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The Intramolecular *Sila*-Pummerer Cyclization: A New Route to Sulfur Heterocycles

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ABSTRACT

The generality of the intramolecular cyclization of suitable nucleophilic sites to a $-S^+=CH_2$ center created by a sila-Pummerer rearrangement has been investigated. Successful nucleophilic sites included the OH group (in alcohols, carboxylic acids, and hydroxylamines) and the NH group (in amines and carbamates): attempts to produce carbon-based nucleophilic sites were not effective. Successful cyclizations were achieved to produce sulfur heterocycles with 5-, 6-, and 7-membered rings.

INTRODUCTION

The classical Pummerer reaction [1,2] has been widely used for the conversion of sulfoxides into α-substituted sulfides, and intramolecular examples of this reaction have been reported [3–5]. The *sila*-Pummerer analogue of this reaction has been extensively investigated by Brook [6], and an elegant application to the cyclization of β-keto sulfoxides in the presence of *t*-butyldimethylsilyl trifluoromethanesulfonate has very recently appeared [7].

Because we had successfully achieved ring closure to a novel 7-membered ring heterocyclic system [8], using a α-trimethylsilyl-substituted sulfoxide under relatively mild conditions (80°C; uncatalyzed), we were interested in exploring the limits of this intramolecular reaction as a potentially useful general route to sulfur-containing heterocycles. We now wish to report the results we obtained when we investigated the creation of various 5- and 6-membered heterocyclic rings employing this approach.

RESULTS AND DISCUSSION

We felt that an interesting example to initiate our investigation was provided by methyl S-(trimethylsilylmethyl)-L-cysteinate S-oxide **4**, which was readily prepared from methyl S-(trimethylsilyl)-L-cysteinate [8], as shown in Scheme 1. When **4** was refluxed in dry acetonitrile for 2 hours, the expected methyl L-thiazolidine-4-carboxylate **5a** was obtained, as the hydrochloride, in 65% yield (Table 1). Interestingly, when the N-protected sulfoxide **3** was subjected to similar *sila*-Pummerer conditions, but for a longer time (16 hours), the analogous thiazolidine derivative **5b** was obtained, in 47% yield (Table 1).

Encouraged by these results, we attempted to extend the *sila*-Pummerer cyclization to the construction of the 5- and 6-membered heterocycles obtained by nucleophilic attack of an alcoholic OH group upon the $-S^+=CH_2$ moiety. To this end, we have prepared 3-(trimethylsilylmethylthio)-1-propanol S-oxide **7** and 2-(trimethylsilylmethylthio)ethanol S-oxide **9**, starting from methyl 3-mercaptopropanoate **6a** and 2-mercaptoethanol **8**, respectively, by the routes shown in Scheme 2.

Refluxing the hydroxy-sulfoxide **7** in acetonitrile for 2 hours afforded the expected 1,3-oxathiane **10** in 58% yield, and, similarly, 1,3-oxathiolane **11a** was obtained from **9**, in 64% yield (Table

Dedicated to Prof. Adrian Gibbs Brook on the occasion of his seventieth birthday.

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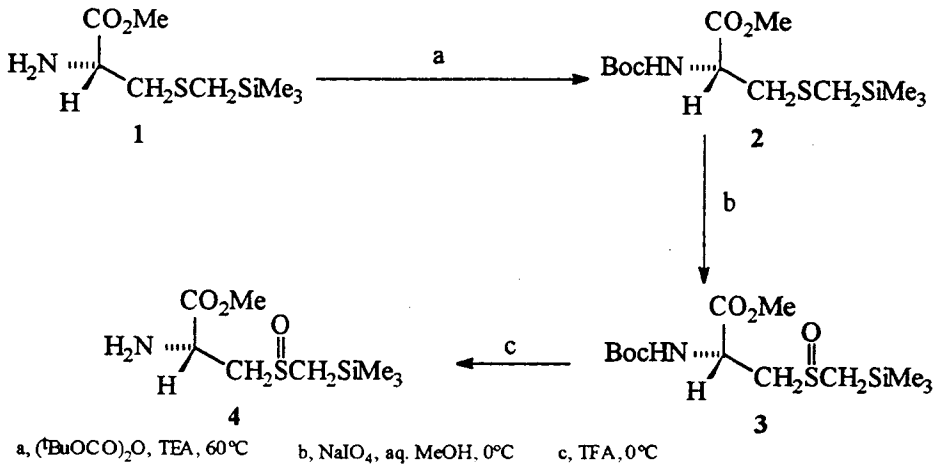
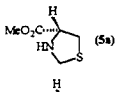
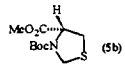
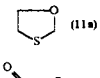
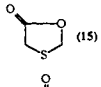
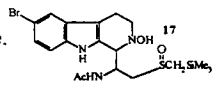


SCHEME 1 Preparation of cysteine-derived sulfoxides **3**, **4**.

