, dissolved in acetone-d_6/TMS and analyzed by ^{1}H-NMR spectroscopy). Absolute concentrations of **1** (or **4**), **2**, and **3** (or benzaldehyde) were determined from HPLC or ^{1}H-NMR integrations (corrected for response factors) and the known initial concentration of the alcohol. The unreacted amount of MnO_2 at each analysis time was calculated from its known initial amount less the total amount of aldehyde product(s) formed. Thus in the reaction of benzyl alcohol (moles of MnO_2/L of original reaction mixture) = (initial moles of MnO_2/L of original reaction mixture) − [benzaldehyde] and in the reaction of the diols (moles of MnO_2/L of original reaction mixture) = (initial moles of MnO_2/L of original reaction mixture) − [2] − 2[3].

The apparent rate constant k for the reaction of benzyl alcohol was determined by a usual second-order rate plot. The determination of the apparent rate constants for the consecutive-competitive reactions of *p*-1 and *m*-1 was performed as before[2,3] by the graphical integration method of Wideqvist.[10] For each data point the value of ln ($[1]_0/[1]$) and Θ ($\equiv\int_0^t$ {unreacted moles of MnO_2/L of original reaction mixture} d*t*) were determined. The value of k_1 was found as the slope of a linear plot of ln ($[1]_0/[1]$) versus Θ. Then for each data point, the value of κ ($=k_2/k_1$) was determined from the equation

$$\frac{1}{\kappa - 1}\left[1 - \left(\frac{[1]}{[1]_0}\right)^{\kappa-1}\right] - \frac{[2]}{[1]} = 0$$

The κ value for a given run was the mean of the point-by-point κ values. From this value, k_2 was calculated ($k_2 = \kappa k_1$). The value of κ was determined also by a computational method, the details of which can be found in ref 11. For the kinetic analysis of the reaction of *o*-1 the concentrations of *o*-1, *o*-2, *o*-3, **5**, and **6** were determined from ^{1}H-NMR integrations and the known initial amount of *o*-1. The unreacted amount of MnO_2 was calculated from the equation (moles of MnO_2/L of reaction mixture) = (moles of MnO_2 initially added/L of reaction mixture) − [*o*-2] − 2[*o*-3] − [5] − 2[6]. The value of k_1 was determined graphically as described above. The κ value in this reaction (Scheme IV) defined as $\kappa = (k_2 + k_2')/k_1$ was determined from the equation

$$\frac{1}{\kappa - 1}\left[1 - \left(\frac{[o\text{-}1]}{[o\text{-}1]_0}\right)^{\kappa-1}\right] - \frac{[o\text{-}2] + [5]}{[1]} = 0$$

The κ value for a given run was again the mean of the point-by-point κ values.

Partial 250-MHz proton NMR and mass spectral data of the species involved in this reaction are given below. In each case these data were consistent with previously published lower resolution spectra. Spectra of pure material in acetone-d_6/TMS were obtained for *o*-1 and *o*-3, whereas the data for *o*-2, **5**, and **6** were obtained by GC/MS and ^{1}H-NMR analysis of the reaction mixture after the appropriate treatment. Acetone-d_6/TMS was used for all NMR analyses; peaks marked with an asterisk are those used for determining relative amounts of reactants and products. Acetone or THF was used as a solvent for the GC/MS analyses. The numbers in parentheses in the MS spectra are relative abundances.

***o*-1**: ^{1}H NMR[20] δ 4.31* (t, J = 4.8 Hz, 2 H), 4.71 (d, J = 4.8 Hz, 4 H). For the MS spectrum, see ref 2a.

***o*-2**: ^{1}H NMR[21] δ 4.47 (t, J = 5 Hz, 1 H), 5.03* (d, J = 5 Hz, 2 H), 10.28* (s, 1 H); MS *m*/*z* 136 (10), 135 (13), 119 (13), 118 (97), 92 (11), 91 (21), 90 (82), 89 (100), 87 (8), 86 (9), 85 (5), 79 (15), 77 (28), 74 (7), 65 (7), 64 (13), 63 (65), 62 (34), 61 (14), 59 (13), 53 (7), 52 (7), 51 (25), 50 (24), 49 (7), 43 (5), 40 (8), 39 (48), 38 (17), 37 (12).

***o*-3**: ^{1}H NMR[22] δ 10.54* (s, 2 H); MS *m*/*z* 135 (3), 134 (26), 133 (15), 107 (3), 106 (36), 105 (100), 79 (2), 78 (19), 77 (99), 76 (13), 75 (8), 74 (18), 73 (4), 63 (6), 62 (6), 61 (4), 53 (5), 52 (14), 51 (72), 50 (50), 49 (7), 39 (16), 38 (11), 37 (9).

