

Total Synthesis of (–)- α -Kainic Acid by (–)-Sparteine-Mediated Asymmetric Deprotonation–Cycloalkylation[†]

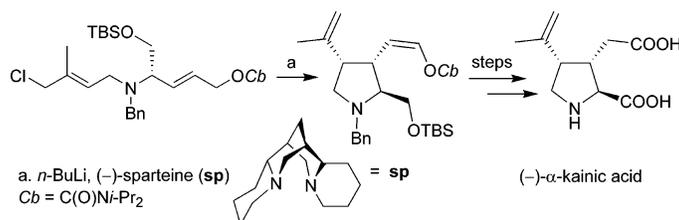
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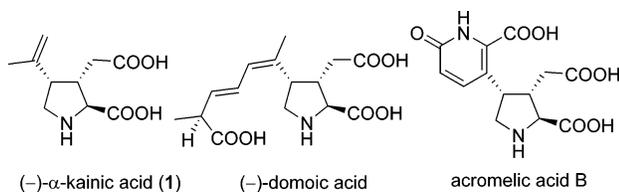
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ABSTRACT



We report a new enantioselective synthesis of (–)- α -kainic acid from *D*-serine methyl ester hydrochloride, based on a (–)-sparteine-mediated asymmetric deprotonation of an intermediate carbamate that, by stereospecific *anti* S_N'S_E' intramolecular cycloalkylation, leads to the pyrrolidine ring precursor of (–)- α -kainic acid, in high yield and diastereoselectivity. The intermediate pyrrolidine was further transformed to (–)- α -kainic acid in three steps.

The natural marine product (–)- α -kainic acid (**1**), a potent neurotransmitter activity inhibitor for the central nervous system,¹ is the parent member of kainoids, an important class of compounds with interesting biological properties.



Synthesis of kainoids needs to address the formation of a pyrrolidine-2-carboxylic acid with defined stereochemistry at the three continuous chiral centers of the ring, where is essential to achieve a *cis* stereochemistry for the 3- and 4-positions. Subsequent to the first synthesis of (–)- α -kainic

acid carried out by Oppolzer,² several total syntheses of this compound were published,³ although only a few lead to the enantiopure product. Here, we report a new diastereoselective (–)-sparteine-mediated total synthesis of (–)- α -kainic acid.

Recently, we have reported that sparteine-mediated carbocyclizations of allyllithium compounds lead to cyclopentanes with the favored *cis* stereochemistry at the newly formed bond.⁴ Later, this method was extended to the synthesis of a *cis*-3,4-divinylpyrrolidine with high enantio- and diastereoselectivity.⁵ We now report the use of this

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(3) (a) Williams, M. R. *Synthesis of Optical Active α -Amino Acids*; Pergamon: Oxford, 1989; p 306. Reviews: (b) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. For selected recent syntheses: (c) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181. (d) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485. (e) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727. (f) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199. (g) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467. (h) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139. (i) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, *19*, 3194. (j) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587.

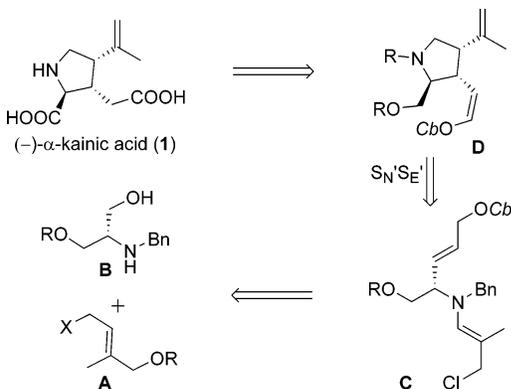
(4) Deiters, A.; Hoppe, D. *J. Org. Chem.* **2001**, *66*, 2842.

(5) Deiters, A.; Wibbeling, B.; Hoppe, D. *Adv. Synth. Catal.* **2001**, *343*, 181.

[†] Dedicated to Professor Th. Kauffmann on the occasion of his 80th birthday.

(1) (a) Foster, A. C.; Fagg, G. E. *Brain Res. Rev.* **1984**, *7*, 103. (b) Watkins, J. C.; Olverman, H. J. *Trends Neurosci.* **1987**, *10*, 265. (c) Hansen, J. J.; Krosgaard-Larsen, P. *Med. Res. Rev.* **1990**, *10*, 55.

