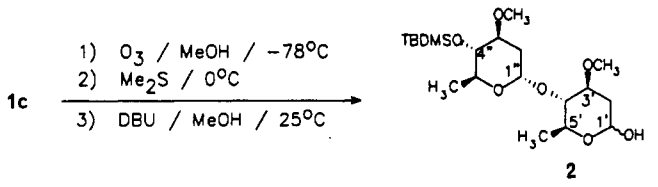
Scheme I



to provide a source of aglycon fragments to be used in a relay synthesis. Their route started with base-catalyzed saponification of avermectin B_1 followed by diazomethane esterification. The resulting seco-acid ester was then silylated and treated with one equivalent of ozone ($NaBH_4$ workup) to cleave the 10,11 double bond.[3e] The northern half fragment was isolated and oxidized (PCC) to an aldehyde. The aldehyde was isolated and treated with a strong base ($KN(TMS)_2$) to effect β-elimination of the disaccharide **2**. Although **2** can be obtained by this approach a more direct route involving fewer isolation and chromatography steps would require less time and would be much more convenient. Examination of the Hanessian route revealed that the saponification–esterification step could be eliminated from the sequence. Furthermore, a methyl sulfide workup (rather than $NaBH_4$ workup) of the ozonolysis reaction would afford a suitable aldehyde directly, thus eliminating the need for the PCC oxidation. Finally, isolation of the aldehyde fragment should not be necessary since it should be possible to effect β-elimination in situ by adding a strong base to the reaction mixture. We therefore concluded that the five-step sequence could be reduced to only two steps (silylation followed by a one-pot ozonolysis–elimination sequence). This modified procedure would afford the disaccharide more directly (albeit at the cost of total destruction of the aglycone portion) and would thus require less time than the previous method. We are pleased to report that the shorter route does in fact work quite well and describe the details herein.

A methanol solution of 4″,5-bis-*O*-(TBDMS)avermectin B_1 (**1c**, prepared in one step from avermectin B_1 using the published procedures)[4] was treated sequentially (one pot) with ozone, methyl sulfide, and DBU (Scheme I, see Experimental Section for details). After workup and chromatography the desired disaccharide derivative **2** was obtained in 57% yield from **1c**. The ozonolysis–elimination sequence (starting from **1c**) can be carried out in a single day and is amenable to preparation of reasonably large amounts of **2**. Thus our improved procedure is considerably more convenient than the previous procedures.[5] Future publications from this laboratory will describe the use of **2** in the synthesis of several interesting avermectin analogues.

Experimental Section

Proton (^1H) NMR spectra were measured in $CDCl_3$ solution at 300 MHz on a Varian XL-300 instrument. Chemical shifts are reported in δ units with the 7.24 ppm resonance of residual chloroform as an internal standard. Signal assignments were made with the assistance of ^1H–^1H correlation spectroscopy (COSY). Mass spectra were measured on a Varian MAT 731 instrument.

