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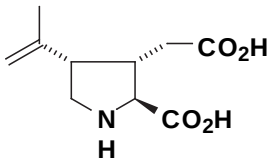
FORMAL SYNTHESIS OF FPA, A KAINOID AMINO ACID, *VIA* KETYL RADICAL CYCLIZATION

Mitsuru Kamabe, Takayuki Miyazaki, Kimiko Hashimoto*[2], and Haruhisa Shirahama*[1]

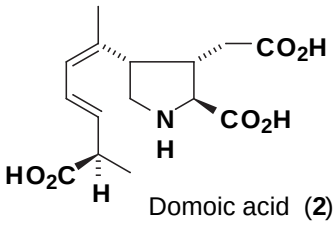
School of Science, Kwansei Gakuin University, Uegahara Nishinomiya, 662-8501, Japan
e-mail (H.S.): shiraham@sci.hokudai.ac.jp; (K. H.) kimikoh@postman.riken.go.jp

Abstract - The formal synthesis of FPA, a kainoid amino acid, was performed through the SmI_2 induced ketyl radical cyclization as the key step. The stereoselectivity was inverted in the presence or absence of the proton source.

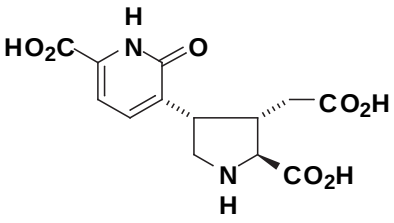
Kainoid amino acids, such as kainic acid (**1**), domoic acid (**2**), acromelic acids A and B (**3**, **4**), MFPA (**5**), and FPA (**6**), show potent neuroexcitatory activity in mammalian central nervous systems.[1] Due to their activity, they are useful probes in the neuroscience fields. Recently, a shortage of kainic acid, which has



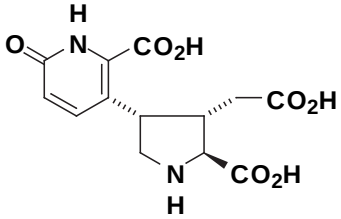
Kainic acid (**1**)



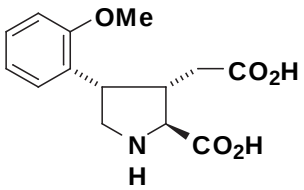
Domoic acid (**2**)



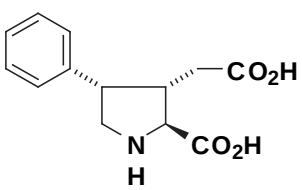
Acromelic acid A (**3**)



Acromelic acid B (**4**)



MFPA (**5**)



FPA (**6**)

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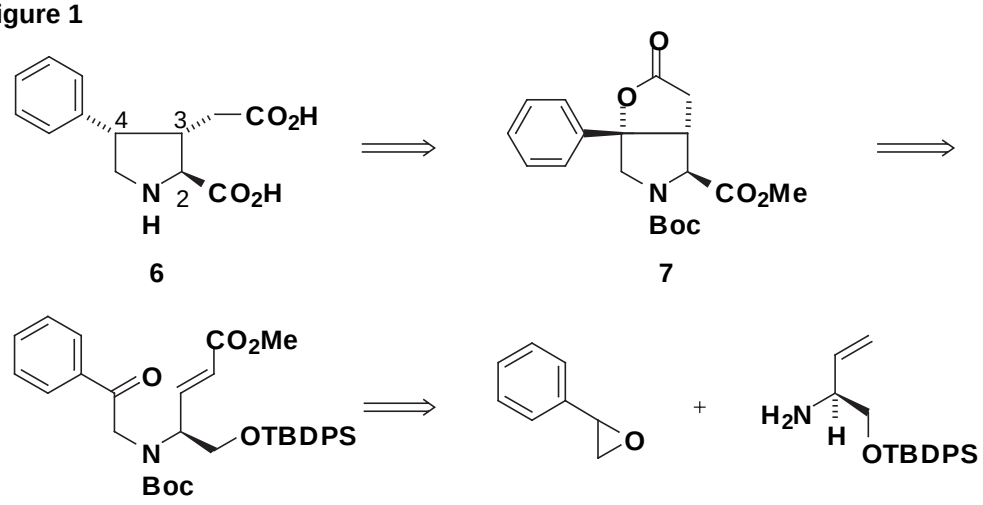
†Dedicated to Professor James P. Kutney in celebration of his 70th birthday.

