A Stereodivergent Approach to (−)-α-Kainic Acid and (+)-α-Allokainic Acid Utilizing the Complementarity of Alkyne and Allene Cyclizations

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Abstract: A formal synthesis of (+)-α-allokainic acid and a total synthesis of (−)-α-kainic acid were carried out using a short, efficient, and highly stereoselective approach. From an alkyne precursor, a nickel-catalyzed cyclization and a palladium-catalyzed rearrangement were utilized in the synthesis of (+)-α-allokainic acid. From an allene precursor, a nickel-catalyzed cyclization was utilized in the synthesis of (−)-α-kainic acid. The allene cyclization used in the latter sequence was the first example of a metal-catalyzed cyclization of this type.

Introduction

Excitatory amino acids have been widely studied due to their role in the mediation of synaptic excitation.[1] L-Glutamic acid is the major excitatory neurotransmitter in the mammalian central nervous system, and its signals are mediated through a combination of receptors. The recognition of L-glutamic acid by several receptor classes has been attributed to its flexibility in adopting numorous low-energy conformations. The kainic acid class of neuroexcitatory amino acid receptor was originally characterized by its selective interaction with a marine natural product α-kainic acid.[2] Kainic acid (**1**) is the simplest member of a family of related natural products that include the C-4 epimer α-allokainic acid (**2**)[2] and more structurally complex members such as domoic acid,[3] acromelic acid A,[4] and related structures (eq 1). The neuroexcitatory properties of α-kainic acid and its selective recognition by the kainic acid receptor are derived from its ability to function as a conformationally restricted analogue of L-glutamate. Studies of the interaction of kainic acid with the kainic acid receptor have played an important role in characterization of the kainic acid receptor[5] and elucidation of the requirements for kainic acid receptor agonist activity.[1] Those studies demonstrated that the C-4 isopropenyl substituent is the principal site at which structural variation is allowed without compromising neuroexcitatory activity.

(-)-α-kainic acid (**1**)

(+)-α-allokainic acid (**2**)   (1)

(-)-domoic acid

acromelic acid A
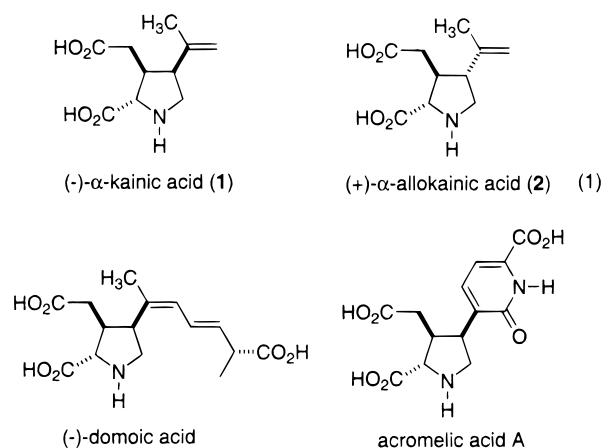
The importance of these natural products in pharmacological investigations has attracted the attention of a number of synthetic groups.[6] Numerous approaches to kainic acid and allokainic acid have been reported, including ene reactions,[7] Claisen rearrangements,[8] free-radical cyclizations,[9] azomethine ylide cycloadditions,[10] Pauson Khand cyclizations,[11] iminium ion cyclizations,[12]

