oil (2.4 g, 71% yield): bp 100 °C (0.25 mmHg), 98% pure by GC (retention time 3.8 min at 200 °C); ^{1}H NMR (C_6D_6) δ 7.27 (d, 1 H, J = 1.7 Hz), 7.06 (d, 1 H, 8.4 Hz), 6.80 (dd, 1 H, J = 8.4, 1.7 Hz) 3.55 (s, 1 H), 3.41 (s, 1 H), 1.10 (s, 9 H); ^{13}C NMR (C_6D_6) δ 149.93, 131.48, 131.24, 128.11, 127.97, 124.02, 34.13, 30.99; IR (neat) 2960, 2910, 2870, 2550, 1480, 1460, 1380, 1260 cm^{-1}; GC-MS, m/e 198 (M^+, 38), 183 (100). Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.56; H, 7.11. Found: C, 60.91; H, 7.29.

Bis(2-mercaptophenyl) Sulfide (35). As in procedure 3 for **13**, dilithio salt **16** was prepared from thiophenol (8.8 g, 0.08 mol), dissolved in THF, and treated at −78 °C during a period of 10 min with a solution of freshly distilled sulfur dichloride (4.08 g, 0.04 mol) in pentane (10 mL). The solution was slowly warmed to room temperature, $LiAlH_4$ (3.0 g, 0.08 mol) was *carefully* added after fitting the flask with a reflux condenser, and the suspension was refluxed for 4 h. The mixture was then cooled to 0 °C and poured into ice-cold HCl (50 mL of concentrated acid diluted with 400 mL of ice water). The aqueous phase was extracted with ether (4 × 200 mL), and the ether extracts were combined and extracted with 10% NaOH solution (3 × 200 mL). The combined NaOH extract was acidified with concentrated HCl and extracted with CH_2Cl_2 (3 × 200 mL), and the CH_2Cl_2 extract was dried ($MgSO_4$), filtered, and concentrated in vacuo, affording a dark brown oil (ca. 10 g) which analyzed by GC-MS for ca. 40% of the title compound, 15% thiophenol, 40% 1,2-benzenedithiol (**32a**), and several minor products. Purification using a Chromatotron (silica gel, hexanes) gave an analytical sample of the title compound (4% yield; 10% yield based on unrecovered starting material) as a colorless solid: mp 90-91 °C; ^{1}H NMR δ 7.42-7.38 (m, 2 H), 7.20-7.05 (m, 6 H), 4.08 (s, 2 H, SH); ^{13}C NMR δ 134.93, 132.37, 132.31, 130.13, 128.23, 126.52; IR (KBr) 3050, 2510 (SH), 1570, 1450, 1430, 1260, 750 cm^{-1}; GC-MS, m/e 250 (M^+, 100), 217 (52), 216 (51), 184 (83), 140 (84). Anal. Calcd for $C_{12}H_{10}S_3$: C, 57.56; H, 4.02. Found: C, 57.59; H, 4.03.

Acknowledgment. We are most grateful to Professor J. C. Martin for generously sharing his results with us and agreeing to delay publication until our own work could be completed and to Professor Gary Posner for helpful suggestions. We thank Dr. Jon Rich for a sample of 1,2-dichlorotetramethyldisilane. We gratefully acknowledge support from the National Science Foundation, the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Herman Frasch Fund, Société Nationale Elf Aquitaine, and the McCormick Co. Funding for the 300-MHz NMR facility was provided by the National Science Foundation.

Registry No. 11, 20965-36-0; **12**, 117526-61-1; **13**, 33356-45-5; **14**, 117526-62-2; **15**, 117526-63-3; **16**, 117526-82-6; **17**, 117526-83-7; **18**, 117526-64-4; **19**, 117526-65-5; **20**, 117526-66-6; **21**, 117526-67-7; **22**, 117526-68-8; **23**, 117526-69-9; **24**, 117526-70-2; **25**, 117526-71-3; **26**, 117526-72-4; **27**, 117526-73-5; **28**, 117526-74-6; **29**, 117526-75-7; **30**, 117526-84-8; **31**, 117526-76-8; **32a**, 117526-15-5; **32b**, 117526-80-4; **33**, 117526-85-9; **34**, 89375-31-5; **35**, 117526-77-9; dihydropyran, 110-87-2; thiophenol, 108-98-5; chlorotrimethylsilane, 75-77-4; 2-trimethylsilylbenzenethiol, silver(I) salt, 117526-81-5; chlorotriethylsilane, 994-30-9; 2-(*tert*-butyldimethylsilyl)benzenethiol, 117526-58-6; 2-[[*tert*-butyl[(*tert*-butyldimethylsilyl)methyl]methyl]silyl]benzenethiol, 117526-59-7; chloro-*tert*-butyldimethylsilane, 18162-48-6; 2-(triphenylsilyl)benzenethiol, 117526-60-0; chlorotriphenylsilane, 76-86-8; 4-(*tert*-butyl)benzenethiol, 2396-68-1; dichlorodimethylsilane, 75-78-5; dichlorodiethylsilane, 1719-53-5; 1,2-dichlorotetramethyldisilane, 4342-61-4; 10,13-di-*tert*-butyl-5,5-diethyldibenzo[*b*,*e*]-5-sila-1,2-dithiepin, 117526-78-0; dichlorodiphenylsilane, 80-10-4; 2-naphthalenethiol, 91-60-1; sulfur, 10544-50-0; 1,2,3,4-benzenetetrathiol, 117526-79-1; 1,2,3-tris(thiomethyl)benzene, 65516-81-6; sulfur dichloride, 10545-99-0.

Supplementary Material Available: General experimental procedures and that for 2-(triethylsilyl)benzenethiol (**14**) (procedure 2), 2-(*tert*-butyldimethylsilyl)benzenethiol (procedure 2), and 1,2-bis[(2′-mercaptophenyl)dimethylsilyl]ethane (**25b**) (1 page). Ordering information is given on any current masthead page.

