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A NEW SYNTHESIS OF α-METHYLSERINE BY NUCLEOPHILIC RING-OPENING OF *N*-SULFONYL AZIRIDINES#

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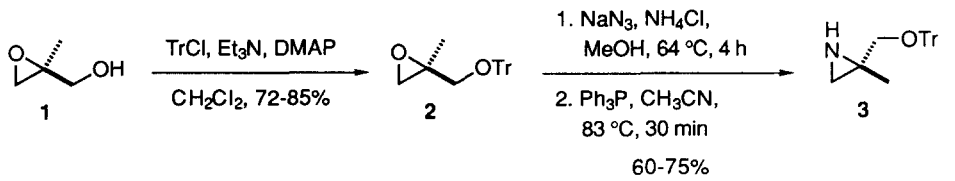
Abstract: Conversion of tritylated 2-methylglycidol to the corresponding aziridine occurs by Staudinger cyclization of the intermediate azido alcohol. After *N*-sulfonylation with Ses-Cl and ring-opening with benzyl alcohol, oxidation of the primary alcohol provides *N,O*-bisprotected α-methylserine directly suitable for repetitive peptide synthesis. This sequence represents a general enantioselective protocol for the synthesis of α-methylserine and other α,α-disubstituted amino acids.

Aziridines are useful building blocks for the preparation of amino alcohols and amino acids, and many pathways employing a range of nucleophiles in the ring-opening reaction have been explored.[2] Neutral and base-catalyzed alcoholysis of aziridines, however, requires *N*-activation with strongly electron-withdrawing substituents such as the *p*-toluenesulfonyl group that are difficult to deprotect for subsequent transformations.[3] In this paper, we report a new synthesis of the non-proteinogenic amino acid α-methylserine[4] that employs ring activation of an optically active aziridine with protective groups that are easily and selectively removed under standard peptide synthesis conditions.

O-Tritylation of commercially available (S)-(-)-2-methylglycidol (**1**, 93% ee) with trityl chloride gave oxirane **2** in 72-85% yield (Scheme 1). Ring opening of the oxirane with sodium azide in methanol in the presence of NH_4Cl followed by Staudinger reaction of the intermediate azido alcohol in hot acetonitrile led to efficient aziridine formation.[5] The enantiomeric excess of **3** was determined as >92% by HPLC analysis of the *N*-benzoyl derivative on a Chiralcel OD column.

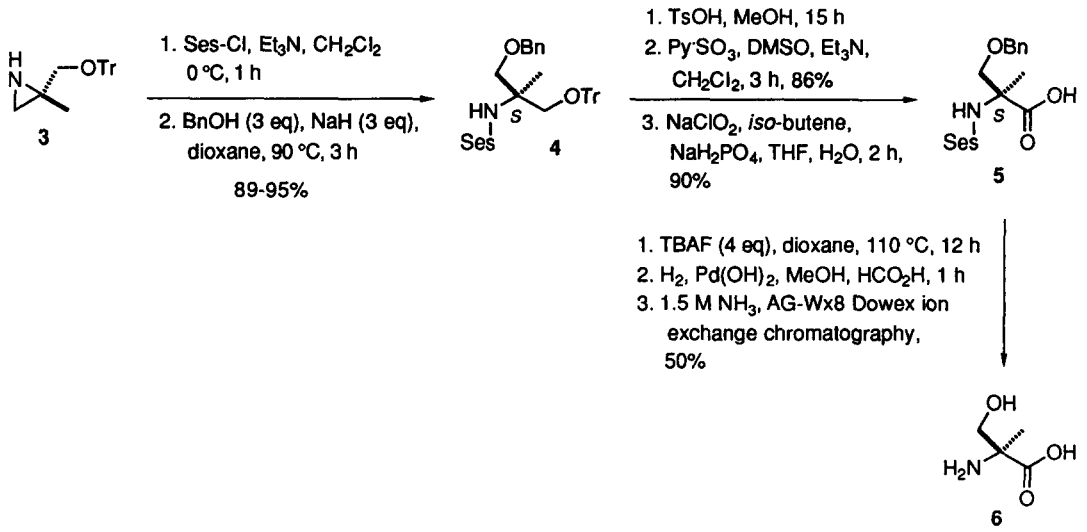
Scheme 1



1 2 3

N-Protection of aziridine **3** with β-trimethylsilylethanesulfonylchloride (Ses-Cl)[6] followed by treatment with 3 eq of the sodium benzyloxide in dioxane at 90 °C for 3 h led to an efficient ring-opening of the activated aziridine in 89-95% overall yield (Scheme 2).[7] This protocol provided a superior regioselectivity and yield than Lewis acid activation of the aziridine. The use of *N*-carbamoyl protective groups in the reaction with alcoholates led mostly to deacylation in preference to ring opening.

