New Enantioselective Approach to the Total Synthesis of (-)-α-Kainic Acid

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Abstract: The total synthesis of (-)-α-Kainic Acid **1** has been accomplished using ethyl N-Boc-pyroglutamate **2** as starting material. The isopropenyl appendage was achieved from the elimination of the dimethylcarbinol introduced at C-4 via an aldol condensation of the lactam enolate of **2** and acetone. The acetate group at C-3 of the kainic acid structure was introduced via diethyl malonate Michael addition reaction to the 2,3-didehydroprolinate **8**. This Michael addition reaction proceeds with complete stereocontrol over the newly generated stereogenic centres. Inversion of the configuration at C-3 in **9** through double bond formation followed by hydrogenation, neutral decarboxylation and further epimerization of the C-2 stereogenic centre in **12**, gave rise to the desired natural product.
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Kainic acid **1** (Figure 1) was first isolated in 1953 from the marine algae *Digenea simplex Ag,*[1] and since then it has attracted the interest of the scientific community due to its neuroexcitatory activity.[2] Other naturally occurring kainoids[3] such as domoic acid and acromelic acid have also shown important biological properties which are attributed to their action as conformationally restricted analogues of the endogenous mammalian neurotransmitter glutamic acid.[4]

Since the first enantioselective synthesis of kainic acid, reported by Oppolzer[5a] in 1982, a number of laboratories have completed total synthesis of **1**.[5] The common feature of all these syntheses is the construction of the pyrrolidine ring during the synthesis, overlooking any synthetic strategy where the heterocycle is present at the beginning of the synthesis. In this paper we wish to describe a new approach to the synthesis of kainic acid based on the stereocontrolled functionalization of *N*-BOC protected pyroglutamate ester **2**.

In planning the synthesis of **1** we wished to extend our earlier work on the reactions of the lactam lithium enolate of **2** with electrophiles[6] and the Michael addition of diethyl malonate to 2,3-didehydroprolinate **3**,[7] both of considerable value for the generation of the side chains at C-4 and C-3 respectively. Throughout the investigation of these key reactions in the kainic acid field, we have developed a flexible strategy for the synthesis of α-allokainoid **4**[7] and β-kainoid **5**.[8]
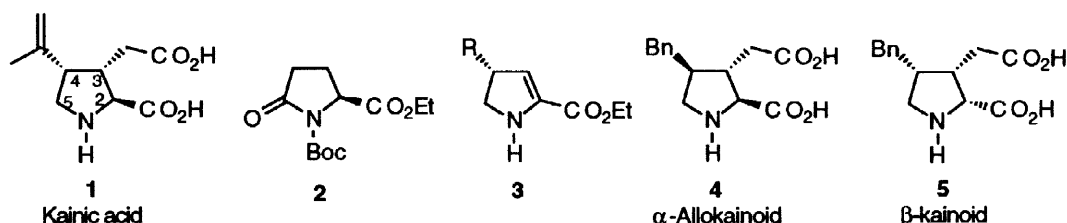

Figure 1

In applying this strategy to the total synthesis of kainic acid two primary concerns remained: (a) stereocontrolled introduction of the isopropenyl group and (b) epimerization of the C-2 stereogenic center.

