

8H, 2-adamantanol CH), 0.45 (s, 4H, 2-adamantanol CH), 0.24 (d, 8H, $J = 12.5$ Hz, 2-adamantanol CH_2), 0.10 (d, 8H, $J = 12.5$ Hz, 2-adamantanol CH_2), 0.06 (d, 8H, $J = 12.5$ Hz, 2-adamantanol CH_2), -0.10 (s, 4H, 2-adamantanol CH), -0.43 (s, 8H, 2-adamantanol CH_2); ^{13}C NMR (125 MHz, D_2O): $\delta = 170.1$ (Cq), 153.4 (CH), 145.2 (Cq), 126.0 (CH), 74.0 (2-adamantanol CH), 47.8 (CH_2), 37.2 (2-adamantanol CH_2), 36.1 (2-adamantanol CH_2), 31.0 (2-adamantanol CH_2), 27.3 (2-adamantanol CH), 26.8 (2-adamantanol CH).

1·(6)₄: ^1H NMR (500 MHz, D_2O): $\delta = 9.29$ (d, $J = 6.6$ Hz, 24H, Py H α), 8.65 (d, $J = 6.6$ Hz, 24H, Py H β), 4.09 (s, 12H, trimethoxybenzene CH), 2.98 (s, 24H, $-\text{NCH}_2\text{CH}_2\text{N}-$), 2.43 (br s, 36H, CH_3O); ^{13}C NMR (125 MHz, D_2O): $\delta = 169.9$ (Cq), 160.6 (trimethoxybenzene Cq), 153.3 (CH) 145.9 (Cq), 126.2 (CH), 92.0 (trimethoxybenzene CH), 54.5 (CH_3O) 47.8 ($-\text{NCH}_2\text{CH}_2\text{N}-$).

1·7: ^1H NMR (500 MHz, D_2O): $\delta = 9.28$ (br s, 24H, Py H α), 8.72 (br s, 24H, Py H β), 4.8 (s, 3H, 7 Ar CH), 2.99 (s, 24H, $-\text{NCH}_2\text{CH}_2\text{N}-$), -0.12 (s, 27H, $t\text{Bu}$); ^{13}C NMR (125 MHz, D_2O): $\delta = 170.1$ (Cq), 153.3 (CH) 149.0 (7 Ar Cq), 146.3 (Cq), 126.0 (CH), 47.8 ($-\text{NCH}_2\text{CH}_2\text{N}-$), 33.8 ($t\text{Bu}$ Cq), 30.4 ($t\text{Bu}$ CH_3).

Received: June 2, 1998 [Z11936IE]

German version: *Angew. Chem.* **1998**, *110*, 3327–3329

Keywords: adamantanes • boron • clusters • molecular recognition • palladium

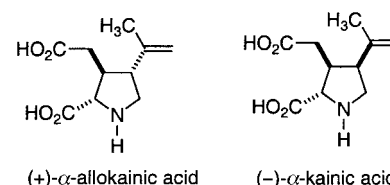
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- [18] The broadening of the signals is probably due to a slow exchange on the NMR time scale between the free and complexed host.
- [19] The assignment of the signals was confirmed by H–H COSY, C–H COSY, NOESY, H–C HMBC.
- [20] The 1:4 stoichiometry was estimated by the Job plot method.
- [21] Force-field calculation clearly shows that tri-*tert*-butylbenzene is slightly larger than the portals of **1**.

Nickel and Palladium Catalysis in the Stereoselective Synthesis of Functionalized Pyrrolidines: Enantioselective Formal Synthesis of (+)- α -Allokainic Acid

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(+)- α -Allokainic acid and (–)- α -kainic acid are representative members of the kainoid family of neuroexcitatory amino acids whose biological activity has been attributed to their action as conformationally restricted analogues of glutamate (Scheme 1).^[1] Extensive structure–activity studies have demonstrated that the C-4 isopropenyl substituent is the



Scheme 1. Kainoid natural products.

