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New Enantioselective Approach to α-Allokainoids by Michael Addition to Chiral 4-Substituted 2,3-Didehydroprolinate

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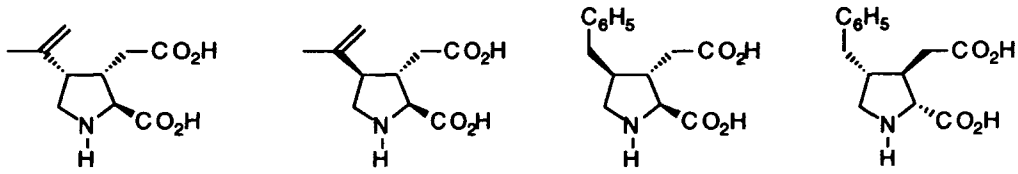
Abstract: (-) and (+) α–Allokainoids hydrochlorides **3** and **4** were obtained by hydrolysis of the corresponding Michael adducts resulting from the addition of diethyl malonate to chiral N-urethane protected ethyl 4-benzyl-2,3-didehydroprolinates **9** and **13** respectively.

The term kainoid refers to a group of natural nonproteinogenic amino acids possesing a pyrrolidinedicarboxylic acid structure, which can be considered as a conformationally contrained glutamic acid, having three contiguous stereogenic centres.[1] (-)-α-Kainic (**1**) (Figure 1) occurs with its C-4 epimer, (+)-allokainic acid (**2**) in the marine alga *Digenea simplex Ag.*[2] From the biological point of view, kainic acid, allokainic acid and other structurally related compounds[3] of this family of natural products have been found to exhibit a powerful neuroexcitatory activity.[1] Recently the total synthesis of different kainoids has attracted the attention of several groups,[4] using different approaches to establish the proper stereochemistry at the pyrrolidine core. In this communication we would like to report a new approach to α-allokainoids **3** and **4** (Figure 1) based on the Michael addition of diethyl malonate to chiral 4-substituted 2,3-didehydroprolinate. The synthesis of **3** and its enantiomer **4** rests on the high stereocontrol exercised by the C-4 substituent of the 2,3-didehydroprolinate.

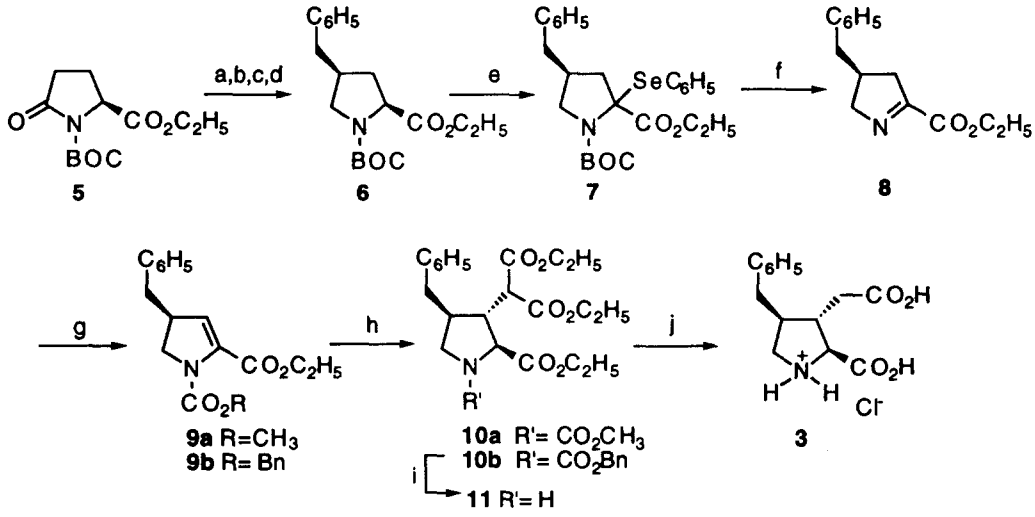


1 **2** **3** **4**

Figure 1

Ethyl N-BOC-pyroglutamate **5** (Scheme 1) was prepared according to literature procedures.[5] Ethyl (2*S*, 4*S*)-4-benzylprolinate (**6**) was prepared following a synthetic pathway recently developed by us.[6] Thus, $BF_3.OEt_2$ mediated aldol condensation of the lactam enolate (LiHMDS/THF/-78ºC) of **5** and benzaldehyde gave a mixture of aldols (72% yield). This mixture was treated with mesyl chloride in the presence of an

