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Design and synthesis of a novel cyclo-β-tetrapeptide

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Abstract

N-Substituted tetralactams (cyclo-β-tetrapeptides) have been identified as potential molecular scaffolds by computer-aided design; compound **2**, arising from L-β-homophenylalanine, has been prepared as a model system and its structure elucidated by single crystal X-ray analysis and NMR spectroscopy. © 1999 Elsevier Science Ltd. All rights reserved.

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Even though natural products provide an excellent source of potential scaffolds[1] for molecular recognition and combinatorial techniques, there is a clear need for alternative systems which display similar properties whilst allowing for greater structural variation.[2] In this context we, as part of a collaborative effort,[3] have embarked on a project to generate new molecular catalysts. The adopted strategy involves a configurationally rigid, chiral scaffold with conveniently oriented functional handles for subsequent diversification.

Given our experience in macrolactam chemistry[4] we envisaged that a macrocycle, containing several amide bonds, might provide a suitably rigid framework, possessing pseudoaxially located functionalities and, if desired, a point of attachment to a solid support. Furthermore, such a system might also be amenable from standard peptide methodology. Thus, we evaluated a range of polyamide macrocycles derived from α-, β- and γ-amino acids by means of molecular mechanics,[5] exploring the effect of ring size and of the number, position and configuration of methyl groups (chosen as a simplified model for appendages). Most molecules generated in this way were found to be conformationally flexible and their methyl groups tended to be located in pseudoequatorial positions. We were gratified, however, to observe that the most stable conformer of (*S,S,S,S*)-tetralactam **1** possessed both rigidity and pseudoaxially located methyl groups on the nitrogen atoms and also resulted in a C_2-symmetrical structure (Fig. 1, a and b); intramolecular CO···HN hydrogen bonds were observed within **1** that may provide enhanced structural rigidity. Therefore, we assumed that other scaffolds related to **1** could show the same patterns. We report herein the synthesis and three-dimensional structure elucidation of a prototype, tetralactam **2** (drawn in Scheme 2), which may be seen as a tetramer of L-β-homophenylalanine (β-hPhe) and which, in comparison with **1**, contains *N*-allyl groups as latent sources of functionality, as well as solubility-enhancing phenyl groups.

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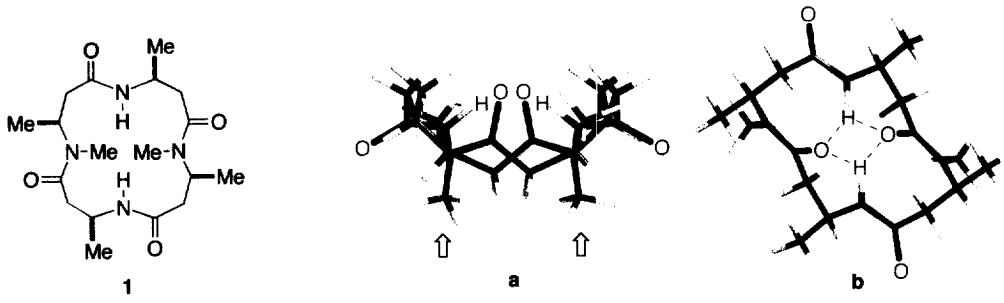
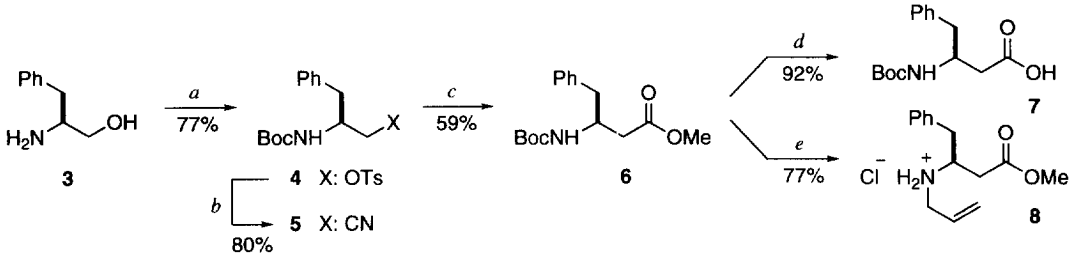


Figure 1. MM2 lowest energy conformer of (*S,S,S,S*)-1,9-di-*N*-methylcyclotetra-β-homoalanine (**1**). (a) Side view; arrows indicate the axially oriented *N*-Me. (b) Top view, showing hydrogen bonding.

