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The Synthesis of 4,5-Methano Congeners of α-Kainic and *α-allo*-Kainic Acids as Probes for Glutamate Receptors

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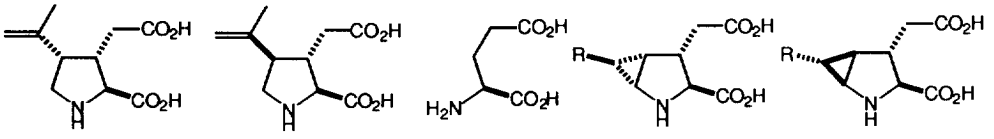
Abstract: *The synthesis of diastereomeric 4,5-methano-L-proline 3-acetic acids is described starting from D-serine. The key reactions include a free-radical carbocyclization and an acid-catalyzed destannylative cyclopropanation of an iminium ion intermediate.*

The synthesis of biologically relevant α-amino acids in which the carbon skeleton has been rigidified has been an area of active research for some years.[1] 2,3-Methano amino acids, also known as "methanologs" have attracted considerable attention in this regard.[2] Many of these compounds were prepared with the intention of probing spatial, conformational and functional features of the natural substrates at their biological receptor sites. Methano[2,3] and related[4] analogs of L-glutamic acid have been of particular interest because of the importance of this amino acid in the CNS. Indeed, the glutamate receptor is considered to be an important target in the quest for therapeutically effective drugs in the cardiovascular and related areas[5] Cyclopropane α-amino acids are also natural products[2] or components of more elaborate structures.[6]

Receptors to excitatory amino acids include among others, those that have an affinity to α-kainic acid **1**,[7] which, viewed in a different perspective, can be considered as a constrained L-glutamic acid **3**. Indeed, in addition to a plethora of total[8] and partial syntheses[8] of α-kainic acid **1** and *allo*-kainic acid **2**, there are several reports of kainoid analogs[8,9] aimed at finding new bioactive compounds in this series.

We report in this Letter, the design and synthesis of structurally novel 4,5-methanoproline 3-acetic acid analogs **4** and **5** in enantiomerically pure form (Figure 1). Examples of methanoprolines are rare,[10,11] and to the best of our knowledge compounds like **4** and **5** which are structurally and stereochemically related to α-kainic and *allo*-kainic acids, are unprecedented.

Figure 1



1, α - kainic acid **2**, *allo*-kainic acid **3**, *L*-Glutamic acid **4**, R=H **4a**, R=vinyl **5**, R=H **5a**, R=vinyl

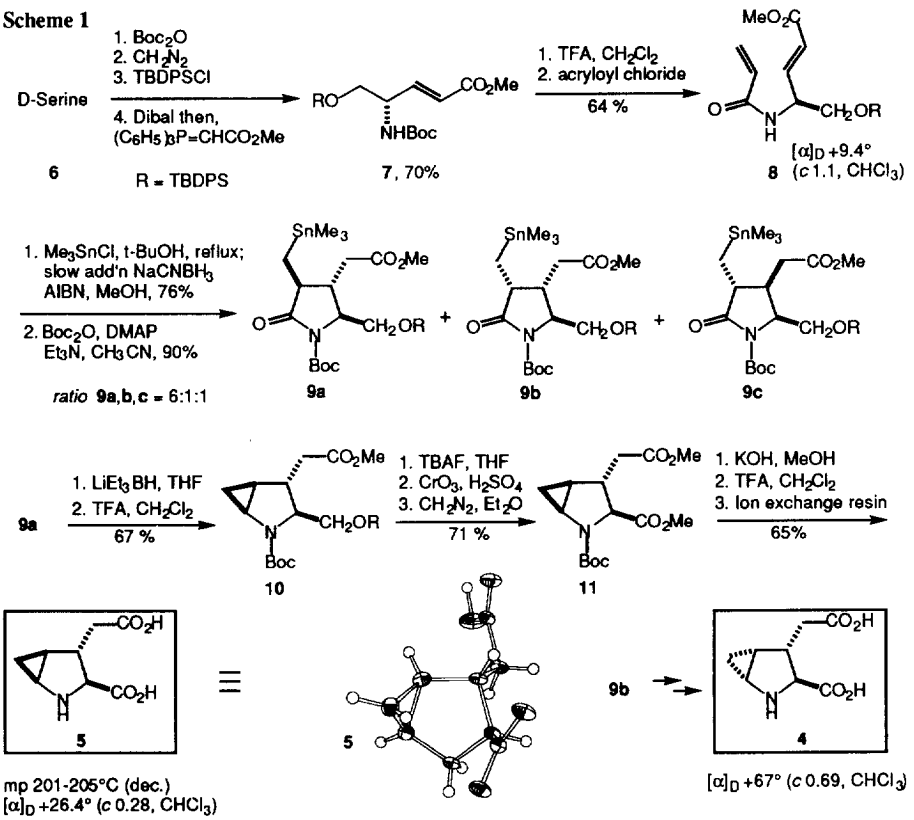
In order to have access to both isomers **4** and **5**, we chose a method of synthesis that produced stereoisomeric intermediates from a common precursor (Scheme 1). D-Serine **6** was elaborated upon by a series of standard manipulations to give the diene **8**. Treatment with trimethyltin hydride[12,13] led to a mixture of pyrrolidinones, which could be separated into the three isomers **9a**, **9b**, and **9c** after conversion to

