Table I. ^{13}C (75 MHz) and ^{1}H (300 MHz) Nuclear Magnetic Resonance Data for Shermilamine A (1) and B (2) (DMSO-d_6)

	shermilamine A: chemical shift, ppm			shermilamine B: chemical shift, ppm	
atom	^{13}C (mult)	^{1}H (mult, J (Hz), intgrtn)	atom	^{13}C (mult)	^{1}H (mult, J (Hz), intgrtn)
2	150.57 (d)	8.43 (d, 4.8 1 H)	2	150.56 (d)	8.50 (d, 5.1, 1 H)
3	107.46 (d)	7.39 (d, 4.8, 1 H)	3	107.07 (d)	7.49 (d, 5.1, 1 H)
3a	138.49 (s)		3a	139.30 (s)	
3b	114.71 (s)		3b	115.34 (s)	
4	125.90 (d)	7.86 (d, 8.7, 1 H)	4	123.87 (d)	8.01 (dd, 7.8, 1.2, 1 H)
5	123.33 (d)	7.07 (dd, 8.7, 1.8, 1 H)	5	120.76 (d)	7.02 (ddd, 7.8, 7.8, 1.2, 1 H)
6	124.97 (s)		6	131.80 (d)	7.44 (ddd, 7.8, 7.8, 1.2, 1 H)
7	118.22 (d)	7.49 (d, 1.8, 1 H)	7	116.43 (d)	7.39 (dd, 7.8, 1.2, 1 H)
7a	141.10 (s)		7a	139.90 (s)	
8		10.17 (s, 1 H)	8		10.24 (s, 1 H)
8a	130.44 (s)		8a	131.07 (s)	
9	109.32 (s)		9	108.56 (s)	
9a	122.01 (s)		9a	121.40 (s)	
11	29.26 (t)	3.54 (s, 2 H)	11	29.25 (t)	3.33 (s, 2 H)
12	163.48 (s)		12	163.41 (s)	
13		9.22 (s, 1 H)	13		9.26 (s, 1 H)
13a	121.31 (s)		13a	121.21 (s)	
13b	136.55 (s)		13b	136.60 (s)	
13c	116.27 (s)		13c	116.27 (s)	
14	27.62 (t)	2.80 (m, 2 H)	14	27.66 (t)	2.82 (m, 2 H)
15	37.03 (t)	3.05 (m, 2 H)	15	37.07 (t)	3.00 (m, 2 H)
16		8.55 (t, 4.8, 1 H)	16		8.57 (t, 4.8, 1 H)
17	171.53 (s)		17	171.62 (s)	
18	22.45 (q)	1.90 (s, 3 H)	18	22.38 (q)	1.92 (s, 3 H)

Table II. $^{2-3}J_{C-H}$ Correlations from HMBC Experiment for Shermilamine A (1) (DMSO-d_6)[a]

proton no.	long-range correlations to carbon no.
H-2	C3, C3a, C13b
H-3	C2, C3b, C13c
H-4	C3a, C3b, C6, C7, C7a
H-5	C3b, C7
H-7	C3b, C5
H_2-11	C9a, C12
H-13	C9a
H_2-14	C8a, C9, C9a
H_3-18	C17

[a] Spectra were recorded on a General Electric GN OMEGA 500 spectrometer.

could then be assigned by direct comparison with the ^{13}C assignments for 1.

Experimental Section

General Procedures. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1420 spectrometer and ultraviolet spectra on a Hewlett-Packard Model 8452A diode array spectrophotometer. Mass spectra were measured on a VG-70SE instrument and NMR spectra on a General Electric QE-300 instrument at 300 MHz (^{1}H) and 75 MHz (^{13}C) respectively and on a General Electric GN OMEGA 500 instrument for the HMBC experiment. Solvents were freshly distilled before use.

