

Enantiospecific Synthesis of Acromelic Acid A via a Cobalt-mediated Cyclisation Reaction

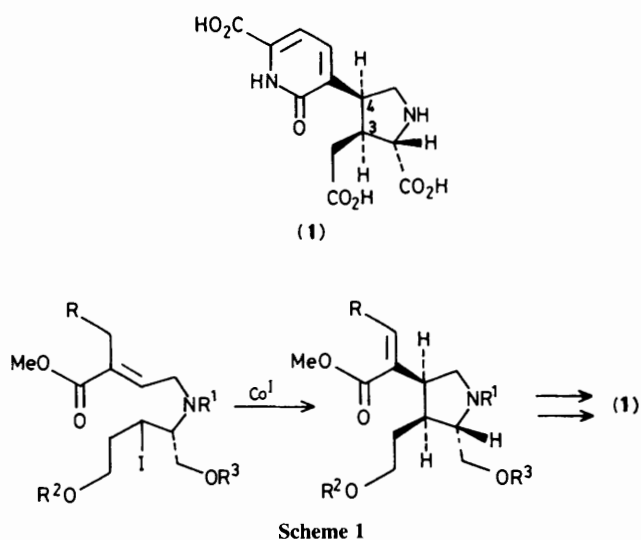
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The potent neurotoxin, Acromelic Acid A, has been synthesised by an enantiospecific route employing a cobalt-mediated cyclisation reaction as the key step.

Acromelic Acid A (**1**), from the poisonous mushroom *Clitocybe acromelalga*, possesses extremely potent depolarising activity on glutamate-mediated neurotransmission.¹ Matsumoto *et al.* have converted kainic acid into this substance.² Following the development of a cobalt-mediated cyclisation

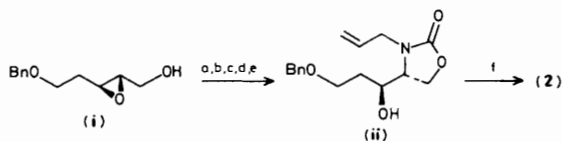
route to the kainic acids³ we now describe how this chemistry can provide an enantiospecific route to Acromelic Acid A. The key step in this strategy involves the cyclisation of a chiral amino acid derivative to a trisubstituted pyrrolidine using a Co^I reagent, Scheme 1. We had previously shown that the two



new centres, at C-3 and C-4, were formed predominantly with the correct stereochemistry required by (1). The new route is shown in Scheme 2.

Thus, reaction of aldehyde (2)[†] and ylide (3)⁴ gave alkene (4)[‡] which was converted into the iodide (5)[§] as before.³ The cobalt-mediated cyclisation of (5) gave the required (2*S*,3*S*,4*S*) isomer (6) as a mixture (1:1) of the two side chain double bond isomers, in 64% yield along with the C-4 epimer (11%). This represented a better stereocontrol at C-4 than in the previous kainic acid synthesis (4*S*:4*R* = 1.7:1).³ Deketalisation gave predominantly the *trans*-double bond isomer of ketone (7) (*trans*:*cis* = 4:1) which, with ammonium acetate (120–125 °C, 2 h), gave pyridone (8). || U.v. (CHCl₃) λ_{max} 236 (log ε 3.90), 310 (3.97) nm; ¹H n.m.r. δH (CDCl₃, 300 MHz) 7.40–7.25 (m, 5H), 7.12 (d, 1H, *J* 7.2 Hz), 6.0 (d, 1H, *J* 7.2 Hz), 4.42 (m, 3H), 4.20 (m, 2H), 3.95 (dd, 1H, *J* 11.4 and 8.8

[†] The aldehyde (2) was prepared according to the following sequence.