Figure 1



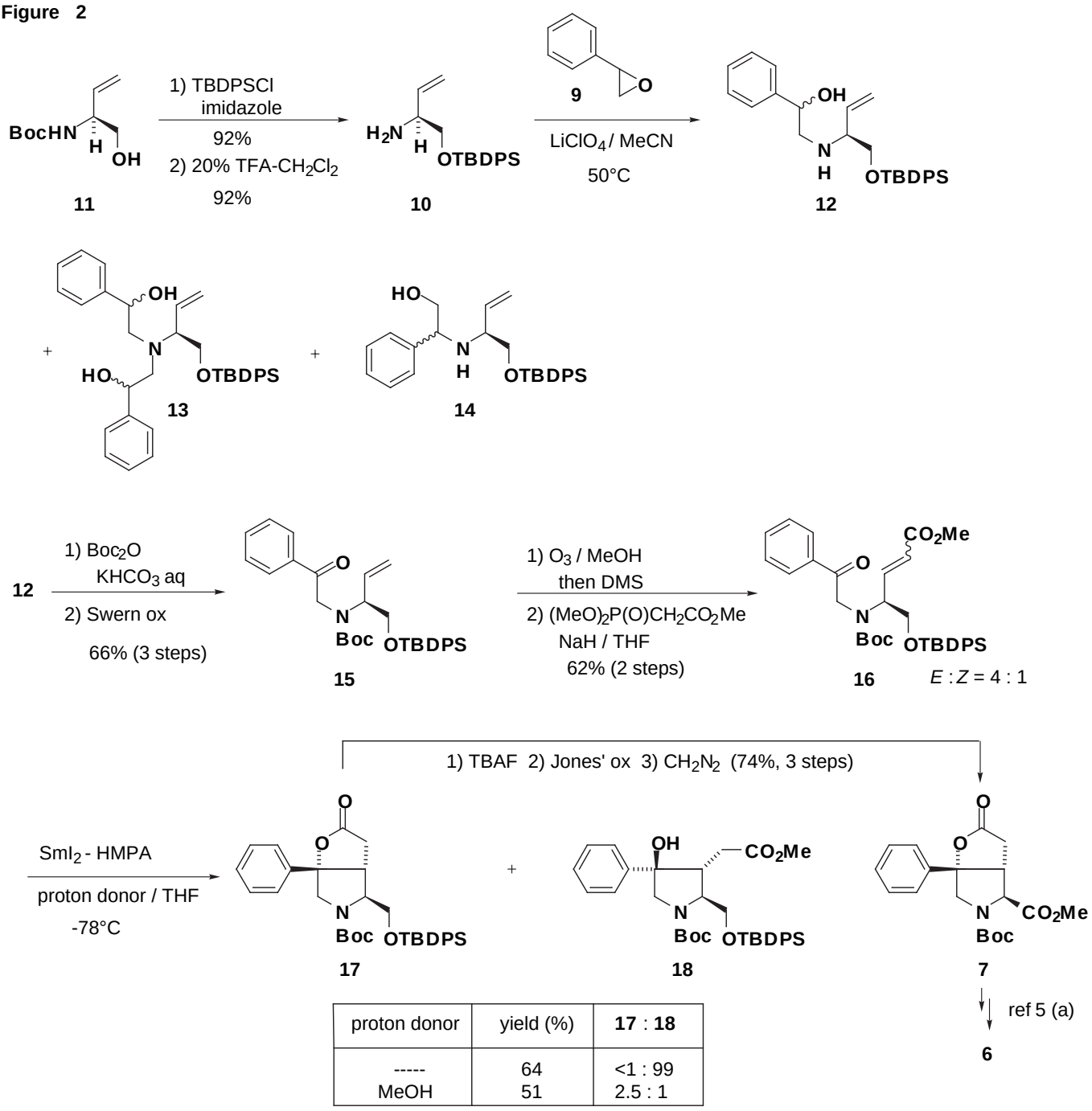
been long supplied from natural sources, began to limit the progress in neuroscience.[2] However it is again being supplied by chemical synthesis.[3] The aromatic kainoids show more potent depolarizing activity than **1** and some of them exhibit a different selectivity to the receptor subtypes.[4] Accordingly, the development of a new synthetic scheme for the kainoids is now required.[5] We now describe the formal synthesis of FPA (**6**) using SmI_2 mediated radical cyclization as the key step,[6] and also show the preliminary results for the cyclization of a pyiridine derivative.

The retrosynthetic scheme is outlined in Figure 1. FPA (**6**) has been previously prepared[7] from lactone (**7**)[7(b)] through hydrogenation with inversion of the configuration[8] at C4. Accordingly, synthesis of lactone (**7**) should be a formal synthesis of **6**. The key reaction is the intramolecular ketyl radical cyclization of **8**. The precursor (**8**) would be synthesized from styrene oxide (**9**) and the vinylglycinol derivative (**10**).

