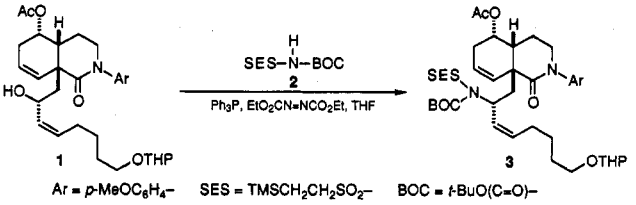
tert-Butyl [[2-(Trimethylsilyl)ethyl]sulfonyl]carbamate: A New Reagent for Use in Mitsunobu Reactions

Jeffrey A. Campbell and David J. Hart*

Department of Chemistry, The Ohio State University, 120 W. 18th Avenue, Columbus, Ohio 43210

Received January 5, 1993

As part of an approach to the manzamine family of alkaloids, we needed to convert alcohol **1** into a protected primary amine that could serve as a precursor to either a carbamate or a sulfonamide that could be easily deblocked.[1] On the basis of the studies reported by Weinreb, it appeared that a Mitsunobu reaction using *N*-acyl sulfonamide **2** might accomplish this objective.[2-4] In fact, treatment of **1** with **2** gave **3** (86%) which was used to

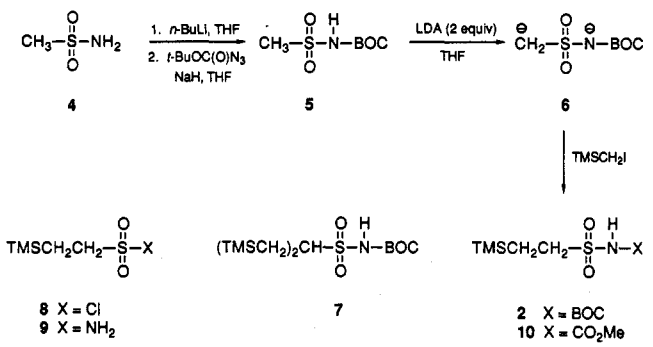


prepare a tetracyclic substructure of manzamine A.[1] This note describes the synthesis of *N*-acyl sulfonamide **2**, presents additional examples of its use in Mitsunobu reactions, and provides conditions for removal of either the 2-[(trimethylsilyl)ethyl]sulfonyl (SES) or *tert*-butoxycarbonyl (BOC) protecting groups.[5,6]

The procedure used to prepare **2** is outlined in Scheme I. Treatment of methanesulfonamide (**4**) with *n*-butyllithium in tetrahydrofuran, followed by acylation of the resulting anion with *tert*-butyl azidoformate in the presence of NaH and TMEDA, gave sulfonamide **5** in 81% yield. Conversion of **5** to dianion **6** was accomplished with 2 equiv of LDA, and addition of **6** to (iodomethyl)-trimethylsilane gave *N*-acyl sulfonamide **2** in 76% yield.[7]

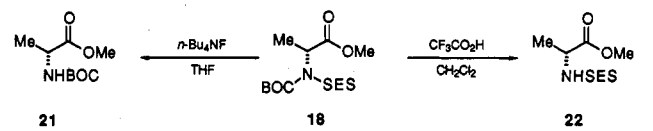
Two aspects of this sequence are notable. Addition of (iodomethyl)trimethylsilane to **6** gave **7** (12%) in addition to **2** (64%). Thus, dianion **6** and the monoanion of **2** appear to react at a rate fast enough to cause problems when the concentration of alkylating agent is low.[8] It is also notable that **5** is a new source of a sulfonamide-derived dianion.[9,10]

Scheme I



An alternate route to **2** was also developed. Thus, deprotonation of the known sulfonamide **9** with methyllithium, followed by acylation with *tert*-butyl azidoformate in the presence of sodium hydride, gave **2** in 86–88% yield.[11] Similar acylation of **9** using methyl chloroformate afforded *N*-acyl sulfonamide **10** in 83% yield (99% based on converted **9**). Although both procedures are satisfactory, we prefer the sulfonamide alkylation route (**4** → **5** → **2**) because of its brevity and higher overall yields.

Treatment of a variety of alcohols with 2 to 3 equiv of **2** under Mitsunobu conditions gave the expected *N*-acyl sulfonamides in excellent yields as shown in Table I.[12] Entries 4 and 5 are particularly notable. To establish that the conversion of **17** to **18** (entry 4) had occured with inversion of configuration and that removal of the SES group could be accomplished without racemization, **18** was converted to known D-alanine derivative **21** in 94% yield



using tetra-*n*-butylammonium fluoride.[13] On the other hand, treatment of **18** with trifluoroacetic acid selectively removed the BOC group to afford **22** in 96% yield.[14] Thus, removal of either the carbamate or sulfonamide protecting groups is possible under mild conditions. The conversion of **19** to **20** (entry 5) was performed on a 7:3 mixture of diastereomers at the carbinol center with the major diastereomer as depicted in Table I. This reaction proceeded with net retention of configuration due to neighboring group participation of the proximal tertiary amide.[1,15] Finally, we note that selective deprotection conditions also succeeded with allylic *N*-acyl sulfonamide **3**. For example, treatment of **3** with a mixture of (trichloro)methylsilane and sodium iodide in acetonitrile

(1) Campbell, J. A.; Hart, D. J. *Tetrahedron Lett.* **1992**, *33*, 6247. The conversion of **1** to **3** proceeds with net retention of configuration as described in this paper.

