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

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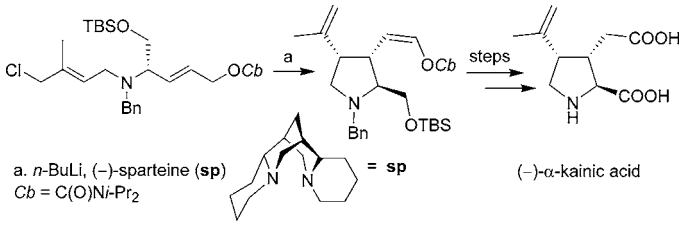
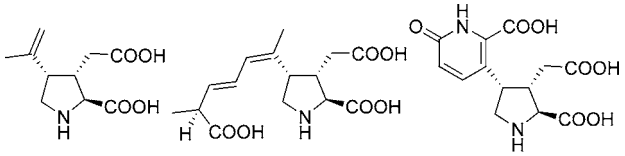
ABSTRACT



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 neurotransmitting 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

† 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.; Krogsgaard-Larsen, P. *Med. Res. Rev.* **1990**, *10*, 55.

(2) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.

(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 recently 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.

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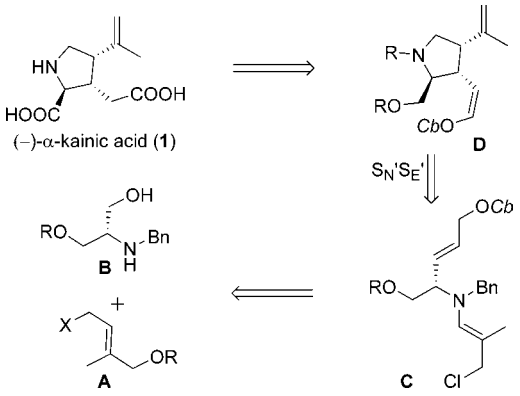
Scheme 1. Retrosynthesis of (−)-α-Kainic Acid by Using an Intramolecular *Anti* $S_N'S_E'$ Reaction



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 ^{1}H 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 (carbethoxymethylene)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 ≥95% enantiomeric excess was determined for **8** by ^{1}H 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.

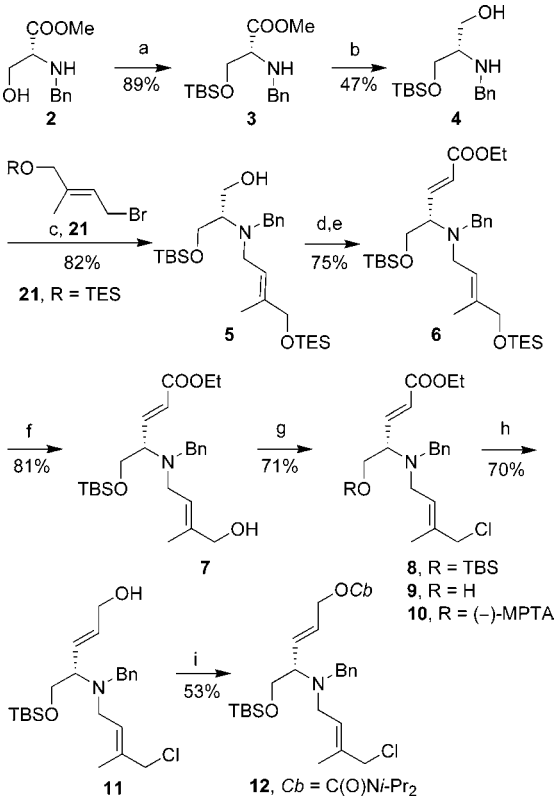
(7) N-Benzylation was carried out first by reductive amination; see: Barco, A.; Benetti, S.; Spalluto, G. *J. Org. Chem.* **1992**, *57*, 6279.

(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) $LiBH_4$, THF/toluene, reflux, 20 min. (c) CH_3CN, $NaHCO_3$, rt, 30 min, **21**, reflux, 3 h. (d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, NEt_3, −15 °C, 1 h. (e) (Carbethoxymethylene)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, *Cb*Cl,THF, reflux, 12 h.