excess of Et_3N (r.t./2 days) to give ethyl N-BOC-4-benzylidenepyroglutamate (62% yield) which was hydrogenated (H_2/PtO_2) to produce the ethyl (2*S*, 4*S*)-N-BOC-4-benzylpyroglutamate (77% yield). Chemoselective reduction[7] ($LiEt_3BH/Et_3SiH/BF_3.OEt_2$) of the pyroglutamate lactam carbonyl group gave rise to **6** (84% yield). The prolinate **6** was subjected to a set of reactions in order to obtain the Michael acceptors **9a,b**. Thus, α-selenation of the ester moiety (LiHMDS/THF/0°C/PhSeCl) by addition of the enolate to the electrophile gave **7** (80% yield). Oxidation ($NaIO_4/MeOH/H_2O$)[8] of the selenide led to a complex mixture rather than clean *syn* elimination. However, to our surprise, N-BOC deprotection (TFA/CH_2Cl_2/r.t.) gave the Δ^1-pyrroline **8**[9] (61% overall yield from **6**) by a β-elimination process of the selenide. For our synthetic purposes, **8** could be transformed into the Michael acceptor **9a** (90% yield) by treatment with methyl chloroformate in the presence of pyridine.[10]

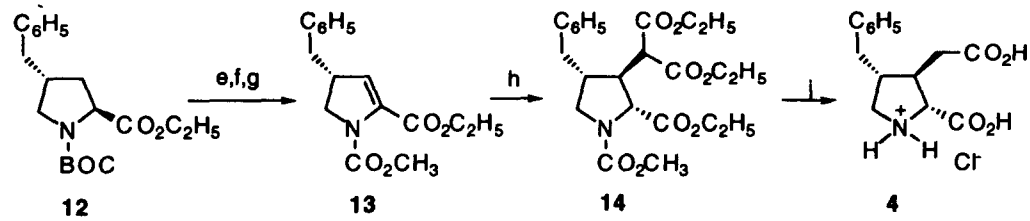


a: 1. LiHMDS/THF/-78°C. 2. $C_6H_5CHO/BF_3.OEt_2$. **b:** $MsCl/Et_3N$. **c:** H_2/PtO_2. **d:** 1. $LiEt_3BH$. 2. $Et_3SiH/ BF_3.OEt_2$. **e:** 1. LiHMDS/THF/0°C. 2. C_6H_5SeCl (inverse addition). **f:** TFA/CH_2Cl_2. **g:** $RCO_2Cl/Py/CH_2Cl_2$ reflux. **h:** $NaH/CH_2(CO_2Et)_2$/THF/0° to r.t. 7 h. **i:** H_2/10% Pd/C. **j:** 6N HCl reflux.

Scheme 1

Michael addition of diethyl malonate[11] anion (NaH/THF/0°C) to **9a**[12] gave the corresponding adduct **10a** (70% yield). In order to determine the level of stereoinduction of the conjugate addition reaction, it was necessary to remove the carbamate, since the presence of rotamers complicated the NMR analysis. As this selective deprotection could not be performed without affecting the other functionality present in **10a**, a parallel experiment was done using benzyl chloroformate[13] to obtain **10b** (yield for **9b** 40% and for **10b** 50%). Removal of the CBz protecting group by hydrogenolysis (10%Pd/C) gave **11** as a single diastereomer.[14] As the use of the CBz protecting group gave lower yields compared with the methyl carbamate, for our synthetic purposes **10a** was hydrolysed to the α-allokainoid hydrochloride **3**[15] [60% yield, $[\alpha]_D$= -10.3° (c, 0.22, H_2O)].

After these results, we decided to obtain the enantiomer **4** (Scheme 2) by the same methodology but starting from the readily available ethyl (2*S*, 4*R*)-4-benzyl prolinate **12** prepared by stereoselective alkylation[16] of the lactam enolate derived from **5** with benzyl bromide (60% yield) and subsequent reduction[7] of the lactam carbonyl group (80% yield). Prolinate **12** was subjected to the same set of reactions as its C-4 epimer **6**, obtaining α-allokainoid hydrochloride **4** [$[\alpha]_D$= +10.4° (c, 0.22, H_2O)].



Scheme 2

The main feature for the synthesis of **3** and **4** resides in the high degree of stereocontrol that the C-4 substituent of the Δ^2-pyrrolines **9** and **13** exercises during the Michael addition reaction. While the stereogenic centre of the starting pyroglutamate **5** induces the stereoselective functionalitation[6,16] at the C-4 position, this stereogenic centre gains an sp^2 status during the generation of the Michael substrates **9** and **13**. In the case of **9** the stereogenic centre at C-2 was regenerated after the conjugate addition of the diethyl malonate. This was not the case for compound **13** were the chirality of the C-2 position was inverted due to the attack of the malonate from the less hindered face of the cyclic system.

A similar methodology based in the Michael conjugate addition to different 3,4-didehydropyroglutamate derivatives have been reported where the pyroglutamate carboxylic moiety was transformed into a protected alcohol[17] or as its *N,O*-acetal,[18] in order to prevent the racemization of the stereogenic centre and to ensure the asymmetric induction. While in these transformations the protected alcohol or the *N,O*-acetal functionality are responsible for the stereochemical reaction outcome, in our approach the reaction stereocontrol is driven by the chiral C-4 substituent of the Michael acceptor, allowing the enantioselective synthesis of these allokainoids.

