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Two Syntheses of (−)-Kainic Acid via Highly Stereoselective Zinc-ene Cyclizations

Justin M. Chalker,*,† Ao Yang, Kai Deng,‡ and Theodore Cohen*

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

justin.chalker@chem.ox.ac.uk; cohen@pitt.edu

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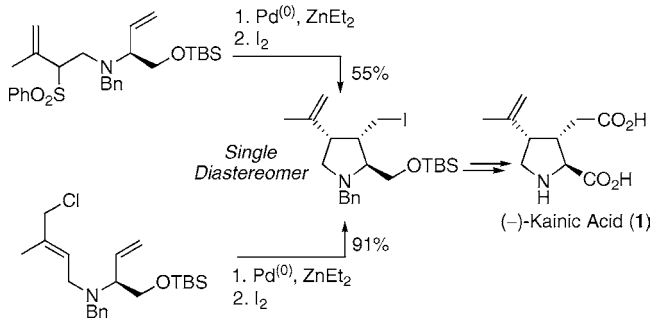
ABSTRACT



Two concise, high-yielding syntheses of enantioenriched (−)-kainic acid are presented. Both routes feature a Pd-catalyzed Zn-ene cyclization that proceeds with complete diastereoselectivity. The key step can be carried out on a multigram scale, and the overall yields are among the highest to date for this marine alkaloid.

(−)-Kainic acid (**1**) is a conformationally restricted glutamate analogue found in *Digenea simplex* and related marine algae.[1] This alkaloid exhibits potent anthelmintic[2] and insecticidal[3] properties but is used primarily as a neuroexcitatory agent[4] by the neuroscience community in modeling afflictions such as epilepsy,[5] Alzheimer's disease,[6] and Huntington's chorea.[7] A halt in commercial production of (−)-kainic acid in 1995 led to a severe shortage of the natural product, hampering neurobiological research.[8] The immediate supply issue has since been resolved,[9] but the natural product remains the target of intense synthetic investigation due to looming depletion of natural sources and its high cost ($6000−$10 000/g). Kainic acid's three contiguous stereocenters and high functional density pose a significant challenge, and despite more than 60 publications devoted to its synthesis, most are limited in yield, stereoselectivity, and scale.[10] We report herein our efforts to address these challenges.

Zinc-ene cyclizations have provided a reliable route to cis-substituted carbo- and heterocycles.[11] Pioneering work by Oppolzer in a Pd-catalyzed Zn-ene cyclization of allyl

† Current Address: University of Oxford, Chemical Research Laboratory, Mansfield Road, Oxford, OX1 3TA, U.K.

‡ Current Address: Memorial Sloan-Kettering Cancer Center, Department of Molecular Pharmacology and Chemistry, 1275 York Avenue, New York, NY, 10021.

(1) (a) Murakami, S.; Takemoto, T.; Shimizu, Z.; Daigo, K. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026. (b) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piatelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549. (c) Balansard, G.; Pellegrini, M.; Cavilli, C.; Timon-David, P. *Ann. Pharm. Fr.* **1983**, *41*, 77.

(2) Nitta, I.; Watase, H.; Tomiie, Y. *Nature (London)* **1958**, *181*, 761.

(3) Sakai, M. *Takeda Kenkhyusho Nempo* **1960**, *19*, 27.

(4) (a) MacGeer, E. G.; Olney, J. W.; MacGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven: New York, 1978. (b) For a recent review, see: Wang, Q.; Yu, S.; Simonyi, A.; Sun, G.; Sun, A. *Mol. Neurobiol.* **2005**, *31*, 3.

(5) Sperk, G. *Prog. Neurobiol. (Oxford)* **1994**, *42*, 1.

(6) (a) Mohmmad, A.; Sultana, R.; Keller, J.; St. Clair, D.; Markesbery, W.; Butterfield, D. *J. Neurochem.* **2006**, *96*, 1322. (b) Goodenough, S.; Schleusner, D.; Pietrzik, C.; Skutella, T.; Behl, C. *Neuroscience* **2005**, *132*, 581.

(7) (a) Coyle, J. T.; Schwarcz, R. *Nature* **1976**, *263*, 244. (b) McGeer, E.; McGeer, R. *Nature* **1976**, *263*, 517.