Isolation. Animals that were collected in September 1987 in Pago Bay, Guam, were frozen until examined. The frozen tunicates (1.73 kg) were extracted, first with methanol, followed by repeated extraction with chloroform/methanol (1:1) containing 1% of a 30% ammonium hydroxide solution. The extracts were combined and concentrated. The aqueous residue was acidified with 1 M hydrochloric acid and partitioned against hexane and chloroform. The aqueous layer was basified with 10% ammonium hydroxide and partitioned against chloroform. The basic chloroform extract was concentrated, yielding an orange/red solid (1.20 g). This residue was filtered through silica gel (BondElut, elution with chloroform) and then subjected to MPLC on silica gel (elution with chloroform/methanol, 97:3), resulting in shermilamine A (1, 98 mg, 0.006%) and shermilamine B (2, 340 mg, 0.019%).

Shermilamine A (1): orange prisms from chloroform/methanol (96:4); mp >300 °C; UV (MeOH) λ_{max} 238 (log ϵ = 4.52), 282 (4.45), 298 (4.39), 350 (3.90), 392 (3.71), 470 nm (3.76); UV ($MeOH_2^+$) λ_{max} 242 (log ϵ = 4.40), 286 (4.36), 312 (4.55), 320 (4.54), 364 (3.74), 382 (3.75), 536 nm (3.77); IR (solution in chloroform) ν_{max} 3680, 1665, 1650, 1630, 1605, 1595, 1500, 1460, 1435, 1375, 1335, 1010, 930, 830 cm^{-1}; HREIMS, m/z 468.0260 ($C_{21}H_{17}{}^{79}BrN_4O_2S$ requires 468.0255); EIMS, m/z 470 (85), 468 (82), 398 (55), 396 (65), 207 (60), 177 (100), 147 (30), 135 (40), 91 (25), 73 (30), 57 (68).

Shermilamine B (2): fine orange prisms from methanol; mp 254 °C dec; UV (MeOH) λ_{max} 234 (log ϵ = 4.54), 282 (4.45), 298 (4.39), 348 (3.97), 390 (3.76), 468 nm (3.81); UV ($MeOH_2^+$) λ_{max} 232 (log ϵ = 4.44), 282 (4.40), 302 (4.53), 318 (4.69), 364 (3.78), 382 (3.79), 536 nm (3.83); IR (film from chloroform) ν_{max} 3290, 3265, 2980, 1640, 1630, 1600, 1580, 1550, 1450, 1420, 1350, 1310, 1190, 1120, 1070, 900, 840, 800, 740, 650 cm^{-1}; HREIMS, m/z 390.1204 ($C_{21}H_{18}N_4O_2S$ requires 390.1259), 318.0645 ($C_{18}H_{12}N_3OS$ requires 318.0590); EIMS, m/z 390 (100), 318 (80), 212 (45), 162 (90).

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Generation and Cycloaddition Reactions of Phenylsulfonyl-Substituted 1,3-Butadienes

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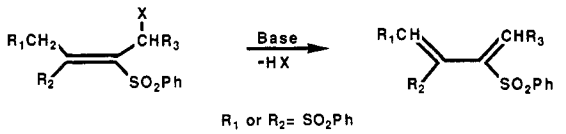
Phenylsulfonyl-substituted 1,3-dienes exhibit high regio- and stereoselectivity toward dienophiles, and consequently these dienes are becoming well established as useful intermediates in organic synthesis.[1] Some of the procedures

(1) Eisch, J. J.; Galle, J. E.; Hallenbeck, L. E. *J. Org. Chem.* **1982**, *47*, 1608. Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335. Bäckvall, J. E.; Juntunen, S. K. *J. Am. Chem. Soc.* **1987**, *109*, 6396. Chou, T. S.; Hung, S. C.; Tso, H. H. *J. Org. Chem.* **1987**, *52*, 3394. Hung, S. C.; Chou, T. S. *J. Org. Chem.* **1988**, *53*, 3020.