The enantiomeric purities of both **3** and **4** were established independently by ^{1}H-NMR of the Mosher amides[19] of the corresponding dimethyl esters. Thus, esterification (CH_3OH/HCl(g)) followed by Mosher amide formation ((S)-(+)- and (R)-(-)-methoxy-α-(trifluoromethyl)phenylacetyl chloride in the presence of propylene oxide) gave an *ee*≥95%.

In summary, the presented synthesis of α-allokainoids opens a new entry to these derivatives in a highly enantioselective fashion. Further studies on this methodology are in progress in our laboratories and will be reported on due course.

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References and Notes

1 McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic acid as a Tool in Neurobiology*; Raven Press: New York, 1983.

2 Murukami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026-1028.

3 (a) (-)-Domoic acid; Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513. (b) Acromelic acids A & B; Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939-942.

4 (a) For a review of total synthesis of different kainoids see: Coppola, G. M. and Schuster, H. F. in *"Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids"*. John Wiley & Sons Inc. New York. **1987**. Synthesis of (+) and (-)-α-Allokainic acid: (b) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279-6286. (-)-α-Allokainic acid: (c) Agami, C.; Cases, M.; Couty, F. *J. Org. Chem.* **1994**, *59*, 7937-7940. (+)-α-Allokainic acid and (-)-α-Kainic acid: (d) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc. Perkin Trans 1* **1992**, 553-559. (-)-α-Kainic acid: (e) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem Soc.; Chem. Commun.* **1992**, 169-170. (f) Yoo, S-e.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968-6972. (±)-α-Kainic acid: (g) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773-2778.

5 Ethyl pyroglutamate: (a) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815-818. (b) The urethane was protected using Grieco's procedure. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.

6 Ezquerra, J.; Pedregal, C.; Yruretagoyena, B.; Rubio, A.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *J. Org. Chem.* **1995**, *60*, 2925-2930.

7 Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053-2056.

8 Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.

9 This type of Δ^1-pyrrolines have been prepared by N-chlorination (^{t}BuOCl) followed by dehydrochlorination (Et_3N); Häusler, J.; Schmidt, U. *Liebigs Ann. Chem.* **1979**, 1881-1889.

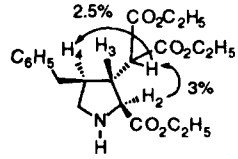
10 Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2625-2628.

11 For a Michael addition reaction of diethyl malonate to Benzyl N-methyl-N-*tert*-butoxycarbonyl methylene glycinate see: Danishefsky, S.; O'Neill, B. T.; Taniyama, E.; Vaughan, K. *Tetrahedron lett.* **1984**, *25*, 4199-4202.

12 The Michael addition reaction has been reported for methyl Δ^2-pyrrolinyl-2-carboxylate with heteronucleophiles; Häusler, J. *Liebigs Ann. Chem.* **1981**, 1073-1088.

13 Switzer, F. L.; Halbeek, H. V.; Holt, E. M.; Stammer, C. H. *Tetrahedron* **1989**, *45*, 6091-6100

14 The stereochemical assignment was made on the basis of n.O.e experiments and coupling constants analysis:



H_2: 3.78 ppm (d, J=5.2 Hz)
H_3: 2.67 ppm (dt, J=7.2 , 5.2 Hz)
H_4: 2.31-2.15 ppm (m)
$J_{3,4} = J_{2,3} = 5.2$ Hz

15 Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR and C, H, N combustion analysis) have been obtained for all compounds reported in this communication. For **3**: m. p.: 58-60°C. ^{1}H NMR (200 MHz, D_2O) 7.19-6.97 (m, 5H); 3.91 (d, J = 5.8 Hz, 1H); 3.18 (dd, J = 6.3 and 11.1 Hz, 1H); 2.91 (dd, J = 8.3 and 11.1 Hz, 1H); 2.63 (dd, J = 5.1 and 13.4 Hz, 1H); 2.51-2.28 (m, 5H). ^{13}C NMR (50 MHz, D_2O) 176.0, 172.4, 139.3, 129.5 (2C), 129.4 (2C), 127.4, 64.4, 50.1, 44.7, 44.0, 37.2, 35.8. IR (KBr) 3422, 2924, 1724, 1406 cm^{-1}. Anal. Cald. for: $C_{14}H_{18}ClNO_4$ C, 56.08; H, 6.06; N, 4.67. Found: C, 55.85; H, 6.26; N, 4.43.

16 Ezquerra, J.; Pedregal, C.; Rubio, A.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665-8678.

17 Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett.* **1991**, *32*, 3057-3058.

18 (a) Hanessian, S.; Rotovelomanana, V. *Synlett*, **1990**, 501-503. (b) Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379-1380.

19 Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

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