Directed Lithiation of Arenethiols

Keith Smith,* Charles M. Lindsay, and Gareth J. Pritchard

Contribution from the Department of Chemistry, University College of Swansea, Swansea SA2 8PP, U.K. *Received July 26, 1988*

Abstract: Benzenethiol, toluene-4-thiol, and 3,5-dimethylbenzenethiol are doubly lithiated (on sulfur and on carbon) by *n*-butyllithium in tetramethylethylenediamine. C-Lithiation occurs ortho to the thiol group, and subsequent treatment with electrophiles provides a convenient approach to ortho-substituted arenethiol derivatives. The reactions with tetraisopropylthiuram disulfide provide direct access to the corresponding *o*-phenylene trithiocarbonates. Double lithiation of 4-methoxybenzenethiol results in C-lithiation adjacent to the methoxy group rather than the thiolate residue, indicating that methoxy is a more powerfully ortho-directing substituent in this type of metalation reaction. 3-Methoxybenzenethiol is lithiated between the methoxy and thiolate groups.

Lithiation of aromatic compounds can often be directed to occur ortho to substituents that possess oxygen or nitrogen atoms.[1,2] Apparently, complexation occurs between the substituent group and the lithium reagent prior to metalation, and this serves to bring the metalating agent into closer proximity with the ortho proton, which is then selectively removed. Groups that encourage such ortho-metalation include SO_2NR_2, $CONR_2$, $OCONR_2$, CH_2NMe_2, OCH_2OMe, and OMe.[1-3] There are occasions when it would be extremely useful to be able to direct lithiation ortho to a simple thiol group as a means of producing ortho-substituted arenethiols. However, an early attempt at lithiation of benzenethiol resulted in only a 3% yield of the appropriate product after trapping with carbon dioxide.[4] A more recent literature statement implied that lithiation ortho to a simple thiol group was possible, but gave no details.[5] We therefore decided to explore the possibility of effecting such ortho-lithiation in a synthetically useful manner by appropriate choice of solvent, reagent, or reaction conditions[6] and now report success in this endeavor. Since completion of our work we have become aware of parallel studied by

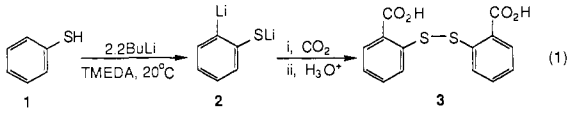
(1) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-360. Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957-986.
(2) Smith, K. *Chem. Br.* **1982**, 29-36. Snieckus, V. *Bull. Soc. Chim. Fr.* **1988**, 67-78.
(3) Fraser, R. R.; Bresse, M.; Mansour, T. S. *J. Am. Chem. Soc.* **1983**, *105*, 7790-7791.
(4) Gilman, H.; Arntzen, C. E.; Webb, F. J. *J. Org. Chem.* **1945**, *10*, 374-379.
(5) Streitwiser, A. *Acc. Chem. Res.* **1984**, *17*, 353-357; see p 357 and ref 38.
(6) Based in part on: Lindsay, C. M. Ph.D. Thesis, Swansea, 1985.

0002-7863/89/1511-0665$01.50/0

the groups of Martin[7] and Block,[8] which are published alongside this article.

Results and Discussion

Generation of Doubly Lithiated Arenethiols. Benzenethiol (**1**) was treated with several different organolithium reagents in several different solvents and under a variety of different conditions in order to try to establish an optimum procedure for generation of its dianion. The reaction mixture was quenched with excess carbon dioxide in order to provide an estimate of the extent of metalation. In most cases the yield of the product following trapping with carbon dioxide was low, even for reactions carried out in solvent mixtures known to favor metalation,[1,2] such as mixtures of THF and diethyl ether, with or without hydrocarbon, and THF–HMPA. However, in tetramethylethylenediamine (TMEDA) benzenethiol was quantitatively converted into its doubly lithiated derivative by stirring overnight at ambient temperature with 2.2 equiv of *n*-butyllithium. Treatment of the dilithio intermediate with carbon dioxide, followed by acidification, gave 2,2′-dithiobis(benzoic acid) (**3**) in 90% yield (isolated), thus demonstrating that C-lithiation occurred ortho to the initial thiol group (eq 1).

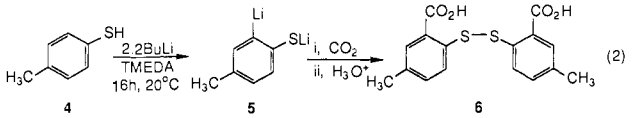


(1)

1 2 3

The yield of **3** was much lower (18%) with *sec*-butyllithium as metalating agent. It was also lower with *n*-butyllithium in a solvent composed of THF to which 1 or 2 equiv of TMEDA had been added. Thus, metalation with *n*-butyllithium (2.2 equiv) in TMEDA at 20 °C (initial addition at −78 °C) for 16 h was adopted as a standard procedure for production of **2**. (It should be noted that the actual final solvent mixture for the metalation reaction contains up to 50% of hexane, the solvent in which the *n*-butyllithium is added.)

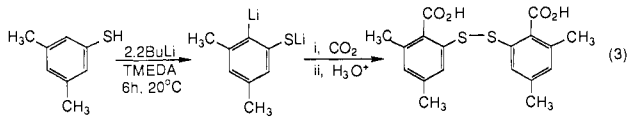
The same procedure was also employed for double metalation of toluene-4-thiol (**4**, eq 2). A good yield of **6** was obtained, thus demonstrating that the procedure was suitable for generation of



(2)

4 5 6

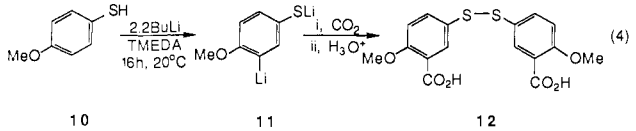
5. However, application of the identical procedure for double metalation of 3,5-dimethylbenzenethiol (**7**) gave a substantially poorer yield of **9**. Thus, the reaction time was varied somewhat in order to optimize the yield of dianion **8**. A reaction period of ca. 6 h at ambient temperature (ca. 20 °C) appeared to give the highest yield (eq 3), although this was still lower than for the reactions of **1** and **4**.