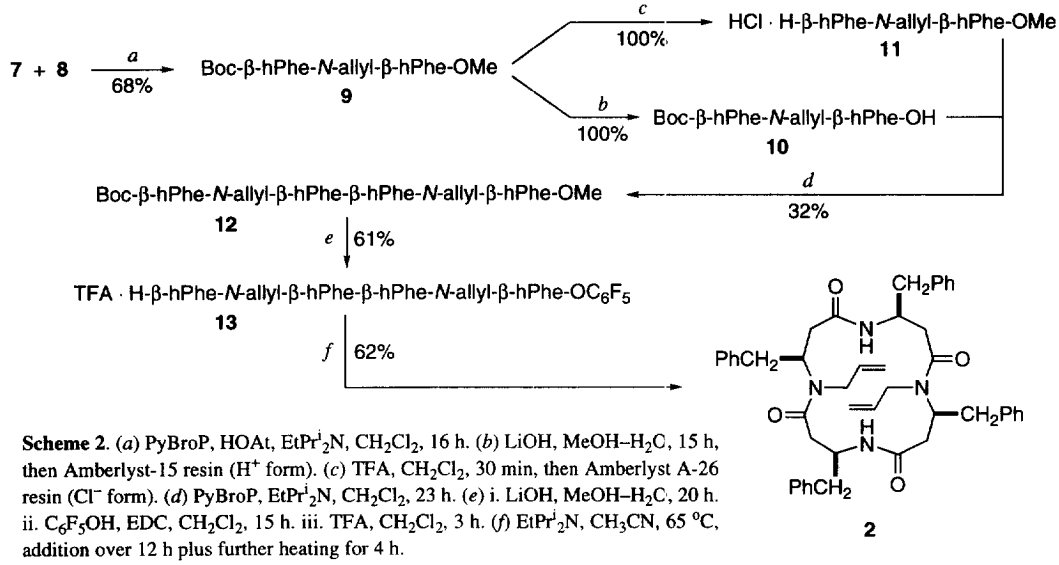
The synthesis of tetralactam **2** is summarised in Schemes 1 and 2. Starting from the easily accessible amino alcohol **3** derived from L-α-phenylalanine,[6] β-homophenylalanine derivatives **6** and **7** were readily prepared on a multigram scale by means of a high-yielding homologation procedure[7] through *O*-tosyl derivative **4** and nitrile **5**.[8] Allylation of **6** turned out to be troublesome, but eventually deprotonation with potassium hexamethyldisilylamide (KHMDS) in DMF at –20 °C and fast addition of allyl iodide, followed by Boc-deprotection with TFA and elution of the crude product through Amberlyst A-26 resin (Cl^- form), afforded pure **8** in 77% overall yield.



Scheme 1. (*a*) i. Boc_2O, THF–H_2O, 17 h. ii. TsCl, pyridine, $CHCl_3$, 22 h. (*b*) NaCN, DMF, 55 °C, 22 h. (*c*) i. H_2O_2, NaOH, MeOH–H_2O, 2 h. ii. $(MeO)_2CHNMe_2$, MeOH, 5 h. (*d*) LiOH, dioxan–H_2O, 20 h, then Amberlyst-15 resin (H^+ form). (*e*) i. KHMDS, DMF, –20 °C, 5 min, then allyl iodide, –20 °C, 30 min. ii. TFA, CH_2Cl_2, 30 min, then Amberlyst A-26 resin (Cl^- form).

Coupling of **7** and **8** using PyBroP–HOAt[9] provided the dipeptide **9** in 68% yield. Appropriate deprotections of **9** and coupling of the resultant products (**10** and **11**) gave the linear tetrapeptide **12** (32%) from which the active ester **13** was readily accessed. Finally, the tetralactam **2** was prepared, in good yield (62%), by slow addition of a 0.01 M solution of **13** in acetonitrile to a 0.003 M solution of $EtPr^i_2N$ (5 equiv.) in acetonitrile at 65 °C.[10] This highly convergent approach only requires seven synthetic steps from **7**[11] and very few chromatographical purifications. Its main advantage is that it may allow access to a large variety of scaffolds by the proper choice of the starting amino acids.

