Pergamon

Tetrahedron Letters 40 (1999) 8701–8704

TETRAHEDRON LETTERS

New pyrazole containing bicarboxylic α-amino acids: mimics of the *cis* amide bond

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Received 15 July 1999; accepted 28 September 1999

Abstract

A series of novel optically active α-amino acids, containing a pyrazole ring, which can be regarded as building blocks for peptidomimetics, have been prepared starting from readily available α-amino acids. The synthetic strategy employed allows the regio- and stereoselective preparation of 1,3- or 1,5-substituted pyrazolyl rings. The pyrazole containing peptidomimetics can be considered as analogues of peptides with a *cis* amide bond.

Keywords: amino acids; amino acid derivatives; cycloadditions; pyrazoles.

Replacement of the peptide bond by surrogates to enhance metabolic stability and/or probe receptor specificity has become an increasingly important topic of research as the central biological role of peptides becomes more understood.[1] The presence of the *N*-methyl amino acid and proline residue in naturally occurring peptides causes *cis–trans* isomerization of amide bonds leading to conformational changes which may be important for their biological activity.[2] In several cases the quantity of *cis* isomer in aqueous solution has been correlated with the biological activity. Some authors have proposed heterocyclic ring systems[3] as peptide bond surrogates for the *cis* amide bond in order to lock the dipeptide analogue into a geometry corresponding to the *cis* isomer.

Recently, we have reported the preparation of heterocycle-containing optically active amino acids as chiral building blocks for the design of peptidomimetics with defined and predictable conformations:[4,5] in this context we decided to prepare new unnatural bis-carboxylic α-amino acids containing pyrazole moieties as possible substitutes for *cis* amide bonds and for the construction of conformationally constrained peptidic receptor probes.

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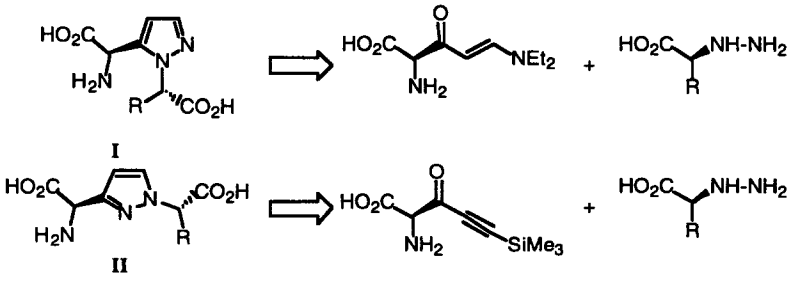
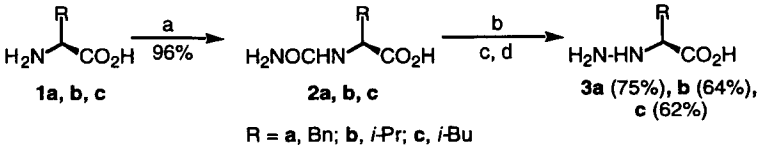
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01847-X



A reliable retrosynthetic analysis for compound **I** suggested the cyclocondensation of a suitable enamino ketone with an α-hydrazinoalkanoic acid whereas the preparation of **II** could start from a silylacetylenic ketone and the same α-hydrazinoalkanoic acid.[6]

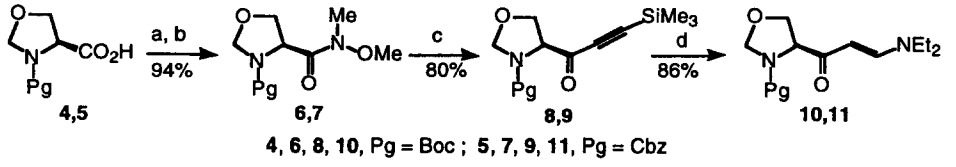
Enantiomerically pure α-hydrazino acids have been prepared by several methods,[7] that suffered from long and tedious reaction steps or were of low practical value in view of the very poor yields. We found it convenient to carry out the preparation of compounds **3** via Hoffman rearrangement[8] with NaOCl of the intermediate acid **2**, prepared from unprotected α-amino acid **1** by treatment with KOCN (Scheme 1). The reactions occurred under mild conditions and the α-hydrazino acid could be recovered in satisfactory yields (>60%) by simple lyophylisation of the aqueous solution, dissolving the residue in ethanol and successive salting out by slow addition of diethylamine.