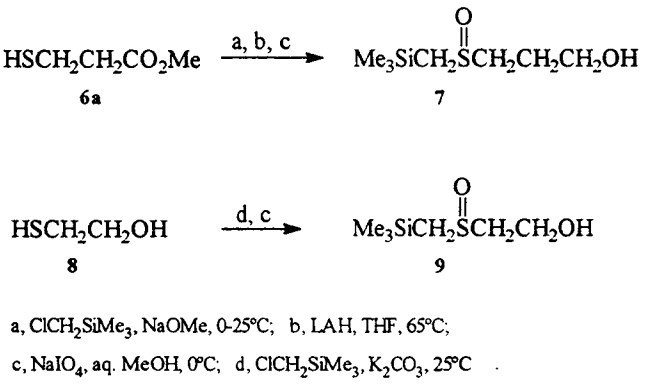
TABLE 1 Intramolecular *sila*-Pummerer Cyclizations

Starting Sulfoxide	*Time of Reaction*[a] *(h)*	*Product*	*Yield (%)*
4	2	 (5a)	95 (65)[b]
3	16	 (5b)	47
7	2	 (10)	58
9	2	 (11a)	64[c]
14	16	 (15)	28
12	16	 (16)	—
17	1	N(10)-Acetyleudistomin L[d]  17	20

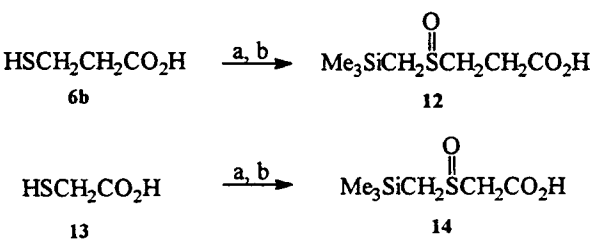
[a]In refluxing CH_3CN.
[b]Following conversion to the hydrochloride.
[c]Characterized as the sulfone analogue.
[d]Ref. [8].

1). To assist with its identification, **11a** was converted to the known, crystalline sulfone **11b** by oxidation with *m*-chloroperoxybenzoic acid (MCPBA).

As these results have shown, the construction of 5- and 6-membered sulfur heterocycles, using OH or NH groups, in the *sila*-Pummerer cyclization appears to be quite general. We were also interested in establishing whether the more weakly nucleophilic carboxylic acid group could function in a similar fashion to generate analogous oxo-substituted heterocycles. We thus prepared 3-(trimethylsilylmethylthio)propanoic acid S-oxide **12** from 3-mercaptopropanoic acid **6b**, using the normal trimethylsilylmethylation method, followed by oxidation of the sulfide with H_2O_2 catalyzed by vanadyl acetylacetonate, $VO(acac)_2$, according to a literature procedure [9]. The analogous 2-(trimethylsilylmethylthio)acetic acid S-oxide **14** was similarly prepared from 2-mercaptoacetic acid **13** (Scheme 3). No significant problems were encountered with introduction of the trimethylsilyl-



SCHEME 2 Preparation of hydroxy-sulfoxides **7**, **9**.



SCHEME 3 Preparation of carboxy-sulfoxides **12**, **14**.

methylthio group at the SH site in either case (90% yields) in spite of the potential for O-alkylation of the carboxylic acid group.

Cyclization of sulfoxide **14** to produce the expected 1,3-oxathiolan-5-one **15** (Table 1) was achieved only after refluxing in acetonitrile for 16 hours, and the yield of pure **15** was only 28%. Attempts to increase this yield by deprotonation of the acid using cesium carbonate were unsuccessful. Given this result, in the presumably more favorable 5-membered ring case, it was not entirely surprising to discover that, for sulfoxide **12**, none of the expected 1,3-oxathian-6-one **16** was isolated, even after prolonged refluxing.

Our attempts to prepare the silyl enol ether derivative of the keto-sulfide 4-(trimethylsilylmethylthio)-2-butanone in order to explore the potential for C-cyclization in the corresponding sulfoxide consistently met with failure. Hunter and Simon [10] have reported the successful intermolecular reaction, in moderate yields, of silyl enol ethers with species $C_6H_5S^+{=}CHR$, generated by TMS-triflate catalyzed Pummerer reactions of the corresponding sulfoxides. Because our lack of success may have been attributed in part to a problem with the regioselectivity of enolate ion formation, we next turned our attention to the preparation of the silyl enol ether derivative of the keto-sulfide **20**, prepared in 75% overall yield in four steps from 2-mercaptobenzoic acid (thiosalicylic acid) **18**, via the Weinreb amide **19**, as shown in Scheme 4. Once again, problems were encountered with the O-silylation of the enolate ion of **20**. Spectroscopic evidence indicated that the problems involved loss of the $SiMe_3$ group from the trimethylsilylmethylthio moiety under the strongly basic conditions (LDA or NaH) involved, even at −78°C. As a result, we reluctantly abandoned further attempts to develop a C-cyclization pathway for the *sila*-Pummerer cyclization.