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Scheme 1. Formal Synthesis of (+)-α-allokainic Acid[a]
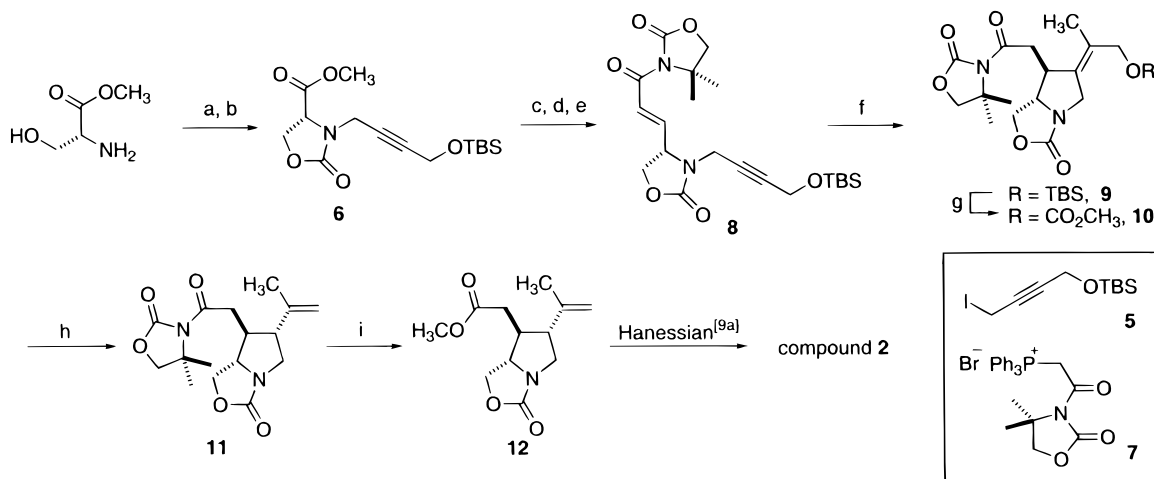
[a] Conditions: (a) Triphosgene, THF, 65 °C, 4 h; (b) 1.1 equiv of KHMDS, THF, 0 °C, 30 min; then 3 equiv of **5** in THF; 40 °C, 24 h, 49 % (2 steps); (c) NaBH₄, EtOH, 0−25 °C, 3 h, 91 %; (d) 1.5 equiv of (COCl)₂, 3 equiv of DMSO, 4 equiv of Et₃N, CH₂Cl₂, −78 °C; (e) 1.5 equiv of **7**, 3 equiv of DMAP, CH₂Cl₂, −20 to 25 °C, 1.5 h, 81 % (two steps); (f) 3 equiv of Me₃Al, 10 mol % Ni(COD)₂, THF, 0 °C, 40 min, 73 % (97:3 diastereoisomeric ratio); (g) HF·Pyr, THF, 0−25 °C, 24 h, 86 %; then 3 equiv of methylchloroformate, 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) 3 equiv of MeOMgBr, 25 °C, 3 h, 54 %

intramolecular Michael additions,[13] hetero-Diels-Alder cyclo-additions,[14] and cobalt-mediated cyclizations[15] as the key ring-closing and stereochemistry-determining steps. However, few approaches allowed the highly stereoselective construction of the pyrrolidine core, and none provided a highly selective stereodivergent entry to both the kainic acid and allokainic acid stereochemical relationships without extensive protecting group manipulations. Furthermore, the flexibility to readily modify the C-4 position is not allowed by most routes. Therefore, we set out to develop a stereodivergent strategy that would allow the preparation of both α-kainic acid and α-allokainic acid as well as provide a versatile route to new analogues of this natural product class.[16]

Results and Discussion

Our initial strategy focused on the preparation of compound **3** as a late-stage common intermediate for the preparation of both kainic acid and allokainic acid (eq 2). We envisioned that
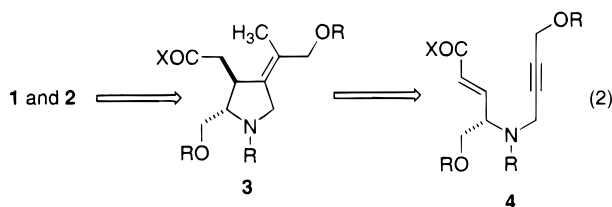
a formal S$_N$2′ displacement of an allylic alcohol derivative at C-4 with a hydride donor would directly produce the desired C-4 isopropenyl unit. Reduction from the β-face of **3** would afford the trans stereochemistry of allokainic acid, whereas reduction from the α-face of **3** would afford the cis stereochemistry of kainic acid. Common intermediate **3** could be

produced by a cyclization of compound **4** utilizing nickel cyclization methodology previously developed in our laboratory.[17]

