A Facile Allylic 1,3-Rearrangement of a Sulfonyl Group and Its Application to a Synthesis of α,β-Unsaturated Ketones

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A *p*-tolylsulfonyl group undergoes a SiO_2-catalyzed 1,3-rearrangement in a sulfenylated allylic system and this rearrangement can be utilized in novel and convenient syntheses of α,β-unsaturated ketones **6** using 3-(methylthio)-2-propenyl *p*-tolyl sulfone (**1**) and (methylthio)methyl *p*-tolyl sulfone (**7**).

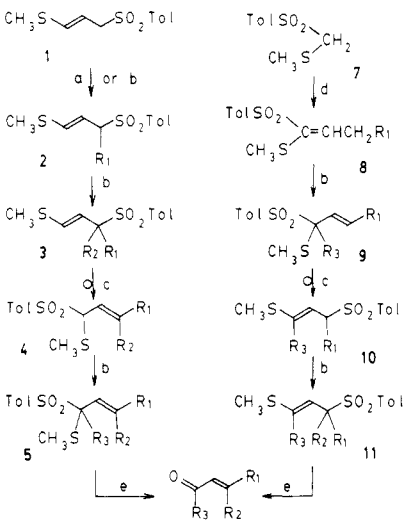
To date, there are several descriptions in the literature of 1,3-rearrangement of allylic sulfonyl groups.[1-5] Baechler et al. reported that, in a metallylic system, thermal 1,3-rearrangement of a phenylsulfonyl group is much slower than those of phenylthio and phenylsulfinyl groups.[4] Further, acceleration of 1,3-rearrangement of a sulfonyl group with an acid, [1,2,6] Pd(0) metal,[3] and a radical initiator[5,6] have been observed. Among these in the literature, we were interested in Bordwell's account which briefly reported on an acid-catalyzed 1,3-rearrangement of *p*-tolylsulfonyl group of 3-methyl-1-(phenylthio)-1-(*p*-tolylsulfonyl)-2-butene leading to 3-methyl-1-(phenylthio)-3-(*p*-tolylsulfonyl)-1-butene,[1] but scant attention has been paid to the rearrangement from theoretical and synthetic points of view. Now we wish to report a novel 1,3-rearrangement of a *p*-tolylsulfonyl group in a sulfenylated allylic system I ⇄ II in Table I) and its application to the synthesis of highly substituted α,β-unsaturated ketones **6** depicted in Scheme I.

Results and Discussion

When I (R_1 = R_2 = alkyl; R_3 = H)[7] was passed through a SiO_2-packed column, the corresponding II was produced at equilibrium with I. The results are summarized in Table I. Since a protic acid such as *p*-toluenesulfonic acid or acetic acid exhibits a catalytic activity for this rearrangement in $CHCl_3$ at an ambient temperature, it may be reasonable to assume that the present rearrangement occurs via a cationic intermediate (III). Table I shows that the equilibrium lies to the side of II when the position α to the sulfonyl group in I is much congested by two alkyls (entries 3-6). In contrast, monoalkylated I (R_1 = alkyl; R_2 = R_3 = H)[7] apparently does not undergo the allylic 1,3-rearrangement (entries 7 and 8). This is accounted for in terms of the stabilizing effect of a methylthio group on an adjacent C=C bond to allow exclusive production of thermodynamically more stable I (R_1 = alkyl; R_2 = R_3 = H) at equilibrium with II. Complete rearrangement of IIh to Ih supports this explanation: When Ih was briefly irradiated with 254-nm light in dioxane–water (19:1) in the presence of $NaHCO_3$ (3 equiv), a 49:51 mixture of Ih and IIh was produced.[8,9] Overnight exposure[10] of this mixture to SiO_2 at room temperature caused slow migration of the *p*-tolylsulfonyl group to afford Ih (78%) with no contamination of IIh. Analogously, irradiation of Ib gave a 38:62 mixture of Ib and IIb (73%). The ratio changed to the thermodynamically controlled one (91:9) after being eluted through a SiO_2-packed column. It should be noted that both Ia (=1 of Scheme I) and IIa were insensitive to SiO_2.[11] This may be attributable to the lack of any alkyl substituent which facilitates the rearrangement by stabilizing the transient cation (III).

Further, II (R_1 = H or alkyl; R_2 = H; R_3 = alkyl) was prepared from (methylthio)methyl *p*-tolyl sulfone (**7**)[12]

Scheme I[a]

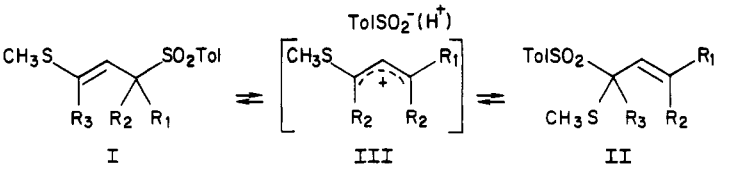


[a] (a) Alkyl halide–KOH–TOMAC (cat.) in DMF; (b) alkyl halide–NaH in DMF; (c) SiO_2; (d) $R_1CH_2CH_2Br$–TOMAC (cat.) in 50% aq NaOH–$PhCH_3$ → SO_2Cl_2 in $CHCl_3$ → heat in $PhCH_3$ (N_2 bubbling); (e) $CuCl_2$ in MeOH–H_2O.

(1) Bordwell, F. G.; Pagani, G. A. *J. Am. Chem. Soc.* **1975**, *97*, 118.
(2) Manchand, P. S.; Rosenberger, M.; Saucy, G.; Wehrli, P. A.; Wong, G.; Chambers, L.; Ferro, M. P.; Jackson, W. *Helv. Chim. Acta* **1976**, *59*, 387.
(3) Inomata, K.; Yamamoto, T.; Kotake, H. *Chem. Lett.* **1981**, 1357.
(4) Baechler, R. D.; Bentley, P.; Deuring, L.; Fisk, S. *Tetrahedron Lett.* **1982**, *23*, 2269.
(5) Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 945.
(6) Lin, P.; Whitham, G. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1102.
(7) Ogura, K.; Iihama, T.; Takahashi, K.; Iida, H. *Tetrahedron Lett.* **1984**, *25*, 2671.
(8) For 30 min with a 10-W low-pressure mercury lamp through a Vycor filter under bubbling with N_2 and external cooling with tap water. Prolonged irradiation (60 min) afforded a 20:80 mixture of Ih and IIh in 45% yield.
(9) Analogous heterolytic fission of a C–SO_2 bond has been noted in the photoinduced hydrolysis of dithioacetal *S,S*-dioxides: Ogura, K.; Ohtsuki, K.; Nakamura, M.; Yahata, N.; Takahasi, K.; Iida, H. *Tetrahedron Lett.* **1985**, *26*, 2455.
(10) Rapid chromatography of the irradiated mixture on SiO_2 afforded IIh in almost pure form: ^1H NMR ($CDCl_3$) δ 0.89 (diffused t, 3 H), 1.1–1.6 (br s, 16 H), 1.7–2.3 (m, 2 H), 2.36 (s, 3 H), 2.46 (s, 3 H), 4.9–6.0 (m, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 7.77 (d, *J* = 8.4 Hz, 2 H).
(11) Irradiation of Ia (=1) with 254-nm light for 20 min gave Ia and IIa, which were separately isolated in yields of 49% and 24%, respectively, by column chromatography on SiO_2 (see Experimental Section). IIa remained unchanged on exposure to SiO_2 for 2 days.
(12) Ogura, K.; Yahata, N.; Takahashi, K.; Iida, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3543.