(3)

7 8 9

The metalation reaction was also applied to 4-methoxybenzenethiol (**10**) in an attempt to assess the relative abilities of thiolate and methoxy groups to direct metalation to their ortho positions. Under the standard conditions the major product was **12** (eq 4), thus demonstrating that the methoxy group is the more



(4)

10 11 12

(7) Figuly, G. D.; Loop, C. K.; Martin, J. C. *J. Am. Chem. Soc.*, preceding ref 8 in this issue.

(8) Block, E.; Eswarakrishnan, V.; Gernon, M.; Kang, H.; Ofori-Okai, G.; Saha, C.; Tang, K.; Zubieta, J. *J. Am. Chem. Soc.*, preceding paper in this issue. See also for a review that includes a passing reference to the work: Block, E.; Aslam, M. *Tetrahedron* **1988**, *44*, 281–324.

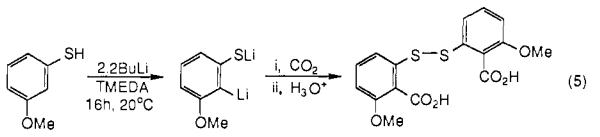
Table I. Products Obtained via Lithiation of Arenethiols

arenethiol	electrophile	product	yield,[a] %
1	CO_2	**3**	90
4	CO_2	**6**	87
7	CO_2	**9**	60
10	CO_2	**12**	65
13	CO_2	**15**	80
1	D_2O	**16**	87
4	D_2O	**17**	98
1	MeI	**18**	40
4	MeI	**19**	42
1	Me_3SiCl	**20**	87
4	Me_3SiCl	**21**	80
7	Me_3SiCl	**22**	30
10	Me_3SiCl	**23**	45
13	Me_3SiCl	**24**	85
1	TITD (Pr^i_2NCS–S–S–$CSNPr^i_2$)	**25**	67
4	TITD (Pr^i_2NCS–S–S–$CSNPr^i_2$)	**26**	61

[a] Yield of isolated, purified material; byproducts were not identified, but did not appear to be derived from metalation at other sites.

powerfully ortho-directing, giving **11** as the intermediate dianion. The isolated yield of **12** was only ca. 65%, and the byproducts were not characterized. However, none of the product expected from metalation ortho to the thiolate group was detected in the mixture.

Finally, 3-methoxybenzenethiol (**13**) was doubly metalated in an analogous manner. The product, isolated in high yield, was **15**, indicating the clean production of dianion **14** (eq 5).[23]



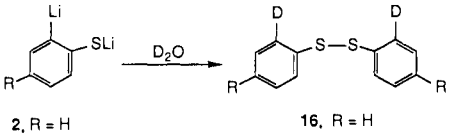
(5)

13 14 15

Reactions of Doubly Lithiated Arenethiols with Electrophiles. Carbon dioxide, deuterium oxide, iodomethane, chlorotrimethylsilane, and tetraisopropylthiuram disulfide (TITD)[9] were chosen as representative electrophiles for investigation of the general synthetic utility of doubly lithiated arenethiols. The dianions **2** and **5** were reacted with each of these elctrophiles while **8**, **11**, and **14** were reacted only with carbon dioxide and chlorotrimethylsilane.

The reactions with carbon dioxide resulted in isolation of the corresponding disulfide dicarboxylic acids, as described in the preceding section. Autoxidation to the disulfide presumably occurs during workup and it should be possible to prevent this by use of appropriate precautions. Indeed, thiosalicylic acid was isolated directly from the similar reaction mixture obtained with Martin's procedure.[7] However, there are simple methods for converting disulfides into thiols,[10] so isolation of the disulfides presents no problem.

In our hands the reactions with D_2O also gave rise to disulfides as the isolated products (eq 6). Yields were good (Table I). Again, it should be possible to obtain the thiols directly by appropriate modification of the workup conditions, but we have not attempted to do so.



(6)

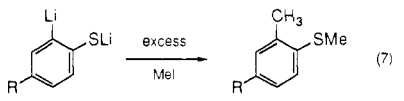
2, R = H
5, R = CH_3

16, R = H
17, R = CH_3

(9) Jen, K.-Y.; Cava, M. P. *Tetrahedron Lett.* **1982**, *23*, 2001–2004.

(10) For listings of reagents that have been used, see: Wardell, J. L. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; Wiley: London, 1974; pp 220–229. Field, L. In *Organic Chemistry of Sulfur*; Oae, S., Ed.; Plenum: New York, 1977; pp 346–348.

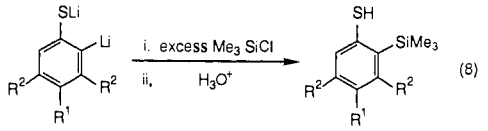
Reactions with iodomethane gave rise to doubly methylated compounds (eq 7). The isolated yields were rather lower (table).



2, R = H 18, R = H

5, R = CH_3 19, R = CH_3

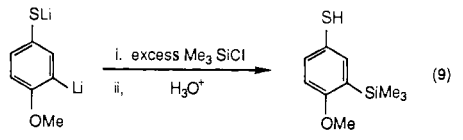
Reactions with chlorotrimethylsilane produced the corresponding trimethylsilyl-substituted arenethiols (equations 8–10). Yields for the reactions of **2**, **5**, and **14** were good, but those for reactions of **8** and **11** were poorer (table).