With this plan in mind, D-serine methyl ester was efficiently converted to cyclization substrate **8** in straightforward fashion (Scheme 1). Condensation of D-serine methyl ester with triphosgene[18] followed by *N*-propargylation with iodide **5** using KHMDS afforded **6** in 49% yield over two steps. Chemo-selective ester reduction with NaBH₄,[19] oxidation under Swern conditions, and Wittig olefination with oxazolidinone **7**[20] gave substrate **8** in 74% overall yield from **6**.[21]

Cyclization of **8** with MeLi/ZnCl₂ and 10 mol % Ni(COD)₂ employing conditions previously reported afforded high yields but moderate diastereoselectivities (ca. 3:1). Commercial tri-methylaluminum or dimethylzinc, however, were found to be superior to MeLi/ZnCl₂ in achieving the desired trans stereo-chemical relationship of the C-2 and C-3 substituents. Cycliza-tion of **8** with commercial trimethylaluminum and Ni(COD)₂ (10 mol %) in THF afforded a 73% yield of **9** with a diastereomeric ratio >97:3 in favor of the desired trans stereochemistry, and commercial dimethylzinc under identical conditions afforded a 67% yield of **9**, also with a >97:3 diastereomeric ratio.

With compound **9** in hand, we were first attracted to the palladium-catalyzed procedure reported by Tsuji for the desired reduction with allylic transposition.[22] A silyl to carbonate protecting group transposition was carried out in 73% yield to prepare substrate **10** for the palladium-catalyzed reduction.

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Scheme 2. Total Synthesis of (−)-α-Kainic Acid[a]
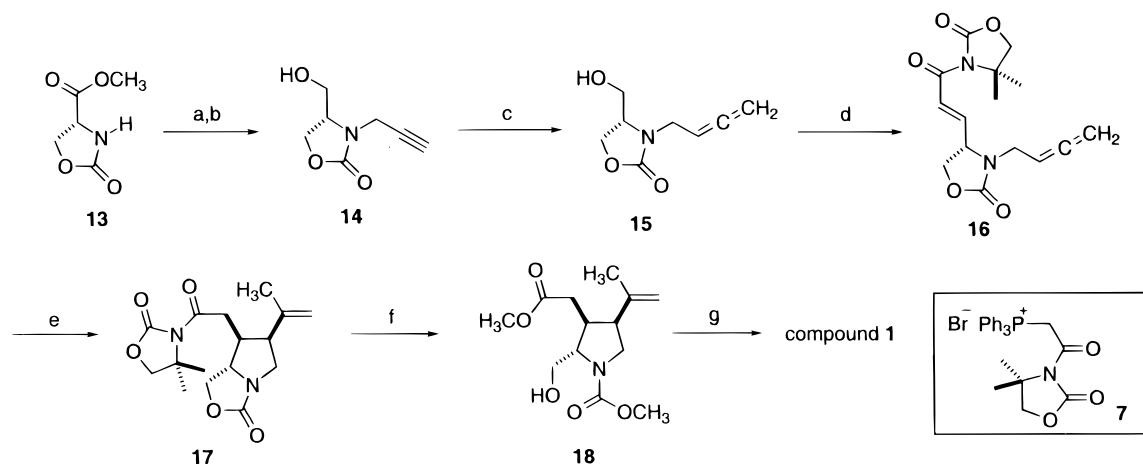
[a] Conditions: (a) KHMDS, propargyl bromide, THF, 0 to 25 °C, 73 %; (b) NaBH$_4$, EtOH, 0−25 °C, 82 %; (c) paraformaldehyde, CuI, HN(iPr)$_2$, dioxane, 100 °C, 76 %; (d) (i) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −78 °C, (ii) reagent **7**, DMAP, CH$_2$Cl$_2$, −20 to 25 °C, 62%, 2 steps; (e) MeLi/ZnCl$_2$, Ni(COD)$_2$ (10 mol %), Ti(O-iPr)$_4$, 57 % (98:2 diastereomeric ratio); (f) (i) MeOMgBr, 25 °C, 60 %, (ii) MeONa, 25 °C, 73 %; (g) (i) CrO$_3$, H$_2$SO$_4$, 0 °C; (ii) NaOH/H$_2$O/MeOH, reflux; (iii) ion exchange chromatography (40% from **18**)