0022-3263/86/1951-0700$01.50/0

Table I. Thermodynamic Ratio between I and II on Treatment with SiO_2[a]



I III II

entry		compds I and II R_1	R_2	R_3	I:II[b]	yield, %
1	a	H	H	H	c	
2	b	Me	Me	H	91:9	100[d]
3	c	Et	Et	H	11:89	96[d]
4	d	*n*-Pr	*n*-Pr	H	6:94	93[d]
5	e	*n*-Bu	*n*-Bu	H	0:100	90[d]
6	f	$PhCH_2$	$PhCH_2$	H	0:100	96[d]
7	g	*n*-Bu	H	H	100:0	91[d]
8	h	*n*-$C_{10}H_{21}$	H	H	100:0	72[d]
9	i	H	H	Me	100:0[f]	58[e]
10	j	H	H	$PhCH_2$	100:0[g]	69[e]
11	k	Me	H	Me	100:0[h]	86[e]
12	l	Me	H	$PhCH_2$	100:0[i]	97[e]
13	m	Ph	H	$PhCH_2$	100:0[j]	92[e]

[a] Column chromatography on SiO_2 using benzene–hexane as an eluent. [b] The value of 100:0 implies that the existence of one isomer was not observed within the limit of ^1H NMR measurement. [c] Not determined (see text). [d] Overall yield from Ia (=1 of Scheme I). [e] Overall yield from 8 of Scheme I. [f] Z:E = 4:1. [g] Z:E = 7:1. [h] Z:E = 6:1. [i] Z:E = 9:1. [j] Z:E = 47:53.

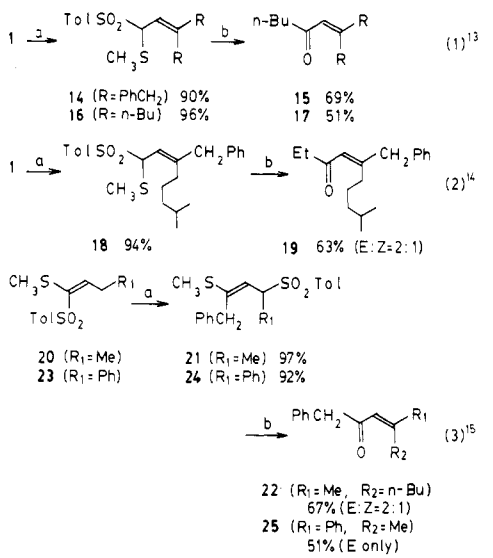
Table II. The Equilibrium between I and II

R_1	R_2	R_3	favorable side
alkyl	H	H	I
alkyl	alkyl	H	II[a]
alkyl	H	alkyl	I
H	H	alkyl	I

[a] Except the case of $R_1 = R_2 = Me$

according to the procedure of Scheme I. Chromatography of the thus-obtained IIi–m on SiO_2 produced Ii–m exclusively. In conclusion, the SiO_2-catalyzed equilibrium position between I and II was much influenced by the number and the position of alkyl substituents as summarized in Table II.

These tendencies are desirable to introducing the third alkyl group to produce a trialkylated I or II ($R_1 = R_2 = R_3$ = alkyl) which realizes a convenient and efficient synthesis of highly substituted α,β-unsaturated ketones **6** of Scheme I. As recently reported by us,[7] two alkyls could be regiospecifically introduced at the position α to the sulfonyl group of 3-(methylthio)-2-propen-1-yl *p*-tolyl sulfone (**1**) to give the corresponding dialkylated product **3**, which smoothly rearranged to **4** on SiO_2. Treatment of the thus-obtained **4** with NaH and an alkyl halide in DMF afforded a trialkylated product **5**. Another trialkylated product **11** was also prepared by alkylation of **10**. When the trialkylated **5** or **11**, without any purification, was subjected to the reaction with $CuCl_2$ in methanol–water, hydrolysis of the vinyl sulfide part and the subsequent dehydrosulfinylation took place concurrently to yield **6**. The methods of Scheme I are characterized by the following features: (i) it is widely applicable to making various α,β-unsaturated ketones (**6**), three substituents (R_1, R_2, R_3) of which are optionally and regiospecifically selected as shown in eq 1–3; (ii) the alkylation steps use such



an inexpensive and easily handled base as NaH or KOH, which enable us to practice the present methods on a large scale; (iii) all of the reactions proceed under mild and convenient conditions.

Thus, we have established novel synthetic routes to highly substituted α,β-unsaturated ketones by the use of the equilibratory allylic 1,3-rearrangement of a sulfonyl group, wherein **1** and **8** are utilized as synthetic equivalents of a trianion (**12**) and a dianion (**13**), respectively.

$$1 = O{=}C^{-}CH{=}C^{2-} \text{ (12)} \qquad 8 = O{=}C^{-}CH{=}C^{-}R_1 \text{ (13)}$$

Experimental Section

General Procedures. Melting points were determined on a hot stage microscope apparatus (Yanagimoto) and are uncorrected. Analytical thin-layer chromatography (TLC) was performed with 0.2-mm SiO_2-coated plastic sheets (Merck Art. 5748). All column chromatography was done with Wako Gel C-200. Proton magnetic resonance (^1H NMR) spectra were recorded on Hitachi R-600 (60-MHz) spectrometer in deuteriochloroform. Chemical shifts are reported in part per million down field from tetramethylsilane

(13) (a) *n*-BuI (3 equiv) or $PhCH_2Br$ (3.2 equiv)–NaH (2.8–3.2 equiv) in DMF, −15 °C → column chromatography on SiO_2. (b) *n*-BuI (1.5 equiv)–NaH (1.5–1.6 equiv) in DMF, −15 °C–room temperature → $CuCl_2$ (2 mol equiv) in MeOH–H_2O (9:1), 40–50 °C.

(14) (a) $Me_2CH(CH_2)_2Br$ (1.5 equiv)–KOH (2 equiv)–TOMAC (0.05 equiv) in DMF, −15 °C → $PhCH_2Br$ (1.7 equiv)–NaH (2.1 equiv) in DMF, room temperature → column chromatography on SiO_2. (b) EtI (2 equiv)–NaH (2.2 equiv) in DMF, room temperature → $CuCl_2$ (2 mol equiv) in MeOH–H_2O (9:1), 40 °C.

(15) (a) $PhCH_2Br$ (1.4–1.8 equiv)–NaH (1.5–1.6 equiv) in DMF, −20 °C → column chromatography on SiO_2. (b) *n*-BuI (2.1 equiv) or MeI (2.4 equiv)–NaH (1.7–1.8 equiv) in DMF, room temperature → $CuCl_2$ (2 mol equiv) in MeOH–H_2O (9:1), 40 °C.

as the internal standard (δ scale). Infrared spectra were determined with JASCO A-200 spectrometer and data are presented in cm^{-1} for important diagnostic absorptions. Mass spectra (MS) were determined on a Hitachi RMU-6E spectrometer at 70 eV. Data are presented in the form m/e (intensity relative to base peak = 100). Microanalytical data were provided by the Analytical Center of Chiba University.

Unless otherwise noted, other materials were obtained from commercial suppliers (Aldrich Chemical Co., Tokyo Kasei Chemical Industry Co., Wako Pure Chemical Industries Co., and Kanto Chemical Co.) and used after being purified by distillation and being dried over molecular sieves (3–4 Å). (Methylthio)methyl *p*-tolyl sulfone (7), which was purchased from Nissan Chemical Industries Co., was recrystallized from benzene–hexane and dried over phosphorus pentoxide.