We believe that the results in Table 1 have established the versatility of the intramolecular *sila*-Pummerer cyclization strategy as a useful general route to sulfur-heterocycles of the 5-, 6-, and 7-membered type. The greater success observed with the OH and NH nucleophiles may be attributed to their greater nucleophilicity as compared to RCO_2H/RCO_2^- [11] or, possibly, to the conformational change in the transition state produced by the additional sp^2 (C=O) center in the carboxylic acid.

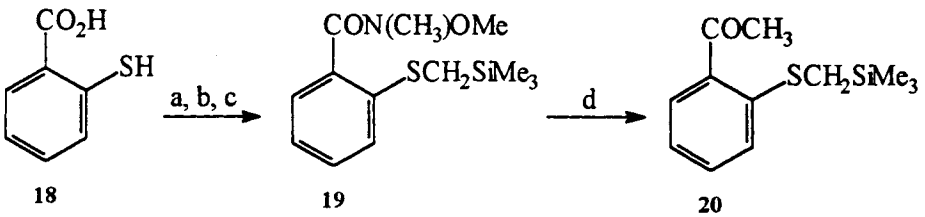
EXPERIMENTAL

Dry DMF, nitromethane, and chlorotrimethylsilane were redistilled from P_2O_5 and stored over 3 Å molecular sieves. Methanol and ethanol were distilled from magnesium methoxide. Acetonitrile, triethylamine, and diisopropylamine were distilled from calcium hydride. THF was dried over 3 Å molecular sieves overnight and then freshly distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was also redistilled prior to use.

Infrared spectra were run as KBr pellets or neat films on NaCl discs on a Nicolet 5DXB Fourier transform infrared spectrometer. ^1H NMR spectra were routinely run at 60 MHz on a Varian EM360-L spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane as the internal standard. ^{13}C and 400 MHz ^1H NMR spectra were run on a Varian XL 400 instrument. Mass spectra were routinely run under electron impact (EIMS) conditions at 70 eV or, occasionally, under fast atom bombardment (FABMS) or chemical ionization (CIMS) conditions on a VG11-250S instrument. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Methyl N-(Boc)-S-(trimethylsilylmethyl)-L-cysteinate, **2**

To the cysteinate ester **1** (6.81 g, 0.031 mol) in dry DMF (75 mL) was added dry triethylamine (TEA) (10.7 mL, 0.077 mol), and the solution was stirred at 60°C under nitrogen. Di-*tert*-butyl dicarbonate (7.38 g, 0.034 mol), was then added to the reaction mixture, and the solution was stirred vigorously



18 **19** **20**

a, $ClCH_2SiMe_3$, $NaHCO_3$ (DMSO-CH_3CN), 25°C; b, $SOCl_2$ refl.;
c, $H_2\overset{+}{N}(CH_3)OMe\ Cl^-$, TEA, 0-25°C; d, MeMgBr, THF, 0-25°C

SCHEME 4 Preparation of 2-(trimethylsilylmethylthio)acetophenone.

(bath temperature of 60°C) for 1 hour. After cooling to 25°C, the orange solution was concentrated under reduced pressure, and the resulting oil was dissolved in water (50 mL) and extracted with diethyl ether (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield an orange oil. Kugelrohr distillation at 180–185°C/0.20 Torr yielded a slightly yellow, mobile oil (8.85 g, 89%). IR (NaCl): ν 3375, 2977, 2957, 1748, 1715, 1250, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.13 (s, 9H, $Si(CH_3)_3$) 1.50 (s, 9H, $OC(CH_3)_3$), 1.70 (dd, J = 11.7, 1.5 Hz, 1H, SCH_2Si), 1.77 (dd, J = 11.7, 3.2 Hz, 1H, SCH_2Si), 2.84 (m, 2H, CH_2S), 3.71 (s, 3H, OCH_3), 4.45 (dd, J = 7.3, 5.8 Hz, 1H, *CH*), 5.34 (d, J = 7.6 Hz, 1H, *NH*). ^{13}C NMR ($CDCl_3$): δ −1.60 ($Si(CH_3)_3$), 19.06 (SCH_2Si), 28.52 ($(\underline{C}H_3)_3CO$), 38.61 (CH_2S), 50.15 (CH), 52.53 (OCH_3), 80.06 ($(CH_3)_3\underline{C}O$), 155.35 ($^tBuO_2C$), 172.03 ($\underline{C}O_2Me$). FABMS: m/z (%) 322 (33) (MH^+), 266 (92), 250 (30), 222 (64), 205 (100), 188 (8), 174 (16), 162 (41), 133 (54). HR–FABMS calcd. for $C_{13}H_{27}NO_4SSi$: 321.1430; found: 321.1422.