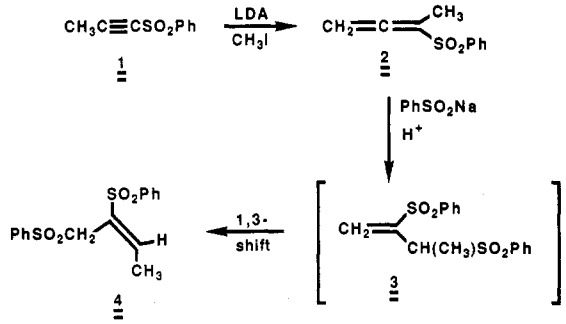
0022-3263/89/1954-4232$01.50/0

Scheme I

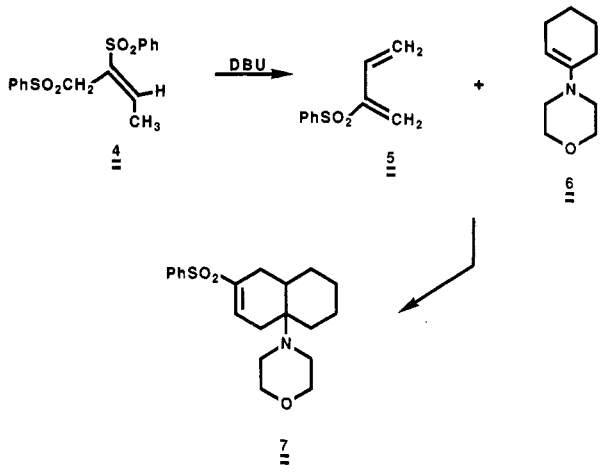


currently available for their preparation include phenylsulfonylmercuration of 1,3-dienes,[2] condensation of allyl sulfones with aldehydes followed by acetylation and subsequent elimination,[3] thermal SO_2 extrusion from 2-(arylsulfonyl)sulfolenes,[4,5] cheletropic ring-opening of sulfolanes,[6] palladium(II)-catalyzed chloroacetoxylation of 1,3-dienes,[7] and the 2-tosylvinyl sulfone coupling with vinylstannanes.[8] Methods of preparing bis(phenylsulfonyl)-substituted 1,3-dienes, however, are limited to relatively few routes.[9,10] As part of a program directed toward the use of activated dienes in heterocyclic synthesis,[11] we decided to explore an alternate synthetic path to these substrates. Herein we report an especially direct route to bis(phenylsulfonyl) substituted dienes based on the strategy shown in Scheme I.

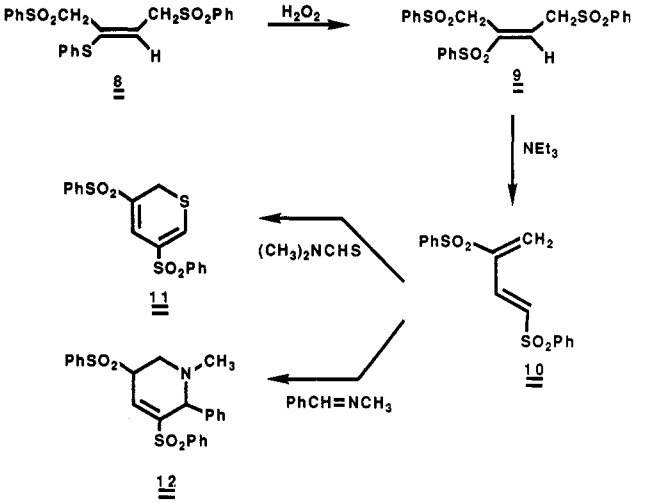
The first system studied involved the preparation of 2-(phenylsulfonyl)-1,3-butadiene[2] (**5**) from 1-methyl-1-(phenylsulfonyl)allene (**2**). The activated allene was obtained by methylation of 1-(phenylsulfonyl)propyne (**1**) using LDA as the base.[12] Treatment of **2** with sodium benzenesulfinate in THF that contained an equivalent of acetic acid afforded (*E*)-1,2-bis(phenylsulfonyl)-2-butene (**4**) in 93% yield.[13] The formation of this material can be rationalized in terms of addition of benzenesulfinate anion



onto the central carbon atom of the activated allene to give disulfone **3** as a transient intermediate. This material undergoes a subsequent 1,3-(phenylsulfonyl) shift to produce the rearranged alkene **4**.[14] Treatment of **4** with DBU in benzene at 25 °C afforded diene **5**, which was found to undergo Diels–Alder dimerization on standing.[2] Reaction of **4** with DBU in the presence of enamine **6** proceeded smoothly to produce the expected Diels–Alder cycloadduct **7** in 80% yield.[15]



