Pergamon

Tetrahedron Letters, Vol. 37, No. 29, pp. 5225-5226, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01061-1

Syntheses of (*S*)-β-Pyrazolylalanine and (*S*)-Quisqualic Acid from a Serine-derived Aziridine

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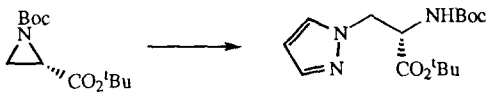
Abstract: The naturally occurring amino acids (*S*)-β-pyrazolylalanine and (*S*)-quisqualic acid are synthesised *via* the nucleophilic ring-openings of an optically active aziridine by pyrazole and 1,2,4-oxadiazolidine-3,5-dione, respectively. Copyright © 1996 Published by Elsevier Science Ltd

Of the known, naturally occurring α-amino acids a significant proportion are derivatives of β-aminoalanine. Many of these have been shown to be biosynthesised from *O*-acetyl serine in the presence of the appropriate nitrogen nucleophile and one of a variety of enzymes[1]. Several useful general routes to β-amino acids have been described[2]. The majority[2c,d,e] of these can be considered to be 'biomimetic' processes, since they are based on a reaction between a nitrogen nucleophile and an alanine β-cation equivalent. We have reported a concise synthesis of (*S*)-*tert*-butyl-*N*-*tert*-butoxycarbonylaziridine-2-carboxylate **1** and its use for the preparation of α-amino acid derivatives *via* its ring-opening with copper 'catalysed' Grignard reagents[3]. Herein, we exemplify the use of **1** for the preparation of heterocyclic α-amino acids by the syntheses of (*S*)-β-pyrazolylalanine **2** and (*S*)-quisqualic acid **3**.

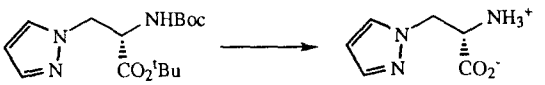
β-Pyrazolylalanine **2**, which is isosteric with histidine[5], was first isolated from *Citrullus vulgaris*, a water melon, in 1957[4]. Several racemic syntheses and resolution procedures for the preparation of **2** have been described, but only one enantiospecific synthesis has been reported[2c]. We found that treatment of aziridine **1** with pyrazole results in the isolation of protected β-pyrazolylalanine **4** in good yield (Scheme 1).



1 **4**

Scheme 1. Reagents and conditions: pyrazole (2 eq.), PhMe, reflux, 48hr, 65-80%

Deprotection of **4** to give **2** (mp 245°C, lit[6] 239-244°C) was effected by CF_3CO_2H followed by ion-exchange chromatography (Scheme 2). The optical rotation of **2** was determined to be +68.5° (c 0.35, H_2O), compared to the literature value[6] of +72.0° (c 1.0, H_2O).



4 **2**

Scheme 2. Reagents and conditions: CF_3CO_2H, 0°C→RT 14hr, then ion-exchange chromatography (Dowex® 50W-X8), 75%

(*S*)-Quisqualic acid **3** is the active ingredient of the ancient Chinese drug Shihchuntze, an anthelmintic made from seeds of *Quisqualis indica*[7]. Quisqualic acid **3** is unique in that it is the only known compound to act as an agonist at multiple excitatory amino acid receptor subtypes in the central nervous system[8]. The first enantiospecific synthesis of quisqualic acid employed *N*-Boc-(*S*)-serine as starting material, and proceeded in an overall yield of 36% over 7 steps[2a]. More recently, Guibourdenche *et al.*[9] reported an asymmetric synthesis based on a previous racemic study by Bycroft *et al.*[10], with an overall yield of 17% over 11 steps.

Treatment of **1** with 1,2,4-oxadiazolidine-3,5-dione[11] gave the protected quisqualic acid **5** after chromatography in moderate yield (Scheme 3).

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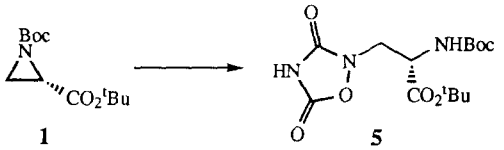
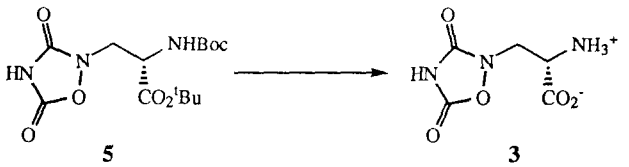


Scheme 3. Reagents and conditions: 1,2,4 oxadiazolidine-3,5-dione, DMF, 98°C, 18hr, 49%

Acidic deprotection (CF_3CO_2H, anisole) of **5** gave (*S*)-quisqualic acid **3** as a white powder (mp 190-192°C, lit[2a] 190-191°C) in high yield (Scheme 4). The identity of the product was confirmed by mixed melting point and spectroscopic comparisons with an authentic sample[12]. The optical rotation of **3** prepared *via* **1** was determined to be +14.5° (c 0.66, 6N HCl), compared with the reported value[2a] of +17.0° (c 2.0, 6N HCl).



Scheme 4. Reagents and conditions: CF_3CO_2H, anisole, 0°C, 16hr, then ion-exchange chromatography (Amberlite® IR-45), quant.

In summary, optically enriched natural products (*S*)-β-pyrazolylalanine **2** and (*S*)-quisqualic acid **3** have been synthesised by a route involving the ring-opening of an optically active aziridine[13]. In the case of **3** the synthesis proceeds in an overall yield comparable with the best previously reported route[2a], and utilises less steps. The syntheses of **2** and **3** exemplify the use of aziridine **1** for the synthesis of β-aminoalanine derivatives.

Acknowledgements

We thank Roche Products Ltd. for a C.A.S.E. award (to C.N.F.) and the E.P.S.R.C. for support (to A.C.S. and C.N.F.).

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13. Racemic aziridine (±)-**1** reacted with other nitrogen based nucleophiles to produce β-substituted alanines in good yields. For example, reaction of (±)-**1** with sodium azide led to the isolation of protected β-azidoalanine in quantitative yield, and reaction with imidazole resulted in the isolation of protected β-imidazolylalanine in 57% yield.

(*Received in UK* 21 *May* 1996; *accepted* 31 *May* 1996)