Methyl N-(Boc)-S-(trimethylsilylmethyl)-L-cysteinate S-Oxide, **3**

To a mixture of the sulfide **2** (0.50 g, 1.54 mmol) in methanol (20 mL) was added a solution of sodium periodate (0.36 g, 1.68 mmol) in distilled water (12 mL). After having been stirred overnight at 0°C, a solution of sodium thiosulfate (3.0 g) in water (50 mL) was added, and the solution was extracted with dichloromethane (4 × 15 L). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a slightly yellow solid (0.54 g). Recrystallization from dichloromethane:hexanes yielded shiny, white fibrous crystals (0.48 g, 92%), mp 118–119°C. IR (KBr): ν 3203, 3050, 2977, 2957, 1755, 1702, 1257, 1025, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.09 (s, 9H, $Si(CH_3)_3$), 1.37 (s, 9H, $OC(CH_3)_3$), 2.13 (d, J = 13.55 Hz, 1H, $S(O)CH_2Si$, 2.39 (d, J = 13.55 Hz, 1H, $S(O)CH_2Si$), 3.04 (dd, J = 12.82, 3.66 Hz, 1H, CH_2S), 3.22 (dd, J = 13.18, 7.33 Hz, 1H, CH_2S), 3.72 (s, 3H, OCH_3), 4.64 (m, 1H, *CH*), 5.87 (d, J = 8.06 Hz, 1H, *NH*). ^{13}C NMR ($CDCl_3$): δ −0.83 ($Si(CH_3)_3$), 28.26 ($(\underline{C}H_3)_3CO$), 43.28 ($(O)SCH_2Si$), 50.90 (CH), 52.78 (OCH_3), 56.97 ($CH_2S(O)$), 80.25 ($(CH_3)_3\underline{C}O$), 155.35 (-$BuO_2\underline{C}$), 170.85 ($\underline{C}O_2Me$); FABMS: m/z (%) 338 (74) (MH^+), 282 (100), 266 (7), 238 (51), 154 (14), 136 (19), 102 (78). HR–FABMS calcd. for $C_{13}H_{28}NO_5SSi$: 338.1457; found: 338.1490. Anal. calcd. for $C_{13}H_{27}NO_5SSi$: C, 46.27; H, 8.07; N, 4.15; S, 9.48. Found: C, 46.16; H, 8.14; N, 4.18; S, 9.52.

Methyl S-(Trimethylsilylmethyl)-L-cysteinate S-Oxide, **4**

A mixture of the sulfoxide **3** (0.52 g, 1.54 mmol) in dichloromethane (10 mL) was slowly treated with trifluoroacetic acid (4.25 mL, 0.055 mol), and the solution was stirred for 1.5 hours at 0°C under nitrogen. The resulting clear yellow mixture was partioned between saturated sodium bicarbonate (25 mL) and dichloromethane (25 mL). To the remaining aqueous layer was slowly added sodium carbonate (to pH ≈ 8), and the aqueous layer was further extracted with dichloromethane (2 × 15 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a slightly orange oil (0.24 g, 67%), which was used without further purification. IR (NaCl): ν 3375, 2957, 2897, 1735, 1682, 1250, 1011, 852 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2.1 (s, 2H, NH_2, *exch*), 2.4 (m, 2H, $S(O)CH_2Si$), 3.1 (m, 2H, $CH_2S(O)$), 3.8 (s, 3H, OCH_3), 4.2 (m, 1H, *CH*).

Methyl L-Thiazolidine-4-carboxylate, **5a**

A solution of the sulfoxide **4** (0.25 g, 1.01 mmol) in dry acetonitrile (40 mL) was refluxed under nitrogen for 2 hours. The orange solution was then concentrated to yield an oil (0.14 g, 95%). Kugelrohr distillation at 75–80°C/0.20 Torr yielded a colorless oil. IR (NaCl): ν 3316, 2997, 2950, 2877, 1742 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.38 (s, 1H, *NH*, *exch*), 2.75 (m, 1H, CH_2S), 3.11 (m, 1H, CH_2S), 3.66 (s, 3H, OCH_3), 3.74 (m, 1H, *CH*), 3.99 (m, 1H, NCH_2S), 4.24 (m, 1H, NCH_2S); ^{13}C NMR ($CDCl_3$): δ 36.65 (CH_2S), 52.21 (OCH_3), 54.13 (NCH_2S), 64.89 (CH), 171.46 (CO_2Me). EIMS: m/z (%) 147 (55) (MH^+), 132 (18), 114 (8), 101 (14), 88 (100), 69 (13), 61 (32), 59 (28).

HCl gas was bubbled through a solution of the free base (0.14 g, 0.95 mmol) in dry methanol (10 mL) and diethyl ether (25 mL), followed by stirring for 0.5 hours. The solution was concentrated to yield an orange paste, which was recrystallized from methanol:diethyl ether yielding the hydrochloride (0.11 g, 65%) as shiny white plates, mp 160–163°C. Ref. [12]: mp 164–165°C. IR (NaCl): ν 3475, 2917, 2804, 2711, 2552, 1748, 1543 cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.28 (m, 1H, CH_2S), 3.34 (m, 1H, CH_2S), 3.75 (s, 3H, OCH_3), 4.28 (d, J = 9.5 Hz, 1H, NCH_2S), 4.31 (d, J = 9.3 Hz, 1H, NCH_2S), 4.78 (s, 1H, CH), 10.61 (br s, 2H, NH_2^+). Anal. calcd. for $C_5H_{10}ClNO_2S$: C, 32.78; H, 5.51; N, 7.65; S, 17.48. Found: C, 32.55; H, 5.52; N, 7.52; S, 17.54.