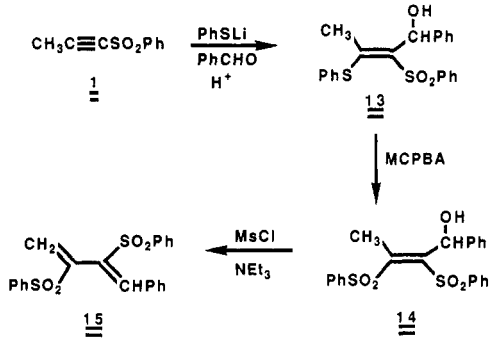
A related elimination sequence was used for the synthesis of 1,3-bis(phenylsulfonyl)-1,3-butadiene (**10**). A sample of 1,4-bis(phenylsulfonyl)-2-(phenylthio)-2-butene (**8**)[16] was oxidized to the corresponding sulfone **9** by using a 30% hydrogen peroxide solution. Elimination of benzenesulfinate to give diene **10** was accomplished by stirring **9** with triethylamine in benzene at 25 °C. This diene is highly activated toward nucleophilic addition because of its markedly lowered LUMO energy level compared with that of the mono(phenylsulfonyl)-substituted diene **5**. We have studied the reaction of **10** with several dienophiles and find that it participates as the diene component with *N*-benzylidenemethylamine as well as with *N*,*N*-dimethylthioformamide. In both cases, the reaction afforded a single product (i.e., **11** or **12**) which can be attributed to an initial Diels–Alder cycloaddition followed by either elimination of dimethylamine or a 1,3-hydrogen shift.



A convenient synthesis of 1-aryl-2,3-bis(phenylsulfonyl)-1,3-butadienes from (phenylsulfonyl)-1-propyne was also developed. Conjugate addition of the lithium salt of benzenethiol to **1** in the presence of benzaldehyde gave an adduct (i.e., **13**) incorporating the three components with an *E* disposition of nucleophile and incorporated benzaldehyde.[17] Oxidation of **13** with MCPBA at −78 °C

(2) Andell, O. A.; Bäckvall, J. E. *Tetrahedron Lett.* **1985**, 4555.
(3) Cuvigny, T.; Hervee du Penhoat, C.; Julia, M. *Tetrahedron* **1986**, *42*, 5329; *Tetrahedron Lett.* **1983**, 4315.
(4) Inomata, K.; Kinoshita, H.; Takemoto, H. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3341.
(5) Chou, T.; Lee, S. J.; Peng, M. L.; Sun, D. J.; Chou, S. S. P. *J. Org. Chem.* **1988**, *53*, 3027.
(6) Naf, F.; Decorzant, R.; Escher, S. D. *Tetrahedron Lett.* **1982**, 5043.
(7) Akermark, B.; Nystrom, J. E.; Rein, T.; Bäckvall, J. E. *Tetrahedron Lett.* **1984**, 5719.
(8) Marino, J. P.; Long, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 7916.
(9) Jeganathan, S.; Okamura, W. H. *Tetrahedron Lett.* **1982**, 4763.
(10) Masuyama, Y.; Sato, H.; Rurusu, Y. *Tetrahedron Lett.* **1985**, 67.
(11) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, 2417; *Ibid.* **1988**, 3041.
(12) Cadiot, P.; Pourcelot, G. *Bull. Soc. Chim. Fr.* **1966**, 3016.
(13) The stereochemistry of compound **4** was assigned on the basis of NOE experiments.
(14) There have been several reports in the literature that indicate that substituted allylic sulfones can undergo 1,3-rearrangement, thereby providing good support for this suggestion; for leading references, see: Padwa, A.; Craig, S. P.; Chiacchio, U.; Kline, D. N. *J. Org. Chem.* **1988**, *53*, 2232.
(15) The stereochemistry of the Diels–Alder cycloadduct **7** has been previously assigned.[2]
(16) Thyagarajan, B. S.; Majundar, K. C.; Bates, D. K. *J. Heterocycl. Chem.* **1975**, *12*, 59. Thyagarajan, B. S.; Wood, B. F.; Glowienka, J. A.; Delgado, P. *Phosphorus Sulfur* **1985**, *25*, 1.

