Enantioselective Routes to Protected *syn*- and *anti*-β-Phenylcysteines[1]

M. Amparo Lago,*,† James Samanen,‡ and John D. Elliott†

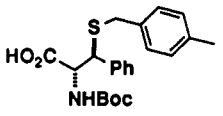
Departments of Medicinal Chemistry and Peptidomimetic Research, SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, Swedeland, Pennsylvania 19479

Received December 17, 1991

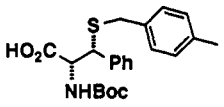
Introduction

Conformational constraint provides a useful approach to enhance receptor affinity for flexible peptides and is often used for the investigation of peptide–receptor interactions.[2] A common way to introduce that restriction is via disulfide bridge cyclization, generally accomplished by replacing two amino acids by two cysteinyl residues. This process, however, removes the respective side chains, which may in themselves be important for receptor affinity. These side chains could be preserved by introducing the corresponding 3-substituted cysteines into the sequence.[3] Asymmetric synthesis of the appropriately substituted cysteines is therefore an important goal.

In this note, we report the enantiospecific syntheses of suitably protected derivatives of *anti*- and *syn*-β-phenylcysteines **1** and **2** via the stereoselective aldol condensation of the appropriate glycine enolate synthon with benzaldehyde followed by the bimolecular displacement of the corresponding mesylate with a sulfur nucleophile.[4]



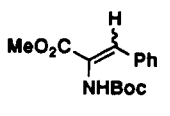
1



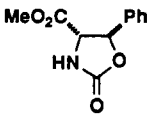
2

Results and Discussion

The syntheses of the *syn*- and *anti*-phenylserines **6** and **14** were based directly on Evans methodology[5] as shown in Schemes I and II, respectively. Thus, the stannous triflate-mediated asymmetric aldol addition reaction of *N*-(isothiocyanoacetyl)oxazolidinone **3** with benzaldehyde was highly stereoselective, providing **4** exclusively. Straightforward manipulations of **4** led to its transformation into *syn*-phenylserine **6** (Scheme I). The next step involved the S_N2 displacement of the corresponding benzylic mesylate **7** with the DBU salt of thiolacetic acid in the presence of excess thiolacetic acid to produce the acetylated thiol **8** in 87% yield together with a small amount (6%) of elimination product **9** (as a single geometrical isomer). The aforementioned conditions proved to be critical for the success of the displacement since the use of different thiolacetic acid salts (potassium, cesium[6]) or other sulfur nucleophiles (potassium ethyl xanthate,[7a] thiourea[7b]) produced mainly the elimination product **9**. Treatment of **8** with 5 equiv of NaOH in the presence of *p*-methylbenzyl bromide accomplished, in one step, removal of the acetyl group, protection of the thiol as the *p*-methylbenzyl thioether, and hydrolysis of the methyl ester to produce acid **1** in 81% yield.[8]



9



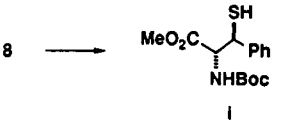
10

In the case of the *anti*-phenylserine **14** (Scheme II), the dibutylboron triflate-mediated aldol reaction of *N*-(bromoacetyl)oxazolidinone **11** with benzaldehyde proceeded in 65% yield with 97% diastereoselectivity. The lower yield in this process is due to partial formation of an unreactive *E*-enolate during the enolization process.[5b] Standard transformations yielded the azide **13** that was converted in one step to the *N*-Boc-protected β-phenylserine **14**.[9] S_N2 displacement of the corresponding mesylate **15** was carried out in this case with the potassium salt of thiolacetic acid (3.5 equiv, 1 M solution in DMF, 20 h at rt) to afford a 69% yield of the desired acetylated thiol **16** together with a minor amount of oxazolidinone **10** (12% yield).[10,11] Treatment of **16** with 3 equiv of NaOH in the presence of *p*-methylbenzyl bromide for 20 min produced the corresponding thiol-protected ester **17** in 91% yield. Deprotection of the methyl ester was carried out in this case with LiCl (DMF, 90 °C, 4 days in 77% yield) since saponification of **17** with base caused elimination.