(2) Weinreb has shown that the 2-[(trimethylsilyl)ethyl]sulfonyl group (SES) is an easily removable amine blocking group, and that *N*-acyl sulfonamides (TsNHBOC) work well in Mitsunobu reactions.[3,4]

(3) Weinreb, S. M.; Demko, D. M.; Lessen, T. A.; Demers, J. P. *Tetrahedron Lett.* **1986**, *27*, 2099.

(4) Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D. Jr.; Weinreb, S. M. *Tetrahedron Lett.* **1989**, *30*, 5709.

(5) For reviews see Mitsunobu, O. *Synthesis* **1981**, 1. Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1991**, *24*, 285.

(6) For other nitrogen nucleophiles see Arnould, J. C.; Landier, F.; Pasquet, M. J. *Tetrahedron Lett.* **1992**, *33*, 7133 and references cited therein.

(7) Dianion **6** has not been characterized and its intermediacy is only inferred from the results.

(8) Controlled generation and alkylation of the dianion of **2** and other reactions of dianion **6** are under investigation.

(9) For the dianion of an *N*-alkyl sulfonamide see Szymonifka, M. J.; Heck, J. V. *Tetrahedron Lett.* **1989**, *30*, 2873.

(10) For the dianion of an *N*-alkylidene sulfonamide see Davis, F. A.; Weismiller, M. C.; Lal, G. S.; Chen, B. C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, *30*, 1613.

(11) For **9** see Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 3475. Our overall yield of **9** from starting from vinyltrimethylsilane via sulfonyl chloride **8**[3] was 31%.

(12) The yield of **18** was 80% when 1.5 equiv of **2** was used (entry 4).

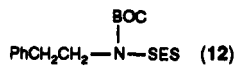
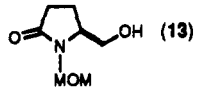
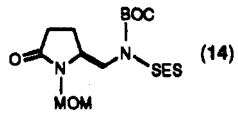
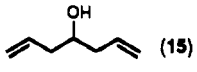
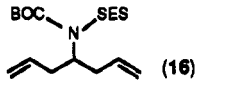
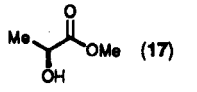
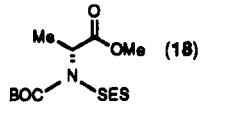
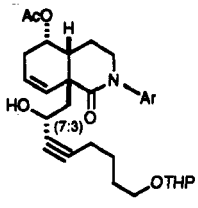
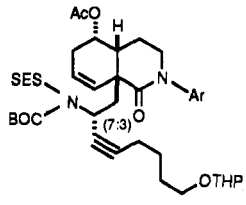
(13) Keglevic, D.; Kornhauser, A.; Valentekovic, S. *Carbohyd. Res.* **1972**, *22*, 245.

(14) Conversion of **18** to **22** was also accomplished using Me_3SiCl–NaI–CH_3CN in 82% yield (99% based on converted **18**): Olah, G. O.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(15) *N*-Acyl sulfonamide **10** was not studied extensively in Mitsunobu reactions, but it appears to behave much as *N*-acyl sulfonamide **2**. For example, treatment of **19** with **10** (2.5 equiv) gave the sulfonamide corresponding to **20** (BOC → MOC) in 96% yield.

0022-3263/93/1958-2900$04.00/0

Table I. Mitsunobu Reactions of 2

entry	alcohol	product	% yield
1		 (12)	100
2	 (13)	 (14)	90
3	 (15)	 (16)	79
4	 (17)	 (18)	100
5	 (19)	 (20)	92

removed both the BOC and THP groups in 86% yield.[16] Warming **3** in DMSO at 178 °C for 20 min also removed both the BOC and THP protecting groups in 77% yield. Alternatively, treatment of **3** with tetra-*n*-butylammonium fluoride in tetrahydrofuran, followed by *p*-toluenesulfonic acid in methanol–dichloromethane, sequentially removed the SES and THP groups in 96% overall yield.

In summary, an efficient synthesis of *tert*-butyl [[2-(trimethylsilyl)ethyl]sulfonyl]carbamate (**2**) has been developed using an *N*-acyl sulfonamide dianion alkylation and the use of this reagent in Mitsunobu reactions has been described.

Experimental Section

General. All melting points are uncorrected. ^{1}H-NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants in hertz, integration, interpretation). ^{13}C-NMR data are reported as follows: chemical shift (multiplicity determined by DEPT). All specific rotations were determined using the sodium D-line at ambient temperature. Solvents and reagents were dried and purified prior to use: THF, ether, and benzene were distilled from sodium metal; CH_2Cl_2 was distilled from CaH_2. Reactions requiring an inert atmosphere were run under argon. Column chromatography was performed using 70–230 mesh silica gel unless stated otherwise. Alcohols **11** and **17** were purchased and alcohols **13** and **15** were prepared from (*S*)-pyroglutamic acid and ethyl formate, respectively.

