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Tandem approaches for the synthesis of functionalized pyrrolidones: efficient routes toward allokainic acid and kainic acid

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ABSTRACT

Tandem approaches for the synthesis of pyrrolidone precursor of allokainic acid and kainic acid are described. The synthesis of pyrrolidone intermediate of allokainic acid is achieved by tandem Wittig–Michael reaction and tandem amidation-Michael reaction while one pot amidation—Ene-esterification is employed for the synthesis of Ganem intermediate (2:1) of kainic acid.

Substituted five member heterocycles 2-oxopyrrolidines or pyrrolidin-2-ones, popularly known as γ-lactams are prevalent structural motifs present in various natural products.[1] They constitute an important role in pharmacological[2] studies due to their application in the treatment of cancers, diabetes, and hepatitis.[3] The SAR studies confirmed the usefulness of these moieties for binding with the receptor proteins.[4] They have also been used as a source of monomers for the synthesis of various functional polymers.[5] Several syntheses have shown that pyrrolidin-2-ones serve as an efficient precursor for the synthesis of pyrrolidines[6] and γ-aminoacids.[7] Due to its unique structure and intriguing biological activities, it is a target of synthetic studies.[8] Most of the strategies involve mainly radical cyclization,[9] ring expansion,[10] metal mediated cyclization reactions,[11] cycloaddition,[12] or intramolecular cyclization of esters.[13] Many tandem approaches, which nowadays an important synthetic tool,[14] have also been investigated.[15] Majority of them include metal mediated, radical cyclization or cycloaddition.

Earlier we had approached the synthesis of kainic acid[16] through tandem Wittig–Ene reaction.[16b] We envisioned that a similar tandem Wittig–Michael reaction can lead us to a pyrrolidone moiety for the synthesis of allokainic acid. Herein we report two domino and one 'one pot' processes for the synthesis of pyrrolidone precursor of allokainic acid. Allokainic acid **1** was isolated along with its C-4 epimer kainic acid **2** from the Japanese marine algae *Digenea simplex AG*[17] in 1953. Over the last few decades several members of kainoids (Fig. 1) have attracted synthetic chemists due to their powerful neuroexcitatory activity[18] in the central nervous system (CNS). A highly functionalized trisubstituted pyrrolidine ring with three contiguous stereogenic centers[18] and global deficiency[19] are the other factors which makes the synthesis of these molecules challenging. Numerous reports are available for the synthesis of allokainic acid.[20] Some of the recent examples include palladium-catalyzed carbocyclization by Cook and Sun,[20v] diastereoselective Rh(II)-carbenoid *C–H* insertion by Zhang and Wee.[20y] Jung et al. achieved the synthesis of allokainic acid by Rh(II)-catalyzed intramolecular *C–H* insertion through control of stereochemistry over 3, 4 positions.[20x] It is stereoselectively synthesized by trimethylstannyl-mediated radical carbocyclization and oxidative destannylation by Hanessian and Ninkovic[20o] and tandem aza-Cope/Mannich reaction by Couty and co-workers.[20m] Allokainic acid was also synthesized by tandem Michael reaction methodology by Barco et al.[20k] Momose and co-workers achieved the formal synthesis of allokainic acid by synthesizing a useful functionalized pyrrolidone through intramolecular Michael reaction[20h].

Our syntheses use readily available starting materials. The first synthesis involved tandem Wittig–Michael reaction as a key step (Scheme 1). The *p*-methoxybenzylamine (PMB) was alkylated with methyl vinyl ketone (MVK) to form amine **5** which was immediately converted into bromoamide **6** by reacting with bromoacetyl chloride in a biphasic medium of water/chloroform (4:1) in 80% yield. In organic solvents the acylation was unsatisfactory. The bromoamide **6** was then converted into phosphonium salt **7**. The attempted conversion of it to the corresponding phosphorane in aqueous basic medium always resulted in its decomposition. So it was decided to prepare the phosphorane in situ. Thus the salt

