Pergamon

Tetrahedron Letters 43 (2002) 3499–3501

TETRAHEDRON LETTERS

Synthesis of benzyl (6*S*)-1,3-dichloro-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-*a*]pyrazine-6-carboxylic ester, a new conformationally constrained peptidomimetic derivative

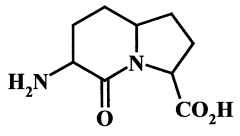
Philippe Gloanec,[a,*] Yolande Hervé,[b] Nathalie Brémand,[b] Jean-Pierre Lecouvé,[b] Fabienne Bréard[b] and Guillaume De Nanteuil[a]

[a]*Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France*
[b]*Oril Industries, 13 rue Auguste Desgenétais, 76210 Bolbec, France*

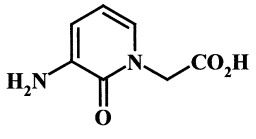
Accepted 21 March 2002

Abstract—We describe the synthesis of benzyl (6*S*)-1,3-dichloro-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-*a*]pyrazine-6-carboxylic ester, a new conformationally constrained peptidomimetic derivative. This compound is prepared in seven steps from (*S*)-pyroglutamic acid as starting material.

The design of peptidomimetic derivatives is currently an area of active investigation and has generated a considerable amount of work in the synthesis of high affinity and selective new therapeutic agents.[1] Conformationally constrained dipeptides analogs are expected to possess the same properties as their highly flexible peptidic counterparts, with the added advantages of increased metabolic stability and improved absorption properties. This can be effectively realized by the systematic replacement of backbone amide bonds by constrained elements such as a cyclic[2] or bicyclic lactam[3] **1** or heterocyclic isosteres[4] **2** in order to reduce the conformational flexibility;[5] (3-amino-2-oxopyridin-1(2*H*)-yl)acetic acid **2** was used to mimic the alanylproline sequence in the design of human leukocyte elastase inhibitors,[4] allowing the maintenance of the bioactive interactions as the original peptidic substrate.



1



2

Keywords: peptidomimetic; pyroglutamic acid; 4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-*a*]pyrazine.

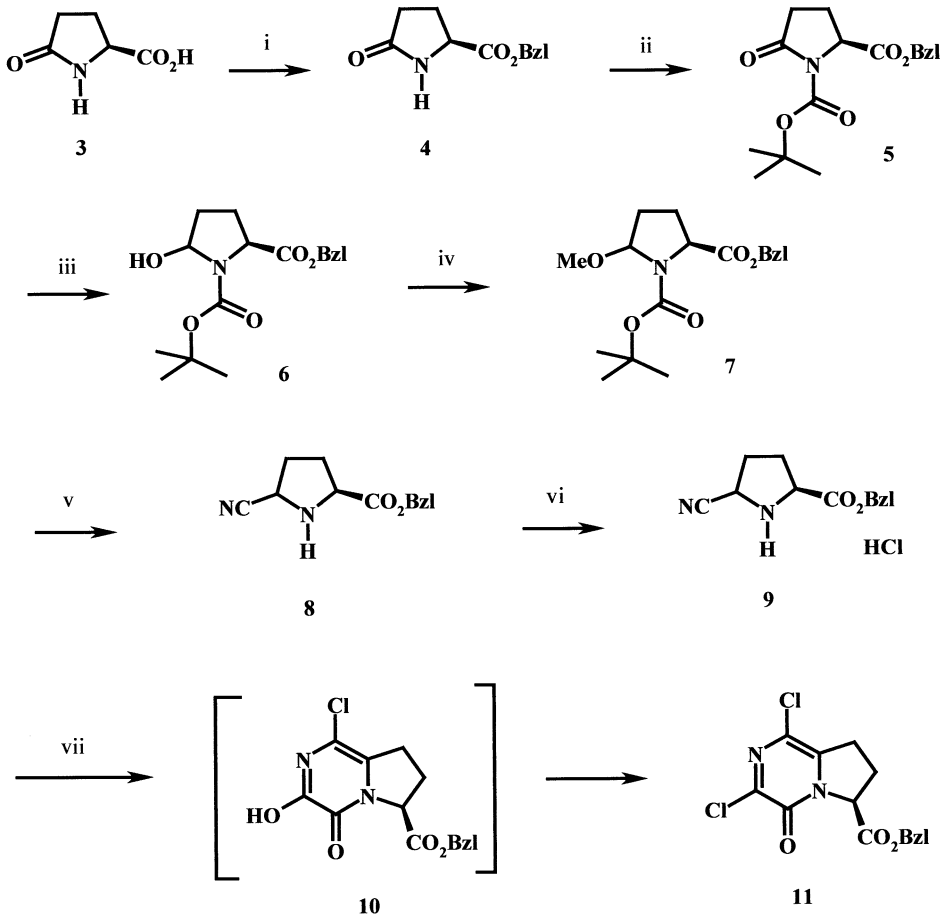
* Corresponding author. Tel.: 33.1.55.72.25.23; fax: 33.1.55.72.24.30; e-mail: philippe.gloanec@fr.netgrs.com

