Pergamon

Tetrahedron Letters 39 (1998) 7159–7162

TETRAHEDRON LETTERS

A New Ligand α-Amino Acid: (*S*)-2-Amino-3-[1-(1,4,7-Triazacyclononane)]Propanoic Acid

Paola Rossi,[a] Fulvia Felluga,[a] and Paolo Scrimin*[b]

[a] *University of Trieste, Department of Chemical Sciences, Via Giorgieri, 1 - 34127 Trieste, Italy.*

[b] *University of Padova, Department of Organic Chemistry and CNR-CMRO, Via Marzolo, 1 - 35131 Padova, Italy*

Received 27 May 1998; accepted 20 July 1998

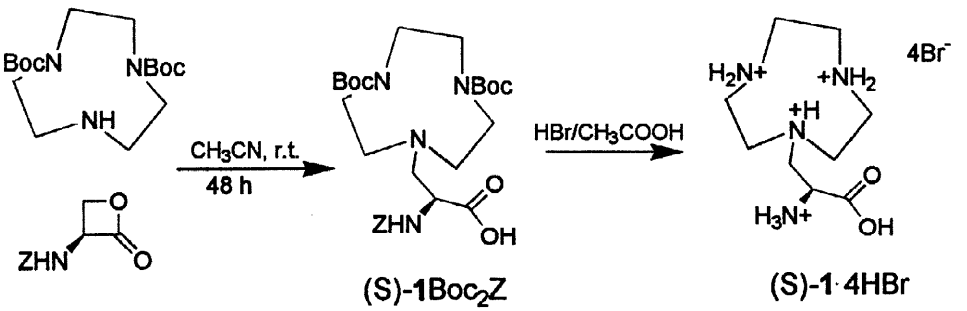
Abstract: The title amino acid was obtained by regiospecific ring-opening reaction of Boc-diprotected 1,4,7-triazacyclononane with (*S*)-2-benzyloxycarbonylamino-β-lactone (80% isolated yield) followed by deprotection. It strongly binds transition metal ions like Zn^{II} and Cu^{II} and can be incorporated in peptide sequences without affecting the metal ion affinity of the triazamacrocycle.

Recent developments in supramolecular chemistry point to the realization of highly organized systems to obtain synthetic catalysts and molecular devices.[1] In this context, the recognition of the peptide framework as an excellent scaffold to obtain supramolecular structures[2] has spurred increasing interest in the control of the conformation of peptides and in the synthesis of new amino acids. The final goal is the proper placement of functional groups in key relative positions to trigger, in the supramolecular architecture of the polypeptide, new functions. Among the possible functional groups, ligands for transition metal ions appear quite interesting also because they may be used in the construction of *de novo* metalloproteins[3] taking advantage of a larger library of amino acids than those provided by the natural pool. These new amino acids may allow larger binding constants, enhanced selectivity and may widen the range of coordination geometries to the metal centre. Several laboratories have recently reported contributions to the construction of this new library.[2,4] Yet, ligand-functionalized amino acids with large affinity constants for transition metal ions and at the same time a coordination sphere not fully saturated, are apparently missing. For this reason, we argued that a triazacyclononane-functionalized amino acid would be a particularly interesting target because: i) reported complexation constants[5] for the binding of Cu^{II} and Zn^{II} by this macrocycle are $10^{15.5}$ and $10^{11.6}$, respectively; ii) the three nitrogens do not saturate the coordination sphere of the metal ions allowing the coordination of a potentially useful reactant and/or a substrate. Furthermore, recent

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01532-9

reports by the laboratory of Burstyn have highlighted the effectiveness of the Cu^{II} complex of this macrocycle in the catalytic hydrolysis of phosphate diesters[6] and carboxamides as well.[7]

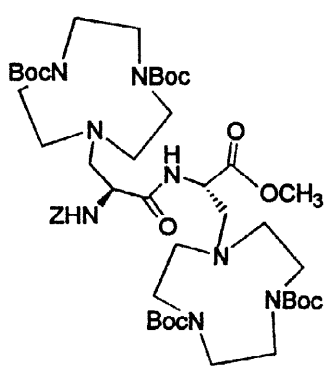
The synthetic route followed for triazacyclononane-functionalized amino acid **1** is reported in the Scheme.[8]



Scheme

Key steps are the Boc-protection of two nitrogens[9] of triazacyclononane and its subsequent reaction with the Z-protected (L)-serine β-lactone.[10] Although reactions of amines with this lactone are known[10] to afford a mixture of functionalized amino acid and amide of serine, corresponding to the attack of the amine to the β- or C=O-carbon, respectively, the present transformation occurs regiospecifically to afford the desired product in 80% isolated yield. This regiospecificity is likely connected to the bulkiness of diprotected triazacyclononane. Noteworthy, because the lactone opening does not involve attack at the chiral carbon and no racemization was observed under the reaction conditions, a single enantiomer of the new amino acid is obtained with this synthetic procedure.

The new amino acid binds strongly Cu^{II} and Zn^{II} ions with 1:1 stoichiometry as highlighted by the formation of an absorption band at 640 nm in the UV-Vis spectrum (Cu^{II}) or by the spectral changes in the ^{1}H-NMR spectrum in D_2O (Zn^{II}) (Figure).