Summary

We have developed enantioselective routes to both (2*R*,3*S*)- and (2*R*,3*R*)-3-phenylcysteine derivatives usefully protected for peptide synthesis via solid-phase metho-

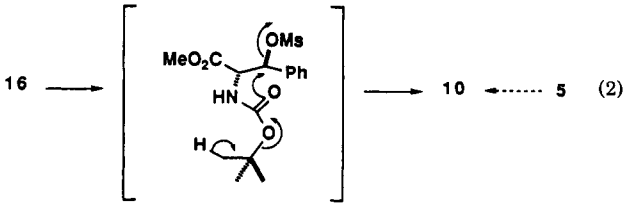
(1) Work presented as a poster at the Fourth Chemical Congress of North America, New York, NY, August 25–30, 1991.
(2) Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 512.
(3) Hruby, V. J. *Life Sciences* **1982**, *31*, 189.
(4) While this work was in progress two other syntheses of β-phenylcysteine involving diastereomeric separation or the use of chiral HPLC appeared in the literature: (a) Ploux, O.; Caruso, M.; Chassaing, G.; Marquet, A. *J. Org. Chem.* **1989**, *53*, 3154. (b) Nagai, U., Pavone V. *Peptide Chemistry 1988* **1989**, 247.
(5) (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (b) Evans, D. A.; Sjogran, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39.
(6) Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664.
(7) (a) Beretta, E.; Cinquini, M.; Colonna, S.; Fornasier, R. *Synthesis* **1974**, 425. (b) Arcus, C. L.; Hallgarten, P. A. *J. Chem. Soc.* **1956**, 2987.
(8) Compound **8** was hydrolyzed with 1 equiv of NaOH, 30 min, to yield the free thiol **i** (mp 76–77 °C (ether–hexane); $[\alpha]^{20}_D$ = +92.30° (*c* = 0.96, $CHCl_3$)). The optical purity was verified to be >97% by ^1H NMR analysis using chiral shift reagent $Eu(hfc)_3$, when compared with the racemic thiol obtained from commercially available racemic *threo*-phenylserine using the same reaction sequence as described in Scheme I.



(1)

i

(9) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837.
(10) Compound **10** is the product of internal displacement of the corresponding unstable mesylate by the carbonyl oxygen in the Boc-protecting group and its structure has been proven by comparison with authentic sample obtained as a byproduct from the hydrolysis of **5** (Scheme I).



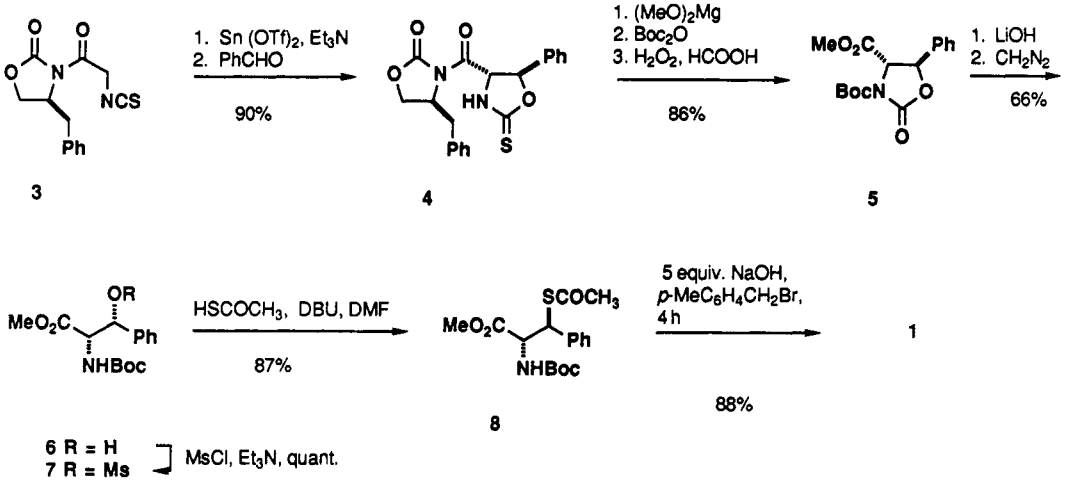
(2)

(11) Treatment of the mesylate **15** with the DBU salt of the thiolacetic acid under analogous conditions as the diastereomeric mesylate **7** also produced the desired compound **16** in 59% yield together with 19% of **10**.

