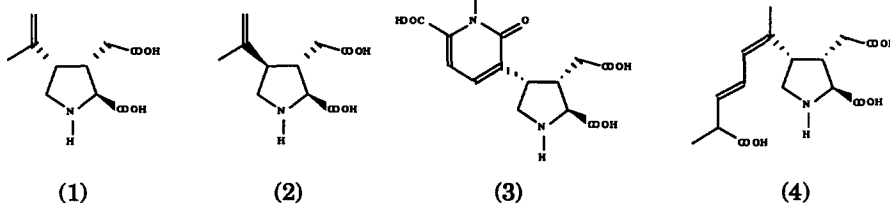


## SYNTHESIS OF $\alpha$ -KAINIC ACID AND $\alpha$ -ALLOKAINIC ACID BY Pd(0) MEDIATED OLEFIN INSERTION-CARBONYLATION REACTION

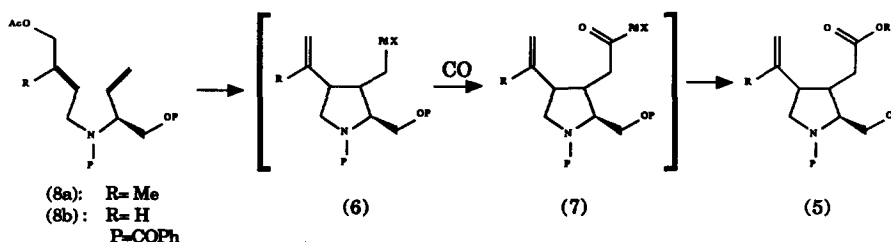
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**Abstract:**  $\alpha$ -Kainic acid and  $\alpha$ -allokainic acid were synthesized by Pd(0) mediated olefin insertion into allylic acetate followed by carbonylation reaction.

$\alpha$ -Kainic acid(1), isolated from the algae *Digenea simplex*<sup>1a</sup> and *Centrocerus clavalatum*<sup>1b</sup> has shown to possess an interesting neuronal excitatory activity.<sup>2</sup> Other structurally related compounds also have been isolated, namely  $\alpha$ -allokainic acid(2) from the same source, acromelic acid A(3) and B from the toxic principles of *Citocybe acromelalga*,<sup>3</sup> and domoic acid(4) and its family from the red algae *Chondria armata*.<sup>4</sup>

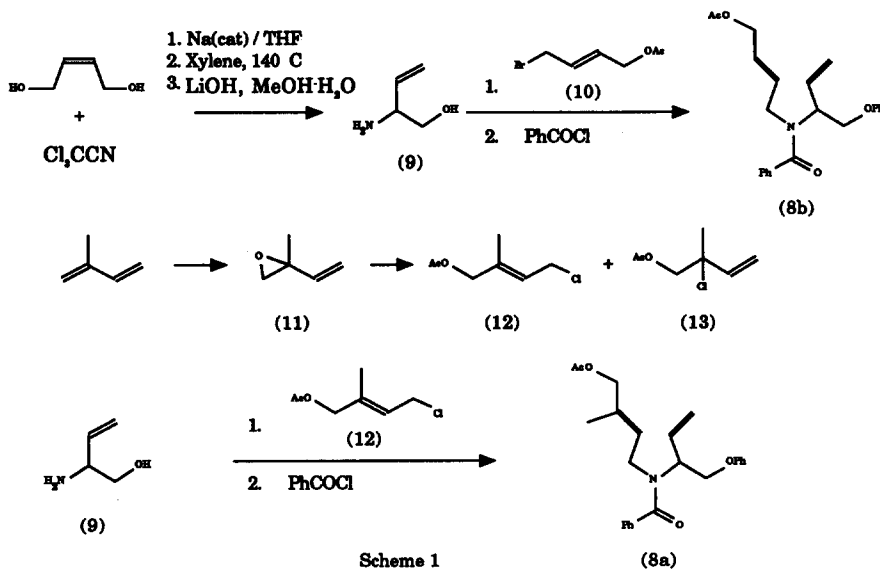


$\alpha$ -Kainic acid has attracted considerable amounts of interests in recent years due to its potent neurotransmitting activity in the central nervous system. A number of total syntheses of and synthetic strategies towards  $\alpha$ -kainic acid and  $\alpha$ -allokainic acid have appeared in the literature.<sup>5</sup> And we also have reported previously a strategy employing intramolecular Michael reaction.<sup>6</sup> In continuing efforts to develop a new methodology for the kainoid ring system, we envisioned that the intramolecular olefin insertion into  $\pi$ -allyl palladium complex would open a new strategy for vinyl substituted cyclic compounds.<sup>7</sup> Specifically in the case of  $\alpha$ -kainic acid(1) 'Pd(0) catalyzed formal "ene" reaction' starting with properly functionalized vinyl-allylic acetate (e.g.8) followed by carbonylation<sup>8</sup> would construct a 3-carboxymethyl-4-vinyl pyrrolidine ring system common to kainoids.