Scheme 1. Retrosynthesis of (–)- α -Kainic Acid by Using an Intramolecular *Anti* $S_N'S_E'$ Reaction



methodology to synthesize (–)- α -kainic acid following the strategy described in Scheme 1.

In our synthesis, the desired configuration of (–)- α -kainic acid, is achieved via asymmetric *anti* $S_N'S_E'$ cycloalkylation reaction of key precursor **C**, synthesized from building blocks **A** and **B**.⁶

Synthesis of key precursor **C** (**12** in Scheme 2) has been carried out starting from *N*-benzyl-protected D-serine methyl ester hydrochloride,⁷ first transformed into silyl ether **3** ($[\alpha]_D^{+3.9}$, c 0.94, CHCl_3) in 89% yield. Reduction of ester **3** with LiBH_4 led to alcohol **4** ($[\alpha]_D^{-8.2}$ (c 1.10, CHCl_3)) in 47%.⁸ Further, the synthesis required the elaboration of intermediate **6** from **4** containing two stereogenic double bonds, both achieved with an *E/Z* ratio >99% (determined by ^1H NMR). *N*-Alkylation of alcohol **4** was carried out by refluxing (*E*)-configured isoprenoid **21**⁹ using NaHCO_3 in acetonitrile, yielding alcohol **5** ($[\alpha]_D^{-3.6}$ (c 0.91, CHCl_3)) in 82%. **5** was converted to **6** with 75% overall yield by Swern oxidation followed in situ olefination using (carboxymethylene)triphenylphosphorane, in a single operation to avoid racemization. The next step of the synthesis consisted of the selective removal of TES group in **6** with TBAF, which was achieved in 81% yield. Allylic alcohol **7** ($[\alpha]_D^{+14.7}$ (c 0.61, CHCl_3)) was then submitted to chlorine-substitution, giving (*E,E*)-allylic chloride **8** ($[\alpha]_D^{+22.0}$ (c 0.78, CHCl_3)) in 71%. An optical purity of $\geq 95\%$ enantiomeric excess was determined for **8** by ^1H NMR analysis of the corresponding (–)-MPTA ester **10**.¹⁰

Desired carbamate **12** was prepared from **8** via 1,2-reduction of its ester moiety by treatment with DIBAL-H (70% yield), followed by standard carbamoylation of **11**, yielding **12** ($[\alpha]_D^{+9.7}$ (c 0.71, CHCl_3)) in 53%.

(6) This synthetic route could be also applicable for the synthesis of (–)-domoic acid by modifying precursor **A** with a dienoic side chain.

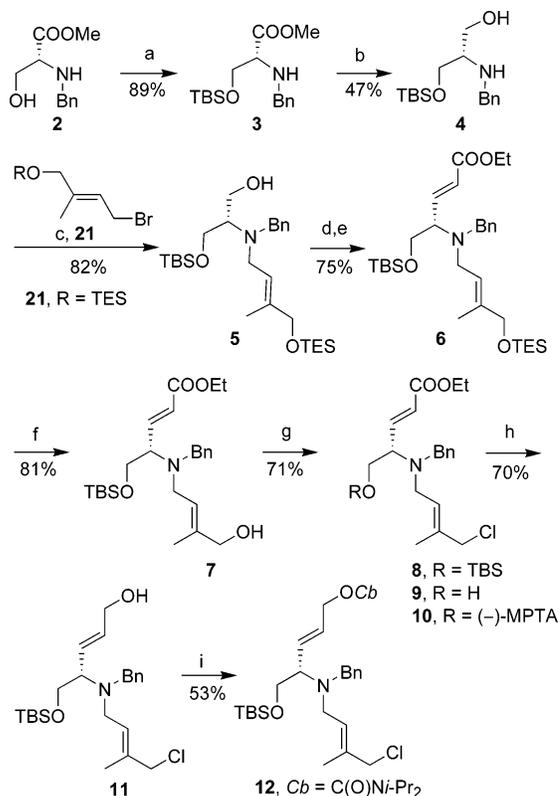
(7) *N*-Benzylation was carried out first by reductive amination; see: Barco, A.; Benetti, S.; Spalluto, G. *J. Org. Chem.* **1992**, *57*, 6279.

(8) Low yield was obtained due to simultaneous occurrence of deprotection of silyl ether. Other reducing agents were checked (LiAlH_4 , NaBH_4) unsuccessfully.