The C_2 symmetry of **2** was clearly demonstrated in solution ($CDCl_3$) by the presence of only half of all the possible peaks in the ^{13}C NMR spectrum. Furthermore, the ^1H NMR spectrum was surprisingly simple and well resolved, with respect to those of its linear precursors **12** and **13**, implying a highly ordered structure. In fact, successive ^1H NMR spectra, obtained by the slow, stepwise cooling of a sample to –70 °C, showed little change in the appearance and shift of the proton signals associated with the macrocyclic core, thus suggesting that the 16-membered ring is fixed in a single conformation.



Scheme 2. (*a*) PyBroP, HOAt, $EtPr^{i}_{2}N$, CH_2Cl_2, 16 h. (*b*) LiOH, MeOH–H_2C, 15 h, then Amberlyst-15 resin (H^+ form). (*c*) TFA, CH_2Cl_2, 30 min, then Amberlyst A-26 resin (Cl^- form). (*d*) PyBroP, $EtPr^{i}_{2}N$, CH_2Cl_2, 23 h. (*e*) i. LiOH, MeOH–H_2C, 20 h. ii. C_6F_5OH, EDC, CH_2Cl_2, 15 h. iii. TFA, CH_2Cl_2, 3 h. (*f*) $EtPr^{i}_{2}N$, CH_3CN, 65 °C, addition over 12 h plus further heating for 4 h.

X-Ray analysis[12] of a single crystal of **2** (Fig. 2), obtained by slow evaporation of a saturated solution of the tetralactam dissolved in cyclohexane, shows a unit cell containing two practically identical conformations of **2**. Their core tetralactam rings fit very well those obtained for **1** from molecular modelling calculations (compare Fig. 2 and Fig. 1). Moreover, the *N*-allyl substituents of **2** are oriented in the desired pseudoaxial manner (Fig. 2a). Two weak intramolecular C=O···H–N hydrogen bonds (but no intermolecular hydrogen bonds), with O–H distances of 218–222 pm, are also observed.

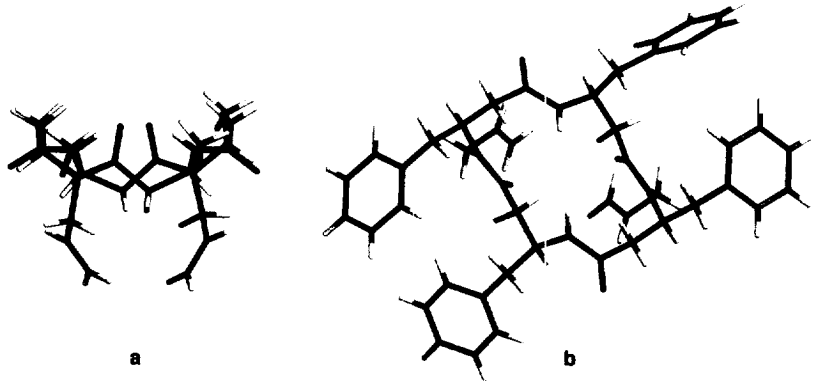


Figure 2. X-Ray crystal structure of compound **2**. (a) Side view, with phenyl groups omitted for clarity. (b) Top view.

In summary, we have synthesised tetralactam **2**, the prototype of a new family of scaffolds potentially useful for the generation of libraries of molecular catalysts;[13] the spectroscopic and physical data of **2** are in accordance with the structure predicted by the computer-aided design. Modification of the allyl chains of **2** and preparation of scaffold molecules based on different amino acids as precursors are the subject of current investigation in our laboratories.

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References and notes

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[1] Davis, A. P. *Chem. Soc. Rev.* **1993**, 243. Boyce, R.; Li, G.; Nestler, H. P.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1994**, *116*, 7955. Cheng, Y.; Suenaga, T.; Still, W. C. *J. Am. Chem. Soc.* **1996**, *118*, 1813.

[2] See, *e.g.*: Kocis, P.; Issakova, O.; Sepetov, N. F.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6623. Mink, D.; Mecozzi, S.; Rebek, J. *Tetrahedron Lett.* **1998**, *39*, 5709.

