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A Biomimetic Synthesis of Stizolobinic Acid

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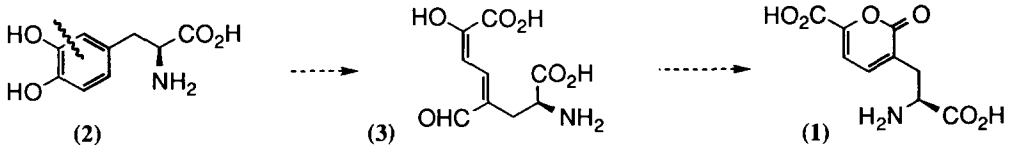
Abstract: Stizolobinic acid (**1**) was synthesized in a biomimetic fashion from an analogue of *L*-DOPA *via* an oxidative cleavage reaction. © 1997 Elsevier Science Ltd.

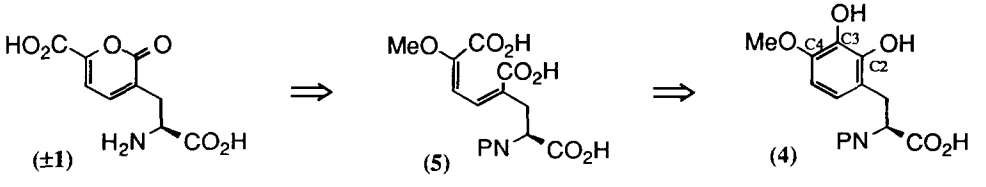
Stizolobinic acid (**1**) is one of many non-proteinogenic amino acids which have been isolated from plant extracts.[1] It is often found to co-exist with its isomeric counterpart stizolobic acid[2,3,4] and has been proposed to be a biosynthetic precursor to acromelic acid A (an extremely potent neurotoxin).[5] (**1**) is mildly neurotoxic, showing weak depolarizing activity in the newborn rat spinal cord.[6,7] Radio-labelling studies have shown that stizolobinic acid (**1**) is biosynthesized from *L*-DOPA (**2**) (Scheme 1).[8] The key feature of the proposed biogenesis is a proximal extradiol oxidative cleavage of the catechol moiety of *L*-DOPA (**2**), catalysed by a dioxygenase, to give an alanyl muconic semi-aldehyde derivative (**3**). Oxidative recyclization of (**3**) produces stizolobinic acid (**1**).

Scheme 1



Further to an earlier communication describing the biomimetic total synthesis of stizolobic acid,[9] we wish to report the asymmetric biomimetic total synthesis of stizolobinic acid (**1**).

Scheme 2



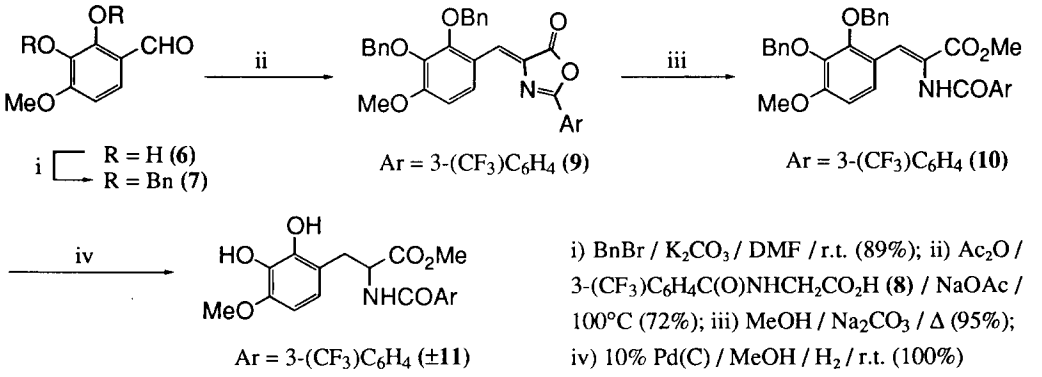
P = a protecting group

A synthetic strategy was devised whereby specific cleavage of the C2-C3 bond of the aromatic ring of a DOPA analogue (**4**) could be controlled by incorporation of free hydroxyl goups at C2 and C3 (Scheme 2).

