New Access to Kainic Acid via Intramolecular Palladium-Catalyzed Allylic Alkylation

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Dedicated to Dr. Pierre Mangeney in honor of his 60th birthday

Abstract: The formal synthesis of kainic acid was carried out in eleven steps. The key cyclization step was accomplished through an intramolecular palladium-catalyzed allylic alkylation of an allylic sulfone. Further functionalization of the resulting pyrrolidone featured, inter alia, a N-heterocyclic carbene–copper hydride (NHC–CuH)-mediated stereoconvergent conjugate reduction.

Key words: kainic acid, synthesis, palladium, allylic alkylation, ring closure

(–)-α-Kainic acid is the parent member of kainoids, an important class of natural nonproteinogenic amino acids (Figure 1). It was first isolated in 1953 from *Digenea simplex*.[1] In addition to its insecticidal and anthelmintic properties, it has been shown to display powerful neuroexcitatory activity in the mammalian central nervous system, where it acts as conformationally restricted analogue of L-glutamate. For these reasons, it has found fundamental applications in the study of neurodegenerative disorders[2] such as Alzheimer's disease,[3] Huntington's chorea[4] and epilepsy.[5] Since the first synthesis of (–)-kainic acid, carried out by Oppolzer,[6] numerous total syntheses of this compound have been described, most of them being of chiral pool derivation.[7,8] Interest in the synthesis of such a target amazingly increased in recent years, due to a temporary halt on the extraction from the above alga, which brought about shortage of this natural product.[9]

Following our ongoing interest in the synthesis of nitrogen-based heterocycles, we reported that pyrrolidones could be built up regio- and stereoselectively via the intramolecular 5-*exo* interaction between a stabilized acetamide enolate anion and a properly tethered η^3-allylpalladium appendage (Scheme 1).[10] Moreover, we subsequently showed that this reaction could take place under biphasic conditions, which are milder and higher yielding than those previously reported in monophasic media.[11]

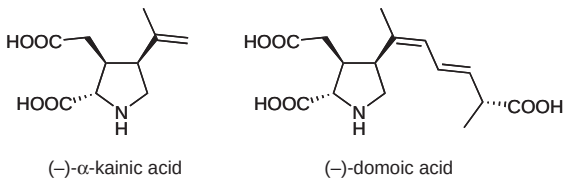
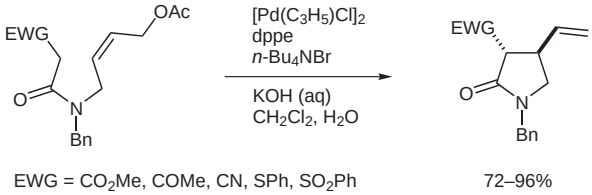
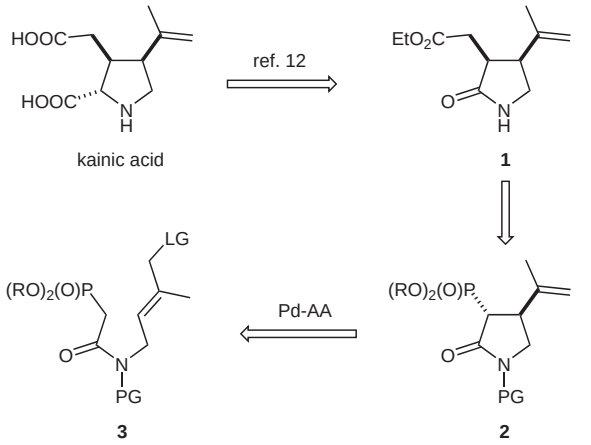


Figure 1 (–)-α-Kainic acid and (–)-domoic acid structures



Scheme 1 Palladium-catalyzed intramolecular allylic alkylation under biphasic conditions

In order to further test the value of the above methodology, we next envisioned to exploit our strategy in the synthesis of kainic acid. Accordingly, since one of the most efficient total syntheses reported to date entails pyrrolidone **1** as an advanced intermediate,[12] we focused on the latter structure as our synthetic goal. We report herein the formal synthesis of (±)-kainic acid according to the retrosynthetic path depicted in Scheme 2.