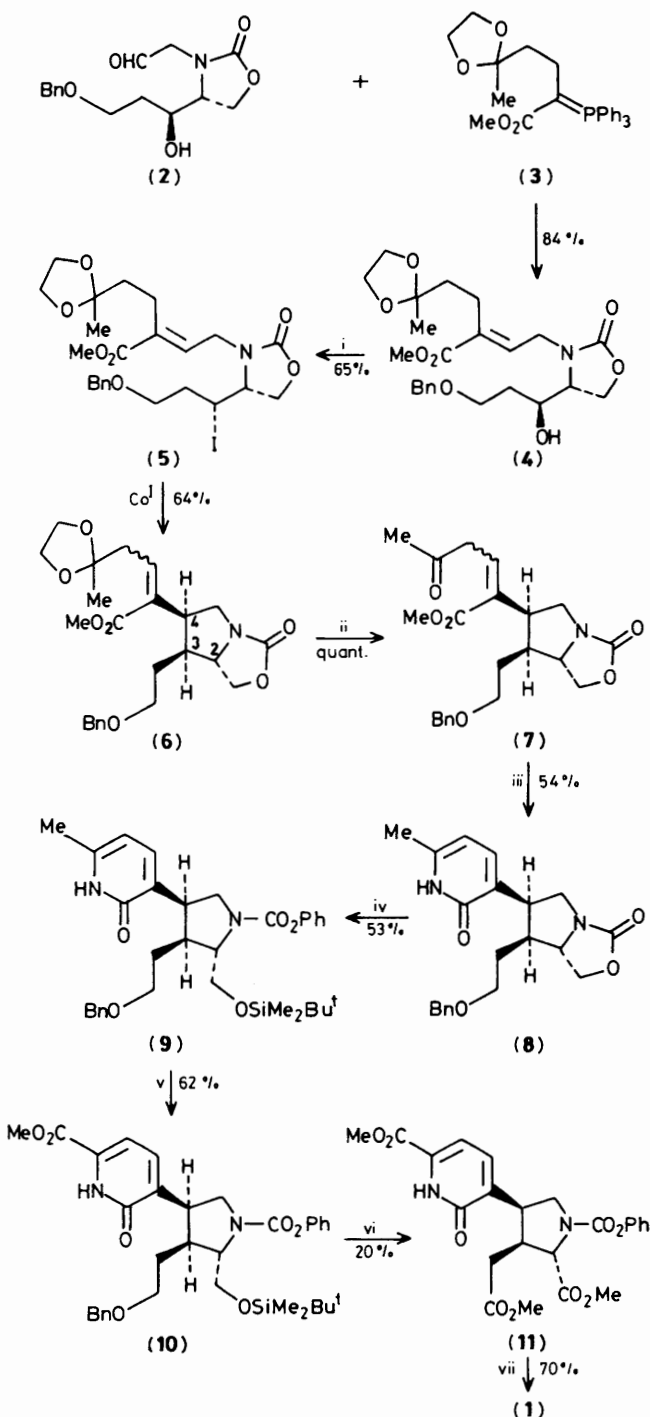
Reagents: a, allyl isocyanate, Et₃N; b, NaH; c, NaOH; d, ClCO₂Me; e, K₂CO₃, MeOH; f, O₃, Me₂S.

Sodium hydride cyclisation of the carbamate, formed by the reaction of allyl isocyanate and epoxy alcohol (i), gave two regioisomeric oxazolidones. However, this mixture could be converted into the desired oxazolidone (ii) by the three-step sequence shown. Ozonolysis of (ii) then yielded the aldehyde (2) in >80% yield.

[‡] The Wittig product (4) was difficult to separate from triphenylphosphine oxide and so was etherified to the ethoxyethyl ether, chromatographed as such, and then hydrolysed (*p*-toluenesulphonic acid, ethylene glycol, 2-methoxy-1,3-dioxalane) to pure (4). All new compounds have given satisfactory n.m.r. and mass spectral data.

[§] The cyclisation conditions differed somewhat from those previously reported³ to minimise reduction of the products α,β-unsaturation. Thus sodium borohydride solution [0.25 equiv. for each equivalent of (5), 1 M in 2 M aq. NaOH] was added dropwise to the mixture of (5), chlorocobaloxime (iii), and sodium hydroxide in methanol at 0 °C. After stirring (10 min) the reaction was worked up.

|| Stereochemistry was confirmed by nuclear Overhauser enhancement experiments.



