Synthesis of 1,3-dioxo-hexahydropyrido[1,2-*c*][1,3]diazepine carboxylates, a new bicyclic skeleton formed by ring expansion–RCM methodology†

Nicolai Dieltiens,[a] Diederica D. Claeys,[a] Bart Allaert,[b] Francis Verpoort[b] and Christian V. Stevens*[a]

Received (in Cambridge, UK) 20th June 2005, Accepted 14th July 2005
First published as an Advance Article on the web 4th August 2005
DOI: 10.1039/b508663a

A short and elegant synthetic pathway was developed for the synthesis of 1,3-dioxo-hexahydropyrido[1,2-*c*][1,3]diazepine carboxylates, a new 1,3-diazepan-2,4-dione containing bicyclic moiety, starting from pyroglutamate esters.

Ever since the importance of diazepines in psychotherapy was discovered in the early 1960s, this class of azaheterocyclic compounds has received a lot of attention from the scientific community. Besides their CNS depressant properties, a wide variety of derivatives possess activities ranging from anxiolytic[1] to anticonvulsant[2] and from antitumor[3] to herbicidal properties.[4] Very recently, 1,4-diazepan-2,5-diones were disclosed as novel inhibitors of LFA-1 (lymphocyte function-associated antigen-1).[5] Among the different classes of diazepines, the 1,3-diazepines have been studied to a minor extent although their derivatives show some interesting activities too, *i.e.* inhibition of the HIV-1 protease,[6,7] adenosine deaminase and guanase.[8] 1,3-Diazepan-2,4-diones, or perhydro-1,3-diazepine-2,4-diones, however, are rare and no straightforward synthetic method for their preparation existed until recently we discovered that this interesting skeleton can be prepared in one step by intramolecular transamidation of pyroglutamates after reaction with isocyanates.[9] During our ongoing research to use ring-closing metathesis for the construction of agrochemically and pharmaceutically interesting azaheterocyclic skeletons,[10] we wanted to evaluate the possibility of using RCM for the construction of hexahydropyridodiazepines, because most of the bioactive diazepines contain one or more fused rings in order to reduce the flexibility of the 7-membered ring. This would produce a new interesting heterocyclic skeleton **1** (Fig. 1), since very similar skeletons are described in the literature with very promising properties.

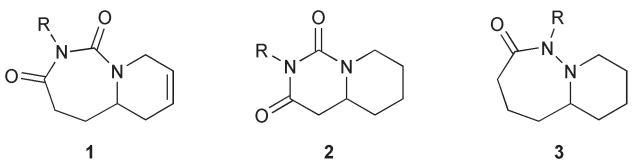


Fig. 1

The six-membered analogue **2**, for example, is a crucial part of a variety of compounds that are CCK (cholecystokinin) receptor antagonists,[11] ligands for 5-HT (5-hydroxytryptamine) receptors,[12] antibacterial agents,[13] antiarrhythmics[14] and herbicides.[15] Derivatives containing the diazepinone core **3** are patented as inhibitors of neutral endopeptidase and angiotensin converting enzyme.[16]

Our strategy to synthesise this heterocyclic skeleton **1**, started from a pyroglutamate ester **4** (Fig. 2). The first step is functionalisation at the C2 position **5**. Carbamoylation and immediate ring expansion would provide the seven-membered motif **6**. Subsequent *N*-alkylation **7** and RCM would provide the envisaged compounds **8**. This strategy provides the possibility of introducing a variety of substituents at four positions and thus would be ideal to synthesise a library of highly functionalised molecules.

Although alkylation of pyroglutamates at the C2 position has been described before,[17] this method is rather impractical with the need for stringent time and temperature control. It was found that excellent results can be obtained when a mixture of the pyroglutamate and the electrophile is treated with 2.1 equivalents of LiHMDS at −40 °C (Scheme 1). When using several equivalents of electrophile, no *N*-alkylation was observed. This methodology, however, cannot be followed if base-sensitive electrophiles are used (*e.g.* in the case of **5e** and **5f**). When using the benzyl ester, however, small amounts of benzyl alcohol were formed caused by fragmentation of the ester.[18] Therefore, all subsequent reactions were carried out on the ethyl ester.

