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AZIRIDINE 2-CARBOXYLATE ESTER MEDIATED ASYMMETRIC SYNTHESIS OF α-ALKYL β-AMINO ACIDS

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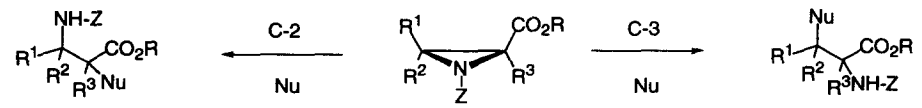
Summary: The highly stereoselective ring opening of N-tosylaziridine 2-carboxylate esters with $LiAlH_4$ followed by oxidation of the ensuing *syn* alcohols results in a highly efficient 4 step asymmetric synthesis of α-methyl β-amino acids from N-sulfinylaziridine 2-carboxylate esters. © 1997 Elsevier Science Ltd.

The asymmetric synthesis of α-alkyl β-amino acids is of current interest because they are constituents of biologically active natural products[1] and precursors of the β-lactam class of antibiotics. Furthermore, substitution of α-amino acids by β-amino acids is useful in the preparation of peptide analogs with increased activity and enzymatic stability.[2] Methods for their synthesis[3] include the Michael addition of chiral secondary amines to α,β-unsaturated esters,[4] the homologation of α-amino acids,[5] alkylation of enolates derived from perhydropyrimidin-4-ones[6], additions to imines,[7] and enzymatic resolution.[8] Many of these procedures are multi-step, affording the product in low overall conversions or requiring separation of diastereoisomers. For these reasons the development of more efficient methods for the asymmetric synthesis of this important class of β-amino acids is highly desirable.

N-Activated aziridine 2-carboxylate esters **1** are useful building blocks for the asymmetric construction of α-amino acids because they undergo stereocontrolled ring-opening at C-3 with inversion of configuration to give β-substituted α-amino acid (Scheme 1).[9,10] Indeed, recent studies in our laboratory have demonstrated the application of cis-N-sulfinylaziridine 2-carboxylate esters **1** (Z = ArS(O)-) in highly stereoselective asymmetric synthesis of α-amino acids,[10] α-methyl[11] and β-substituted α-amino acids,[12] the antibiotic thiamphenacol,[13] β-hydroxy α-amino acids,[14] β-hydroxy α-methyl α-amino acids,[11] the protein kinase C inhibitors D-*erythro* and L-*threo*-sphingosine,[14] and

Scheme 1



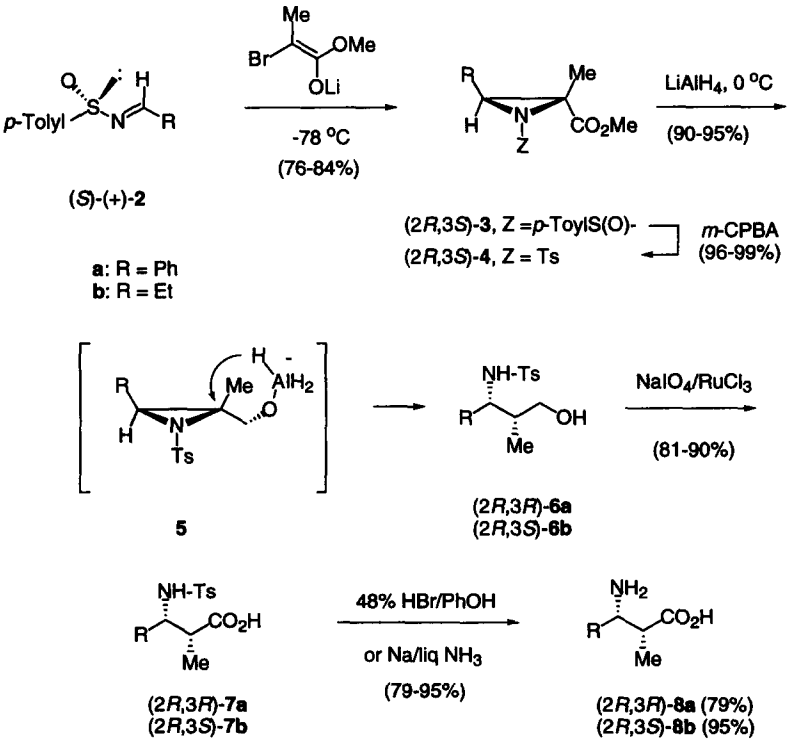
1

β-amino acid — Z = Ts, *p*-TolylS(O) — α-amino acid

the cytotoxic antibiotic (*R*)-(-)-dysidazirine.[15] However, to prepare β-amino acids from **1**, requires ring-opening at C-2 which is relatively rare.[16] On the other hand, Tanner[17] and others[18] have shown that C-2 aziridine ring-opening occurs in the corresponding aziridino alcohols **1** (CO_2R = CH_2OH). We make use of this strategy in the first asymmetric synthesis of α-methyl-β-amino acids from aziridine-2-carboxylate esters.