These considerations guided our retrosynthetic analysis (Scheme 1). In the synthetic plan, the isopropenyl moiety would arise from the elimination of the dimethylcarbinol introduced at C-4 *via* an aldol[6d] reaction on 2. The acetate group at C-3 would be introduced *via* a Michael addition to the 2,3-didehydroprolinate 8. Inversion of the configuration at C-3 in 9 through double bond formation followed by hydrogenation, neutral decarboxylation and further epimerization of C-2 in 12, would furnish the natural product 1.
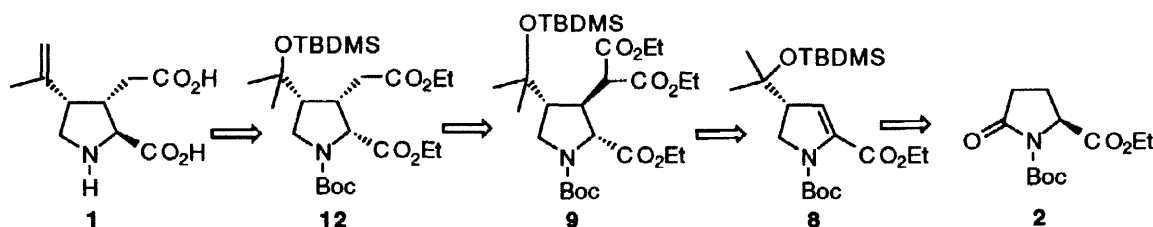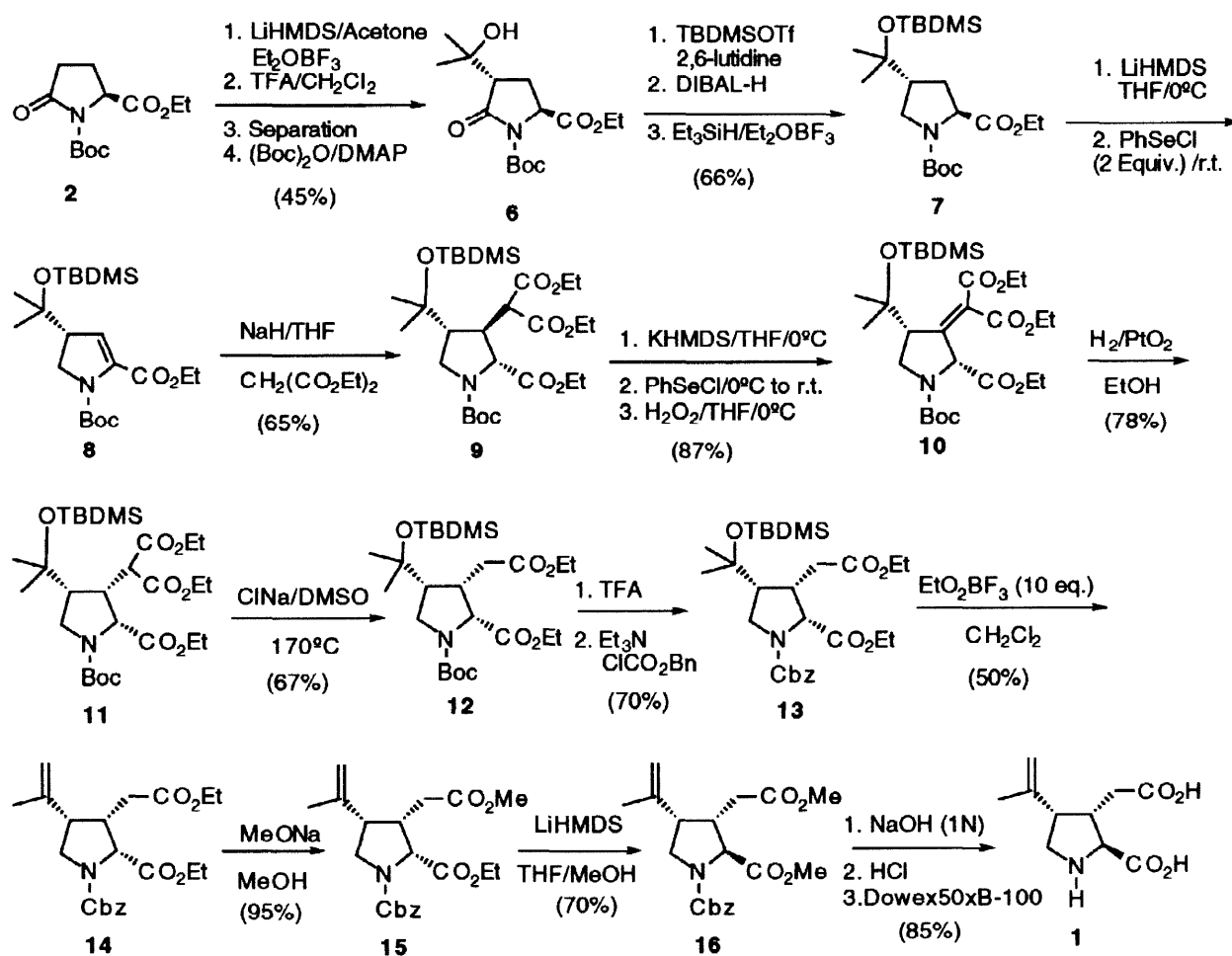