Related systems were reported by Tsuji to rearrange with palladium catalysis via intermediate π-allyl complexes to give the terminal alkene by hydride delivery to the more hindered allyl terminus. 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 stereochemistry. We initially anticipated that oxidative addition might occur from the α-face, opposite the adjacent C-3 side chain, to afford the stereochemistry observed in α-kainic acid. However, treatment of **10** with Pd$_2$(dba)$_3$/PBu$_3$ and HCO$_2$H/Et$_3$N cleanly produced **11** in 74% yield with a 95:5 diastereomeric ratio in favor of the all-trans stereochemical relationship of the three pyrrolidine substituents, 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 **10a** (eq 3). Alternate

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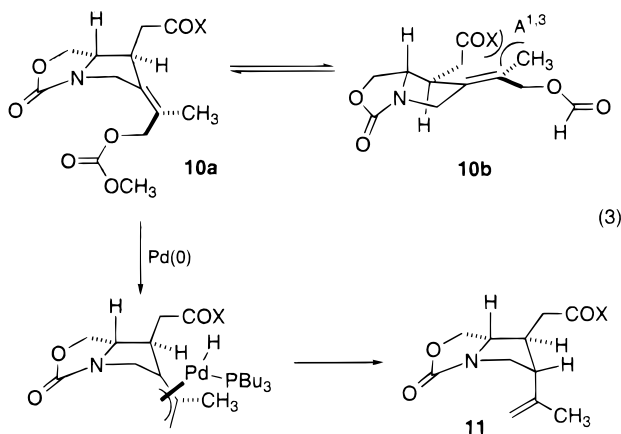
conformation **10b** with a more accessible concave (α) face is destabilized by severe A^{1,3} strain associated with the exocyclic double bond. The formal synthesis of (+)-α-allokainic acid was then completed by converting the acyloxazolidinone unit to the corresponding methyl ester **12** upon treatment with CH$_3$OMgBr (Scheme 1).[23] Compound **12** was previously converted to (+)-α-allokainic acid (**2**) by Hanessian.[9a]

Whereas endo-selective hydride addition to **10** would afford the α-kainic stereochemistry, the conformational bias toward exo-selective hydride addition would likely be difficult to reverse with any hydride delivery agent. Choice of acyclic protecting groups in place of the internal oxazolidinone would remove the conformational biases associated with the [3.3.0] bicycle; however, such a strategy would destroy the divergent nature of the synthetic plan and potentially compromise the high stereoselectivity of the nickel-catalyzed cyclization. Therefore, a simple reversal of chemical steps was instead considered for completing the synthesis of α-kainic acid. Rather than cyclization of an alkyne followed by double bond isomerization as described in the synthesis of α-allokainic acid, we anticipated that isomerization of an alkyne to an allene followed by cyclization should result in the identical introduction of a C-4 isopropenyl unit.[24] Furthermore, our prior studies on cyclizations of bis-enones demonstrated a preference for formation of cis-fused products via an eclipsed conformation of the two reactive π-components when two sp^2-hybridized units were involved (eq 4).[17b,25] A similar transition structure for an allene/alkene

(4)
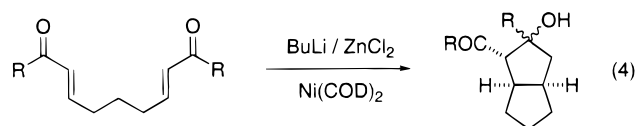
cyclization would directly afford the α-kainic acid stereochemistry.