4′-*O*-[4″-*O*-(*tert*-Butyldimethylsilyl)oleandrosyl]oleandrose (2). Ozone (in a stream of oxygen from a Wellsbach ozone generator) was bubbled through a cold (−78 °C) solution of 2.75 g (2.5 mmol) of 4″,5-bis-*O*-(TBDMS)avermectin B_1 (**1c**)[4] in 40 mL of methanol until the blue ozone color persisted (ca. 13 min). Nitrogen gas was then bubbled through the solution for 2 min (blue color disappeared). Methyl sulfide (1.28 mL, 17.5 mmol) was added, and the solution was warmed to 0 °C. The solution was stirred at 0 °C for 50 min, and then 1.87 mL (12.5 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. The solution was warmed to room temperature and stirred for 2 h. The dark (almost black) solution was then partitioned between ether (100 mL) and 0.5 N HCl (40 mL). The aqueous layer was extracted with ether (50 mL), and the combined organic layers were washed sequentially with 2% $NaHCO_3$ (25 mL) and saturated NaCl (25 mL), dried ($MgSO_4$), filtered, and evaporated to an amber oil (2.30 g). Analytical TLC (silica gel, eluted with 3.5% methanol in methylene chloride, stained with 4% ethanolic phosphomolybdic acid and charred) of this crude product showed only one major product spot (R_f 0.26) plus a few minor spots in addition to baseline material. The crude product was purified by flash chromatography[6] (50 mm column, 8 in. of 230–400 mesh silica gel, eluted with 3.5% methanol in methylene chloride). The fractions containing the desired product (R_f 0.26) were combined and evaporated to a light yellow oil (0.815 g). This material was further purified by flash chromatography (50-mm column, 7 in. of 230–400 mesh silica gel, eluted with 3:2 hexane–ether). The fractions containing the desired product (R_f 0.16) were combined and evaporated to a colorless oil (0.603 g, analytically pure, 57% yield from **1c**), which is a 2:1 mixture of the 1′-α and -β anomers of 4′-*O*-[4″-*O*-(*tert*-butyldimethylsilyl)oleandrosyl]oleandrose (**2**): ^1N NMR (300 MHz, $CDCl_3$) δ 5.32 (0.66 H, br s, $H_{1'}$ (1′-α-anomer)), 5.29 (1 H, d, J = 3 Hz, $H_{1''}$), 4.77 (0.34 H, ddd, J = 9, 7, 2 Hz, $H_{1'}$ (1′-β-anomer)), 3.90 (0.66 H, dq, J = 9, 6 Hz, $H_{5'}$ (1′-α-anomer)), 3.73–3.58 (1.66 H, m, $H_{3'}$ (1′-α-anomer) + $H_{5''}$), 3.38–3.25 (1.68 H, m, $H_{5'}$ (1′-β-anomer) + $H_{3'}$ (1′-β-anomer) + $H_{3''}$), 3.35 (3 H, s, 3″-OCH_3), 3.30 (1.98 H, s, 3′-OCH_3 (1′-α-anomer)), 3.29 (1.02 H, s, 3′-OCH_3 (1′-β-anomer)), 3.20 (0.34 H, dd, J = 9, 9 Hz, $H_{4'}$ (1′-β-anomer)), 3.19 (0.66 H, dd, J = 9, 9 Hz, $H_{4'}$ (1′-α-anomer)), 3.11 (1 H, dd, J = 9, 9 Hz, $H_{4''}$), 3.05 (0.34 H, d, J = 7 Hz, OH (1′-β-anomer)), 2.52 (0.66 H, dd, J = 2, 2 Hz, OH (1′-α-anomer)), 2.39 (0.34 H, ddd, J = 12, 5, 2 Hz, $H_{2'eq}$ (1′-β-anomer)), 2.31–2.21 (1.66 H, m, $H_{2'eq}$ (1′-α-anomer) + $H_{2''eq}$), 1.56–1.37 (2 H, m, $H_{2'ax}$ + $H_{2''ax}$), 1.32 (1.02 H, d, J = 6 Hz, $H_{6'}$ (1′-β-anomer)), 1.26 (1.98 H, d, J = 6 Hz, $H_{6'}$ (1′-α-anomer)), 1.19 (3H, d, J = 6 Hz, $H_{6''}$), 0.87 (s, 9 H, ^{t}BuSi), 0.07 and 0.05 (6 H, 2 s, $Si(Me)_2$); FAB mass spectrum, m/e 427 (M + Li); Anal. Calcd for $C_{20}H_{40}O_7Si$: C, 57.11; H, 9.56. Found: C, 57.47; H, 9.70.

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Registry No. **1c**, 81924-42-7; α-**2**, 119245-51-1; β-**2**, 119245-52-2.

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(5) Note that this procedure should work equally well with the minor components (such as avermectin B_2 and the avermectin A series) isolated from fermentation of *S. avermitilis*. In principle, the procedure could also be used to prepare 4-*O*-TBDMS-oleandrose by using 4″,5-bis-*O*-(TBDMS)avermectin B_1 monosaccharide as the starting material.

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1,1-Bis(methylthio)-2-(phenylsulfonyl)ethene: A Useful Ketene Anion Enolate Synthon

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Sulfur-stabilized acyl anion equivalents and their Michael-accepting homologues are very useful reagents in organic synthesis.[1] For example, 2-lithio-1,3-dithiane,[2] the

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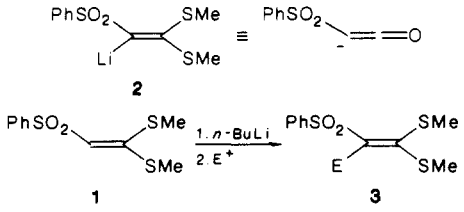
most common acyl anion synthon, 2-alkylidene-1,3-dithiane,[3] and ketene thioacetal monoxide[4] have proved their merit as useful synthons in organic syntheses.

While developing a new methodology, we have designed a new ketene anion synthon. Ketenes, being highly reactive, are difficult to metalate under normal reaction conditions. However, masked ketenes can be stabilized and metalated under controlled conditions. Introduction of a strong electron-withdrawing group at the α-carbon atom of the masked ketene molecule can stabilize an α-ketene anion.[5]

This paper describes the lithiation of a 2-(phenylsulfonyl)thioketene *S,S*-acetal (**1**)[6] to give the vinyllithium **2** and the use of anion **2** as an α-ketene anion synthon, which, in turn, is a doubly umpolunged enolate equivalent.

