oxygen atom is probably more favorable for acylation.

Acylation of $[SiW_{11}O_{39}Cu(H_2O)]^{6-}$. The IR spectrum of the acylated product (Product C) of $[SiW_{11}O_{39}Cu(H_2O)]^{6-}$ is quite similar to that of Product Z with new bands at 1760 and 1200-1300 cm^{-1} ascribable to the acetyl groups. Elemental analysis shows that all four bridging oxygen atoms between the copper and tungsten atoms have been acylated. No NMR spectrum was observed for Product C which is paramagnetic. The frozen solution EPR spectra show that both g_{II} and A_{II} values of the Cu^{2+} ion change when the heteropolyanion is acylated. However, no further useful information about the acylated product could be derived from the EPR spectra.

Reactions of the Acylated Products. The acyl group in Product Z can be removed easily be hydrolysis or reaction with aniline. After these reactions the IR bands at 1700 and 1200-1300 cm^{-1} and the ^1H-NMR lines at 1.92-1.98 ppm disappear from the spectra of the heteropolyanion, indicating that the acetyl group has been detached from the heteropolyanion. These reactions may be represented as follows:

$$\begin{array}{l} R-C=O \\ \quad | \\ Zn-O-W \end{array} \quad + H_2O \longrightarrow Zn-\overset{H}{O}-W + RCOOH$$

$$\begin{array}{l} R-C=O \\ \quad | \\ Zn-O-W \\ (R=CH_3) \end{array} \quad + C_6H_5NH_2 \longrightarrow Zn-\overset{H}{O}-W + C_6H_5NHCOR$$

So all our experimental results are consistent with acylation of the bridging oxygen atoms between a divalent metal ion and tungsten ions in the heteropolyanions. The mechanism of acylation is probably an acid-catalyzed nucleophilic substitution with the bridging oxygen atom acting as the nucleophile.

$$\begin{array}{l} X \\ | \\ R-C=O \end{array} + H^+ \longrightarrow \begin{array}{l} X \\ | \\ R-C-OH \\ + \end{array} \xrightarrow{Zn-O-W} \begin{array}{l} R-C=O+XH \\ \quad\quad | \\ \quad\quad Zn-O-W \end{array}$$

$(X=CH_3COO)$

We have shown that the bridging oxygen atoms between a divalent metal ion and oxotungsten ions in some heteropolyanions can be acylated. This result suggests that the basicity of the surface oxygen atoms of heteropolyanions and metal oxides, which may play a crucial role in some reactions, can be controlled by choosing appropriate metal ions. It seems that the sum of the formal charges on two groups connected by the bridging oxygen atom is useful in estimating the basicity of the oxygen atom. For $[SiW_{12}O_{40}]^{4-}$ and $[SiW_{11}VO_{40}]^{5-}$, which do not react with acetic anhydride in the presence of acid,[7] the bridging oxygen atoms connect two $[W=O]^{4+}$ groups or one $[W=O]^{4+}$ group and one $[V=O]^{3+}$ group. For $[SiW_{10}V_2O_{40}]^{6-}$ and $[SiW_{11}O_{39}M(H_2O)]^{6-}$ ($M=Zn^{2+}$ or Cu^{2+}), which can be acylated, there are bridging oxygen atoms connecting two $[V=O]^{3+}$ groups or one $[W=O]^{4+}$ group and M^{2+} ($M=Zn$ or Cu). So the bridging oxygen atoms in these heteropolyanions can be acylated when the sum of the formal charges on two oxometal or metal groups are less than 7. More work on other systems is needed to confirm this generalization.

Acknowledgement. The support of this research by the Ministry of Education is gratefully acknowledged.

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12. See, for example, D. L. Pavia, G. M. Lampman, and G. S. Kriz, Jr., "Introduction to Spectroscopy", W. B. Saunders Co., Philadelphia, 1979, p. 57.
13. We have observed only one ^1H-NMR line at 1.90 ppm for acylated $[Nb_2W_4O_{19}]^{4-}$ at which one bridging oxygen atom between two niobium atoms is available for acylation.
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15. Water-free solvents were used to prevent hydrolysis of the acylated product. Ether and dichloromethane were refluxed in the presence of CaH_2, and acetonitrile was stored with a molecular sieve. The reaction was carried out under a nitrogen atomosphere.