5: ^{1}H NMR[21] δ 4.91 (d, J = 13 Hz, 1 H), 5.12* (dd, J_1 = 2 Hz, J_2 = 13 Hz, 1 H), 5.58 (d, J = 7.5 Hz, 1 H), 6.41 (dd, J_1 = 2 Hz, J_2 = 7.5 Hz, 1 H); MS *m*/*z* 119 (12), 118 (96), 91 (5), 90 (63), 89 (100), 87 (14), 86 (8), 85 (4), 64 (12), 63 (54), 62 (25), 61 (12), 59 (17), 51 (10), 50 (13), 43 (12), 41 (8), 40 (5), 39 (37), 38 (16), 37 (12).

6: ^{1}H NMR[23,24b] δ 5.36* (s, 2 H); MS[24] *m*/*z* 134 (33), 133 (16), 106 (29), 105 (85), 89 (8), 78 (18), 77 (100), 76 (14), 75 (10), 74 (19), 73 (7), 63 (10), 62 (8), 61 (6), 53 (8), 52 (16), 51 (71), 50 (48), 49 (9), 39 (19), 38 (13), 37 (13).

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Stereoselectivity of the α-Sulfenylation of 4-Phenylbutyrolactone. Configurational and Conformational Analyses by ^{1}H NMR Spectroscopy[1]

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γ-Butyrolactones have emerged as important synthons and building blocks for the synthesis of complex natural products.[2] Their stereochemistry and conformational

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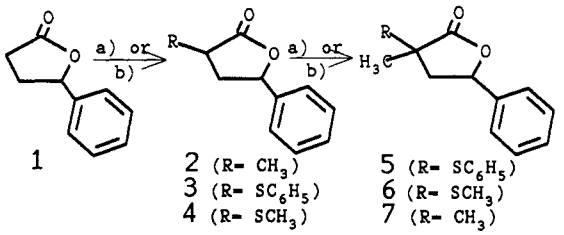

Figure 1. (a) Sulfenylation: (1) LDA/THF, (2) RSSR. (b) Methylation: (1) LDA/THF, (2) CH_3I.

behavior are interesting because of their potential as optically active reagents.[2-4] Highly diastereofacial alkylations of electrophiles at C-2 of substituted γ-butyrolactones have been reported, showing that reactions occur preferentially anti to the C-4 substituent.[5-7] Herein, we present our results on stereoselective α-sulfenylations of 4-phenylbutyrolactone (1). These reactions are noteworthy because they give a high proportion of the cis isomers: 2-(phenylthio)- or 2-(methylthio)-4-phenylbutyrolactones (3-cis and 4-cis). In contrast, the same sulfenylation reactions performed on 2-methyl-4-phenylbutyrolactone (2) as well as methylation of 1 and 3 proceed trans to the phenyl group with high stereoselectivity. The stereochemistry and the conformational equilibria of the substituted butyrolactones are also reported.

Results and Discussion

The sulfenyl derivatives were prepared by reaction of the lithium enolates of 4-phenylbutyrolactone (1) and 2-methyl-4-phenylbutyrolactone (2) with diphenyl disulfide or dimethyl disulfide under different reaction conditions as described in the Experimental Section, Figure 1. The reaction of the lithium enolate of 1 with diphenyl disulfide afforded a mixture of cis and trans isomers (3-cis and 3-trans) in a 60/40 ratio. On the other hand, the reaction of the same lithium enolate of 1 with dimethyl disulfide gave a mixture of cis and trans isomers (4-cis and 4-trans) in a 80/20 ratio. We considered it important to understand why the sulfenylation reactions of 1 afforded unexpected proportions of the cis isomers and so decided to analyze the methylation of the enolate of 1 that gives 2-trans and 2-cis in a 94/6 ratio. These contrasting results eliminate the possibility that the phenyl group acts as a directing group for a cis attack.

Another explanation for the stereochemistry of α-sulfenylation is based on a base-catalyzed equilibration of the initially formed α-sulfenyl compounds. In order to check this idea, we treated the isomer mixture of 2-trans and 2-cis (94/6%) with lithium diisopropylamide (LDA) followed by hydrolysis at −78 °C and obtained predominantly 2-cis (90%), indicating that at this temperature the protonolysis of the enolate is diastereoselective and anti to the phenyl group. However, the protonolysis at room temperature loses its stereoselectivity and gives a 46/54 isomer ratio (cis/trans).