Scheme 1

Ethyl *N*-Boc pyroglutamate 2 was prepared from L-glutamic acid following standard reaction conditions.[9] $BF_3 \cdot OEt_2$ mediated aldol condensation of the pyroglutamate lactam enolate,[6d] generated with LiHMDS in THF at -78°C, with acetone gave rise to a mixture of *cis* and *trans* aldols (1:4 ratio), which could not be separated by chromatography. In order to obtain the *trans* aldol 6, it was neccessary to remove the urethane protecting group with TFA in CH_2Cl_2 and perform the chromatography on the corresponding pyroglutamate. Once the separation was achieved, the Boc protecting group was reintroduced under standard conditions. Thus, 6 was prepared in a 45% yield from 2 (Scheme 2). Once the desired functionality with the appropriate stereochemistry was introduced at C-4, the next step in the synthesis was the chemoselective reduction of the lactam carbonyl group. Thus, the alcohol was protected as its TBDMS ether and the lactam carbonyl group was reduced in a two steps sequence reduction, first partial reduction with DIBALH to the corresponding hemiaminal,[10] followed by further reduction of this intermediate with Et_3SiH/BF_3Et_2O *via* an *N*-acyliminium intermediate.[11] Prolinate 7 could be prepared in a 66% isolated yield from 6.

The Michael acceptor 8[12] was prepared using the optimised reaction conditions recently described by us,[8] generating the ester enolate with LiHMDS at 0°C in THF and reacting with 2 equivalents of PhSeCl at room temperature. The addition of diethyl malonate anion to 8, produced the Michael adduct 9 in 65% yield as a single diastereomer. With all the substituents attached to the prolinate ring, it was then time to generate the isopropenyl functionality at C-4 and to adjust the stereochemistry at both the C-2 and C-3 positions. Thus, 9 was deprotonated with KHMDS in dry THF at 0°C and reacted with PhSeCl. The selenated product was oxidised with hydrogen peroxide[13] in THF at 0°C, yielding the olefine 10 in 87% yield. Hydrogenation of the double bond was achieved in ethanol with PtO_2 as catalyst at 80 psi, the reaction requiring 15 days for completion. Under these reaction conditions the all-*cis* prolinate 11 was obtained in 78% yield. Ethylmalonate decarboxylation was carried out under neutral reaction conditions, using NaCl in a mixture of $DMSO/H_2O$ heating at 170°C over 2 hours, in order to avoid the deprotection of the urethane and ester hydrolysis. Under these reaction conditions, the β-kainoid diester 12 was obtained in 67% yield.

The next steps in the synthesis were the generation of the isopropenyl appendage. Attempts to deprotect the TBDMS group in 12, using ammonium fluoride or tetrabutyl ammonium fluoride did not prove effective, the silylated alcohol being recovering. This unreactive behaviour is probably the result of the high steric hindrance imposed by the C-2 and C-3 substituents. The same result was obtained when 12 was treated with BF_3OEt_2 (10 equiv.) at 0°C. When the reaction was run at room temperature, the Boc protecting group was hydrolysed by the action of the Lewis acid. At this point we decided to change the urethane protecting group to CBz, which is stable to acidic reaction conditions. Thus, removal of the Boc protecting group of 12 with TFA, followed by reprotection with benzyloxycarbonyl chloride (CBz-Cl) under standard conditions, gave rise to the β-kainoid 13 in 70% yield. Deprotection of the TBDMS group and dehydratation was

achieved when **13** was treated with BF₃OEt₂ (15 equiv.) in dichloromethane at room temperature resulting in the formation of the β-kainate **14** in 50% yield.

In order to complete the synthesis, the last step was to invert the configuration of the C-2 stereogenic center. This epimerization step has been reported by Takano[5c] on a related substrate (dimethyl diester) using NaH and DBU in benzene at room temperature over 24 hours. Surprisingly, under the same reaction conditions, the diethyl diester **14** was recovered without any sign of C-2 epimerization. After this unexpected result, we decided to prepare the same intermediate reported by Takano by transesterification using sodium methoxide in methanol at room temperature over 4 hours. To our surprise, under these reaction conditions, only one out of the two diethyl esters was transesterified, compound **15** being obtained in 95% yield. Longer reaction times, to complete the reaction, did not result into the desired product. However, when **15** was treated with a stronger base (LiHMDS) in THF at 0°C, the α-kainate **16**[14] was obtained in 70% yield. This intermediate displayed the same optical rotation and spectroscopic data to the one described by Takano.[5c] It is noteworthy, the methyl ester has to be present at the C-3 acetate substituent for the epimerization of C-2 to take place. In fact, when **14** was treated under the same reaction conditions as **15** we only observed a mixture of decomposition products.