(8) Tremblay, J.-F. *Chem. Eng. News* **2000**, January 3rd, 14.

(9) (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, March 6th, 131. (b) Tremblay, J.-F. *Chem. Eng. News* **2001**, January 29th, 19.

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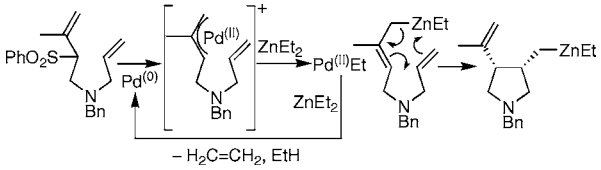
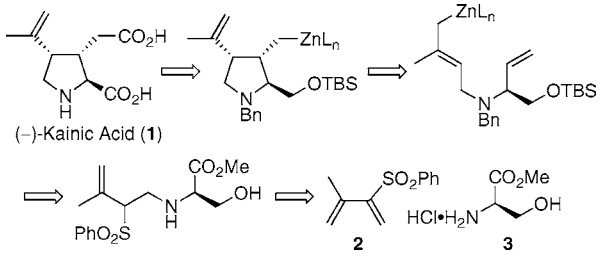
acetates offers an attractive strategy for installing these cis substitutions through a mild, functionally compatible allyl zinc intermediate.[11a] We recently extended this transformation to allyl phenyl sulfones and have shown that the concept is well-suited for the synthesis of cis-substituted pyrrolidines[11d] (Scheme 1).

Scheme 1. Cis-Substituted Pyrrolidines via Pd-Catalyzed Zn-ene Cyclization



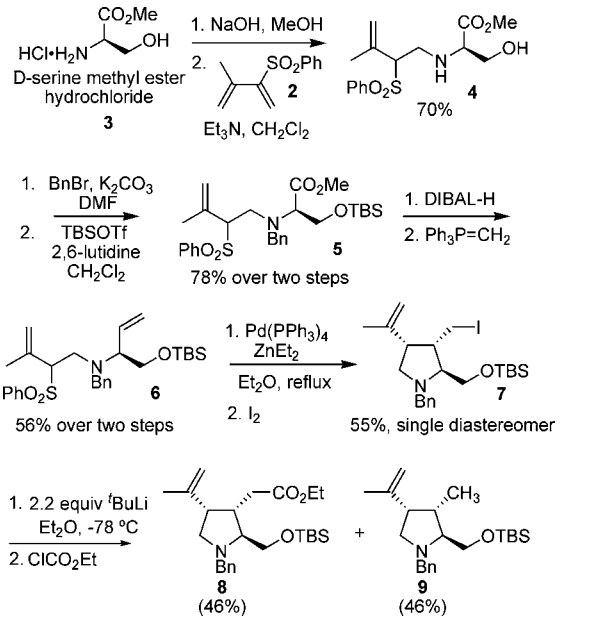
We envisioned installing the cis C3−C4 side chains of kainic acid through this methodology with the trans C2−C3 relationship induced by a bulky TBS ether. The cyclization substrate could be derived from readily prepared sulfone **2**[12] and commercially available D-serine methyl ester hydrochloride **3** (Scheme 2).

Scheme 2. Retrosynthesis of (−)-Kainic Acid



Addition of D-serine methyl ester to **2** proved somewhat problematic, and early attempts resulted in low conversion and polymerization of the diene. This was somewhat surprising given that simple amines such as benzylamine add readily to **2**.[11d] Only when using 2 equiv of the neutralized amino acid ester in refluxing dichloromethane did the reaction go to completion to give adduct **4** in 70% yield as a mixture of diastereomers (Scheme 3). Protection of the secondary amine[13] and primary alcohol with benzyl bromide and TBSOTf, respectively, gave **5** in 78% yield over two steps. The cyclization substrate **6** was then prepared in a two-step reduction−olefination sequence converting ester **5** to the desired terminal olefin in 56% yield. The stage was then set for the key cyclization. Accordingly, a solution of **6** in diethyl ether was heated at reflux in the presence of a catalytic amount of $Pd(PPh_3)_4$ and 10 equiv of diethylzinc. The palladium was added in three portions of 5 mol % each over the 24 h reaction period because a single palladium loading never resulted in complete consumption of **6**. The reaction was quenched with iodine to provide pyrrolidine **7** in 55% yield *as a single diastereomer*, demonstrating both the high cis fidelity of the zinc-ene cyclization and the exquisite substrate control by the TBS ether in directing the formation of the desired trans C2−C3 isomer.