Methyl N-(Boc)-L-thiazolidine-4-carboxylate, **5b**

A solution of the sulfoxide **3** (0.23 g, 0.68 mmol) in dry acetonitrile (20 mL) was refluxed (bath temperature 100–110°C) under nitrogen overnight. The resulting mixture was concentrated to produce a yellow oil (0.19 g). Flash chromatography on silica gel, eluting with 95:5 dichloromethane:methanol, gave the cyclized product (0.08 g, 47%) as a slightly yellow oil. IR (NaCl): ν 2977, 2950, 2884, 1742, 1702 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.32 (s, 9H, $OC(CH_3)_3$), 2.72 (dd, J = 10.26, 7.69 Hz, 1H, CH_2S), 3.08 (dd, J = 10.26, 7.32 Hz, 1H, CH_2S), 3.61 (s, 3H, OCH_3),

3.71 (dd collapsed into t, J = 7.69, 7.32 Hz, 1H, *CH*), 3.95 (d, J = 9.52 Hz, 1H, NCH_2S), 4.20 (d, J = 9.52 Hz, 1H, NCH_2S). ^{13}C NMR ($CDCl_3$): δ 27.88 ($OC(\underline{C}H_3)_3$) 36.53 (CH_2S), 52.07 (OCH_3), 54.02 (NCH_2S), 64.80 (CH), 80.68 ($O\underline{C}(CH_3)_3$), 152.60 ($\underline{C}O_2$-Bu), 171.35 ($\underline{C}O_2Me$). FABMS: m/z (%) 248 (8) (MH^+), 246 (11), 192 (36), 160 (35), 148 (41), 146 (56), 132 (6), 116 (9), 88 (19), 57 (100), 41 (21). HR–FABMS calcd. for $C_{10}H_{18}NO_4S$: 248.0956; found: 248.0954.

3-(Trimethylsilylmethylthio)-1-propanol S-Oxide, **7**

Methyl 3-(trimethylsilylmethylthio)propanoate (5.63 g, 67%) was obtained as a colorless mobile oil from methyl 3-mercaptopropanoate **6a** (4.60 mL, 0.047 mol) and chloromethyltrimethylsilane (6.10 mL, 0.044 mol) using the procedure described for **12** but substituting dry methanol for dry ethanol. IR (NaCl): ν 2957, 2924, 2897, 1742, 1250, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.1 (s, 9H, $Si(CH_3)_3$), 1.8 (s, 2H, SCH_2Si), 2.7 (t, J = 4 Hz, 4H, CH_2S and CH_2CO_2Me), 3.7 (s, 3H, CO_2CH_3).

To a slurry of LAH (0.73 g, 19.23 mmol) in dry THF (20 mL) was slowly added the methyl ester obtained above (1 g, 4.80 mmol) in dry THF (30 mL) over a period of 15 minutes, at 0°C. The resulting solution was brought to gentle reflux and stirred an additional 3 hours. The reaction was quenched by the slow addition of dilute ethyl acetate (in THF), resulting in a thick white slurry which was filtered through Celite and washed with diethyl ether (3 × 15 mL). The ether extracts were combined, washed (NaCl), dried (Na_2SO_4), and concentrated, yielding a slightly yellow oil. Kugelrohr distillation at 110–115°C/0.20 Torr yielded a colorless oil (0.64 g, 81%). IR (NaCl): ν 3349, 2950, 2877, 1390, 1250, 1064, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 1.9 (s, 2H, SCH_2Si), 2 (m, 2H, $HOCH_2CH_2$), 2.8 (t, J = 6 Hz, 2H, CH_2S), 3.2–3.6 (br s, 1H, *OH, exch*), 3.8 (t, J = 6 Hz, 2H, $HOCH_2$).

3-(Trimethylsilylmethylthio)-1-propanol S-oxide **7** (0.44, 81%) was obtained as a colorless oil by treatment of the sulfide described above (0.50 g, 2.80 mmol) with sodium periodate (0.65 g, 3.08 mmol) using the procedure described previously. IR (NaCl): ν 3359, 2957, 2897, 1250, 1011, 839 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.14 (s, 9H, $Si(CH_3)_3$), 1.79 (m, 1H, $CH_2CH_2S(O)$), 2.03 (m, 1H, $CH_2CH_2S(O)$), 2.06 (dd, J = 13.55, 4.76 Hz, 1H, $S(O)CH_2Si$), 2.26 (dd, J = 13.55, 1.83 Hz, 1H, $S(O)CH_2Si$), 2.73 (m, 2H, $CH_2S(O)$), 3.65 (m, 2H, CH_2O), 4.66 (m, 1H, *OH, exch*). CIMS: m/z (%) 195 (26) (MH^+), 179 (58), 163 (9), 130 (34), 121 (11), 115 (16), 105 (100), 89 (19), 73 (37). HR–CIMS calcd. for $C_7H_{19}O_2SSi$: 195.0875; found: 195.0866.

