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Concise Syntheses of Acromelic Acid A and *Allo*-Acromelic Acid A

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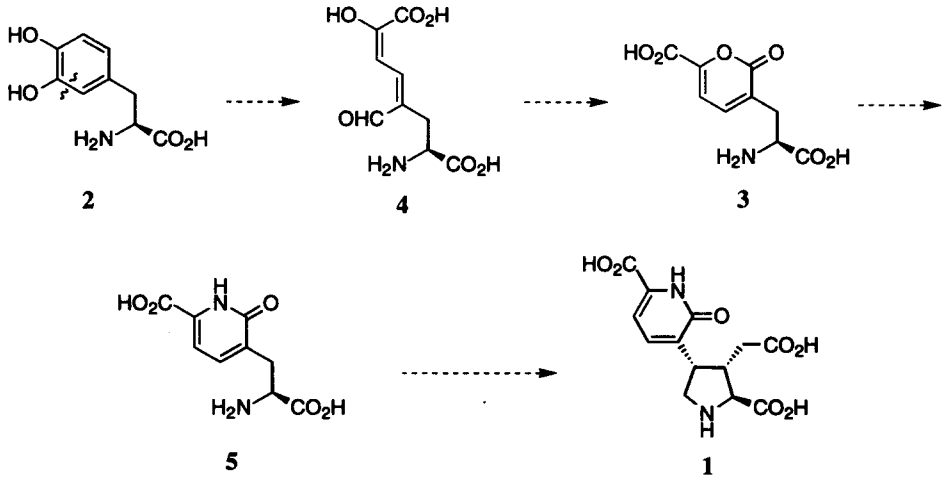
Abstract: Acromelic acid A **1** and *allo*-acromelic acid A **12** were synthesised in a biomimetic fashion. An oxidative cleavage - recyclisation strategy was used to construct the requisite C-4 pyridone from an intermediate catechol.

Acromelic acid A **1** was isolated from a poisonous mushroom, *Clitocybe acromelalga* (CA), in 1983.[1] Since then much interest has been generated owing to its extremely potent neuroexcitatory activity at the glutamate receptor and it is much sought after as a tool in exploratory neurophysiology.[2,3,4] Extraction of **1** from CA is not an efficient process and supply of material has not met this demand. Reported syntheses of **1** thus far have not demonstrated amenability to large scale preparation.[5]



Scheme 1

Herein we report a concise synthesis of **1** based on a biomimetic approach.[6] The biogenesis of **1** features the oxidative cleavage and recyclisation of L-DOPA **2** to give stizolobinic acid **3**, *via* **4** (Scheme 1).[7,8] Ammonolysis of **3** derives **5** which is thought to then condense with glutamic acid to give **1**.[3]