Scheme 3. Formal Synthesis of (−)-Kainic Acid Using a Pd-Catalyzed Zn-ene Cyclization of an Allyl Sulfone



Although iodide **7** is a known precursor to kainic acid, its conversion to **1** suffers a low-yielding acylation, wherein after lithium−halogen exchange and quenching with ethylchloroformate, a 1:1 mixture of desired ester **8** and reduced compound **9** is obtained.[14] This problem arises from quenching of the alkyllithium by the acidic α proton of the product ester.[15] Despite this drawback,[16] the synthesis of known ester **8** verified the stereochemical outcome of the cyclization by comparison to previously published spectroscopic data.[17] Unfortunately, after removal of the TBS ether of **8** (TBAF, THF), chiral HPLC revealed low optical purity of the cy-

(10) For reviews, see: (a) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. (b) Moloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. For recent syntheses, see: (c) Thuong, M.; Sottocornola, S.; Prestat, G.; Broggini, G.; Madec, D.; Poli, G. *Synlett* **2007**, 1521. (d) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 1635. (e) Pandy, S.; Orellana, A.; Greene, A.; Poison, J.-F. *Org. Lett.* **2006**, *8*, 5665. (f) Scott, M.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (g) Hodgson, D.; Hachisu, S.; Andrews, M. *J. Org. Chem.* **2005**, *70*, 8866. (h) Anderson, J.; O'Loughlin, J.; Tornos, J. *Org. Biomol. Chem.* **2005**, *3*, 2741. (i) Martinez, M.; Hoppe, D. *Eur. J. Org. Chem.* **2005**, 1427. (j) Poisson, J.-F.; Orellana, A.; Greene, A. *J. Org. Chem.* **2005**, *70*, 10860. (k) Hodgson, D.; Hachisu, S.; Andrews, M. *Org. Lett.* **2005**, *7*, 815. (l) Trost, B. M.; Rudd, M. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (m) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337.

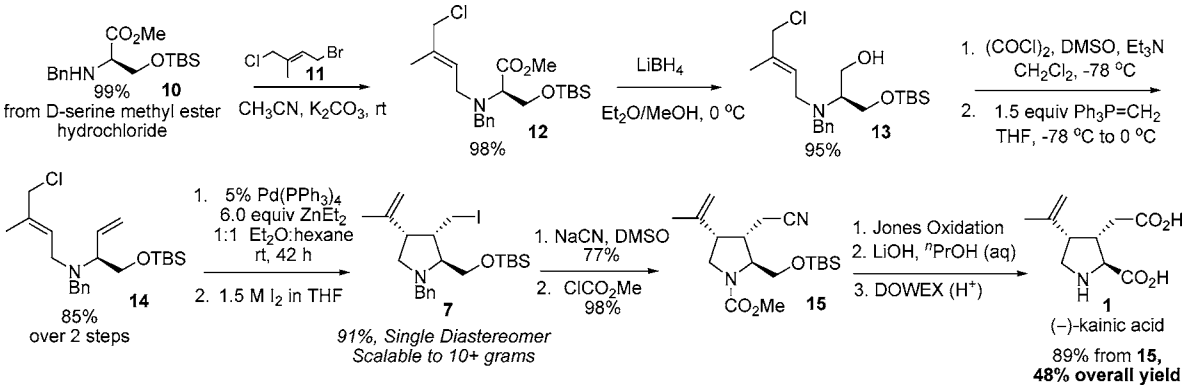
(11) For previous examples of zinc-ene cyclizations, see: (a) Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* **1994**, *35*, 7939. (b) Millot, N.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 7779. (c) Unger, R.; Cohen, T.; Marek, I. *Org. Lett.* **2005**, *7*, 5313. (d) Deng, K.; Chalker, J.; Yang, A.; Cohen, T. *Org. Lett.* **2005**, *7*, 3637.

(12) Bäckvall, J.-E.; Ericsson, A. *J. Org. Chem.* **1994**, *59*, 5850.