In order to establish the diastereoselectivity of the

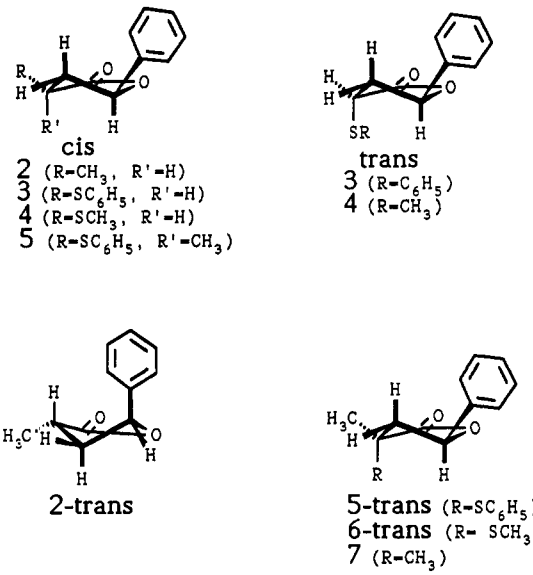

Figure 2. Configuration and conformation of the studied lactones.

protonation of 3, the mixture of 3-cis and 3-trans was separated by chromatography on a silica gel column. Each isomer was converted to the enolate with LDA and protonated with a mixture of AcOH/MeOH/THF at −78 °C to give the same isomer ratio (60/40 of cis/trans, respectively). The methyl sulfenylation isomers (4-cis and 4-trans, 80/20 ratio) could not be separated, but the mixture was submitted to the same protonation conditions described previously, affording 68/32 ratios of the cis/trans isomers, respectively. The results of the protonations clearly show that the initial products of the sulfenylation reaction undergo base-catalyzed equilibration. The role of the acidic proton at C-2 in the stereochemistry of sulfenylation reaction was investigated through the reaction of the lithium enolate of 2-trans with diphenyl disulfide or with dimethyl disulfide in the reaction conditions mentioned before. The reactions were completely stereoselective, affording the 5-trans or 6-trans isomers. Also, α-methylation of both the 3-cis and 3-trans isomers was carried out using the lithium enolate anion prepared by reaction with LDA in THF. Each isomer separately afforded a mixture of methylated isomers 5-cis and 5-trans in a ratio of 90/10. It was observed that sulfenylation and methylation reactions as well as protonation of 2 proceed by attack from the face opposite to the phenyl group. In all these molecules the absence of a proton in C-2 avoids the re-enolization, giving stereoselective substitution trans to the phenyl group.

As was reported before for other lactones,[7] it is remarkable that lactone 1 can give both methylated isomers 2-trans or 2-cis in high yield either by direct alkylation or by protonation at low temperature and that both isomers 5-trans or 5-cis can be obtained from the methylation and sulfenylation reactions by changing the sequence of the reactions. Sulfenyl derivatives 3 and 4 were found to be stable under acidic conditions at room temperature and several hours at 140 °C in DMSO solution. But 3-cis or 3-trans can be epimerized at room temperature in a THF solution with diisopropylamine to give a ratio of isomers cis/trans of 60:40. Also the 80:20 mixture of 4-cis and 4-trans gave, under the same conditions, an isomer ratio of 55:45, evidencing the acidity of the C2-H.

Slow crystallization of the mixture (about 2 months) of 3-cis/3-trans (60/40, respectively) yielded pure cis or trans isomers, through an asymmetric transformation of second order,[8] which has been shown to occur when crystallization

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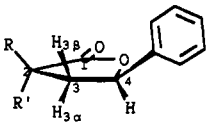
Table I. Coupling Constants and Calculated Dihedral Angles Based on Vicinal Hydrogen Coupling Constants (^3J)[10]



	J (Hz)/dihedral angles (deg)				
compound	H_2–$H_{3\alpha}$	H_2–$H_{3\beta}$	$H_{3\alpha}$–H_4	$H_{3\beta}$–H_4	$H_{3\alpha}$–$H_{3\beta}$
2-cis	8.6/26	15.2/160[e]	5.3/38	10.6/155	15.2
2-trans[c,d]	8.5/143	8.5/27	7.5/54	4.8/21	12.7
3-cis[a]	8.6/26	11.2/160	6.6/29	9.9/148	13.2
3-trans[b]	1.0/91	7.6/33	5.9/34	9.6/146	13.5
3-trans[c,d]	4.0/53	7.9/31	6.6/29	7.9/136	13.8
4-cis[a]	8.8/24	10.9/158	6.2/31	9.6/146	13.1
4-trans[a,d]	3.2/60	7.6/33	6.4/30	9.0/142	12.6
5-cis[a,g]			7.3/23	9.2/145	13.9
5-trans[f]			5.3/34	10.5/155	13.9
5-trans[c]			5.6/36	10.5/155	13.9
6-trans			5.6/36	10.7/156	13.7
7			6.2/32	9.9/148	12.8

[a] Same coupling constants in C_6D_6 and $CDCl_3$. [b] THF-d_8 at −105 °C. [c] C_6D_6. [d] In conformational equilibrium. [e] This coupling constant has an abnormally high value; we have assumed the dihedral angle based on examination of Dreiding stereomodels. [g] $^2J_{gem}$ = 13.2 Hz in $CDCl_3$. [f] $CDCl_3$.

is slower than the interconvertion rate of isomers. At present, we have not been able to direct the crystallization to a specific isomer by seeding the isomeric mixture with crystals of a pure isomer.