In this paper, we report our preliminary results in the design and synthesis of a novel peptidomimetic moiety, benzyl (6*S*)-1,3-dichloro-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-*a*]pyrazine-6-carboxylic ester **11**. Thus, the proline-containing ring of the bicyclic lactam **1** was combined with the insatured pattern of (3-amino-2-oxopyridin-1(2*H*)-yl)acetic acid **2**, to afford the novel heterobicyclic ester **11** that could be used as a potential dipeptide surrogate.

As shown in Scheme 1, the benzyl (6*S*)-1,3-dichloro-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic ester **11** was prepared from (*S*)-pyroglutamic acid in seven steps with a 22% overall yield.

The key intermediate in this synthesis was the aminonitrile **8**, obtained according to a modification of the preparation described by Langlois.[6] Commercially available (*S*)-pyroglutamic acid was treated with thionyl chloride in benzyl alcohol and a catalytic amount of DMF under standard conditions[7] to provide the benzyl ester **4** in good yield (90%). Protection of the intermediate lactam **4** as a *tert*-butyloxy carbamate was performed in dichloromethane in the presence of dimethylaminopyridine to give **5** in quantitative yield and without any racemization at the adjacent carbon atom. Regioselective reduction of compound **5** with DIBAL-H in THF at −78°C afforded α-hydroxy carba-

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00574-9



Scheme 1. *Reagents and conditions*: (i) $PhCH_2OH$, $SOCl_2$, DMF, rt, overnight, 90%; (ii) Boc_2O, DMAP, CH_2Cl_2, 0°C to rt, overnight, 98%; (iii) DIBAL-H, THF, –78°C, 70%; (iv) MeOH, TsOH, 98%; (v) TMSCN, $SnCl_4$, CH_2Cl_2, –40°C, 60%; (vi) 4 M HCl sol. in dioxane, AcOEt, 95%; (vii) oxalyl chloride, 1,2-dichlorobenzene, 65%.

mate **6** as a racemic mixture of diastereomers in 70% yield. The α-methoxy derivative **7** was then obtained quantitatively from **6** by treatment with a methanolic solution of *p*-toluene sulfonic acid. Compound **7** was further treated with trimethylsilylcyanide in the presence of tin tetrachloride in dichloromethane at –40°C, leading to the aminonitrile **8**. The mixture of two diastereomers was purified by silica gel chromatography (MERCK silica gel 60 230–400 mesh, CH_2Cl_2/AcOEt, 95:5) and chlorohydrated with 1.1 equiv. of a 4 M HCl–dioxane solution to provide the aminonitrile **9**. Treatment of the hydrochloride **9** with oxalyl chloride in 1,2-dichlorobenzene at room temperature[8] gave the intermediate benzyl (6*S*)-1-chloro-3-hydroxy-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic ester **10** which was not isolated. Reaction with a second equivalent of oxalyl chloride gave the desired compound **11**, which was obtained after crystallisation in methanol without any racemization in 65% yield.[9]

In summary, we have prepared the new benzyl (6*S*)-1,3-dichloro-4-oxo-4,6,7,8-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carboxylic ester as a potential substitute for a dipeptidic sequence. This novel peptidomimetic has recently been used for the design of enzyme inhibitors,[10] and work is ongoing to evaluate **11** in other biological active systems.