Scheme 2 Retrosynthetic approach to kainic acid; Pd-AA = palladium-catalyzed allylic alkylation

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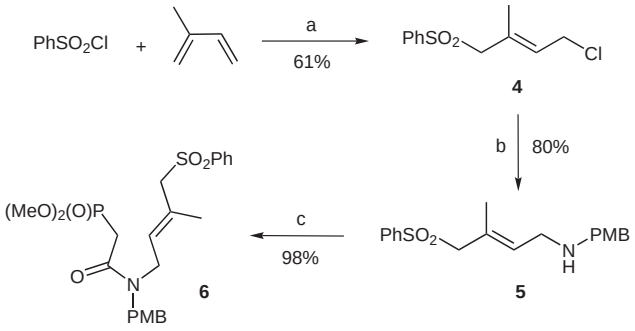
Key precursor **1** would arise from the *trans*-substituted pyrrolidone **2** via Horner–Wadsworth–Emmons olefination with ethyl glyoxalate, followed by reduction of the electron-poor double bond. Pyrrolidone **2** could in turn be derived from an intramolecular palladium-catalyzed allylic alkylation of the unsaturated α-phosphonoamide **3**.

1-Acetoxy-4-chloro-2-methyl-2-butene was first recognized as a reasonable intermediate in the synthesis of the cyclization precursor **6**.[13] However, in view of the difficulties in preparing and isolating this reagent in satisfactory yield[14] we decided to look for an alternative precursor. A quick perusal of the literature suggested that chlorosulfone (*E*)-**4** could be an ideal choice. Indeed, allylic sulfones are known to generate η^3-allyl-palladium complexes, although their use is still rather underdeveloped with respect to the more popular allyl acetates or carbonates.[15] Copper-catalyzed condensation between phenylsulfonyl chloride and isoprene afforded **4** in 61% yield on multigram scale.[16] Reaction of the latter with excess *p*-methoxybenzylamine afforded allylic amine **5** in 80% yield. Subsequent acylation with dimethylphosphonoacetic acid gave the cyclization precursor **6** in 98% yield (Scheme 3).

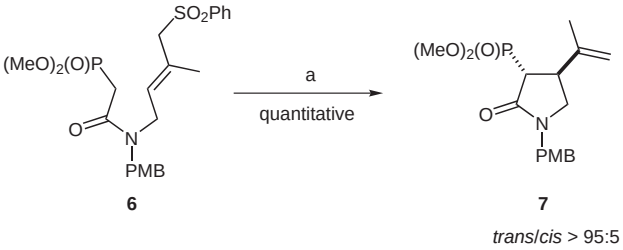


Scheme 3 *Reagents and conditions:* (a) CuCl (5 mol%), Et_3NHCl (5 mol%), MeCN, 60 °C, 16 h; (b) *p*-$MeOC_6H_4CH_2NH_2$ (3 equiv), MeCN, reflux, 4 h; (c) $(MeO)_2P(O)CH_2COOH$ (1.2 equiv), DCC (1.5 equiv), DMAP (5 mol%), THF, r.t., 16 h.

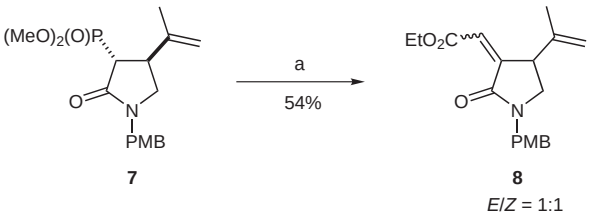
Intramolecular palladium-catalyzed allylic alkylation of the phosphonoacetamide **6** was next tested (Scheme 4). Much to our satisfaction, treatment of the substrate **6** with $[Pd(C_3H_5)Cl]_2$ (5 mol%), 1,2-bis(diphenylphosphino)ethane (dppe; 12.5 mol%), *n*-Bu_4NBr (10 mol%) and KOH (4.0 equiv) in 1:1 CH_2Cl_2–H_2O gave, after 16 hours at room temperature, the expected pyrrolidone **7** in quantitative yield and a >95:5 *trans*/*cis* diastereomeric ratio.[17]

Horner–Wadsworth–Emmons olefination was next undertaken. Deprotonation of **7** with NaH at 0 °C in THF followed by condensation with excess ethyl glyoxalate in toluene afforded the expected diene pyrrolidone **8** (54% yield) as a 1:1 *E*/*Z* mixture, separable by flash chromatography (Scheme 5).