Scheme 2. Reagents and conditions: i, (CF₃SO₂)₂O, pyridine, NaI; ii, *p*-TsOH, acetone; iii, NH₄OAc, 120–125 °C, 2 h; iv, Ba(OH)₂, aq. EtOH, reflux 1 h, then phenyl chloroformate, NaHCO₃, then Bu^tMe₂SiCl, dimethylaminopyridine (DMAP), Et₃N, then HOAc, aq. tetrahydrofuran; v, SeO₂, 1,4-dioxane, reflux 20 h, then NaOCl₂, NaH₂PO₄, 2-methyl-but-2-ene (*cf. ref. 5*), then CH₂N₂; vi, *p*-TsOH, MeOH, then pyridinium chlorochromate (PCC), dimethylformamide (DMF) 40 °C, 24 h, then CH₂N₂, then H₂/5% Pd-C, then PCC, DMF, then CH₂N₂; vii, aq. NaOH, 90 °C, 12 h.

H₂), 3.69 (dt, 1H, *J* 8.8 and 4.4 Hz), 3.41 (m, 2H), 3.39 (dd, 1H, *J* 11.4 and 4.4 Hz), 2.28 (s, 3H), 2.23 (m, 1H), 1.80–1.40 (m, 2H); *m/z* (NH₃-direct chemical ionisation) 369 (MH⁺);

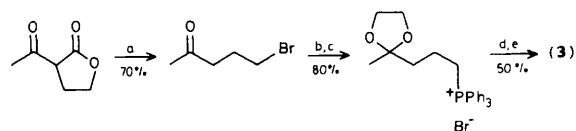
$[\alpha]_D + 5.8^\circ$ (c 0.28, CHCl_3). The oxazolidone moiety of (**8**) was now removed, in preparation for the oxidation sequence, and replaced by a phenylcarbamate group and the hydroxyl silylated to give (**9**). Oxidation of the 6-methyl group of the 2-pyridone was achieved in a two-step sequence, by way of initial selenium dioxide conversion into aldehyde followed by sodium chlorite oxidation and then esterification to (**10**). Finally, oxidation of the potential primary alcohols of (**10**) was achieved as before³ and deprotection of the pyrrolidine nitrogen and saponification in a single step gave Acromelic Acid A (**1**): m.p. 285—290 °C (decomp.) (lit.² m.p. > 310 °C); U.v. (H_2O) λ_{max} 315 (log ϵ 3.98), 244 (3.74) nm; ^1H n.m.r. δ_{H} (D_2O , 300 MHz), 7.41 (d, 1H, J 7.2 Hz), 6.87 (d, 1H, J 7.2 Hz), 4.10 (d, 1H, J 7.6 Hz), 3.72 (q, 1H, J 7.6 Hz), 3.61 (m, 2H), 3.10 (m, 1H), 2.58 (dd, J 17.2 and 5.0 Hz), 2.16 (dd, 1H, J 17.2 and 10.2 Hz); m/z (fast atom bombardment) 311 (MH^+); $[\alpha]_D + 37^\circ$ (c 0.26, H_2O) [lit.² $+27.8^\circ$ (c 0.35, H_2O)]. The n.m.r. spectrum (D_2O , 500 MHz) of the synthetic sample was identical with that of an authentic specimen kindly supplied by Professor Shirahama (Hokkaido University).

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- 2 K. Konno, K. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1986, **27**, 607. During the preparation of this manuscript a new synthesis of Acromelic Acid A has appeared, cf. S. Takano, Y. Iwabuchi, and K. Ogasawara, *J. Am. Chem. Soc.*, 1987, **109**, 5523.
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- 4 The stabilised ylide (**3**) was synthesised by the acylation and transylation reaction developed by Bestmann. For a review, see H. J. Bestmann, *Angew. Chem., Int. Ed. Engl.*, 1965, **4**, 583, 645, 830.



Reagents: a, HBr; b, H^+ , ethylene glycol; c, Ph_3P ; d, lithium di-isopropylamide; e, ClCO_2Me .

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