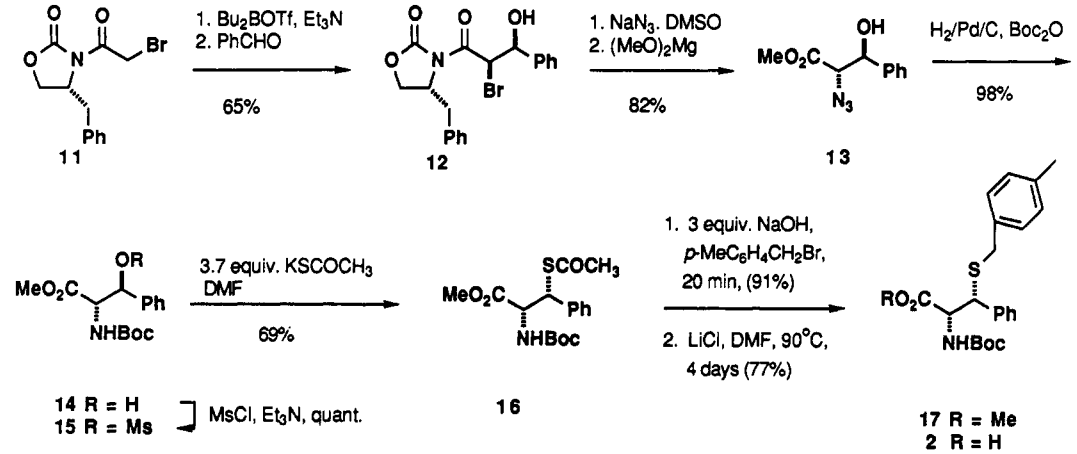
* To whom correspondence should be addressed.
† Department of Medicinal Chemistry.
‡ Department of Peptidomimetic Research.

0022-3263/92/1957-3493$03.00/0

Scheme I



Scheme II



dology. The final hydrogen fluoride treatment used to remove the peptide from the support has been shown to bring about sulfur deprotection without affecting the integrity of the incorporated β-phenylcysteines.[12] In addition, the aforementioned approaches for the synthesis of the protected amino acids **1** and **2** would seemingly be applicable to the enantioselective preparation of other 3-substituted cysteines.

Experimental Section

General Methods. Oxazolidines **4** and **12** were prepared in a similar manner as reported in the literature.[5] THF was distilled from Na/benzophenone ketyl and all other reagents and materials were obtained from commercial suppliers and were used without further purification. All reactions were conducted under an Ar atmosphere unless otherwise noted. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Analytical TLC was performed on precoated silica gel plates (Merck 60 F-254). ^1H and ^{13}C NMR spectra were obtained on a Bruker AM-250 (250 MHz and 62.9 MHz, respectively) instrument in $CDCl_3$. Me_4Si was used as internal standard reference, the chemical shifts are reported as ppm on the δ scale, and coupling constants are given in hertz. Mass spectra were obtained with a Finnigan-MAT quadrupole instrument with desorptive chemical ionization. IR spectra were recorded on a Perkin Elmer Model 783.

Methyl (2*S*,3*R*)-2-((*tert*-Butyloxycarbonyl)amino)-3-hydroxy-3-phenylpropionate (6). To a room-temperature solution of methyl ester **5** (5.6 g, 17.6 mmol) in dioxane (300 mL) was added 44 mL (88 mmol, 5 equiv) of freshly prepared 2 N aqueous LiOH solution. The resultant suspension was stirred at rt overnight. Volatiles were removed in vacuo. The residue was dissolved in 300 mL of 1 N aqueous $NaHSO_4$ and extracted with three portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated, the residue was then redissolved in Et_2O (300 mL), and after cooling to 0 °C, a solution of ethereal diazomethane was added until a pale yellow color persisted. The solution was stirred at 0 °C for 15 min and at rt for 30 min. The solvent was removed and the residual foamy oil was purified by flash column chromatography eluting with 30% EtOAc–hexane to give the desired Boc-protected amino alcohol **6** (4.01 g, 81%) followed by (1/1 EtOAc/hexane) the oxazolidinone **10**[10] (460 mg, 12%). The amino alcohol **6** was obtained as a white solid which crystallized: mp 101–102 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = −15.10° (*c* = 0.93, $CHCl_3$); ^1H NMR δ 7.29–7.36 (m, 5 H), 5.27–5.35 (m, 1 H), 5.24 (dd, *J* = 3.5, 3.4 Hz, 1 H), 4.50 (bd, *J* = 6.6 Hz, 1 H), 3.76 (s, 3 H), 2.70 (bs, 1 H, OH), 1.33 (s, 9 H); ^{13}C NMR δ 171.5, 155.5, 139.9, 128.2, 127.9, 126.0, 80.0, 73.8, 59.5, 52.4, 28.1; IR (KBr) 3440 (b), 1745, 1705 cm^{-1}; MS *m*/*z* 296 (M + 1, 40). Anal. Calcd for $C_{15}H_{21}O_5N$: C, 61.02; H, 7.12. Found: C, 59.96; H, 6.94.