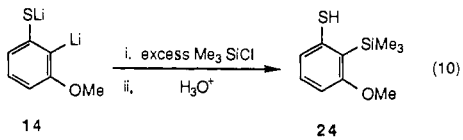
2, $R^1 = R^2 = H$ 20, $R^1 = R^2 = H$

5, $R^1 = CH_3$, $R^2 = H$ 21, $R^1 = CH_3$, $R^2 = H$

8, $R^1 = H$, $R^2 = CH_3$ 22, $R^1 = H$, $R^2 = CH_3$

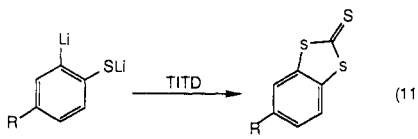


11 23



14 24

The reactions of dianions **2** and **5** with TITD produced *o*-phenylene trithiocarbonates (eq 11). These could be isolated directly in quite good yields. Such compounds can be converted into *o*-dithiols.[11]



2, R = H 25, R = H

5, R = CH_3 26, R = CH_3

Conclusion

Arenethiols are efficiently lithiated by *n*-butyllithium in TMEDA–hexane at ambient temperature over periods ranging from ca. 5 to 20 h for solutions that are ~0.5 M in concentration. The dianions then react in the expected manner with electrophiles such as CO_2, D_2O, Me_3SiCl, MeI, and TITD. The products are generally obtained in good yield, although yields with MeI as electrophile are somewhat lower. In the cases of CO_2 and D_2O the products were usually isolated as disulfides, while MeI gave dimethyl products, and TITD gave cyclic trithiocarbonates.

The methoxy group is a more powerful group for ortho-directing metalation than is the thiolate group and 4-methoxybenzenethiol therefore gives rise to 3-substituted 4-methoxybenzenethiol derivatives. However, in the case of 3-methoxybenzenethiol, metalation occurs cleanly between the two substituents.

The availability of a method for ortho-metalation of arenethiols should be of general significance for the synthesis of substituted arenethiols.

(11) For a general listing of methods for cleavage of cyclic trithiocarbonates, see: Breslow, D. S.; Skolnik, H. *Multi-Sulfur and Sulfur and Oxygen 5- and 6-Membered Heterocycles*; Wiley-Interscience: New York, 1966; p 541.

Experimental Section

General Procedures. Elemental analyses (C, H, N) were obtained for all new compounds, on a Carlo Erba 1106 instrument, and all data were accurate to within 0.4% of the calculated values. Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh) silica gel. TLC was carried out on aluminum-backed Kieselgel plates. TMEDA was distilled from CaH_2, THF from sodium benzophenone ketyl. Other solvents were all distilled as appropriate.[12] 3,5-Dimethylthiophenol was obtained from Courtaulds Sulphur Chemicals.[13] Other thiols were obtained from Aldrich. *n*-BuLi was also obtained from Aldrich and standardized by literature procedures.[14] Tetraisopropylthiuram disulfide was prepared by the method of Rothstein and Binovic.[15]

Lithium 2-Lithiobenzenethiolate (2). Typically, to a solution of thiophenol (1.07 g, 1.00 mL, 9.7 mmol) in *N,N,N′,N′*-tetramethylethylethylenediamine (TMEDA, 15 mL) at −78 °C, was added *n*-butyllithium (13.3 mL of a 1.58 M solution in hexane, 21 mmol). The resulting solid matrix was allowed to warm to room temperature to give a pale yellow solution which, when stirred overnight, gave a very fine white suspension. This suspension was used directly in reactions with electrophiles.

Lithium 2-Lithio-4-methylbenzenethiolate (5). The procedure was identical with that described for **2**, starting from *p*-thiocresol (**4**; 1.19 g, 9.3 mmol) and *n*-butyllithium (12.7 mL, 1.58 M, 20 mmol). The final suspension was pale yellow.

Lithium 2-Lithio-3,5-dimethylbenzenethiolate (8). The procedure was very similar to that described for **2**, starting from 3,5-dimethylbenzenethiol (**7**; 1.08 g, 1.00 mL, 7.8 mmol), TMEDA (15 mL), and *n*-butyllithium (10.8 mL of 1.58 M). The mixture was stirred for only 6 h at ambient temperature. The suspension obtained was white.

Lithium 3-Lithio-4-methoxybenzenethiolate (11). The procedure was identical with that described for **2**, starting from 4-methoxybenzenethiol (**10**; 0.50 g, 3.6 mmol), TMEDA (8 mL), and *n*-butyllithium (5.0 mL, 1.58 M, 7.9 mmol). A deep yellow solution was obtained.

Lithium 2-Lithio-3-methoxybenzenethiolate (14). The procedure was identical with that described for **2**, starting from 3-methoxybenzenethiol (**13**; 0.50 g, 3.6 mmol), TMEDA (8 mL), and *n*-butyllithium (5.0 mL, 1.58 M, 7.9 mmol). A fine white suspension was obtained.

Reactions of Doubly Lithiated Arenethiols with Carbon Dioxide: General Procedure. A round-bottomed flask was charged with a large excess of powdered solid carbon dioxide and fitted with a septum vented via a needle attached to a paraffin oil bubbler. The flask was allowed to vent for several minutes in order to ensure complete displacement of air, and then the solution or suspension of the dianion (**2**, **5**, **8**, **11**, or **14**), prepared as described above, was added via a 16-gauge double-ended needle. The mixture was allowed to warm to room temperature following evaporation of all of the CO_2 and was then opened to air, acidified with 3 M aqueous HCl, and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The crude product was taken up into $NaHCO_3$ solution and washed twice with diethyl ether. The aqueous layer was then acidified and extracted into ethyl acetate, and the organic extract was washed with water, dried ($MgSO_4$), and evaporated to give the product.

The products obtained are described below.