Reduction of the conjugate double bond was next tackled for each isomer, separately. The use of L-Selectride®[18] was rather disappointing, leading to complete degradation of starting material in the case of (*E*)-**8**, and to a moderate

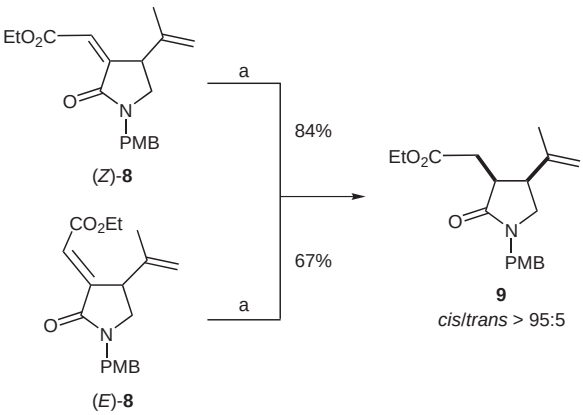


Scheme 4 *Reagents and conditions:* (a) $[Pd(C_3H_5)Cl]_2$ (5 mol%), dppe (12.5 mol%), *n*-Bu_4NBr (10 mol%), aq KOH (4 equiv), CH_2Cl_2–H_2O (1:1), r.t., 16 h.



Scheme 5 *Reagents and conditions*: (a) NaH (1.2 equiv), THF, 0 °C then ethyl glyoxalate (50% solution in toluene, 2 equiv), r.t., 1 h.

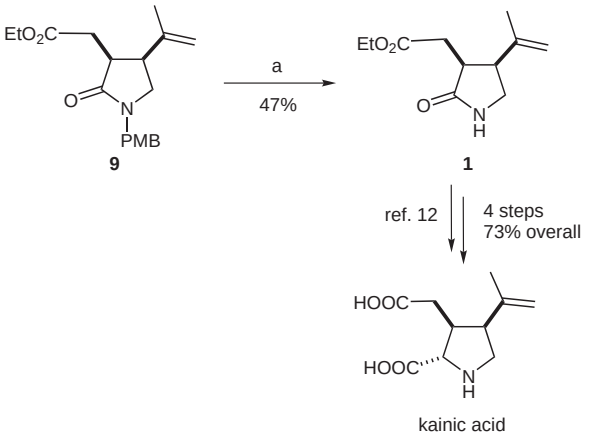
yield (52%) of the desired pyrrolidone **9** with a poor 65:35 *cis*/*trans* diastereomeric ratio, when starting from (*Z*)-**8**. Conversely, N-heterocyclic carbene–copper hydride (NHC–CuH) efficiently promoted the reduction step.[19] Indeed, treatment of (*Z*)-**8** or (*E*)-**8** with 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr)-CuCl (2 mol%), *t*-BuONa (10 mol%), and excess poly(methylhydrosiloxane) (PMHS) as the hydride source, gave the *cis*-pyrrolidone **9** as the only product in 84% and 67% yields, respectively (Scheme 6). A similar result was obtained starting from an equimolar *E*/*Z* mixture of **8** (72% yield).[20]



Scheme 6 *Reagents and conditions*: (a) IPr-CuCl (2 mol%), *t*-BuONa (10 mol%), PMHS (4 equiv), toluene, r.t., 16 h.

PMB deprotection completed the formal synthesis of kainic acid. Thus, treatment of **9** with CAN in MeOH gave rise to Ganem's intermediate **1** (47% yield, i.e. 6 steps and 14% overall yield from the known chlorosulfone **4**), whose spectroscopic data were in agreement with those reported in the literature.[12] According to Ganem's

procedure, a four-step sequence can convert pyrrolidone **1** into kainic acid in an overall 73% yield (Scheme 7). Moreover, the two enantiomers may be further separated via a (+)-ephedrine-mediated resolution, according to Oppolzer's protocol.[21]



Scheme 7 *Reagents and conditions*: (a) $(NH_4)_2Ce(NO_3)_6$ (4 equiv), MeOH, 0 °C then r.t., 16 h.