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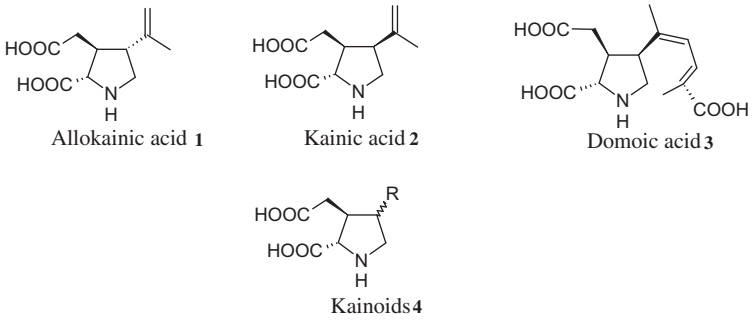
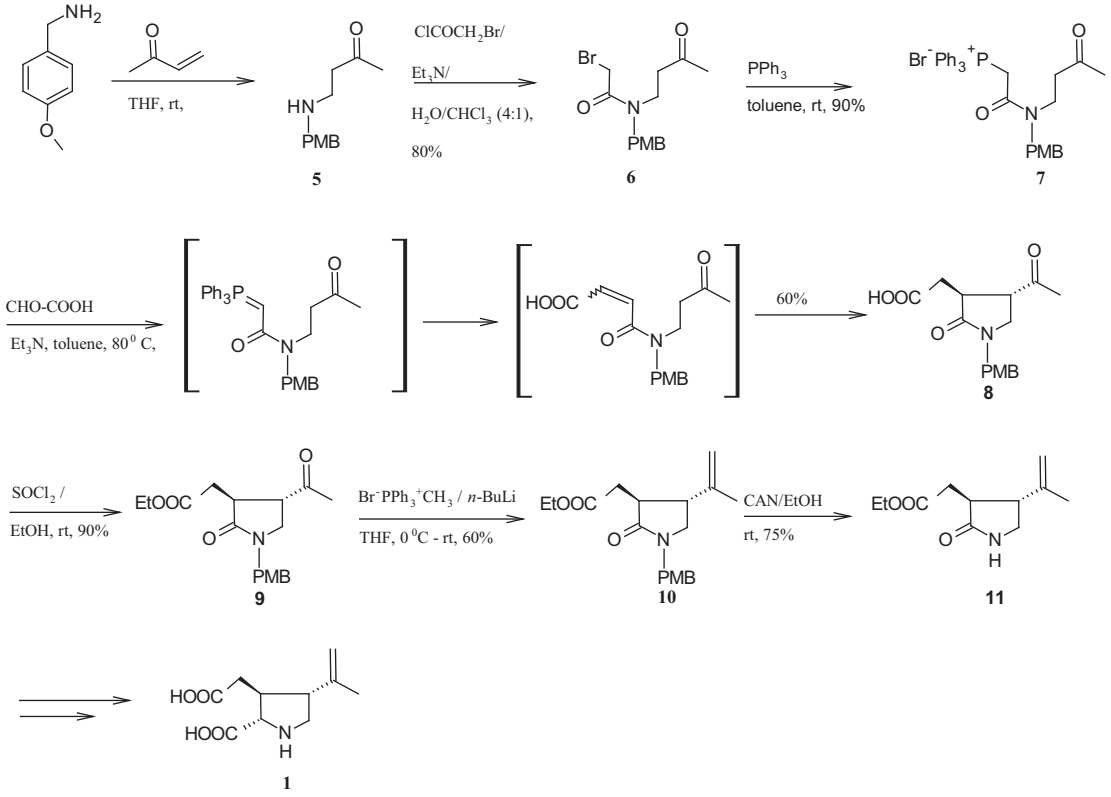


Figure 1. Members of kainoids.



Scheme 1. Tandem Wittig–Michael approach.

7 was treated with excess triethylamine in the presence of ethyl glyoxalate. The reaction took place displaying three close spots on TLC, of the product, the decomposed phosphorane product and triphenylphosphine oxide making it difficult for separation. Hence to make the separation process easy, the Wittig reaction was carried out with glyoxalic acid with excess triethylamine in toluene at 80 °C. The expected Wittig product **8** was then separated by chemical separation without involving column chromatography. The ^{1}H NMR of the crude acid confirmed the formation of domino Wittig–Michael reaction; however at this stage we could not assign the configuration at C3–C4. The crude acid **8** as such was esterified using $SOCl_2$ in ethanol to give ester **9** in 54% overall yield. The product obtained was purified by column chromatography and characterized by spectroscopic methods. The compound **9** was then alkenated to give **10**. The PMB group was easily deprotected using ceric ammonium nitrate (CAN) in EtOH to get the compound **11**.

At this stage we compared the ^{1}H NMR of **11** with that reported in the literature.[16b,c] The differentiation of the *cis* and *trans* isomers

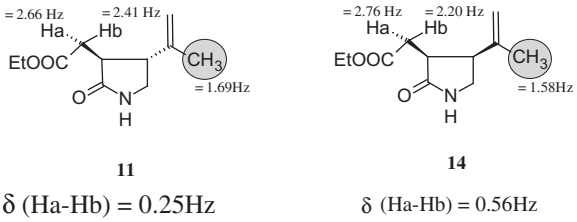
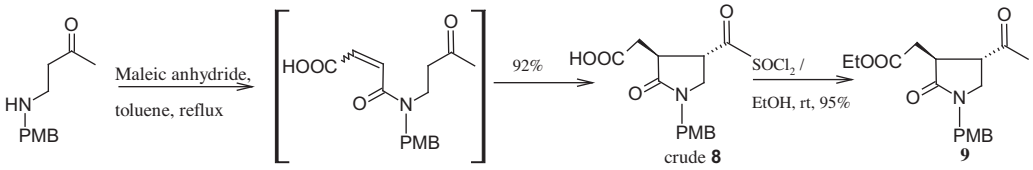
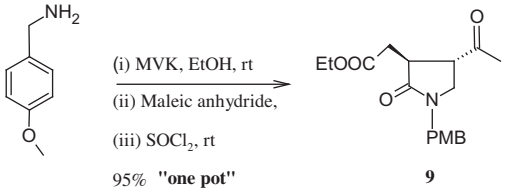


Figure 2. The differentiation of *cis* and *trans* isomer.