Methyl (2*S*,3*R*)-2-((*tert*-Butyloxycarbonyl)amino)-3-((methanesulfonyl)oxy)-3-phenylpropionate (7). To a solution of alcohol **6** (0.94 g, 3.18 mmol) and Et_3N (0.73 g, 7.18 mmol) at 0 °C in CH_2Cl_2 (10 mL) was added MsCl (418 mg, 3.65 mmol). The reaction mixture was stirred at 0 °C for 45 min and then quenched with cold dilute HCl and extracted with CH_2Cl_2. The organic layer was washed with aqueous $NaHCO_3$ followed by brine and dried over Na_2SO_4. The solvent was removed in vacuo and the crude mesylate **7** was obtained as a foamy white solid that was used in the next step without further purification: ^1H NMR δ 7.39–7.40 (m, 5 H), 5.89 (d, *J* = 6.6 Hz, 1 H), 5.17 (bd, *J* = 9.6 Hz, 1 H, HN), 4.85 (dd, *J* = 9.6, 6.6 Hz, 1 H), 3.71 (s, 3 H), 2.91 (s, 3 H), 1.42 (s, 9 H); IR (KBr) 3400, 1745, 1715 cm^{-1}.

(12) To be published elsewhere.

Methyl (2*R*,3*S*)-3-(Acetylthio)-2-((*tert*-butyloxycarbonyl)amino)-3-phenylpropionate (8). To a solution of mesylate **7** (1.18 g, 3.16 mmol) in DMF (10 mL) was added a preformed solution of the DBU salt of thiolacetic acid [formed by the addition of thiolacetic acid (1.2 g, 15.8 mmol) to DBU (1.68 g, 11.07 mmol) in DMF (5 mL)]. The reaction mixture was stirred at rt for 30 h and was then quenched with water, diluted with CH_2Cl_2, and washed 4 more times with water. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the crude oil was purified by flash column chromatography eluting with 8% EtOAc–toluene to give the desired acetylated thiol **8** (0.97 g, 87%) as a colorless liquid followed by a small amount of elimination compound **9** (50 mg, 6%). **8**: $[\alpha]^{20}_D$ = +143.60° (*c* = 2.50, $CHCl_3$); ^{1}H NMR δ 7.29–7.40 (m, 5 H), 5.14 (d, *J* = 4.7 H, 1 H, H-3), 5.07 (bd, *J* = 9.6 Hz, 1 H, HN), 4.90 (dd, *J* = 9.6, 4.7 Hz, 1 H, H-2), 3.69 (s, 3 H, CH_3O), 2.33 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR δ 193.3, 170.1, 155.1, 136.6, 128.6, 128.4, 128.2, 80.2, 57.3, 52.2, 49.9, 30.2, 28.1; IR (neat) 3380, 1750, 1690 cm^{-1}; MS *m*/*z* 354 (M + 1, 25). Anal. Calcd for $C_{17}H_{23}O_5NS$: C, 57.79; H, 6.51. Found: C, 57.64; H, 6.59.

(2*R*,3*S*)-2-((*tert*-Butyloxycarbonyl)amino)-3-((4-methylbenzyl)thio)-3-phenylpropionic Acid (1). To acetylated thiol **8** (520 mg, 1.47 mmol) dissolved in MeOH (8 mL) was added aqueous NaOH (1.62 mL of a 1 M solution) followed by 4-methylbenzyl bromide (300 mg, 1.62 mmol). After 20 min an additional 2.5 equiv of base was added. The reaction was stirred at rt for 3 h (TLC). The solution was then carefully neutralized with dilute HCl. The volatiles were removed in vacuo and the residue was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 2% AcOH–20% EtOAc–hexane to give the desired acid **1** (480 mg, 79%) as a white solid which crystallized: mp 131–132 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = +211.70° (*c* = 0.99, $CHCl_3$); ^{1}H NMR δ 7.29–7.31 (m, 5 H), 7.08 (s, 4 H), 5.05–5.35 (bs, 1 H), 4.93–5.05 (m, 1 H), 4.79 (bs, 1 H), 4.19 (d, *J* = 13 Hz, 1 H), 3.51 (d, *J* = 13 Hz, 1 H), 2.31 (s, 3 H), 1.40 (s, 9 H); IR (KBr) 3380, 1700 cm^{-1}; MS *m*/*z* 402 (M + 1, 30). Anal. Calcd for $C_{22}H_{27}O_4NS$: C, 65.81; H, 6.78. Found: C, 65.91; H, 7.00.