afforded disulfone **14** in 92% yield. Reaction of **14** with mesyl chloride in the presence of triethylamine gave 1-phenyl-2,3-bis(phenylsulfonyl)-1,3-butadiene (**15**) in 95% yield. The simplicity of this procedure for preparing 1-substituted 2,3-bis(phenylsulfonyl)butadienes has obvious synthetic potential, and we are further examining the range of aldehydes that can be used with this method.[18]



In summary, phenylsulfonyl-substituted 1,3-dienes can readily be prepared by the eliminative route shown in Scheme I. These activated dienes are versatile synthetic reagents that can be used as substrates for Michael-type additions as well as in cycloaddition chemistry. The generalization of these findings and the use of these dienes for the synthesis of various heterocyclic compounds are the objects of ongoing investigations.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390 and General Electric QE 300 spectrometer. ^{13}C NMR spectra were recorded on a GE QE 300 spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Preparation and Cycloaddition Reaction of 2-(Phenylsulfonyl)-1,3-butadiene (5). A solution containing 0.4 mL of diisopropylamine in 10 mL of tetrahydrofuran was treated with 1.7 mL of a 1.67 M *n*-butyllithium solution at 0 °C. After stirring for 15 min, the solution was cooled to −78 °C and 0.5 g of 1-(phenylsulfonyl)-1-propyne in 3 mL of tetrahydrofuran was added dropwise to the solution. The solution was stirred for 15 min and then cannulated into a solution containing 0.5 mL of iodomethane in 1 mL of tetrahydrofuran at −78 °C. The mixture was allowed to warm to −20 °C and was quenched with a saturated solution of ammonium chloride. The two layers were separated, and the aqueous layer was extracted with 10 mL of ether. The combined extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography using a hexane–ethyl acetate mixture as the eluent to give 0.45 g (83%) of 3-(phenylsulfonyl)-1,2-butadiene (**2**)[12] as a clear oil: IR (neat) 3060, 2985, 2920, 1960, 1940, 1590, 1450, 1320, 1310, 1150, 730, and 695 cm^{-1}; ^1H NMR (CCl_4, 90 MHz) δ 1.85 (t, 2 H, J = 3.0 Hz), 5.20 (q, 2 H, J = 3.0 Hz), 7.50–7.60 (m, 3 H), and 7.70–7.90 (m, 2 H).

A solution containing 1.0 g of **2**, 2.54 g of benzenesulfinic acid sodium salt, and 0.32 mL of glacial acetic acid in 10 mL of tetrahydrofuran was heated at reflux for 12 h. The solution was cooled to room temperature and filtered through a Celite pad. The organic solution was washed with brine and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave 1.47 g (85%) of a white solid, mp 137–138 °C, which was identified as (*E*)-1,2-bis(phenylsulfonyl)-2-butene (**4**) on the basis of its spectral properties: IR (CCl_4) 3080, 3015, 2940, 1645, 1600, 1450, 1320, 1150, 1080, and 870 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.97 (d, 3 H, J = 7.2 Hz), 4.21 (s, 2 H), 7.37 (q, 1 H, J = 7.2 Hz), 7.49–7.69 (m, 6 H), and 7.77–7.82 (m, 4 H). Anal. Calcd for $C_{16}H_{16}O_4S$: C, 57.12; H, 4.79. Found: C, 56.90; H, 4.80.

To a stirred solution containing 100 mg of **4** and 0.50 mL of 1-morpholino-1-cyclohexene (**6**) in 6 mL of benzene under a nitrogen atmosphere was added 54 μL of DBU via syringe. The reaction mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. The crude residue was subjected to silica gel chromatography using a 30% ethyl acetate–hexane mixture as the eluent. The major fraction contained 94 mg of a clear oil (80%), whose spectral characteristics were identical with those of a known sample of 4-[1,3,4,5,8,8a-hexahydro-7-(phenylsulfonyl)-4a(2*H*)-naphthalenyl]morpholine (**7**):[2] IR (neat) 3060, 2940, 2870, 1450, 1310, 1160, and 1095 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.10–1.42 (m, 4 H), 1.45–1.77 (m, 4 H), 1.87–2.38 (m, 5 H), 2.42 (br s, 4 H), 3.49 (br s, 4 H), 6.91 (br s, 1 H), 7.42–7.62 (m, 3 H), and 7.80–7.90 (m, 2 H).