2-Methyl-N-sulfinylaziridines **3a-b** were prepared as previously described by addition of the lithium enolate of methyl α-bromopropionate to sulfinimines (*S*)-**2a-b** (Scheme 2).[10] (*S*)-(+)-N-(propylidene)-*p*-toluenesulfinamide (**2b**) was prepared in 67% yield by reaction of (1*R*,2*R*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (Andersen reagent) with 1.3 equivalents of LiHMDS and 1.1 equiv. *n*-propanal at -78 °C as present earlier.[19,20] Following separation of the diastereomeric E/Z-aziridines by flash column chromatography (+)-(2*R*,3*S*)-**3a** and (+)-(2*R*,3*S*)-**3b** were isolated in 84 an 76% yield, respectively.[20] Oxidation of the N-sulfinyl aziridines **3** was accomplished using 2.0 equiv. of 60 % *m*-chloroperbenzoic acid (*m*-CPBA) in $CHCl_3$ to give the N-tosyl derivatives **4** in nearly quantitative yield. Reduction of **4** at 0 °C with 1.0-1.2 equiv. of lithium aluminum hydride ($LiAlH_4$) afforded exclusively the *syn* alcohols (2*R*,3*R*)-**6a** and (2*R*,3*S*)-**6b** in 90-95% yield.[20] 2-Methyl-3-(*N*-tolylamino)-3-phenyl-1-propanol (**6a**) has been prepared in racemic form as a 1:1 *syn*:*anti* mixture

Scheme 2



via the hydroboration of 2-methyl-1-(N-tolylamino)-1-phenyl-2-propene,[21] and (2*S*,3*R*)-2-methyl-3-(tosylamino)pentanol (**6b**) was prepared in 10 steps from L-aspartic acid.[22] The fact that the reductive ring-opening of **4** occurs at C-2 with inversion of configuration strongly supports the suggestion by Tanner et al.[17] that hydride is delivered intramolecularly via the aluminum hydride complex of the intermediate aziridino alcohol; e.g. **5**.

Next the amino alcohols **6** were oxidized to the β-amino acid derivatives **7** in good to excellent yield by treatment with 4.4 equiv. of $NaIO_4$ and a catalytic amount of $RuCl_3$. Attempts to remove the tosyl group in **7a**, as previously described,[12] by heating with 48% HBr/PhOH gave uncharacterizable materials. However, reduction with Na/liq. NH_3 afforded (2*R*,3*R*)-(+)-2-methyl-3-amino-3-phenylpropanoic acid (**8a**)[22] in 79% isolated yield. The tosyl group in **7b** was removed uneventfully with 48% HBr/PhOH to give (2*R*,3*S*)-(-)-2-methyl-3-aminopentanoic acid (**8b**)[23] in 95% isolated yield. The fact that the **8a** and **8b** were obtained as single diastereoisomers (^1H NMR of the crude mixtures) indicates that removal of the tosyl group occured without epimerization at the C-3 nitrogen stereogenic center. The crude amino acids were purified using a Dowex 50X8-100 ion exchange resin and isolated as the hydrochloride salts by dissolving in conc. HCl and concentrating. Their properties were identical to authentic samples and obtained in >97% ee.[22-24] Amino acid **8b** is the enantiomer of the β-amino acid found in the marine cytotoxic antitumor desipepties dolastatin D,[1e] 10 and 11.[1a] This enantiomer can be readily prepared starting from (*R*)-(-)-**2**.[19]

In summary, a short, highly efficient four-step stereoselective asymmetric synthesis of α-alkyl β-amino acids **8a** and **8b** in 57-81% overall yield from N-sulfinylaziridine-2-carboxylate esters **3a** and **3b** is described.

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20. Selected physical properties: *(S)*-(+)-**2b**: oil, $[\alpha]^{20}_D$ +385 (c 2, $CHCl_3$); *E*-(*Ss,2R,3S*)-(+)-**3b**: oil; $[\alpha]^{20}_D$ +72.0 (c 0.30, $CHCl_3$); *E*-(*2R,3S*)-(+)-**4b**: mp 84-86 °C, $[\alpha]^{20}_D$ +24.4 (c 0.55, $CHCl_3$);*syn-(2R,3R)*-(+)-**6a:** mp 159-61 °C, $[\alpha]^{20}_D$ = +26.1 (c 1.0, CH_3OH); *syn-(2R,S)*-(-)-**6b**: mp 73-75 °C, $[\alpha]^{20}_D$ -35.0 (c 0.60, $CHCl_3$); *syn-(2R,3R)*-(+)-**7a**: mp 144-46 °C, $[\alpha]^{20}_D$ = +49.1 (c 1.1, $CHCl_3$); *syn-(2R,3S)*-(-)-**7b**: oil; $[\alpha]^{20}_D$ -36.5 (c 0.62, $CHCl_3$).
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