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Simple Analogs of Acromelic Acid, Which Are Highly Active Agonists of Kainate Type Neuroexcitant

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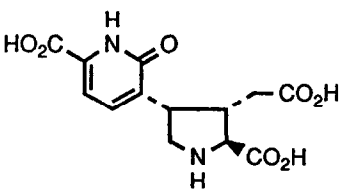
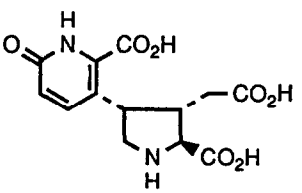
Summary: The highly stereoselective synthesis of acromelic acid analogs; **3a** and **3b**, was achieved. The new kainoid **3b** was found to be the strongest neuroexcitant among the kainoids known so far.

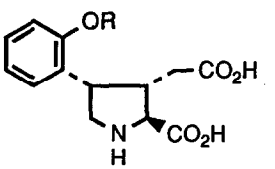
Recently neuropharmacological studies demonstrated that glutamic acid was a putative excitatory neurotransmitter and a glutamate recepter was probably involved in higher brain function such as memory and learnning.[1] Glutamic acid causes a marked depolarization of mammalian central neurons which lead to specific neuronal death in the brain.[2] It plays a key role in ischemic brain damage presumably.[3] Neurodegeneration sickness and Huntington's and Alzheimer's diseases, could arise from the abnormal function of the glutamatergic systems.[4] The actions of glutamate are mediated by mainly three subtypes of receptors: kainate, quisqualate, and NMDA(N-methyl-D-aspartate) types based on their sensitivities for the above three agonists.[5] Thus far,



acromelic acid A (1)



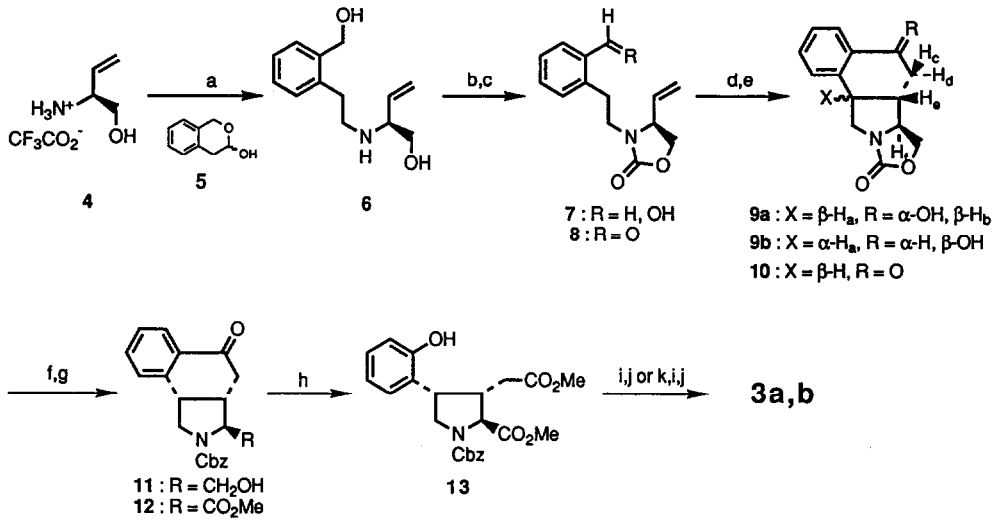
acromelic acid B (2)



3a : R = H
3b : R = Me

there has been little progress in neuropharmacological studies on each subtype[6] except the NMDA. This is due to the lack of selective reagents, which serve as pure agonists or antagonists. Owing recent studies, we have uncovered the kainoids, acromelic acids A(**1**) and B(**2**),[7] which show remarkable neuroexcitatory effects on kainate type receptor[8] and different modes of action from kainic acid.[9] Their depolarizing effect is about 100 times more potent than kainic acid and 10 times more potent than domoic acid in the crayfish neuromuscular junction,[10] moreover, acromelic acid A shows the strongest activity among the L-glutamic acid related compounds(the acid B is slightly less potent than A) in rat and frog spinal cords.[11] A dependence of the activity of these substances on the C-4 position of the pyrrolidine residue of kainoids was demonstrated in the course of our synthetic studies on acromelic acids.[12] This information prompted a design and synthesis of new strongly excitatory and more easily obtainable kainoids. Here we wish to describe an highly stereoselective synthesis of an extraordinary potent neuroexcitatory kainoid **3b**. The potency of newly synthesized compound **3b** is now beyond that of any known natural products.