Generation and Diels–Alder Cycloaddition of 1,3-Bis(phenylsulfonyl)-1,3-butadiene (10). A solution containing 0.62 mL of thiophenol and 0.21 mL of triethylamine in 20 mL of benzene was added to a vigorously stirred solution containing 2.0 g of 1,4-bis(phenylsulfonyl)-2-butyne[16] in 60 mL of benzene. The mixture was stirred under nitrogen for 2 h at 25 °C, then diluted with 100 mL of benzene, washed with water, and dried over sodium sulfate. Concentration of the solution under reduced pressure left a white solid, which was crystallized from methylene chloride–ether to give 1.95 g (73%) of 1,4-bis(phenylsulfonyl)-2-(phenylthio)-2-butene (**8**):[16] mp 144–145 °C; IR (KBr) 3060, 2970, 2935, 1620, 1585, 1475, 1445, 1425, 1315, 1300, 1245, 1190, 1145, 1135, 1085, 990, 755, 735, and 690 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.87 (s, 2 H), 4.04 (d, 2 H, J = 8.2 Hz), 5.63 (t, 1 H, J = 8.2 Hz), 7.05–7.15 (m, 2 H), 7.25–7.40 (m, 3 H), 7.52–7.63 (m, 4 H), 7.64–7.75 (m, 2 H), and 7.78–7.92 (m, 4 H). Anal. Calcd for $C_{22}H_{20}O_4S_3$: C, 59.44; H, 4.53. Found: C, 59.33; H, 4.53.

To a solution containing 0.80 g of the above compound in 10 mL of glacial acetic acid was added 0.62 mL of a 30% hydrogen peroxide solution. The mixture was heated at 90 °C for 1.5 h, diluted with water, and allowed to crystallize on cooling. The residue obtained was recrystallized from chloroform–ether to give 0.65 g (76%) of a white solid, whose structure was assigned as 1,2,4-tris(phenylsulfonyl)-2-butene (**9**): mp 124–125 °C; IR (KBr) 3070, 2990, 2940, 1645, 1585, 1480, 1445, 1320, 1305, 1240, 1215, 1145, 1080, 995, 750, 725, and 685 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 4.00 (s, 2 H), 4.39 (d, 2 H, J = 8.1 Hz), 7.16 (t, 1 H, J = 8.1 Hz), and 7.45–7.90 (m, 15 H). Anal. Calcd for $C_{22}H_{20}O_6S_3$: C, 55.45; H, 4.23. Found: C, 55.44; H, 4.27.

To a solution containing 85 mg of **9** and 0.02 mL of *N*,*N*-dimethylthioformamide in 7 mL of benzene was added 1 equiv of triethylamine in 1 mL of benzene. The solution was heated at reflux under nitrogen for 20 h. The reaction mixture was filtered through a pad of silica gel followed by removal of the solvent to leave behind an orange oil. Purification of the oil by silica gel chromatography using an ethyl acetate–hexane (30:70) mixture as the eluent afforded 53 mg (78%) of 3,5-bis(phenylsulfonyl)-2*H*-thiopyran (**11**): mp 187–188 °C; IR (KBr) 3060, 1620, 1585, 1530, 1450, 1320, 1155, 1090, 790, 755, and 695 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.50 (s, 2 H), 7.32 (s, 1 H), 7.50–7.70 (m, 6 H), and 7.78–7.98 (m, 5 H). Anal. Calcd for $C_{16}H_{14}O_4S_3$: C, 53.95; H, 3.73. Found: C, 53.81; H, 3.76.