(4*R*)-3-((2′*S*,3′*S*)-2′-Azido-3′-hydroxy-3′-phenylpropanoyl)-4-(phenylmethyl)-2-oxazolidinone (18). A solution of aldol adduct **12** (3.1 g, 7.67 mmol) and NaN_3 (0.99 g, 15.3 mmol) in DMSO (26 mL) was stirred at rt for 5 h. The resultant dark solution was diluted with 1:1 hexane/CH_2Cl_2, washed four times with water, dried over Na_2SO_4, and concentrated in vacuo to give a pale oil which crystallized. Purification by recrystallization from Et_2O/hexane gave 2.2 g (80%) of the azide as a white solid: mp 115–116 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = –6.60° (*c* = 2.2, $CHCl_3$); ^{1}H NMR δ 7.20–7.53 (m, 10 H), 5.38 (d, *J* = 8.5 Hz, 1 H), 5.08 (dd, *J* = 8.5, 6.6 Hz, 1 H), 4.71–4.75 (m, 1 H, H-4), 4.20–4.27 (m, 2 H, H-5), 3.31 (dd, *J* = 13.6, 3.4 Hz, 1 H), 2.95 (d, *J* = 6.6 Hz, 1 H, OH), 2.75 (dd, *J* = 13.6, 9.6 Hz, 1 H); ^{13}C NMR δ 169.6, 153.3, 139.5, 134.8, 129.3, 128.9, 128.8, 128.7, 127.3, 126.7, 74.8, 66.5, 63.1, 55.5, 37.3; IR (KBr) 3420, 2100, 2760, 1700 cm^{-1}; MS *m*/*z* 349 (M + 1 – H_2O, 25). Anal. Calcd for $C_{19}H_{18}O_4N_4$: C, 62.29; H, 4.95; N, 15.29. Found: C, 62.03; H, 5.06; N, 15.23.

Methyl (2*S*,3*S*)-2-Azido-3-hydroxy-3-phenylpropionate (13). To a solution of the azide **18** (1.52 g, 4.15 mmol) in anhydrous MeOH (8 mL) and CH_2Cl_2 (8 mL) at 0 °C was added via cannula a suspension formed by the addition of MeMgBr (5.2 mL, 4.5 mmol, 1.1 equiv, 0.88 M in Et_2O) to anhydrous MeOH (5 mL). After stirring for 3 min, the reaction was quenched by the addition of aqueous $NaHSO_4$ (20 mL, 1 N) and extracted three times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography eluting with CH_2Cl_2 to afford 807 mg (88%) of the title compound **13** as a white solid which crystallized: mp 40–41 °C (Et_2O–hexane); ^{1}H NMR δ 7.37 (s, 5 H), 5.00 (bd, *J* = 6.4 Hz, 1 H), 4.11 (d, *J* = 7 Hz, 1 H), 3.77 (s, 3 H), 3.08 (bs, 1 H, OH); ^{13}C NMR δ 169.3, 136.1, 128.7, 128.6, 126.6, 74.5, 52.6; IR (KBr) 3500, 2120, 1740 cm^{-1}; MS *m*/*z* 238 (M + NH_4, 83). Anal. Calcd for $C_{10}H_{11}O_3N_3$: C, 54.30; H, 5.01; N, 19.00. Found: C, 54.31; H, 5.08; N, 18.78.

Methyl (2*S*,3*S*)-2-((*tert*-Butyloxycarbonyl)amino)-3-hydroxy-3-phenylpropionate (14). Palladium on charcoal (10%) (80 mg) in EtOAc (4 mL) was vigorously stirred under H_2 for 15 min. To this suspension was added a mixture of the azido alcohol **13** (800 mg, 3.6 mmol) and di-*tert*-butyl dicarbonate (943 mg, 4.32 mmol) in EtOAc (4 mL). The resulting mixture was stirred under H_2 at rt for 2 h (TLC) and then filtered through a plug of Celite. The filtrate was concentrated in vacuo and the resulting white solid was purified by a short flash column chromatography eluting with 30% EtOAc–hexane to give the desired Boc-protected amino alcohol **14** (1.04 g, 98%) as a white solid which crystallized: mp 101–102 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = +83.30° (*c* = 1.05, $CHCl_3$); ^{1}H NMR δ 7.25–7.38 (m, 5 H), 5.19–5.31 (m, 1 H), 5.17–5.19 (m, 1 H), 4.71–4.76 (m, 1 H), 3.93 (bd, *J* = 5.3 Hz, 1 H, HO), 3.70 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR δ 170.1, 156.1, 139.3, 128.2, 127.9, 126.0, 80.5, 74.9, 59.7, 52.2, 28.2; IR (KBr) 3450, 3390, 1760, 1710 cm^{-1}; MS *m*/*z* 296 (M + 1, 32). Anal. Calcd for $C_{15}H_{21}O_5N$: C, 61.02; H, 7.12. Found: C, 60.96; H, 6.96.