In an excess of LDA and methyl iodide the lactone 1 gave the C-2 dimethylated compound 7; this compound was very useful in the assignment of the configuration of the methyl derivatives.

NMR Stereochemical Analyses. Particular attention was placed on elucidating the configuration and conformation of all lactones prepared in this work, Figure 2. This information was deduced from the ^1H NMR chemical shifts and coupling patterns of the spectra as well as from dihedral angles calculated from J(H–H)[9] (Table I). Additional information was obtained from J(C–H) and NOESY experiments on the methylated compounds. In some cases the ^1H NMR spectra in C_6D_6 showed a strong upfield benzene-induced solvent shift effect for all ring protons, in particular for H-3β which is on the same face as the phenyl group. Improved resolution was attained in C_6D_6 which allowed observation of the CH_2 AB system.

The ^1H NMR spectrum of 3-cis shows that the heterocycle exists predominantly in one conformation. The two large coupling constants between H-2 and H-3β (11.2 Hz, 160°) and H-3β and H-4 (9.9 Hz, 148°) are indicative of the cis structure (Table I). The data allow us to conclude that both substituents are pseudoequatorial, based on calculated dihedral angles between the ring hydrogens and from the fact that the alternative conformation with the two substituents in pseudoaxial position is very unlikely and should exhibit smaller coupling constants.

The 3-trans diastereomer is in conformational equilibrium between two conformers having substituents in pseudoaxial and pseudoequatorial positions (in $CDCl_3$ or THF-d_8, at 27 °C and at 270 MHz). At −90 °C in THF-d_8 the molecule is frozen and complex coupling patterns are observed. The assignment of the ^1H NMR spectra were confirmed by comparison with the calculated spectrum.[10]

Analysis of the coupling constants of 3-trans gave us the dihedral angles between hydrogen atoms and allows us to propose the structure of the anchored conformation (J(H2–H3α) = 1 Hz, 91°; J(H2–H3β) = 7.6 Hz, 33°; J(H3β–H4) = 9.6 Hz, 146°) in which the phenylthio group is pseudoaxial and the phenyl group is pseudoequatorial. The predominance of this conformer can be rationalized in terms of the longer C–S bond length compared to the C–C bond which renders the sulfur more stable in the axial position than the phenyl group. The coalescence temperature (−10 °C) of the AB system allowed us to calculate the energy for the ring inversion as $\Delta G^* = 12.9$ kcal/mol in THF.

It is noteworthy that the same compound in C_6D_6 at 27 °C appears in a conformational equilibrium shifted largely to the conformer observed at −105 °C (THF-d_8), which has the sulfenyl group in pseudoaxial position and the phenyl group in pseudoequatorial position. In this case it is reasonable to assume that benzene forms a stacking complex with the phenyl group of the molecule, slowing ring inversion.

The *cis*-methylthio compound 4-cis presents the same preferred conformation as compound 3-cis, as can be observed from data in the table. The corresponding trans lactone (4-trans) was observed in conformational equilibrium at probe temperature in $CDCl_3$ and its coupling pattern is very similar to that of 3-trans recorded under the same conditions.

The lactone 2-cis was found in the same preferred conformation as compounds 3-cis and 4-cis. The corresponding 2-trans compound presents a complex ^1H NMR spectrum in THF-d_8. Addition of C_6D_6 induces complete separation of all the lines and thus coupling constants can be obtained. The molecule seems to be frozen in one conformation with the methyl group in pseudoequatorial position and the phenyl group in pseudoaxial position. The trans configuration was established on the basis of coupling pattern and was confirmed by a NOESY phase-sensitive experiment.[11]

The conformation of 5-cis is locked, according to the ^1H NMR spectrum in $CDCl_3$ or C_6D_6 at 270 MHz. Its configuration was established by a NOESY experiment which shows an interaction between H-4 and the methyl group, establishing their proximity and therefore their axial position. Also, the methyl group shows interaction with H-3α. 3-cis and 5-cis show the same coupling pattern.

The NOESY experiment shows that the methyl group of 5-trans interacts with H-3β and that H-4 is next to H-3α. There is no shielding of the methyl by the phenyl group, evidencing that neither of these groups is in axial position. The coupling pattern again is similar to that of the 3-trans isomer. The NOESY experiment shows for 6-trans that the methyl group and H-3β are interacting with the phenyl group and therefore that it is the trans isomer. The coupling constants and chemical shifts support the assignment. Compound 7 was found anchored at room temperature. The preferred conformer has the phenyl group in pseudoequatorial position.

