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AN EFFICIENT SYNTHESIS OF THE BASIC PYRROLIDINE RING FOR THE KAINOIDS

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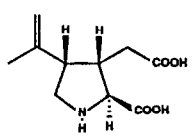
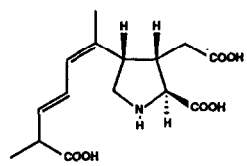
Abstract: A new synthetic approach to the 3-carboxymethylproline ring system common to the kainoids via intramolecular Michael reaction is described.

α-Kainic acid, isolated from the algae *Digenea simplex*[1] and *Centrocerus clavulatum*[2] has been shown to possess an interesting neuronal excitatory activity.[3] Other structurally related compounds also have been isolated, namely acromelic acid A & B from the toxic principles of *Clitocybe acromelalga*[4] and domoic acid and its family from the red algae *Chondria armata*[5]. On the other hand, α-kainic acid has attracted considerable interests in recent years due to its potent neurotransmitting activity in the central nervous system[3] and domoic acid for its insecticidal activity.[5b]

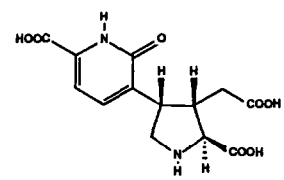
All of the aforementioned compounds contain interesting common amino acid moiety, 3-carboxymethylproline. Some synthetic works have been done on this family by Oppolzer[6], by Baldwin[7] and by Takano.[8]



α- Kainic acid

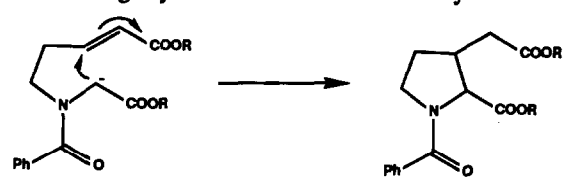


Domoic acid



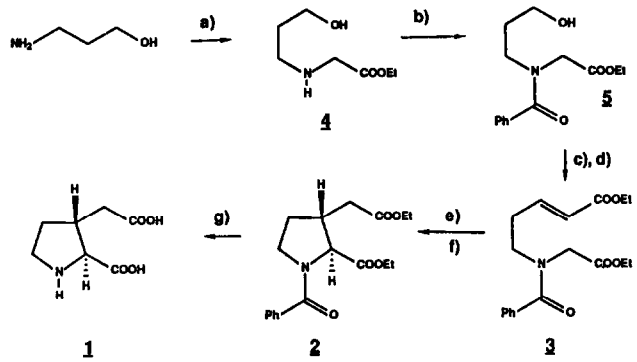
Acromelic acid A

Their interesting structures and biological activities have prompted us to investigate a more efficient synthesis of the basic ring system of these compounds. We envisioned that the pyrrolidine ring system can be formed by the intramolecular Michael reaction as shown.



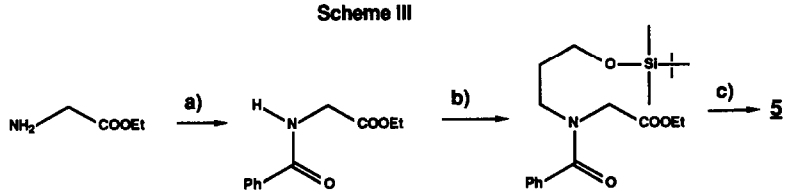
The preparation of the key intermediate 3[9] is illustrated in scheme II & III. When 3 was treated with a catalytic amount of NaOEt (20 mole %) in benzene at room temperature, the cyclization took place and was completed in 0.5 hr to give a mixture of isomers (trans:cis=70:30) which was further equilibrated (NaOEt in refluxing ethanol, 2 hr) to give an equilibrium mixture (trans:cis=95:5) of 2 in 94% yield. The acid hydrolysis of the trans isomer of 2 (4N HCl, reflux for 15 hr) gave 3-carboxymethylproline which showed yellow coloration by ninhydrin.[10]

Scheme II



a) $BrCH_2COOEt$, neat, rt/2 hr, 60% b) Benzoyl chloride, Na_2CO_3, H_2O, 4°C/1 hr, 84%
c) DMSO/$(COCl)_2$, CH_2CL_2, -50°C, Et_3N, -50°-rt/1 hr, 78%
d) Ph_3P=CHCOOEt, benzene, rt/4 hr, 72% e) NaOEt, benzene, rt, 0.5 hr
f) NaOEt, ethanol, reflux/2 hr g) 4N HCl, reflux/15 hr

Scheme III



a) Benzoyl chloride, pyridine, THF, rt/16 hr, 77%
b) $Br(CH_2)_3OSi(t\text{-}Bu)(Me)_2$, NaH, DMF, 0°C-rt/4 hr, 72%
c) 1N HCl, acetic acid, THF, 0°C/1 hr, 98%

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References and Notes

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9. It is a mixture of trans and cis isomers (85:15) but both isomers cyclize to give 2. Therefore, it is not necessary to separate them at this stage.
10. In the NMR spectrum of 2 (in $CDCl_3$), the methine proton at 2 position of the cis isomer appeares at δ4.73, but that of the trans isomer is obscured by the presence of protons from ethyl groups. But the presence of the methine proton from the trans isomer was evident on 1 (δ4.06 in CD_3OD).

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