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Stereoselective Synthesis of Conformationally Restricted Analogues of Aspartic and Glutamic Acids from Endocyclic Enecarbamates.

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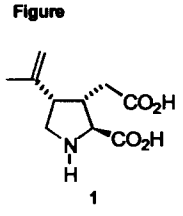
Abstract: The stereoselective synthesis of cyclic amino acids incorporating the core framework of aspartic acid and glutamic acids were accomplished from a common intermediate. Oxidative cleavage of an aza-bicyclic-dichlorocyclobutanone/pentanone with Me_2CuLi/Ac_2O followed by ozonolysis furnished the amino acid derivatives in good overall yields in a three-step sequence. This protocol was also applied to the synthesis of a *cis*-β-amino acid and to the enantioselective construction of a chimeric amino acid incorporating the basic skeleton of four different naturally occurring amino acids into a single structure.

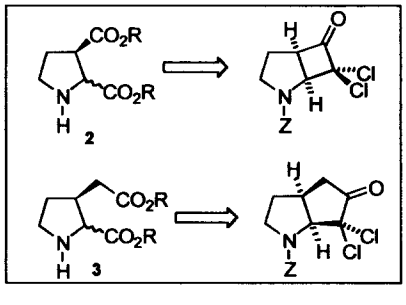
Conformationally restricted α-amino acids are important probes for molecular biology studies. The affinity of an α-amino acid or a peptide for its molecular receptor, as well as its agonist or antagonist activity, are strongly influenced by its conformational bias during molecular recognition.[1] For example, the neuroexcitatory activity of kainic acid **1** (Figure) is intrinsically associated to its action as a conformationally constrained glutamate, a well-known neurotransmitter.[2,3] Glutamate and the several glutamate receptor subtypes are implicated in normal neurophysiological processes such as learning and memory, and in pathological processes such as epilepsy, Alzheimer's and Huntington's diseases.[4] Additionally, the synthesis and use of α-amino acids incorporating structural characteristics of other amino acids (chimeras) have been attracting much attention as molecular probes, for they have proved to be useful substrates for determining the spatial requirements for receptor binding and physiological responses.[5] The remarkable physiological and pharmacological activities of these conformationally locked and chimeric α-amino acids have been the main impetus for research in this exciting and rapidly expanding research area.

In this communication we present our preliminary results concerning the stereoselective synthesis of cyclic and chimeric amino acids from endocyclic enecarbamates.[6] The preparation of aspartates **2** and glutamates **3** were envisioned (Figure) from an oxidative cleavage process on a 2-aza-dichlorocyclobutanone or cyclopentanone intermediate (obtainable by [2+2] cycloaddition of dichloroketene to a common five-membered endocyclic enecarbamate[7]), a process potentially applicable to the synthesis of other kainoid compounds as well.[2]