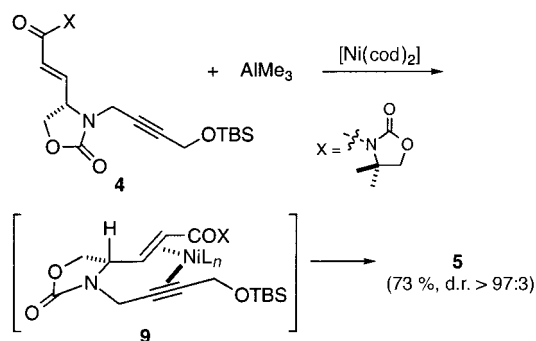
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[**] This work was supported by the National Institutes of Health. J.M. acknowledges receipt of a National Science Foundation CAREER Award, a Camille Dreyfus Teacher-Scholar Award, and a 3M Pharmaceuticals New Faculty Award. M.V.C. acknowledges receipt of a Graduate Research Assistantship Award from Wayne State University. The authors thank H  l  ne Fain for helpful suggestions.

principal site at which structural variation is allowed without compromising neuroexcitatory activity.^[2] Given the important role of these natural products in pharmacological investigations, we set out to develop a synthetic entry to this class of compounds that allows facile late-stage modification of the C-4 substituent and access to both the kainic acid and allokainic acid configurations.^[3] Herein, we report our initial studies in this regard with a direct and highly stereoselective formal total synthesis of (+)- α -allokainic acid. The strategy involves the nickel-catalyzed cyclization of a D-serine-derived alkynyl enone with trimethyl aluminum followed by a palladium-catalyzed allylic carbonate reductive transposition (Scheme 2).

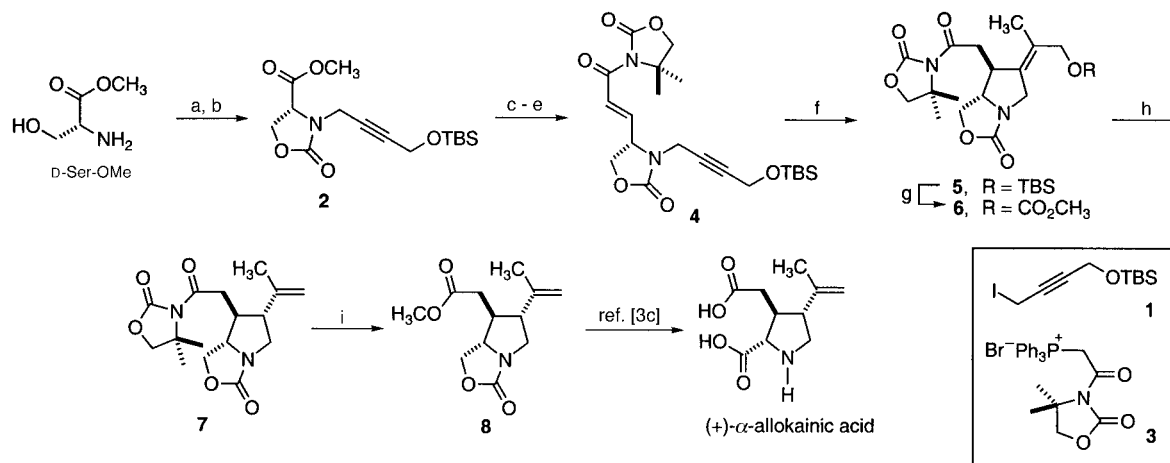
D-Serine methyl ester was efficiently converted to the central cyclization substrate **4** in straightforward fashion (Scheme 2). Condensation of D-serine methyl ester with triphosgene,^[4] followed by N-propargylation with iodide **1** using KHMDS afforded **2** in 49% yield over two steps. Chemoselective ester reduction with NaBH₄,^[5] oxidation under Swern conditions, and Wittig olefination with oxazolidinone **3**^[6] gave substrate **4** in 74% overall yield from **2**.

Cyclization of **4** with MeLi/ZnCl₂ and 10 mol % [Ni(cod)₂] by employing conditions previously reported^[7–8] afforded high yields but moderate diastereoselectivities (ca. 3:1). Commercial trimethylaluminum or dimethylzinc, however, were found to be superior to MeLi/ZnCl₂ in achieving the desired *trans* stereochemical relationship of the C-2 and C-3 substituents. Cyclization of **4** with commercial trimethylaluminum and [Ni(cod)₂] (10 mol %) in THF afforded a 73% yield of **5** with a diastereomeric ratio (d.r.) of >97:3 in favor of the desired *trans* isomer, and commercial dimethylzinc under identical conditions afforded a 67% yield of **5**, also with a >97:3 diastereomeric ratio. We believe that a parallel orientation of the two reactive π components in chelated structure **9** is responsible for the *trans* relationship of the two substituents in product **5** (Scheme 3).

