Enantioselective Synthesis of Optically Pure (*R*)- and (*S*)-β-Lysine *via* Nitrone Cycloaddition

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Optically pure (*R*)- and (*S*)-β-lysines have been obtained *via* cycloaddition of chiral nitrone (**4**) to vinyl acetate, followed by facile chromatographic separation of the four resulting acetates (**5**) into two pairs of C-5 epimers and conversion of each pair into diastereoisomerically pure isoxazolidinone (**7a** or **b**).

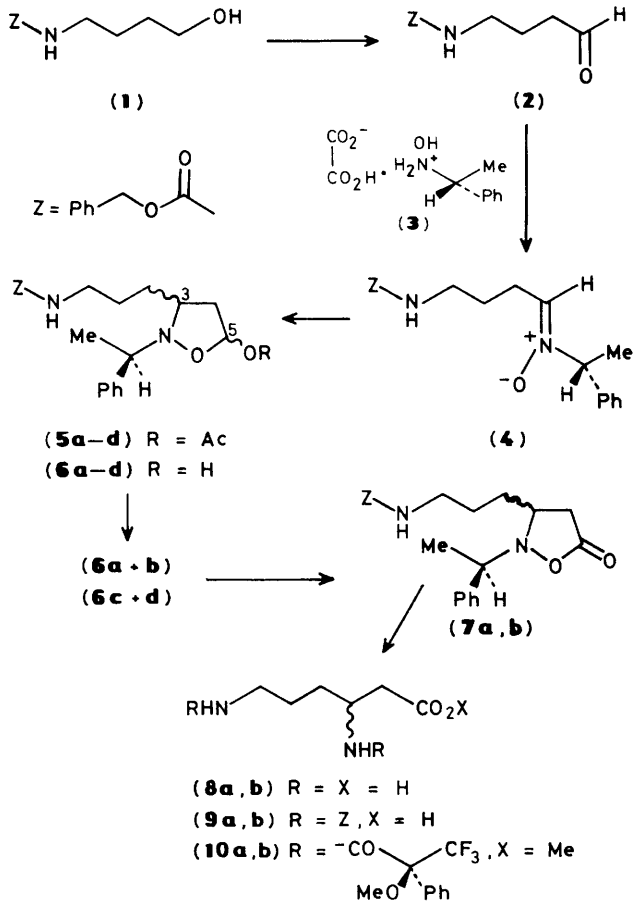
β-Amino acids are important in both primary and secondary metabolism.[1] Pre-eminent among them is β-lysine. (3*S*)-β-Lysine is the first intermediate in the anaerobic catabolism of (2*S*)-α-lysine in *Clostridia*, which terminates in the formation of butyric acid, acetic acid, and ammonia.[2] (3*S*)-β-Lysine is also widely produced by *Streptomyces* species and incorporated into a large family of broad-spectrum antibiotics.[3] Of these, streptothrycin F which contains one β-lysine residue, has been most intensively studied,[4] but the racemomycins (RM–A ≡ streptothrycin F) form an homologous series with up to seven β-lysine residues linked in a peptide chain.[3]

In previous asymmetric syntheses of β-amino acids, the new chiral centre at C_β was generated either by nucleophilic addition at sp^2 carbon or by hydrogenation of α,β-dehydro-β-amino esters. Optical yields have not exceeded 50% and have generally been below 20%. We now report the enantioselective synthesis of optically pure (*R*)- and (*S*)-β-lysine *via* cycloaddition of a chiral nitrone to vinyl acetate, based on previous reports that chiral nitrones can cyclo-add to alkenes with good diastereoselectivity.[5–7]