***tert*-Butyl (Methylsulfonyl)carbamate (5).** To a solution of 16 g (168 mmol) of methanesulfonamide (**4**) in 400 mL of THF at −55 °C was added 67.3 mL (168 mmol) of 2.5 M *n*-BuLi in hexanes over a 5–10-min period. The resulting white suspension was cooled to −78 °C and stirred for 30 min. To the white slurry was added 13.5 g (263 mmol) of 78% KH in oil followed by 46 mL (305 mmol) of TMEDA. The mixture was then slowly warmed to rt over 1 h. The slurry was cooled to −78 °C, 30.2 g (210 mmol) of *tert*-butyl azidoformate added over a 1–2-min period, and the mixture was slowly allowed to warm to rt over a 140-min period. The slurry was heated at 45–50 °C for 17 h and then the majority of the excess KH was quenched by carefully adding 10 mL of *tert*-butyl alcohol. The mixture was then cooled to 5 °C and an additional 20 mL of *tert*-butyl alcohol was added over a 10-min period. To the resulting yellow suspension was added 5 mL of water dropwise over a 15-min period, followed by an additional 15 mL of water over a 10-min period, and finally 80 mL of water in one portion. The orange emulsion was mixed with 200 mL of water. The THF layer was washed with three additional 200-mL portions of water. The combined water layers were cooled to 0 °C and acidified to pH 2–3 using concentrated HCl. The aqueous layer was extracted with four 300-mL portions of CH_2Cl_2. The combined organic extracts were washed with 200 mL of 3 N aqueous HCl, dried ($MgSO_4$), and concentrated in vacuo to afford 28.3 g of a light yellow solid. The solid was diluted with 154 mL of ether–CH_2Cl_2–MeOH (68:8:1) and 80 mL of hexane was added immediately. The resulting slurry was refrigerated for 1.5 h and the resulting solid was collected and dried to give 22.3 g (68%) of **5** as a white crystalline solid. The mother liquor was repeatedly recrystallized in similar fashion (using charcoal) to afford an additional 4.17 g (13%) of sulfonamide **5** as clear colorless needles: mp 107.5–108 °C; IR (CH_2Cl_2) 3373, 3251, 1738 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.50 (s, 9 H, CH_3), 3.25 (s, 3 H, CH_3S), 7.35 (s, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 27.9 (q), 41.1 (q), 84.3 (s), 149.8 (s); mass spectrum (FAB) *m/z* (rel inten) 196.2 ($M^+ + 1$, 56), 137 (100). Anal. calcd for $C_6H_{13}NO_4S$: C, 36.91: H, 6.71. Found: C, 36.96, H, 6.68. On one occasion (72-mmol scale) a 60% oil dispersion of NaH was used in place of KH with no effect on the yield.

***tert*-Butyl [[2-(Trimethylsilyl)ethyl]sulfonyl]carbamate (2). From 5.** To a solution of 15.1 mL (108 mmol) of diisopropylamine in 100 mL of THF at −78 °C was added 42 mL (105 mmol) of a 2.5 M solution of *n*-BuLi in hexane over a 5-min period. The solution was stirred for 15 min and then a solution of 10.25 g (52.5 mmol) of **5** in 100 mL of THF was added over a 16-min period. The mixture was stirred for 6 min and then transferred by cannula into a solution of 8.4 mL (56.7 mmol) of (iodomethyl)trimethylsilane in 60 mL of THF at −78 °C over a 15-min period. The solution was stirred for 105 min and then allowed to warm to rt over a 105-min period. The mixture was poured into 500 mL of ice–water containing 130 mL of 2 M aqueous HCl. The aqueous solution was extracted with four 300-mL portions of CH_2Cl_2. The combined extracts were washed with 200 mL of saturated aqueous sodium bisulfite and 150 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 14.8 g of an off-white solid. The residue was dissolved in 390 mL of hexane–ether (9:1) and the solution was heated until the volume was approximately 330 mL. The solution was cooled to rt, seeded, and stored at 0 °C overnight. The resulting crystals were collected to give 10.9 g (74%) of **2** (mp 82–82.5 °C). The mother liquor was concentrated in vacuo and recrystallized in similar fashion to afford an additional 0.28 g (2%) of **2** (mp 82 °C): IR (CH_2Cl_2) 3375, 1745 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 0.99–1.06 (m, 2 H, CH_2Si), 1.49 (s, 9 H, $C(CH_3)_3$), 3.27–3.34 (m, 2 H, CH_2SO_2), 7.35 (s, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 10.2 (t), 27.9 (q), 49.4 (t), 84.1 (s), 149.9 (s); mass spectrum (FAB) *m/z* (relative intensity) 282 ($M^+ + 1$, 3), 73 (100). Anal. calcd for $C_{10}H_{23}NO_4SiS$: C, 42.68: H, 8.24. Found: C, 42.79, H, 8.27.