2,2′-Dithiobis(benzoic acid) (3): yield 1.34 g (4.37 mmol, 90%); off-white solid; mp 289–291 °C (lit.[4] 289–290 °C); ^{1}H NMR (DMSO-d_6) δ 7.3–7.7 (m, 8 H), 8.0 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.5 (singlet in the off-resonance decoupled spectrum), 138.9 (s), 133.1 (d), 131.5 (d), 128.1 (s), 125.8 (d), 124.9 (d); mass spectrum (70 eV), *m/z* (relative intensity) 306 (1, M^+), 154 (25), 152 (74), 136 (100), 108 (60), 96 (27), 69 (33), 50 (18); IR (KBr disc), ν_{max} 3000, 1690, 1470, 1420, 1270 cm^{-1}.

2,2′-Dithiobis(5-methylbenzoic acid) (6):[16] yield 1.36 g (4.07 mmol, 87%); mp 288 °C dec; ^{1}H NMR (DMSO-d_6) δ 2.28 (s, 6 H), 7.3 (dd, J = 2, 8 Hz, 2 H), 7.51 (d, J = 8 Hz, 2 H), 7.85 (d, J = 2 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 167.7 (s), 135.8 (d), 135.4 (s), 133.8 (d), 131.9 (s), 128.0 (d), 125.2 (s), 20.0 (q); mass spectrum (70 eV), *m/z* (relative intensity) 334 (0.5, M^+), 168 (24), 166 (84), 150 (100), 121 (64), 110 (24), 78 (31), 77 (22), 66 (19); accurate mass of M^+, found *m/z*

(12) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1966.

(13) We thank Courtaulds for this free sample: Courtaulds Research, Lockhurst Road, Coventry, U.K.; Sulphur Chemicals, Barton Dock Road, Stretford, Manchester, M32 OTD, U.K.

(14) Brown, H. C. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975. Gilman, H.; Haubein, S. H. *J. Am. Chem. Soc.* **1944**, *66*, 1515–1516. Eberly, K. C. *J. Org. Chem.* **1961**, *26*, 1309–1310. Gilman, H.; Cartledge, F. K. *J. Organomet. Chem.* **1964**, *2*, 441–454.

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334.0334, calcd for $C_{16}H_{14}O_4S_2$ 334.0333; IR (KBr disc), ν_{max} 2950, 1690, 1560, 1480, 1420, 1320, 1270, 1220, 1060 cm^{-1}.

2,2'-Dithiobis(4,6-dimethylbenzoic acid) (9): yield 0.83 g, (2.28 mmol, 60%); from acetic acid; mp 202–206 °C; ^1H NMR (DMSO-d_6) δ 2.30 (s, 6 H), 2.37 (s, 6 H), 7.02 (d, J = 1 Hz, 2 H), 7.46 (d, J = 1 Hz, 2 H), 12.0–14.0 (v br, 2 H); ^{13}C NMR (DMSO-d_6) δ 168.8 (s), 139.9 (s), 135.8 (s), 134.6 (s), 131.3 (s), 130.2 (d), 125.7 (d), 20.7 (q), 19.7 (q); mass spectrum (70 eV), m/z (relative intensity) 180 (55), 164 (100), 151 (82), 135 (49), 121 (24), 104 (13), 91 (37), 77 (23), 62 (27), 50 (35), 47 (33); IR (KBr disc), ν_{max} 3000 (v br), 1670, 1600, 1450, 1300, 1280, 1170, 1100, 850, 780 cm^{-1}.

3,3'-Dithiobis(6-methoxybenzoic acid) (12): yield 0.43 g (1.17 mmol, 65%); from methanol–water; mp 205–206 °C; ^1H NMR (DMSO-d_6) δ 3.78 (s, 6 H), 7.1 (d, J = 9 Hz, 2 H), 7.55 (dd, J = 3, 9 Hz, 2 H), 7.7 (d, J = 3 Hz, 2 H), 12.7 (br s, 2 H); ^{13}C NMR (DMSO-d_6) δ 166.2 (s), 158.4 (s), 134.7 (d), 132.3 (d), 126.3 (s), 122.2 (s), 113.7 (d), 66 (q); mass spectrum (70 eV), m/z (relative intensity) 366 (24, M^+), 183 (100), 166 (8), 151 (57), 123 (12), 109 (10), 107 (10), 96 (17), 95 (59), 70 (14), 69 (31), 63 (16), 45 (37); IR (KBr disc), ν_{max} 2900 (v br), 1700, 1600, 1320, 1290, 1260 cm^{-1}.

2,2'-Dithiobis(6-methoxybenzoic acid) (15): yield 0.53 g (1.44 mmol, 80%); from acetic acid; mp 188 °C (lit.[17] mp 187 °C); ^1H NMR (DMSO-d_6) δ 3.88 (s, 6 H), 7.09 (d, J = 8 Hz, 2 H), 7.34 (d, J = 9 Hz, 2 H), 7.46 (dd, J = 8, 9 Hz, 2 H, overlapping with proton at 7.34), 11.8–12.8 (v br, 1 H); ^{13}C NMR (DMSO-d_6) δ 166.8 (s), 156.0 (s), 134.3 (s), 130.9 (d), 124.2 (s), 119.0 (d), 110.7 (d), 56.0 (q); mass spectrum (70 eV), m/z (relative intensity) (no M^+) 182 (34), 166 (100), 152 (36), 137 (16), 136 (16), 123 (26), 108 (14), 107 (15), 96 (15), 95 (25), 75 (29), 69 (56), 63 (34), 62 (39), 61 (26), 53 (18), 52 (18), 51 (25), 50 (29), 45 (33); IR (KBr disc), ν_{max} 3000 (v br), 1720, 1590, 1460, 1440, 1275, 1030 cm^{-1}.