Swern oxidation [dimethyl sulphoxide (DMSO)–oxalyl chloride in CH_2Cl_2, −60 °C, then triethylamine (TEA)] of the *N*-protected 4-aminobutan-1-ol (**1**),† m.p. 58—61 °C, (5M NaOH, $PhCH_2OCOCl$, 1 equiv., 0 °C) afforded the aldehyde (**2**) [^{1}H n.m.r. ($CDCl_3$): δ 1.85 (2H, q), 2.54 (2H, t), 3.25 (2H, q), 5.09 (2H, s), 7.31 (5H, s), and 9.8 (1H, s)] as an unstable yellow oil. This was treated immediately with the crystalline hydroxylamine oxalate (**3**)[8] (1 equiv. in CH_2Cl_2–TEA, 20 °C, 5 h) to furnish the nitrone (**4**), m.p. 92—96 °C, in 91% overall yield from (**1**). Reaction of (**4**) with vinyl acetate (excess, reflux, 16 h) furnished the four diastereoisomeric C-5 acetates (no C-4 acetates) (**5a—d**) (68% yield), which were cleanly separable by flash chromatography (SiO_2)[9] into two pairs (ratio 7 : 3; eluted with 35—55% ethyl acetate–hexane). Each pair consisted of C-5 epimers but had only one configuration at C-3, as subsequently revealed by the homogeneity of the C-3-epimeric isoxazolidinones (**7a,b**). Hydrolysis [K_2CO_3 in MeOH–H_2O (4 : 1), 20 °C, 1 h] of each acetate pair [^{1}H n.m.r. δ 6.42 and 6.25 (O-C*H*-OAc)] afforded (>98%) the corresponding pair of isoxazolidinols (**6a + b**) [δ 5.61 (1H, m)] and (**6c + d**) [δ 5.35 (1H, m, O-C*H*-OH)]. They were individually oxidised (CrO_3, CH_2Cl_2, pyridine, 0 °C) to the isoxazolidinones (**7a,b**)‡ (*ca.* 40%) which were purified by silica gel chromatography. In each case the ^{1}H and ^{13}C n.m.r. spectra showed complete absence of the C-3 isomeric isoxazolidinone.

Hydrogenolysis of (**7a**) (20% $Pd(OH)_2$/C, H_2, EtOH; 20 h at 20 °C then 5 h at 70 °C) afforded (*R*)-(−)-β-lysine (**8a**)§ (98% yield). Hydrogenolysis of (**7b**) as for (**7a**) afforded (*S*)-(+)-β-lysine (**8b**)§ (99% yield).

The optical purity of the (*R*)- and (*S*)-β-lysines (**8a,b**) from hydrogenolysis of (**7a,b**) was checked by conversion of the total hydrogenolysis product into the methyl ester bis-(*S*)-methoxy(trifluoromethyl)phenylacetyl (MTPA) amides (**10a,b**). These could not be clearly identified in the ^{19}F n.m.r. spectrum because other fluorine-containing products were formed, but they were readily separated by g.c.–mass spectrometry (OV-1; 25 m, 290 °C, 3 ml per min): retention time (**10a**) 16.68, (**10b**) 16.12 min; *m/z* 592 [M^+], 403 (100%)



Scheme 1

† All new compounds gave spectroscopic and micro-analytical data in accord with the assigned structures.

‡ *Spectral data* for (**7a**): i.r. (CCl_4) ν_{max} 1790, 1728 cm^{-1}; *m/z* ($C_{22}H_{26}O_4N_2$) 382.1894; ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.53 (3H, d, CH_3CHPh), 4.00 (1H, q, CH_3CHPh), 5.06 (2H, s, PhCH_2O); ^{13}C n.m.r. (90.56 MHz, $CDCl_3$) δ 156.27 (NH*C*OO), 176.52 (CH_2*C*OO).

For (**7b**) i.r. (CCl_4) ν_{max} 1790, 1728 cm^{-1}; *m/z* 382.1912; ^{1}H n.m.r. δ 1.60 (3H, d), 4.04 (1H, q), 5.10 (2H, s); ^{13}C n.m.r. δ 156.41, 175.24.

§ (**8a**): $[\alpha]_D$ −19.5° (*c* 1.0, 1 M HCl) (lit.[10] +24° for (*S*)-(+)-β-lysine); ^{1}H n.m.r. (90 MHz, D_2O) δ 1.72 (4H, m), 2.49 (2H, d), 3.05 (2H, br. t), 3.82 (^{1}H, m); *N,N*-dibenzyloxycarbonyl derivative (**9a**), m.p. 153—156 °C (lit.[11] 155 °C).

(**8b**): $[\alpha]_D$ +18° (*c* 0.2); ^{1}H n.m.r. as for (**8a**); *N,N*-dibenzyloxycarbonyl derivative (**9b**), m.p. 153—156 °C.

[M^+ – $C_9H_8F_3O$]. In each case the other isomer was completely absent.

Authentic specimens of (*R*)- and (*S*)-β-lysine were prepared by Arndt–Eistert homologation of (*R*)- or (*S*)-dibenzyloxycarbonyl ornithine,[11] respectively and were converted into derivatives (**9a,b**) and (**10a,b**) for direct comparison with the compounds prepared above *via* nitrone cycloaddition. There was complete correspondence in all physical and spectroscopic properties of the substances prepared by the two routes.
routes.

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