Conclusion

It was found that the sulfenylation of 2-methyl-4-phenylbutyrolactone and methylation reactions of 4-phenylbutyrolactone afford predominantly the trans isomers, as was found in other alkylation reactions of 4-sub-

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stituted γ-lactones.[7] In contrast sulfenylation reactions of 4-phenylbutyrolactone give the cis isomers predominantly, evidently as a result of a base-catalyzed equilibration of the C-2 sulfenylated lactones. A very interesting observation of a second-order asymmetric transformation of compounds 3-cis and 3-trans was made. A very careful NMR study allowed the configuration and conformation of the lactones to be established.

Experimental Section

All melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz, respectively. The isomeric mixtures were separated using medium pressure column chromatography by using silica gel (60 G) as an adsorbent and hexane–CH_2Cl_2 mixtures as the eluent. NMR NOESY spectra were recorded on a JEOL 270-GXS (270 MHz), at 27 °C, using a 90° pulse for ^1H, with 64 scans and mixing times of 500 ms, and double FT was performed using FT-POWER with the sine-bell function. The NOESY phase-sensitive experiment was performed according to ref 11.

Phenylsulfenylation of Dihydro-5-phenyl-2(3*H*)-furanone (4-Phenylbutyrolactone, 1). To a solution of diisopropylamine (0.33 mL, 2.35 mmol) in dry THF (10 mL) was added 0.67 mL of *n*-butyllithium (2.35 mmol, 3.4 M in THF) at −78 °C under nitrogen. The mixture was stirred for 30 min at this temperature. The lactone 1 (0.346 g, 2.13 mmol) was dissolved in dry THF (5 mL), cooled to −78 °C, and added to the LDA solution, and the reaction mixture was stirred at −78 °C over 30 min. Diphenyl disulfide (0.55 g, 2.56 mmol) was dissolved in 5 mL of THF at −78 °C and was added dropwise to the reaction mixture. After the mixture was stirred at −78 °C for 3 h, the reaction was quenched with 1.0 mL of a cool solution (78 °C) of AcOH/MeOH/THF (1:1:1). The organic phase was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. The crude reaction product was a yellow crystalline powder (0.575 g, 90%) consisting of a 60/40 isomer ratio of cis/trans isomers as established by proton NMR on the basis of the signals of H-2 obtained in CW mode at 90 MHz. Separation of 1 g of the reaction mixture by column chromatography afforded 0.55 g (55%) of the known[12] 3-cis and 0.36 g (36%) of 3-trans. Similar reactions but with a different order of addition of the reagents (LDA over the lactone 1) or different stoichiometry of the LDA/lactone (0.5:1; 1:1; 1.5:1, respectively) or different dilution or different reaction times afforded the same ratio of isomers.

***cis*-Dihydro-5-phenyl-3-(phenylthio)-2(3*H*)-furanone (*cis*-2-(phenylthio)-4-phenylbutyrolactone, 3-cis):** mp 90–93 °C; IR (KBr) 1775 and 1769 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.39 (C=O), 79.08 (C-4), 46.72 (C-2), 38.37 (C-3), phenyl group 138.32 (C_i), 129.30 (C_o), 128.77 (C_p), 125.62 (C_m), phenylthio group 131.77 (C_i), 133.83 (C_o), 128.67 (C_p), 128.73 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 4.07 (1 H, dd, H-2), 5.33 (1 H, dd, H-4), 2.97 (1 H, ddd, H-3α), 2.2 (1 H, ddd, H-3β); (C_6D_6) δ 2.90 (1 H, dd, H-2), 4.00 (1 H, dd, H-4), 1.54 (1 H, ddd, H-3α), 1.25 (1 H, ddd, H-3β). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.85; H, 5.11.

***trans*-Dihydro-5-phenyl-3-(phenylthio)-2(3*H*)-furanone (*trans*-2-(phenylthio)-4-phenylbutyrolactone, 3-trans):** mp 81–82 °C; IR (KBr) 1777 and 1760 cm^{-1}; ^{13}C NMR (C_4D_8O, −105 °C) 174.60 (C=O), 80.70 (C-4), 45.05 (C-2), 38.47 (C-3), phenyl group 139.42 (C_i), 129.38 (C_o), 128.60 (C_p), 125.51 (C_m), phenylthio group 132.94 (C_i), 133.41 (C_o), 128.82 (C_m), 128.48 (C_p) ppm; ^1H NMR ($CDCl_3$) δ 3.96 (1 H, m, H-2), 5.39 (1 H, m, H-4), 2.57 (2 H, m, H-3α and H-3β); (C_4D_8O, −105 °C δ 4.38 (1 H, dd, H-2), 5.55 (1 H, dd, H-4), 2.54 (1 H, ddd, H-3α), 2.65 (1 H, ddd, H-3β); (C_6D_6) δ 3.51 (1 H, dd, H-2), 5.01 (1 H, dd, H-4), 2.04 (1 H, ddd, H-3α), 1.84 (1 H, ddd, H-3β). Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 70.98; H, 5.15.

