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2-Methyl *N*-(*p*-Toluenesulfinyl)aziridine-2-carboxylic Acid: Asymmetric Synthesis of α-Methylphenylalanine and α-Methyl-β-phenylserine

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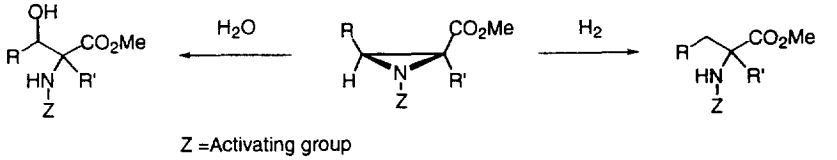
Summary: 2-Substituted aziridine **2a**, prepared from sulfinimine **1** via a Darzens-type condensation, undergoes a highly regio- and stereocontrolled ring-opening to give α-methylphenylalanine and α-methyl-β-phenylserine in high enantiomeric purity. Copyright © 1996 Elsevier Science Ltd

The high level of interest in α-alkylated α-amino acids[1] stems from their biological stability,[2] their utility in studies of enzyme mechanisms,[3] and their use as enzyme inhibitors.[4] Furthermore, once incorporated into peptides, these amino acids influence the conformation of the protein, thereby altering its properties.[5] Most of the methods developed for the enantioselective syntheses of the α-alkylated α-amino acids[1c] involve the alkylation of chiral nonracemic enolates derived from β-lactams,[6] bis-lactims,[7] oxazinones,[8] imidazolidinones,[9] oxazaborolidinone,[10] alanine dianions[11] and other methods.[12] The direct α-alkylation of alanine and phenylalanine enolates in good to excellent ee's has also been described.[13]

N-Activated aziridine-2-carboxylic acids are playing increasingly important roles in strategies for the asymmetric synthesis of proteinogenic and nonproteinogenic α-amino acids because they undergo highly regio- and stereocontrolled ring-opening with nucleophiles (Scheme 1).[14,15] However, the only report of their application to the asymmetric synthesis of α-alkylated α-amino acids is the conversion of 2-methyl aziridine-2-carboxylic acid, prepared in several steps from an optically active oxirane, to α-methyl cysteine derivatives.[16] That there are so few aziridine mediated syntheses of α-alkylated α-amino acids is undoubtedly due to the lack of convenient routes to these heterocycles.[17] In this letter we report methodology for the enantioselective synthesis of 2-substituted aziridine-2-carboxylic acids and their application to the asymmetric synthesis of α-alkyl-α-amino acid derivatives.

Scheme 1

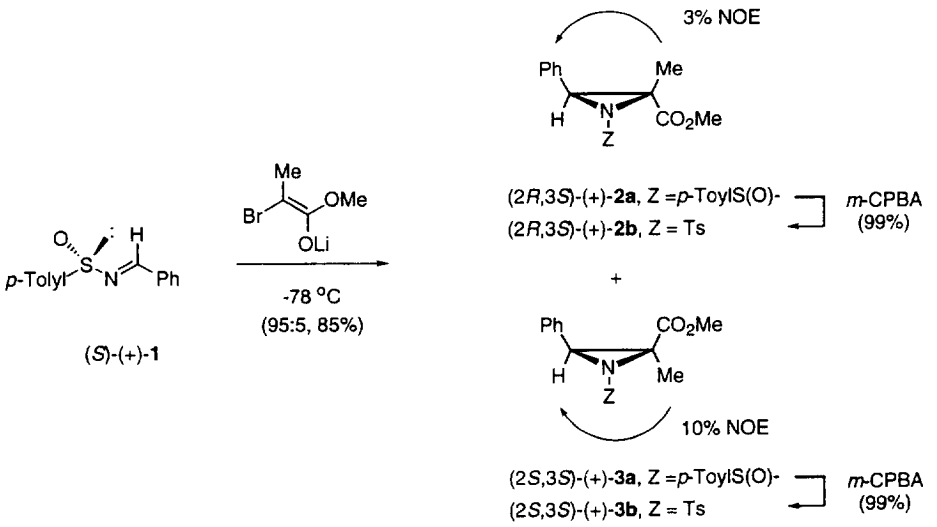


Z =Activating group

Earlier studies from these laboratories reported the application of *cis*-*N*-sulfinylaziridine 2-carboxylic acids in the asymmetric synthesis of α-amino acids, β-hydroxy α-amino acids,[15] the antibiotic thiamphenacol,[18] the