Scheme 2

Finally, kainic acid **1** was obtained by basic hydrolysis (NaOH 1N) of the esters and the urethane protecting group of **16**, followed by purification (Dowex).

We have developed a new total synthesis of (-)-α-kainic acid starting from *N*-Boc ethyl pyroglutamate, where the pyroglutamate stereogenic center is used to gain the desired stereoselective functionalisation of the C-4 position of the kainate. This stereogenic center is then lost during the generation of the Michael acceptor **8**, which is used to introduce the acetate substituent present in the target molecule. As a result of this reaction the configurations at the C-2 and C-3 positions were the opposite to the ones desired. Selective manipulations permitted us to recover the original stereochemistry at C-2 while fixing properly the C-3 stereogenic center. The use of ethyl pyroglutamate as starting material and diethyl malonate as nucleophile for the Michael addition step, allowed us to observe the role of the ester groups in the epimerization step of the β-kainate **14**. As the ester groups would not be expected to influence either the aldol or the Michael addition reactions, a more convenient total synthesis would use methyl ester from the outset. Further applications of this novel methodology and an improved approach to α-kainic, β- kainic and allokainic acids are in progress in these laboratories and will be reported in due course.[15]

References and Notes

1. Murukami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026-1028.
2. (a) McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic acid as a Tool in Neurobiology*; Raven Press: New York, 1983. (b) *"Excitatory Amino Acid receptors"* Krogsgaard-Larsen, P.: Hansen, J. J.; Ed. Ellis Horwood, New York, 1992
3. For reviews on total synthesis of kainoids see: (a) Williams, R. M. in *"Synthesis of Optically Active Amino Acids"*. Pergamon Press. **1989**. (b) Parsons, A. F. *"Tetrahedron Report number 393"Tetrahedron* **1996**, *52*, 4149-4174.
4. Lodge, D. in *"Excitatory Amino Acids in Health and Disease"*, John Wiley & Sons, Inc.: New York, 1988.
5. (a) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978-4979. (c) Baldwin, J. E.; Li, C-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166-168. (c) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204-1206. (d) Takano, S.; Sugihara, T.; Sotoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467-6471. (e) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc. Perkin Trans 1* **1992**, 553-559. (f) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279-6286. (g) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169-170. (h) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125-127. (i) Yoo, S-e.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968-6972. (j) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418-5424. (k) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60-62. (l) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *61*, 2773-2778. (m) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896-1898.
6. Alkylations: (a) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665-8678. (b) Ezquerra, J.; Pedregal, C.; Rubio, A.; Vaquero, J. J.; Matía, M. P.; Martín, J.; Diaz, A.; García Navío, J. L.; Deeter, J. B. *J. Org. Chem.* **1994**, *59*, 4327-4331. (c) Ezquerra, J.; Pedregal, C.; Micó, I.; Nájera, C. *Tetrahedron: Asymmetry* **1994**, *5*, 921-926. Aldol condensations (d) Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Carreño, M. C.; Escribano, A.; García Ruano, J. L. *J. Org. Chem.* **1995**, *60*, 2925-2930.
7. Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149-6152.
8. Ezquerra, J.; Escribano, A.; Rubio, A.; Remuiñán, M. J.; Vaquero, J. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2613-2626.
9. (a) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815-818. (b) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.
10. Langlois, N; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477-2480.
11. Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053-2056.
12. A related approach, starting from 4-hydroxiproline, to C-4 aryl kainoids, which emplys a similar intermediate to **8**, has been reported by Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625-2628.
13. Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.
14. This compound was also prepared form comercially (-)-kainic acid, displaying the same optical rotation. All compounds described in this communication gave satisfactory combustion analysis or HRMS and were characterised on the bases of their ^{1}H-NMR and ^{13}C-NMR spectra.
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