[3] *E.g.*: Paterson, I.; Scott, J. P. *Tetrahedron Lett.* **1997**, *38*, 7441. Gennari, C.; Ceccarelli, S.; Piarulli, U.; Montalbetti, C. A. G. N.; Jackson, R. F. W. *J. Org. Chem.* **1998**, *63*, 5312. Broderick, S.; Davis, A. P.; Williams, R. P. *Tetrahedron Lett.* **1998**, *39*, 6083. Gennari, C.; Ceccarelli, S.; Piarulli, U.; Aboutayab, K.; Donghi, M.; Paterson, I. *Tetrahedron* **1998**, *54*, 14999.

[4] Bartra, M.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1992**, *33*, 3669. Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671.

[5] Calculations have been carried on a SGI Power Indigo-2 workstation using both SYBYL (Clark, M.; Cramer III, R. D.; van Opdensch, N. *J. Comput. Chem.* **1989**, *10*, 982) and MM2 (for a review see: Burket, U.; Allinger, N. L. "Molecular Mechanics", ACS monograph 177, American Chemical Society, Washington D.C., 1982) force fields as implemented in Spartan 4.1/5.0 (Wavefunction, Inc.). Osawa algorithm (Osawa, E. J. *J. Am. Chem. Soc.* **1989**, *111*, 8950) was used for conformational search in cyclic systems.

[6] Meyers, A. I.; McKennon, M. J.; Drauz, K.; Schawrm, M. *J. Org. Chem.* **1993**, *58*, 3568.

[7] Kaseda, K.; Kikuchi, T.; Kibayashi, C. *Tetrahedron Lett.* **1989**, *30*, 4539.

[8] All new compounds have spectroscopical and analytical data consistent with the assigned structure.

[9] Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243. Also see: Coste, J.; Frérott, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437 (PyBroP). Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397 (HOAt).

[10] Seebach, D.; Matthews, J. L. *Helv. Chim. Acta.* **1997**, *80*, 173. Seebach, D.; Matthews, J. L. *J. Chem. Soc., Chem. Commun.* **1997**, 2015.

[11] This compound had been previously prepared according to the Arndt–Eistert procedure: Bankowski, K.; Misicka, A.; Barth, T.; Slaninova, J. *Collect. Czech. Chem. Commun.* **1989**, *54*, 2795. Ondetti, M. A.; Engel, S. L. *J. Med. Chem.* **1975**, *18*, 761.

[12] *Crystal data* for **2**: $C_{46}H_{52}N_4O_4$, M = 724.92; a = 10.6308(6), b = 19.1724(11), c = 19.7640(11) Å, β = 94.779(2)°, U = 4014.3(4) Å^3; monoclinic, space group $P2_1$, Z = 4; D_c = 1.199 g cm^{-3}; T = 160(2) K; colourless tablet, crystal dimensions, 0.66 × 0.59 × 0.32 mm; μ(Mo-Kα) = 0.077 mm^{-1}. *Data collection and processing:* Bruker SMART CCD area detector diffractometer; $2\Theta_{max}$ = 57.5°; graphite monochromated Mo-Kα radiation, λ = 0.71073 Å; ω rotation with narrow frames; 25758 reflections measured, 17581 independent reflections (R_{int} = 0.0184) all of which were included in the refinement; data corrected for Lorentz and polarisation effects. *Structure solution and refinement:* solution by direct methods, anisotropic refinement of all non-H atoms on F^2 by full-matrix least-squares to give: $R_w = \{\Sigma[w(F_o^2 - F_c^2)/\Sigma[w(F_o^2)^2]\}^{1/2}$ = 0.0849 (all data), conventional R = 0.0390 for 14669 reflections having $F_o^2 > 2\sigma(F_o^2)$, goodness of fit on F^2 values = 1.014 for 974 refined parameters. H-atoms were constrained. An extinction correction refined to 0.0026(3) and the final difference electron density map features were within the range –0.163 to 0.184 e Å^{-3}. Programs: *Bruker SMART* and *SAINT* for diffractometer control and frame integration (Bruker Analytical X-Ray Instruments, Madison, WI, 1994), *Bruker SHELXTL* for structure solution, refinement and molecular graphics (G. M. Sheldrick, SHELXTL manual, version 5, Bruker Analytical X-Ray Instruments, Madison, WI, 1994) and local programs.

[13] For very recent reviews, see: Balkenhohl, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288. Gennari, C.; Nestler, H. P.; Piarulli, U.; Salom, B. *Liebigs Ann./Recueil* **1997**, 637.