Methylsulfenylation of Dihydro-5-phenyl-2(3*H*)-furanone (1). A solution of lactone 1 (0.34 g, 2.13 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at −78 °C over 30 min. Dimethyl disulfide (0.22 g, 2.35 mmol) was dissolved in 5 mL of dry THF, at −78 °C, and was added dropwise to the reaction mixture. After the mixture was stirred at −78 °C for 3 h, the reaction was quenched as reported for phenylsulfenylation. The mixture was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. The crude product was a yellow liquid (0.40 g) that after purification by column chromatography afforded the cis/trans mixture as a viscous liquid (0.28 g, 70% yield). Separation of isomers could not be attained. The mixture was observed directly by proton NMR and the isomer ratio (80/20 of cis/trans) was measured from the analyses of the signals of H-4.

***cis*-Dihydro-3-(methylthio)-5-phenyl-2(3*H*)-furanone (cis-2-(methylthio)-4-phenylbutyrolactone, 4-cis):** IR ($CHCl_3$) 1774 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.96 (C=O), 78.88 (C-4), 43.28 (C-2), 33.77 (C-3), 13.88 (methylthio), phenyl group 138.63 (C_i), 128.70 (C_p), 128.57 (C_o), 125.38 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 2.21 (3 H, s, CH_3S), 2.07 (1 H, dd, H-3β), 2.93 (1 H, ddd, H-3α), 3.72 (1 H, dd, H-2), 5.34 (1 H, dd, H-4), 7.30 (5 H, m, H-aromatic) ppm.

***trans*-Dihydro-3-(methylthio)-5-phenyl-2(3*H*)-furanone (*trans*-2-(methylthio)-4-phenylbutyrolactone, 4-trans):** IR ($CHCl_3$) 1775 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.29 (C=O), 79.84 (C-4), 41.99 (C-2), 38.03 (C-3), 14.58 (methylthio), phenyl group 138.48 (C_i), 128.43 (C_o), 128.31 (C_p), 125.52 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 2.27 (3 H, s, CH_3S), 2.48 (1 H, dd, H-3β), 2.44 (1 H, dd, H-3α), 3.52 (1 H, dd, H-2), 5.60 (1 H, dd, H-4), 7.30 (5 H, m, H-aromatic) ppm.

Methylation of Dihydro-5-phenyl-2(3*H*)-furanone (1). A solution of the lactone 1 (0.34 g, 2.13 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-Buli (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at the same temperature over 30 min. Methyl iodide (0.16 g, 2.56 mmol) was dissolved in 5 mL of dry THF, cooled to −78 °C, and added dropwise to the reaction mixture. After the mixture was stirred at −78 °C for 3 h, the reaction was quenched as reported for the phenylsulfenylation, extracted with $CHCl_3$ (10 mL), and washed with water (4 × 5 mL) and the solvent was dried and removed. The crude product was a yellow liquid (0.37 g) that was observed directly by ^1H NMR (CW, 90 MHz) and the isomer ratio was measured from the analyses of the signals of H-4. After purification of the reaction mixture by column chromatography, 0.33 g of the trans isomer was obtained (90%).

***trans*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-methyl-4-phenylbutyrolactone, 2-trans):** IR ($CHCl_3$) 1768 cm^{-1}; MS *m/z* (rel intensity) 176 (M^+, 90), 132 (48), 117 (100), 105 (80), 77 (37) 42 (50); ^{13}C NMR ($CDCl_3$) 179.19 (C=O), 78.57 (C-4), 38.92 (C-2), 34.10 (C-3), 15.60 (CH_3), phenyl group 141.69 (C_i), 129.22 (C_o), 128.50 (C_p), 125.85 (C_m) ppm; ^1H NMR (C_6D_6) δ 1.20 (3 H, d, CH_3), 2.11 (1 H, ddd, H-3β), 2.20 (1 H, ddd, H-3α), 2.53 (1 H, tq, H-2), 5.40 (1 H, dd, H-4), 7.28 (5 H, m, H-aromatic) ppm.

Methylation of Dihydro-5-phenyl-3-(phenylthio)-2-(3*H*)-furanone (3). The lactone 3-cis or 3-trans (0.50 g, 1.85 mmol) and LDA (2 mmol) in 50 mL of dry THF were maintained at −78 °C for 1.5 h. A solution of methyl iodide (1.43 mL, 2.30 mmol) in dry THF (10 mL) was added and the reaction mixture was stirred for 8 h at −78 °C and then allowed to reach room temperature before being quenched using a saturated aqueous solution of NH_4Cl. The mixture was extracted with CH_2Cl_2, dried, concentrated, and separated by column chromatography. In both cases the reaction yield was 97% (0.51 g) and the isomer ratio 90/10 of cis/trans (0.45 and 0.05 g, respectively).