antitumor agent (*R*)-(−)-dysidazirine,[19] and D-*erythro* and L-*threo*-sphingosine.[20] The requisite aziridines were prepared in modest yield via a Darzens-type synthesis involving the addition of the lithium enolate of methyl α-bromoacetate to enantiopure sulfinimines (thiooxime S-oxides). As an extension of this protocol we prepared trans-(2*R*,3*S*)-(+)-*N*-(*p*-toluenesulfinyl)-2-methyl-2-carbomethoxy-3-phenylaziridine (**2**) by treatment of (*S*)-(+)-benzylidene-*p*-toluenesulfinamide (**1**)[21] with the lithium enolate of methyl α-bromopropionate. Thus, methyl α-bromopropionate (11.1 mmol) was treated with an equivalent amount of lithium bis(trimethylsilylamide) in THF at -78 °C. After 30 min., a solution of 4.1 mmol of (+)-**1** was added to the enolate at -78 °C via cannula (Scheme 2). After 1 h the reaction mixture was quenched by addition of H_2O. The ratio of (2*R*,3*S*)-(+)-**2a**/(2*S*,3*S*)-(+)-**3a** was 95:5. Products were isolated by flash chromatography (EtOAc:*n*-pentane, 20:80) affording (2*R*,3*S*)-(+)-**2a** ($[\alpha]^{20}_D$ +99.6 (c 0.22, $CHCl_3$)) in better than 84% yield and the minor aziridine, (2*S*,3*S*)-(+)-**3a** ($[\alpha]^{20}_D$ +23.4 (c 0.95, $CHCl_3$)), in 2-3% yield. It is worth noting that higher yields of **2** (84%) for the propionate enolate are better than for the corresponding acetate enolate (65%),[15] presumably due to greater enolate stability in the former case. It proved difficult to establish the relative configurations of the N-sulfinylaziridines by NOE experiments because they exist as syn and anti mixtures. Treatment of **2a/3a** with 2 equivalents of *m*-chloroperbenzoic acid (*m*-CPBA) readily afforded the corresponding N-tosyl aziridines **2b/3b** in near quantitative yield which exist as single isomers. The fact that irradiation of the Me protons in **2b/3b** produces NOE enhancements of 3 and 10 percent in the C-3 phenyl and C-3 hydrogen, respectively, is consistent with the anti nature of the groups in (2*R*,3*S*)-(+)-**2b** ($[\alpha]^{20}_D$ +44.14 (c 0.28, $CHCl_3$)).

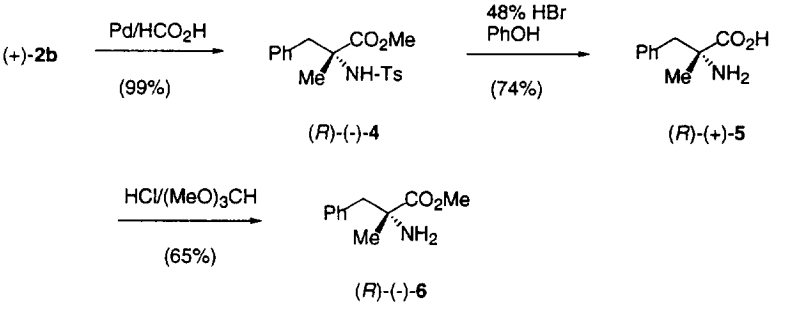
Scheme 2



Aziridine ring opening requires activation at nitrogen and N-tosyl activation often affords superior reactivity and selectivity. As noted earlier this key aziridine activating group is readily installed simply by oxidation of the N-sulfinyl aziridine.[15] Hydrogenation of (+)-**2b** gave a quantitative yield of the α-methylphenylalanine derivative (-)-**4** and was accomplished by treatment with Pd(black)/HCO_2H in ethanol for 8 h at rt and then for 1.5 h at 75 °C (Scheme 3). If the reaction was carried out from the beginning at 75 °C there