With this plan in mind, oxazolidinone **13** was *N*-propargylated with propargyl bromide followed by one-carbon homologation with formaldehyde, diisopropylamine, and copper bromide to afford allene **15** (Scheme 2). This novel method for allene introduction, initially described by Crabbé, was proposed to involve an acetylide Mannich condensation/sigmatropic rearrangement sequence.[26] Swern oxidation followed by Wittig olefination with oxazolidinone **7**[20] afforded cyclization substrate **16**. Treatment of **16** with MeLi/ZnCl$_2$ in the presence of

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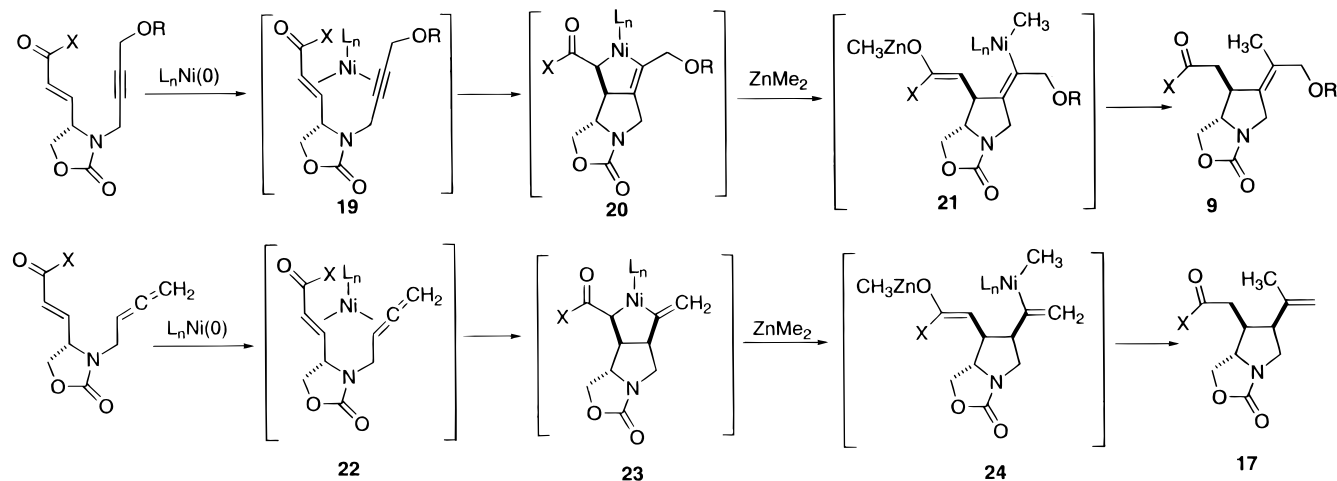
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Scheme 3

Ni(COD)$_2$ and Ti(Oi-pr)$_4$ directly afforded compound **17** in 57% yield with a diastereomeric ratio of 97:3 in favor of the α-kainic acid stereochemistry. Deprotection was accomplished most efficiently with a two-step procedure in which the counterion was varied. Cleavage of the acyl linkage to the external oxazolidinone was accomplished with MeOMgBr,[23] then the internal oxazolidone was converted to the methylcarbamate with NaOMe in methanol to generate compound **18**. Jones oxidation followed by hydrolysis with KOH and ion exchange chromatography afforded (−)-α-kainic acid (**1**) that displayed ^{1}H and ^{13}C NMR data, optical rotation data, and melting point identical with that previously reported.