2-(Trimethylsilylmethylthio)ethanol S-Oxide, **9**

A mixture of 2-mercaptoethanol **8** (6 g, 0.076 mol) and potassium carbonate (15.6 g, 0.113 mol) in dry acetonitrile (80 mL) was slowly treated with chloromethyltrimethylsilane (9.8 g, 0.080 mol) via an addition funnel. The reaction mixture was stirred at 25°C overnight under nitrogen. The resulting white suspension was concentrated to a white solid, which was dissolved in water (50 mL) and extracted with dichloromethane (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a slightly orange oil. Kugelrohr distillation at 105–110°C/0.20 Torr yielded a colorless mobile oil (7.90 g, 63%). IR (NaCl): ν 3369, 2957, 2884, 1250, 858 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.20 (s, 9H, $Si(CH_3)_3$), 1.9 (s, 2H, SCH_2Si), 2.8 (t, J = 6 Hz, 2H, CH_2S), 3.3 (br s, 1H, *OH, exch*), 3.8 (t, J = 6 Hz, 2H, OCH_2).

The oxidation of this sulfide (0.60 g, 3.65 mmol) using sodium periodate was carried out as described previously, affording 2-(trimethylsilylmethylthio)ethanol S-oxide **9** (0.55 g, 84%) as a white solid. The solid was recrystallized from dichloromethane:petroleum ether yielding white needles (70% recovery), mp 49–50°C. IR (KBr): ν 3236, 2950, 2897, 2857, 1250, 991, 839 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.10 (s, 9H, $Si(CH_3)_3$), 2.17 (d, J = 13.6 Hz, 1H, $S(O)CH_2Si$), 2.46 (d, J = 13.2 Hz, 1H, $S(O)CH_2Si$), 2.80 (ddd, J = 13.2, 5.9, 3.3 Hz, 1H, CH_2S), 2.96 (ddd, J = 13.2, 8.1, 4 Hz, 1H, CH_2S), 3.85 (dd, J = 6.6, 4.8 Hz, 1H, *OH, exch*), 4.1 (m, 2H, OCH_2); EIMS: m/z (%) 181 (100) (MH^+), 163 (9), 154 (6), 136 (14), 119 (9). HR–EIMS calcd. for $C_6H_{17}O_2SSi$: 181.0719; found: 181.0725.

1,3-Oxathiane, **10**

A solution of the sulfoxide **7** (0.27 g, 1.51 mmol) in dry acetonitrile (10 mL) was refluxed for 2 hours (bath temperature 100–110°C) under nitrogen. Concentration of the orange solution afforded a yellow oil (0.20 g), which was distilled at 70–75°C/15 Torr to yield the cyclized product (0.09 g, 58%) as a slightly yellow oil. Ref. [13]: bp 96–100°C/100 Torr. ^1H NMR ($CDCl_3$): δ 1.8 (m, 2H, CH_2CH_2S), 2.8 (t, 2H, CH_2S), 3.8 (t, 2H, OCH_2), 4.7 (s, 2H, OCH_2S). EIMS: m/z (%) 104 (100) (MH^+), 92 (6), 74 (64), 61 (9), 58 (14).

1,3-Oxathiolane, **11a**

A solution of the sulfoxide **9** (0.25 g, 1.38 mmol) in dry acetonitrile (10 mL) was refluxed for 2 hours (bath temperature 100°C) under nitrogen. Concentration of the resulting solution yielded a slightly yellow oil (0.11 g). Subsequent Kugelrohr distillation at 30°C/12 Torr yielded a colorless oil (0.08 g, 64%). IR (NaCl): ν 2973, 2944, 2867, 1074, 951 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.8 (t, J = 7 Hz, 2H, CH_2S), 3.8 (t, J = 7 Hz, 2H, CH_2O), 4.7 (s, 2H, OCH_2S). EIMS: m/z (%) 90 (43), 69 (5), 60 (50), 59 (20), 45 (32), 32 (54), 28 (65), 18 (100). HR–EIMS calcd. for C_3H_6OS: 90.01339; found: 90.01340.

1,3-Oxathiolane, 3,3-Dioxide, **11b**

A solution of the sulfide **11a** (0.22 g, 2.44 mmol) in dichloromethane (20 mL) was treated with MCPBA (1.95 g, 7.32 mmol), and the mixture was heated gently overnight. To the resulting dichloromethane solution was added sodium bicarbonate (1.00 g), and the mixture was allowed to stand at 25°C for 1 hour. After the addition of distilled water (50 mL), the two-layer system was extracted with dichloromethane (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a white solid (0.17 g, 59%). Recrystallization from methanol (71% recovery) afforded the sulfone as white plates, mp 82–84°C. Ref. [14]: mp 86–88°C. IR (KBr): ν 2972, 2926, 1421, 1316, 1284, 1131, 1065 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.20 (t, J = 6.95 Hz, 2H, CH_2SO_2), 4.37 (t, J = 6.95 Hz, 2H, OCH_2), 4.40 (s, 2H, OCH_2SO_2).