To a solution containing 100 mg of **9** and 0.02 mL of *N*-benzylidenemethylamine in 7 mL of benzene was added 1 equiv of triethylamine in 1 mL of benzene. The solution was stirred at room temperature under nitrogen for 6 h. The reaction mixture was filtered through a pad of silica gel followed by removal of the solvent to leave behind an orange oil. Purification of the oil by silica gel chromatography using an ethyl acetate–hexane (30:70) mixture as the eluent afforded 3,5-bis(phenylsulfonyl)-1-methyl-2-phenyl-1,2,5,6-tetrahydropyridine (**12**) in 81% yield: mp 172–173 °C; IR (KBr) 3105, 3000, 2890, 2810, 1590, 1475, 1450, 1325, 1310, 1210, 1150, 1090, 1060, 950, 770, 730, 700, and 625 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.18 (s, 3 H), 2.86 (dd, 1 H, J = 13.3 and 6.1 Hz), 3.00 (dd, 1 H, J = 13.3 and 8.1 Hz), 4.29 (m, 1 H),

(17) Bury, A.; Joag, S. D.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1986**, 124. The stereochemical assignment of compound **13** is based on NOE experiments.

(18) The Diels–Alder cycloaddition chemistry of several alkyl and aryl 1,3- and 2,3-substituted bis(phenylsulfonyl)butadienes will be reported on at a later date.

4.48 (s, 1 H), 6.32 (d, 2 H, J = 7.5 Hz), 6.83 (t, 2 H, J = 7.5 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 7.42 (t, 1 H, J = 7.6 Hz), 7.48 (d, 1 H, J = 3.4 Hz), 7.61 (t, 2 H, J = 7.5 Hz), 7.78 (t, 1 H, J = 7.5 Hz), and 7.95 (d, 2 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 41.8, 44.8, 60.7, 63.3, 127.7, 127.8, 128.5, 129.4, 129.5, 130.1, 132.9, 134.2, 134.4, 137.0, 139.3, and 147.5. Anal. Calcd for $C_{24}H_{23}NO_4S_2$: C, 63.55; H, 5.11; N, 3.09. Found: C, 63.52; H, 5.16; N, 3.06.

Preparation of 1-Phenyl-2,3-bis(phenylsulfonyl)-1,3-butadiene (15). To a stirred solution containing (*Z*)-1-phenyl-2-(phenylsulfonyl)-3-(phenylthio)-2-buten-1-ol (**13**)[17] in 20 mL of dichloromethane at −78 °C was added 1.84 g of MCPBA (65%). The mixture was stirred for 15 min at −78 °C and then allowed to warm to room temperature, after which stirring was continued for an additional 5 h. The reaction mixture was poured into a separatory funnel containing a 10% aqueous sodium sulfite solution. The aqueous layer was extracted twice with dichloromethane, and the combined organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure to give a white solid, which was recrystallized from methanol–ether to give (*Z*)-1-phenyl-2,3-bis(phenylsulfonyl)-2-buten-1-ol (**14**) as a white crystalline solid in 92% yield, mp 191–192 °C, which exhibits the following spectroscopic characteristics: IR (KBr) 3480, 3060, 1440, 1290, 1140, 1070, 930, 760, 730, 690, 570, and 630 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 2.04 (s, 3 H), 4.07 (d, 1 H, J = 9.6 Hz), and 7.20–8.00 (m, 15 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.7, 70.4, 124.9, 127.1, 127.3, 127.5, 128.1, 128.9, 129.2, 133.6, 134.1, 139.4, 140.8, 141.2, 151.5, and 151.9. Anal. Calcd for $C_{22}H_{20}S_2O_5$: C, 61.66; H, 4.70. Found: C, 61.59; H, 4.73.

To a solution containing 0.2 g of 1-phenyl-2,3-bis(phenylsulfonyl)-2-buten-1-ol (**14**) and 0.1 mL of triethylamine in 5 mL of dichloromethane at 0 °C was added 0.04 mL of mesyl chloride. The reaction mixture was allowed to warm to room temperature and was stirred for an additional 4 h, after which it was poured into cold water. The aqueous layer was extracted with methylene chloride. The organic portion was washed consecutively with a 10% hydrochloric acid solution, a saturated sodium bicarbonate solution, and brine, then dried, and concentrated under reduced pressure to give a 95% yield of 1-phenyl-2,3-bis(phenylsulfonyl)-1,3-butadiene (**15**). Crystallization of the oil from chloroform–hexane gave a white solid, mp 104–105 °C, which exhibits the following spectroscopic properties: IR (KBr) 3060, 1630, 1590, 1580, 1440, 1310, 1160, 1140, 1080, 970, 740, 680, and 520 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 1 H), 6.74 (s, 1 H), and 7.20–8.10 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.0, 128.1, 128.3, 128.4, 128.5, 129.8, 130.5, 131.6, 132.2, 133.1, 133.1, 134.1, 137.5, 138.5, 143.5, and 144.3. Anal. Calcd for $C_{22}H_{18}S_2O_4$: C, 64.37; H, 4.42. Found: C, 64.28; H, 4.45.