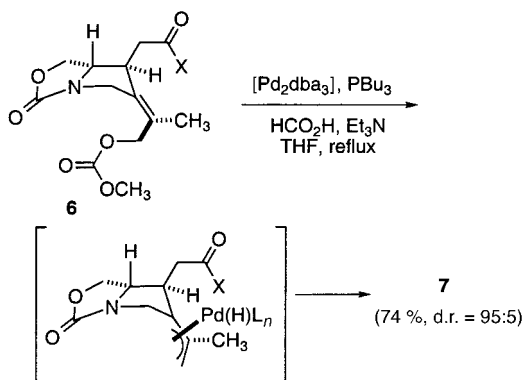


Scheme 3. Stereoselectivity of nickel-catalyzed alkylative cyclization.

A silyl to carbonate protecting group transposition was carried out in 73% yield to prepare substrate **6** for a palladium-catalyzed reduction with allylic transposition. Related systems were reported by Tsuji et al. to rearrange with palladium catalysis via intermediate π -allyl complexes to give the terminal alkene by hydride delivery to the more hindered allyl terminus.^[9] The stereochemistry of oxidative addition ultimately sets the stereochemistry of the overall process, since decarboxylation and C–H bond reductive elimination both proceed with overall retention of configuration. Treatment of **6** with [Pd₂(dba)₃]/PBu₃ and HCO₂H/Et₃N cleanly produced **7** in 74% yield with a 95:5 diastereomeric ratio in favor of the all-*trans* stereochemical relationship of the three substituents at the pyrrolidine ring, as seen in allokainic acid. This result is consistent with *exo*-selective oxidative addition, *syn* to the adjacent side chain, to ultimately deliver hydride to the β -face of **6** (Scheme 4). The formal total synthesis of (+)- α -allokainic acid was then completed by converting the acyloxazolidinone unit to the corresponding methyl ester **8** upon treatment with CH₃OMgBr (Scheme 2).^[10] Compound **8** was previously converted to (+)- α -allokainic acid by Hanesian et al.^[3c]



Scheme 2. Formal synthesis of (+)- α -allokainic acid. a) Triphosgene, THF, 65 °C, 4 h; b) KHMDS (1.1 equiv), THF, 0 °C, 30 min; then **1** (3 equiv) in THF; 40 °C, 24 h, 49% (2 steps); c) NaBH₄, EtOH, 0–25 °C, 3 h, 91%; d) (COCl)₂ (1.5 equiv), DMSO (3 equiv), Et₃N (4 equiv), CH₂Cl₂, –78 °C; e) **3** (1.5 equiv), DMAP (3 equiv), CH₂Cl₂, –20 to 25 °C, 1.5 h, 81% (two steps); f) Me₃Al (3 equiv), 10 mol % [Ni(cod)₂], THF, 0 °C, 40 min., 73% (97:3 diastereoisomeric ratio); g) HF·pyridine, THF, 0–25 °C, 24 h, 86%; then methylchloroformate (3 equiv), pyridine, CH₂Cl₂, 0–25 °C, 3 h, 83%; h) 10 mol % [Pd₂(dba)₃], 40 mol % PBu₃, Et₃N (1.5 equiv), HCO₂H (1.5 equiv), THF, 65 °C, 74%, (95:5 diastereomeric ratio); i) MeOMgBr (3 equiv), 25 °C, 3 h, 54%. cod = cycloocta-1,5-diene, dba = 1,5-diphenylpenta-1,4-dien-3-one, DMAP = 4-dimethylaminopyridine, HMDS = hexamethyldisilazane, TBS = *tert*-butydimethylsilyl.



Scheme 4. Palladium-catalyzed reductive transposition.