scheme 1[a]

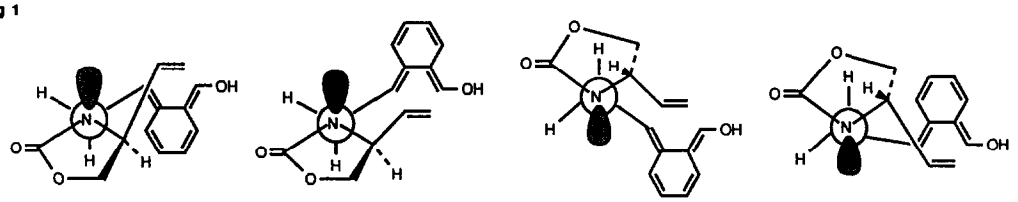


[a](a) 1N KOH/MeOH(pH 6), and then $NaBH_3CN$, 5; (b) CbzCl, K_2CO_3 , and then KOH, MeOH; (c) MnO_2 ; (d) hv, toluene, 15°C; (e) MnO_2; (f) $Ba(OH)_2$, H_2O, MeOH, and then CbzCl; (g) PDC, DMF, MS 4A, 45°C, and then CH_2N_2 /ether; (h) mCPBA, CH_2Cl_2, and then CH_2N_2/erther; (i) KOH,H_2O, MeOH; (j) TMSOTf, PhSMe, TFA, 0°C; (k) MeI, NaH, DMF.

The synthesis was performed through the photo induced intramolecular Diels-Alder reaction[13] as a key step which assembled a suitably substituted pyrrolidine ring. TFA salt of optically active vinyl glycinol **4**[14] was coupled with lactol **5** by reductive amination[15] with $NaBH_3CN$ in MeOH at pH 6 adjusted by 1N KOH (72%). The resulting secondary amine **6**(mp 68-69°C, $[\alpha]^{24}_D$-4.50°(c 1.00, $CHCl_3$)) was protected as a cyclic carbamate **7** which was then oxidized to aldehyde **8** (75% yield over three steps). The intramolecular Diels-Alder reaction was carried out under by irradiation using a medium-pressure mercury lamp in toluene at 15°C to afford a mixture of cyclic alcohols which consisted of **9a**[16](mp 166-168°C, $[a]^{22}_D$ 13.8°(c 0.50, $CHCl_3$)) and its C-4 epimer **9b**[16](mp 172-175°C, $[a]^{24}_D$-47.3°(c 0.40, $CHCl_3$)) in the ratio of 99 : 1 (64%). The cyclic carbamate assembly was essential to control the transition-state conformation of Diels-Alder reaction to give cyclic compound **9a** with desired configuration(Fig 1). Among four possible transition states, two 2, 3-cis form(**14c, d**) were most unlikely to be involved in the Diels-Alder reaction because oxazolidone rings would be extremely strained in these conformations.[17] Between two 2, 3-trans conformers, endo-type **14a**, which would be converted to the desired isomer **9a**, appears to be the most favourable. The major isomer **9a** was oxidized to ketone **10** (89%). Hydrolysis of the carbamate group of **10** with $Ba(OH)_2$ followed by treatment with CbzCl gave alcohol **11** which was then oxidized and esterified to give ketoester **12** (48% yield over four steps). The ketoester **12** was subjected to Baeyer-Villiger oxidation and next treatment with diazomethane and phenol derivative **13** was obtained (90% for two steps). Finally **13** was converted to acromelic acid congener **3a**[18](mp >300°C, $[\alpha]^{24}_D$ 22.4°(c 0.25, H_2O)) through hydrolysis of ester and removal of Cbz-group (43% for two steps). Moreover, after methylation of phenol hydroxyl group, methoxyphenyl derivative **3b**[18](mp >300°C, $[\alpha]^{24}_D$ 4.99°(c 0.30, H_2O)) was also obtained by the same deprotection procedure (46% for two steps).