Reactions of Doubly Lithiated Arenethiols with D_2O: General Procedure. The suspension of the dianion, prepared as described above, was stirred and cooled to −10 °C. A solution of D_2O (1 mL) in THF (10 mL) was then added by syringe. The reaction mixture was allowed to warm to ambient temperature and then stirred for 1 h. It was then opened to air, acidified with 3 M aqueous hydrochloric acid, and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave the product. The following products were obtained in this way.

Bis(2-deuteriophenyl) disulfide (16): yield 0.93 g (4.22 mmol, 87%); low-melting solid; mp 61 °C; ^1H NMR ($CDCl_3$) δ 7.0 (m); mass spectrum (70 eV), m/z (relative intensity) 220 (62, M^+), 219 (34), 110 (100), 109 (35), 45 (40); accurate mass of M^+, found m/z 220.0350, calcd for $C_{12}H_8D_2S_2$ 220.0349.

Bis(2-deuterio-4-methylphenyl) disulfide (17): yield 1.12 g (9.1 mmol, 98%); white crystals; ^1H NMR ($CDCl_3$) δ 2.2 (s, 6 H), 6.9 (m, 6 H); mass spectrum (70 eV), m/z (relative intensity) 248 (60, M^+), 247 (30), 124 (100), 123 (33), 92 (17), 80 (21), 78 (20), 45 (41); accurate mass of M^+, found m/z 248.0669, calcd for $C_{14}H_{12}D_2S_2$ 248.0662.

Reactions of Doubly Lithiated Arenethiols with MeI: General Procedure. The solution of the appropriate dianion, prepared as described, was cooled to −78 °C, and iodomethane (5.4 g, 38 mmol, large excess) in THF (10 mL) was added by syringe. The reaction mixture was allowed to warm to room temperature over 1 h and then stirred for a further 3 h. It was acidified by addition of 3 M hydrochloric acid and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by bulb-to-bulb distillation. The following products were obtained in this way.

2-Methylthioanisole (18): yield 0.566 g (4.1 mmol, 40%); colorless liquid; bp 50 °C (oven temperature) (0.1 mmHg) [lit.[18] bp 55–56 °C (1.5 mmHg)]; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3 H), 2.31 (s, 3 H), 7.0–7.25 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 137.7 (s), 135.6 (s), 129.7 (d), 126.4 (d), 124.9 (d), 124.5 (d), 19.9 (q), 15.0 (q); mass spectrum (70 eV), m/z (relative intensity) 138 (62, M^+), 124 (24), 123 (46), 91 (60), 89 (12), 78 (13), 77 (18), 69 (13), 65 (15), 62 (12), 50 (16), 45 (100); IR (neat), ν_{max} 3090, 3000, 2920, 1590, 1470, 1440, 1380, 1070, 1050, 740 cm^{-1}.

2,4-Dimethylthioanisole (19): yield 0.593 g (3.9 mmol, 42%); colorless liquid; bp 60 °C (oven temperature) (0.1 mmHg) [lit.[19] bp 234–236 °C (760 mmHg)]; ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 2.28 (s, 3 H), 2.30 (s, 3 H), 6.8–7.1 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 135.9 (s), 134.3 (s), 130.7 (d), 129.5 (s), 127.2 (d), 125.6 (d), 20.7 (q), 19.8 (q), 15.6 (q); mass spectrum (70 eV), m/z (relative intensity) 152 (74, M^+), 138 (31), 137 (47), 105 (50), 93 (12), 91 (50), 79 (12), 78 (13), 77 (27), 51 (19), 45 (100); IR (neat), ν_{max} 3090, 3000, 2940, 1590, 1450, 1380, 1060, 800 cm^{-1}.

Reactions with Chlorotrimethylsilane: General Procedure. The solution of the appropriate dianion, prepared as above, was cooled to −78 °C, and chlorotrimethylsilane (at least 2.2 mol/mol of dianion) in THF (5–10 mL) was added by syringe. The reaction mixture was allowed to warm slowly to room temperature over 1 h and stirred for a further 1.5 h. It was then acidified by addition of 3 M hydrochloric acid and extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated, and the crude product was purified by bulb-to-bulb distillation. The following products were obtained in this way.

2-(Trimethylsilyl)benzenethiol (20):[20] yield 1.53 g (8.4 mmol, 87%); colorless liquid; bp 100 °C (oven temperature) (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.70 (s, 9 H), 3.76 (s, 1 H), 7.3–7.6 (m, 3 H), 7.65–7.80 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 139.6 (s), 137.3 (s), 135.2 (d), 131.7 (d), 129.7 (d), 125.3 (d), −0.2 (q); mass spectrum (70 eV), m/z (relative intensity) 182 (13, M^+), 168 (17), 167 (74), 166 (78), 151 (100), 105 (12), 91 (65), 89 (14), 77 (41), 76 (26), 75 (66), 73 (28), 65 (21), 63 (11), 53 (17), 51 (15), 50 (11), 45 (22), 43 (29); accurate mass of M^+, found 182.0579, calcd for $C_9H_{14}SSi$ 182.0586; IR (neat), ν_{max} 2960, 2580, 1580, 1500, 1480, 1380, 1280, 1240, 1170, 1150, 1080, 1040, 840 cm^{-1}.

4-Methyl-2-(trimethylsilyl)benzenethiol (21): yield 1.54 g (7.4 mmol, 80%); colorless liquid; bp 115 °C (oven temperature) (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.58 (s, 9 H), 2.48 (s, 3 H), 3.61 (s, 1 H), 7.20 (dd, J = 8, 2 Hz, 1 H), 7.42 (d, J = 8 Hz, 1 H), 7.49 (d, J = 2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 140.1 (s), 135.9 (d), 134.9 (s), 133.1 (s), 132.2 (d), 130.5 (d), 21.1 (q), − 0.1 (q); mass spectrum (70 eV), m/z (relative intensity) 196 (17, M^+), 182 (13), 181 (50), 180 (89), 166 (17), 165 (100), 105 (34), 91 (87), 89 (23), 86 (45), 83 (72), 79 (20), 77 (39), 75 (39), 73 (50), 51 (39), 49 (94), 43 (34); accurate mass of M^+, found 196.0742, calcd for $C_{10}H_{16}SSi$ 196.0742; IR (neat), ν_{max} 2970, 2580, 1580, 1500, 1460, 1380, 1290, 1240, 1180, 1150, 1080, 1030, 840 cm^{-1}.