(9) Synthesized from hydroxyacetone in 67% overall yield over four steps: silylation followed by Horner–Wadsworth–Emmons reaction, 1,2-reduction of the ester moiety, and bromination.

(10) (–)-MPTA ester **10** was derived from racemic and enantiomerically enriched **9** by esterification using (–)-MPTACl in 70% overall yield.

Scheme 2. Synthesis of Cyclization Precursor **12**^a



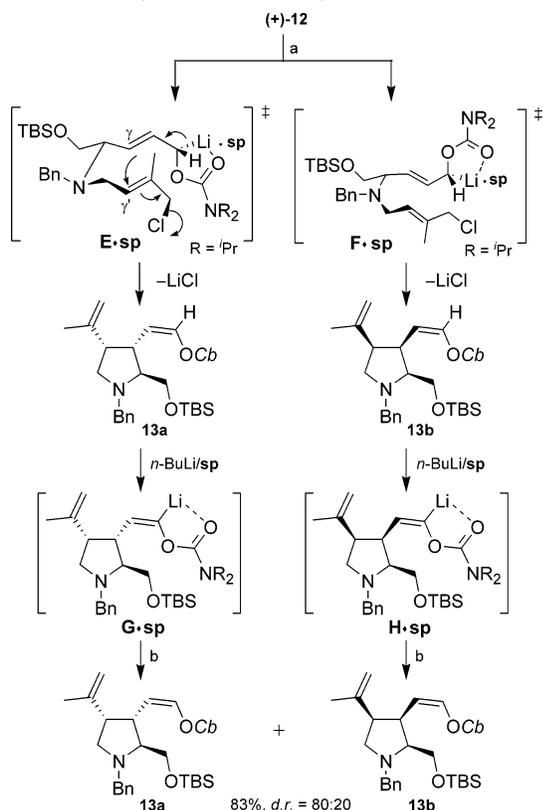
^a Conditions: (a) TBSCl , NEt_3 , DMAP , CH_2Cl_2 , rt, 12 h. (b) LiBH_4 , $\text{THF}/\text{toluene}$, reflux, 20 min. (c) CH_3CN , NaHCO_3 , rt, 30 min, **21**, reflux, 3 h. (d) $(\text{COCl})_2$, DMSO , CH_2Cl_2 , -78°C , NEt_3 , -15°C , 1 h. (e) (Carboxymethylene)triphenylphosphorane, -15°C to room temperature, 3 h. (f) TBAF, THF , 0°C , 5 min. (g) NEt_3 , CH_2Cl_2 , -40°C , MsCl , 1 h, LiCl , THF , rt, 3 h. (h) DIBAL-H, CH_2Cl_2 , -78°C , 2 h. (i) NaH , CbCl , THF , reflux, 12 h.

Intramolecular *anti* $S_N'S_E'$ cycloalkylation of (*E,E*)-carbamate **12** (Scheme 3), the key step for the synthesis of (–)- α -kainic acid, commenced with α -deprotonation by means of *n*-BuLi/(–)-sparteine at -78°C in toluene.¹¹ This reaction took place under kinetic control, providing after 1 h the cyclization products **13a** ($[\alpha]_D^{-22.6}$ (c 0.57, CHCl_3)) and **13b** ($[\alpha]_D^{-6.4}$ (c 0.75, CHCl_3)) in 83% yield¹² (**13a**:**13b**, dr 80:20, as determined by ^1H NMR). As expected, a high C3–C4 *cis* selectivity was achieved giving the two separable diastereomers **13a** and **13b**, without formation of *trans* products with respect to the C3–C4 bond, as evidenced by ^1H NMR.

Since the relative configuration of pyrrolidines **13a** and **13b** could not be determined by NOE studies, the stereochemical assignment of structures to **13a** and **13b** is based on the fact that the two olefinic protons of the isopropenyl chain appear as two singlets in the ^1H NMR spectra, as is typical for similar kainoids.¹³ In addition, experimental vicinal coupling constants ($^3J_{2,3}$ and $^3J_{3,4}$) observed for **13a**

(11) Deiters, A.; Mück-Lichtenfeld, C.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2000**, *2*, 2415.

(12) Other conditions for the asymmetric cyclization, as well as other key precursors, were tried with less success.