Dibenzylation of 3-(Methylthio)-2-propenyl *p*-Tolyl Sulfone (Ia = 1) and the Subsequent Treatment with SiO_2. A Typical Procedure. To a solution of benzyl bromide (3.33 g, 13.6 mmol) and 3-(methylthio)-2-propen-1-yl *p*-tolyl sulfone (1)[16] (1.08 g, 4.20 mmol) in DMF (30 mL) was added NaH (60% dispersion in an oil) (551 mg, 13.8 mmol) at −15 °C, and the resulting mixture was stirred at the same temperature for 4 h. An aqueous NH_4Cl solution (60 mL) was added, and extraction with diethyl ether (50 mL × 3) was performed. The extracts were combined, washed with brine (100 mL), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a yellow solid (2.73 g), which was shown by its ^1H NMR spectrum to consist mainly of the dibenzylated derivative.[17] The yellow solid (1.03 g) was subjected to column chromatography on SiO_2 using benzene–hexane (2:1) as an eluent to give 645 mg (96%) of IIf (= 14 of eq 1): colorless crystals; mp 80.5–81 °C (from hexane–benzene); ^1H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.42 (s, 3 H), 3.16 (s, 4 H), 4.67 (d, J = 11 Hz, 1 H), 5.30 (d, J = 11 Hz, 1 H), 6.90–7.40 (m, 12 H), 7.68 (d, J = 8.6 Hz, 2 H); IR (KBr) 1320, 1291, 1144, 1082 cm^{-1}. Calcd for $C_{25}H_{26}O_2S_2$: C, 71.05; H, 6.20. Found: C, 70.77; H, 6.18.

2-Methyl-4-(methylthio)-3-buten-2-yl *p*-Tolyl Sulfone (Ib). This was given as a 91:9 mixture of Ib and IIb by column chromatography on SiO_2: colorless crystals; mp 86–88.5 °C (without recrystallization); ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H), 2.23 (s, 3 H), 2.44 (s, 3 H), 5.37 (d, J = 15.4 Hz, 1 H), 6.08 (d, J = 15.4 Hz, 1 H), 7.31 (d, J = 8.4 Hz, 2 H), 7.69 (d, J = 8.4 Hz, 2 H); IR (KBr) 1648, 1601, 1301, 1284, 1132, 1068 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2S_2$: C, 57.75; H, 6.71. Found: C, 57.94; H, 6.68. IIb showed ^1H NMR signals at δ 1.43 (s, 3 H), 1.68 (s, 3 H), 2.29 (s, 3 H), 4.48 (d, J = 10.8 Hz, 1 H), and 4.92 (d, J = 10.8 Hz, 1 H).

3-Ethyl-1-(methylthio)-2-penten-1-yl *p*-Tolyl Sulfone (IIc). This was given as a 89:11 mixture of IIc and Ic by column chromatography on SiO_2: colorless oil; ^1H NMR ($CDCl_3$) δ 0.6–1.2 (m, 6 H), 1.7–2.15 (m, 4 H), 2.37 (s, 3 H), 2.43 (s, 3 H), 4.61 (d, J = 10.9 Hz, 1 H), 5.03 (d, J = 10.9 Hz, 1 H), 7.31 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H); IR (liquid film) 1658, 1600, 1322, 1318, 1304, 1280, 1158, 1138, 1122, 1084 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2S_2$: C, 60.36; H, 7.43. Found: C, 60.43; H, 7.38. Ic showed ^1H NMR signals at δ 2.20 (s, 3 H), 5.04 (d, J = 15.6 Hz, 1 H), and 5.98 (d, J = 15.6 Hz, 1 H).

3-Propyl-1-(methylthio)-2-hexen-1-yl *p*-Tolyl Sulfone (IId). This was given as a 94:6 mixture of IId and Id by column chromatography on SiO_2: colorless oil: ^1H NMR ($CDCl_3$) δ 0.7–1.0 (m, 6 H), 1.2–2.1 (m, 8 H), 2.37 (s, 3 H), 2.46 (s, 3 H), 4.58 (d, J = 10.6 Hz, 1 H), 5.05 (d, J = 10.6 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.76 (d, J = 8.2 Hz, 2 H); IR (liquid film) 1600, 1316, 1304, 1296, 1144, 1084 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_2S_2$: C, 62.54; H, 8.03. Found: C, 62.62; H, 8.00. Id showed ^1H NMR signals at δ 2.19 (s, 3 H), 5.05 (d, J = 15.7 Hz, 1 H), and 5.97 (d, J = 15.7 Hz, 1 H).

3-Butyl-1-(methylthio)-2-hepten-1-yl *p*-Tolyl Sulfone (IIe = 16). This was isolated in a pure form by column chromatography on SiO_2: colorless oil; ^1H NMR ($CDCl_3$) δ 0.7–1.0 (m, 6 H), 1.1–1.5 (m, 8 H), 1.7–2.1 (m, 4 H), 2.36 (s, 3 H), 2.43 (s, 3 H), 4.58 (d, J = 10.4 Hz, 1 H), 5.12 (d, J = 10.4 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.78 (d, J = 8.2 Hz, 2 H); IR (liquid film) 1600, 1325, 1306, 1290, 1076 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_2$: C, 64.36; H, 8.52. Found: C, 64.50; H, 8.47.

Butylation of 3-(Methylthio)-2-propenyl *p*-Tolyl Sulfone (Ia = 1) and the Subsequent Treatment with SiO_2. Typical Procedure. To a suspension of NaH (60% dispersion in an oil) (143 mg, 3.0 mmol) in DMF (10 mL) were successively added butyl iodide (454 mg, 2.5 mmol) and Ia (=1) (599 mg, 2.5 mmol) at −15 °C, and the resulting mixture was stirred at the same temperature for 2 h. After addition of an aqueous NH_4Cl solution (3 mL), the mixture was extracted with diisopropyl ether (40 mL × 3). The extracts were combined, washed with brine (100 mL), and dried (Na_2SO_4). Removal of the solvent and column chromatography on SiO_2 using benzene–hexane (2:1) as an eluent to give 674 mg (91%) of Ig as a geometric mixture (*E*:*Z* = 7:3). The *E* isomer was isolated by recrystallization from hexane–benzene: colorless crystals; mp 69–70 °C; ^1H NMR ($CDCl_3$) δ 0.89 (diffused t, 3 H), 1.0–1.6 (m, 6 H), 2.19 (s, 3 H), 2.43 (s, 3 H), 3.2–3.8 (m, 1 H), 5.00 (dd, J = 15.0, 9.0 Hz, 1 H), 6.00 (d, J = 15.0 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.63 (d, J = 8.2 Hz, 2 H); IR (KBr) 1595, 1302, 1292, 1140, 1082 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2S_2$: C, 60.37; H, 7.43. Found: C, 60.36; H, 7.40. The *Z* isomer showed ^1H NMR signals at δ 2.05 (s, 3 H) and 6.18 (d, J = 9.6 Hz, 1 H).

