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A new synthetic method for an acromelic acid analog, a potent neuroexcitatory kainoid amino acid, via photoinduced benzyl radical cyclization

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Abstract—A new synthetic method for an acromelic acid analog, MFPA, was developed. The key step is the photoinduced benzyl radical cyclization with excellent stereoselectivity. © 2002 Published by Elsevier Science Ltd.

Acromelic acids A and B (**1** and **2**) are potent neuroexcitatory amino acids isolated as toxic compounds from the poisonous mushroom *Clitocybe acromelalga* by us (Fig. 1).[1] These amino acids are members of the kainoid amino acids which act on excitatory amino acid (EAA) receptors in mammalian central nervous systems as potent agonists.[2] Among the EAA receptors, the kainate subtype, one of the subtypes of the EAA ionotropic receptors, are specifically depolarized by these amino acids.[3] We have developed various synthetic methods for the kainoid amino acids in order to find a more efficient method.[4] During the course of these studies, we synthesized the most potent analog, the methoxyphenyl derivative (MFPA, **3**), among the kainate type agonists.[4a,b] The potency of the depolarization depends on the nature of the C4-substituent of the kainoid.[3c] The compound showing the more potent depolarization activity has a C4-substituent with the higher HOMO energy.[5] Accordingly, we developed a new synthetic method suitable for synthesizing the analogs with a C4-substituent having the higher HOMO energy, which is exemplified in the synthesis of MFPA (**3**).

The tosylate **4** prepared from 2-(2-methoxyphenyl)-acetic acid by reduction with $LiAlH_4$ followed by tosylation with TsCl and pyridine was coupled with vinyloxazolidinone **5**[6] prepared from L-methionine to give **6** in 83% yield (Scheme 1). The vinyl group of **6** was converted to the unsaturated ester **7** by successive ozonolysis and Horner–Emmons reactions. An acetonitrile or benzene solution of **7** was irradiated using a high-pressure mercury lamp in a quartz test tube at room temperature in the presence of α-trifluoroacetophenone and KF to afford the cyclized products **8** and **9** in a 1:1 ratio in 50% combined yield. In the model studies of the photoreaction in acetonitrile, some acyclic ethers are cyclized into THF rings with *trans*-

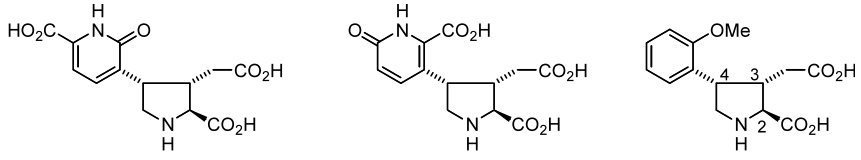

Figure 1.

Keywords: benzyl radical; radical cyclization; photoreaction; salt effect; kainoid.