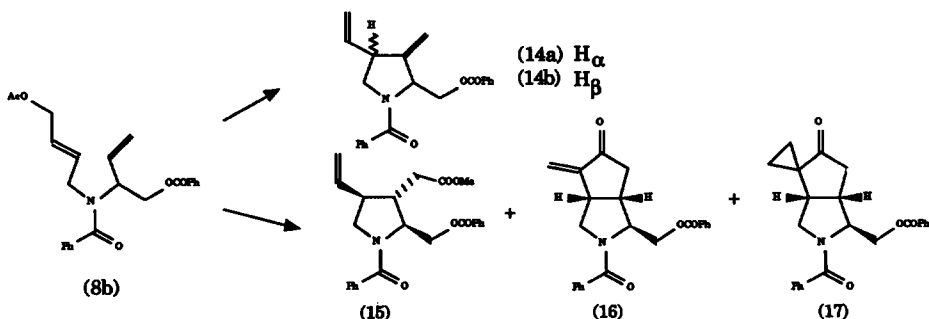


In this letter, we would like to report our results on this work. The key substrates 8a and 8b were prepared as summarized in Scheme 1. Vinylamino alcohol(9) was obtained as described in the literature.<sup>9</sup> Coupling of 9 and 10<sup>10</sup> followed by quenching with benzoyl chloride produced compound 8b. To prepare compound 8a, isoprene was first epoxidized with

mCPBA to vinyl epoxide (11) (regioselectivity > 10 : 1) and then epoxide (11) was treated with acetyl chloride/LiCl in acetonitrile to give a mixture of 12 and 13 (60% yield, 12 : 13 = 3 : 2). Coupling of 9 with 12 and benzoylation provided a fully functionalized compound 8a.

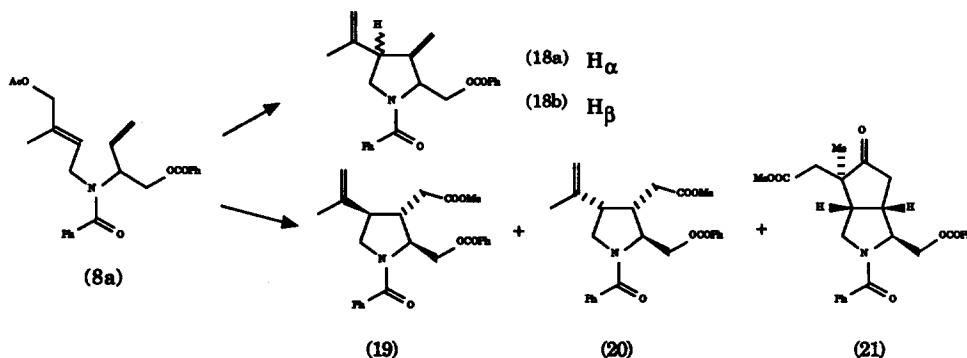


One of the key processes, a Pd(0) mediated cyclization reaction, was first studied with a simpler substrate 8b. Cyclization was effected by treatment of 8b with either Pd(PPh<sub>3</sub>)<sub>4</sub> or Pd(dba)<sub>2</sub> in acetic acid at 80°C to give a 1 : 1 mixture of the cyclized products, 14a and 14b in 60% yield. Then we turned our attention to cyclization followed by carbonylation reaction. A subsequent carbonylation was turned out to be more complex and sensitive to the ligand on palladium. For example, no major product was obtained when Pd(PPh<sub>3</sub>)<sub>4</sub> was used as a palladium species. On the other hand Pd(dba)<sub>2</sub> was turned out to be a very effective catalyst. Thus treatment of 8b with a catalytic amount of Pd(dba)<sub>2</sub> under CO(1 atm) in acetic acid at 45°C for 2hr followed by hydrolysis and subsequent esterification (CH<sub>2</sub>N<sub>2</sub>) produced two major products 15<sup>11</sup> (35% yield) and 16 (24% yield) and one minor product 17 (ca.10% yield).<sup>12</sup>



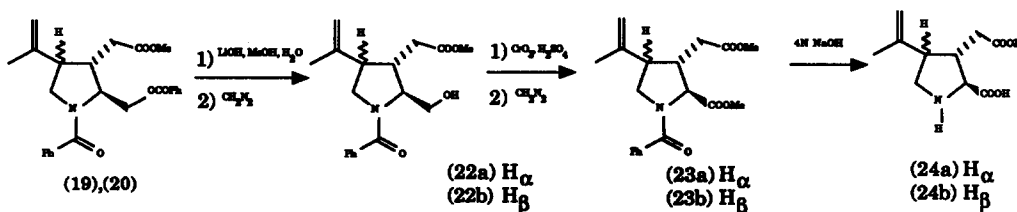
A few things are worthwhile to mention about this reaction. First, substituent at C-2 controls the stereochemistry at C-3 trans but not on the stereochemistry at C-4, from the fact that a mixture of *cis*(3,4) and *trans*(3,4) was obtained in a 1 : 1 ratio.<sup>13</sup> Second, only the *cis*(3,4) product underwent further reactions (insertion of Pd-acyl complex into olefin intramolecularly followed by  $\beta$ -hydride elimination) to give bicyclic compounds **16** and **17**.