Scheme 2

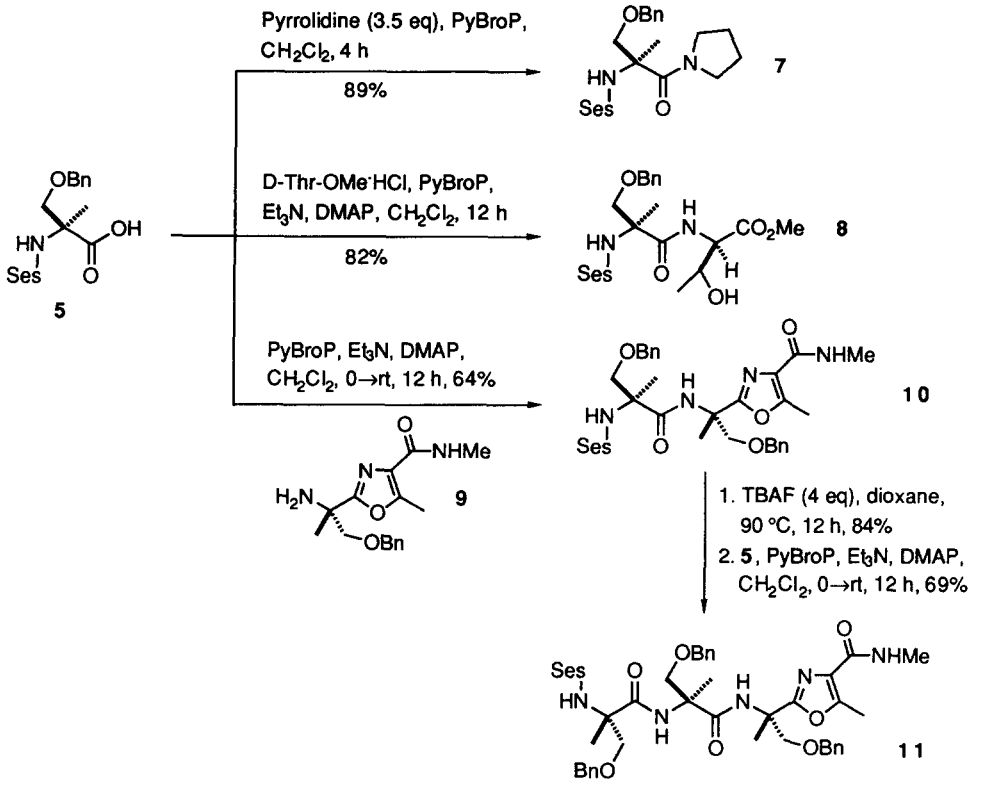


Removal of the trityl group with tosic acid in methanol and oxidation of the primary alcohol with sulfur trioxide pyridine complex[8] provided 86% of the intermediate aldehyde that was further oxidized with sodium chlorite[9] to give α-methylserine **5** in 90% yield and high optical purity.[10] Cleavage of both *N*- and *O*-protective groups with TBAF and catalytic hydrogenation, respectively, gave (*S*)-(+)-α-methylserine (**6**) in 50% yield after ion-exchange chromatography. However, the bisprotected amino acid building block **5** can be directly used for subsequent synthetic transformations and repetitive peptide synthesis (Scheme 3).

Coupling of α-methylserine **5** with the secondary amine pyrrolidine and the amino acid D-threonine in the presence of bromotripyrrolydinophosphonium hexafluorophosphate (PyBroP)[11] provided amide **7** and dipeptide **8** in 89% and 82% yield, respectively. Under similar conditions, condensation with the sterically highly hindered amine **9** gave dipeptide **10** in 64% yield. Removal of the *N*-sulfonyl protective group with tetrabutylammonium fluoride occurred smoothly in 84% yield to give an intermediate amine that was further acylated with acid **5** to provide the highly functionalized tripeptide **11** in 69% yield.

