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[A012]

TOTAL SYNTHESIS OF (–)-α-KAINIC ACID BY (–)-SPARTEINE-MEDIATED ASYMMETRIC DEPROTONATION/CYCLOALKYLATION

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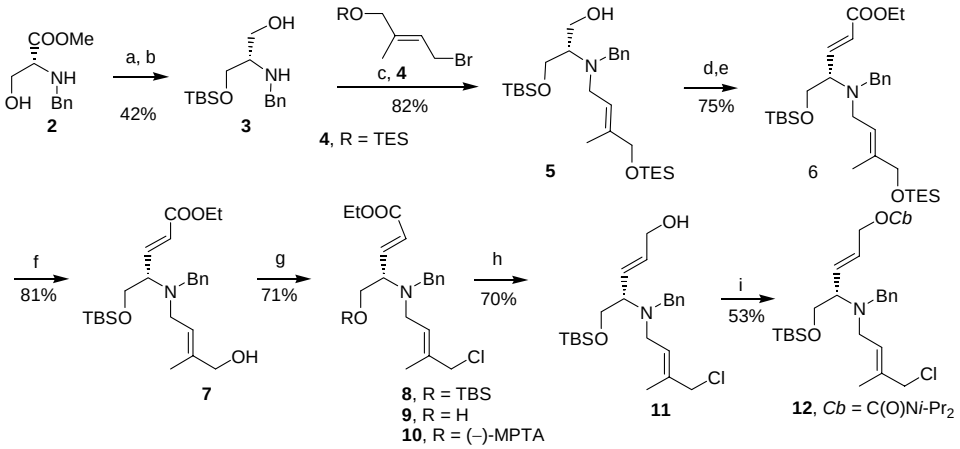
The marine product (–)-α-kainic acid (**1**)[1] has attracted considerable interest mainly because of its potent neurotransmitting activity inhibition in the central nervous system. Several total syntheses are known[2] which have involved 10-21 steps with overall yields ranging from 0.7% to 6%.

In our group, a method for the asymmetric synthesis of 3,4-divinylpyrrolidines was developed[3] with complete enantio- and diastereoselectivity *via* asymmetric deprotonation of the *O*-allyl carbamate by S_N'S_E' cycloalkylation, and recently we have communicated our results to the synthesis of kainoids.[4]

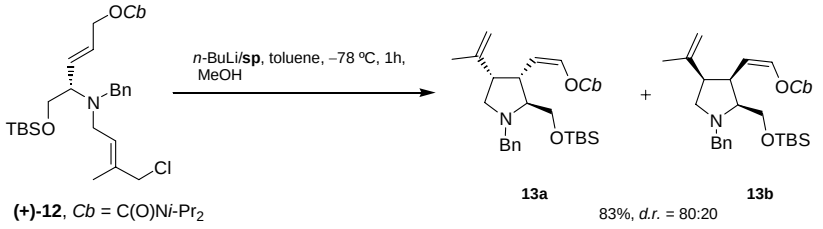
Our synthesis starts from *N*-benzyl protected D-serine methyl ester hydrochloride (Scheme 1), firstly transformed into a silyl ether followed by reduction with $LiBH_4$ leading to alcohol **3** in 42% yield. Further, the synthesis required the elaboration of intermediate **6** from **3** containing two stereogenic double bonds, both achieved with an *E/Z* ratio >99% (determined by ^{1}H NMR). *N*-Alkylation of alcohol **3** was carried out by refluxing *E*-configured isoprenoid **4**[5] using $NaHCO_3$ in acetonitrile, yielding alcohol **5** 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. Selective removal of TES group in **6** with TBAF (81% yield), followed by chlorine-substitution of alcohol **7** gave (*E*,*E*)-allylic chloride (**8**) in 71%. An optical purity of ≥95% enantiomeric excess was determined for **8** by ^{1}H NMR analysis of the MPTA ester **10** (Scheme 1). Required 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** in 53%.