Acknowledgements

The authors are grateful to Sophie Cornet, Camille Poindron, Danièle Heno for their expert technical assistance and thank the Division of Analytical Chemistry for their helpful assistance.

References

1. (a) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699; (b) Adang, A. E. P.; Hermkens, P. H. H.; Lindres, J. T. M.; Ottenheijm, H. C. J.; Van Staveren, C. J. *Rec. Trav. Chim. Pays Bas* **1994**, *113*, 63; (c) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cokk, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusieski, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039; (d) Gianis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *33*, 1244.

2. (a) Tamura, S. Y.; Goldman, E. A.; Bergum, P. W.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2573; (b) Tamura, S. Y.; Goldman, E. A.; Brunck, T. K.; Ripka, W. C.; Semple, J. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 331.
3. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.
4. (a) Brown, F. J.; Andisik, D. W.; Bernstein, P. R.; Bryant, C. B.; Ceccarelli, C.; Damewood, J. R.; Edwards, P. D.; Earley, R. A.; Feeney, S.; Green, R. C.; Gomes, B.; Kosmider, B. J.; Krell, R. D.; Shaw, A.; Steelman, G. B.; Thomas, R. M.; Vacek, E. P.; Veale, C. A.; Tuthill, P. A.; Warner, P.; Williams, J. C.; Wolanin, D. J.; Woolson, S. A. *J. Med. Chem.* **1994**, *37*, 1259; (b) Sanderson, P. E. J.; Lyle, T. A.; Cutrona, K. J.; Dyer, D. L.; Dorsey, B. D.; McDonough, C. M.; Naylor-Olsen, A. M.; Chen, I.-W.; Chen, Z.; Cook, J. J.; Cooper, C. M.; Gardell, S. J.; Hare, T. R.; Krueger, J. A.; Lewis, S. D.; Lin, J. H.; Lucas, B. J., Jr.; Lyle, E. A.; Lynch, J. J., Jr.; Stranieri, M. T.; Vastag, K.; Yan, Y.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem.* **1998**, *41*, 4466.
5. Souers, A. J.; Ellman, J. A. *Tetrahedron* **2001**, *57*, 7431.
6. (a) Langlois, N.; Rojas, A.; Decavallas, O. *Tetrahedron: Asymmetry* **1996**, *7*, 1095; (b) Langlois, N.; Rojas, A. *Tetrahedron: Asymmetry* **1993**, *49*, 77.
7. Effenberger, F.; Muller, W.; Isak, H. *Chem. Ber.* **1987**, *120*, 45.
8. Vekemans, J.; Pollers-Wieers, C.; Hoornaert, G. *J. Heterocyclic Chem.* **1983**, *20*, 919.
9. Spectral data for **11**: $[\alpha]_D^{20} = -244$ ($c = 1$, $CHCl_3$); ee = 98% determined using chiral HPLC (Chiracel OD, EtOH, 240 nm); mp 101–102°C; IR (Nujol): 1753 and 1671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ ppm 2.40 (m, 1H, CH), 2.60 (m, 1H, CH), 3.15 (m, 2H, CH_2), 5.20 (dd, 1H, CH), 5.22 (m, 2H, CH_2), 7.35 (m, 5H, aromatic); elemental analysis: calcd for $C_{15}H_{12}Cl_2N_2O_3$: C, 53.12; H, 3.57; N, 8.26; Cl, 20.91. Found: C, 53.24; H, 3.67; N, 8.22; Cl, 20.62.
10. De Nanteuil, G.; Gloanec, P.; Verbeuren, T.; Rupin, A.; Vallez, M. O. Int. Pat. App. EP 1069132.