Figure



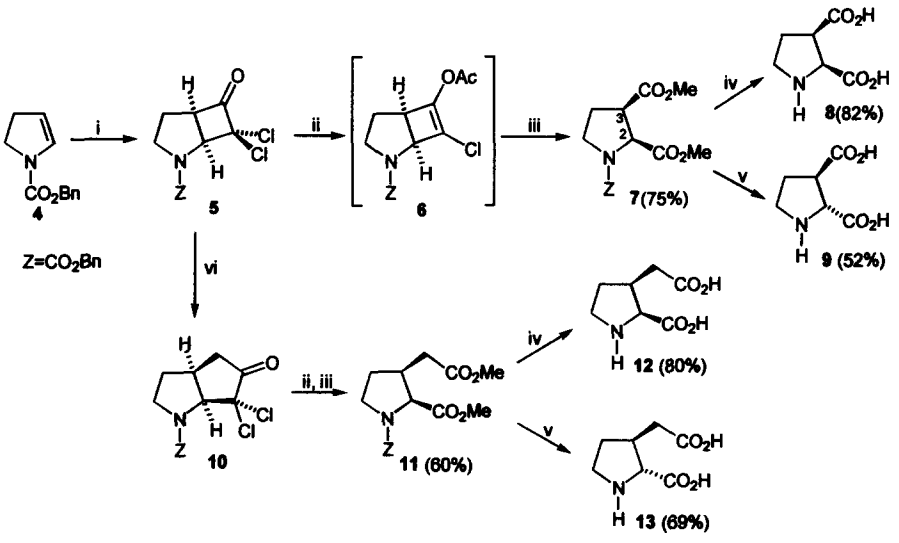
1



Positioning of the key C-C bonds α and β to the pyrrolidine nitrogen was accomplished by a [2+2] cycloaddition reaction of endocyclic enecarbamate **4** to dichloroketene to provide the aza-bicyclic dichlorocyclobutanone **5** as the only observable product in 87-92% isolated yield (Scheme 1). Dicarboxylation of the pyrrolidine ring was initially carried out using the following sequence adapted from the work of Greene and coworkers:[8] a) formation of an enolacetate **6** employing n-BuLi, followed by addition of acetic anhydride, and b) oxidative cleavage of the previously formed enolacetate with $RuCl_3/NaIO_4$. To facilitate isolation and purification, the crude product was esterified with diazomethane to produce the corresponding methyl esters. Application of this protocol to cyclobutanone **5** produced a mixture of (±)-*cis* and *trans* 2,3-dicarbomethoxy pyrrolidines **7** (~1:3 ratio), isolated in 15-25% yield from other unidentified products. The *trans*-**7** compound was probably formed from the *cis*-**7** derivative by epimerization during basic hydrolysis using Greene's protocol.

Much better results were obtained when we used Greene's alternative protocol that involved enolacetate formation with Me_2CuLi/Ac_2O.[9] We found it advantageous to use O_3 instead of $RuCl_3/NaIO_4$ and also to eliminate the recommended hydrolysis after oxidation. Enolacetate **6** was then formed from **5** with Me_2CuLi/Ac_2O and extracted with hexanes/Et_2O. The extracted enolacetate **6** was immediately cleaved with O_3 and the crude product esterified with CH_2N_2. This procedure permitted the stereoselective preparation of the *cis*-2,3-dicarbomethoxy pyrrolidine **7** ($J_{2,3}$= 8.4 Hz) in 75% overall yield from aza-dichlorocyclobutanone **5** without isolation of intermediates. Conversion of N-Cbz-diOMe α-amino acid **7** to the known *cis*-aspartic acid analogue **8** ($J_{2,3}$= 7 Hz) was effected in high overall yield (82%) as described in the literature (i: hydrogenolysis; ii: hydrolysis; iii: Dowex 50-X8).[10]

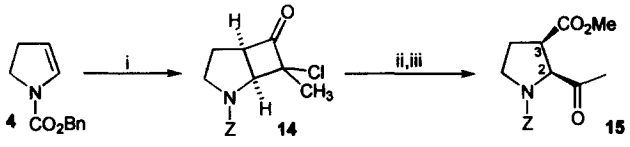
As the *trans* aspartic acid analogue **9** was also of interest, we carried out epimerization of the *cis*-diester **7** to the more stable *trans*-epimer by refluxing **7** with MeONa in MeOH for 5h, followed by hydrogenolysis and ion-exchange chromatography, to afford the known *trans*-aspartic acid analogue **9** ($J_{2,3}$= 5.2 Hz) in 52% yield.[10]



Scheme 1. Reagents and Conditions: i) $CHCl_2COCl$, Et_3N, hex. (92%); ii)a: Me_2CuLi, THF, -50 °C, 50 min; b: Ac_2O, -50 °C to rt, 3h; iii) a: O_3, CH_2Cl_2/MeOH, -78 °C; b: Me_2S, -78 °C to rt, 12h; c: CH_2N_2, MeOH/Et_2O, 0 °C, 15 min; iv) a: H_2, $Pd(OH)_2$, MeOH, rt, 12 h; b: HCl 6M, 70°C, 12h; c: Dowex 50-X8; v) a: MeOH, MeONa, reflux, 5h; b:H_2, $Pd(OH)_2$, MeOH, rt, 12 h; c: Dowex 50-X8; vi)CH_2N_2, MeOH, rt (80%)

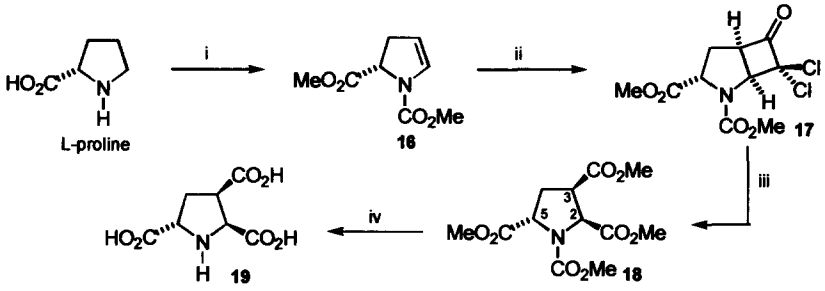
In order to prepare the glutamate derivatives, the aza-dichlorocyclobutanone **5** was ring-expanded with CH_2N_2 to give the dichlorocyclopentanone **10** in 80% yield with total regiocontrol (Scheme 1). Reaction conditions were somewhat critical at this stage (35-80% yield). However, consistently high yields of **10** (75-80%) were obtained using 1.5 equiv. of CH_2N_2 in the presence of MeOH (3%). Dichlorocyclopentanone **10** could be carried on to the next step without further purification (**10** is unstable towards column chromatography). Oxidative cleavage employing the same sequence used on dichlorocyclobutanone **5** (i: Me_2CuLi/Ac_2O; ii: O_3 then Me_2S; iii: CH_2N_2) furnished the *cis*-3-carbomethoxymethy-proline **11** ($J_{2,3}$= 8.8 Hz) in 60% yield. Hydrogenolysis of **11** followed by acidic hydrolysis cleanly afforded the *cis*-glutamic acid analogue **12** ($J_{2,3}$= 8.1 Hz) in 80% yield. Conversion of the *cis*-diester **11** to the *trans*-glutamic acid analogue was carried out by first effecting hydrogenolysis and then basic hydrolysis of the adduct to produce the *trans*-glutamic acid analogue **13** ($J_{2,3}$= 3.7 Hz)[10] in 69% yield.