1-(Methylthio)-1-tridecen-3-yl *p*-Tolyl Sulfone (Ih). This was given as a mixture of *E* and *Z* geometric isomers, and the *E* isomer was isolated by recrystallization from ethanol: colorless crystals; mp 72–73 °C; ^1H NMR ($CDCl_3$) δ 0.88 (diffused t, 3 H), 1.05–1.6 (m, 18 H), 2.22 (s, 3 H), 2.45 (s, 3 H), 3.0–3.8 (m, 1 H), 5.04 (dd, J = 15.0, 9.0 Hz, 1 H), 6.00 (d, J = 15.0 Hz, 1 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.4 Hz, 2 H); IR (KBr) 1595, 1302, 1292, 1140, 1082 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_2S_2$: C, 60.37; H, 7.43. Found: C, 60.36; H, 7.40. The *Z* isomer showed ^1H NMR signals at δ 2.06 (s, 3 H) and 6.20 (d, J = 9.6 Hz, 1 H).

3-(Methylthio)-2-buten-1-yl *p*-Tolyl Sulfone (Ii). Typical Procedure. To a solution of 1-(methylthio)-1-propen-1-yl *p*-tolyl sulfone (see below) (490 mg, 2.0 mmol) and methyl iodide (595 mg, 4.2 mmol) in DMF (5 mL) was added NaH (60% content) (128 mg, 3.2 mmol) at 0 °C, and the resulting mixture was stirred at the same temperature for 6 h and then at room temperature for 18 h. After the addition of an aqueous NH_4Cl solution (50 mL), the mixture was extracted with diethyl ether (50 mL × 4). The extracts were combined, washed with brine (50 mL × 2), and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a pale yellow oil, which was shown by a ^1H NMR analysis to consist mainly of 2-(methylthio)-3-buten-2-yl *p*-tolyl sulfone (IIi). This was subjected to column chromatography on SiO_2 using benzene–hexane (2:1) as an eluent to give Ii (299 mg, 58% yield) as a mixture of two geometric isomers (*Z*:*E* = 7:1). The *Z* isomer was isolated in a pure form by recrystallization from benzene–hexane: colorless crystals; mp 79–79.5 °C; ^1H NMR ($CDCl_3$) δ 1.59 (s, 3 H), 2.21 (s, 3 H), 2.46 (s, 3 H), 3.87 (d, J = 7.8 Hz, 2 H), 4.97 (t, J = 7.8 Hz, 1 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.76 (d, J = 8.4 Hz, 2 H); IR (KBr) 1290, 1137, 745, 522, 500 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.18; H, 6.30. Found: C, 56.22; H, 6.29. The *E* isomer showed ^1H NMR signals at δ 2.03 (s, 6 H), 4.03 (d, J = 7.8 Hz, 2 H), and 5.53 (t, J = 8 Hz, 1 H).

3-(Methylthio)-4-phenyl-2-buten-1-yl *p*-Tolyl Sulfone (Ij). In the similar manner, Ij was obtained as a 7:1 mixture of the *Z* and *E* isomers, and the *Z* isomer was isolated in a pure form by recrystallization from benzene–hexane: colorless crystals; mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 2.11 (s, 3 H), 2.38 (s, 3 H), 3.33 (s, 2 H), 3.85 (d, J = 7.2 Hz, 2 H), 5.05 (t, J = 7.2 Hz, 1 H), 7.0–7.4 (m, 7 H), 7.75 (d, J = 7.8 Hz, 2 H); IR (kBr) 1295, 1157, 1137, 1084, 580, 515 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_2S_2$: C, 65.03; H. 6.06. Found: C, 65.13; H, 6.10. The *E* isomer showed ^1H NMR signals at δ 1.89 (s, 3 H) and 5.53 (t, J = 8 Hz, 1 H).

4-(Methylthio)-3-penten-2-yl *p*-Tolyl Sulfone (Ik). Analogously, Ik was prepared as a geometric mixture (*Z*:*E* = 6:1) from 1-(methylthio)-1-buten-1-yl *p*-tolyl sulfone (see below) followed by treatment with SiO_2. The *Z* isomer was isolated in a pure form by recrystallization from benzene–hexane: colorless crystals; mp 130.5–131.5 °C; ^1H NMR ($CDCl_3$) δ 1.47 (d, J = 7.8

(16) Ogura, K.; Iihama, T.; Takahasi, K.; Iida, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3347.

(17) This was isolated in a pure form by recrystallization: colorless crystals; mp 103–104 °C (from diisopropyl ether–benzene); ^1H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 2.36 (s, 3 H), 3.30 (s, 4 H), 5.21 (d, J = 16 Hz, 1 H), 6.18 (d, J = 16 Hz, 1 H), 6.95–7.30 (m, 12 H), 7.59 (d, J = 8 Hz, 2 H); IR (KBr) 1594, 1492, 1455, 1282, 1136, 1082 cm^{-1}. Anal. Calcd for $C_{25}H_{26}O_2S_2$: C, 71.05; H, 6.20. Found: C, 70.92; H, 6.22.

Hz, 3 H), 1.55 (s, 3 H), 2.21 (s, 3 H), 2.45 (s, 3 H), 4.00 (dq, J = 7.8, 10.2 Hz, 1 H), 4.77 (d, J = 10.2 Hz, 1 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H); IR (KBr) 1602, 1286, 1080, 820, 712, 684, 562 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_2S_2$: C, 57.74; H, 6.71. Found: C, 57.76; H, 6.70. The E isomer showed ^1H NMR signals at δ 1.99 (s, 3 H) and 5.38 (d, J = 10 Hz, 1 H).

4-(Methylthio)-5-phenyl-3-penten-2-yl *p*-Tolyl Sulfone (Il = 21). This compound (Z:E = 9:1) was also prepared from 1-(methylthio)-1-buten-1-yl *p*-tolyl sulfone by the above method, and the Z isomer was isolated in a pure form by recrystallization: colorless crystals; mp 110–111 °C; ^1H NMR ($CDCl_3$) δ 1.38 (d, J = 6.6 Hz, 3 H), 2.21 (s, 3 H), 2.47 (s, 3 H), 3.07 (d, J = 15.6 Hz, 1 H), 3.47 (d, J = 15.6 Hz, 1 H), 4.00 (dq, J = 6.6, 9.6 Hz, 1 H), 4.93 (d, J = 9.6 Hz, 1 H), 6.9–7.4 (m, 7 H), 7.74 (d, J = 8.4 Hz, 2 H); IR (KBr) 1624, 1600, 1496, 1288, 1132, 1084, 726, 526 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_2S_2$: C, 65.86; H, 6.40. Found: C, 65.73; H, 6.39. The E isomer showed ^1H NMR signals at δ 1.96 (s, 3 H) and 5.52 (d, J = 9.6 Hz, 1 H).

3-(Methylthio)-1,4-diphenyl-2-buten-1-yl *p*-Tolyl Sulfone (Im = 24). Analogously, this was obtained as a geometric mixture (E:Z = 53:47) by benzylation of 1-(methylthio)-3-phenyl-1-propen-1-yl *p*-tolyl sulfone and subsequent treatment with SiO_2. The E isomer was isolated in a pure form by crystallization from methanol: colorless crystals; mp 118–119 °C; ^1H NMR ($CDCl_3$) δ 1.97 (s, 3 H), 2.41 (s, 3 H), 3.63 (s, 2 H), 5.54 (d, J = 10.8 Hz, 1 H), 6.07 (d, J = 10.8 Hz, 1 H), 7.06–7.40 (m, 12 H), 7.54 (d, J = 7.8 Hz, 2 H); IR (KBr) 1600, 1495, 1140, 1085, 700, 575 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_2S_2$: C, 70.55; H, 5.92. Found: C, 70.34; H, 5.97. The E isomer showed ^1H NMR signals at δ 2.25 (s, 3 H), 3.32 (d, J = 15.6 Hz, 1 H), 3.54 (d, J = 15.6 Hz, 1 H), 5.00 (d, J = 10.8 Hz, 1 H), and 5.57 (d, J = 10.8 Hz, 1 H).

