Synthesis of L-Quisqualic Acid: A General Method for Enantio-efficient Synthesis of β-Aminoalanine Derivatives

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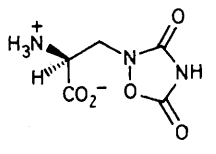
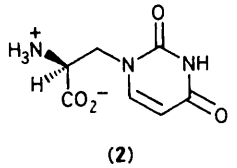
A general method for the enantio-efficient synthesis of β-aminoalanine derivatives, which involves intramolecular transfer of the amino substituent from the α-carboxy to the β-carbon atom *via* an azetidinone is described with its application to an efficient synthesis of the neuroexcitatory quisqualic acid in an optically pure state.

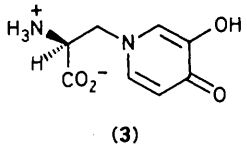
The natural occurrence of β-substituted alanine derivatives, such as the neuroexcitatory quisqualic acid (**1**)[1—5] and the non-protein amino acids willardiine (**2**)[6] and mimosine (**3**),[7] prompted us to search for general procedures for enantio-efficient syntheses of such compounds. Present methods,[7] such as displacement reactions on β-substituted alanines, path a, Scheme 1, or conjugate additions to dehydroalanine derivatives, path b, Scheme 1, are neither efficient nor stereospecific, frequently giving racemic materials which then require resolution. Consequently we have examined the intramolecular delivery of a nucleophile, attached initially to the carboxy group, onto the β-carbon atom of serine, to provide thereby a cyclic intermediate which in principle should be readily hydrolysed to the required β-substituted alanine, as in Scheme 2. Since L-quisqualic acid (**1**) is an exceptionally potent agonist of the neurotransmitter L-glutamate and is not readily accessible either from natural sources



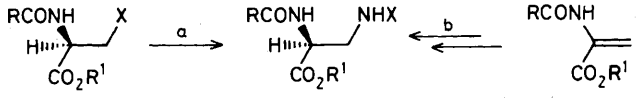
(**1**)



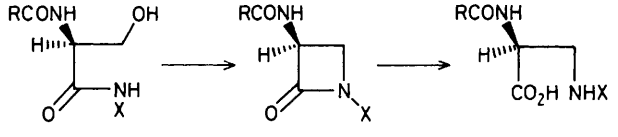
(**2**)



(**3**)



Scheme 1



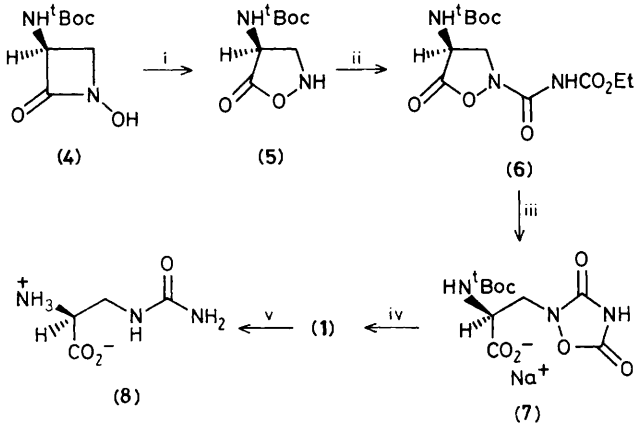
Scheme 2

or from synthesis[3,8] we chose this as our initial target for reduction to practice of our proposal as in Scheme 2.†