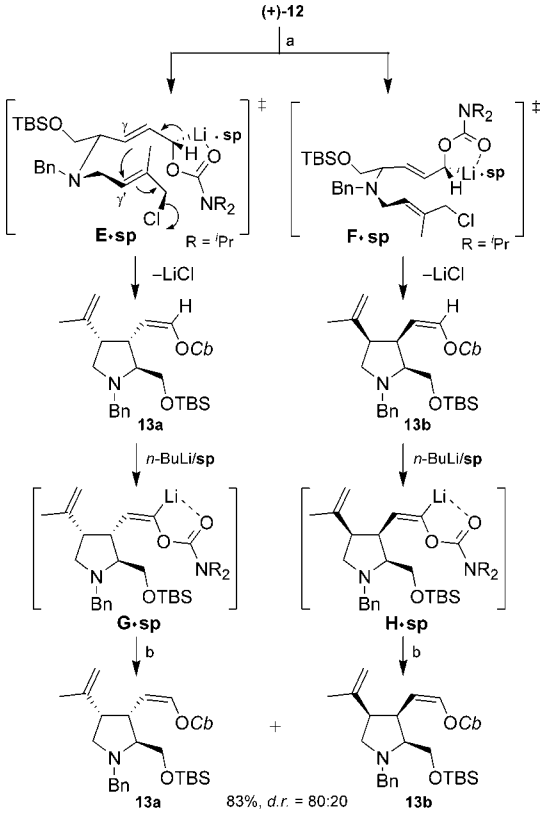
Intramolecular *anti* $S_N'S_E'$ cycloalkylation of (*E*,*E*)-carbamate **12** (Scheme 3), the key step for the synthesis of (−)-α-kainic acid, commenced with α-deprotonation by means of *n*-BuLi/(−)-sparteine at −78 °C in toluene.[11] This reaction took place under kinetic control, providing after 1 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% yield[12] (**13a**:**13b**, dr 80:20, as determined by ^{1}H 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 ^{1}H 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 ^{1}H 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.

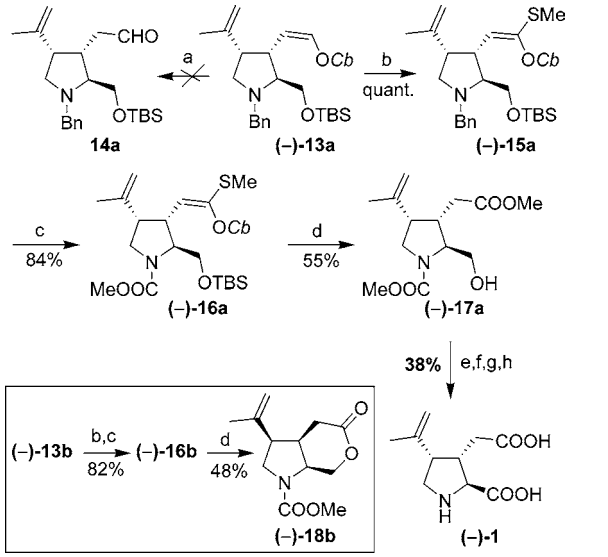
(12) Other conditions for the asymmetric cyclization, as well as other key precursors, were tried with less success.

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



[a] Conditions: (a) *n*-BuLi/**sp** (2.2 equiv), toluene, −78 °C, 1 h. (b) MeOH.

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 °C, 1 h, MeSSMe, 1 h, rt. (c) MeOC(═O)Cl, $ClCH_2CH_2Cl$, reflux, 3 h. (d) $MeSO_3H$, MeOH, H_2O, reflux, 16 h. (e) Jones reagent. (f) 40% NaOH aq, reflux, 18 h. (g) Dowex 50WX-200 (elution with NH_4OH (1 N)), Amberlite CG- 50 (elution with H_2O). (h) Recrystallization, EtOH aq.

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*-proton[15] of carbamate **12**, generating the configurationally labile intermediate **E·sp**. Intramolecular cycloalkylation of **E** occurs under 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 $\pi-\pi^*$ 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 methods[17] 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 methyllithium[18] or TMSOTf[19] 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

(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.

(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, $CHCl_3$)) 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 ^{1}H 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, CH_2Cl_2)) versus ($[\alpha]_D$[3i] −43.0 (*c* 1.25, CH_2Cl_2)) and for **18b** ($[\alpha]_D$ −28.1 (*c* 0.30, $CHCl_3$)) versus *ent*-**18b** ($[\alpha]_D$[3j] +32.1 (*c* 1.20, $CHCl_3$)).

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, H_2O) versus lit.[4i] $[\alpha]_D$ −14.6 (*c* 0.25, H_2O).

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