Preparation of 1-(Methylthio)-1-propen-1-yl *p*-Tolyl Sulfone. Typical Procedure. To a solution of (methylthio)-methyl *p*-tolyl sulfone (5.00 g, 23.1 mmol) and ethyl bromide (3.84 g, 35 mmol) in toluene (50 mL) were added methyltrioctylammonium chloride (200 mg, 0.50 mmol) and a 50% aqueous solution (50 mL) of NaOH, and the resulting mixture was stirred at an ambient temperature for 5 days. After the addition of 10% hydrochloric acid (100 mL), the resulting mixture was extracted with diisopropyl ether (50 mL × 4). The extracts were combined, washed with water (250 mL × 3), and dried ($MgSO_4$). Evaporation of the solvent followed by recrystallization from benzene–hexane gave 1-(methylthio)-1-propyl *p*-tolyl sulfone as colorless crystals (4.33 g, 77%): mp 103–105 °C; ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 6.6 Hz, 3 H), 1.3–1.85 (2 H, m), 2.20 (s, 3 H), 2.44 (s, 3 H), 3.60 (dd, J = 4.0, 10.3 Hz, 1 H), 7.37 (2 H, d, J = 8.4 Hz), 7.82 (2 H, d, J = 8.4 Hz); IR (KBr) 1595, 1280, 1120, 805, 765, 565, 515 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2S_2$: C, 54.06; H, 6.60. Found: C, 54.07; H, 6.56.

Further, evaporation of the mother liquor and the subsequent column chromatography on SiO_2 using benzene–hexane (3:1) as an eluent afforded 1-(methylthio)-1-propyl *p*-tolyl sulfone (0.80 g, 14%). The total yield was 91%. To a solution of 1-(methylthio)-1-propyl *p*-tolyl sulfone (501 mg, 2.05 mmol) in chloroform (10 mL) was dropwise added sulfuryl chloride (447 mg, 3.3 mmol) under cooling with ice, and the resulting mixture was stirred at the same temperature for 1.5 h and then at an ambient temperature for 2 h. After the removal of volatile compounds under reduced pressure, the residue was separated by column chromatography on SiO_2 using benzene–hexane (2:1) as an eluent to give a colorless oil (551 mg, 96%), which showed ^1H NMR and IR spectra characteristic of 1-chloro-1-(methylthio)-1-propyl *p*-tolyl sulfone: ^1H NMR ($CDCl_3$) δ 1.17 (t, 3 H, J = 6.6 Hz), 2.0–2.4 (m, 2 H), 2.42 (3 H, s), 2.46 (3 H, s), 7.38 (d, J = 8.4 Hz, 2 H), 7.87 (d, J = 8.4 Hz, 2 H); IR (liquid film) 1600, 1330, 1155, 1080, 650, 535 cm^{-1}.

A solution of 1-chloro-1-(methylthio)-1-propyl *p*-tolyl sulfone (544 mg, 1.95 mmol) in toluene (10 mL) was refluxed under bubbling with N_2 for 22.5 h. Then water (30 mL) was added, and the mixture was extracted with diisopropyl ether (20 mL × 4). The extracts were combined, dried ($MgSO_4$), evaporated, and subjected to column chromatography on SiO_2 using benzene–hexane (2:1) as an eluent to give 1-(methylthio)-1-propen-1-yl *p*-tolyl sulfone (409 mg, 87% yield) as colorless crystals: mp 71–72.5 °C (benzene–hexane); ^1H NMR ($CDCl_3$) δ 2.10 (d, J = 6.6 Hz, 3 H), 2.18 (s, 3 H), 2.42 (s, 3 H), 7.31 (d, J = 7.8 Hz, 2 H), 7.58 (q, J = 6.6 Hz, 1 H), 7.78 (d, J = 7.8 Hz, 2 H); IR (KBr) 1590, 1400, 1305, 1285, 1145, 665 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.51; H, 5.82. Found: C, 54.61; H, 5.83.

Similarly, 1-(methylthio)-1-buten-1-yl *p*-tolyl sulfone (**20**) and 1-(methylthio)-3-phenyl-1-propen-1-yl *p*-tolyl sulfone (**23**) were synthesized.

1-(Methylthio)-1-butyl *p*-tolyl sulfone: ^1H NMR ($CDCl_3$) δ 0.73–1.18 (diffused t, 3 H), 1.2–2.0 (m, 4 H), 2.21 (s, 3 H), 2.45 (s, 3 H), 3.66 (dd, J = 3.0, 10.8 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.82 (d, J = 8.4 Hz, 2 H); IR (liquid film) 1290, 1145, 1090 cm^{-1}; Anal. Calcd for $C_{12}H_{18}O_2S_2$: C, 55.78; H, 7.02. Found: C, 55.89; H, 6.93.

1-Chloro-1-(methylthio)-1-butyl *p*-tolyl sulfone: colorless crystals; mp 88–89 °C; ^1H NMR ($CDCl_3$) δ 0.78–1.18 (diffused t, 3 H), 1.33–1.92 (m, 2 H), 1.92–2.27 (m, 2 H), 2.42 (s, 3 H), 2.47 (s, 3 H), 7.33 (d, J = 8.4 Hz, 2 H), 7.82 (d, J = 8.4 Hz, 2 H); IR (KBr) 1325, 1150, 1080 cm^{-1}. Anal. Calcd for $C_{12}H_{17}ClO_2S_2$: C, 49.22; H, 5.85. Found: C, 49.32; H, 5.82.

1-(Methylthio)-1-buten-1-yl *p*-Tolyl Sulfone (20). This was given as a geometric mixture (E:Z = 3:2), and the E isomer was isolated by crystallization from benzene–hexane as colorless crystals: mp 47–48 °C; ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3 H), 2.23 (s, 3 H), 2.40 (s, 3 H), 2.36–2.90 (m, 2 H), 7.23 (d, J = 7.8 Hz, d), 7.38 (t, J = 8.0 Hz, t), 7.82 (d, J = 7.8 Hz, 2 H); IR (KBr) 1290, 1140, 1084 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_2S_2$: C, 56.22; H, 6.29. Found: C, 56.47; H, 6.31. The ^1H NMR spectrum of the Z isomer showed two characteristic signals at δ 2.31 (s, 3 H) and 6.43 (t, J = 7.8 Hz, 1 H).

1-(Methylthio)-3-phenyl-1-propyl *p*-tolyl sulfone: colorless crystals; mp 78–79 °C; ^1H NMR ($CDCl_3$) δ 1.53–2.11 (m, 2 H), 2.20 (s, 3 H), 2.42 (s, 3 H), 2.64–3.04 (m, 2 H), 3.57 (dd, J = 2.7, 11.1 Hz, 1 H), 7.20 (s, 5 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 8.4 Hz, 2 H); IR (KBr) 1285, 1135, 1080 cm^{-1}. Anal. Calcd for $C_{17}H_{20}O_2S_2$: C, 63.72; H, 6.29. Found: C, 63.84; H, 6.31.