When (iodomethyl)trimethylsilane was added to the dianion derived from **5**, dialkylation product **7** was also obtained and characterized as follows: mp 73.2–74.2 °C (from hexane–ether, 25:1); IR (CH_2Cl_2) 3376, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.10 (s, 18 H, CH_3Si), 0.98 (dd, J = 15.1, 7.6 Hz, 2 H, CHSi), 1.23 (dd, J = 15.1, 5.7 Hz, 2 H, CHSi), 1.49 (s, 9 H, CH_3), 3.77 (tt, J = 7.6, 5.7 Hz, 1 H, CHS), 7.07 (s, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −0.7 (q), 19.6 (t), 28.0 (q), 57.6 (d), 83.8 (s), 149.8 (s); mass spectrum (FAB) *m/z* (rel inten) 368.2 ($M^+ + 1$, 3), 187.2 (100). Anal. calcd for $C_{14}H_{33}NO_4Si_2S$: C, 45.74: H, 9.05. Found: C, 45.90, H, 9.20.

From 9. To a solution of 2.77 g (15.3 mmol) of 2-(trimethylsilyl)ethanesulfonamide (**9**) in 21 mL of THF cooled to −78 °C was added 11.4 mL (15.2 mmol) of a 1.33 M solution of MeLi in ether. The resulting white slurry was warmed to rt and 0.95 g (39.7 mmol) of NaH was added, followed by 3.6 mL (23.7 mmol)

(16) Olah, G. O.; Husaing, A.; Singh, B. P.; Mehotra, A. K. *J. Org. Chem.* 1983, *48*, 3667.

of TMEDA. The mixture was cooled to −78 °C, the resulting grey slurry was stirred for 5 min, 2.97 g (20.6 mmol) of *tert*-butyl azidoformate was added, and the mixture was slowly allowed to warm to rt overnight. The resulting yellow suspension was diluted with 20 mL of THF, cooled to 0 °C, and 5 mL of *tert*-butyl alcohol was added. The solution was stirred for 5 min, followed by careful dropwise addition of 5 mL of water. The solution was acidified to pH 1 using 6 N aqueous HCl and diluted with 50 mL of water. The solution was warmed to rt and extracted with three 100-mL portions of CH_2Cl_2. The combined extracts were washed with 100 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to give 4.24 g of a pale yellow solid. The solid was recrystallized from 52 mL of hexane–ether (9:2) to afford 3.30 g (77%) of sulfonamide **2** as white needles (mp 82–83 °C). An additional 0.47 g (11%) of **2** was obtained through recrystallization of the mother liquor in similar fashion (mp 81–83 °C).

Methyl [[2-(Trimethylsilyl)ethyl]sulfonyl]carbamate (10). To a solution of 1.00 g (5.5 mmol) of sulfonamide **9** in 8 mL of THF cooled to −78 °C was added 4.1 mL (5.7 mmol) of 1.4 M MeLi in ether. The resulting yellow slurry was warmed to rt, 0.34 g (14.2 mmol) of NaH was added, and the mixture was cooled to −78 °C. The grey slurry was stirred for 5 min, 636 mg (14.2 mmol) of methyl chloroformate was added, and the mixture was warmed to rt overnight. The resulting yellow suspension was cooled to 0 °C and 1–2 mL of MeOH was added. The solution was stirred for 5 min and 20 mL of water was carefully added dropwise. The solution was warmed to rt and extracted with five 45-mL portions of CH_2Cl_2. The combined extracts were washed with 80 mL of 1 M aqueous HCl and 50 mL of brine, dried ($MgSO_4$), and concentrated in vacuo. The residual yellow oil (1.39 g) was chromatographed over 50 g of activity grade II *basic* alumina and eluted sequentially with 500 mL of EtOAc–hexane (1:1) and 250 mL of EtOAc–hexane (35:65) to afford 162 mg (16%) of recovered 2-(trimethylsilyl)ethanesulfonamide (**9**). Further elution with AcOH–EtOAc–hexane (1:20:10) gave 1.22 g of crude **10**. This material was partitioned between 150 mL of EtOAc and 20 mL of 2 M aqueous HCl. The aqueous layer was extracted with two 75-mL portions of EtOAc. The combined organic layers were washed with 25 mL of brine, dried ($MgSO_4$), and concentrated in vacuo to afford 1.1 g (83%) of *N*-acyl sulfonamide **10** as a pale off-white waxy solid. A small portion was recrystallized from ether–hexane (1:1) to obtain an analytically pure sample: mp 75–75.8 °C; IR (crystal, microscope) 1724 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.05 (s, 9 H, $(CH_3)_3Si$), 1.0–1.07 (m, 2 H, CH_2Si), 3.30–3.37 (m, 2 H, CH_2SO_2), 3.80 (s, 3 H, OCH_3), 7.88 (s, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 9.9 (t), 49.7 (t), 53.7 (q), 151.7 (s); mass spectrum (FAB) *m/z* (rel inten) 240 (M^+ + 1, 17), 73 (100). Anal. calcd for $C_7H_{17}NO_4SiS$: C, 35.13: H, 7,16. Found: C, 35.23, H, 7.18.