In summary, the above described sequence represents a successful eleven-step formal synthesis of kainic acid. The key cyclization step was accomplished through an intramolecular palladium-catalyzed allylic alkylation from an allylic sulfone. Further functionalization of the resulting pyrrolidone exploited a stereoconvergent NHC–CuH-mediated conjugate reduction. Extension of the present strategy to an enantioselective synthesis of (–)-kainic acid is currently under investigation.

Acknowledgment

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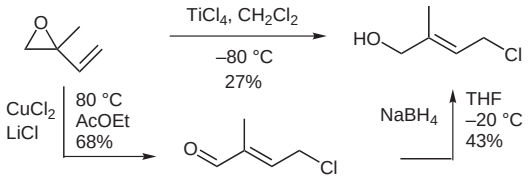

Scheme 8

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(17) **Procedure for the Palladium-Catalyzed Cyclization Reaction**: To a solution of tetrabutylammonium bromide (10 mol%) in CH_2Cl_2 (1 mL) were added in this order allylpalladium chloride dimer (5 mol%) and dppe (12.5 mol%). After 5 min stirring, to the thus formed catalytic

system were added successively a CH_2Cl_2 (5 mL) solution of **6** (795 mg, 1.6 mmol), H_2O (6.0 mL), and a 50% aq KOH solution (6.4 mmol). The resulting biphasic system was stirred vigorously at r.t. for 16 h. The aqueous phase was extracted with CH_2Cl_2 (3 ×). The collected organic phases were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by flash chromatography to afford **7** in quantitative yield as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 4.78 (br s, 2 H), 4.46 (d, *J* = 14.6 Hz, 1 H), 4.40 (d, *J* = 14.6 Hz, 1 H), 3.87 (d, *J* = 10.8 Hz, 3 H), 3.81 (d, *J* = 10.8 Hz, 3 H), 3.80 (s, 3 H), 3.55 (dd, *J* = 8.3, 9.6 Hz, 1 H), 3.20–3.32 (m, 1 H), 2.98–3.07 (m, 1 H), 2.94 (dd, *J* = 4.5, 22.8 Hz, 1 H), 1.63 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 159.2, 144.3, 129.6, 127.4, 114.1, 112.3, 55.3, 53.5 (*J* = 100 Hz), 50.1, 46.4, 46.0 (*J* = 140 Hz), 39.7, 19.2. IR: 2955, 2360, 1688, 1514, 1247, 1031 cm^{-1}. MS (ESI$^+$): *m*/*z* = 392 [M + K$^+$], 376 [M + Na$^+$], 354 [M + H$^+$].

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(20) **Procedure for the Hydride Conjugate Addition**: An oven-dried flask under an argon atmosphere was charged with IPr-CuCl (2 mol%), *t*-BuONa (10 mol%) and anhydrous toluene (1 mL). After 10 min stirring at r.t., PMHS (90 μL) was added and the resulting orange solution was stirred at r.t. for 5 min. Then toluene (1 mL), and further PMHS (270 μL) were added. A solution of **8** (1:1 *E*/*Z* mixture) (508 mg, 1.54 mmol) in toluene (8 mL) was added via cannula to the thus generated reducing system and the reaction mixture was stirred at r.t. for 16 h. H_2O was added, the aqueous phase was extracted with EtOAc (3 ×). The collected organic phases were washed with brine, dried over $MgSO_4$ and the solvents were removed in vacuo. The crude product was purified by flash chromatography to afford pure **9** as an oil (72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.6 Hz, 2 H), 6.83 (d, *J* = 8.6 Hz, 2 H), 4.74 (br s, 1 H), 4.65 (br s, 1 H), 4.39 (d, *J* = 14.2 Hz, 1 H), 4.35 (d, *J* = 14.2 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 3 H), 3.36–3.42 (m, 1 H), 3.10–3.15 (m, 2 H), 3.03 (dd, *J* = 1.3, 10.1 Hz, 1 H), 2.83 (dd, *J* = 3.5, 17.2 Hz, 1 H), 2.21–2.32 (m, 1 H), 1.42 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 172.5, 159.2, 143.1, 130.0, 128.1, 114.9, 114.0, 60.6, 55.3, 49.0, 46.3, 42.0, 41.6, 31.0, 19.8, 14.3. IR: 2936, 1731, 1687, 1513, 1246, 1175, 1032 cm^{-1}.

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