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# Biomimetic Syntheses of Stizolobic Acid and 3-(6-Carboxy-2-oxo-4-pyridyl)alanine

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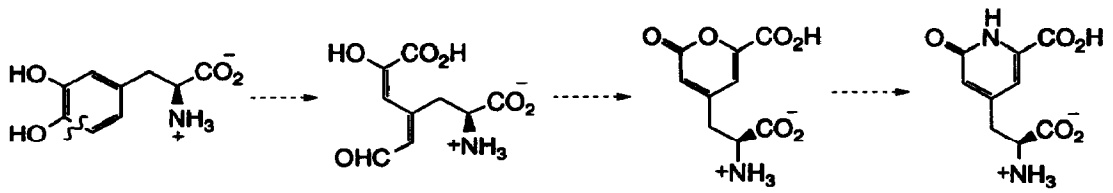
*Abstract:* (±) Stizolobic acid (1) and (±) 3-(6-carboxy-2-oxo-4-pyridyl)alanine (2) were synthesized in a biomimetic fashion from a catechol *via* an iron (III) catalysed oxidative cleavage.

Stizolobic acid (1) and 3-(6-carboxy-2-oxo-4-pyridyl)-*L*-alanine (2) (which we refer to as acromelobic acid) are among many non-proteinogenic amino acids which have been isolated from plant extracts[1]. Stizolobic acid (1) is a competitive antagonist of the quisqualate type receptor at the crayfish neuromuscular junction[2] and shows depolarizing activity in the mammalian central nervous system, binding preferentially to receptors other than the NMDA-type[3]. Acromelobic acid (2) shows weak depolarizing activity in the newborn rat spinal cord[4].

Radio-labelling studies[5] have shown that stizolobic acid (1) is biosynthesized from *L*-DOPA (3). The key feature of the biogenesis is a distal extradiol oxidative cleavage of the catechol moiety of *L*-DOPA (3), catalysed by an iron dependent dioxygenase, to give an alanyl muconic semi-aldehyde derivative (4). Subsequent recyclization of (4) followed by oxidation of the corresponding lactol produces stizolobic acid (1). Ammonolysis[4] of the pyrone ring of (1) gives acromelobic acid (2) (scheme 1).



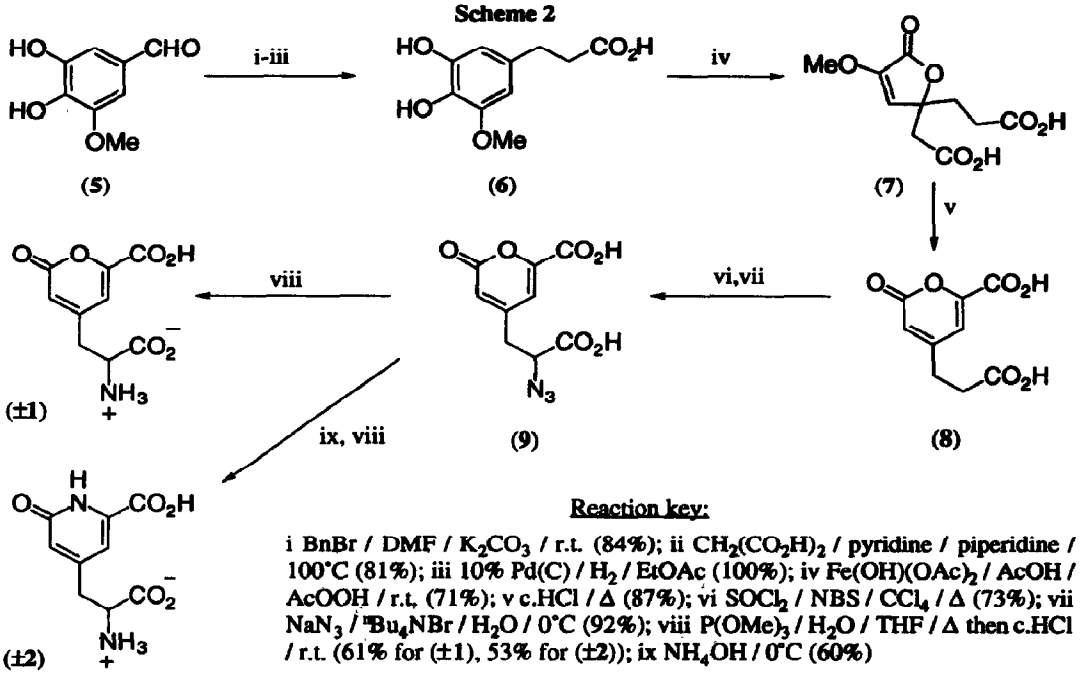
(3) (4) (1) (2)

**Scheme 1**

Supplementary to earlier syntheses of (±1)[6] biogenetic considerations have led to the development of the total biomimetic syntheses of (±1) and (±2) (scheme 2). The biomimetic nature of the synthetic strategy centres around the transformation of a catechol to a 2-pyrone-6-carboxylic acid.

Key intermediate (6) was obtained in satisfactory yield by homologation of the starting aldehydic catechol (5)[7]. This was achieved *via* bis-benzyl protection of the catechol and subsequent Doebner modified Perkin condensation[8] followed by catalytic hydrogenation. Iron (III) catalysed peracetic acid oxidation[9] of dihydrocaffeic acid derivative (6) afforded the butenolide (7) (a cyclized muconic acid derivative) cleanly and in good yield. Prolonged treatment of (7) with hot concentrated hydrochloric acid effected methyl vinyl ether hydrolysis with concomitant rearrangement to afford des-aminostizolobic acid (8) in good yield. *In situ* formation of the di-acid chloride in the presence of *N*-bromosuccinimide[10] gave an alpha-bromo acid after hydrolytic work-up. Azidation of the alpha-bromo acid was achieved in excellent yield with sodium azide in

**Scheme 2**




Reaction key:

i BnBr / DMF / $K_2CO_3$ / r.t. (84%); ii $CH_2(CO_2H)_2$ / pyridine / piperidine / 100°C (81%); iii 10% Pd(C) / $H_2$ / EtOAc (100%); iv $Fe(OH)(OAc)_2$ / AcOH / AcOOH / r.t. (71%); v c.HCl / Δ (87%); vi $SOCl_2$ / NBS / $CCl_4$ / Δ (73%); vii $NaN_3$ / $^nBu_4NBr$ / $H_2O$ / 0°C (92%); viii $P(OMe)_3$ / $H_2O$ / THF / Δ then c.HCl / r.t. (61% for (±1), 53% for (±2)); ix $NH_4OH$ / 0°C (60%)

cold water, under phase transfer conditions. The convergent azide intermediate (**9**) was reduced with trimethyl phosphite[11] to afford an intermediate phosphoramidate which gave stizolobic acid (±**1**) upon treatment with concentrated hydrochloric acid. Treatment of (**9**) with cold aqueous ammonia solution followed by an identical reduction protocol gave acromelobic acid (±**2**). Although resolution[12] of (±**1**) has been reported, enantiospecific syntheses of (**1**) and (**2**) are under investigation.

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