Synthetic Studies on Kainoids

Sung-eun Yoo*, Kyu Yang Yi, Sang-Hee Lee, and Nak-Jung Kim

Korea Research Institute of Chemical Technology, Chungnam 305-606

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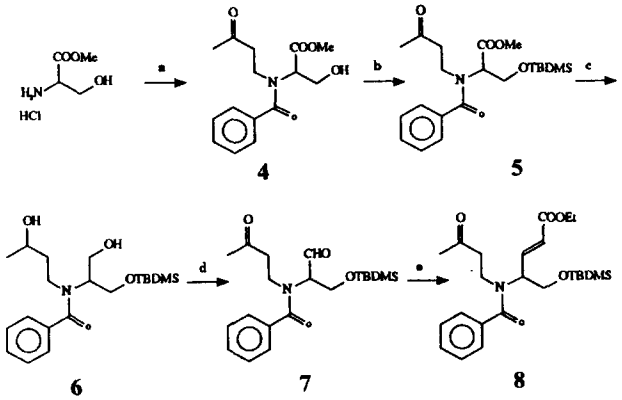
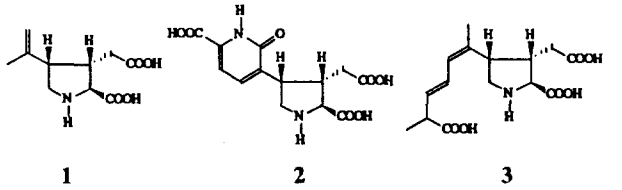
α-Kainic acid (**1**), isolated from the algae *Digenea simplex*[4] and *Centrocerus clavulatum*[2] has shown to possess an interesting neuronal excitatory activity.[3] Other structurally related compounds also have been isolated, namely acromelic acid (**2**) from the toxic principles of *Clitocybe acromelalga*[4] and domoic acid (**3**) and its family from the red algae *Chondria aromata*.[5a] In recent years, α-kainic acid has attracted consi-



a) i) methyl vinyl ketone, K_2CO_3, CH_3CN-H_2O, rt
ii) PhCOCl, K_2CO_3, CH_3CN-H_2O (2 : 1), rt, 30 min.
b) *t*-butyldimethylsily chloride, imidazole, DMF, rt, 1 hr.
c) $NaBH_4$, LiCl, MeOH, rt, 10 hr.
d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −50℃, 1 hr.
e) Ph_3P=CHCOOEt, benzene, rt, 1 hr.

Scheme 1

derable interests due to its potent neurotransmitting activity in the central nervous system[3] and domoic acid for its insecticidal activity.[5b]



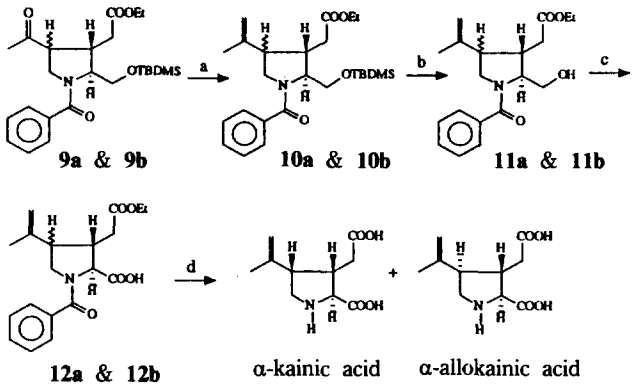
Interesting structural features of kainoids and their biological activities have promoted us[6] and others[7] to investigate the more general synthetic methodology for these compounds. Previously we have demonstrated that the common ring system of kainoids, 3-carboxymethylproline, could be generated *via* the intramolecular Michael reaction.[8]

In this paper we would like to report the synthetic studies on more elaborated system, namely 4-acetyl-3-carboxymethylproline, which is a key intermediate for the synthesis of α-kainic acid and other related compounds using again the intramolecular Michael reaction as the key reaction.