3-(Trimethylsilylmethylthio)propanoic Acid S-Oxide, **12**

To 3-mercaptopropanoic acid **6b** (4.12 mL, 0.047 mol) in dry ethanol (100 mL), under nitrogen at 0°C, was slowly added sodium (2.70 g, 0.117 mol). The reaction mixture was warmed to 25°C, and chloromethyltrimethylsilane (6.90 mL, 0.049 mol) was slowly added to the reaction mixture over a period of 10 minutes. After having been stirred for 1.5 hours, the cloudy white suspension was concentrated to yield a white solid. This was dissolved in 1M HCl (75 mL) and then extracted with dichloromethane (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a colorless oil (8.10 g, 89%), which crystallized on storing at 0°C. IR (NaCl): ν 3031, 2958, 2919, 1713, 1252, 844 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 1.9 (s, 2H, SCH_2Si), 2.8 (t, J = 2 Hz, 4H, CH_2S and CH_2CO_2H), 11.8 (s, 1H, CO_2H).

A stirred solution of the sulfide (0.50 g, 2.56 mmol) in dry acetone (10 mL) maintained at 0°C was treated with 30% H_2O_2 (0.44 g, 3.87 mmol), followed by a catalytic amount of vanadyl acetylacetonate (<0.01 g) [9]. The resulting orange solution was stirred at 0°C until it became blue (3 hours); then distilled water (25 mL) was added, and the solution was extracted with dichloromethane (4 × 15 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a colorless oil (0.49 g, 91%). IR (NaCl): ν 2957, 2924, 2904, 1722, 1250, 998, 852 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2.4 (two d, J = 12 Hz, 2H, $S(O)CH_2Si$), 2.8–3.1 (m, 4H, $CH_2S(O)$ and CH_2CO_2H), 10.8 (s, 1H, CO_2H). EIMS: m/z (%) 209 (20) (MH^+), 190 (18), 179 (12), 163 (20), 147 (48), 129 (52), 118 (21), 103 (25), 88 (19), 75 (100), 73 (75), 55 (42).

2-(Trimethylsilylmethylthio)acetic Acid S-Oxide, **14**

The reaction of mercaptoacetic acid **13** (1.50 g, 16.3 mmol) with chloromethyltrimethylsilane (2.4 mL, 17.1 mmol) in the presence of sodium ethoxide following the procedure detailed above for the preparation of **12** led to the isolation of the S-protected acid as an essentially colorless oil (2.64 g, 92%), purified by Kugelrohr distillation at 110°C/0.20 Torr. IR (NaCl): ν 3442, 3070, 2957, 2897, 1709, 1250, 845 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.1 (s, 9H, $Si(CH_3)_3$), 1.9 (s, 2H, SCH_2Si), 3.2 (s, 2H, SCH_2CO_2H), 9.9 (s, 1H, CO_2H).

Compound **14** was prepared by the vanadyl acetylacetonate catalyzed oxidation [9] of the sulfide so obtained with 30% hydrogen peroxide by the method described above for **12**. The sulfoxide (0.40 g, 78%) was obtained as white crystals, recrystallized from dichloromethane:petroleum ether, mp 94–95°C. IR (KBr): ν 3415, 2957, 2917, 2897, 1709, 1250, 991, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2.5 (two d, J = 12 Hz, 2H, $S(O)CH_2Si$), 3.7 (s, 2H, $S(O)CH_2CO_2H$), 9.1 (br s, 1H, CO_2H). EIMS: m/z (%) 193 (6) (MH^+), 177 (14), 147 (22), 135 (23), 117 (15), 103 (28), 86 (6), 75 (100), 59 (14).

1,3-Oxathiolan-5-one, **15**

A solution of the sulfoxide **14** (0.40 g, 2.06 mmol) in dry acetonitrile (10 mL) was refluxed (bath temperature 110–120°C) under nitrogen overnight. The resulting solution was concentrated to yield a slightly yellow oil. The desired product (0.06 g, 28%) was obtained as a colorless oil by flash chromatography of the residual oil, by eluting with dichloromethane:methanol (95:5) [15], or, alternatively, by Kugelrohr distillation at 100°C/15 Torr. Ref. [15]: bp 84°C/12 Torr. IR (NaCl): ν 3003, 2957, 2924, 2897, 1768, 1735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.6 (s, 2H, SCH_2CO_2), 5.2 (s, 2H, OCH_2S). EIMS: m/z (%) 104 (100) (M^+), 74 (54), 60 (17). HR–EIMS calcd. for $C_3H_4O_2S$: 103.9932; found: 103.9936.