The strategy of utilizing an alkyne cyclization/alkene isomerization sequence in the preparation of allokainic acid and an alkyne isomerization/allene cyclization sequence in the preparation of kainic acid effectively leads to a stereodivergent route to these two epimeric natural products. Significantly, the same general reaction, the nickel-catalyzed cyclization of a doubly unsaturated substrate in the presence of dimethylzinc, could be utilized in both approaches. We believe that the same mechanism is likely operative in both instances (Scheme 3). Initial oxidative cyclization of nickel(0) complexes **19** and **22** would afford metallacycles **20** and **23**.[27] Transmetalation of dimethylzinc would afford nickel alkenyl species **21** and **24**. Carbon−carbon bond reductive elimination would then afford products **9** and **17** upon hydrolysis of the crude reaction mixtures. The stereodivergent nature of the parallel sequences is allowed since the allene cyclization directly introduces the C-4 stereocenter, whereas the alkyne cyclization defers introduction of that stereocenter until a later step.

To our knowledge, this represents the first example of a metal-catalyzed allene/alkene cyclization of this type. Rhodium-catalyzed intramolecular [5+2] cycloadditions involving allenes and vinylcyclopropanes were reported by Wender,[28] and a ruthenium-catalyzed intermolecular cycloisomerization involving an electron-deficient alkene and an allene to produce 1,3-dienes was recently reported by Trost.[29] Several allene/alkyne cycliza-

tions have been reported,[30] including extensive work from Brummond[31] on Pauson Khand cyclizations involving a number of transition metals and from Sato[32] on titanium-mediated stoichiometric reductive cyclizations. Interestingly, the methods reported by Brummond and Sato likely involve metallacycles analogous to structure **23** (Scheme 3), and the models advanced by these authors for predicting the regiochemistry of allene cyclizations are completely consistent with our observations. In contrast, metal-catalyzed cyclizations of ω-haloallenes extensively studied by Negishi typically occur at the internal allene carbon in an exo- or endocyclization,[33] although some exceptions have been noted in related reaction classes.[34]

An eclipsed orientation of the two reactive π-components in nickel(0) complexes **25** or **26** should give rise to the lowest activation barriers in the oxidative rearrangement to metallacycles **20** and **23** (eq 5).[35] Hence, formation of the reactive

(5)
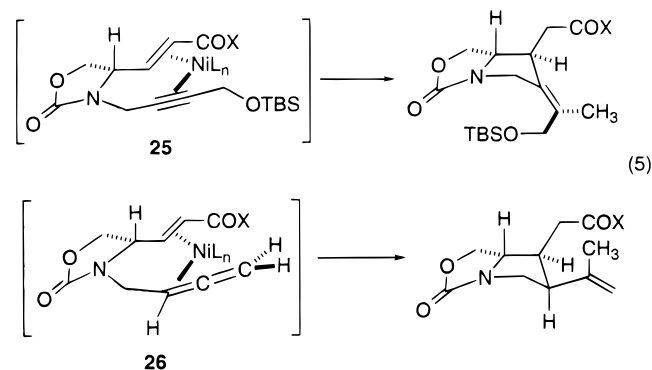
conformers **25** and **26** could explain the stereoselectivities observed in the nickel-catalyzed reactions of alkynes and allenes. It should be noted that the distal π-system of the allene in

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conformation **26** is orthogonal to the unsaturated acyloxazoli-dinone carbon/carbon double bond, thus precluding formation of a chelated complex that would lead to cyclization onto the central allene carbon. An analysis of molecular models suggests that formation of a chelated complex involving the distal π-system would require bond rotations that would introduce significant nonbonded interactions.

Conclusions

An efficient stereodivergent entry to both (−)-α-kainic acid (**1**) and (+)-α-allokainic acid (**2**) was developed. The strategy is highlighted by the stereochemical complementarity of an alkyne cyclization/alkene isomerization sequence to produce allokainic acid and an alkyne isomerization/allene cyclization sequence to produce kainic acid. Both routes were highly diastereoselective. Whereas related alkyne cyclizations have previously been extensively investigated,[17] this report describes the first example of an allene cyclization of this type. Future work will be devoted to further investigating nickel-catalyzed cyclizations of allenes and to the preparation of more structurally complex natural and unnatural members of the kainic acid class.

Supporting Information Available: Full experimental details, ^{1}H NMR spectra of all compounds, and additional correlations with known compounds to confirm stereochemical assignments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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