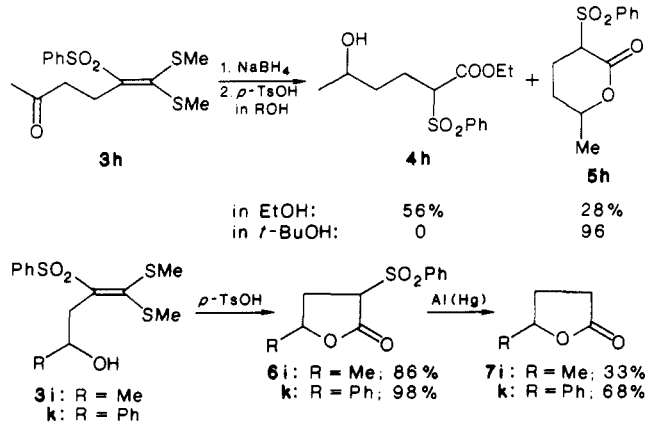


Initially, we examined the formation and stability of **2**. Ketene acetal **1** was treated with an equimolar amount of *n*-BuLi in tetrahydrofuran (THF) at various temperatures to generate the lithioketene acetal **2**, which was subsequently treated with an equimolar amount of benzyl bromide to form **3b**. Under the optimized conditions, **1** was treated with *n*-BuLi between −78 and −20 °C and kept for about 1–4 h for complete lithiation. At higher temperatures (>−20 °C), **2** gradually decomposed. Various electrophiles were reacted with **2**, and the results are listed in Table I.

Alkylation and benzoylation (entries a–c) of **2** proceeded in good yields. Carbonyl compounds and epoxides (entries d–f, i–k) also reacted readily, to give α-, β-, and γ-hydroxy derivatives, respectively. Though the epoxides reacted very slowly, good yields were obtained when the reaction mixtures were stored under an inert atmosphere at −20 °C for a week. Silylation (entry 1) and amination (entries m, n) also proceeded smoothly.

Conventional methods[7] to generate carbonyl compounds from sulfur compounds were unsuccessful in effecting desulfurization of **3**. However, when **3h** was reduced to the alcohol and subsequently treated with *p*-toluenesulfonic acid in refluxing ethanol, it gave **4h** (56%) along with significant formation of the δ-lactone **5h** (28%).[8] Interestingly, use of *tert*-butyl alcohol instead of ethanol resulted in almost quantitative formation (96%) of **5h**. Use of mercuric chloride/mercuric oxide[9] also gave **5h**, in 41% yield.

This unique observation, in which a γ-hydroxy thioketene *S,S*-acetal was converted directly into a δ-lactone (**5h**),[9,10] was also applied to **3i** and **3k**. The γ-lactones **6i** and **6k** were obtained in good yields (86, 98%).



Finally, desulfurization of γ-lactones **6i** and **6k** was accomplished by using aluminum amalgam in THF–H_2O[11,12] to afford the sulfur-free lactones **7i** (33%) and **7k** (68%).

Thus, the synthetic potential of the ketene anion synthon was explored and applied to a unique synthesis of lactones. Further application to the synthesis of a natural product is in progress.

Experimental Section

Melting points were measured on a Yanako MP-S3 apparatus and are uncorrected. ^{1}H NMR spectra were observed with Hitachi R-24B and R-600 and JEOL JNM-JX 270 and JNM-FX 270 spectrometers. Chemical shifts are reported in parts per million (δ; ppm) relative to Me_4Si as an internal standard in $CDCl_3$ or CCl_4. Infrared spectra were obtained on Hitachi 215 and JASCO A-202 infrared spectrophotometers. Mass spectra were taken with an RNU-7M mass spectrometer at 70 eV. Column chromatography was performed on Merck Art. No. 7734, Wako gel C-200, and Fujigel BW-200 and BW-820MH. Centrifugal liquid chromatography was performed on Fujigel KT-2061. All solvents were freshly distilled and stored under nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride and stored over molecular sieves, 5A 1/16. Ether, benzene, and *n*-hexane were dried over sodium wire. Unless otherwise noted, other solvents were used after simple distillation.

1,1-Bis(methylthio)-2-(phenylsulfonyl)ethene (1). Compound **1** was prepared by the known method:[6] mp 122–123 °C (recrystallized from ethanol) (lit.[6] mp 119–121 °C).

Selection of the optimum reaction condition: A three-neck flask was equipped with a magnetic spin bar, a serum cap, a thermometer, and a calcium chloride tube, solid **1** (10 mmol) in dry THF (70 mL) was cooled to −40 °C under N_2, and 1.05 molar equiv of *n*-BuLi (1.6 M in hexane) was added dropwise from a microsyringe. After 1 h, the lithio derivative **2** was quenched with 1.05 equiv of benzyl bromide, and again the reaction mixture was stirred for 1 h at −40 °C. Saturated aqueous NH_4Cl solution was added to the reaction mixture, which was then acidified with a 1 N HCl aqueous solution. The organic layer was separated. The aqueous layer was extracted with chloroform several times. The combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure, and the crude products were purified by chromatography on a silica gel column with benzene–ethyl acetate (10:1 v/v) to give **3b**. The temperature dependency of **2** was checked under the same reaction conditions described above: the best yield of **3b** (78%) was obtained at −40 °C and −20 °C. At 0 °C, **3b** was obtained in 48% yield together with the starting material (**1**) (13%). At −78 °C for 1 h, only 24%

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of **3b** was obtained, with recovery of 69% of the starting material (1), but a longer reaction time (4 h) improved the yield of **3b** to 77%.