3,5-Dimethyl-2-(trimethylsilyl)benzenethiol (22): yield 0.49 g, (2.34 mmol, 30%); colorless liquid; bp 80 °C (oven temperature) (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 2.30 (s, 3 H), 3.40 (s, 1 H), 6.80 (s, 1 H), 6.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 141.7 (s), 138.7 (s), 130.0 (s), 126.6 (s), 126.1 (d), 126.0 (d), 27.0 (q), 21.3 (q), −1.7 (q); mass spectrum (70 eV), m/z (relative intensity) 210 (5, M^+), 121 (30), 119 (97), 117 (100), 84 (18), 82 (30), 73 (35), 47 (47); IR (neat), ν_{max} 2990, 2580, 1590, 1470, 1440, 1250, 1170, 850, 700 cm^{-1}.

4-Methoxy-3-(trimethylsilyl)benzenethiol (23): yield 0.34 g (1.62 mmol, 45%); colorless liquid; bp 95 °C (oven temperature) (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.48 (s, 9 H), 3.56 (s, 1 H), 3.94 (s, 3 H), 6.86 (d, J = 9 Hz, 1 H), 7.4–7.6 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 163.2 (s), 137.9 (d), 134.7 (s), 133.5 (d), 114.6 (s), 110.4 (d), 55.1 (q), −0.9 (q); mass spectrum (70 eV), m/z (relative intensity) 212 (27, M^+), 197 (29), 196 (26), 182 (15), 181 (23.9), 168 (13), 167 (100), 91 (14), 77 (11), 75 (40), 73 (23), 59 (19), 49 (12), 45 (20), 43 (17); IR (neat), ν_{max} 2900, 2590, 1590, 1470, 1380, 1290, 1240, 1185, 1160, 1120, 1090, 1030, 840 cm^{-1}.

3-Methoxy-2-(trimethylsilyl)benzenethiol (24): yield 0.65 g (3.06 mmol, 85%); colorless liquid; bp 90 °C (oven temperature) (0.1 mmHg); ^1H NMR ($CDCl_3$) δ 0.62 (s, 9 H), 3.65 (s, 1 H), 3.92 (s, 3 H), 6.79 (d, J = 9 Hz, 1 H), 6.99 (d, J = 8 Hz, 1 H), 7.30 (dd, J = 8, 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.2 (s), 139.5 (s), 135.5 (s), 130.5 (d), 124.1 (d), 107.2 (d), 55.0 (q), 2.4 (q); mass spectrum (70 eV), m/z (relative intensity) 212 (27, M^+), 197 (29), 196 (26), 182 (15), 181 (24), 168 (13), 167 (100), 75 (41), 73 (23), 59 (20), 45 (20); IR (neat), ν_{max} 2990, 2590, 1590, 1460, 1430, 1250, 1050, 840, 780, 710 cm^{-1}.

Reactions with Tetraisopropylthiuram Disulfide (TITD): General Procedure. The solution of the appropriate dianion was cooled to −10 °C, and a solution of TITD (1 mol/mol of dianion; i.e., 3.41 g, 9.7 mmol for dianion **2**, 3.27 g, 9.3 mmol for dianion **5**) in THF (10 mL) was added. The mixture was stirred for 1 h at −10 °C, then acidified by addition of 3 M hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to leave a dark oil. The crude product was purified by flash chromatography on silica (eluted with dichloromethane–hexane 1:1) to give a yellow crystalline product which was recrystallized. The following products were obtained in this way.

1,3-Benzodithiole-2-thione (25): yield 1.20 g (6.5 mmol, 67%), from acetic acid; mp 166 °C (lit.[21] mp 165 °C); ^1H NMR (DMSO-d_6) δ 7.4 (m, 2 H), 7.8 (m, 2 H); IR (KBr disc), 1440, 1290, 1265, 1140, 1120 cm^{-1}; mass spectrum (70 eV), m/z (relative intensity) 184 (100, M^+), 140 (78), 108 (18), 69 (33), 63 (13).

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5-Methyl-1,3-benzodithiole-2-thione (26): yield 1.12 g (5.7 mmol, 61%), from ethanol; mp 85 °C (lit.[22] mp 84 °C); ^{13}C NMR ($CDCl_3$) δ 141.0, 137.9, 137.6, 128.4, 121.7, 121.3, 21.1; mass spectrum (70 eV), m/z (relative intensity) 194 (100, M^+), 154 (57), 153 (22), 121 (40), 69 (21); IR (KBr disc), ν_{max} 1460, 1120, 1070, 900, 810 cm^{-1}.

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Registry No. 1, 108-98-5; **3**, 119-80-2; **4**, 106-45-6; **6**, 13616-79-0; **7**, 38360-81-5; **9**, 117371-40-1; **10**, 696-63-9; **12**, 71993-03-8; **13**, 15570-12-4; **15**, 19532-68-4; **16**, 117371-41-2; **17**, 117371-42-3; **18**, 14092-00-3; **19**, 34678-67-6; **20**, 33356-45-5; **21**, 117371-43-4; **22**, 117371-44-5; **23**, 117371-45-6; **24**, 117371-46-7; **25**, 934-36-1; **26**, 54199-61-0.