***tert*-Butyl (±)-[(1*R**,2*Z*)-1-[[(4a*R**,5*S**,8a*R**)-2,3,4,4a,5,6-Hexahydro-5-hydroxy-2-(*p*-methoxyphenyl)-1-oxo-8a(1*H*)-isoquinolyl]methyl]-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-heptenyl][[2-(trimethylsilyl)ethyl]sulfonyl]carbamate, Acetate Ester (3).** To a solution of 1.89 g (6.71 mmol) of carbamate **2** and 1.78 g (6.77 mmol) of triphenylphosphine in 16 mL of THF was added dropwise 1.22 g (2.26 mmol) of alcohol **1**[1] in 28 mL of THF over a 5-min period. To the colorless mixture was added dropwise a solution of 0.89 mL (5.64 mmol) of neat DEAD over a 10-min period, and the resulting orange solution was stirred for an additional 4 h. The solution was concentrated in vacuo, and most of the triphenylphosphine oxide and diethyl hydrazinedicarboxylate was removed by repeated crystallization of the reaction mixture from 12 mL of hexane–EtOAc (3:1) at 0 °C. To separate the product from excess **2**, the residue was chromatographed over 400 g of activity grade II *basic* alumina and eluted with 1700 mL of hexane–EtOAc (78:22) to afford 1.66 g (91%) of slightly impure sulfonamide **3** as a colorless oil. This material was subjected to medium pressure chromatography over a Lobar size C column and eluted with hexane–EtOAc (79:21 → 70:30) to afford 1.55 g (86%) of desired acyl sulfonamide **3**: IR (CH_2Cl_2) 1730, 1641 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 9 H, $SiCH_3$), 0.97 (t, J = 9.2 Hz, 2 H, CH_2Si), 1.37–2.18 (m with s (*t*-Bu) and s ($COCH_3$) at δ 1.52 and 2.04, 27 H), 2.40 (dd, J = 14.8, 7.8 Hz, 1 H, CHCN(BOC)SES), 2.46–2.60 (m with dd (CHCN(BOC)SES), J = 15, 5.3 Hz at δ 2.5, 2 H), 2.73 (dt, J = 12.0, 3.0 Hz, 1 H, CH), 3.23–3.50 (m, 5 H), 3.67 (dt, J = 9.7, 6.6 Hz, 1 H, OCH or CHNAr), 3.77–3.93 (m with s ($ArOCH_3$) at δ 3.78, 5 H), 4.52 (t, J = 2.8 Hz, 1 H, OCHO), 5.17 (ddd, J = 10.2, 6.0, 3.9 Hz, 1 H, CHOAc), 5.18–5.29 (m, 1 H, =CHC*H*N), 5.44 (dt, J = 10.7, 7.3 Hz, 1 H, *H*C=CHCHN), 5.58 (dm, J = 10.0 Hz, 1 H, =C*H*CH_2), 5.65–5.77 (m, 2 H, HC=C*H*CHN, =CH), 6.88 (d, J = 8.9 Hz, 2 H, ArH), 7.21 (d, J = 8.9 Hz, 2 H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 10.0 (t), 19.6 (t, THP diastereomer 1), 19.6 (t, THP diastereomer 2), 20.5 (t), 21.2 (q), 25.5 (t), 26.1 (t), 26.8 (t), 27.5 (t), 28.0 (q), 29.4 (t), 30.7 (t), 36.8 (d), 40.7 (t), 50.4 (t), 50.9 (s), 51.1 (t), 53.1 (d), 55.3 (q), 62.2 (t, THP diastereomer 1), 62.2 (t, THP diastereomer 2), 67.3 (t), 69.0 (d), 84.5 (s), 98.7 (d, THP diastereomer 1), 98.8 (d, THP diastereomer 2), 114.1 (d), 122.8 (d), 127.4 (d), 128.4 (d), 132.6 (d), 133.2 (d), 137.0 (s), 151.6 (s), 157.9 (s), 170.0 (s), 171.5 (s); mass spectrum (FAB), *m/z* (rel inten) 804.48 (M^+, 0.12).

***tert*-Butyl Phenethyl[[2-(trimethylsilyl)ethyl]sulfonyl]carbamate (12).** To a solution of 800 mg (3.07 mmol) of triphenylphosphine, 576 mg (2.05 mmol) of carbamate **2**, and 125 mg (1.023 mmol) of 2-phenylethanol (**11**) in 10 mL of THF cooled to 0 °C was added dropwise 387 μL (2.46 mmol) of neat DEAD over a 5-min period. The solution was stirred for 5 min, concentrated in vacuo, chromatographed over 40 g of silica gel, and eluted sequentially with 760 mL of hexane and 420 mL of hexane–EtOAc (85:15) to afford 396 mg (100%) of sulfonamide **12** as a colorless oil: IR (CH_2Cl_2) 1721 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.39 (s, 9 H, CH_3Si), 0.90–0.96 (m, 2 H, CH_2Si), 1.52 (s, 9 H, CH_3), 2.96 (t, J = 7.7 Hz, 2 H, CH_2N), 3.21–3.27 (m, 2 H, CH_2S), 3.88 (t, J = 7.7 Hz, 2 H, CH_2Ar), 7.19–7.32 (m, 5 H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.0 (q), 10.2 (t), 28.0 (q), 36.4 (t), 48.0 (t), 50.7 (t), 84.1 (s), 126.6 (d), 128.5 (d), 129.1 (d), 138.2 (s), 151.5 (s); mass spectrum (FAB) *m/z* (rel inten) 387.3 (M^+ + 1, 2), 330.2 (100).