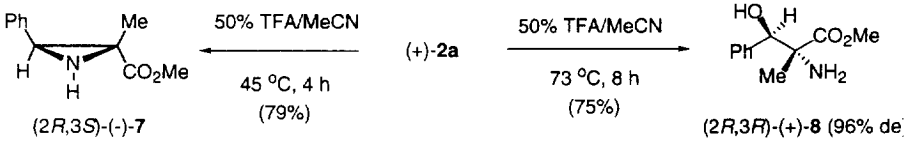
was only 68% yield of (-)-**4** after 4 days. This suggests that precomplexation of the substrate with the catalyst is required prior to hydrogenation and is hampered at the elevated temperature. Refluxing (-)-**4** with 48% HBr and phenol efficiently removed the N-tosyl group to give an 74% isolated yield of (*R*)-(+)-α-methylphenylalanine (**5**) [$[\alpha]^{20}_D$ +19.01 (c 0.51, H_2O), lit.[12d] $[\alpha]^{20}_D$ +20.5 (c 1.0, H_2O)] following isolation by ion exchange (Dowex 50x8-100, acid).[21] To further establish the enantiomeric purity of (+)-**5** it was converted to the methyl ester **6** in 65% yield according to the method of Jain.[23] Chiral shift reagent experiments with $Eu(hfc)_3$ indicate that (-)-methyl α-methylphenylalanine (**6**) ($[\alpha]^{20}_D$ -2.4 (c 0.75, EtOH)) is >95% enantiomerically pure.[24]

Scheme 3



An important advantage of the *N*-sulfinyl auxiliary is that it is easily removed under acid or base conditions thus providing the opportunity to introduce other *N*-aziridines substituents or activating groups.[15] When N-sulfinylaziridine 2-carboxylic acid (+)-**2a** was stirred at 45 °C with 50% aqueous trifluoroacetic acid in acetonitrile for 4 h, aziridine (2*R*,3*S*)-(-)-**7** was isolated in 79% yield (Scheme 4). Alternatively when the reaction was heated at 73 °C for 8 h methyl (2*R*,3*R*)-(+)-α-methyl-β-phenylserine (**8**) was obtained in 75% yield by flash chromatography. In an earlier synthesis of this material, via the reaction of benzaldehyde with a lithiated bis-lactim, Schollkopf et. al reported that the asymmetric induction at C-3 was poor (ca 41%) and that it was a thermally labile oil.[7a,24] By contrast we found methyl (2*R*,3*R*)-(+)-α-methyl-β-phenylserine (**8**) to be a stable, white crystalline solid mp 93-95 °C, ($[\alpha]^{20}_D$ +5.0 (c 0.68, $CHCl_3$)) with IR and NMR consistent with reported values.[25,26]

Scheme 4



In summary, a new methodology is described for the preparation of 2-substituted aziridine 2-carboxylic acids **2** via the highly diastereoselective Darzens-type addition of α-bromo enolates to enantiopure sulfinimines **1**. Regio- and stereocontrolled ring-opening of **2** affords α-methylphenylalanine (**5**) and α-methylphenylserine (**8**) in high enantiomeric purity. The enantiomers of **5** and **8** are similarly available from (*R*)-(-)-**1**. The extension of this methodology to the preparation of other 2-substituted aziridine 2-carboxylic acids is in progress.

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26. This compound was fully characterized and had spectral properties consistent with its structure.

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