Efficient Total Synthesis of Didemnins A and B†,1

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Abstract: Didemnins A and B (**1** and **2**), cytotoxic cyclic peptides from a Caribbean tunicate *Tridemnum solidum*, have been efficiently prepared by a convergent scheme from two key eastern and western fragments. Efficient routes to derivatives of the constituents of didemnins were explored. Benzyl (2*RS*,4*S*)-[*O*-(*tert*-butyldimethylsilyl)hydroxyisovaleryl]propionate (Hip derivative) was prepared from 2-hydroxyisovaleric acid by use of C-acylation of Meldrum's acid with diethyl phosphorocyanidate as a key step. Derivatives of (3*S*,4*R*,5*S*)-isostatine (Ist) were prepared from Boc-(*R*)-alloisoleucine. Methylation of Boc-(*R*)-Leu-OH and Z-(*S*)-Tyr-OH respectively afforded the corresponding *N*-methyl and *N*,*O*-dimethyl derivatives. The key eastern fragment, (2*RS*,4*S*)-Hip-(*S*)-Leu-(*S*)-Pro-OBzl (**3**), was prepared stepwise from (*S*)-Pro-OBzl, while Boc-(*R*)-MeLeu-(*S*)-Thr[Z-(*S*)-MeTyr(Me)]-(3*S*,4*R*,5*S*)-Ist(TBDMS)-OH (**4**), the key western fragment for didemnin A (**1**), was prepared from Ist derivatives. Coupling of **3** with **4** and cyclization, followed by deprotection, afforded didemnin A (**1**), which was converted to didemnin B (**2**).

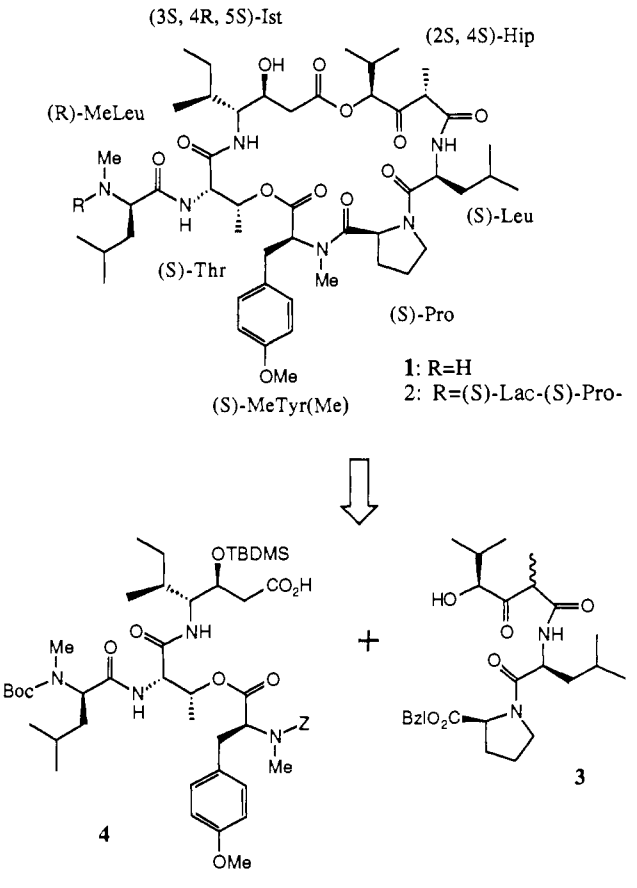
Didemnins were isolated by Rinehart and co-workers[2] from a Caribbean tunicate *Tridemnum solidum*. These structurally unique cyclic depsipeptides have quite interesting cytotoxic, antiviral, and immunosuppressive activities.[2,3] The structures of didemnins A and B have been firmly established as **1** and **2**, respectively, through their total synthesis.[2c] We have already reported[1a] a preparation of [(3*S*,4*R*)-Sta]didemnin A (the second proposed structure of didemnin A)[2b] in which the isostatine part of **1** is replaced with (3*S*,4*R*)-statine. We now describe a total synthesis of didemnins A and B, which will promise an efficient route to prepare these medicinally interesting compounds on a large scale.[4] Our synthetic strategy leading to **1** was based upon a convergent scheme involving the key eastern and western fragments **3** and **4**, which contained the (hydroxyisovaleryl)-propionyl (Hip) and isostatine (Ist) units, respectively, as shown in Scheme I.

Preparation of the Hip derivative **7b** originated with (*S*)-2-hydroxyisovaleric acid (**5a**)[5] (Scheme II). Treatment of **5a** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) followed by alkaline treatment afforded **5b**, which was condensed with Meldrum's acid by use of diethyl phosphorocyanidate (DEPC).[6] Without purification, the product **6** was refluxed with benzyl alcohol in benzene to give the β-keto ester **7a** ($[\alpha]^{23}_D$ −19.8° (*c* 0.53, MeOH)), which was methylated to produce **7b** as a mixture of diastereomers.[7] Our method is much superior to the reported ones[2c,8] in both overall yield and simplicity of the reaction workups.

The required Ist derivative **9d** was prepared from Boc-(*R*)-alloisoleucine (**8**)[9] (Scheme III). After activation of its carboxyl group as the imidazolide by use of carbonyldiimidazole, treatment with ethyl lithioacetate according to the method of Joullie[10] afforded the β-keto ester **9a** ($[\alpha]^{23}_D$ −31.1° (*c* 0.33, $CHCl_3$)) in 78% yield. Alternatively, **8** was transformed to Boc-(*R*)-alloisoleucinal via Boc-(*R*)-alloisoleucinol (mp 42-45 °C, $[\alpha]^{23}_D$ −1.2° (*c* 1, MeOH)) by our own method.[11] Condensation of Boc-(*R*)-alloisoleucinal with ethyl lithioacetate gave Boc-(3*RS*,4*R*,5*S*)-Ist-OEt

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

Scheme I



(**9b** and **9c**, 51% yield from Boc-(*R*)-alloisoleucinol), which was oxidized with pyridinium dichromate (PDC)[12] to give the β-keto

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