Thus L-serine was converted by known procedures into 3*S*-azetidinone (**4**)[9] which was isomerised cleanly to the isooxazolidin-5-one (**5**)‡ by treatment with a catalytic amount of lithium ethanethiolate [3 mol %, tetrahydrofuran (THF), 20 °C, 72 h, 83%]. Treatment of this substance with ethoxycarbonyl isocyanate[10] (1.05 equiv., THF, 20 °C) gave the urea (**6**) which was immediately ring opened [NaOH (2.0 equiv.), THF: water (1 : 1), 20 min, 20 °C] and freeze dried to the salt (**7**). Upon treatment of (**7**) with trifluoroacetic acid (20 °C, 1 h) followed by ion-exchange chromatography [Dowex 50W-X8(H)] there was obtained L-quisqualic acid (**1**) {89% from (**5**), m.p. 190—191 °C (from water–ethanol) (lit.,[2] 187—188 °C), $[\alpha]_D^{20}$ + 17.0 (*c* 2.0, 6 M HCl) [lit.,[2] + 17.3 (*c* 2.0, 6M HCl)], ν_{max} (KBr) 3400—2750s, 1830s, 1775s, 1745s, and 1605s cm^{-1} (lit.,[2] 3400—2750, 1830, 1775, 1740, and 1605

† During the course of this work a synthesis of *racemic* (**1**) (20% from the enol formed from ethyl hippurate and ethyl formate) was reported. An enzymic resolution procedure was employed to obtain the L-isomer, 'identical with the natural product.' However neither the yield nor specific rotation of L-(**1**) was reported, see B. W. Bycroft, S. R. Chhabra, R. J. Grout, and P. J. Crowley, *J. Chem. Soc., Chem. Commun.*, 1984, 1156.

‡ The structure (**5**) was characterised by full spectral and analytical data. An uncatalysed rearrangement of (**4**) to (**5**), achieved by reflux in ethyl acetate gave only a 20% yield of (**5**), see T. Hirose, K. Chiba, S. Mishio, J. Nakano, and H. Uno, *Heterocycles*, 1982, **19**, 1019.



Scheme 3. *Reagents and conditions:* i, LiSEt (3 mol %), THF, 20 °C, 72 h; ii, EtO·CO·NCO (1.05 equiv.), THF, 20 °C, 5 min; iii, NaOH (2 equiv.), THF, H_2O, 20 °C, 20 min; iv, trifluoroacetic acid, 20 °C, 1h, then Dowex 50W-X(8)H; v, H_2–PtO_2–H_2O, 20 °C, 3 h.

cm^{-1}), δ_H§ (300 MHz, D_2O/NaOD, pH 13) 3.55—3.57 (1H, m, X part of ABX, 2-H), 3.72—3.85 (2H, m, AB part of ABX, 3-H), δ_C (62.9 MHz, D_2O) 50.1(t), 53.4(d), 154.8, 159.7, and 171.3(3 × s), *m/z* (positive argon fast-atom bombardment) 190 (MH^+, base peak), satisfactory elemental analysis obtained} (Scheme 3).

An identical procedure applied to 3*R*-(**4**) gave D-quisqualic acid, m.p. 190—191 °C, $[\alpha]_D^{20}$ −16.8° (*c* 2.0, 6M HCl).

The optical purity of L-quisqualic acid (**1**) was further confirmed by chemical degradation. Thus catalytic reduction (H_2–PtO_2–H_2O, 20 °C, 3 h) gave L-2-amino-3-ureidopropanoic acid (**8**), m.p. 216—217 °C (from water–ethanol), $[\alpha]_D^{20}$ −67.7° (*c* 1, H_2O), δ_H § (300 MHz, D_2O/NaOD, pH 13) 3.20—3.42 (3H, m), *m/z* (positive argon fast-atom bombardment) 148 (MH^+, base peak) [lit.,[8] m.p. 214—215 °C, $[\alpha]_D^{20}$ −68.8° (c 1.1, H_2O); lit.,[11] m.p. 218—220 °C, $[\alpha]_D^{20}$ −66.2° (*c* 2.6, H_2O)].

In summary, our method has permitted a relatively simple synthesis of both enantiomers of quisqualic acid, with an overall efficiency far in excess of any prior methodology, and in principle should provide access to a variety of unusual β-substituted amino acids in the optically pure state.

Received, 19th November 1984; Com. 1634

§ Chemical shifts are referenced to internal sodium [2,2,3,3-$^2H_4$]-3-trimethylsilylpropionate = 0.00 p.p.m.

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