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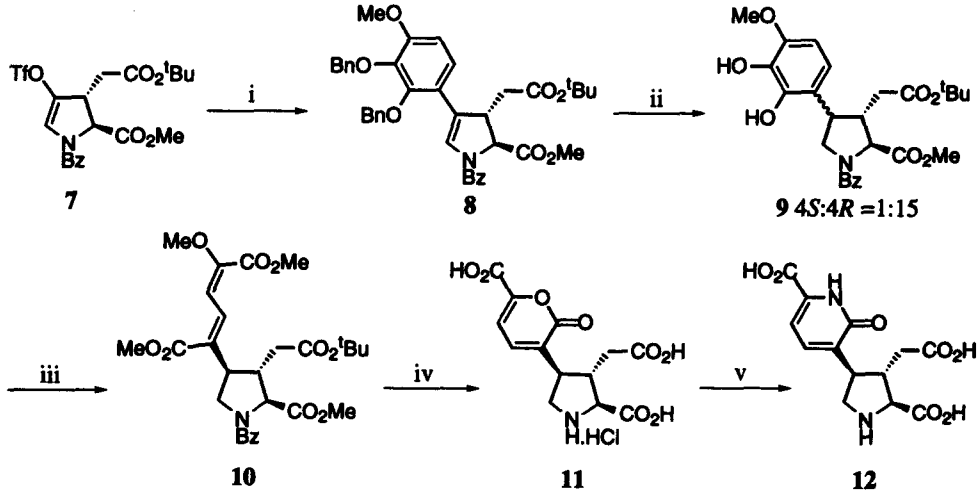
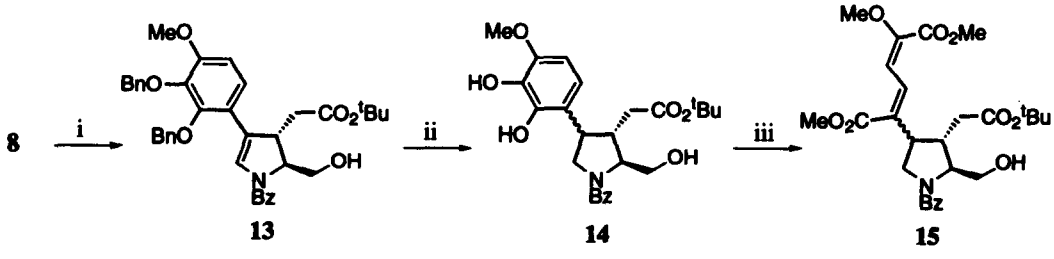
A palladium catalysed cross-coupling[9] of the boronic acid **6**[10] with the vinyl triflate **7**[11] proceeded smoothly to give **8** in 67% yield (Scheme 2). Hydrogenation of **8** in the presence of palladium black gave **9** (15:1 ratio of C-4 epimers in favour of the 4*R* isomer). No reduction of **8** was observed when subjected to hydrogenation under homogeneous catalysis.[12] Oxidative cleavage of **9** (as a mixture of C-4 epimers), by sequential treatment with Fétizon's reagent (silver carbonate on Celite®)[13] then lead tetraacetate and methanol,[14] gave a good yield of the 4*R* isomer **10** after chromatographic purification on silica gel. Hydrolysis of **10** with hot concentrated hydrochloric acid gave the desired pyrone **11**. Treatment of the crude pyrone **11** with aqueous ammonia at room temperature gave *allo*-acromelic acid A **12** (approximately 15% yield over 11 steps from commercially available *trans*-4-hydroxy-L-proline).



Reagents: i) **6**, $Pd(PPh_3)_4$ / DME / 2M $Na_2CO_{3(aq)}$ / LiCl / Δ (67%); ii) H_2 / Palladium black / EtOAc / r.t. (quant.); iii) Ag_2CO_3 on Celite® / DCM / r.t., then $Pb(OAc)_4$ / MeOH / DCM / 0°C (81%); iv) conc. HCl / 100°C; v) $NH_3(aq)$ / r.t. (quant.).

Scheme 2

The successful completion of the synthesis of **12** encouraged us to seek means of controlling the diastereoselectivity in the reduction of the dehydroproline **8** to allow access to acromelic acid A **1**. It has been reported that the stereochemical outcome of olefin hydrogenations can be influenced by the presence of a neighbouring functional group.[15] In particular, primary amines and hydroxyl groups are known to direct hydrogenation from the same face of the molecule.[16] .



Reagents: i) $NaBH_4$ / MeOH / 0°C (78%); ii) H_2 / Catalyst / Solvent; iii) $Pb(OAc)_4$ / MeOH / 0°C (95%).