We then focused our attention to a fully elaborated substrate **8a**. We found that 2-methylallylic acetate (**8a**) did behave quite differently from **8b**. For example, under the usual cyclization / carbonylation condition (Pd(dba)<sub>2</sub> (7%), PPh<sub>3</sub> (15%), CO(1atm), at 45°C in acetic acid) **8a** was inert. A more vigorous reaction condition (same condition as described previously except for the reaction temperature, 80°C) required even to produce the cyclized products, **18a** and **18b** (1:1). For the subsequent carbonylation, more forcing conditions (Pd(dba)<sub>2</sub> (7%), PPh<sub>3</sub> (15%), CO(3 atm), 80°C in acetic acid) were necessary to give two major products **19** and **20**<sup>14</sup> in 35% and 25% yield, respectively, and one minor product **21**<sup>12</sup> in 10% yield after usual workup (i. hydrolysis with H<sub>2</sub>O, ii. esterification with CH<sub>2</sub>N<sub>2</sub>) and separation by preparative thin layer chromatography (silica gel, hexane:ethyl acetate=1:1).



Stereoselectivity between C2-C3 and C3-C4 is similar to that of the previous model system. However, the existence of the methyl group slowed down substantially the initial cyclization reaction as well as the second cyclization reaction (cyclization of Pd-acyl complex to the newly formed olefin) which can be explained as the steric effect of the methyl group.

Transformation of **19** and **20** into  $\alpha$ -allokainic acid(**24a**) and  $\alpha$ -kainic acid(**24b**) was done by 1) LiOH, MeOH/H<sub>2</sub>O (2:1), rt, 1 hr then CH<sub>2</sub>N<sub>2</sub> 2) CrO<sub>3</sub>/H<sub>2</sub>SO<sub>4</sub>, acetone, rt, 30 min. then CH<sub>2</sub>N<sub>2</sub> 3) 4N NaOH, reflux, 3 hrs (Scheme 2).<sup>15</sup>



Scheme 2

## References and Notes

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8. Although there was no report on Pd(O) catalyzed cyclization/carbonylation at the inception of this work, following communications have appeared soon after. a) Yamamoto, K. et al., *Chem. Lett.* 955 (1989) b) Oppolzer, W. et al., *Tet. Lett.* 5883 (1989)
9. Vyas, D. M., Chiang, Y., Doyle, T. W.; *J. Org. Chem.* **49**, 2037 (1984)
10. The substrate (10) was obtained by treatment of 1,4-dibromo-2-butene with sodium acetate.
11. Structure and stereochemistry of 15 were fully elucidated spectroscopically. Trans(2,3), trans(3,4) relationship was confirmed by NOE experiments done by Dr. S. G. Lee (KRICT).
12. The structure of 17 & 21 was assigned tentatively based on <sup>1</sup>H NMR, IR and mass spectra. 17 might be derived from the cyclopropanation of 16 in the presence of Pd(II) and CH<sub>2</sub>N<sub>2</sub>.
13. While this manuscript was in preparation, a communication dealing with stereoselectivity has been reported. Oppolzer, W. et al.; *Tet. Lett.* 1265 (1990)
14. Spectroscopic data for new compounds; Compound 19: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz)  $\delta$  1.70 (s, 3H), 2.45-2.63 (m, 3H), 2.81 (m, 1H), 3.49 (m, 1H), 3.60 (m, 1H), 3.63 (s, 3H), 4.48 (m, 1H), 4.59 (m, 1H), 4.85 (d, 2H, J=7.4Hz), 4.94 (m, 1H), 7.37-7.63 (m, 8H), 8.09 (d, 2H, J=7.4Hz); IR (neat) 1724, 1635 cm<sup>-1</sup>; MS (70 ev) m/e 421 (M<sup>+</sup>), 105 (100%); Exact mass: calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>5</sub>, 421.1889, found: 421.1871.  
Compound 20: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300MHz)  $\delta$  1.64 (s, 3H), 2.31-2.44 (m, 2H), 2.96 (m, 1H), 3.12 (m, 1H), 3.46 (m, 1H), 3.67 (m, 1H), 3.46 (m, 1H), 3.67 (s, 3H), 3.71 (m, 1H), 4.02-5.10 (m, 5H), 7.35-8.17 (m, 10H); IR (neat) 1724, 1635 cm<sup>-1</sup>; MS (70 ev) m/e 421 (M<sup>+</sup>), 286 (100%); Exact mass: calcd. for C<sub>25</sub>H<sub>27</sub>NO<sub>5</sub>, 421.1889, found: 421.1894.
15. The reason for the stepwise transformation was to confirm the structure of the intermediates. A more direct conversion of 19 & 20 into 24a and 24b can be done by basic hydrolysis followed by oxidation.