***tert*-Butyl [[(2*S*)-1-(Methoxymethyl)-5-oxo-2-pyrrolidinyl]methyl][[2-(trimethylsilyl)ethyl]sulfonyl]carbamate (14).** To a solution of 1.04 g (3.96 mmol) of triphenylphosphine, 746 mg (2.65 mmol) of carbamate **2**, and 211 mg (1.32 mmol) of (*S*)-(+)-*N*-(methoxymethyl)-5-(hydroxymethyl)-2-pyrrolidinone (**13**) in 13 mL of THF cooled to 0 °C was added dropwise 500 μL (2.46 mmol) of neat DEAD over a 5-min period. The solution was stirred for 10 min and concentrated in vacuo. The majority of the triphenylphosphine oxide and diethyl hydrazinedicarboxylate was removed by repeated crystallization of the reaction mixture from 9 mL of hexane–EtOAc (8:2) cooled to 0 °C over a 24-h period. The mother liquor was concentrated in vacuo and the residue subjected to medium pressure chromatography, eluting with hexane–EtOAc (7:3) followed by hexane–EtOAc (6:4), to afford 546 mg (90%) of sulfonamide **14** as a pale yellow oil contaminated with diethyl hydrazinedicarboxylate (6 mol% by ^1H NMR): IR (CH_2Cl_2) 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.14 (s, 9 H, CH_3Si), 0.81–1.10 (m, 2 H, CH_2Si), 1.50 (s, 9 H, CH_3) 1.97–2.10 (m, 2 H), 2.30 (ddd, J = 17.2, 7.5, 5.0 Hz, 1 H, CHCO), 2.50 (dt, J = 17.2, 9.0 Hz, 1 H, CHCO), 3.25 (s, 3 H, OCH_3), 3.23–3.47 (m, 2 H, CH_2S), 3.68 (dd, J = 14, 8.9 Hz, 1 H, CHN(SES)BOC), 3.88 (dd, J = 14, 3.9 Hz, 1 H, CHN(SES)BOC), 3.88–3.97 (m, 1 H, NCH), 4.65 (d, J = 10.5 Hz, 1 H, NCHO), 4.71 (d, J = 10.5 Hz, 1 H, NCHO); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −2.3 (q), 10.1 (t), 22.1 (t), 27.6 (t), 29.2 (t), 48.1 (t), 50.4 (t), 55.7 (q), 56.9 (d), 72.9 (t), 84.6 (s), 151.3 (s), 175.9 (s); exact mass calcd for $C_{17}H_{34}N_2O_6SiS$ *m/z* 422.1907, found *m/z* 422.1849.

***tert*-Butyl (1-Allyl-3-butenyl)[[2-(trimethylsilyl)ethyl]sulfonyl]carbamate (16).** To a solution of 793 mg (3.0 mmol) of triphenylphosphine, 567 mg (2.0 mmol) of carbamate **2**, and 113 mg (1.0 mmol) of diallylcarbinol (**15**) in 10 mL of THF cooled to 0 °C was added 381 μL (2.42 mmol) of neat DEAD dropwise over a 5-min period. The solution was stirred for 30 min, concentrated in vacuo, and chromatographed over 40 g of silica gel, eluting sequentially with 860 mL of hexane and 280 mL of hexane-EtOAc (9:1), to afford 298 mg (79%) of sulfonamide **16** as a colorless oil: IR (CH_2Cl_2) 1719 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 9 H, CH_3Si), 0.90–1.07 (m, 2 H, CH_2Si), 1.51 (s, 9 H, CH_3), 2.42 (dt, J = 14.1, 6.4 Hz, 2 H, =CCH), 2.66 (dt, J = 14.1, 8.8 Hz, 2 H, =CCH), 3.31–3.39 (m, 2 H, CH_2S), 4.25 (m, 1 H, CHN), 5.03–5.11 (m, 4 H, $=CH_2$), 5.67–5.84 (m, 2 H, =CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 10.1 (t), 28.0 (q), 37.7 (t),

51.4 (t), 58.1 (d), 83.9 (s), 117.6 (t), 135.2 (d), 151.1 (s); mass spectrum (FAB), *m/z* (rel inten) 376.2 ($M^+ + 1$, 8), 320.2 (100).

***N*-(*tert*-Butoxycarbonyl)-*N*-[[2-(trimethylsilyl)ethyl]sulfonyl]-D-alanine, Methyl Ester (18).** To a solution of 826 mg (3.15 mmol) of triphenylphosphine, 590 mg (2.10 mmol) of carbamate, **2**, and 114.5 mg (1.05 mmol) of (*S*)-methyl lactate (**17**) in 10 mL of THF cooled to 0 °C was added dropwise 397 μL (2.52 mmol) of neat DEAD over a 5-min period. The solution was stirred for 30 min, concentrated in vacuo, and chromatographed over 40 g of silica gel, eluting sequentially with 760 mL of hexane and 560 mL of hexane–EtOAc (9:1), to give 388 mg (100%) of sulfonamide **18** as a colorless oil: $[\alpha] = 46.6°$ ($c = 2.93$, MeOH); IR (CH_2Cl_2) 1748, 1731 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.06 (s, 9 H, CH_3Si), 0.94–1.26 (m, 2 H, CH_2Si), 1.48 (s, 9 H, CH_3), 1.60 (d, $J = 7$ Hz, 3 H, CH_3), 3.37–3.80 (m, 2 H, CH_2S), 3.73 (s, 3 H, OCH_3), 4.88 (q, $J = 7$ Hz, 1 H, CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 9.9 (t), 17.1 (q), 27.9 (q), 50.8 (t), 52.4 (q), 54.6 (d), 84.9 (s), 150.7 (s), 170.8 (s); mass spectrum (FAB) *m/z* (rel inten) 368.2 ($M^+ + 1$, 15), 312.2 (100).