Pandell's intradiol iron (III) catalysed peracid oxidation protocol[10] was initially chosen as a means of effecting selective fission of the C2-C3 bond. A methoxyl group was included at C4 to serve as an acid labile "masked" hydroxyl group in the oxidation product (**5**). Subsequent hydrolysis and recyclization of (**5**) under strongly acidic conditions would give the desired pyrone (an appropriately selected protecting group on nitrogen being removed simultaneously).

Aldehydic catechol (**6**)[11] was chosen as a starting material and protected as its bis-benzyl ether (**7**) (Scheme 3). An Erlenmeyer condensation[12] of (**7**) with *N*-3-(trifluoromethylbenzoyl)glycine (**8**)[13,14] gave azlactone (**9**). Base catalysed methanolysis[15] of (**9**) afforded the amidocinnamate (**10**) which was reduced to the *DL*-DOPA analogue (±**11**) by catalytic hydrogenation.

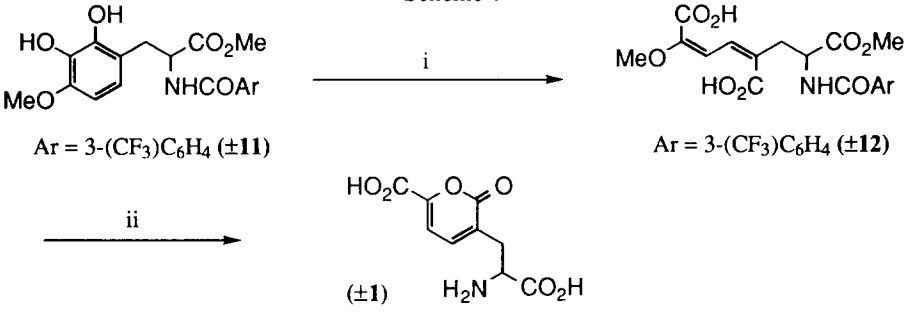
Scheme 3



i) BnBr / K_2CO_3 / DMF / r.t. (89%); ii) Ac_2O / 3-$(CF_3)C_6H_4C(O)NHCH_2CO_2H$ (**8**) / NaOAc / 100°C (72%); iii) MeOH / Na_2CO_3 / Δ (95%); iv) 10% Pd(C) / MeOH / H_2 / r.t. (100%)

Oxidative cleavage of the catechol moiety of (±**11**) with peracetic acid in the presence of a catalytic amount of iron (III) acetate (basic) gave the desired alanyl muconic acid (±**12**) (Scheme 4). Treatment of crude (±**12**) with hot concentrated hydrochloric acid gave *DL*-stizolobinic acid (±**1**).

Scheme 4

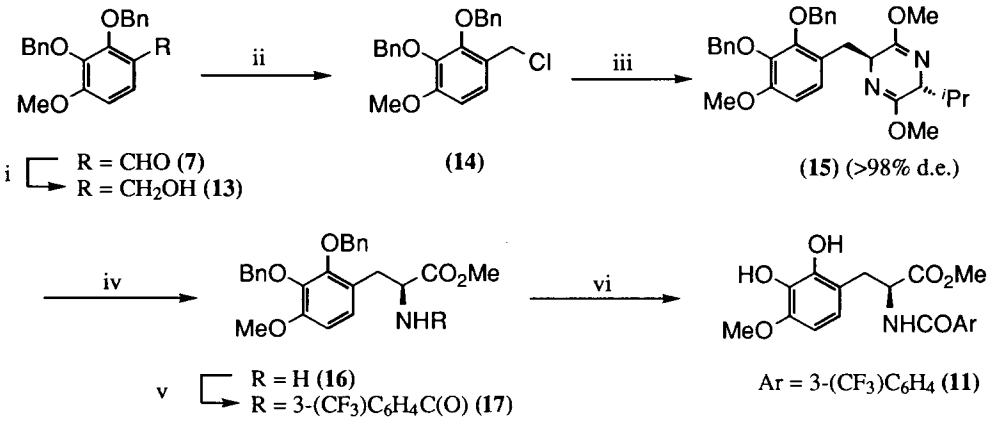


i) AcOH / AcOOH / $Fe(OAc)_2OH_{(cat.)}$ / r.t. (*ca.* 45%); ii) c.HCl / 100°C (*ca.* 65%).