Compound **2** was reacted with various electrophiles under the optimum reaction conditions, and the results are listed in Table I.

1,1-Bis(methylthio)-2-(phenylsulfonyl)-1-propene (3a): IR (neat) 1305, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (s, 3 H), 2.36 (s, 3 H), 2.46 (s, 3 H), 7.35 (m, 3 H), 7.75–8.20 (m, 2 H); high-resolution MS (m/z) found M 274.0144, calcd for $C_{11}H_{14}O_2S_3$ M^+ 274.0419.

1,1-Bis(methylthio)-3-phenyl-2-(phenylsulfonyl)-1-propene (3b): mp 114–115 °C (recrystallized from ethanol); IR ($CHCl_3$) 1303, 1142, 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.32 (s, 3 H), 4.36 (s, 2 H), 7.30 (s, 5 H), 7.10–7.75 (m, 5 H). Anal. Found: C, 58.23; H, 5.15. Calcd for $C_{17}H_{18}O_2S_3$: C, 58.29; H, 5.14.

1,1-Bis(methylthio)-3-phenyl-2-(phenylsulfonyl)-1-propen-3-one (3c): mp 109–111 °C (recrystallized from ethanol); IR ($CHCl_3$) 3235, 1665, 1595, 1308, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, 3 H), 2.01 (s, 3 H), 7.15–7.65 (m, 10 H). Anal. Found: C, 55.92; H, 4.45. Calcd for $C_{17}H_{16}O_3S_3$: C, 56.04; H, 4.40.

3,3-Bis(methylthio)-1-phenyl-2-(phenylsulfonyl)-2-propen-1-ol (3d): IR (CCl_4) 3540, 1500, 1310, 1140, 690 cm^{-1}; ^1H NMR (CCl_4) 1.94 (s, 3 H), 2.29 (s, 3 H), 4.52 (d, 1 H, J = 10 Hz), 6.50 (d, 1 H, J = 10 Hz), 7.09–8.25 (m, 10 H).

4,4-Bis(methylthio)-3-(phenylsulfonyl)-3-buten-2-ol (3e): mp 124.5–125.0 °C (recrystallized from ethanol); IR ($CHCl_3$) 3500, 1510, 1305, 1135, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70 (d, 3 H, J = 7 Hz), 1.78 (s, 3 H), 2.34 (s, 3 H), 4.05 (d, 1 H, J = 10 Hz), 5.08 (dq, 1 H, J = 10 and 7 Hz), 7.27–7.77 (m, 3 H), 7.77–8.24 (m, 2 H). Anal. Found: C, 47.20; H, 5.33. Calcd for $C_{12}H_{16}O_3S_3$: C, 47.37; H, 5.26.

1,1-Bis(methylthio)-2-(phenylsulfonyl)-1,4-pentadien-3-ol (3f): mp 121.0–122.0 °C (recrystallized from CCl_4); IR (CCl_4) 3500, 1305, 1135 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (s, 3 H), 2.38 (s, 3 H), 4.38 (d, 1 H, J = 10 Hz), 5.15–5.64 (m, 2 H), 5.73–6.20 (m, 2 H), 7.40–7.72 (m, 3 H), 7.79–8.23 (m, 2 H). Anal. Found: C, 49.40; H, 5.14. Calcd for $C_{13}H_{16}O_3S_3$: C, 49.37; H, 5.06.

1,1-Bis(methylthio)-3,5-diphenyl-2-(phenylsulfonyl)-1-penten-5-one (3g): mp 144.0–145.0 °C (recrystallized from ethanol); IR ($CHCl_3$) 1695, 1305, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (s, 3 H), 2.37 (s, 3 H), 4.18 (d, 1 H, J = 6.5 Hz), 4.28 (d, 1 H, J = 6.0 Hz), 6.00 (dd, 1 H, J = 6.5 and 6.0 Hz), 7.10–7.80 (m, 11 H), 7.80–8.27 (m, 4 H). Anal. Found: C, 63.90; H, 5.21. Calcd for $C_{25}H_{24}O_3S_3$: C, 64.10; H, 5.16.

