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Facile synthesis of (+)-α-allokainic acid via Pd-catalyzed hydrogenolysis of allyl acetate derived from *trans*-4-hydroxy-L-proline

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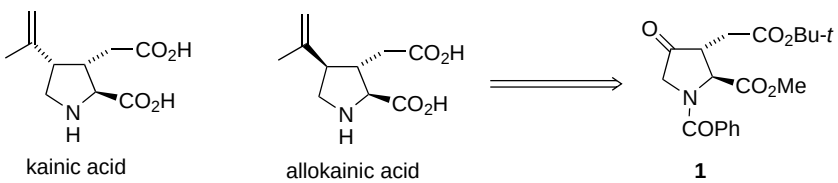
Abstract—$Pd(PPh_3)_4/PPh_3$-catalyzed hydrogenolysis of **3a** derived from *trans*-4-hydroxy-L-proline using ammonium formate as a hydride reagent, provides olefin **4** as a major product, which is hydrolyzed to give (+)-α-allokainic acid.

Due to their marked biological activity in particular neuroexcitatory activity in the mammalian central nervous system, caused by acting at the kainate subtype of ionotropic glutamate receptors, kainic acid and α-allokinaic acid have become attractive synthetic targets in the past two decades.[1,2] Over 20 different synthetic routes to these compounds have been reported, however, most of the reported protocols suffer from taking long steps, using expensive reagents, or handling of the reactions under sensitive conditions.[1,2] Herein, we wish to describe a convenient route to (+)-α-allokainic acid using a known compound **1**[3] as a key intermediate (Scheme 1).

As outlined in Scheme 2, we synthesized the ketone **1** from *trans*-4-hydroxy-L-proline in six steps according to a known procedure.[3] Reaction of **1** with 2-propenylmagnesium bromide afforded allyl alcohol **2** in 62% yield as a mixture of two diastereomers in a ratio of 2/1. Acylation of **2** with acetyl chloride, methyl chloroformate, or benzoyl chloride provided **3a**, **3b** or **3c**, respectively. Obviously, if the *O*-acyl groups of **3** could be cleaved in a regioselective and stereoselective manner, we would obtain protected (−)-kainic acid or (+)-α-allokainic acid efficiently. Thus, a study toward the Pd-catalyzed hydrogenolysis[4] of **3** was undertaken and the results are summarized in Table 1.

As shown in Table 1, in most cases, this hydrogenolysis reaction gave olefin **4** as the major product. Its 4-epimer **5**, and regioisomer **6** were also isolated as minor products. In some cases, diene **7** was isolated. The ratio for these products was dependent on the catalytic systems, hydride reagent, or reaction temperature. The best selectivity was observed when $Pd(PPh_3)_4/PPh_3$ was used as a catalytic system, HCO_2NH_4 was used as a hydride reagent, and the reaction was carried out in refluxing THF. In this case the olefin **4** was isolated in 69% yield (entry 1). Changing the palladium source or the hydride reagent slightly reduced the selectivity (compare entries 1–4). When dppp was used as the ligand, the major product was the diene **7**, which indicated that this ligand promoted β-hydrogen elimination in this case (entry 5). It was reported that tri-*n*-



Scheme 1.

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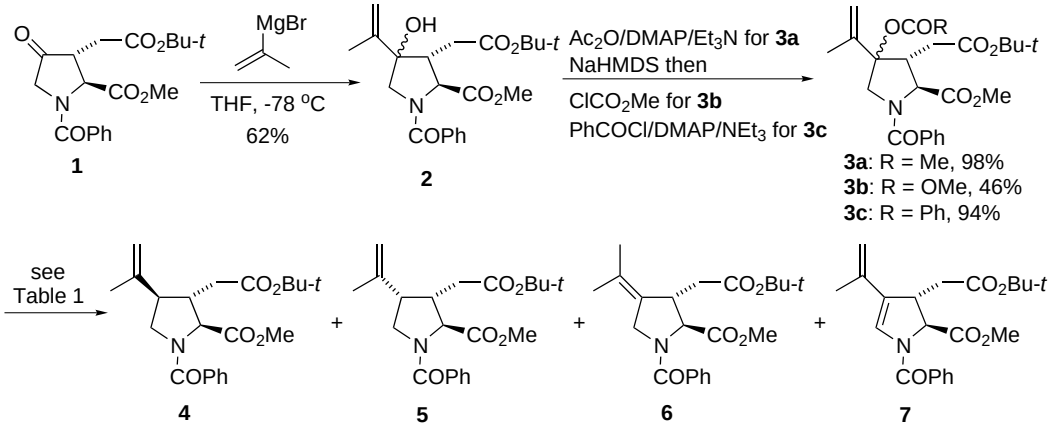


Scheme 2.