The above strategy should provide simple variation of the C-4 substituent of allokinic acid simply by selection of a more complex organoaluminum or organozinc reagent. In addition, the introduction of chirality in sequential operations provides the opportunity for modification of the above strategy to allow preparation of the epimeric series of kainoids typified by kainic acid itself through a late-stage common intermediate.^[11]

Experimental Section

5: Trimethylaluminum (2.0 M in hexanes, 1.44 mmol) was added dropwise to a solution of $[\text{Ni}(\text{cod})_2]$ (13.2 mg, 0.05 mmol) in THF (1.5 mL) at 0 °C. After 5 min, the mixture was transferred to a solution of **4** (210 mg, 0.48 mmol) at 0 °C in THF (3 mL) by cannula, and stirring was continued for 40 min at 0 °C. The reaction was quenched with $\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$ pH 8 buffer, extracted with EtOAc (four times), dried over MgSO_4 , filtered, and concentrated. Flash chromatography (EtOAc/hexanes 1/1) afforded **5** (160 mg, 0.35 mmol, 73%) in a 97:3 diastereomeric ratio: $[\alpha]_D^{25} = -90.9$ ($c = 0.5$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 4.64$ (dd, $J = 4.5$, 3.5 Hz, 1H), 4.41–4.48 (m, 2H), 4.01–4.09 (m, 4H), 3.73 (dt, $J = 8.0$, 4.5 Hz, 1H), 3.59 (d, $J = 15$ Hz, 1H), 3.36 (d, $J = 16$ Hz, 1H), 2.91–3.02 (m, 2H), 1.68 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 173.0$, 161.1, 154.0, 132.8, 130.2, 75.4, 70.5, 65.1, 64.8, 60.5, 48.5, 44.2, 41.1, 25.9, 24.85, 24.81, 18.3, 16.3, –5.3, –5.4; IR (film): $\tilde{\nu} = 2928$, 1772, 1695, 1396, 1311; HRMS: m/z : calcd. for $\text{C}_{18}\text{H}_{27}\text{N}_2\text{O}_6\text{Si}$ 395.1639, found 395.1642 $[M - \text{C}(\text{CH}_3)_3]^+$.

7: Tributylphosphane (6.1 mg, 0.03 mmol) was added to a solution of $[\text{Pd}_2(\text{dba})_3]$ (6.4 mg, 0.007 mmol) in THF (0.3 mL) at 0 °C. Formic acid (4.83 mg, 0.1 mmol) and triethylamine (10.6 mg, 0.1 mmol) were added neat, followed by carbonate **6** (25 mg, 0.06 mmol) in THF (0.3 mL), and the reaction mixture was refluxed (bath temperature 80–85 °C) for 3 h. The mixture was filtered through florisil, and the solvent was removed. Flash chromatography (EtOAc/hexanes 1/1) afforded **7** (15 mg, 0.05 mmol, 74%) in a 95:5 diastereomeric ratio: $[\alpha]_D^{25} = -22.4$ ($c = 1.45$ in CHCl_3); ^1H NMR (500 MHz, CDCl_3): $\delta = 4.87$ (br. s, 1H), 4.85 (t, $J = 1.5$ Hz, 1H), 4.45–4.49 (m, 2H), 4.02 (s, 2H), 3.74 (m, 1H), 3.47 (dd, $J = 8.5$, 11.0 Hz, 1H), 3.38 (dd, $J = 9.5$, 11.5 Hz, 1H), 3.20 (dd, $J = 17.0$, 4.0 Hz, 1H), 2.75 (m, 2H), 2.25 (dq, $J = 9.5$, 4.0 Hz, 1H), 1.70 (s, 3H), 1.54 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 172.4$, 160.7, 154.0, 141.6, 114.7, 75.3, 68.0, 64.8, 60.6, 54.9, 48.6, 42.9, 38.2, 24.7, 24.6, 18.2; IR (film): $\tilde{\nu} = 1774$, 1696, 1381, 1308; HRMS (EI): m/z : calcd. for $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ 322.1529, found 322.1535 $[M^+]$.

Received: June 22, 1998 [Z12026IE]

German version: *Angew. Chem.* **1998**, *110*, 3346–3348

Keywords: cyclizations • neurotoxins • nickel • palladium • pyrrolidines

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Acrylate-Assisted Arene–Chromium Bond Cleavage: Generation of a $[\text{Cr}(\text{CO})_2]$ Fragment under Mild Conditions*

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Ligand exchange is a key reaction in stoichiometric and catalytic applications of transition metal compounds. It is instrumental in the coordination of a substrate and, following metal-mediated reactions, in the release of the product. Therefore the rate of these processes often determines the efficiency of the overall transformation. Acceleration of ligand exchange and the increase in selectivity that results

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[**] We thank the Swiss National Science Foundation for support of this work (SNSF grants 20-045291.95 and 20-52478.97) and Dr. Allan Cunningham Jr., Ciba Specialty Chemicals for valuable discussions.