1,1-Bis(methylthio)-2-(phenylsulfonyl)-1-hexen-5-one (3h): mp 133.0–134.0 °C (recrystallized from ethanol); IR ($CHCl_3$) 1715, 1305, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 3 H), 2.16 (s, 3 H), 2.34 (s, 3 H), 2.55–3.40 (m, 4 H), 7.35–8.20 (m, 5 H). Anal. Found: C, 50.77; H, 5.48. Calcd for $C_{14}H_{18}O_3S_3$: C, 50.91; H, 5.45.

5,5-Bis(methylthio)-4-(phenylsulfonyl)-4-penten-2-ol (3i): IR ($CHCl_3$) 3540, 1300, 1140, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6 Hz), 1.75 (s, 3 H), 2.30 (s, 3 H), 2.95 (s, 1 H), 3.14 (d, 2 H, J = 6 Hz), 4.25 (m, 1 H), 7.35–7.80 (m, 3 H), 7.80–8.32 (m, 2 H); ^{13}C NMR ($CDCl_3$) 17.02 (q, 2 SCH_3), 17.48 (q), 24.04 (t), 68.33 (d), 128.05 (d), 128.36 (d), 132.63 (d), 142.44 (s), 143.71 (s), 152.35 (s).

6,6-Bis(methylthio)-5-(phenylsulfonyl)-5-hexen-3-ol (3j): IR (neat) 3520, 2940, 1300, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (t, 3 H, J = 6 Hz), 1.37–1.95 (m, 2 H), 1.75 (s, 3 H), 2.34 (s, 3 H), 2.58 (s, 1 H), 3.14 (d, 2 H, J = 6 Hz), 3.60–4.23 (m, 1 H), 7.25–7.73 (m, 3 H), 7.85–8.27 (m, 2 H); high-resolution MS (m/z) found M 332.02582, calcd for $C_{14}H_{20}O_3S_3$ M^+ 332.0573.

4,4-Bis(methylthio)-1-phenyl-3-(phenylsulfonyl)-3-buten-1-ol (3k): mp 125.0–125.5 °C (recrystallized from ethanol); IR ($CHCl_3$) 3520, 1300, 1140 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (s, 3 H), 2.27 (s, 3 H), 3.21 (d, 1 H, J = 6 Hz), 3.40 (dd, 2 H, J = 7 and 8 Hz), 5.14 (m, 1 H), 7.15–7.85 (m, 8 H), 7.85–8.37 (m, 2 H); ^{13}C NMR ($CDCl_3$) 17.62 (q), 17.48 (q), 42.76 (t), 73.94 (d), 125.71 (d), 127.59 (d), 128.08 (d), 128.39 (d), 128.77 (d), 132.71 (d), 142.39 (s), 142.79 (s), 144.17 (s), 153.24 (s). Anal. Found: C, 56.53; H, 5.26. Calcd for $C_{18}H_{20}O_3S_3$: C, 56.84; H, 5.26.

1,1-Bis(methylthio)-2-(trimethylsilyl)-2-(phenylsulfonyl)ethene (3l): mp 120.0–121.0 °C (recrystallized from ethanol); IR ($CHCl_3$) 1135, 752 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.49 (s, 9 H), 1.68 (s, 3 H), 2.31 (s, 3 H), 7.25–7.67 (m, 3 H), 7.75–8.12 (m, 2 H). Anal. Found: C, 46.98; H, 6.11. Calcd for $C_{13}H_{20}O_2S_3Si$: C, 46.99; H, 6.02.

1,1-Bis(methylthio)-3-phenyl-3-(phenylamino)-2-(phenylsulfonyl)-1-propene (3m): mp 144–145 °C (recrystallized from ethanol); IR ($CHCl_3$) 3420, 1600, 1500, 1300, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 2.40 (s, 3 H), 5.62 (br s, 1 H), 6.74 (br s, 1 H), 6.77–6.90 (m, 3 H), 7.18–7.56 (m, 12 H); ^{13}C NMR ($CDCl_3$) 17.77 (q, 2 SCH_3), 59.40 (d), 114.11 (d), 118.31 (d), 126.58 (d), 127.18 (d), 128.05 (d), 128.13 (d), 128.42 (d), 129.49 (d), 132.57 (d), 140.05 (s), 141.95 (s), 146.53 (s), 146.79 (s), 153.24 (s); high-resolution MS (m/z) M found 441.0884, calcd for $C_{23}H_{23}NO_2S_3$ M^+ 441.0888. Anal. Found: C, 62.47; H, 5.29; N, 3.18. Calcd for $C_{23}H_{23}NO_2S_3$: C, 62.58; H, 5.25; N, 3.17.

***N*-Phenyl-3,3-bis(methylthio)-2-(phenylsulfonyl)-propenamide (3n)**: mp 185–186 °C (recrystallized from ethanol); ^1H NMR (DMSO-d_6) δ 2.14 (s, 3 H), 2.35 (s, 3 H), 6.94–8.19 (m, 11 H). Anal. Found: C, 53.81; H, 4.59; N, 3.75. Calcd for $C_{17}H_{17}O_3NS_3$: C, 53.80; H, 4.51; N, 3.69.