(13) Protection of the amine was probably necessary because attempted cyclization of the N-unprotected version of the cyclization substrate shown in Scheme 1 was unsucessful.

(14) Campbell, A.; Raynham, T.; Taylor, R. *J. Chem. Soc., Perkin Trans. 1.* **2000**, 3194.

Scheme 4. Total Synthesis of (−)-Kainic Acid Using a Pd-Catalyzed Zn-ene Cyclization of an Allyl Chloride



clized material (e.r. = 2:1).[18] This is likely due to epimerization of the configurationally labile α-amino aldehyde intermediate obtained after DIBAL-H reduction of ester **5**.[19]

While the synthesis of **1** was accomplished in the formal sense and the suitability of the key cyclization established, there are several limitations to this first generation route. First, while unhindered amines are known to add smoothly to diene **2**,[20] D-serine methyl ester does not and an equivalent of chiral starting material is wasted because it is needed in excess. Second, the reduction−olefination route to **6** and the acylation route to **8** are relatively low yielding. Third, while the cyclization gives the correct relative stereochemistry, **8** was not optically pure. A different strategy was therefore necessary if the route was to be amenable to a scalable, enantiopure synthesis. Addressing these limitations, and motivated by the high diastereoselectivity of the zinc-ene cyclization, we revised our approach.

Returning to **3**, protection was carried out by reductive benzylation and TBS protection to give **10** quantitatively (Scheme 4).[17] Chemoselective allylation with chloro bromide **11**,[21] generated in two steps from isoprene, proceeded smoothly to provide allyl chloride **12**. While we originally set out to use **12** as a substrate for sulfonylation by sodium benzenesulfinate to obtain the allylic isomer of **5**, it was apparent that an allyl chloride would be suitable in the cyclization,[11a] provided it could survive conversion of the methyl ester of **12** to the terminal olefin. Gratifyingly, the chloride survived such a manipulation and chemoselective reduction with $LiBH_4$ provided alcohol **13** in high yield. Subsequent Swern oxidation and Wittig olefination provided diene **14** in 85% yield. Unfortunately, while it was possible to carry out the oxidation and olefination on a large scale (up to 30 g), significant racemization was again observed.[22] This result was disappointing in light of instances where Swern oxidations of very similar substrates were carried out with little or no epimerization reported.[17,23,24]

Although **14** was not optically pure, the ease in accessing large amounts of the material facilitated investigation of the key step as well as a revised end game. Thus, with cyclization substrate **14** in hand, we subjected the allyl chloride to $Pd(PPh_3)_4$ and $ZnEt_2$ in a mixture of diethyl ether and hexane. After the mixture had been stirred at room temperature for 42 h and quenched with iodine, pyrrolidine **7** was obtained in *91% yield as a single diastereomer*.[25]

While both the allylic sulfone **6** and allylic chloride **14** undergo cyclization with complete diastereoselectivity, the yield and mild conditions of the chloride approach provide a distinct advantage over the sulfone strategy.[26] Furthermore, the cyclization of **14** could be carried out on a 10 g scale without significant deterioration in stereoselectivity and yield.

(15) Other mechanisms of quenching, such as 1,5 proton transfer to give an allyllithium, were ruled out by D_2O quenching after lithiation. For an example of such a proton transfer, see: Cheng, D.; Zhu, S.; Liu, X.; Norton, S.H.; Cohen, T. *J. Am. Chem. Soc.* **1999**, *121*, 10241. Standard precautions to prevent the formation of **9** (e.g., reverse quench) were ineffective. Excess ^{t}BuLi (>5 equiv) improved the yield of **8** slightly, but this measure is impractical for a scalable process.

(16) Our original plan, designed to both facilitate the cyclization and save steps, was to use the conjugated unsaturated methyl ester as the enophile, readily prepared by using the suitable Wittig reagent, instead of the alkene in **6**. However, the result was a surprise. The cyclization was considerably more sluggish, requiring an elevated temperature, and the major product had a trans C3−C4 relationship. The sluggish cyclization suggests that this Zn-ene reaction should be considered an ambiphilic rather than a nucleophilic addition. The origin of the trans selectivity is not yet fully understood, but optimizing this transformation provides a route to other kainoid stereoisomers.

(17) Barco, A.; Benetti, S.; Spalluto, G. *J. Org. Chem.* **1992**, *57*, 6279.