1-Chloro-1-(methylthio)-3-phenyl-1-propyl *p*-tolyl sulfone: colorless crystals; mp 99.5–100.5 °C; ^1H NMR ($CDCl_3$) δ 2.29–2.63 (m, 2 H), 2.45 (s, 3 H), 2.47 (s, 3 H), 2.77–3.04 (m, 2 H), 7.22 (s, 5 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.85 (d, J = 8.4 Hz, 2 H); IR (KBr) 1325, 1145, 1085 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClO_2S_2$: C, 57.53; H, 5.40. Found: C, 57.53; H, 5.41.

1-(Methylthio)-3-phenyl-1-propen-1-yl *p*-Tolyl Sulfone (23). This compound was given as a geometric mixture (E:Z = 3:2). The E isomer was isolated by crystallization from benzene–hexane as colorless crystals: mp 98.8–99.2 °C; ^1H NMR ($CDCl_3$) δ 2.26 (s, 3 H), 2.40 (s, 3 H), 4.11 (d, J = 7.8 Hz, 2 H), 6.51 (t, J = 7.8 Hz, 1 H), 7.22 (s, 5 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.87 (d, J = 8.4 Hz, 2 H); IR (KBr) 1290, 1140, 1084 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_2S_2$: C, 64.12; H, 5.70. Found: C, 64.46; H, 5.78. The Z isomer showed ^1H NMR signals at δ 2.26 (s, 3 H), 4.11 (d, J = 7.8 Hz, 2 H), and 6.51 (t, J = 7.8 Hz, 1 H).

Photolysis of 3-(Methylthio)-2-propenyl *p*-Tolyl Sulfone (Ia). Typical Procedure. A solution of Ia (301 mg, 1.2 mmol) and sodium hydrogen carbonate (314 mg, 3.7 mmol) in dioxane (190 mL) and water (10 mL) was irradiated for 20 min with a low-pressure Hg lamp (10 W) through a Vycor filter under bubbling with N_2 and external cooling with tap water. After addition of water (50 mL), the mixture was extracted with dichloromethane (50 mL × 4), and the combined extract was dried ($MgSO_4$) and evaporated to give a yellow oil. Column chromatography of this oil on SiO_2 using benzene–hexane (1:1) as an eluent afforded Ia (155 mg, 51%) and IIa (76 mg, 25%). IIa: colorless crystals; mp 66.5–67 °C; ^1H NMR ($CDCl_3$) δ 2.34 (3 H, s), 2.44 (3 H s), 4.36 (d, J = 7.8 Hz, 1 H), 5.0–6.0 (m, 3 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.77 (d, J = 8.4 Hz, 2 H); IR (KBr) 1594, 1424, 1285, 1176, 1130, 1119, 1080, 974, 946 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2S_2$: C, 54.52; H, 5.82. Found: C, 54.52; H, 5.98.

Synthesis of 2-Benzyl-1-phenyl-2-octen-4-one (15). To a solution of butyl iodide (488 mg, 2.65 mmol) and 14 (=IIf) (739 mg, 1.75 mmol) in DMF (10 mL) was added NaH (60% content) at −15 °C, and the resulting mixture was stirred at −15 °C for 9 h under an atmosphere of N_2. After the reaction was quenched by the addition of an aqueous NH_4Cl solution (50 mL), the mixture was extracted with diisopropyl ether (50 mL × 3). The extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), and evaporated to give a yellow oil (968 mg). The oil (469 mg) was dissolved in methanol (9 mL). Then, water (1 mL)

and cupric chloride (229 mg, 1.70 mmol) were added. After the resulting mixture was stirred at 50 °C for 3 h, water (50 mL) was added, and the mixture was extracted with dichloromethane (50 mL × 3). The extracts were combined, washed with water (100 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue on SiO_2 using benzene–hexane (1:5) as an eluent gave **15** (173 mg; 69% overall yield from **14**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.91 (diffused t, 3 H), 1.0–1.8 (m, 4 H), 2.43 (t, J = 6.6 Hz, 2 H), 3.32 (s, 2 H), 3.94 (s, 2 H), 6.08 (s, 1 H), 7.24 (s, 10 H); IR (liquid film) 1692, 1620, 1604, 1495, 1453 cm^{-1}; MS (70 eV), m/e (relative intensity) 293 (12, $M^+ + 1$), 292 (45, M^+), 207 (11), 129 (10), 115 (21), 105 (21), 92 (16), 91 (100), 85 (34), 77 (14), 57 (28).

Synthesis of 7-Butyl-6-decen-5-one (17). To a solution of butyl iodide (342 mg, 1.86 mmol) and **16** (=IIe) (444 mg, 1.25 mmol) in DMF (10 mL) was added NaH (60% content) (758 mg, 1.89 mmol) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h and at room temperature for 6 h under an atmosphere of N_2. The reaction was quenched by the addition of a aqueous NH_4Cl solution (40 mL), and then the mixture was extracted with diethyl ether (40 mL × 3). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and evaporated to give a yellow oil. This oil was dissolved in methanol (9 mL), and water (1 mL) and cupric chloride (338 mg, 2.51 mmol) were added. After the resulting mixture was stirred at 40 °C for 2 h, water (50 mL) was added, and the mixture was extracted with diethyl ether (40 mL × 3). The extracts were combined, washed with water (100 mL), dried (Na_2SO_4), and evaporated. Column chromatography of the residue on SiO_2 using benzene–hexane (1:5) as an eluent afforded **17** (145 mg; 51% overall yield for **15**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.9–1.05 (9 H, m), 1.1–1.8 (12 H, m), 2.0–2.8 (6 H, m), 6.02 (1 H, s); IR (liquid film) 1693, 1614 cm^{21}; MS (70 eV), m/e (relative intensity) 224 (18, M^+), 195 (24), 168 (100), 140 (21), 125 (25), 85 (24), 83 (20), 57 (28), 55 (46), 43 (24), 41 (34), 29 (25).

Synthesis of 5-Benzyl-9-methyl-4-decen-3-one (19). As described in ref 3, **1** (Ia) was alkylated with 4-methylpentyl bromide to afford 7-methyl-1-(methylthio)-1-octen-3-yl p-tolyl sulfone in 63% yield. After this product (145 mg, 0.44 mmol) was dissolved in DMF (5 mL), benzyl bromide (130 mg, 0.76 mmol) and NaH (60% content) (37.5 mg, 0.94 mmol) were added under cooling with ice. The resulting mixture was stirred at the same temperature for 8 h, and the reaction was quenched by the addition of an aqueous NH_4Cl solution (30 mL). The mixture was extracted with diisopropyl ether (30 mL × 3), and the extracts were combined, washed with brine (100 mL), and dried (An_2SO_4). Removal of the solvent under reduced pressure gave a yellow oil (286 mg), which was subjected to column chromatography on SiO_2 using benzene–hexane (1:1) as an eluent to give **18** (177 mg, 94% yield) as a colorless oil. This oil was shown by ^1H NMR ($CDCl_3$) analysis to be a 1:1 mixture of two geometric isomers: δ 0.83 (6 H, d, J = 5.8 Hz), 1.0–1.5 (5 H + 2/2 H, m), 1.6–2.1 (2/2 H, m), 2.33 (3/2 H, s), 2.36 (3/2 H, s), 2.42 (3/2 H, s), 2.47 (3/2 H, s), 3.25 (2/2 H, s), 3.33 (2/2 H, s), 4.58 (1/2 H, d, J = 10.6 Hz), 4.62 (1/2 H, d, J = 10.6 Hz), 5.15 (1/2 H, d, J = 10.6 Hz), 5.28 (1/2 H, d, J = 10.6 Hz), 6.8–7.4 (7 H, m), 7.69 (2/2 H, d, J = 8.3 Hz), 7.74 (2/2 H, d, J = 8.3 Hz). Anal. Calcd for $C_{24}H_{32}O_2S_2 \cdot {}^1/_4C_6H_6$: C, 70.22; H, 7.74. Found: C, 70.27; H, 7.61.