Ethyl 5-Hydroxy-2-(phenylsulfonyl)hexanoate (4h). Ketone **3h** (1.56 g, 4.72 mmol) was treated with excess $NaBH_4$ in methanol at room temperature. Ethanol was removed under reduced pressure, and then the reaction residue was added to saturated NH_4Cl and extracted with $CHCl_3$. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo to give crude alcohol. The reaction products were recrystallized from carbon tetrachloride to give the corresponding alcohol (1.813 g, quantitative yield): mp 76.0–77.0 °C; IR (CCl_4) 3540, 1300, 1140, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (d, 3 H, J = 7 Hz), 1.78 (s, 3 H), 1.55–2.10 (m, 2 H), 2.35 (s, 3 H), 2.34–3.27 (m, 3 H), 3.65–4.25 (m, 1 H), 7.35–8.18 (m, 5 H). Anal. Found: C, 50.43; H, 6.03. Calcd for $C_{14}H_{20}O_3S_3$: C, 50.60; H, 6.02.

The mixture of this alcohol (498 mg, 1.5 mmol) and *p*-TsOH (1.2 g, 6.0 mmol, 4 equiv) in ethanol (40 mL) was heated to reflux for 24 h. Ethanol was evaporated, and the residue obtained was chromatographed on a silica gel column with benzene–ethyl acetate (5:1 v/v) as eluant to give the former fraction (**5h**) (107 mg, 28.1%) and the latter fraction (**4h**) (250 mg, 55.6%). IR of **4h** (neat): 3550–3400, 1740, 1450, 1150, 690 cm^{-1}. NMR of **4h** ($CDCl_3$): δ 1.06 (t, 3 H, J = 6 Hz), 1.12 (d, 3 H, J = 6 Hz), 1.3–1.6 (m, 2 H), 1.95–2.30 (m, 2 H), 3.45–3.80 (m, 3 H), 4.06 (q, 2 H), 7.40–8.00 (m, 5 H).

6-Methyl-3-(phenylsulfonyl)tetrahydropyran-2-one (5h). This alcohol (1.023 g, 3.1 mmol) and *p*-toluenesulfonic acid (2.5 g, 12.5 mmol) were dissolved in *tert*-butyl alcohol (100 mL), and the resultant mixture was heated to reflux for 4 days. The solvent was removed under reduced pressure, and the residue was purified by chromatography on a silica gel column (benzene–ethyl acetate, 10:1 v/v) to afford δ-lactone **5h** (0.758 g, 96% yield) as a diastereomeric mixture: IR (neat) 1730, 1450, 1315, 1155, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (d, J = 6.5 Hz, CH_3, minor), 1.42 (d, J = 6.5 Hz, CH_3, major), 1.52–2.89 (m, 4 H), 4.02 (dd, J = 4.3 and 3.1 Hz, SO_2CH, minor), 4.12 (dd, J = 9.2 and 7.6 Hz, SO_2CH, major), 7.54–7.96 (m, 5 H); ^{13}C NMR ($CDCl_3$) 19.81 (t), 20.07 (t), 21.34 (q), 27.04 (t), 28.65 (t), 63.49 (d), 64.35 (d), 77.46 (d), 78.29 (d), 129.00 (d), 129.06 (d), 129.26 (d), 129.34 (d), 134.18 (d), 134.30 (d), 137.89 (s), 138.35 (s), 163.06 (s), 163.32 (s).

3-(Phenylsulfonyl)-5-methyltetrahydrofuran-2-one (6i). Alcohol **3i** (1.75 g, 5.5 mmol) and *p*-toluenesulfonic acid (4.2 g, 22.0 mmol) were refluxed in ethanol for 48 h. The ethanol was removed under reduced pressure, and the residue was purified by chromatography on silica gel (benzene–ethyl acetate, 10:1 v/v, R_f 0.25) to afford γ-lactone **6i** (1.134 g, 86% yield) as a 4:6 cis–trans mixture: mp 104.0–104.5 °C (recrystallized from ethanol); IR ($CHCl_3$) 1780, 1450, 1335, 1150, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) trans isomer δ 1.43 (d, 3 H, J = 6.4 Hz), 2.28 (ddd, 1 H, J = 14.4, 10.1, and 9.0 Hz), 3.16 (ddd, 1 H, J = 14.4, 6.4, and 2.8 Hz), 7.28–8.05 (m, 5 H), cis isomer δ 1.49 (d, 3 H, J = 6.4 Hz), 2.53 (ddd, 1 H, J = 14.0, 9.5, and 7.9 Hz), 2.84 (ddd, 1 H, J = 14.0, 10.1, and 6.7 Hz), 4.25 (dd, 1 H, J = 10.1 and 9.5 Hz), 4.62 (dqd, 1 H, J = 7.9, 6.7, and 6.4 Hz), 7.28–8.05 (m, 5 H); ^{13}C NMR ($CDCl_3$) trans isomer 21.04 (q), 31.67 (t), 65.48 (d), 76.65 (d), 129.23 (d), 129.31 (d), 134.70 (d), 136.92 (s), 167.70 (s), cis isomer 20.93 (q), 30.67 (t), 64.53 (d),