the N-boc derivatives and column chromatography.[14] The stereochemical outcome favoring the major *trans*-isomer **10a** has been rationalized based on the prevalence of a late transition state.[11,15]

In a key transformation, the lactam was sequentially reduced to the hemiaminal, then treated with acid to give the 4,5-methano derivative **10** *via* intermolecular alkylation of the corresponding N-Boc iminium ion.[11] Subsequent steps relied on functional group manipulations to afford the diester **11** which was in turn hydrolyzed to the crystalline 4*S*,5*S*-methano-3*S*-carboxylmethyl-L-proline, **5**. An X-ray crystal analysis provided conclusive proof for its structure and stereochemistry.

The isomeric 4*R*,5*R*-analog **4** was prepared in a similar manner, to give an amorphous product, whose stereochemistry was rigorously assigned by detailed n.O.e. studies.

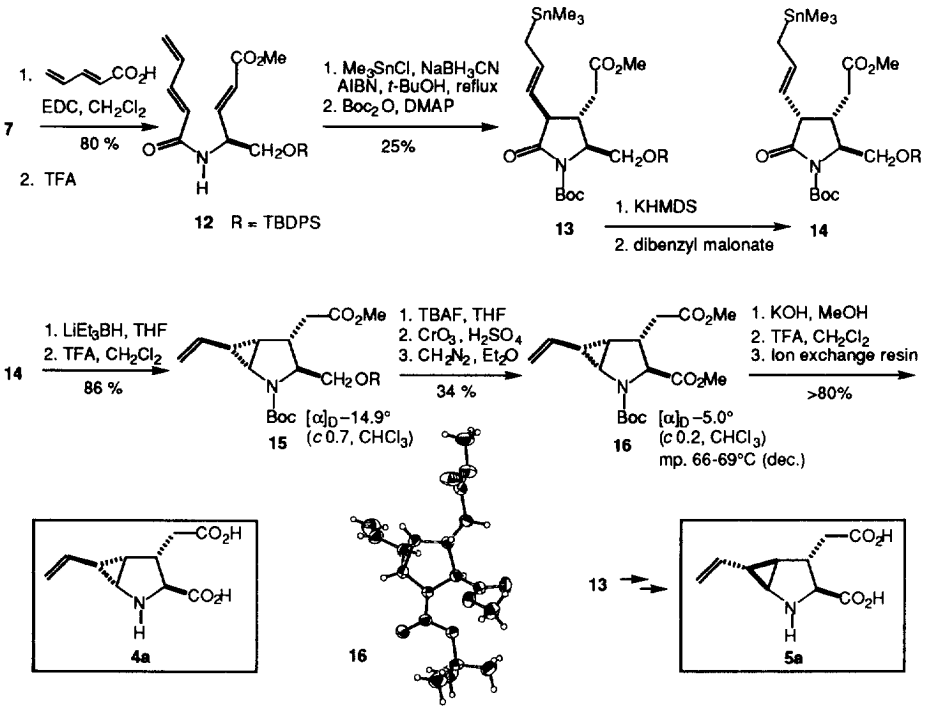
Scheme 1



The radical carbocyclization reaction can also be done on an extended dienic system[12a] which can eventually lead to the functionalized 4,5-methano analogs **4a** and **5a** (Figure 1).

