A Formal Synthesis of (-)-α-Kainic Acid

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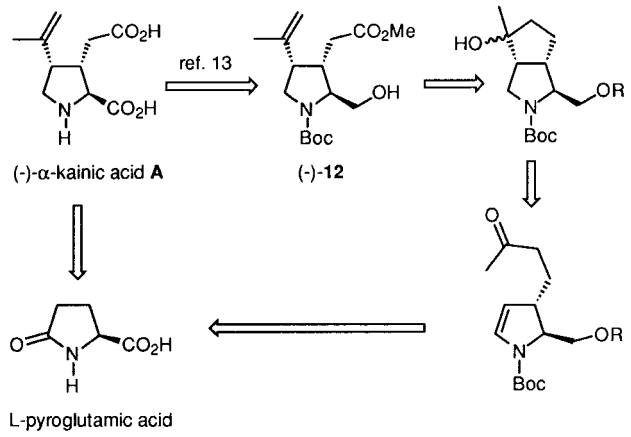
Abstract: The formal synthesis of (-)-α-kainic acid was achieved from L-pyroglutamic acid. The C-4 substituent of the pyrrolidine ring was introduced by using a ketyl radical cyclization on an enecarbamate.

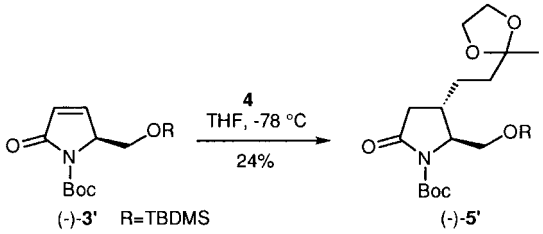
(-)-α-Kainic acid **A**, first isolated in 1953 from the marine alga *Digenea simplex*[1], is the parent member of kainoids displaying potent anthelmintic properties and neurotransmitting activity[2] in the central nervous system. Among these properties, the neuroexcitatory activity is attributed to their *trans* C-2/C-3: *cis* C-3/C-4 structure and the functionality at the C-4 center beside the 2-carboxy and 3-carboxymethyl functionalities. Because of its biological importance as well as its synthetic interest, several enantiocontrolled syntheses have been disclosed. Oppolzer's synthesis of (-)-α-kainic acid relying on an intramolecular ene reaction stands as the first and, as yet remains, the most efficient approach in terms of the number of steps and overall yield.[3] In other approaches, intramolecular Pauson-Khand reaction,[4] tandem Michael reactions,[5] thiazolium[6] or azomethine[7] ylide cycloadditions, Diels-Alder addition,[8] retro Diels-Alder reaction of keto dicyclopentadiene,[9] palladium-induced cyclization,[10] or enolate Claisen rearrangement[11] have been used. More recently, syntheses of several kainoids using free radical cyclization reaction have been presented.[12, 13] We report here a procedure for the construction of (-)-α-kainic acid by synthesizing the key intermediate (-)-**12**, using an intramolecular radical cyclization of a ketyl radical. The method allows the introduction of the C-4 substituent on the pyrrolidine ring. The synthesis of (-)-α-kainic acid was planned from L-pyroglutamic acid according to the following retrosynthetic Scheme.



Scheme 1

L-Pyroglutamic acid (-)-**1** was transformed into the protected amido alcohol (+)-**2** [m.p.= 70 °C, $[\alpha]_D^{20}$ + 57.1 (*c* 0.25, THF)][14] in 3 steps with an overall yield of 63% (Scheme 2). Compound (+)-**2** was tosylated in the presence of LiHMDS, followed by the addition of *p*-toluenesulfonyl chloride[15] (yield: 98%). In order to introduce the 3-oxobutyl side chain at C-3, the obtained tosylamide was transformed into the corresponding enamide (-)-**3**[15a] via phenylselenylation (LiHMDS, PhSeCl, -78 °C, 85%) and subsequent oxidation with H_2O_2 in ethyl acetate (yield: 75%). Conjugate addition of the organocupromagnesium derivative **4**[16] in THF at -78 °C furnished the expected C-3 alkylated pyrrolidine (-)-**5** in 71% yield.