Scheme 1. (a) KOCN, 60°C, 4 h (b) NaOCl 0.5N/KOH, 90°C, 2 h (c) toluene, NH_2–NH_2 aq, HCl, 80°C, 30 min (d) EtOH abs, Et_2NH

Our strategy was based on the possibility of building the amino acid functionality from L-serine into the corresponding *N*-protected (*S*)-4-carboxy-1,3-oxazolidine, also known as 4-oxaproline.[9] This seemed to be suitable as the chiral starting material since cleavage of the oxazolidine ring followed by oxidation should allow the formation of the amino acid functionality.

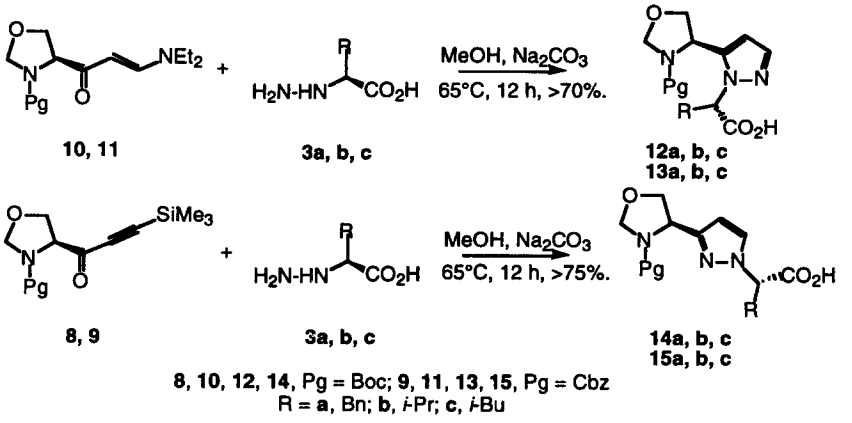
Compounds **4**, **5**, prepared quantitatively from L-serine, were converted into the corresponding Weinreb amides (**6**, **7**) through reaction with 2 equiv. of *N*,*O*-dimethylhydroxyl amine (94% yield), after treatment with ethyl chloroformate (Scheme 2). The synthesis of *N*-Boc (**8**) - and *N*-Cbz protected (*S*)-1-oxazolidin-4-yl-3-(trimethylsilanyl)-propynones (**9**) was performed by reacting compounds **6**, **7** with trimethylsilylethynyl magnesium bromide (80% yield).[4] Then, compounds **8**, **9** could be efficiently and quantitatively transformed to the corresponding (*S*)(*E*)-3-diethylamino-1-oxazolidin-4-yl-propenones (**10**, **11**) with diethylamine.[10]



Scheme 2. (a) $ClCO_2Et$, NMM, CH_2Cl_2, –20°C (b) HON(OMe)Me, 25°C (c) Me_3Si-C≡C-MgBr, Et_2O, 25°C (d) Et_2NH, EtOH, 25°C, 12 h

The successive cyclocondensations were carried out in methanol, at 65°C for 12 h, by reacting the α-hydrazino acid **3** with the enamino ketones **10**, **11** or the trimethylsilyl ketones **8**, **9** (Scheme 3). The

yields were good (>70%) and the pyrazolyl derivatives **12**, **13** and **14**, **15** could be recovered as pure compounds, simply by acidifying the reaction mixtures and extracting with EtOAc. The reactions were found to be highly regioselective and no trace of the isomeric pyrazolyl derivatives were detected.



Scheme 3.

In order to obtain the target compounds **I** and **II**, it appeared convenient to perform the cleavage of the oxazolidine ring without affecting the protection of the amino group. We have already found that the 2,2-dimethyl-3-*tert*-butoxycarbonyloxazolidine ring can be cleaved using *p*-toluenesulfonic acid (PTSA) in dry methanol at room temperature albeit in low conversion (25%).[5]