The readily available diene **12** was subjected to the free radical carbocyclization reaction to give mainly the all-*trans*-pyrrolidinone which was isolated as the N-Boc derivative **13** (Scheme 2). Quenching the potassium dienolate of the all-*trans*-isomer **13** with dibenzylmalonate[16] as a proton source led to the isomeric product **14** as the major product. Formation of the N-Boc iminium ion by the method described above led to the vinyl cyclopropane **15** which was in turn converted into the α-kainic acid congener **4a**, isolated as an amorphous solid. Application of the same methodology to the isomeric **13** gave **5a**, also isolated as an amorphous solid. The structures in this series were unambiguously established by detailed N.M.R. studies and by an X-ray crystal analysis of **16**.

Scheme 2



Compounds **4**, **4a**, **5** and related amino acids from another series[11] were tested for their binding as antagonists and agonists in five receptor assays.[5a] Unfortunately, no significant binding affinity was found at 1 μM in the DCKA (^{3}H-5,7-dichlorokynurenic acid) assay for the glycine recognition site of the NMDA receptor. When tested in the AMPA, kainate, and other receptor binding assays at concentrations of 1 μM and 10 μM, again, activity was surprisingly low compared to standards.[17]

Clearly, the structural requirements for effective binding to these receptors have not been satisfied by our methano analogs in spite of their novel structures. The lack of activity in the kainate receptor and the glutamate recognition site of N-methyl-D-aspartate receptor (CGP 39653) are reflective of the lack of our understanding for specific spatial requirements and hydrophobic interactions of the appended cyclopropane in analogs **4**, **4a**, **5** vis-a-vis the 2-propenyl group in α-kainic acid itself.

We are presently developing alternative, highly stereocontrolled methods for the synthesis of conformationally constrained analogs of L-proline and L-pipecolic acid. These should find specific applications in the design of peptidomimetics aimed at probing enzymatic reactions that involve *cis/trans* amide-bond isomerization[18] such as in the immunophilins,[19] as well as in the study of secondary and tertiary local structures of certain peptides.[20]