***cis*-Dihydro-3-methyl-5-phenyl-3-(phenylthio)-2(3*H*)-furanone (*cis*-2-methyl-2-(phenylthio)-4-phenylbutyrolactone, 5-cis):** mp 71–73 °C; IR (KBr) 1764 and 1761 cm^{-1}; ^{13}C NMR ($CDCl_3$) 177.36 (C=O), 77.29 (C-4), 52.77 (C-2), 43.99 (C-3), 23.59 (CH_3), phenyl group 138.72 (C_i), 128.62 (C_o), 129.19, (C_p), 125.60 (C_m), phenylthio group 130.36 (C_i), 136.94 (C_o), 129.76 (C_p), 129.19 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 1.65 (3 H, s, CH_3), 5.33 (1 H, dd, H-4), 2.60 (1 H, dd, H-3α), 2.40 (1 H, dd, H-3β); (C_6D_6) δ 1.32 (3 H, s, CH_3), 4.78 (1 H, dd, H-4), 1.96 (1 H, dd, H-3α), 2.18 (1 H, dd, H-3B). Anal. Calcd for $C_{17}H_{16}O_2S$: C, 71.80; H, 5.67. Found: C, 71.54; H, 5.61.

***trans*-Dihydro-3-methyl-5-phenyl-3-(phenylthio)-2-**

(12) Iwai, K.; Kosugi, H.; Uda, H.; Kwai, M. *Bull. Chem. Soc. Jpn.* 1977, *50*, 242.

(3*H*)-furanone (*trans*-2-methyl-2-(phenylthio)-4-phenylbutyrolactone, 5-trans): mp 115 °C; IR (KBr) 1762 cm^{-1}; ^{13}C NMR ($CDCl_3$) 175.67 (C=O), 77.78 (C-4), 51.57 (C-2), 46.22 (C-3), 23.43 (CH_3), phenyl group 138.56 (C_i), 129.07 (C_o), 128.60 (C_p), 125.52 (C_m), phenylthio group 129.32 (C_i), 137.25 (C_o), 130.21 (C_p), 128.78 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 1.55 (3 H, s, CH_3), 5.52 (1 H, dd, H-4), 2.76 (1 H, dd, H-3α), 2.31 (1 H, dd, H-3β); (C_6D_6) δ 1.29 (3 H, s, CH_3), 5.37 (1 H, dd, H-4), 2.24 (1 H, dd, H-3α), 1.75 (1 H, dd, H-3β).

Phenylsulfenylation of *trans*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-methyl-4-phenylbutyrolactone, 2-trans). A solution of lactone **2** (0.4 g, 2.27 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at −78 °C over 1 h. Diphenyl disulfide (0.49 mL, 2.27 mmol) was dissolved in 5 mL of dry THF, cooled to −78 °C, and added dropwise to the reaction mixture. Then, the solution was stirred at −78 °C for 3 h, and the reaction was quenched as reported for phenylsulfenylation of **1**. The mixture was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. After separation of the crude product by column chromatography, 0.60 g of **5**-trans was obtained (93%).

Methylsulfenylation of *trans*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-Methyl-4-phenylbutyrolactone, 2-trans). A solution of lactone **2** (0.4 g, 2.27 mmol) in 5 mL of dry THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.33 mL, 2.35 mmol) and *n*-BuLi (0.67 mL, 2.35 mmol, 3.5 M) in 10 mL of THF], and the reaction mixture was stirred at −78 °C over 1 h. Dimethyl disulfide (0.22 mL, 2.27 mmol) was dissolved in 5 mL of dry THF, cooled to −78 °C, and added dropwise to the reaction mixture. Then the solution was stirred at −78 °C for 3 h, and the reaction was quenched as reported for phenylsulfenylation. The mixture was extracted with $CHCl_3$ (10 mL) and washed with water (4 × 5 mL) and the solvent dried and removed. Purification of the reaction mixture by column chromatography afforded **6**-trans as a liquid (3.88 g, 77%).

***trans*-Dihydro-3-methyl-3-(methylthio)-5-phenyl-2-(3*H*)-furanone (*trans*-2-methyl-2-(methylthio)-4-phenylbutyrolactone, 6-trans)**: IR ($CHCl_3$) 1775 cm^{-1}; ^{13}C NMR ($CDCl_3$) 174.98 (C=O), 77.94 (C-4), 46.69 (C-2), 46.41 (C-3), 21.95 (CH_3), 11.96 (methylthio), phenyl group 138.42 (C_i), 128.73 (C_o), 128.57 (C_p), 125.53 (C_m) ppm; ^1H NMR ($CDCl_3$) δ 1.60 (3 H, s, CH_3), 2.21 (3 H, s, CH_3S), 2.25 (1 H, dd, H-3β), 2.57 (1 H, dd, H-3α), 5.63 (1 H, dd, H-4), 7.30 (5 H, m, H-aromatic) ppm.