The oxidative protocol described above was equally applicable to substrates containing only one chlorine atom in the cyclobutanone ring. To illustrate this point chloromethyl-aza-cyclobutanone **14** was prepared by [2+2] of chloromethylketene to enecarbamate **4** (85% yield)[7] and submitted to the oxidative cleavage sequence. The corresponding *cis*-α-acetyl-β-carbomethoxyl-pyrrolidine **15** ($J_{2,3}$= 8.5 Hz) was obtained in an overall yield of 66% from aza-cyclobutanone **14** (Scheme 2).



Scheme 2. Reagents and Conditions: i) $CH_3CHClCOCl$, Et_3N, hex., 40 °C(Me endo:exo; 5:1 85%); ii)a: Me_2CuLi, THF, -50 °C, 50 min; b: Ac_2O, -50 °C to rt, 3h; iii) a: O_3, CH_2Cl_2/MeOH -78 °C;b: Me_2S, -78 °C to rt, 12h; c: CH_2N_2, CH_2Cl_2/Et_2O, 0 °C, 10 min (66%)

Application of the above methodology to enantiomerically pure endocyclic enecarbamates derived from L-proline allowed the enantioselective preparation of a chimeric amino acid in which the structures of four different amino acids were embedded into a single molecular framework (Scheme 3). Enecarbamate **16** was prepared according to the protocol of Shono[11] (anodic oxidation of protected L-proline followed by elimination of methanol). [2+2] Cycloaddition of enecarbamate **16** to dichloroketene proceeded with high diastereofacial selectivity (~20:1) to provide the *anti* dichlorocyclobutanone **17** in 63% yield.[12] Remarkable at this stage was the stereocontrol exercised by the rather small carbomethoxy group at C-5 of the pyrrolidine nucleus, directing the ketene cycloaddition to the β-face of the enecarbamate double bond. The chimeric arrangement was created, in a stereoselective manner, by the enolacetate formation/oxidative cleavage/esterification described above. Thus, oxidative cleavage of **17** produced the triester chimera **18** ($J_{2,3}$= 8.4 Hz) in 60% yield, which after acid hydrolysis furnished the mixed α-amino acid **19** in 52% yield. Chimera **19** (**2R,3R,5S**) incorporates the structure of the naturally occurring amino acids proline, aspartic acid, glutamic acid and α-amino adipic within a single structure.



Scheme 3. Reagents and Conditions: i) ref. 11(45% overall from proline): ii) $CHCl_2COCl$, Et_3N, Hex. (63%); iii) a: Me_2CuLi, - 50°C THF, then addition of Ac_2O; b: O_3, CH_2Cl_2/CH_3OH, -78°C, then Me_2S; c: CH_2N_2, CH_3OH (60%); iv) HCl 6N, reflux, 17h (52%)

In conclusion, we describe herein a conceptually new approach for the construction of conformationally restricted amino acids that is also amenable to the synthesis of kainoid compounds. In addition, a direct and enantioselective synthesis of a new chimeric structure incorporating four different amino acids is presented. This latter compound could be of interest as a conformationally constrained neurotransmitter or as a conformationally restrained element in oligopeptide synthesis.

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11. Shono, T; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kamazawa, T.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697-6703. We recently developed an alternative methodology for the preparation of optically pure five-membered endocyclic enecarbamates starting from (S)-pyroglutamic acid. A full account of this work will be presented in due course.
12. **16**, $[\alpha]^{25}_D$= −139.0 (c 2.1, acetone); **17**, $[\alpha]^{25}_D$= −144.6 (c 3.4, CH_2Cl_2); **18**, $[\alpha]^{25}_D$= −37.2 (c 1.1, MeOH).

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