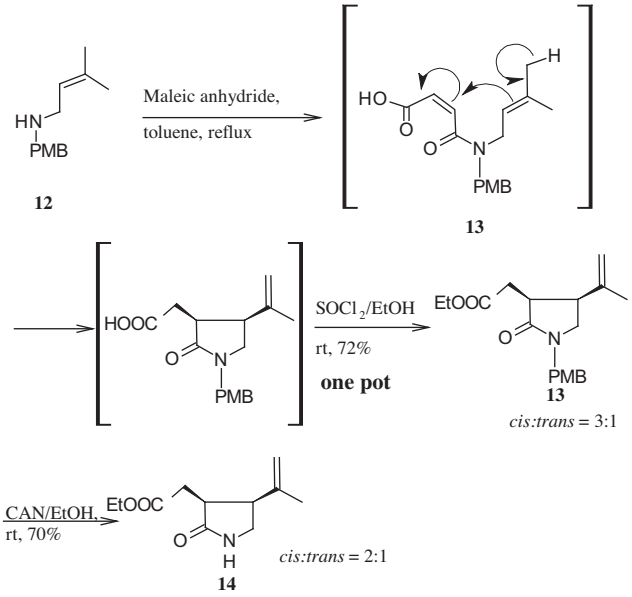
of the kainoids was well explained by Baldwin et al.[21] based on δ values of the methylene protons attached to carboxyl part of the side chain and they demonstrated that (i) one of the protons of CH_2 (either Ha or Hb) shows significantly lower chemical shift in the case of *cis* isomer compared to the corresponding proton in the *trans* isomer due to shielding effect (Ha or Hb of *cis* < Ha or Hb of *trans*) and (ii) The difference in the chemical shift values



Scheme 2. Tandem amidation-Michael approach.



Scheme 3. One-pot approach for allokainic acid precursor.



Scheme 4. One-pot approach for kainic acid precursor.

for these two protons in the *cis* isomer is larger than that for trans that is δ (Ha–Hb) of *cis* > δ (Ha–Hb) of *trans*. The δ values of compound **11** for the protons attached to carboxyl part are 2.66 and 2.4 Hz and the difference is smaller than that reported for *cis* compound which confirmed the formation of *trans* isomer (Fig. 2). And also the higher δ value observed for CH_3 attached to the olefinic part in compound **11** due to less shielding than in the case of *cis* isomer further confirms the formation of *trans* isomer **11** exclusively which is a key building block[20h,16b,c] for allokainic acid **1**.

After achieving the success in getting the precursor of allokainic acid through tandem Wittig–Michael reaction, we thought of a still shorter route via tandem amidation-Michael reaction (Scheme 2). This time amine **5** was directly reacted with maleic anhydride in toluene at 80 °C. The acid **8** formed was separated by chemical separation and further treated with $SOCl_2$ in ethanol to furnish the product **9**.

We then thought of carrying out the entire sequences in one pot (Scheme 3) which nowadays is another emerging tool in synthetic organic chemistry.[22] This time PMB was reacted with MVK in absolute ethanol. Maleic anhydride was added to the reaction mixture once the primary amine was totally consumed and further stirred till the disappearance of the secondary amine. $SOCl_2$ was added in the same pot and stirred further at room temperature to afford the key intermediate **9** in 95% yields.

Further we visualized that similar one pot strategy can be adapted for the synthesis of all important Ganem intermediate **14**[16c] employed in the synthesis of kainic acid. Thus a mixture of prenylated PMB **12** and maleic anhydride was refluxed in toluene and then treated with EtOH and $SOCl_2$ in the same pot. The three reactions namely, amidation, Ene, and esterification took place in one pot to give a mixture of diastereomers **13** and **10** in a 3:1 ratio. The PMB group was then deprotected using CAN to give **14** (Scheme 4).

In summary we have developed metal-free, ligand-free intramolecular tandem, and one pot approaches for the synthesis of a functionalized pyrrolidin-2-one which are effective precursors for allokainic acid and kainic acid. The challenging asymmetric fusion of C3 and C4 which serves as a route for (−)-allokainic acid and (−)-kainic acid is under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.007.

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