Methyl (2*S*,3*S*)-2-((*tert*-Butyloxycarbonyl)amino)-3-((methanesulfonyl)oxy)-3-phenylpropionate (15). To a solution of alcohol **14** (1.94 g, 6.81 mmol) and Et_3N (1.25 g, 12.4 mmol) at 0 °C in CH_2Cl_2 (15 mL) was added MsCl (0.96 g, 8.4 mmol). The reaction mixture was stirred at 0 °C for 20 min. It was then quenched with cold dilute HCl and extracted into CH_2Cl_2. The organic layer was washed with an aqueous solution of $NaHCO_3$ followed by brine and dried over Na_2SO_4. The solvent was removed in vacuo and the crude mesylate **15** was obtained as a foamy white solid that was used in the next step without further purification. **15**: ^{1}H NMR δ 7.38–7.43 (m, 5 H), 5.92 (d, *J* = 5.0 Hz, 1 H, H-3), 5.23 (bd, *J* = 8.7 Hz, 1 H, HN), 4.88 (dd, *J* = 8.7, 5.0 Hz, 1 H, H-2), 3.72 (s, 3 H), 2.92 (s, 3 H), 1.39 (s, 9 H).

Methyl (2*R*,3*R*)-3-(Acetylthio)-2-((*tert*-butyloxycarbonyl)amino)-3-phenylpropionate (16). To a solution of mesylate **15** (2.72 g, 7.29 mmol) in DMF (7 mL) was added the potassium salt of thiolacetic acid (3 g, 29.9 mmol) followed by additional DMF (5 mL). The reaction mixture was stirred at rt for 20 h. The product was partitioned between water and CH_2Cl_2. The organic layer was washed 4 times with water and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product contained a 6:1 mixture of the desired product **16** and oxazolidinone **10** (as indicated by ^{1}H NMR of the crude). The mixture was purified by flash column chromatography gradient elution from 5% to 1:1 EtOAc/hexane to give the desired acetylated thiol **16** (1.65 g, 69%) as a tan solid followed by oxazolidinone **10** (193 mg, 12%). The acetylated thiol **16** was recrystallized to produce a white solid: mp 87–88 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = –97.20° (1.0, $CHCl_3$); ^{1}H NMR δ 7.31 (s, 5 H), 5.26 (bd, *J* = 6.3 Hz, 1 H, HN), 5.03 (bd, *J* = 6.6 Hz, 1 H, H-3), 4.77 (dd, *J* = 6.6, 6.3 Hz, 1 H, H-2), 3.62 (s, 3 H), 2.36 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR δ 193.5, 170.6, 154.9, 137.8, 128.6, 128.3, 128.1, 80.3, 58.5, 52.2, 50.5, 30.2, 28.3; IR (KBr) 3380, 1745, 1690 cm^{-1}; MS *m*/*z* 354 (M + 1, 20). Anal. Calcd for $C_{17}H_{23}O_5NS$: C, 57.77; H, 6.56; N, 3.97. Found: C, 58.05; H, 6.92; N, 3.73.