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 ºC, NEt_3, –15 ºC, 1 h, e) (carbethoxymethylene) triphenylphosphorane, –15 ºC to rt, 3 h, f) TBAF, THF, 0 ºC, 5 min, g) NEt_3, CH_2Cl_2, –40 ºC, MsCl, 1 h, LiCl, THF, rt, 3 h, h) DIBAL-H, CH_2Cl_2, –78 ºC, 2 h, i) NaH, *Cb*Cl,THF, reflux, 12 h

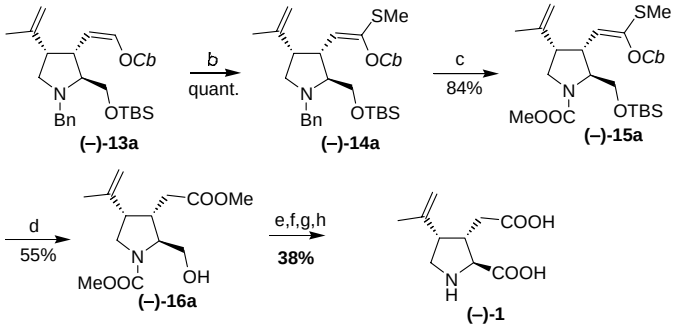
Scheme 1

Intramolecular *anti*-S_N'S_E' cycloalkylation of (*E*,*E*)-carbamate **12** (Scheme 2), commenced with α-deprotonation by means of *n*-BuLi/(–)-sparteine at –78 ºC in toluene.[3,4] This reaction took place under kinetic control providing after 1h the cyclization products **13a** and **13b** in 83% yield (**13a**:**13b**, *d.r.* 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 in respect to the C3-C4 bond, as evidenced by ^{1}H NMR.[6] In addition, experimental vicinal coupling constants ($^3J_{2,3}$ and $^3J_{3,4}$) observed for **13a** were within the range of calculated ones by computational studies based on the Karplus-Conroy equation.[7] 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.[3]



Scheme 2

To complete the synthesis of (–)-α-kainic acid, oxidative removal of the carbamate group in **13a** is necessary (Scheme 3). Indirect oxidation method consisting in a vinylic deprotonation with *t*-BuLi followed by quench with MeSSMe gave the ketene monothioacetal **14a** which was submitted without further purification to *N*-debenzylation by treatment with methyl chloroformate, providing **15a** in 84% overall yield. Treatment of monothioketene acetal **15a** with excess of methanesulfonic acid, resulted in the deprotection of the hydroxyl group and simultaneous hydrolysis of the ketene monothioacetal moiety giving alcohol **16a** in 55% overall yield.



a) MeLi or TMSOTf, b) *t*-BuLi, TMEDA, THF, −78 ºC, 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 (1N)), Amberlite CG- 50 (elution with H_2O), h) recryst. EtOH aq.

Scheme 3

Eludicidation of the structure of **16a** was carried out by ^{1}H NMR spectra and NOE studies.[8] The final steps to the natural product were carried out following literature precedents:[2b] Jones oxidation of the primary alcohol **16a**, followed by hydrolysis with 40% aqueous sodium hydroxide, and purification by using ion-exchange chromatography afforded enantiopure (−)-α-kainic acid (**1**) as colourless needles after recrystalization from aqueous ethanol (38% overall yield). Our final product possessed identical physical properties to that the authentic material:[2b] mp 243-245 ºC (decomp) *versus* mp 241-244 ºC (decomp); ($[\alpha]_D$ −14.3, *c* 0.40, H_2O) *versus* ($[\alpha]_D$ −14.6, *c* 0.25, H_2O).

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[1] Isolation from *Digenea simplex*: S. Murukami, T. Takemoto, Z. Shimizu, *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

[2] Selected syntheses: a) W. Oppolzer, K. Thirring, *J. Am. Chem. Soc.* 1982, *104*, 4978. b) M. V. Chevliakov, J. Montgomery, *J. Am. Chem.* Soc. **1999**, *121*, 11139, and references cited therein. c) J. Clayden, J. C. Menet, K. Tchabanenko, *Tetrahedron* **2002**, *23*, 4727. d) Q. Xia, B. Ganem, *Organic Letters* **2001**, *3*, 485. e) D.A. Campbell, M. T. Raynham, K. J. R. Taylor, *Perkin 1* **2000**, *19*, 3194.

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[5] Synthesized from hydroxyacetone in 67% overall yield over four steps: silylation followed by Horner-Wadsworth-Emmons reaction, 1,2-reduction of ester moiety and bromination.

[6] a) Kondo, K.; Kondo, Y.; Takemoto, T.; Kenoue, T. *Bull Chem. Soc. Jpn.* **1962**, *35*, 1899. b) For a discusion the rotameric distributions of several kainoids: Kozikowski, A. P.; Fauq, A. H. *Tetrahedron Lett*. **1990**, *31*, 2967, and references cited therein.

[7] *NMR-Spectroscopie*; Günther, H., Ed.; Georg Thieme Verlag Stuttgart: New York, 1992. The coupling constants were obtained with the use of packet of programs TURBOMOLE (vers 5.6), University Karlsruhe 2003. The structures were obtimized 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).

[8] The ^{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 refence 6). The NOE studies were carried out at low temperature because of the broad signals.