The known vinylglycinol (**11**) was prepared according to a previous report.[9] The hydroxy group of **11** was protected as the TBDPS ether and the Boc protective group was removed to give the amine (**10**) (Figure 2). The amine was coupled with the epoxide (**9**) using $LiClO_4$ as a catalyst in MeCN[10] to afford the desired coupling product (**12**) as the major product along with trace amounts of **13** and **14**. The regioselectivity could be explained by the steric bulkiness of the nucleophilic amine (**10**). The inseparable mixture of **12** and **10** was separated after treatment with Boc_2O and the Swern oxidation, giving the pure ketone (**15**). The olefin group of **15** was cleaved by ozonolysis and the resulting hemiacetal[11] was directly exposed to the Horner-Emmons reaction without purification to give the unsaturated ester (**16**) as a mixture of geometric isomers (E : Z = 4 : 1). The mixture was treated with SmI_2 (10 equiv.) in THF-HMPA (20 : 1) at -78 °C to produce **18** as the sole product. On the other hand, the cyclization reaction was performed in the presence of MeOH (the same amount with HMPA) as a proton donor to give a mixture of **17** and **18** in a ratio of 2.5 : 1, with the desirable stereoisomer as the

major product. The structure of **17** was confirmed by comparing the ^{1}H NMR spectral data and the optical rotation after conversion to the known (**7**).[7(b)] On the other hand, the stereochemistry of **18** was tentatively estimated from the previous synthetic studies.[12]

Figure 2

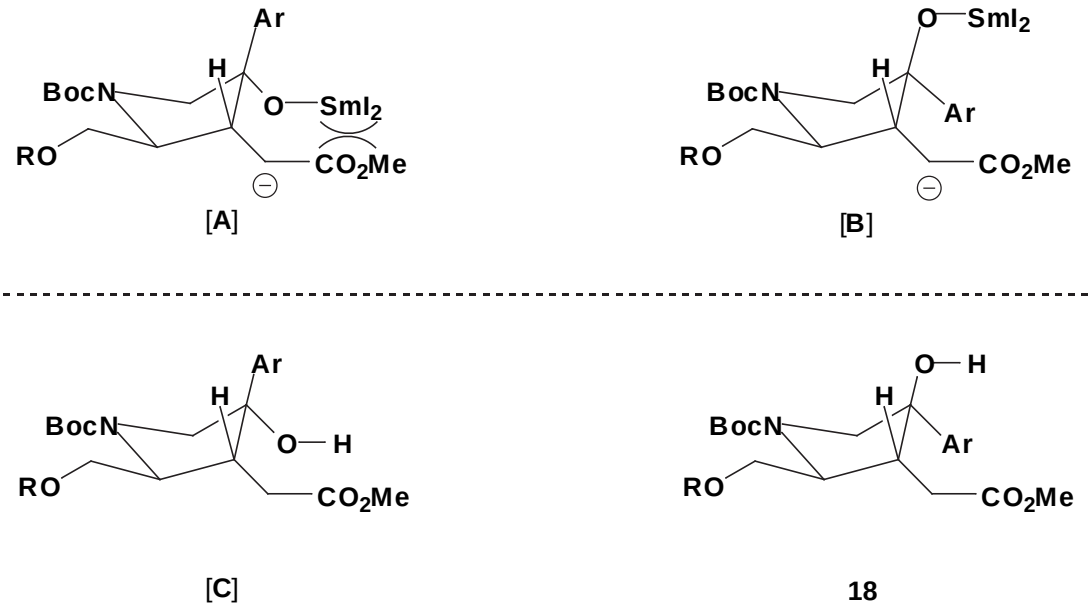


proton donor	yield (%)	**17** : **18**
-----	64	<1 : 99
MeOH	51	2.5 : 1

During the radical cyclization reaction[13] of **16**, the stereoselectivity was inverted depending on the presence or the absence of MeOH. The radical addition reaction to the intramolecular olefin should be a reversible reaction due to the lower electrophilicity of the benzyl radical.[14] Accordingly, the product (**18**) should be a thermodynamic product in the absence of MeOH due to the steric repulsion between the -OSmI$_2$ and the methoxycarbonylmethyl groups of **A**, the precursor of **17**, compared with **B**, the precursor

of **18** (Figure 3). On the other hand, in the presence of MeOH, the free hydroxy group would be produced in the reaction mixture by proton exchange with MeOH. In this case, there exists less steric repulsion between the -OH and the methoxycarbonylmethyl groups in **C** than that between the phenyl and methoxycarbonylmethy group in **18**.