We have to point out that the addition of **4** to the *N*-Boc protected enamide (-)-**3'**[17] led to the alkylated product (-)-**5'** in lower yield (24%). The relative *trans* stereochemistry of the two side-chains at C-2 and C-3 in (-)-**5** and (-)-**5'** was determined by ^{1}H NMR (J H_2-H_3 ≈ 0 Hz).[18]



Scheme 3

Desulfonylation of (-)-**5** by Na in the presence of naphthalene,[19] followed by *tert*-butoxycarbonylation [$(Boc)_2O$] afforded the carbamate (-)-**6** (yield: 83%). The requisite enecarbamate (+)-**7** for the radical cyclization was prepared by reduction of the amide (-)-**6** by Dibal-H (90%), followed by deprotection of the ketone (HCl, H_2O-acetone) and dehydration of the corresponding hydroxycarbamate by quinolinium camphorsulfonate (QCS)[20] (overall yield for the two steps: 42%). We investigated the ketyl radical cyclization by irradiating ketone (+)-**7** in the presence of Et_3N (10 equiv.) at 254 nm in CH_3CN (10^{-2} M).[21] No cyclized product was detected by GC-MS or by ^{1}H NMR. However, when the ketyl radical was generated by using SmI_2 in THF in the presence of HMPA (20 equiv.) and *t*-BuOH[22] (3 equiv.) the bicyclic amine (-)-**8** was isolated in 55% yield together with the corresponding product **B** of pinacolic coupling (32%).[23] Transformation of the bicyclic system into (-)-**12** was realized in 5 steps.

Treatment of the tertiary alcohol (-)-**8** with $POCl_3$ in pyridine afforded alkene (-)-**9** (72% yield). This compound was then treated with RuO_2-$NaIO_4$ to produce a ketocarboxylic acid that was treated directly with CH_3I in the presence of K_2CO_3 to produce intermediate **10**. Methylenation of the methyl ketone into (-)-**11**[24] was achieved by using non-basic conditions such as CH_2I_2, $TiCl_4$, Zn.[6] No purification was performed on compound **10** to avoid its epimerisation at C-4. Finally, the known precursor (-)-**12**[13, 25] of the (-)-α-kainic acid was obtained by treating (-)-**11** with a solution of HF (40%) in THF[11] (yield ≥ 30%).

Since the *trans*, *cis*-trisubstituted pyrrolidine (-)-**12** has been converted into (-)-α-kainic acid **A** without difficulty[13], the present transformation of L-pyroglutamic acid (-)-**1** into (-)-**12** (18 steps) constitutes a new formal synthesis of this natural product.

Our work demonstrates that *cis*-3,4-disubstituted pyrrolidines can be obtained with high stereoselectivity applying a 5-*exo*-trig radical induced cyclization of δ,ε-unsaturated ketones.

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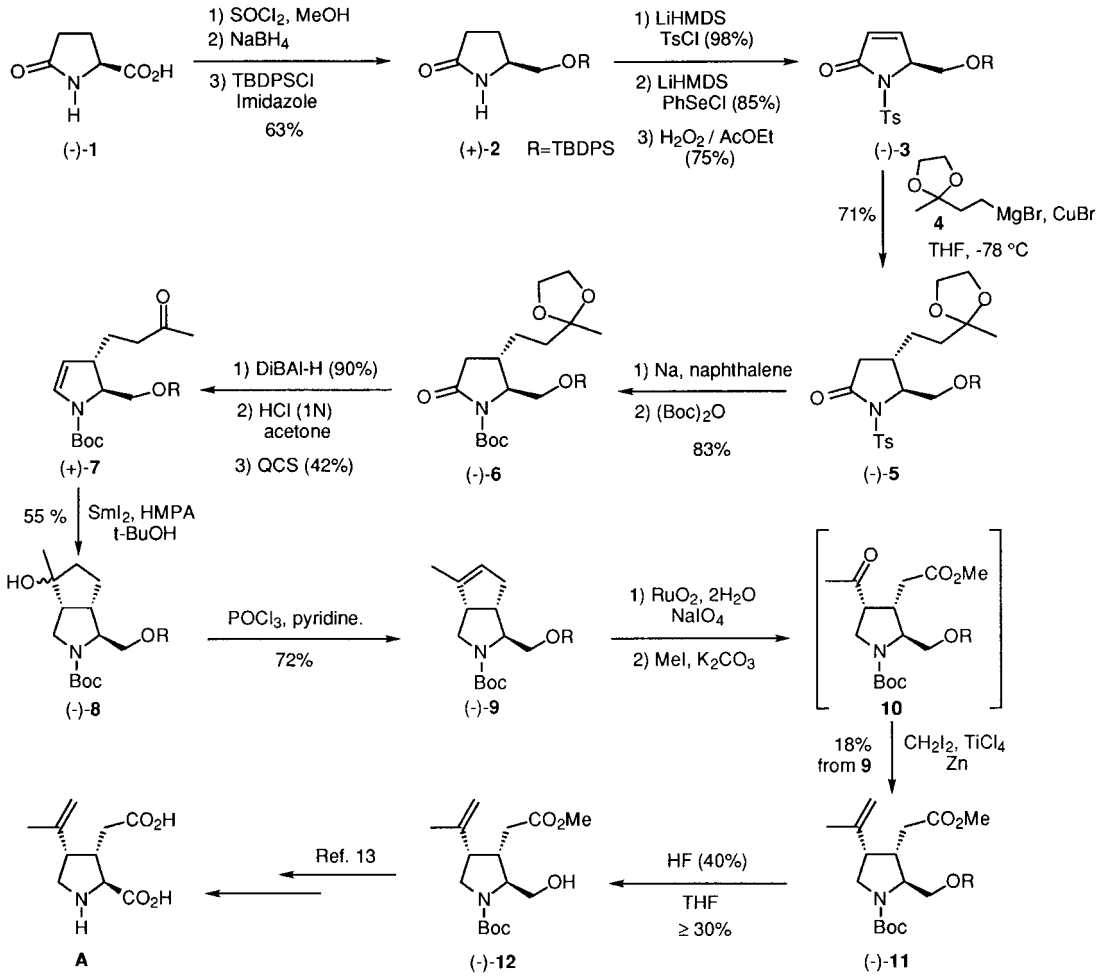