To a solution of ethyl iodide (111 mg, 0.71 mmol) and **18** (152 mg, 0.36 mmol) in DMF (5 mL) was added NaH (60% content) (32 mg, 0.79 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 24 h under an atmosphere of N_2. The reaction was quenched by the addition of an aqueous NH_4Cl solution (30 mL), and then the mixture was extracted with diisopropyl ether (30 mL × 3). The combined extracts were washed with brine (100 mL), dried (Na_2SO_4), and evaporated to give a yellow oil. This oil was dissolved in methanol (9 mL), and water (1 mL) and cupric chloride (96 mg, 0.72 mmol) were added. After the resulting mixture was stirred at 40 °C for 2 h, water (50 mL) was added, and extraction with diethyl ether (30 mL × 3) was performed. The extracts were combined, washed with water (100 mL), dried (Na_2SO_4), and evaporated. Column chromatography of the residue on SiO_2 using benzene–hexane (1:3) as an eluent afforded **19** (E:Z = 2:1) (60 mg; 64% overall yield) as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.85 (6 H, d, J = 6.0 Hz), 0.95–1.8 (8 H, m), 1.8–2.75 (4 H, m), 3.43 (2 H × 2/3, s), 4.01 (2 H × 1/3, s), 5.95 (1 H × 2/3, s), 6.15 (1 H × 1/3, s), 7.19 (5 H, s); IR (liquid film) 1695, 1608, 1602 cm^{-1}; MS (70 eV), m/e (relative intensity) 259 (30, $M^+ + 1$), 258 (81, M^+), 229 (89), 167 (100), 159 (75), 145 (32), 131 (25), 129 (34), 128 (21), 117 (31), 115 (28), 111 (24), 105 (22), 95 (21), 91 (98), 85 (31), 69 (29), 57 (70), 55 (22), 43 (71), 41 (30), 29 (37).

Synthesis of 4-Methyl-1-phenyl-3-octen-2-one (22). To a solution of butyl iodide (695 mg, 3.78 mmol) and **21** (=Il) (698 mg, 1.94 mmol) in DMF (8 mL) was added NaH (60% content) (117 mg, 2.93 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 23.5 h under an atmosphere of N_2. After the reaction was quenched by the addition of an aqueous NH_4Cl solution (50 mL) and water (25 mL), the mixture was extracted with diethyl ether (25 mL × 4). The combined extracts were washed with brine (100 mL × 3), dried ($MgSO_4$), and evaporated to give a yellow oil. This oil was dissolved in methanol (9 mL), and water (1 mL) and cupric chloride (543 mg, 4.04 mmol) were added. Then the resulting mixture was stirred at 40 °C for 2 h, and water (60 mL) was added. After extraction with diethyl ether (25 mL × 3), the extracts were combined, washed with water (50 mL × 3), dried (Na_2SO_4), and evaporated. Column chromatography of the residue on SiO_2 using benzene–hexane (1:2) as an eluent afforded **22** (E:Z = 3:2) (290 mg; 67% overall yield) as a pale yellow oil: ^1H NMR ($CDCl_3$) [of the E isomer] δ 0.91 (3 H, br t), 1.15–1.61 (6 H, m), 2.11 (3 H, d, J = 1.2 Hz), 3.69 (2 H, s), 6.08 (1 H, q, J = 1.2 Hz), 7.25 (5 H, s); IR (liquid film) 1685 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 7.40. Found: C, 83.09; H, 9.07. The Z isomer showed ^1H NMR signals at δ 1.85 (s, 3 H) and 6.13 (s, 1 H).

Synthesis of 1,4-Diphenyl-3-penten-2-one (25). To a solution of methyl iodide (430 mg, 3.03 mmol) and **24** (:Im) (506 mg, 1.23 mmol) in DMF (7 mL) was added NaH (60% content) (87 mg, 2.18 mmol) at room temperature, and the resulting mixture was stirred at room temperature for 14 h under an atmosphere of N_2. After the reaction was quenched by the addition of an aqueous NH_4Cl solution (50 mL), the mixture was extracted with diisopropyl ether (25 mL × 4). The combined extracts were washed with brine (100 mL × 2) and water (100 mL), dried ($MgSO_4$), and evaporated to give an oil. This oil was dissolved in methanol (13.5 mL), and water (1.5 mL) and cupric chloride (336 mg, 2.49 mmol) were added. Then the resulting mixture was stirred at 40 °C for 4 h, and water (60 mL) was added. After extraction with diisopropyl ether (20 mL × 4), the extracts were combined, washed with water (100 mL), dried ($MgSO_4$), and evaporated. Column chromatography of the residue on SiO_2 using benzene–hexane (1:2) as an eluent afforded **25** (148 mg, 51% yield) as a pale yellow oil, which was shown by ^1H NMR to consist of a sole geometric isomer (probably E isomer): ^1H NMR ($CDCl_3$) δ 2.52 (3 H, d, J = 1.2 Hz), 3.78 (2 H, s), 6.52 (1 H, q, J = 1.2 Hz), 7.27 (5 H, s), 7.34 (5 H, s); IR (liquid film) 1690 cm^{-1}. Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.25; H, 6.88.

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Registry No. 1, 92610-41-8; (E)-**2g**, 99946-73-3; (Z)-**2g**, 99946-74-4; (E)-**2h**, 99946-75-5; (Z)-**2h**, 99946-76-6; **3b**, 99946-65-3; **3c**, 99946-67-5; **3d**, 99946-69-7; **3e**, 99946-71-1; **3f**, 99946-63-1; **4a**, 99947-07-6; **4b**, 99946-66-4; **4c**, 99946-68-6; **4d**, 99946-70-0; **4e**, 99946-72-2; **4f**, 99946-64-2; (E)-**4h**, 99946-77-7; (Z)-**4h**, 99946-78-8; (E)-**5** (R_3 = Et, R_1 = CH_2Ph, R_2 = $(CH_2)_3CHMe_2$, 99947-18-9; (Z)-**5** (R_3 = Et, R_1 = CH_2Ph, R_2 = $(CH_2)_3CHMe_2$, 99947-19-0; **5e**, 99947-10-1; **5f**, 99947-08-7; **5m** (R_2 = Me), 99947-26-9; **7**, 59662-65-6; **9i**, 99946-89-1; **9j**, 99946-90-4; (E)-**9k**, 99946-91-5; (Z)-**9k**, 99946-92-6; (E)-**9l**, 99946-93-7; (Z)-**9l**, 99946-94-8; (E)-**9m**, 99946-95-9; (Z)-**9m**, 99946-96-0; (E)-**10i**, 99946-97-1; (Z)-**10i**, 99465-98-2; (E)-**10j**, 99946-99-3; (Z)-**10j**, 99947-00-9; (E)-**10k**, 99947-01-0; (Z)-**10k**, 99947-02-1; (E)-**10l**, 99947-03-2; (Z)-**10l**, 99947-04-3; (E)-**10m**, 99947-05-4; (Z)-**10m**, 99947-06-5; (E)-**11a** (R_2 = $(CH_2)_3CHMe_2$), 99947-12-3; (Z)-**11a** (R_2 = $(CH_2)_3CHMe_2$), 99947-13-4; (E)-**11f** (R_2 = $(CH_2)_3CHMe_2$), 99947-14-5; (Z)-**11f** (R_2 = $(CH_2)_3CHMe_2$), 99947-15-6; (E)-**11f** (R_2 = Bu), 99947-22-5; (Z)-**11l** (R_2 = Bu), 99947-23-6; **15**, 99947-09-8; **17**, 99947-11-2; (E)-**18**, 99947-16-7; (Z)-**18**, 99947-17-8; (E)-**19**, 99947-21-4; (Z)-**19**,