(18) See Supporting Information for details.

(19) For a review discussing the inherent configurational lability of α-amino aldehydes, see: Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

(20) (a) Bäckvall, J.-E.; Juntunen, S. *J. Am. Chem. Soc.* **1987**, *109*, 6396. (b) Ref 11d.

(21) Lee, J.; Jeong, Y.; Ji, M.; Baik, W.; Lee, S.; Koo, S. *Synlett* **2004**, 1937. Apparently, a high *E*/*Z* ratio is critical in the synthesis of **12**. When batches of **11** with low *E*/*Z* were used, yields diminished to 80−90%. We suspect that intramolecular ammonium formation of the *Z* isomer is responsible for the reduced yield in these cases.

(22) Direct determination of the optical purity of **14** was complicated by a minor amount of *Z* olefin. An e.r. of 1.6:1.0 was inferred by chiral HPLC after the cyclization (see Supporting Information). Interestingly, the specific rotation of known compound **8**, when synthesized through the chloride route, was nearly identical to the literature value where a Swern oxidation on a similar amino alcohol substrate was used: $[\alpha]_D = -29.1°$ ($c = 1.16$) vs $[\alpha]_D = -27.2°$ ($c = 0.99$) in ref 17. We consider the optical purity of this material suspect.

(23) Martinez, M. M.; Hoppe, D. *Org. Lett.* **2004**, *6*, 3743.

(24) It is conceivable that silyl transfer in **13** contributes to racemization. However, such a transfer in TBS-protected serinols was not observed in several similar substrates. See: (a) Novachek, K. A.; Meyers, A. I. *Tetrahedron Lett.* **1996**, *37*, 1743. (b) Laïb, T.; Chastanet, J.; Zhu, J. *J. Org. Chem.* **1998**, *63*, 1709. (c) Jurczak, J.; Gryko, D.; Kobrzycka, E.; Grunza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051.

Revising the conversion of **7** to **1**, we turned to cyanation as an alternative to direct acylation.[27] Treatment of **7** with NaCN in DMSO provided the corresponding nitrile in 77% yield.[28] Conversion of the benzyl amine to carbamate **15** proceeded in high yield in the presence of methylchloroformate. One-pot deprotection and Jones oxidation of the TBS ether provided the corresponding carboxylic acid.[29] In the final step, basic hydrolysis removed the carbamate and revealed the carboxylate from the nitrile. The final product, after treatment with ion-exchange resin, was spectroscopically identical to an authentic sample (89% from **15** to **1**).

With a high-yielding end game realized, we returned to the synthesis of **14** in an effort to improve optical purity. Unfortunately, all oxidation/olefination sequences screened for alcohol **13** resulted in low yields and e.r. Therefore, while the allyl chloride route can only be considered an enantioenriched synthesis of kainic acid, this should not detract from the exquisite diastereoselectivity of the key zinc-ene cyclization and the scale, brevity, and overall yield of the synthesis (11% and 48% overall yield for the sulfone and chloride routes, respectively).[30] Finally, the troublesome conversion of **12** to **14** has prompted us to explore new strategies for the conversion of amino acid esters to olefins in such a way that the configurationally labile aldehyde is avoided entirely. Progress to this end will be reported in due course.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) It is interesting that no β-elimination of the intermediate allyl zinc is observed. A minor amount (typically 2−5%) of uncyclized, dechlorinated material is also isolated after quenching. This material is likely the result of protonation of the allyl zinc intermediate where a Pd-H species is the proton source. Without excess diethylzinc as a proton scavenger, the amount of this byproduct increases significantly.

(26) In general, however, allylic sulfones are much more easily prepared than allylic chlorides. See ref 11d.

(27) The direct cyanation of the dialkylzinc cyclization product was explored with limited success despite some precedence. See: (a) ref 11a. (b) Klement, I.; Lennick, K.; Tucker, C.; Knochel, P. *Tetrahedron Lett.* **1993**, *34*, 4623.

(28) The reduced yield is the result of a competitive E2 elimination.

(29) Evans, P. A.; Roseman, J.; Garber, L. *Synth. Commun.* **1996**, *26*, 4685.

(30) The overall yield for the sulfone route was calculated using the revised conversion of iodide **7** to kainic acid shown in Scheme 4.