Figure 3



The same strategy was applied to a pyridine derivative (Figure 4). The lithiation of 2-methoxypyridine (**19**) was performed using α-ethoxyvinyllithium[15] and the resulting anion was trapped with acetaldehyde to give the alcohol (**20**). Dehydration of **20** through mesylation followed by elimination gave the ethylene derivative (**21**) which was then oxidized to the epoxide (**22**). The epoxide (**22**) was then coupled with the amine (**10**) in the same manner as above to afford the amine (**23**). The amino group of **23** was protected by Boc group and then the alcohol was oxidized to the ketone. The resulting ketone (**24**) was exposed to ozonolysis and then the Horner-Emmons reaction to afford the precursor (**25**) for the radical cyclization as a mixture of geometric isomers (E : Z = 2 : 1). The ketyl radical cyclization in the presence of MeOH produced **26** and **27** in a ratio of 1 : 1. The stereochemistry of these products was estimated from the comparison of the ^{1}H NMR spectra with those of the phenyl derivatives (**17** and **18**).

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*[1] Present address: 2-16, Minami 18 Nishi 8, Chuo-ku, Sapporo, 064-0918, Japan

*[2] To whom correspondence should be addressed. Present address: Lab. of Biochemical Resources, Plant Science Center, RIKEN, 2-1 Hirosawa, Wako-shi, Saitama, 351-0198, Japan

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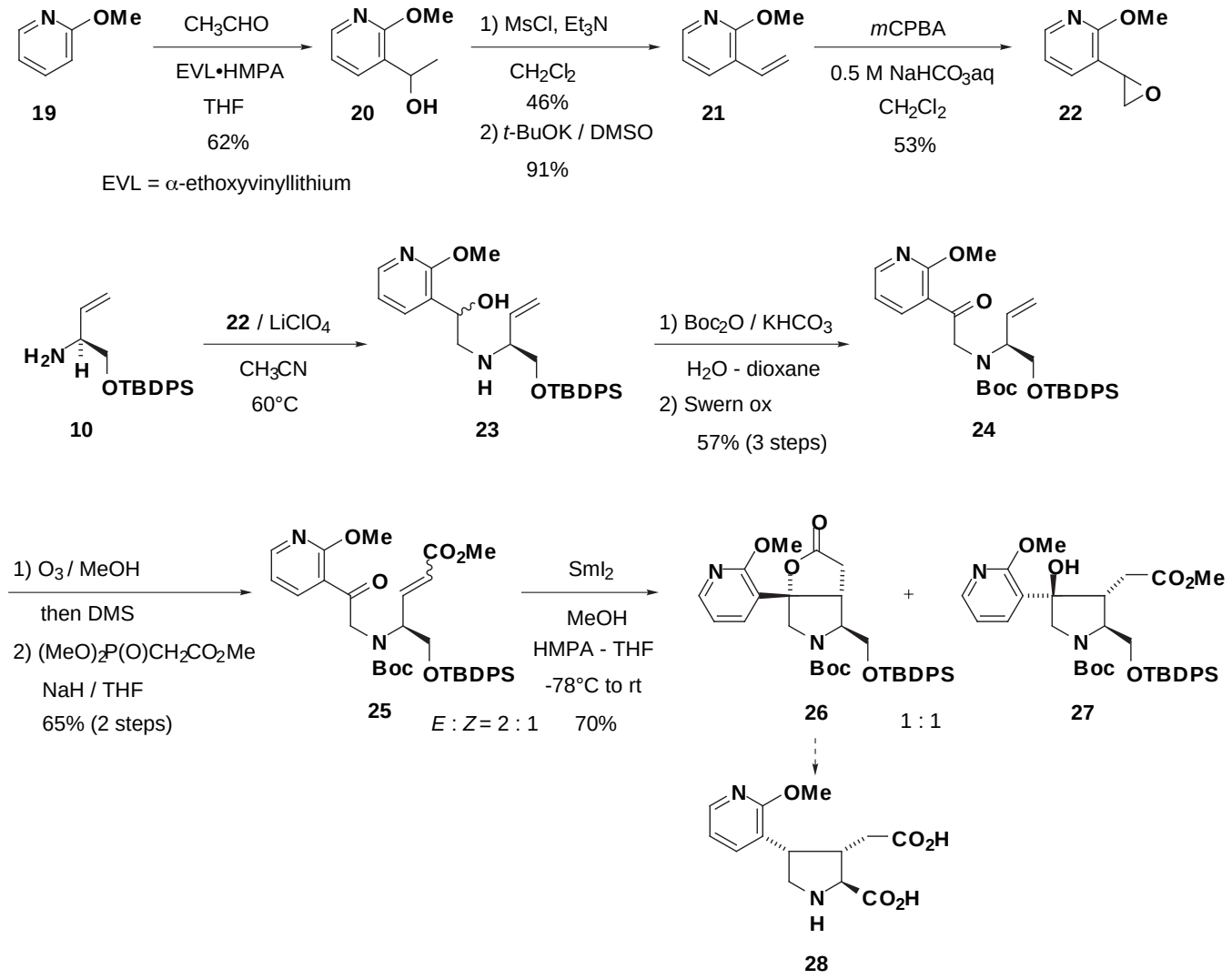
Figure 4



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