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Synthesis of β-Amino-α-hydroxy Acids via Aldol Condensation of a Chiral Glycolate Enolate. Synthesis of (-)-Bestatin

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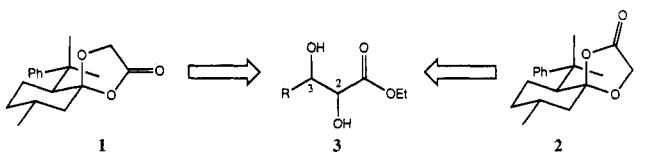
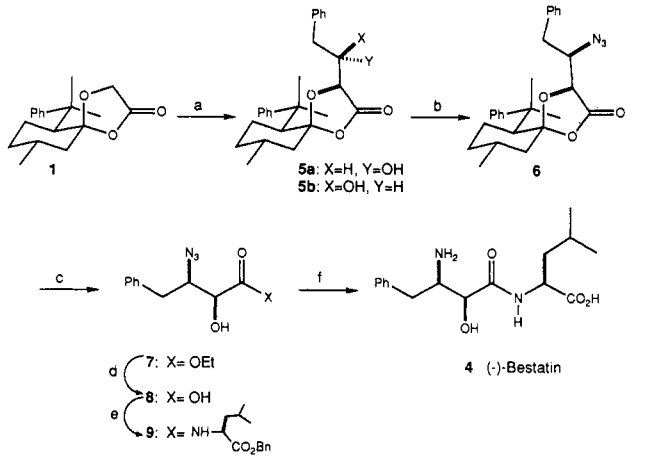
We have recently reported that the enolates of the spirocyclic 1,3-dioxolan-4-ones **1** and **2** undergo aldol condensations with aldehydes to afford, after acidic ethanolysis, α,β-dihydroxy esters **3** (Scheme I).[1] These dioxolanones are derived from 8-phenylmenthone and glycolic acid.[2] A key feature of this method is that any one of the four possible stereoisomers of **3** may be selectively prepared. Hence, the absolute stereochemistry at C-2 is completely controlled by selecting the appropriate dioxolanone **1** or **2**, and moderate to good relative stereocontrol at C-3 is governed by the choice of enolate counterion: Li^+ or Mg^{2+} gives the anti aldol, Zr^{4+} gives the syn aldol. The aldol adducts **3** are potentially useful intermediates for the synthesis of interesting biological substances. Herein, we wish to report an application of this chemistry to the synthesis of (-)-bestatin **4**.

Scheme I



Scheme II[a]



[a] [a] (i) LiHMDS, THF, −78 °C; (ii) phenyl acetaldehyde (56%, 5.7:1, **5a:5b**); [b] Ph_3P, DEAD, DPPA, THF, 0 °C to room temperature, 48 h (79%); [c] EtOH, HCl, reflux, 12 h (59%, 71% based on reacted starting material); [d] (i) LiOH, THF, H_2O, 0 °C, 1 h; (ii) HCl(aq) (91%); [e] L-leucine benzyl ester ·TsOH, HOBT, DCC, THF, 0 °C to room temperature, 16 h (68%); [f] H_2, Pd/C, MeOH, 48 h (86%).

Compounds such as bestatin[3] and amastatin[4] are examples of biologically important compounds with novel β-amino-α-hydroxy acid subunits. Bestatin is a potent aminopeptidase B inhibitor isolated from *Streptomyces*.[3,5] Clinical studies have shown its usefulness in the treatment of cancer through its ability to enhance the cytotoxic activity of known antitumor agents.[6] Since its discovery there has been continual interest in examining bestatin and analogues for biological activity.[7] Previous syntheses of the key subunit (2*S*,3*R*)-3-amino-2-hydroxy-4-phenyl-

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