Methyl (±)-[(1*R)-1-[[(4a*R**,5*S**,8a*R**)-2,3,4,4a,5,6-Hexahydro-5-acetoxy-2-(*p*-methoxyphenyl)-1-oxo-8a(1*H*)-isoquinolyl]methyl]-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-heptynyl][[2-trimethylsilyl)ethyl]sulfonyl]carbamate (20) and Methyl (±)-[(1*S**)-1-[[(4a*R**,5*S**,8a*R**)-2,3,4,4a,5,6-Hexahydro-5-acetoxy-2-(*p*-methoxyphenyl)-1-oxo-8a(1*H*)-isoquinolyl]methyl]-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2-heptynyl][[2-trimethylsilyl)ethyl]sulfonyl]carbamate (1-*epi*-20).** To a solution of 654 mg (2.73 mmol) of sulfonamide **2** and 860 mg (3.28 mmol) of triphenylphosphine in 12.9 mL of tetrahydrofuran was added dropwise a solution of 590 mg (1.09 mmol) of alcohol **19**[1] (2.5:1 mixture of diastereomers at C-1) in 11.1 mL of THF over a 5-min period. To the colorless mixture was added dropwise 0.43 mL (2.73 mmol) of neat DEAD over a 7-min period, and the resulting orange solution was stirred for an additional 3 h. The solution was concentrated in vacuo, and most of the triphenylphosphine oxide and diethyl hydrazinedicarboxylate was removed by repeated crystallization from 10 mL of EtOAc–hexane (1:1) at 0 °C. The residue was chromatographed over 180 g of activity grade II *basic* alumina, eluting with hexane–EtOAc (66:34), to afford a slightly impure mixture of sulfonamides **20** and 1-*epi*-**20** as a colorless oil. This residue was subjected to medium pressure chromatography over a Lobar size C column, eluting with hexane–EtOAc (4:1 → 3:2) to afford 516 mg (62%) of sulfonamide isomer **20**, 100 mg (12%) of a mixture of **20** and 1-*epi*-**20**, and 198 mg (24%) of 1-*epi*-**20**. Data for compound **20**: IR (CCl_4) 1732, 1639 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ −0.08 (s, 9 H, $SiCH_3$), 0.90–1.20 (m, 2 H, CH_2Si), 1.40–2.10 (m with s ($COCH_3$) at δ 2.03, 18 H), 2.38 (td, $J = 16.5, 5.8$, 1 H, =CHC*H*), 2.54 (dd, $J = 15.2, 3.8$ Hz, 1 H, C*H*CHN), 2.65 (dd, $J = 15.1, 9.5$ Hz, 1 H, C*H*CHN), 2.81 (dm, $J = 11.9$ Hz, 1 H, CH), 3.22–3.99 (m, 8 H, OCH_2, $THPOCH_2$, CH_2S, CH_2NAr), 3.77 (s, 3 H, $ArOCH_3$), 3.89 (s, 3 H, OCH_3), 4.52 (t, $J = 3.2$ Hz, 1 H, OCHO), 5.15–5.25 (m, 2 H ≡CHC*H*N, CHOAc), 5.57–5.70 (m, 2 H, =CH, =CH), 6.87 (d, $J = 8.9$ Hz, 2 H, ArH), 7.25 (d, $J = 8.9$ Hz, 2 H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 9.7 (t), 18.3 (t), 19.5 (t), 20.1 (t), 21.1 (q), 25.4 (t), 25.5 (t), 26.7 (t), 28.8 (t), 30.6 (t), 36.5 (d), 40.4 (t), 49.2 (d), 50.0 (t), 50.2 (t), 50.8 (s), 53.9 (q), 55.3 (q), 62.1 (t), 66.7 (t), 68.2 (d), 78.2 (s), 84.1 (s), 98.7 (d), 114.0 (d), 123.4 (d), 127.2 (d), 132.2 (d), 136.7 (s), 153.4 (s), 157.8 (s), 169.9 (s), 171.3 (s); exact mass calcd for $C_{38}H_{56}N_2O_{10}SiS$ *m/z* 760.3425, found *m/z* 760.3435. Data for compound 1-*epi*-**20**: IR (CH_2Cl_2) 1730, 1640 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ −0.05 (s, 9 H, $SiCH_3$), 0.83–1.09 (m, 2 H, CH_2Si), 1.45–2.32 (m, with s ($COCH_3$) at δ 2.03, 19 H), 2.53 (ddd, $J = 16.7, 6.2, 3.3$ Hz, 1 H, =CHC*H*), 2.81–2.91 (m, 2 H, C*H*CHN, CH), 3.23–3.52 (m, 5 H), 3.68–3.89 (m, 3 H), 3.79 (s, 3 H, $ArOCH_3$), 3.83 (s, 3 H, OCH_3), 4.57 (t, $J = 3.1$ Hz, 1 H, OCHO), 5.13 (m, 1 H, ≡CHC*H*N), 5.26 (ddd, $J = 10.2, 6.1, 3.8$ Hz, 1 H, CHOAc), 5.61–5.70 (m, 2 H, =CH, =CH), 6.88 (d, $J = 9.0$ Hz, 2 H, ArH), 7.21 (d, $J = 8.9$ Hz, 2 H, ArH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.2 (q), 9.4 (t), 18.5 (t), 19.6 (t), 20.2 (t), 21.2 (q), 25.4 (t), 25.4 (t), 26.9 (t), 28.9 (t), 30.7 (t), 36.8 (d), 43.1 (t), 46.7 (d), 50.6 (t), 50.8 (t), 50.9 (s), 53.8 (q), 55.3 (t), 62.3 (t), 66.8 (t), 68.2 (d), 78.7 (s), 84.2 (s), 98.8 (d), 114.3 (d), 123.5 (d), 127.8 (d), 131.6 (d), 136.6 (s), 153.0 (s), 158.1 (s), 170.08 (s), 171.10 (s); exact mass calcd for $C_{38}H_{56}N_2O_{10}SiS$ *m/z* 760.3425, found *m/e* 760.3414.