Protonation Reactions. General Procedure. A solution of the lactone **3**-cis (0.10 g, 0.37 mmol) in 5 mL of THF was cooled to −78 °C and added to a solution of LDA prepared as reported before [diisopropylamine (0.037 g, 0.37 mmol) and *n*-Buli 1.4 M (0.26 mL, 0.37 mmol) in 10 mL of THF], and the reaction mixture was stirred at the same temperature over 1 h under a nitrogen atmosphere and quenched at −78 °C with a mixture of AcOH/MeOH/THF (1:1:1). The mixture was extracted with $CHCl_3$ (20 mL) and the solvent dried and removed. The crude product was observed directly by proton NMR (90 MHz, CW) and the isomer ratio measured from the analyses of the signals of H-2 or methyl.

Lactones **3**-cis and **3**-trans afforded a 60/40 (cis/trans) ratio, whereas the **4**-cis and **4**-trans mixture (80/20) gave 68/32, respectively. The reaction of the lactone mixture **2**-cis and **2**-trans gave an isomer ratio cis/trans of 90/10. The cis isomer was separated and analyzed by NMR spectrscopy.

***cis*-Dihydro-3-methyl-5-phenyl-2(3*H*)-furanone (*trans*-2-methyl-4-phenylbutyrolactone, 2-cis)**: IR ($CHCl_3$) 1767 cm^{-1}; MS *m/z* (rel intensity) 176 (M^+, 90), 132 (48), 117 (100), 105 (80), 77 (37), 42 (50); ^{13}C NMR ($CDCl_3$) 179.64 (C=O), 79.60 (C-4), 41.35 (C-2), 36.80 (C-3), 15.40 (CH_3), phenyl group 139.88 (C_i), 129.22 (C_o), 128.88 (C_p), 126.18 (C_m) ppm; ^1H NMR (C_4D_8O/C_6D_6) δ 1.27 (3 H, d, CH_3), 1.78 (1 H, td, H-3β), 2.74 (1 H, ddd, H-3α), 2.76 (1 H, qdd, H-2), 5.29 (1 H, dd, H-4), 7.32 (5 H, m, H-aromatic) ppm.

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Synthesis of 1-Amino-1-(aminomethyl)cyclopropane and Its Monobenzamides†

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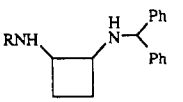
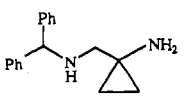
An increasing number of therapeutic agents, including antiarrythmic, antipsychotic, and antitumor compounds, have structures which incorporate a 1,2-diamine function. As an extension of our program[1] dealing with the preparation of cyclopropane compounds of biological interest,[2] we required a method for the synthesis of a series of 1,2-diaminoethanes in which one of the carbon atoms is incorporated into a cyclopropane ring. Here we report on the preparation of the simplest such compound, the previously unknown 1-amino-1-(aminomethyl)cyclopropane, **1**, by a simple and efficient synthetic strategy which allows regiospecific functionalization of *either* primary amine group.

Existing methods for the synthesis of vicinal diamines are rather limited and usually involve the introduction of two nitrogen functions onto a preformed carbon skeleton.[3] We propose an alternative strategy, whereby a variety of target molecules might be constructed from a single C_2N_2 unit, an objective which calls for an ethylenediamine synthon having nonequivalent nitrogen and carbon atom reactivities. A possible candidate was (dibenzylamino)-acetonitrile which can be alkylated with certain electrophiles under strongly basic conditions,[1b] but recent observations indicate that this synthon is not applicable to cyclopropane-forming reactions in which 1,2-dibromoethane is used as the electrophile.[4] We adopted instead the related compound [*N*-(diphenylmethylene)amino]-acetonitrile, **2**, as our 1,2-diamine precursor, since it also has the requisite differential reactivity of all four central atoms. Synthon **2** was first prepared in 1978 by O'Donnell[5a] and has been used by his group[5] and others[6] as a synthetic glycine equivalent in the preparation of a number of amino acid derivatives.

The various approaches to the synthesis of **1** are shown in Scheme I. Double alkylation of **2** with 1,2-dibromoethane and base under phase-transfer conditions according to O'Donnell[5b] gave the cyclopropane derivative **3**. Complete multiple-bond reduction of **3** with lithium aluminum hydride was inefficient, giving a mixture of products from which **4** was isolated only in low yield (35%). A high yield of diamine **4** was obtained using a borane–tetrahydrofuran complex[7] which allowed the reaction to go to completion without complication from reductive decyanation.[8] We were intrigued to find, however, that a small amount (15–20%) of a secondary product was formed, corresponding to a cyclobutanediamine **7a**, which was characterized as its benzamide **7b**.



7a R=H
7b R=PhCO



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