The synthetic pathway used for the preparation of the key intermediate **8** is described in Scheme 1. Serine methyl ester was reacted with methyl vinyl ketone followed by benzoyl chloride in the presence of potassium carbonate in CH_3CN-H_2O to give **4**.

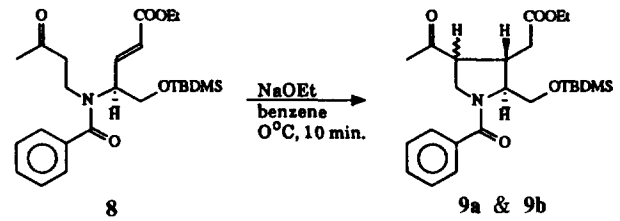
After protecting the alcohol group with a silyl group (*t*-butyldimethylsilyl chloride, imidazole, DMF, rt), ketone and ester groups of **5** were reduced at the same time with $NaBH_4$/LiCl in MeOH to diol **6**. The diol was then oxidized ($(COCl)_2$, DMSO, Et_3N, CH_2Cl_2) to the ketoaldehyde **7**, which was immediately subjected to the Wittig reaction. Thus, the key compound for the crucial cyclization reaction, α,β-unsaturated ester **8**, was obtained in 59% overall yield from serine methyl ester.

When the compound **8** was treated with a catalytic amount of sodium ethoxide (0.2 eq.) in benzene at 0℃, the intramolecular Michael reaction took place smoothly to produce two stereoisomers of the cyclized product in 10 : 1 ratio (88% combined yield) along with some minor compounds. When a different base, such as Triton B, was used a different ratio of the isomers was obtained, indicating that the reaction pathway leading to two stereoisomers is sensitive to condition being used.



a) $Ph_3P^+CH_3I^-$, *n*-BuLi, THF, −78℃
b) *n*-$Bu_4N^+F^-$, THF, rt
c) Jones reagent, acetone, 0℃
d) 4 N HCl, reflux

Scheme 2



The above two isomer, **9a** & **9b**, were separated chromatographically and each isomer was subjected to the extensive structure determination. However, it was not a simple task to determine the sterochemistry only by spectroscopic means such as the coupling patterns of the ^{1}H-NMR spectra. Therefore, both isomers, **9a** & **9b**, were independently transformed to the final compounds not only to complete the synthesis but also to determine the stereochemistry of two isomers, **9a** & **9b**, following steps shown in Scheme 2, namely 1) the Wittig reaction of the carbonyl group to give **10a** & **10b** 2) deprotection (*n*-Bu_4NF, THF, rt) of the silyl protecting group to give **11a** & **11b**, 3) Jones oxidation of the resulting alcohol and 4) the acid hydrolysis of the ester groups.

The final compound derived from the minor isomer, **9b**, was turned out to be identical to natural α-kainic acid and the final compound from the major isomer, **9a**, was identical to α-allokainic acid.[9] Thus, this correlation conclusively determines the stereochemsitry of **9a** & **9b** obtained from the crucial intramolecular Michael reaction. In conclusion, we successfully applied the intramolecular Michael reaction for the total synthesis of α-kainic and α-allokainic acid.

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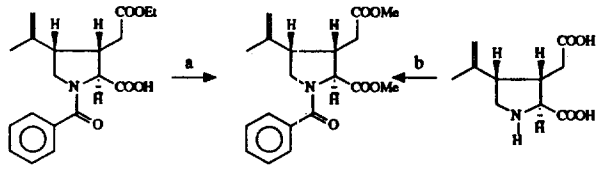
9. The comparison of ^{1}H-NMR spectra was done with the common intermediate, **13b**, derived from the synthetic compound, **12b**, and from the natural α-kainic acid as shown below.