In conclusion, we have demonstrated a novel enantioselective synthesis of the biologically important amino acid α-methylserine via oxirane→aziridine conversion, regioselective ring-opening of the *N*-sulfonated aziridine with alcoholate, and two-step oxidation of the primary alcohol substituent. The major advantage of this protocol vs. earlier procedures[4] is the direct access to an *N,O*-bisprotected derivative suitable for immediate further synthetic manipulations. The *N*-terminal β-silylethylsulfonamide group and the side-chain benzyl ether are orthogonal protective groups and readily removed with fluoride anion and catalytic hydrogenolysis, respectively. The versatility of this approach has been demonstrated by the synthesis of a range of *C*-terminal derivatives of α-methylserine and efficient solution-phase repetitive peptide couplings. Further applications of this methodology in amino acid synthesis will be reported in due course.

Scheme 3



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In part from the Ph.D. thesis of C. P. Miller, University of Pittsburgh, 1993.

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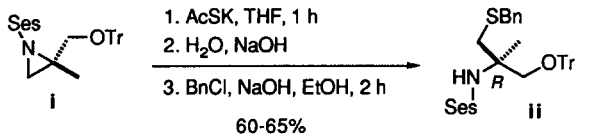
7. Ring opening of *N*-Ses-protected aziridines occurs with a wide range of nucleophiles. For example, reaction of **i** with thioacetate followed by *S*-benzylation led to the α-methylcysteinol derivative **ii**:



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10. **(*S*)-2-Methyl-2-trityloxymethyl-oxirane (2).** A solution of 0.70 g (7.95 mmol) of **1** in 20 mL of CH_2Cl_2 was treated with 1.20 g (11.8 mmol) of Et_3N, 2.70 g (9.71 mmol) of trityl chloride, and 200 mg (1.63 mmol) of DMAP and stirred for 48 h at rt. The reaction mixture was diluted with 20 mL of H_2O and the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 2.02 g (77%) of crystalline **2**: R_f 0.59 (EtOAc/Hexanes, 1:4); Mp 206 °C; $[\alpha]_D$ 15.6° (*c* 0.59, CH_2Cl_2); ^1H NMR δ 7.50-7.24 (m, 15 H), 3.19, 3.12 (AB, 2 H, *J* = 10.3 Hz), 2.78, 2.64 (AB, 2 H, *J* = 4.9 Hz), 1.43 (s, 3 H).

(*S*)-2-Methyl-2-trityloxymethyl-aziridine (3). A solution of 700 mg (2.12 mmol) of **2** and 337 mg (6.35 mmol) of NH_4Cl in 4 mL of MeOH was treated with 415 mg (6.35 mmol) of sodium azide and heated at 64° C for 3 h. The reaction mixture was diluted with 30 mL of H_2O and extracted with EtOAc (3x30 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo to give crude (*S*)-3-azido-2-methyl-1-(triphenylmethoxy)-2-propanol that was used directly for the next reaction: R_f 0.47 (EtOAc/Hexanes, 1:9). A mixture of 740 mg of crude azido alcohol and 630 mg (2.4 mmol) of triphenylphosphine in 4 mL of CH_3CN was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo and chromatographed on SiO_2 (EtOAc/Hexanes, 1:1) to yield 523 mg (74%) of **3** as a colorless solid: R_f 0.30 (EtOAc/Hexanes, 1:1); $[\alpha]_D$ -7.2° (*c* 1.2, $CHCl_3$, 23 °C); ^1H NMR δ 7.53-7.50 (m, 6 H), 7.36-7.23 (m, 9 H), 3.23, 3.17 (AB, 2 H, *J* = 9.4 Hz), 1.85 (b, 1 H), 1.54 (b,1 H), 1.31 (b, 4 H).