2

AcAib-1Boc$_2$-Aib-Aib-1Boc$_2$-Aib-AibOH

3

Its potential application for the construction of functional peptides is demonstrated by its straightforward dimerization into dipeptide **2**[11] or its incorporation in longer peptide sequences. It

has been in fact incorporated *via* conventional solution synthesis in the Aib-containing heptapeptide **3**.[12] Peptides containing α,α-disubstituted amino acids,[13] because of the steric hindrance at the α carbon, are usually more difficult to synthesize[14] and, hence, we predict that its incorporation in peptide sequences containing conventional amino acids should not present

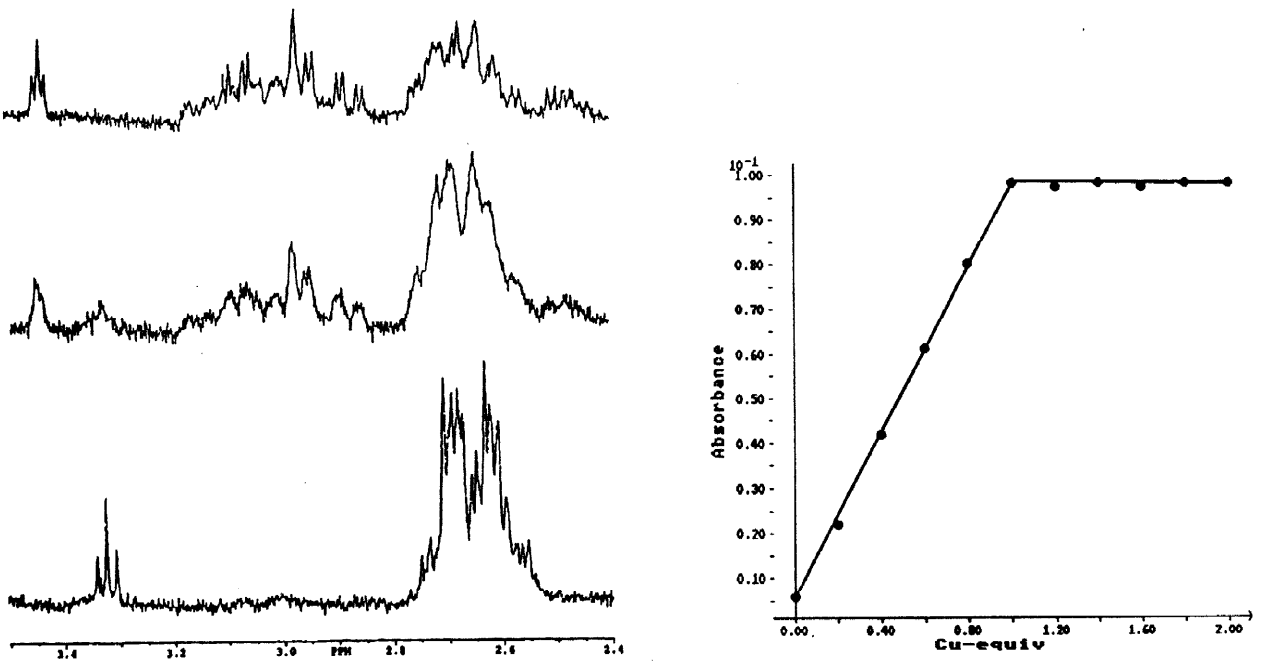


Figure. Spectral changes induced in the ^{1}H-NMR spectrum[15] of **1** (as free base) by complexation of Zn^{II} (left; from bottom to top Zn^{II}:**1** ratio is 0:1, 0.5:1, 1:1) and titration of **1** (as free base) with Cu^{II} as followed spectrophotometrically at 640 nm (right, [**1**]=1×10^{-3} M).

any particular problem. Preliminary results indicate that the affinity of the amino acid towards transition metal ions (Cu^{II} in particular) is not affected by its incorporation into peptide **3** (devoid of the protecting groups) so that its complexes can be studied as potential catalysts in hydrolytic reactions. Work in this direction is currently pursued in our laboratory.

Acknowledgements

The authors are indebted to Prof. G. Pitacco for helpful discussion. They also thank the Ministry of University, Scientific and Technological Research (MURST) and the National Research Council (CNR) for funding.

References and footnotes

* e-mail: scrimin@mail.chor.unipd.it

1. (a) Lehn, J. M. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89; (b) "*Comprehensive Supramolecular Chemistry*" Vol. 10, Reinhoudt, D. N. Ed., Pergamon, Elsevier Science Ltd., Oxford: 1996.

2. Voyer, N.; Lamothe, J. *Tetrahedron* **1995**, *51*, 9241.

3. (a) Handel, T. M.; Williams, S. A.; DeGrado, W. F. *Science* **1993**, *261*, 879; (b) Klemba, M.; Gardner, K. H.; Marino, S.; Clarke, N. D.; Regan, L. *Struct. Biol.* **1995**, *2*, 368.