12b **13b** α-kainic acid

a) i) NaOH, MeOH-H_2O, rt, 2 hr.
ii) CH_2N_2, Et_2O
b) i) PhCOCl, NaOH, H_2O, 0℃
ii) CH_2N_2, Et_2O

Direct Template Synthesis of Iron(III) Polyaza Macrotricyclic Complex

Myunghyun Paik Suh*, Sang-Hee Park, and Do-Uk Kim

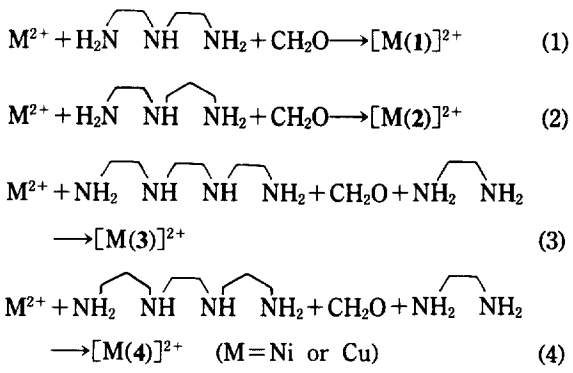
Department of Chemistry Education, Seoul National University, Seoul 151-742

Received August 17, 1991

Metal template syntheses often provide selective routes toward the products that are not obtainable in the absence of metal ions. Especially, template reactions involving formaldehyde and amines facilitate the preparation of saturated polyaza multidentate, macrocyclic and macropolycyclic complexes.[1-8] The reactions are simple ("one-pot reactions"), cheap, and high yielding.

However, iron macrocyclic complexes are not able to be synthesized by the direct template condensation reactions unless the macrocycle to be produced is highly conjugated. The direct template reactions usually lead to iron oxide instead of the desired macrocyclic complexes because Fe(II) intermediate complexes have strong tendency to react with water and a trace of oxygen. Therefore, Fe(II) macrocyclic complexes are generally synthesized by the insertion of Fe (II) ion to the free macrocycle, that is prepared separately, under an oxygen and moisture free condition.

Ni(II) and Cu(II) complexes of macrotricyclic ligands 1-4 have been prepared in our laboratory by the template condensation reactions of amines and aqueous formaldehyde in the presence of Ni(II) or Cu(II) ion as described in eqs 1-4.[6-8] In these cyclization reactions, formaldehyde links two *cis* amine moieties to form methylenediamine (N-C-N) linkages. The complexes contain five-membered or six-membered sub-ring moieties that are located anti and almost perpendicular to the square coordination plane.

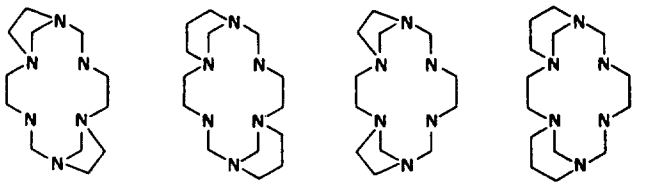


(1)

(2)

(3)

(4)



1 **2** **3** **4**

In order to synthesize Fe(II) complexes of the macrotricyclic ligands **1-4**, we have to obtain the free ligand from the Ni(II) or Cu(II) macrocyclic complexes. However, the free ligands are not able to be isolated because of the instability of N-C-N linkages contained in the macrocyclic ligands. It has been known that N-C-N linkages are unstable when they contain primary or secondary amines.[9] In addition, it has been revealed that N-C-N groups containing secondary nitrogens are stable as long as their nitrogens are coordinated to the metal ion.[2-8]

Therefore, the only way to obtain the Fe(II) complexes of macrocyclic ligands **1-4** is the direct template synthesis that is conducted in the absence of water and oxygen. Formaldehyde or paraformaldehyde cannot be employed in this reaction because water is produced during the Schiff base condensation reactions.

We have attempted to synthesize the Fe(II) complex of macrotricyclic ligand **1** by the direct template condensation re-