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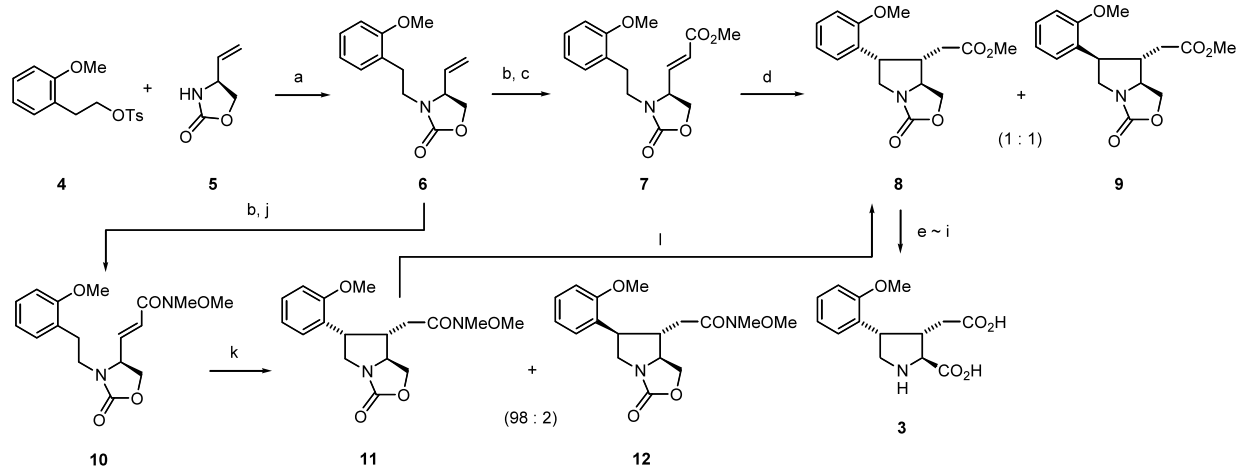
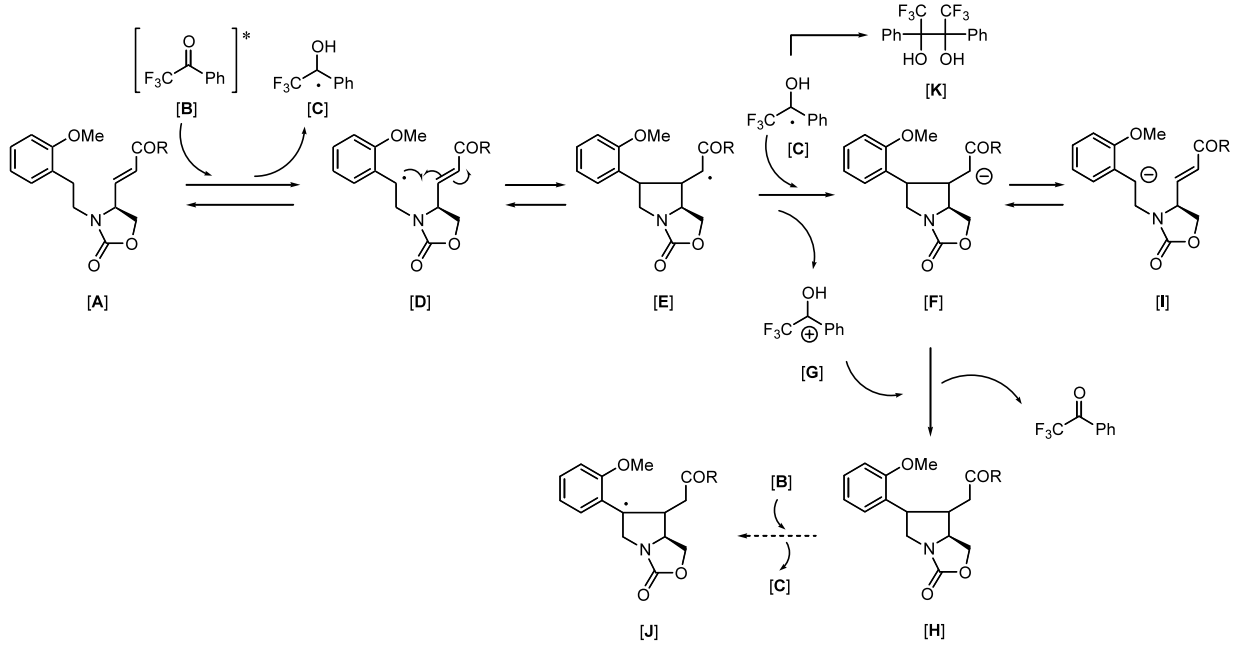


Scheme 1. *Reagents and conditions*: (a) KH/DMF, 0°C, 83%; (b) O_3/MeOH, then DMS; (c) $(MeO)_2P(O)CH_2CO_2Me$, NaH/THF, 96% (two steps); (d) *hv*, CF_3COPh, KF/CH_3CN or benzene, 50% (**8**:**9** = 1:1); (e) 1 M KOH/MeOH, reflux, then Boc_2O; (f) CH_2N_2, 72% (two steps); (g) Jones' oxidation, then CH_2N_2, 76%; (h) 1 M KOH/EtOH, quant.; (i) TFA, quant.; (j) $(EtO)_2P(O)CH_2CONMeOMe$, NaH/THF, 88% (two steps); (k) *hv*, CF_3COPh, KF/benzene, 41%; (l) HCl_{aq}, 66%, then CH_2N_2.

substituents as the major product without KF.[8] On the other hand, the presence of KF or TBAF was essential for the reaction of **7** otherwise the yield was negligible.[9] Thus the obtained *cis*-isomer was converted to MFPA (**3**, $[\alpha]_D$+9.37°(*c* 0.25, H_2O) [lit.:[4a] $[\alpha]_D$ +4.99° (*c* 0.30, H_2O)]) by our previous synthetic reactions with slight modifications.[4a] To improve the stereoselectivity in the cyclization reaction, the radical acceptor was changed from the methyl ester to the Weinreb amide using the amide-type Horner–Emmons reagent prepared according to a previous report.[10] An acetonitrile solution of the amide **10** was irradiated under the same conditions as in the case of **7** to give **11** and **12** in a 1:1 ratio in 41% combined yield. On the other hand, a benzene solution of the amide **10** was exposed to the photoreaction to give cyclized products **11** and **12** in a ratio of 98:2.[11] The yield was 41% with recovery of the starting material (32%), which was rather low but the stereoselectivity was remarkably improved.[12] The amide **11** was hydrolyzed to the acid and the resulting compound was esterified to yield **8** which can be converted to MFPA (**3**) by the same methods as already described.

The plausible mechanism of the photoreaction drawn by consulting Wagner's studies[7] is shown in Scheme 2. The photoexcited α-trifluoroacetophenone [**B**] produces a charge transfer complex (exciplex) with [**A**]. Through the proton transfer reaction, the complex produces two



Scheme 2.