Scheme 3. Cyclization to the Pyrrolidines **13a** and **13b**^a

^a Conditions: (a) *n*-BuLi/sp (2.2 equiv), toluene, $-78\text{ }^{\circ}\text{C}$, 1 h. (b) MeOH.

were within the range of calculated ones from computational studies based on the Karplus–Conroy equation.¹⁴

The (*Z*)-geometry of the enol carbamate moiety is based on the small olefinic coupling constant (5.6 Hz) observed, in agreement with previous studies in our group.^{4,5}

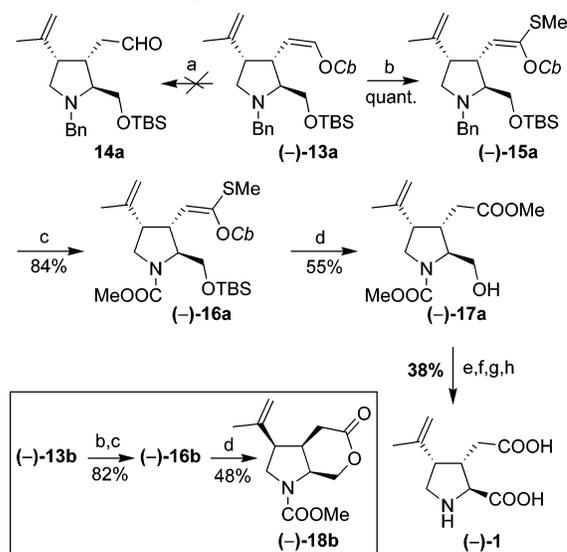
Further support to this assignment is provided by the conversion of **13a** to (–)- α -kainic acid (**1**).

The stereochemical outcome of the asymmetric cycloalkylation reaction is supported by the following mechanistic considerations: (1) The chiral base *n*-BuLi/(–)-sparteine enantioselectively removes the α -*pro-S*-proton¹⁵ of carbamate **12**, generating the configurationally labile intermediate **E·sp**. Intramolecular cycloalkylation of **E** occurs under

(13) (a) Kondo, K.; Kondo, Y.; Takemoto, T.; Kenoue, T. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1899. (b) For a discussion of the rotameric distributions of several kainoids: (c) Conway, G. A.; Park, J. S.; Maggiora, L.; Mertes, M. P.; Galton, N.; Michaelis, E. K. *J. Med. Chem.* **1984**, *27*, 52. (d) Kozikowski, A. P.; Fauq, A. H. *Tetrahedron Lett.* **1990**, *31*, 2967 and references therein.

(14) *NMR-Spectroscopie*; Günther, H., Ed.; Georg Thieme Verlag Stuttgart: New York, 1992. The coupling constants were obtained with the use of the packet of programs TURBOMOLE (version 5.6) (University Karlsruhe: Karlsruhe, Germany, 2003). The structures were optimized with the theoretical function at the DFT level using the pure B-P functional [DFT-(B-P)] and the basis set TZVP (triple-valence-polarized).

(15) In all known examples, deprotonation of *O*-allylic carbamates with *n*-BuLi/sp led to the (*S*)-configured organolithium compound. For reviews: (a) Hoppe, D. *Angw. Chem.* **1984**, *96*, 930; *Angw. Chem., Int. Ed. Engl.* **1984**, *23*, 932. (b) Hoppe, D.; Hense, T. *Angw. Chem., Int. Ed. Engl.* **1997**, *36*, 2282 and references therein.

Scheme 4. Completion of the Synthesis to (–)- α -Kainic Acid and Synthesis of Lactone **18b**^a

^a Conditions: (a) MeLi or TMSOTf. (b) *t*-BuLi, TMEDA, THF, $-78\text{ }^{\circ}\text{C}$, 1 h, MeSSMe, 1 h, rt. (c) MeOC(=O)Cl, ClCH₂CH₂Cl, reflux, 3 h. (d) MeSO₃H, MeOH, H₂O, reflux, 16 h. (e) Jones reagent. (f) 40% NaOH aq, reflux, 18 h. (g) Dowex 50WX-200 (elution with NH₄OH (1 N)), Amberlite CG-50 (elution with H₂O). (h) Recrystallization, EtOH aq.

regioselective C–C bond formation between both γ,γ' -positions and simultaneous elimination of lithium chloride.⁵ Although these (–)-sparteine–lithium ion pairs of primary allyl carbamates have been recognized to have limited configurational stability, the cycloalkylation is more rapid than epimerization. (2) An *endo* conformation of the allylic moiety in an anti mode is required for the S_N'S_E' cycloalkylation.¹⁶ The chairlike transition state **E** allows the π – π^* overlap of the electron-rich and electron-deficient allyl moieties, presumably being the origin of the high *cis* diastereoselectivity. Compound **13b** is most probably formed by intramolecular cycloalkylation of the (*R*)-configured lithium derivative **F·sp**.