4. (a) Torrado, A.; Imperiali, B. *J. Org. Chem.* **1996**, *61*, 8940; (b) Imperiali, B.; Prins, T. J.; Fisher, S. L. *J. Org. Chem.* **1993**, *58*, 1613; (c) Imperiali, B.; Fisher, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 8527; (d) Cheng, R. P.; Fisher, S. L.; Imperiali, B. *J. Am. Chem. Soc.* **1996**, 118, 11349; (e) Yamamoto, H.; Nishina, T.; Nishio, H; Yumoto, N.; Tatsu, Y.; Taguchi, T.; Yoshikawa, S. *Peptide Chem.* **1994**, *41*, 1993; (f) Voyer, N. *J. Am. Chem. Soc.* **1991**,*113*, 1818; (g) Mazaleyrat, J.-P.; Gaucher, A.; Goubard, Y.; Šavrada, J.; Wekselman, M. *Tetrahedron Lett.* **1997**, *38*, 2091.

5. Smith, R. M.; Martell, A. E. "*Critical Stability Constants*", Vol. 6, Plenum: New York, 1989.

6. Deal, K. A.; Burstyn, J. N. *Inorg. Chem.* **1996**, *35*, 2792.

7. Hegg, E. L.; Burstyn, J. N. *J. Am. Chem. Soc.* **1995**, *117*, 7015.

8. Synthetic procedure: to the lactone (300 mg, 1.38 mmol) dissolved in 20 mL of CH_3CN was added the diprotected triazacyclononane (500 mg, 1.52 mmol) and the solution kept at room temp. for 48 h with stirring. Subsequently the solvent was evaporated under reduced pressure and the resulting crude material eluted from a SiO_2 column (eluent: $CHCl_3/CH_3OH$ 9:1) to afford the protected amino acid in 80 % yield. ^{1}H-NMR (δ, $CDCl_3$): 7.29 (m, 5H), 5.85 (br 1H), 5.03 (s, 2H), 4.14 (br, 1H), 3.79-255 (m, 14H), 1.36 (s, 18H); $[\alpha]_D^{25}$ = +18.6 (c=1; $CHCl_3$). Elemental analysis, calculated for $C_{27}H_{42}N_4O_8$: C, 58.89%; H, 7.69%; N, 10.17%. Found: C, 58.31%; H, 7.49%; N, 9.69%. Deprotected **1**·4HBr was obtained quantitatively by treating the above material with HBr/CH_3COOH for 30 min and subsequent precipitation of the salt with Et_2O. ^{1}H-NMR (δ, D_2O/NaOD): 2.55-2.75 (m, 14 H) 3.33 (t, 1H). Evidence of the formation of the tetrahydrobromide salt was obtained from the ^{1}H-NMR spectrum in DMSO d_6. It shows two broad signals at δ 8.4 (3H) and 9.0 (5H) which we assign to the NH_3^+ and to the protons of the nitrogens of the ring, respectively.

9. For analogous partial protection of 1,5,9-triazacyclododecane see: Brandes, S.; Gras, C.; Denat, F.; Pallumbi, P.; Guillard, R. *Bull. Soc. Chim. Fr.* **1996**, *133*, 65.

10. (a) Arnold, L. D.; Kalantar, H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105; (b) Ratemi, E. S.; Vederas, J. C. *Tetrahedron Lett.* **1994**, *35*, 4921.

11. Peptide **2** synthesis: to a stirred solution of $1Boc_2Z$ (100 mg, 0.18 mmol) in 2 ml of distilled CH_2Cl_2 were added HOBt (24 mg, 0.18 mmol), EDC·HCl (40 mg, 0.20 mmol) and the stoichiometric amount of the methyl ester of $1Boc_2$ (Z deprotection was performed by catalytic hydrogenation in MeOH) in CH_2Cl_2. The mixture was stirred at room temp. 18 h, the pH was then adjusted to 8 with Et_3N and the solvent was eventually evaporated under reduced pressure. The resulting oil was dissolved in 50 ml of AcOEt, washed with 0.5M citric acid, H_2O and $NaHCO_3$. The organic phase gave, after evaporation of the solvent, a crude material that was eluted from a SiO_2 column (eluent: $CHCl_3/CH_3OH$ 95:5) to afford dipeptide **2** in 75% yield. ^{1}H-NMR (δ, $CDCl_3$): 7.32 (m, 5H); 5.07 (s, 2H); 4.71-4.04 (m, 2H); 3.64 (s, 3H); 3.60-2.40 (m, 28H); 1.38 (s, 36H).

12. Details of the synthesis of **3** are being published elsewhere. It has been fully characterized by ^{1}H-NMR, FT-IR and FAB-MS (m/z 1297 M^+, 1320 $M+Na^+$).

13. Polese, A.; Formaggio, F.; Crisma, M.; Valle, G.; Toniolo, C.; Bonora, G. M.; Broxterman, Q. B.; Kamphuis, J. *Chem. Eur. J.* **1996**, *2*, 1104.

14. Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268.

15. In D_2O/NaOD (pD>9). Incidentally we note that the exchange of Zn^{II} is slow on the NMR time scale. Such behavior is not unusual for Zn^{II} complexes in aqueous solution.