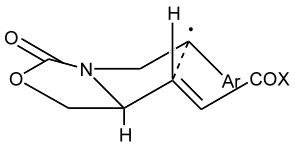


Figure 2.

radical species, [**C**] and [**D**]. The radical [**D**] cyclizes to [**E**]. The radical [**E**] then gets an electron from [**C**] to produce [**F**] which abstracts a proton probably from [**G**] to produce [**H**]. These types of radical cyclizations usually produce a *cis*-substituted five-membered ring, which is explained by the transition state bearing the equatorial substituents at the two carbons of the partly formed bond (Fig. 2).[13]

In the case of **10**, the product ratio was 98:2 in benzene solution giving the *cis*-isomer as the major product for which the above explanation should be applicable. The photoreaction of the same amide **10** in acetonitrile produced a mixture of 1:1 stereoisomers. The anion [**F**] would be more stable in acetonitrile than in benzene because of the solvent polarity; therefore, the anion [**F**] would equilibrate with [**I**] before abstracting a proton from [**G**], resulting in the production of the mixture.

On the other hand, in the case of **7**, the cyclization reactions in both acetonitrile and benzene produce *cis*- and *trans*-isomers in a ratio of 1:1. The stereoselectivity might be attributable to the stability of the anion [**F**] of the ester independent of the solvent.

Comparing the stability of the anions [**F**] of the ester and of the amide, the latter must be rather destabilized by the resonance effect of the nitrogen.

In addition, the cyclized *cis*-isomers could not be converted into the corresponding *trans*-isomers and vice versa under our photoreaction conditions by the epimerization at the benzylic position through the radical intermediate [**J**].[14]

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   In the THF ring cyclization, the photoreaction smoothly proceeded without salt. This might be due to the desirable conformation of the starting ether for the cyclization, which resulted in faster cyclization. On the other hand, the amide derivative contained a nitrogen with sp^2 hybridization, which might be disadvantage to adopt the suitable conformation for the cyclization. Accordingly, the amide derivative fell into equilibration between [**A**] and [**D**]. The salt added might prevent [**D**] to [**A**] by some effects (cf. Ref. 9), which promotes further cyclization.
   In the ether series, the major product had 3,4-*trans* configuration. This might be attributable to the structure of the radical acceptor, i.e. ester, and also the solvent used, i.e. acetonitrile.
9. The role of KF and TBAF (salt effect) might be either or some of the followings: (i) stabilization of radical ion pair (exciplex) (ii) inhibition of back electron transfer ([**D**] to [**A**]) (iii) acceleration of charge separation. See: Santamaria, J. In *Photoinduced Electron Transfer*; Fox, M. A.; Chanon, M., Eds. Solvent and salt effects. Elsevier: Amsterdam, 1988; Chapter 3.1, pp. 483–540.
   We tried some salts in the photoreaction, such as, KBr, LiCl, and LiBr. However, no effect was observed for these salts in the photoreaction. Accordingly, the desirable effect in the reaction probably arose from the fluoride ion. The salt effect was well documented for organic compounds and some inorganic compounds, such as, $LiClO_4$, $Mg(ClO_4)_2$, and Bu_4NClO_4. The effects of fluoride ion to this kind of organic synthesis would be the first example. Fluoride-promoted dye-sensitized photooxidation was reported by Wasserman; however, the role of the fluoride ion seemed to be different from that of our reaction. See Wasserman, H. H.; Pickett, J. E. *J. Am. Chem. Soc*. **1982**, *104*, 4695–4696.

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11. Typical experimental: To a solution of **10** (55 mg, 0.16 mmol) in acetonitrile (2.2 ml) in a quartz test tube were added KF (10.0 mg, 0.17 mmol) and α-trifluoroacetophenone (0.12 ml, 0.82 mmol). The solution was irradiated with stirring under argon atmosphere using high-pressure mercury lamp at rt for 1 h. The mixture was concentrated and the residue was chromatographed on silica gel (40% EtOAc–hexane) to afford a mixture of **11** (22. 5 mg, 41%) and **12** (0.8% from ^{1}H NMR), and recovered **10** (17.5 mg, 32%). The stereochemistries of the products were determined after conversion to the known **3**.
12. The yield was not improved by increasing the quantities of α-trifluoroacetophenone and/or KF. This might be due to the formation of the pinacol [**K**], which disturbs the formation of [**F**]. In the photoreaction, the irradiation for long time made the decrease in the yields both of the products and recovery of the starting material.
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14. The carbonyl group of α-trifluoroacetophenone in the excited state [**B**] is reported to be hard to abstract hydrogen. Accordingly, the direct production of the radical species [**J**] (and also [**E**]) from [**H**] could be excluded. The exciplex formation between [**B**] and [**H**] followed by proton transfer would produce [**J**]; however, such a reaction was not observed.