To complete the synthesis of (–)- α -kainic acid, oxidative removal of the carbamate group in **13a** is necessary (Scheme 4).

The usual oxidative methods¹⁷ are not applicable to vinyl carbamates **13a** and **13b** due to the reactive additional trisubstituted double bond. Moreover, attempts to convert the vinyl carbamate **13a** into aldehyde **14a** by using methyllithium¹⁸ or TMSOTf¹⁹ failed. In light of these results, we used an indirect oxidation method consisting in a vinylic deprotonation with *t*-BuLi followed by quench with MeSSMe.²⁰ The obtained ketene monothioacetal **15a** was submitted

(16) Hoppe, D.; Brönneke, A. *Tetrahedron Lett.* **1983**, *24*, 1687. For review about S_N reactions, see: Magid, M. R. *Tetrahedron* **1980**, *31*, 1901.

(17) (a) Rehders, F.; Hoppe, D. *Synthesis* **1992**, 859. (b) Grieco, A. P.; Oguri, T.; Yokoyama, Y. *Org. Lett.* **1978**, *5*, 419.

(18) Madec, D.; Henryon, V.; Férézou, P. *J. Tetrahedron Lett.* **1999**, *40*, 8103.

without further purification to *N*-debenzylation by treatment with methyl chloroformate,²¹ providing **16a** ($[\alpha]_D -19.0$ (*c* 0.5, CHCl₃)) in 84% overall yield. Similar results were obtained when the minor diastereomer **13b** was treated under the same conditions to provide **16b**.

Treatment of monothioketene acetal **16a** with an excess of methanesulfonic acid resulted in the deprotection of the hydroxyl group and simultaneous hydrolysis of the ketene monothioacetal moiety, giving alcohol **17a** in 55% overall yield. In a similar fashion, lactone **18b** resulted from deprotection of silyl ether in **16b** followed by cyclization of both C-2 and C-3 chains in 48% yield.

Elucidation of the structure of **17a** and **18b** was carried out by ¹H NMR spectra and NOE studies.²² The absolute configuration was confirmed by comparing their respective $[\alpha]_D$ values with published ones: for **17a** ($[\alpha]_D -41.2$ (*c* 0.52, CH₂Cl₂)) versus ($[\alpha]_D^{31} -43.0$ (*c* 1.25, CH₂Cl₂)) and for **18b** ($[\alpha]_D -28.1$ (*c* 0.30, CHCl₃)) versus *ent*-**18b** ($[\alpha]_D^{31} +32.1$ (*c* 1.20, CHCl₃)).

(19) Seppi, M.; Kalkofen, R.; Reupohl, J.; Fröhlich, R.; Hoppe, D. *Angew. Chem.* **2004**, *116*, 1447.

(20) Paulsen, H.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5667.

(21) Campbell, A. D.; Raynham, T. M.; Taylor, R. J. K. *Chem. Commun.* **1999**, 245.

(22) ¹H NMR exhibits two broad singlets at 4.62 and 4.91 ppm for the alkene protons, indicating the C3–C4 *cis* relationship (see references 4i and 12). The NOE studies were carried out at low temperature because of the broad signals.

The final steps to the natural product were carried out following literature precedents:⁴ⁱ Jones oxidation of the primary alcohol **17a**, followed by hydrolysis with 40% aqueous sodium hydroxide, and purification by using ion-exchange chromatography afforded enantiopure (–)-α-kainic acid as colorless needles after recrystallization from aqueous ethanol (38% overall yield). Our final product possessed physical properties identical to those of the authentic material: mp 243–245 °C (decomp) versus lit.³ⁱ mp 241–244 °C (decomp); $[\alpha]_D -14.3$ (*c* 0.40, H₂O) versus lit.⁴ⁱ $[\alpha]_D -14.6$ (*c* 0.25, H₂O).

In conclusion, we have reported a new method to prepare (–)-α-kainic acid via (–)-sparteine-mediated asymmetric lithiation and cycloalkylation synthesis.

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Supporting Information Available: Experimental procedures for the preparation of new compounds and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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