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References and Notes

1. For selected reviews on constrained peptides, see Giannis, A.; Kolter, T. *Angew, Chem. Int. Ed. Engl.* **1993**, *32*, 1244; Kahn, M. *Synlett* **1993**, 821; Rizo, J.; Gierasch, L. M. *Ann. Rev. Biochem.* **1992**, *61*, 387; Fauchére, J.-L. *Adv. Drug Res.* **1986**, *15*, 29.
2. For selected reviews, see Burgess, K.; Ho, K.-K.; Moye-Sherman, D. *Synlett* **1994**, 525; Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, *130*, 5.
3. For some examples, see Pellicciari, R.; Marinozzi, M.; Natalini, B.; Costantino, G.; Luneia, R.; Giorgi, G.; Moroni, F.; Thomsen, C. *J. Med. Chem.* **1996**, *39*, 2259; Sagnard, I.; Sasaki, N. A.; Chiaroni, A.; Riche, C.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 3149; Hanafi, N.; Ortuno, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1657; Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.
4. Raghavan, S.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Tetrahedron Lett.* **1993**, *34*, 5765.
5. a. Knöpfel, T.; Kuhn, R. Allgeier, H. *J. Med. Chem.* **1995**, *38*, 1417; Johnson, R. L.; Koerner, J. F. *J. Med. Chem.* **1988**, *31*, 2058; b. *Glutamate: Transmitter in the Central Nervous System*, Roberts, P. J.; Storm-Mathesen, J.; Johnson, G. A. R. Eds.; Wiley, New-York, N. Y., 1981.
6. See for example, Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721; Jimenez, J. M.; Rifé, J.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1995**, *6*, 1849; Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796; Fourden, L.; Kato, K.; Takita, T.; Umezawa, H. *Tetrahedron Lett.* **1980**, *21*, 4925; Smith, A. Millington, D. S.; Sheppard, R. C. *Phytochemistry*, **1972**, *11*, 1105.
7. McGeer, E. G.; Olney, J. W. in *Kainic Acid as Tool in Neurobiology* ; Raven Press, New York, N. Y., 1978.
8. For a recent review, see Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149 and references cited therein; see also Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Baldwin, J. E.; Magnus, P. D. Eds.; Pergamon Press, New York, N. Y., 1989; pp 306-320; for the first synthesis of α-kainic acid, see Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.
9. For representative examples, see Gill, P.; Lubell, W. D. *J. Org. Chem.* **1995**, *60*, 2658; Baldwin, J. E., Rudolph, M. *Tetrahedron Lett.* **1994**, *35*, 6163; Ezquerra, J.; Escribano, A.; Rubio, A.; Remuinan, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1995**, *36*, 6149; Hashimoto, K.; Harikawa, M.; Shirahawa, H. *Tetrahedron Lett.* **1990**, *31*, 7047; Kozikowski, A. P.; Fang, A. H. *Tetrahedron Lett.* **1990**, *31*, 2967.
10. For the synthesis of racemic and enantiopure 2,3-methanoproline, see Hercouet, A.; Bessières, B.; Le Corre, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1267; Switzer, F. L.; van Halbeek, H.; Holt, E. M.; Stammer, C. H. *Tetrahedron* **1989**, *45*, 6091; for the synthesis of *cis*- and *trans*- 3,4-methanoprolines, see Fujimoto, Y.; Irrevere, F.; Karle, J. M.; Karle, I. L.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3471; for a recent discussion of cyclopropylpyrrolidines, see Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268.
11. For related structures, see Hanessian, S.; Reinhold, U.; Ninkovic, S. *Tetrahedron Lett.*, preceding paper.
12. a. Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5419; b. Hanessian, S.; Leger, R. *J. Am. Chem. Soc.*, **1992**, *114*, 3115; c. Hanessian, S.; Leger, R. *Synlett*, **1992**, 402.
13. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.*, **1986**, *108*, 303.
14. New compounds were adequately characterized by spectoscopic and analytical data.
15. For a recent review on free-radical chemistry, see Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.
16. Dibenzylmalonate afforded the best selectivity compared to other protic and aprotic proton sources (*ratio* **14** : **15** = 1:3.9), see for example Baker, W.; Pratt, J. K. *Tetrahedron* **1993**, *49*, 8739 and references therein.
17. CGP 39653, [^{3}H]-*E*-2-amino-4-phosphonomethy-hept-3-enoic acid, antagonist for the glutamate recognition site of NMDA receptors; [^{3}H]-MK-801, Merck's blocker of NMDA receptor associated ion channels; [^{3}H]-kainic acid, agonist for Kainate receptors.
18. For recent reports, see Curran, T. P.; McEnaney, P. M. *Tetrahedron Lett.* **1995**, *36*, 191; Andres, C. J.; Macdonald, T. L.; Ocain, T. D.; Longhi, D.; *J. Org. Chem.* **1993**, *58*, 6609; Ebenhardt, E. S.; Loh, S. N.; Raines, R. T. *Tetrahedron Lett.* **1993**, *34*, 3055 and references cited therein.
19. Schreiber, S. L. *Science* **1990**, *251*, 283; Freedman, R. B. *Nature* **1989**, *341*, 692; *337*, 407.
20. Bell, J. E.; Bell, T. E.; *Proteins and Enzymes*, Prentice Hall, Englewood Cliff, N. J., 1988; Robson, B.; Garner, J. *Introduction to Proteins and Protein Engineering*, Elsevier, Amsterdam, 1986; see also Bryson, J. W.; Betz, S. F.; Lu, H. S.; Svich, D. J.; Zhau, H. X.; O'Neill, K. T.; De Grado, W. F. *Science* **1995**, *270*, 935; Tramontano, A.; Bianchi, E.; Venturini, S.; Martin, F.; Pessi, A.; Sollazzo, M. *J. Mol. Recogn.* **1994**, *7*, 9; Johnson, W. C., Jr. *Proteins* **1990**, *7*, 205.

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