99947-20-3; **20** (R_1 = H), 99946-84-6; (*E*)-**20** (R_1 = Me), 99946-85-7; (*Z*)-**20** (R_1 = Me), 99946-86-8; (*E*)-**22**, 99947-24-7; (*Z*)-**22**, 99947-25-8; (*E*)-**23** (R_1 = Ph), 99946-87-9; (*Z*)-**23** (R_1 = Ph), 99946-88-0; **25**, 99947-27-0; $MeSCH(SO_2Tol)Et$, 94816-47-4; $MeSCCl(SO_2Tol)Et$, 99946-81-3; $MeSCH(SO_2Tol)Pr$, 99946-79-9; $MeSCCl(SO_2Tol)Pr$, 99946-82-4; $MeSCH(SO_2Tol)(CH_2)_2Ph$, 99946-80-2; $MeSCCl(SO_2Tol)(CH_2)_2Ph$, 99946-83-5; $Me_2CH(CH_2)_3Br$, 626-88-0.

Synthesis and Stereochemistry of Carbinolamine-Containing Pyrrolo[1,4]benzodiazepines by Reductive Cyclization of *N*-(2-Nitrobenzoyl)pyrrolidine-2-carboxaldehydes

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An investigation of the reductive cyclization of *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehydes has been carried out, establishing that (a) electron-donating substituents are apparently required in the aromatic ring for successful carbinolamine formation, (b) this route complements the lactam (hydride) reduction approach which fails to afford carbinolamine products when electron-donating groups are present in the aromatic ring, and (c) carbinolamines are always coproduced with varying amounts of the corresponding secondary amines of type **6**. Five carbinolamine-containing compounds have been prepared by this route and details of the interconversion between the imine, carbinolamine, and carbinolamine methyl ether forms and their corresponding ^1H NMR assignments are described. In addition, the unsubstituted nitro aldehyde **3** afforded a different isolated product (the *N*-hydroxycarbinolamine methyl ether **21**), the yield of which could be increased by the addition of Me_2SO.

The carbinolamine-containing pyrrolo[1,4]benzodiazepine group of antitumor antibiotics are presently attracting increased interest from both the synthetic and biological standpoint. Well-known members of this group[1] include anthramycin, tomaymycin, the neothramycins A and B, and sibiromycin, which are thought to exert their antitumor activity through covalent binding of their N10–C11 carbinolamine functionalities within the minor groove of DNA,[2] and at least in the case of anthramycin, the precise structure of the drug–DNA adduct has been elucidated.[3] A rational approach to the development of clinically useful drugs in this series has been suggested[4] and a few groups, including our own,[5] have embarked upon the preparation of rationally designed analogues in order to test SAR predictions.

Until 1983, there were two major synthetic routes in the literature, one involving hydride reduction of the corresponding dilactam **1**[6] and the other controlled reductive cyclization of an *N*-(2-nitrobenzoyl)pyrrolidine-2-carboxaldehyde (**3**)[7] (Scheme I). These methods have been used for the total syntheses of anthramycin,[6] and tomaymycin[8,9] and neothramycin,[10] respectively. However, more recently Kaneko and co-workers have reported[11,12] an alternative approach involving the aluminum amalgam reduction of an imino thioether of type **2**, prepared from the corresponding dilactam **1**. In addition, work carried out by another group[13] has led to the development of two new techniques involving cyclization of amino acetals **4** and N-protected amino aldehydes **5**. Also, Mori and coworkers[14] have recently reported a new route for the synthesis of secondary amine compounds of type **6**, suggesting that this should open up a new synthetic pathway. However, there are presently no useful techniques in the literature for converting the N10–C11 secondary amine functionality to an N10–C11 carbinolamine or the equivalent.

We recently published the results of an investigation into the generality of the dilactam reduction route (**1** → **7**), demonstrating that product formation is dependent upon the nature and position of substituents in the aromatic ring.[5] We discovered that this route was unsuccessful for analogues containing electron-donating groups in the aromatic ring and only afforded carbinolamine-type products when electron density could be reduced on the N10 nitrogen via an external bridge from N10 to a C9

(1) For a review, see: Hurley, L. H.; Thurston, D. E. *Pharm. Res.* **1984**, *52*. Hurley, L. H. *J. Antibiot.* **1977**, *30*, 349. For newer members of this class of compounds, see: Kunimoto, S.; Masuda, T.; Kanbayashi, N.; Hamada, M.; Naganawa, H.; Miyamoto, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1980**, *33*, 665. Shimizu, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Fujimoto, K. *J. Antibiot.* **1982**, *35*, 972.

(2) Petrusek, R. L.; Anderson, G. L.; Garner, T. F.; Quinton, F. L.; Fannin, L.; Kaplan, D. J.; Zimmer, S. G.; Hurley, L. H. *Biochemistry* **1981**, *20*, 1111.

(3) Graves, D. E.; Pattaroni, C.; Krishnan, B. S.; Ostrander, J. M.; Hurley, L. H.; Krugh, T. R. *J. Biol. Chem.* **1984**, *13*, 8202.

(4) Thurston, D. E.; Hurley, L. H. *Drugs Future* **1983**, *8*, 957.

(5) Thurston, D. E.; Kaumaya, P. T. P.; Hurley, L. H. *Tetrahedron Lett.* **1984**, *25*, 2649.

(6) Leimgruber, W.; Batcho, A. D.; Czajkowski, R. C. *J. Am. Chem. Soc.* **1968**, *90*, 5641.

(7) Lown, J. W.; Joshua, A. V. *Biochem. Pharmacol.* **1979**, *28*, 2017.

(8) Tozuka, Z.; Takasugi, H.; Takaya, T. *J. Antibiot.* **1983**, *36*, 276.

(9) Tozuka, Z.; Yazawa, H.; Murata, M.; Takaya, T. *J. Antibiot.* **1983**, *36*, 1699.

(10) Miyamoto, M.; Kondo, S.; Naganawa, H.; Maeda, K.; Ohno, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 340.

(11) Kaneko, T.; Wong, H.; Doyle, T. W. *Tetrahedron Lett.* **1983**, *24*, 5165. Kaneko, T.; Wong, H.; Doyle, T. W. *J. Antibiot.* **1984**, *37*, 300.

(12) Kaneko, T.; Wong, H.; Doyle, T. W.; Rose, W. C.; Bradner, W. T. *J. Med. Chem.* **1985**, *28*, 388.

(13) Holden, K. G.; Hoover, J. R. E. SmithKline Beckman Corp., personal communication.

(14) Mori, M.; Purvaneckas, G.-E.; Ishikura, M.; Ban, Y. *Chem. Pharm. Bull.* **1984**, *32*, 3840.

0022-3263/86/1951-0705$01.50/0