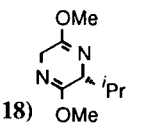
In a subsequent enantiospecific synthesis the *L*-DOPA analogue (**11**) was synthesized stereoselectively in 70% yield over seven steps (Scheme 5). Reduction of (**7**) with sodium borohydride in methanol gave (**13**)

which was reacted with thionyl chloride to produce the benzyl chloride derivative (**14**) cleanly. Chirality was introduced using Schöllkopf's *bis*-lactim ether methodology[16] as a key step to produce (**15**). Hydrolysis of (**15**) with dilute mineral acid gave the free amine (**16**) which was converted into the 3-trifluoromethylbenzoyl derivative (**17**).[14] Hydrogenolysis of the benzyl protecting groups of (**17**) by catalytic hydrogenation gave (**11**) in quantitative yield.

Scheme 5



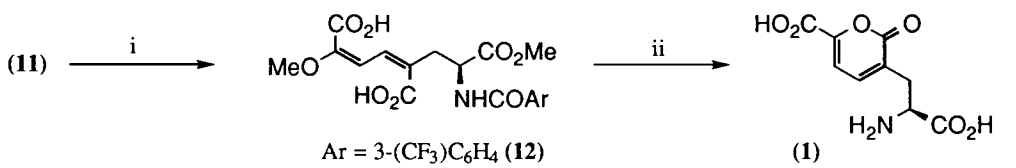
i) $NaBH_4$ / MeOH / r.t. (99%); ii) $SOCl_2$ / DCM / r.t. (100%); iii) (**18**) / ^nBuLi / THF / -78°C (92%); iv) 0.25M HCl / MeCN / r.t. (95%); v) 3-$(CF_3)C_6H_4COCl$ / NEt_3 / DMAP(cat.) / DCM / r.t. (89%); vi) 10% Pd(C) / MeOH / H_2 / r.t. (100%).



(**18**)

Oxidative cleavage of catechol moiety of (**11**) afforded the desired homochiral muconate (**12**) which was converted into *L*-stizolobinic acid (**1**) by heating with strong aqueous acid (Scheme 5). Purification of (**1**) was carried out by ion exchange chromatography.[17]

Scheme 6

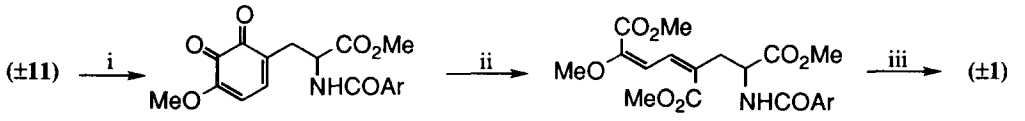


i) $Fe(OAc)_2OH$(cat.) / AcOOH / r.t. (*ca.* 45%); ii) c.HCl / 100°C (*ca.* 65%).

An alternative method of oxidative cleavage of (±**11**) has shown to give much improved yields of muconate product (Scheme 7). This involved a stepwise oxidation of (±**11**) to the corresponding *ortho*-quinone

(±**19**) using Fétizon's reagent (silver carbonate on Celite®),[18] followed by treatment with lead tetraacetate plus methanol,[19] to give triester (±**20**) in 94% yield over the two steps. Hydrolysis of (±**20**) then gave (±**1**).

Scheme 7



Ar = 3-$(CF_3)C_6H_4$ (±**19**) Ar = 3-$(CF_3)C_6H_4$ (±**20**)

i) Ag_2CO_3 / DCM / r.t.; ii) $Pb(OAc)_4$ / MeOH / DCM / 0°C (94% from (±**11**)); iii) c.HCl / Δ (75%).

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