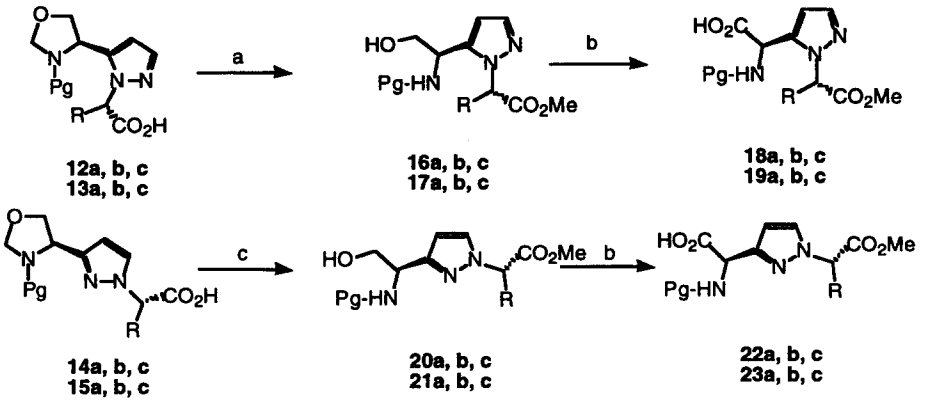
Unfortunately, the *N*-Boc pyrazolyl derivatives, **12** and **14**, were found to be resistant even after prolonged reflux and the only products we could recover were the corresponding methyl esters. The oxazolidine ring of these *N*-Boc protected compounds could be cleaved by $SOCl_2$ in anhydrous methanol at 65°C for 4 h (>60% conversion). In this case, however, we observed methylation of the carboxylic acid and complete deblocking of the *N*-Boc function. Nevertheless, further oxidation with Jones' reagent afforded quantitatively the unprotected amino acids **18** and **22**, which could be recovered in low yields from the reaction mixtures only by careful salting out.

The *N*-Cbz derivatives **13** and **15** were cleaved by PTSA in dry refluxing methanol with good conversions (>50%) to give methyl esters **17** and **21** directly that were recovered as pure compounds by simple acid-base work-up (Scheme 4): the unreacted compounds **13** and **15** could be recovered almost quantitatively and conveniently recycled to increase the conversion up to 90%. Subsequent oxidation using Jones' conditions afforded the *N*-Cbz protected α-amino acids **19** and **23** in almost quantitative yield.[11] The use of the *N*-Cbz protection is thus more convenient, as the pyrazole containing α-amino acids can be introduced directly into a peptidic framework.

In summary, a methodology for the preparation of a new class of optically active α-amino acids has been developed using an inexpensive chiral starting material: moreover, compound **II** can be compared to amino suberic acid while compounds **I** can be regarded as glutamic acid homologues.

Acknowledgements

This work was financially supported by MURST, Roma in the project 40%, Es. Fin. 97, Chimica dei Composti Organici di Interesse Biologico and by CNR, Roma, with the grant no. 98.01856.CT03.



12, **14**, Pg = Boc; **13**, **15**, **17**, **19**, **21**, **23**, Pg = Cbz; **16**, **18**, **20**, **22**, Pg = H; R = **a**, Bn; **b**, *i*-Pr; **c**, *i*-Bu

Scheme 4. (a) **12**: $SOCl_2$, MeOH, 65°C, 4h, >60%; **13**: PTSA, MeOH, reflux, 48 h, >90% (b) Jones' reagent, 0°C, >95% (c) **14**: $SOCl_2$, MeOH, 65°C, 4 h, >60%; **15**: PTSA, MeOH, reflux, 24 h, >90%

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11. All new compounds were fully characterized by ^1H and ^{13}C NMR analyses and gave satisfactory elemental analysis. As representative example: **23a**, ^1H NMR (300 MHz) ($CDCl_3$) δ: 3.64–3.69 (m, 2H), 3.81 (s, 3H), 5.04–5.10 (m, 1H), 5.14 (s, 2H), 5.19–5.29 (m, 1H), 6.98 (bs, 1H) 5.88 (s, 1H), 6.75–6.90 (m, 2H), 7.13–7.41 (m, 8H), 7.45 (s, 1H), 9.58 (bs, 1H); ^{13}C NMR (75.4 MHz) ($CDCl_3$) d: 173.5, 169.3, 166.6, 155.6, 149.5, 135.6, 134.2, 130.9, 128.7, 128.5, 128.3, 128.1, 127.4, 98.5, 79.2, 67.6, 51.6, 47.9, 33.1. Although the synthetic sequences adopted were known to be stereospecific, the absence of any racemization was verified by comparison of the ^1H NMR of the amino acids **19** and **23** with those of the corresponding diastereoisomers, prepared from D-amino acids, through the same synthetic sequences.