(*S*)-2-Trimethylsilanyl-ethanesulfonic acid-(2-benzyloxy-1-methyl-1-trityloxymethyl-ethyl)-amide (4). A solution of 450 mg (1.36 mmol) of **3** in 1 mL of CH_2Cl_2 was added dropwise at 0 °C to a solution of 1.377 g (13.6 mmol) of Et_3N and 402 mg (1.7 mmol) of Ses-Cl in 4 mL of CH_2Cl_2. The reaction mixture was stirred at 0° C for 1 h, concentrated, and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 402 mg (60%) of (*S*)-2-methyl-1-(2-trimethylsilanyl-ethanesulfonyl)-2-trityloxymethyl-aziridine: R_f 0.7 (EtOAc/Hexanes, 2:9); $[\alpha]_D$ -25.8° (*c* 0.56, $CHCl_3$, 25 °C). A solution of 118 mg (0.23 mmol) of Ses-aziridine in 2 mL of dioxane was added to a mixture of 17.0 mg (0.70 mmol) of NaH and 76 mg (0.70 mmol) of benzyl alcohol in 2 mL of dry dioxane. The reaction mixture was heated at reflux for 3 h, quenched with 10 mL of saturated NH_4Cl solution and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 123 mg (89%) of **4**: R_f 0.30 (EtOAc/Hexanes, 1:7); $[\alpha]_D$ 3.7° (*c* 0.46, $CHCl_3$, 25 °C); ^1H NMR δ 7.50-7.46 (m, 6 H), 7.42-7.26 (m, 14 H), 4.70 (s, 1 H), 4.58 (s, 2 H), 3.78, 3.73 (AB, 2 H, *J* = 8.9 Hz), 3.49, 3.17 (AB, 2 H, *J* = 8.7 Hz), 2.93-2.87 (m, 2 H), 1.42 (s, 3 H), 1.05-0.90 (m, 2 H), 0.03 (s, 9 H).

(2*S*)-3-Benzyloxy-2-methyl-2-(2-trimethylsilanyl-ethanesulfonylamino)-propionic acid (5). A solution of 120 mg (0.19 mmol) of **4** in 2 mL of MeOH was treated with 10 mg (0.05 mmol) of $TsOH{\cdot}H_2O$, stirred at rt for 15 h, concentrated in vacuo and chromatographed on SiO_2 (EtOAc/Hexanes, 1:2) to yield 59 mg (87%) of primary alcohol: R_f 0.2 (EtOAc/Hexanes, 1:4); $[\alpha]_D$ -1.2° (*c* 2.2, $CHCl_3$, 23 °C). A solution of 1.5 g (4.3 mmol) of alcohol in 5 mL of CH_2Cl_2 was treated with 1.73 g (17.1 mmol) of Et_3N, cooled to 0 °C, and a solution of 2 g (12.5 mmol) of $Py{\cdot}SO_3$ in 15 mL of DMSO was added. The reaction mixture was stirred at rt for 3 h, treated with 30 mL of H_2O, and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with H_2O (3X30 mL), 1 M HCl (10 mL), and saturated NH_4Cl (20 mL), dried (Na_2SO_4), and chromatographed on SiO_2 (EtOAc/Hexanes 1:4) to yield 1.29 g (86%) of α-methylserinal as a viscous oil: R_f 0.45 (EtOAc/ Hexanes, 1:4); $[\alpha]_{365}$ -2.3° (*c* 1.2, $CHCl_3$, 23 °C). A solution of 49 mg (0.13 mmol) of aldehyde in 0.5 mL of THF and 0.25 mL of H_2O was treated with 0.25 mL (0.75 mmol) of a 3 M solution of isobutene in THF, 53 mg (0.39 mmol) of $NaH_2PO_4{\cdot}H_2O$, and 35 mg (0.39 mmol) of $NaClO_2$, stirred for 2 h, diluted with 20 mL of H_2O and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and chromatographed on SiO_2 (MeOH/CH_2Cl_2, 1:5) to yield 43 mg (90%) of **5** as a viscous oil: R_f 0.77 (MeOH /CH_2Cl_2, 1:5); $[\alpha]_D$ 0.3° (*c* 1.2, $CHCl_3$, 23 °C); ^1H NMR (CD_3OD) δ 7.27-7.16 (m, 5 H), 4.14 (s, 2 H), 3.66 (dd, 2 H, *J* = 3.1 Hz), 2.88-2.82 (m, 2 H), 1.33 (s, 3 H), 0.92-0.86 (m, 2 H), -0.16 (s, 9 H); ^{13}C NMR (CD_3OD/$CDCl_3$) δ 176.0, 137.1, 127.4, 126.7, 73.0, 72.4, 61.7, 50.7, 20.6, 9.4, -3.7.
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