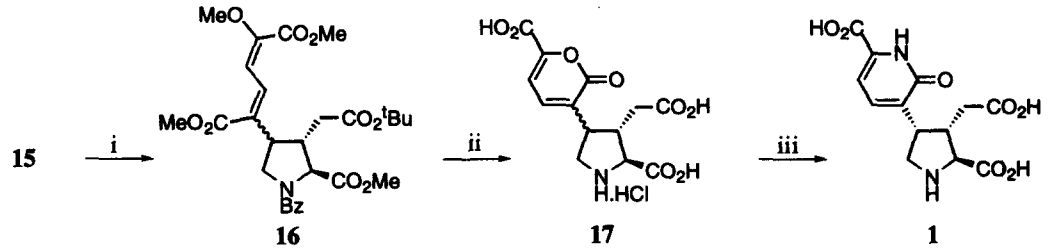
Scheme 3

To this end, the methyl ester of **8** was chemoselectively reduced with sodium borohydride to give alcohol **13** (Scheme 3). Both the solvent and catalyst have been shown to affect substrate haptophilicity and so the stereocontrolled hydrogenation of **13** was attempted using different heterogeneous catalysts and solvents (Table 1). Solvents with low dielectric constants were chosen since these are known to enhance the haptophilicity of the directing group.[15a] Homogeneous hydrogenation of **13** was also attempted using Crabtree's catalyst but the reaction was considerably slower. Separation of the 11:1 mixture of C-4 epimers was not carried out until the last step of the synthesis. Oxidative cleavage of **14** was accomplished using lead tetraacetate to give the muconate derivative **15**. This reaction proceeded much faster than the two-step procedure used for the synthesis of *allo*-acromelic acid A **12**. Jones oxidation of **15** and esterification of the acid with diazomethane gave **16** (Scheme 4). No epimerisation at C-2 was detected by ^{1}H NMR (300MHz).

Catalyst	Solvent	H_2 Pressure (atm)	Ratio of 4*S*:4*R*
Palladium black	Benzene	4.5	11:1
Palladium black	10:1 Hexane/1,4-dioxane	4	11:1
Palladium black	10:1 Hexane/1,4-dioxane	1.5	8:1
Palladium black	Ethyl acetate	4	10:1
10% Palladium on C	10:1 Hexane/1,4-dioxane	1	3:1
10% Palladium on C	Ethyl acetate	1	3:1
Raney® nickel	Ethyl acetate	3.5	No reduction observed

Table 1

Cyclisation to the pyrone **17** was achieved using 6M hydrochloric acid under reflux. Reaction of the crude pyrone **17** with aqueous ammonia gave an 11:1 mixture of **1** and **12**. Purification was achieved by ion-exchange chromatography using Dowex® (50X8), filtration through activated charcoal and cellulose chromatography to give acromelic acid A **1** as a white micro-crystalline solid ($[\alpha]_D^{23}$+27.5 (*c* 0.28, H_2O), Lit.[17] $[\alpha]_D$+27.8 (*c* 0.35, H_2O)).



Reagents: i) CrO_3 / conc. H_2SO_4 / acetone / H_2O, then CH_2N_2 / Et_2O / r.t. (54%); ii) 6M HCl(aq) / 100°C; iii) NH_3(aq) / r.t., ion-exchange chromatography (quant.), activated charcoal, cellulose chromatography (60%).

Scheme 4

This preparation of acromelic acid A **1** is a 13 step procedure, from commercially available *trans*-4-hydroxy-L-proline, proceeding with an overall yield of approximately 9% and is amenable to practice on the multi-gram scale.

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We acknowledge with thanks, grants from the EPSRC (formerly the SERC) and a fellowship from Glaxo-Wellcome in support of this work and the EPSRC mass spectrometry service (Swansea) for high

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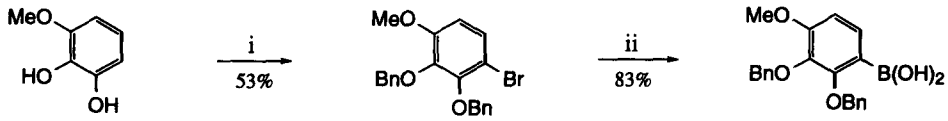
10. The phenylboronic acid derivative **6** was prepared by halogen-metal exchange of **18** followed by sequential quenching with trimethyl borate and aqueous ammonium chloride solution (Scheme 5). The bromobenzene **18** was derived from commercially available 3-methoxycatechol **19**.



19 **18** **6**

Reagents: i) a) NBS / AcOH / r.t., b) BnBr / K_2CO_3 / DMF / r.t.; ii) a) ^{n}BuLi / THF / -78°C, b) $B(OMe)_3$ / -78 to 0°C (c) NH_4Cl(aq).

Scheme 5

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