Table I. Reaction of Lithiothioketene *S,S*-Acetal 2 with Various Electrophiles

entry	electrophile	reactn temp, °C	reactn time	yield, %
a	methyl iodide	−78–rt[a]	24 h	92
b	benzyl bromide	−40	3 h	78
c	benzoyl chloride	−78	4 h	82
d	benzaldehyde	−40	5 h	69
e	acetaldehyde	−78	14 h	60
f	acrolein	−78	3 h	75[b]
g	benzalacetophenone	−78	3 h	74[c]
h	methyl vinyl ketone	−78	3 h	36[c]
i	propene oxide	−20	1 week	80
j	1-butene oxide	−20	1 week	81
k	styrene oxide	−20	1 week	65
l	trimethylchlorosilane	−25	5 h	53
m	benzylideneaniline	−40	4 h	95
n	phenyl isocyanate	−78	3 h	82

[a] Room temperature. [b] Only 1,2-adduct was obtained. [c] 1,4-Adduct was obtained.

74.84 (d), 129.17 (d), 129.52 (d), 134.55 (d), 137.09 (s), 167.47 (s); high-resolution MS (*m/z*) found M^+ 240.0463, calcd for $C_{11}H_{12}O_4S$ M 240.0455. Anal. Found: C, 54.94; H, 5.04. Calcd for $C_{11}H_{12}O_4S$: C, 55.00; H, 5.04.

5-Phenyl-3-(phenylsulfonyl)tetrahydrofuran-2-one (6k). According to a procedure similar to that used for **6i**, from the alcohol **3k** (646 mg, 1.7 mmol) and *p*-TsOH (1.5 g, 6.8 mmol) in *t*-BuOH (30 mL) was obtained γ-lactone **6k** (503 mg, 98%) (cis:trans = 1:9): mp 134–135.5 °C (recrystallized from ethanol); IR ($CHCl_3$) 1780, 1450, 1330, 1150, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) trans isomer δ 2.64 (ddd, 1 H, *J* = 14.7, 9.8, and 9.0 Hz), 3.46 (ddd, 1 H, *J* = 14.7, 6.9, and 3.0 Hz), 4.18 (dd, 1 H, *J* = 9.8 and 3.0 Hz), 5.80 (dd, 1 H, *J* = 9.0 and 6.9 Hz), 7.58–8.02 (m, 10 H), cis isomer δ 2.87 (ddd, 1 H, *J* = 13.8, 10.8, and 9.5 Hz), 3.10 (ddd, 1 H, *J* = 13.8, 9.5, and 6.6 Hz), 4.41 (dd, 1 H, *J* = 10.8 and 9.5 Hz), 5.39 (dd, 1 H, *J* = 9.5 and 6.6 Hz), 7.58–8.02 (m, 10 H); ^{13}C NMR ($CDCl_3$) trans isomer 32.59 (t), 65.25 (d), 80.62 (d), 125.46 (d), 128.94 (d), 129.17 (d), 129.31 (d), 129.37 (d), 134.81 (d), 136.77 (s), 137.95 (s), 167.81 (s), cis isomer 32.16 (t), 64.33 (d), 78.72 (d), 125.86 (d), 128.94 (d), 129.17 (d), 129.23 (d), 129.63 (d), 134.61 (d), 136.92 (s), 137.55 (s), 167.10 (s); high-resolution MS (*m/z*) found M^+ 302.0612, calcd for $C_{16}H_{14}O_4S$ M 302.0612. Anal. Found: C, 63.64; H, 4.70. Calcd for $C_{16}H_{14}O_4S$: C, 63.57; H, 4.64.

5-Methyltetrahydrofuran-2-one (7i). Sulfone **6i** (4.69 g, 19.5 mmol) was dissolved in 10% aqueous THF (300 mL). Aluminum amalgam (0.195 g-atom, 5.0 g in 2% aqueous $HgCl_2$ solution) was added to the stirred solution. The resultant mixture was heated to reflux for 12 h. The resulting solid was then filtered and washed with THF. Most of the THF was removed from the filtrate, the residue was extracted with ether and dried ($MgSO_4$), the solvent was evaporated from the filtrate, and the residue was purified by silica gel column chromatography with benzene–ethyl acetate (20:1 v/v) as eluant to give **7i** as a colorless oil (0.642 g, 33% yield): bp 67–68 °C/5 mmHg; IR (neat) 2990, 1775, 1340, 1175, 940 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (d, 3 H), 1.45–2.70 (m, 4 H), 4.20–4.86 (m, 1 H).