Methyl (2*R*,3*R*)-2-((*tert*-Butyloxycarbonyl)amino)-3-((4-methylbenzyl)thio)-3-phenylpropionic Acid (17). The acetylated thiol **16** (500 mg, 1.4 mmol) was dissolved in MeOH (2 mL), and aqueous NaOH added (1.6 mL, 1 M), followed by 4-methylbenzyl bromide (300 mg, 1.62 mmol). After 20 min most of the starting material was consumed (TLC). The solution was then carefully neutralized with dilute HCl. The volatiles were removed in vacuo and the residue was extracted three times with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography eluting with 5% to 20% EtOAc–hexane to give the desired ester **17** (480 mg, 79%) as a white solid which crystallized: mp 97–98 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = –171.80° (*c* = 1.05, $CHCl_3$); ^{1}H NMR δ 7.29–7.36 (m, 5 H), 7.03–7.11 (m, 4 H), 5.22 (bd, *J* = 8.8 Hz, 1 H, HN), 4.63 (dd, *J* = 8.8, 5.8 Hz, 1 H, H-2), 4.13 (d, *J* = 5.4 Hz, 1 H, H-3), 3.57 (s, 3 H), 3.55 (d, *J* = 13 Hz, 1 H), 3.39 (d, *J* = 13 Hz, 1 H), 2.33 (s, 3 H), 1.38 (s, 9 H); ^{13}C NMR δ 170.8, 154.7, 138.4, 136.9, 134.3, 129.2, 128.9, 128.7, 128.5, 127.8, 80.1, 57.5, 52.1, 51.6, 35.5, 28.3, 21.0; MS *m*/*z* 316 (M + 1, 20). Anal. Calcd for $C_{23}H_{29}O_4NS \cdot {}^1/_4H_2O$: C, 65.76; H, 7.08; N, 3.33. Found: C, 65.59; H, 7.03; N, 3.36.

(2*R*,3*R*)-2-((*tert*-Butyloxycarbonyl)amino)-3-((4-methylbenzyl)thio)-3-phenylpropionic Acid (2). The methyl ester **17** (380 mg, 0.91 mmol) and anhydrous LiCl (376 mg, 8.89

mmol) were dissolved in 10 mL of dry DMF. The reaction mixture was heated at 90 °C for 4 days and then cooled to rt quenched with dilute HCl and extracted several times with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography eluting first with 20% EtOAc–hexane to recover starting material 17 (75 mg, 20%), followed by 25% EtOAc/5% acetic acid/hexane to give the desired carboxylic acid as a white solid that was recrystallized (341 mg, 77%): mp 107–108 °C (Et_2O–hexane); $[\alpha]^{20}_D$ = −143.70° (c = 1.66, $CHCl_3$); ^1H NMR δ 7.25–7.34 (m, 5 H), 7.06 (s, 4 H), 5.27 (bd, J = 8.7 Hz, 1 H, HN), 4.65 (dd, J = 8.7, 5.5 Hz, 1 H, H-2), 4.24 (d, J = 5.5 Hz, H-3), 3.59 (d, J = 13.3 Hz, 1 H), 3.46 (d, J = 13.3 Hz, 1 H), 2.30 (s, 3 H), 1.37 (s, 9 H); ^{13}C NMR δ 174.5, 155.3, 138.1, 136.9, 133.9, 129.2, 128.9, 128.6, 127.9, 80.5, 58.1, 50.8, 35.5, 28.2, 21.1; MS m/z 401 (M + 1, 12). Anal. Calcd for $C_{22}H_{27}O_4NS$: C, 65.81; H, 6.78; N, 3.48. Found: C, 65.83; H, 6.92; N, 3.57.

Acknowledgment. We wish to thank J. I. Luengo and F. Ali for helpful discussions, J. Leber and R. Calvo for technical assistance, E. A. Reich for elemental analyses, and M. Huddleston for mass spectra.

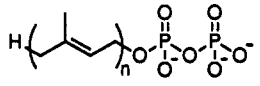
Formation and Alkylation of Anions of Bis(methylsulfonyl)methane

Alfredo Castro and Thomas A. Spencer*

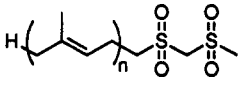
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received September 4, 1991 (Revised Manuscript Received February 21, 1992)

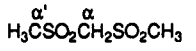
This study of the formation and alkylation of anions of a 1,3-disulfone was undertaken to explore the idea that the disulfone moiety might serve as a surrogate for the diphosphate group in prospective inhibitors of the important enzymatic reactions which have substituted diphosphates as substrates. The diphosphate moiety itself is unsuitable as part of substrate analogue inhibitors in vivo because it is readily hydrolyzed by phosphates and because, being ionic, it presumably would have difficulty crossing cell membranes.[1] Sulfones have previously been proposed as nonionic, nonhydrolyzable substitutes for biological phosphodiesters.[2] The specific context in which it was decided to explore the idea of 1,3-disulfones as diphosphate mimics was that of prenylated diphosphates 1, which are