N,O-Dimethyl-2-(trimethylsilylmethylthio)-benzohydroxamic acid, **19**

To a stirred solution of chloromethyltrimethylsilane (4.75 mL, 34 mmol) and sodium bicarbonate (4.08 g, 48 mmol) was slowly added (30 minutes) a solution of thiosalicylic acid (5.0 g, 32 mmol) in dry acetonitrile (40 mL) and dry DMSO (5 mL). The resulting yellow solution was stirred at 25°C overnight and then concentrated under reduced pressure to a thick yellow paste. The paste was dissolved in 1 M HCl and extracted with ethyl acetate (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a slightly yellow solid (6.16 g, 79%). Recrystallization from 80% ethanol (80–85% recovery) yielded white crystals, mp 135–137°C. IR (KBr): ν 3448, 2957, 2984, 2824, 1682, 1250, 852 cm^{-1}. ^1H NMR ($CDCl_3$/DMSO-d_6): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2.0 (s, 2H, SCH_2Si), 7.1 (m, 1H, *H*-3), 7.4 (d, J = 3 Hz, 2H, *H*-4 and *H*-

5), 8.1 (d, J = 7 Hz, 1H, *H*-6), 11.8 (br s, 1H, CO_2H). EIMS: m/z (%) 240 (42) (M^+), 225 (89), 181 (39), 151 (100), 137 (9), 122 (43), 105 (16), 91 (8), 75 (92), 73 (3), 59 (16). HR–EIMS calcd. for $C_{11}H_{16}O_2SSi$: 240.0640; found: 240.0640.

The S-alkylated acid (3 g, 12.5 mmol) was refluxed in freshly distilled thionyl chloride (10 mL) for 0.5 hours, and the resulting solution was concentrated under reduced pressure to yield the acid chloride (3.23 g, 100%) as a deep orange oil. IR (NaCl): ν 3063, 2957, 2891, 1762, 1250, 852 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2.1 (s, 2H, SCH_2Si), 7.3 (m, 1H, *H*-3), 7.5 (m, 2H, *H*-4 and *H*-5), 8.3 (d, J = 7 Hz, 1H, *H*-6).

The hydroxamic acid **19** was prepared by the method described by Weinreb and Nahm [16] from the acid chloride so obtained (3.23 g, 12.5 mmol) and N,O-dimethylhydroxylamine hydrochloride (1.34 g, 13.7 mmol). The hydroxamic acid was isolated as an oil (3.50 g, 98%), which could be Kugelrohr distilled at 150°C/0.20 Torr to yield a low melting colorless solid (mp < 25°C) that slowly became orange upon storage. IR (NaCl): ν 3057, 2957, 2937, 2897, 1649, 1250, 852 cm^{-1}. ^1H NMR ($CDCl_3$/DMSO-d_6): δ 0.1 (s, 9H, $Si(CH_3)_3$), 2.2 (s, 2H, SCH_2Si), 3.2 (s, 3H, NCH_3), 3.5 (s, 3H, OCH_3), 7.1 (s, 1H, *H*-3), 7.3 (m, 3H, *H*-4, *H*-5, and *H*-6). EIMS: m/z (%) 283 (6) (M^+), 268 (17), 223 (71), 168 (8), 151 (8), 121 (11), 108 (7), 73 (100), 59 (15). HR–EIMS calcd. for $C_{13}H_{21}NO_2SSi$: 283.1062; found: 283.1067.

2-(Trimethylsilylmethylthio)acetophenone, **20**

The hydroxamic acid **19** (2.50 g, 8.82 mmol) was dissolved in dry THF (100 mL), and the reaction mixture was cooled to 0°C under N_2. The reaction mixture was treated with 3 M methylmagnesium bromide in diethyl ether (15 mL, 45.0 mmol). The yellow solution was stirred at 0°C for 1 hour, warmed to 25°C, and stirred at this temperature for 1 hour. The reaction mixture was poured into a precooled solution of 10% HCl in ethanol (40 mL), and the resulting solution was partitioned between a saturated NaCl solution (30 mL) and a 1:1 mixture of diethyl ether:dichloromethane (3 × 40 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to yield a deep orange oil (2.01 g, 96%), which became red upon standing. The ketone was purified by flash chromatography, eluting with CH_2Cl_2. IR (NaCl): ν 3057, 3003, 2957, 2884, 1675, 1244, 845 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.2 (s, 9H, $Si(CH_3)_3$), 2 (s, 2H, SCH_2Si), 2.5 (s, 3H, $COCH_3$), 7.2 (m, 1H, *H*-3), 7.4 (d, J = 3 Hz, 2H, *H*-4, *H*-5), 7.8 (d, J = 7 Hz, 1H, *H*-6). EIMS: m/z (%) 238 (25) (M^+), 223 (100), 177 (8), 165 (17), 151 (34), 137 (9), 134 (9), 115 (13), 91 (10), 75 (68), 59 (15). HR–EIMS calcd. for $C_{12}H_{18}OSSi$: 238.0848; found: 238.0840.

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