Table 1. Pd-catalyzed hydrogenolysis of **3**[a]

Entry	Substrate	Catalyst	Ligand	Hydride reagent[b]	Solvent	Yield (%)[c]			
						4	**5**	**6**	**7**
1	**3a**	$Ph(Ph_3P)_4$	PPh_3	A	THF	69	15	8	–
2	**3a**	$Pd(OAc)_2$	PPh_3	A	THF	62	17	8	–
3	**3a**	$Ph(Ph_3P)_4$	PPh_3	B	THF	57	28	8	–
4	**3a**	$Pd(OAc)_2$	PPh_3	B	THF	53	27	10	–
5	**3a**	$Pd(OAc)_2$	dppp	A	THF	–	–	–	46[d]
6	**3a**	$Ph(Ph_3P)_4$	P(Bu-*n*)$_3$	A	THF	34[d]	–	–	–
7	**3a**	$Pd(OAc)_2$	P(Bu-*n*)$_3$	B	THF	31[d]	–	–	–
8	**3a**	$Ph(Ph_3P)_4$	PPh_3	A	1,4-dioxane	50	20	7	13
9	**3a**	$Pd(OAc)_2$	PPh_3	A	1,4-dioxane	50	19	6	9
10	**3b**	$Ph(Ph_3P)_4$	PPh_3	A	THF	57	20	8	8
11	**3c**	$Ph(Ph_3P)_4$	PPh_3	A	THF	37	16	10	–

[a] Reaction conditions: **3** (0.5 mmol), catalyst (0.025 mmol), ligand (0.1 mmol), hydride reagent (1.0 mmol), refluxed in indicated solvent for 2 h (in 1,4-dioxane) or 6–12 h (in THF).
[b] A: HCO_2NH_4; B: HCO_2H/NEt_3.
[c] Isolated yield.
[d] Some unidentified products were isolated.

butylphosphine was a better ligand for terminal olefin formation,[4b] however, in the present reaction it led to formation of other side products (entries 6 and 7). In addition, either raising the reaction temperature or using other esters also reduced the selectivity (compare entries 1 and 8, 1 and 10, 11).

The stereochemical outcome of this hydrogenolysis reaction is illustrated in Fig. 1. After reaction of allyl esters **3** with Pd(0), two (π-allyl)palladium complexes **A** and **B** might form, which are attacked by hydride from the rear of the Pd species to produce either olefin **4** or **5**. There is a stronger steric interaction between the Pd species and the 3-substituent in the intermediate **B**, and so the intermediate **A** should be more stable than **B**, thereby giving the olefin **4** as the major product.

Refluxing olefin **4** in aqueous sodium hydroxide followed by a purification with Dowex-50W provided (+)-α-allokainic acid[5] in 75% yield. Thus, we have

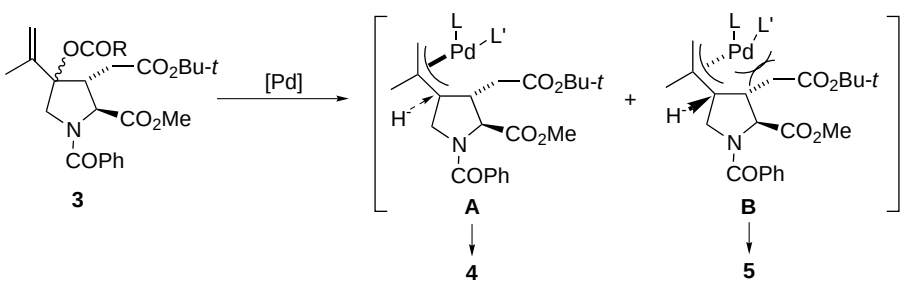
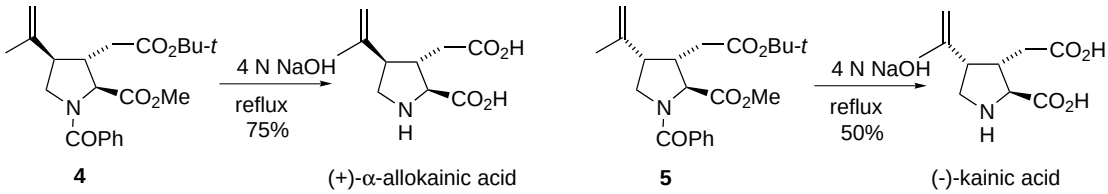


Figure 1.



Scheme 3.

developed a 10-step route to (+)-α-allokainic acid in 12% overall yield. Similarly, the olefin **5** was converted into (−)-kainic acid in 50% yield (Scheme 3). Attempts to improve the selectivity for **5** by changing the substrates in order to develop an efficient synthesis for (−)-kainic acid is being pursued in our laboratory.

Acknowledgements

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5. Selected data: $[\alpha]_D^{20}=+7.4$ (*c* 1.3, H_2O) [lit.[6] $[\alpha]_D^{20}=+7.0$ (*c* 0.2, H_2O)]; ^1H NMR (300 MHz, D_2O): δ 4.95 (s, 2H), 3.90 (d, $J=8.9$ Hz, 1H), 3.48 (dd, $J=11.6$, 7.9 Hz, 1H), 3.28 (dd, $J=11.6$, 11.2 Hz, 1H), 2.89–2.53 (m, 4H), 1.69 (s, 3H); MS *m*/*z* 213 (M^+).
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