Scheme 2

References and Notes

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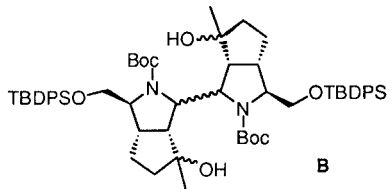
(23) Structure of dimer **B**:



B

Analytical data for **B**: oil; IR (neat): 3420, 1690, 1660 cm^{-1}. ^1H NMR (300 MHz, toluene-d_8, 90 °C) δ: 1.13 (s, 3H), 1.19 (s, 9H), 1.26 (s, 9H), 1.51-1.69 (m, 3H), 2.13-2.23 (m, 1H), 2.27-2.30 (m,1H), 2.99-3.07 (m, 1H), 3.75-3.81 (m, 1H), 4.03 (s, 1H), 4.11-4.17 (m, 1H), 4.22-4.25 (m, 1H), 7.19-7.26 (m, 6H), 7.77-7.82 (m, 4H). ^{13}C NMR (75 MHz, toluene-d_8, 90 °C) δ: 25.0 (q), 27.6 (q), 28.7 (q), 31.5 (t), 42.3 (t), 47.6 (d), 58.3 (d), 64.5 (d), 68.7 (t), 69.5 (d), 79.2 (s), 81.0 (s), 128.0 (d), 128.1 (d), 129.8 (d), 129.9 (d), 135.1 (s), 135.3 (s), 136.2 (d), 136.3 (d), 155.2 (s). MS (FAB^+) *m/z*: 1018 (M^+ + H), 918 (M^+ + H - CH_2=$C(CH_3)_2$ - CO_2), 900 (M^+ + H - CH_2=$C(CH_3)_2$ - CO_2 - H_2O), 862 (M^+ + H - 2 x (CH_2=$C(CH_3)_2$) - CO_2), 844 (M^+ + H - 2 x (CH_2=$C(CH_3)_2$) - CO_2 - H_2O), 818 (M^+ + H - 2 x (CH_2=$C(CH_3)_2$) - 2 x CO_2).

(24) (-)-**11**: oil; $[\alpha]_D^{20}$ -26.3 (*c* 0.4, CH_2Cl_2). IR (neat): 1740, 1700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.07 (s, 9H), 1.27- 1.35 (m, 9H), 1.72-1.76 (m, 3H), 2.12-2.49 (m, 2H), 2.77- 3.19 (m, 2H), 3.40-3.81 (m, 8H), 4.67-4.94 (m, 2H), 7.37- 7.44 (m, 6H), 7.63-7.66 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$)
δ: 19.0 (s), 22.4 (q), 26.7 (q), 28.3 (q), 32.8 (t), 38.6 (d), 44.7 (d), 47.9 (t), 51.4 (q), 63.2 (d), 68.0 (t), 79.4 (s), 112.3 (t), 127.5 (d), 128.6 (d), 133.1 (s), 133.2 (s), 135.4 (d), 141.7 (s), 154.1 (s), 172.9 (s). MS (EI) *m/z*: 494 ($M^{+\cdot}$-$C_4H_9^{\cdot}$), 438 (42), 393 (31), 378 (78), 122 (64), 57 (100). HRMS calculated for $C_{28}H_{36}NO_5Si$ ($M^{+\cdot}$-$C_4H_9^{\cdot}$): 494.2362, found: 494.2361.

(25) (-)-**12**: oil; $[\alpha]_D^{20}$ -35.0 (*c* 0.2, $CHCl_3$) [Lit.[13b] $[\alpha]_D^{21}$ -38.0 (*c* 0.2, $CHCl_3$)]. IR (neat): 3421, 1737, 1690, 1674, 1403 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 1.71 (s, 3H), 2.17-2.37 (m, 2H), 2.46-2.53 (m, 1H), 2.90-2.97 (m, 1H), 3.48 (d, J = 7.7 Hz, 2H), 3.58-3.82 (m, 6H), 4.67-4.69 (m, 1H), 4.89-4.93 (m, 1H).

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