5-Phenyltetrahydrofuran-2-one (7k). Lactone **7k** was obtained in 68% yield by the procedure described above: IR (neat) 1775, 1175, 1140, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.14–2.25 (m, 1 H), 2.60–2.71 (m, 3 H), 5.49–5.54 (m, 1 H), 7.31–7.43 (m, 5 H); high-resolution MS (*m/z*) found M^+ 162.0672, calcd for $C_{10}H_{10}O_2$ M 162.0680.

Registry No. **1**, 41374-14-5; **3a**, 119336-15-1; **3b**, 119336-16-2; **3c**, 65019-70-7; **3d**, 119336-17-3; **3e**, 119336-18-4; **3f**, 119336-19-5; **3g**, 119336-20-8; **3h**, 119336-21-9; **3h** (alcohol analogue), 119336-28-6; **3i**, 119336-22-0; **3j**, 119336-23-1; **3k**, 119336-24-2; **3l**, 119336-25-3; **3m**, 119336-26-4; **3n**, 119336-27-5; **4h**, 119336-29-7; *cis*-**5h**, 119336-30-0; *trans*-**5h**, 119336-31-1; *cis*-**6i**, 119336-32-2; *trans*-**6i**, 119336-33-3; *cis*-**6k**, 72764-75-1; *trans*-**6k**, 72764-76-2; **7i**, 108-29-2; **7k**, 1008-76-0; benzyl bromide, 100-39-0; acetaldehyde, 75-07-0; acrolein, 107-02-8; benzalacetophenone, 94-41-7; methyl vinyl ketone, 78-94-4; propene oxide, 75-56-9; 1-butene oxide, 106-88-7; styrene oxide, 96-09-3; benzylideneaniline, 538-51-2; phenyl isocyanate, 103-71-9.

Reaction of 2,5-Bis(trifluoromethyl)-1,3,4-oxadiazole with Hydrazine. The Synthesis of 4-Amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole

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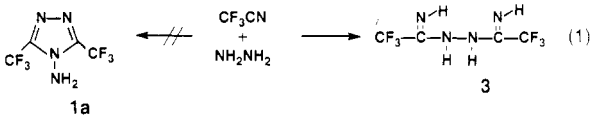
Introduction

Recently, we investigated the reaction of 2,5-bis(trifluoromethyl)-1,3,4-oxadiazole with primary amines to produce the corresponding 4-substituted 3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazoles.[2] In the course of this study, we had the occasion to make 4-amino-3,5-bis(trifluoromethyl)-4*H*-1,2,4-triazole (**1a**). Examination of the literature revealed that the synthesis of **1a** had never been reported for the reaction of 3,5-bis(trifluoromethyl)-1,3,4-oxadiazole (**2a**) with hydrazine, nor had its synthesis by any other method been correctly reported.

Brown and Pilipovich[3] reported in 1960 that trifluoroacetonitrile reacted with hydrazine to produce the 4-aminotriazole **1a**. Later, Brown and Wetzel[4] modified that claim and reported that the product was actually 1,2-bis(*N*-aminotrifluoroacetimidoyl)hydrazine (**3**), as shown in eq 1.



In 1966, Brown et al.[5] reported that the reaction of **2b–d** with hydrazine in methanol at 0 °C produced the corresponding 1-(*N*-aminoperfluoroalkylimidoyl)-2-(perfluoroacyl)hydrazines **4b–d**; these compounds were then treated with acetic acid at reflux to provide the corresponding 4-aminotriazoles **1b–d** in good yields (Scheme I). As means of structure proofs, **1b** and **1c** were deaminated with nitrous acid to the corresponding **5b** and **5c**, respectively, which had been made previously by the reaction of **2b** and **2c** with ammonia.[6] Haszeldine et al.[7] subsequently reported that **2a**, unlike **2b–d** previously reported by Brown et al., reacted with hydrazine in ethanol at 0 °C to afford the dihydrotetrazine **6a** in 30% yield. As means of a structure proof, **6a** (^{19}F δ = 8.4) was oxidized with $FeCl_3$ to the corresponding tetrazine **7a** (^{19}F δ = 10.5).[8] Surprisingly, we isolated **4a** in 76% yield when a methanolic solution of hydrazine at −42 °C was treated with **2a**. The isolation of **4a**, instead of the dihydrotetrazine **6a** as reported by Haszeldine et al., intrigued us so we examined the reaction more closely to determine if **6a** was a consequence of the reaction of **2a** with hydrazine at 0 °C or was

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