The activity of **3a** was in between acromelic acid A and B and the congener **3b** exhibited much more potent neuroexcitatory activity than acromelic acid A in the isolated rat spinal cord.[19]

Fig 1



2,3-trans , 3,4-cis (**14a**) 2,3-trans , 3,4-trans (**14b**) 2,3-cis , 3,4-trans (**14c**) 2,3-cis , 3,4-cis (**14d**)

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(16) Stereochemistry was confirmed by NMR spectra and NOE experiments. ^{1}H NMR for **9a**: (500MHz, $CDCl_3$) δ 1.86 (1H$_d$, ddd, J = 7.3, 7.8, 13.2 Hz), 2.12 (1H$_c$, ddd, J = 3.9, 5.9, 13.2 Hz), 2.42 (1H$_e$, dddd, J = 5.9, 6.4, 7.8, 9.3 Hz), 3.09 (1H, dd, J = 9.3, 11.7 Hz), 3.45 (1H$_a$, ddd, J = 8.3, 9.3, 9.3 Hz) 4.16 (1H$_f$, ddd, J = 3.9, 6.4, 7.8 Hz), 4.23 (1H, dd, J = 3.9, 8.8 Hz), 4.30 (1H, dd, J = 8.3, 11.7 Hz), 4.61 (1H, dd, J = 7.8, 8.8 Hz), 4.85 (1H$_b$, J = 3.9, 7.3 Hz), 7.15 (1H, dd, J = 1.5, 6.8 Hz), 7.28 (1H, ddd, J = 1.5, 7.3, 7.8 Hz), 7.30, ddd, J = 1.5, 6.8, 7.8 Hz), 7.45 (1H, dd, J = 1.5, 7.3 Hz). NOE was observed between protons of H$_a$-H$_b$, H$_a$-H$_c$, H$_a$-H$_e$, H$_c$-H$_e$, H$_d$-H$_f$.; ^{1}H NMR for **9b**: (500MHz, $CDCl_3$) δ 1.83 (1H$_d$, ddd, J = 4.9, 12.7, 13.2 Hz), 2.03 (1H$_e$, dddd, J = 2.4, ~9, 10.3, 12.7 Hz), 2.27 (1H$_c$, ddd, J = 1.5, 2.4, 13.2 Hz), 3.11 (1H$_a$, ddd, J = 8.3, ~9, 10.7 Hz), 3.53 (1H, dd, J = 9.8, 10.7 Hz), 3.83 (1H$_f$, ddd, J = 3.9, 7.8, 10.3 Hz), 3.93 (1H, dd, J = 8.3, 9.8 Hz), 4.33 (1H, dd, J = 3.9, 8.8 Hz), 4.54 (1H, dd, J = 7.8, 8.8 Hz), 4.99 (1H$_b$, dd, J = 1.5, 4.4 Hz), 7.01 (1H, dd, J = 1.5, 6.8 Hz), 7.28 (1H, ddd, J = 1.5, 7.3, 7.8 Hz), 7.30 (1H, ddd, J = 1.5, 6.8, 7.8 Hz), 7.45 (1H, dd, J = 1.5, 7.3 Hz). NOE was observed between protons of H$_a$-H$_d$, H$_a$-H$_f$, H$_c$-H$_e$, H$_d$-H$_f$.

(17) The compound **11** easily gave the corresponding cyclic carbamate while the 2,3-cis-isomers of **11** would not give the oxazolidone ring.

(18) ^{1}H NMR for **3a**: (500MHz, D_2O) δ 1.91 (1H, dd, J = 9.8, 16.1 Hz), 2.37 (1H, dd, J = 5.4, 16.1 Hz), 3.06 (1H, dddd, J = 5.4, 7.8, 9.8, 7~8 Hz), 3.71 (1H, dd, J = 7.3, 11.7 Hz), 3.76 (1H, dd, J = 7.8, 11.7 Hz), 3.83 (1H, ddd, J = 7.3, 7.8, 7~8 Hz), 4.06 (1H, d, J = 7.8 Hz), 6.84 (1H, ddd, J = 1.5, 7.8, 7.8 Hz), 6.86 (1H, dd, J = 1.5, 7.8 Hz), 7.00 (1H, dd, J = 1.5, 7.8 Hz), 7.17 (1H, ddd, J = 1.5, 7.8, 7.8 Hz). ^{1}H NMR for **3b**: (500MHz, D_2O) δ 1.85 (1H, dd, J = 9.8, 16.1 Hz), 2.30 (1H, dd, J = 5.4, 16.1 Hz), 3.08 (1H, dddd, J = 5.4, 7.3, 9.8, ~8 Hz), 3.67 (1H, dd, J = 8.3, 11.7 Hz), 3.75 (1H, dd, J = 7.8, 11.7 Hz), 3.79 (3H, s), 3.89 (1H, ddd, J = 7.8, 8.3, ~8 Hz), 4.00 (1H, d, J = 7.3 Hz), 6.92 (1H, t, J = 7.3 Hz), 7.00 (1H, d, J = 8.3 Hz), 7.04 (1H, d, J = 7.3 Hz), 7.30 (1H, dd, J = 7.3, 8.3 Hz).

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