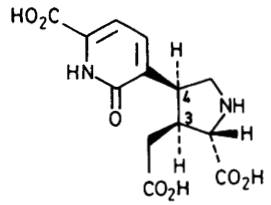
Enantiospecific Synthesis of Acromelic Acid A *via* a Cobalt-mediated Cyclisation Reaction

Jack E. Baldwin* and Chun-Sing Li

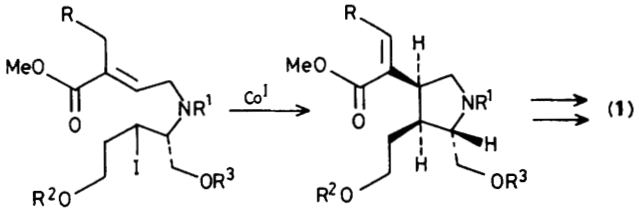
The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford OX1 3QY, U.K.

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 *Clitycybe 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 acids[3] 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



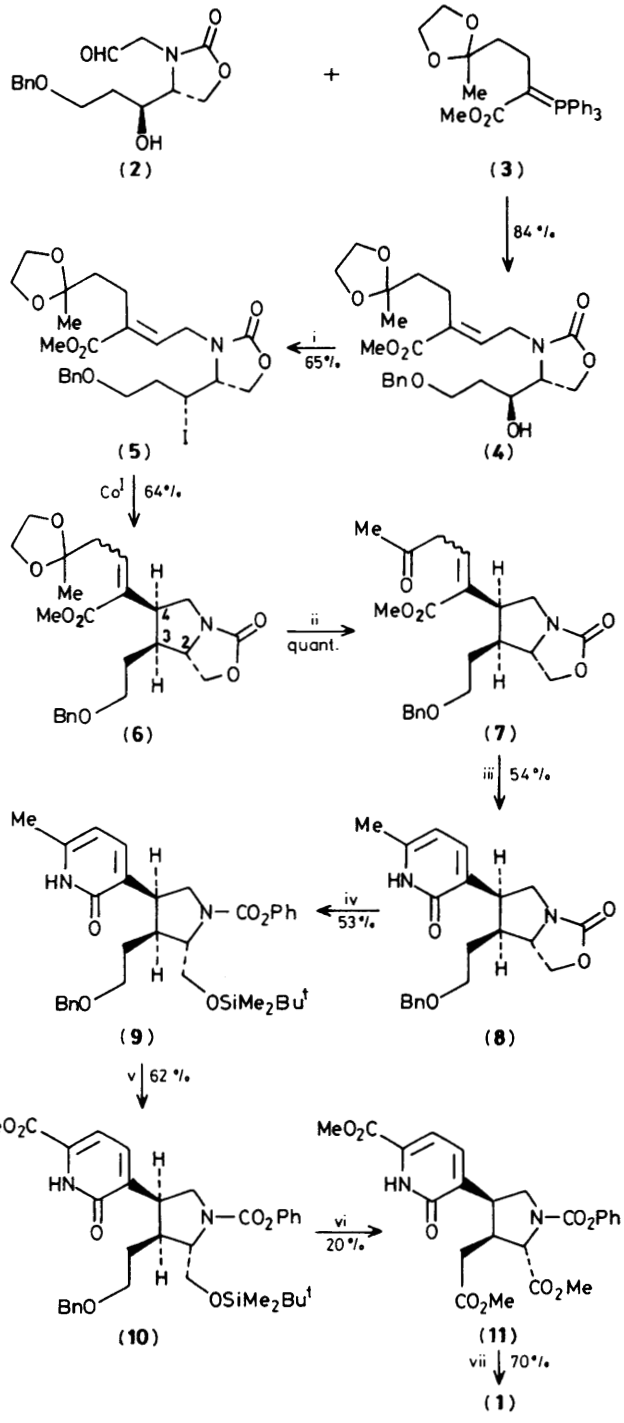
(1)



Scheme 1

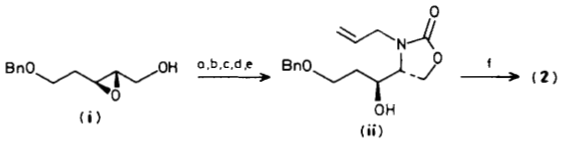
new centres, at C-3 and C-4, were formed predominantly with the correct stereochemistry required by (**1**). The new route is shown in Scheme 2.

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. ($CHCl_3$) λ_{max} 236 (log ε 3.90), 310 (3.97) nm; ^{1}H n.m.r. δH ($CDCl_3$, 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 Hz), 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* (NH_3–direct chemical ionisation) 369 (MH^+);



Scheme 2. *Reagents and conditions:* i, $(CF_3SO_2)_2O$, pyridine, NaI; ii, *p*-TsOH, acetone; iii, NH_4OAc, 120—125 °C, 2 h; iv, $Ba(OH)_2$, aq. EtOH, reflux 1 h, then phenyl chloroformate, $NaHCO_3$, then Bu^tMe_2SiCl, dimethylaminopyridine (DMAP), Et_3N, then HOAc, aq. tetrahydrofuran; v, SeO_2, 1,4-dioxane, reflux 20 h, then $NaOCl_2$, NaH_2PO_4, 2-methyl-but-2- ene (*cf.* ref. 5), then CH_2N_2; vi, *p*-TsOH, MeOH, then pyridinium chlorochromate (PCC), dimethylformamide (DMF) 40 °C, 24 h, then CH_2N_2, then H_2/5% Pd–C, then PCC, DMF, then CH_2N_2; vii, aq. NaOH, 90 °C, 12 h.

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



Reagents: a, allyl isocyanate, Et_3N; b, NaH; c, NaOH; d, $ClCO_2Me$; e, K_2CO_3, MeOH; f, O_3, Me_2S.

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-dioxalone) to pure (**4**). All new compounds have given satisfactory n.m.r. and mass spectral data.

§ The cyclisation conditions differed somewhat from those previously reported[3] 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.

$[\alpha]_D$ + 5.8° (*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 before[3] 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° (*c* 0.26, H_2O) [lit.[2] +27.8° (*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 Shirahame (Hokkaido University).

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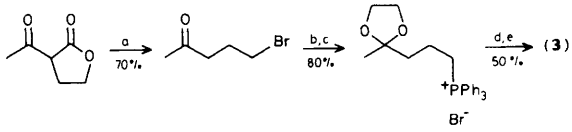
References

1 K. Konno, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, 1983, **24**, 939.

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.

3 J. E. Baldwin and C.-S. Li, *J. Chem. Soc., Chem. Commun.*, 1987, 166.

4 The stabilised ylide (**3**) was synthesised by the acylation and transylidation 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, $ClCO_2Me$.

5 B. O. Lindgren and T. Hilsson, *Acta Chem. Scand.*, 1973, **27**, 880.