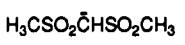
1



2

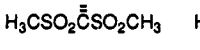


3

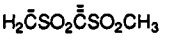


4

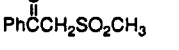
5



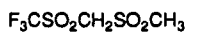
6



7



8



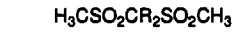
9

key intermediates in the biosynthesis of important natural products such as steroids 1 (n = 1–3)[3,4] and prenylated proteins 1 (n = 3,4).[4,5] The analogous prenylated 1,3-disulfones 2 are very similar in size and shape to the natural substrates, as judged from CPK models and Chem-X modeling program studies; they would clearly not be readily hydrolyzed, and they might be sufficiently polar to bind in the active site in place of the ionic diphosphate moiety.[5]

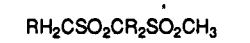
The most direct method for synthesis of the desired 1,3-disulfones 2 appeared to be alkylation with the appropriate allylic halide at the anionic site formed from a methyl group (α′ position) of bis(methylsulfonyl)methane (3).[6] As expected, initial deprotonation of 3 to form an anion occurs at the doubly activated methylene group (pK_a = 12.54)[7] to form α-monoanion 4, but it was unknown whether a second deprotonation would generate the desired nucleophilic properties at the terminal α′-position via formation of dianion 5 or would lead instead to α,α-dianion 6. If the latter were formed, a third deprotonation to form α,α,α′-trianion 7 presumably would be required in order to effect the desired α′-alkylation. Prior studies of alkylation of substrates most closely related to 3 have indicated that the α,α′-dianion is formed in the case of β-keto sulfone 8,[8] but that the α,α-dianion is formed from trifylsulfone 9,[9,10] so that it was unclear what sequence of deprotonation to expect from 3. Accordingly, determination of this sequence was undertaken with 3, which we found can be most conveniently prepared from commercially available methyl methylsulfinylmethyl sulfide by Oxone oxidation.[11]

The first method employed consisted in treatment of THF solutions of 3 with 1, 2, or 3 equiv of n-BuLi at rt for 30 min, followed by rapid addition of a large excess of MeI. After 1 h at rt, these reactions afforded essentially quantitative yields of the α-monomethylated, α,α-dimethylated, and α,α,α′-trimethylated bis(methylsulfonyl)methanes 10, 11, and 12, respectively. If the

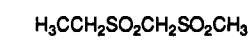
10, R = CH_3
13, R = D



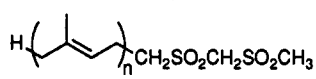
11, R = CH_3
14, R = D



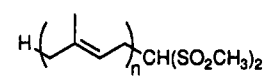
12, R = CH_3
15, R = D



16



17, n = 1
19, n = 2
21, n = 3



18, n = 1
20, n = 2
22, n = 3

reaction time was abbreviated by immediate evaporation of the reaction mixture after addition of excess MeI to the

(1) Bertolino, A.; Altman, L. J.; Vasak, J.; Rilling, H. C. *Biochim. Biophys. Acta* **1978**, *530*, 17.
(2) Huang, Z.; Schneider, K. C.; Benner, S. A. *J. Org. Chem.* **1991**, *56*, 3869.
(3) Rilling, H. C. *Biochem. Soc. Trans.* **1985**, *13*, 997.
(4) Goldstein, J. L.; Brown, M. S. *Nature* **1990**, *343*, 425.
(5) (a) Rilling, H. C.; Breunger, E.; Epstein, W. W.; Crain, P. F. *Science* **1990**, *247*, 318. (b) Farnsworth, C. C.; Gelb, M. H.; Glomset, J. A. *Science* **1990**, *247*, 320. (c) Mumby, S. M.; Casey, P. J.; Gilman, A. G.; Gutowski, S.; Sternweis, P. C. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 5873. (d) Glomset, J. A.; Gelb, M. H.; Farnsworth, C. C. *Trends Biol. Sci.* **1990**, *15*, 139.
(6) Gibson, D. T. *J. Chem. Soc.* **1931**, 2637.
(7) Hine, J.; Philips, J. C.; Maxwell, J. I. *J. Org. Chem.* **1970**, *35*, 3934.
(8) Grossert, J. S.; Hoyle, J.; Hooper, D. L. *Tetrahedron* **1984**, *40*, 1135.
(9) (a) Hendrickson, J. B.; Boudreaux, G. J.; Palumbo, P. S. *Tetrahedron Lett.* **1984**, 4617. (b) Hendrickson, J. B.; Palumbo, P. S. *J. Org. Chem.* **1985**, *50*, 2110.
(10) Boudreaux, G J. Ph.D. Dissertation, Brandeis University, 1986.
(11) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, 1287.

0022-3263/92/1957-3496$03.00/0