***N*-(*tert*-Butoxycarbonyl)-D-alanine, Methyl Ester (21).** To a solution of 92 mg (0.25 mmol) of **18** in 13.6 mL of THF was added 0.75 mL (0.75 mmol) of 1 M tetra-*n*-butylammonium fluoride in THF. The colorless solution was stirred to 10 min and was diluted with 80 mL of ether. The organic layer was washed with four 15-mL portions of water and 30 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 11 g of silica gel, eluting with hexane–EtOAc (3:1), to afford 48 mg (94%) of carbamate **21** as a colorless oil: $[\alpha] = 41.4°$ ($c = 1.91$, MeOH), lit.[13] $[\alpha] = 41°$ (MeOH); IR (CH_2Cl_2) 3438, 1743, 1714 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.36 (d, $J = 7.2$ Hz, H, CH_3), 1.42 (s, 9 H, CH_3), 3.72 (s, 3 H, OCH_3), 4.29 (m, 1 H, CH), 5.05 (s, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 18.6 (q), 28.3 (q), 49.2 (d), 52.2 (q), 79.8 (s), 155.0 (s), 173.8 (s); mass spectrum (FAB), *m/z* (rel inten) 204.2 ($M^+ + 1$, 5.4), 136.1 (100).

***N*-[[2-(Trimethylsilyl)ethyl]sulfonyl]-D-alanine, Methyl Ester (22). Procedure A.** To a solution of 54.3 mg (0.148 mmol) of **18** in 2 mL of CH_2Cl_2 was added 68 μL (0.886 mmol) of TFA. The mixture was stirred for 22 h, an additional 100 μL (1.30 mmol) of TFA was added, and stirring was continued for 30 h. The mixture was dissolved in 50 mL of dichloromethane, washed with 20 mL of saturated aqueous sodium bicarbonate, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 10 g silica gel, eluting with hexane–EtOAc (4:1), to afford 37.8 mg (96%) of sulfonamide **22**. A portion was recrystallized from hexane–ether (20:1) to afford an analytical sample: $[\alpha] = 26.2°$ ($c = 0.89$, MeOH); mp 59–60 °C; IR (CH_2Cl_2) 3686, 3364, 2954, 1744, 1605, 1455, 1437, 1422, 1378 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.03 (s, 9 H, CH_3Si), 0.93–1.14 (m, 2 H, CH_2Si), 1.45 (d, $J = 7$ Hz, 3 H, CH_3), 2.86–2.98 (m, 2 H, CH_2S), 3.76 (s, 3 H, OCH_3), 4.17 (dq, $J = 8, 7$ Hz, 1 H, CH), 4.98 (d, $J = 8$ Hz, 1 H, NH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ −2.1 (q), 10.4 (t), 19.9 (q), 50.0 (t), 51.6 (d), 52.6 (q), 173.2 (s); mass spectrum (FAB), *m/z* (rel inten) 268.10 ($M^+ + 1$, 1.9), 267.11 (M^+, 0.2), 252.1 (100). Anal. calcd for $C_9H_{21}NO_4SiS$: C, 40.42: H, 7.92. Found: C, 40.53, H, 7.96. **Procedure B.** To a solution of 183.5 mg (0.5 mmol) of **18** and 150 mg (0.99 mmol) of sodium iodide in 8 mL of acetonitrile was added 127 μL (0.99 mmol) of chlorotrimethylsilane. The solution was stirred for 30 min, 10 mL of saturated aqueous sodium bicarbonate was added, and the aqueous solution was extracted with 50 mL of CH_2Cl_2. The organic layer was washed with 10 mL of saturated aqueous sodium bisulfite and 20 mL of brine and dried ($MgSO_4$). The solution was concentrated in vacuo and the residual yellow oil (146 mg) was chromatographed over 30 g of silica gel, eluting with hexane–EtOAc (7:3), to afford 35 mg (17%) of recovered **18** and 108 mg (82%) of **22** as a waxy off-white solid.

Acknowledgment. We thank the National Institutes of Health (GM-27647) for generous support and Dr. Kurt Loening for help with nomenclature.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all compounds (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.