Next the ring expansion was performed with different isocyanates (Scheme 2). In almost all cases, small amounts of carbamoyllactam **9** were formed together with the desired

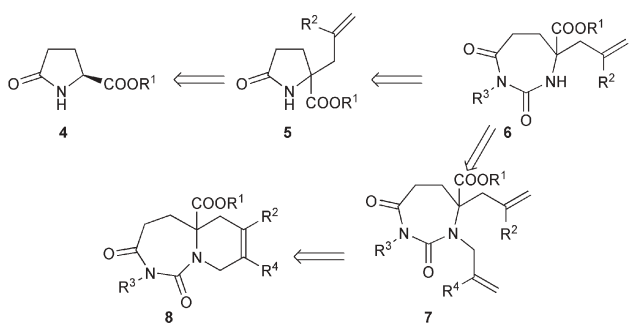
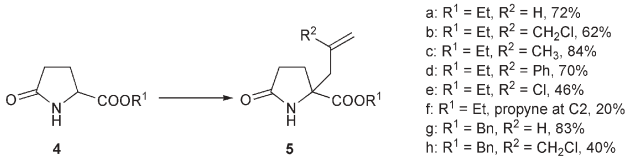


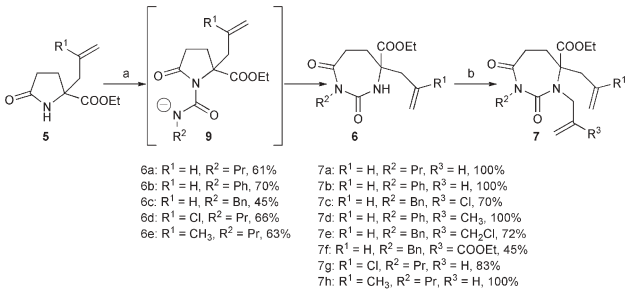
Fig. 2 Retrosynthetic analysis of bicyclic skeleton **8**.

[a]*Research group SynBioC, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000, Ghent, Belgium. E-mail: chris.stevens@ugent.be; Fax: +32-9-2646243; Tel: +32-9-2645957*
[b]*Division of Organometallics and Catalysis, Department of Inorganic and Physical Chemistry, Ghent University, Krijgslaan 281 (S-3), B-9000, Ghent, Belgium*

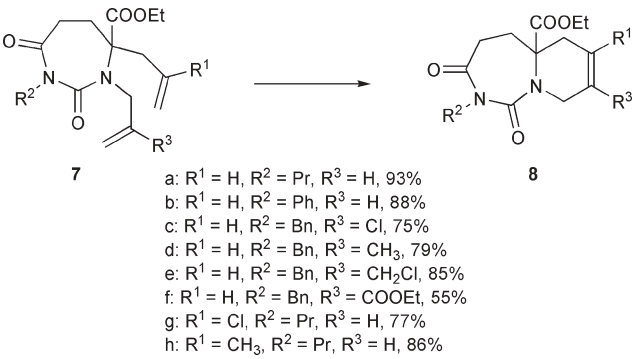
† Electronic supplementary information (ESI) available: experimental section, complete spectral characterisation of all compounds and copies of carbon spectra of the end compounds. See http://dx.doi.org/10.1039/b508663a



Scheme 1 *Reagents and conditions*: 4 equiv. electrophile, 2.1 equiv. LiHMDS, THF, 30 min at −40 °C then 2 h at rt.



Scheme 2 *Reagents and conditions*: (a) R^2NCO, NaH, THF, rt; (b) electrophile, K_2CO_3, acetone, reflux.



Scheme 3 *Reagents and conditions*: for entries a, b, d, e and h: 5% Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 2 h; for entry f: 5% Hoveyda–Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 2 h; for entries c and g: 5% Grubbs' 2nd generation catalyst, benzene, reflux, 14 h.

7-membered ring **6** thus requiring purification. It was observed that bulky R^1 substituents (*e.g.* phenyl, morpholinomethyl) prevent the pyroglutamate from reacting with the isocyanate even under more drastic conditions (reflux in DMF). In these cases only unreacted starting material could be recovered.

Also compound **5f**, with a propyne substituent at C2, gave a mixture of compounds upon reaction with isocyanates and was therefore not further used. The 1,4-functionalised 1,3-diazepan-2,4-diones **6** obtained in this fashion proved to be rather poor nucleophiles. Treatment with strong bases did not lead to alkylation but resulted in partial decomposition of the starting material. The only way to alkylate these intermediates at N3 in good yield was to reflux them with 2 equivalents of electrophile and 5 equivalents of finely ground K_2CO_3 in acetone for several days (Scheme 2). Finally, ring-closing metathesis on substrates **7** provided the envisaged bicyclic structures **8** in excellent yield (Scheme 3).

The second generation Grubbs' and Hoveyda–Grubbs' catalysts provide the possibility of performing RCM on a variety of substrates with different substituents on the double bond. Substrates with a vinylic[19] or allylic chloride (**8c**, **8e**, **8g**) or an extra ester-functionality (**8f**) thus provide the possibility of further functionalisation.

In short, we have developed an efficient four step protocol for the synthesis of highly functionalised 1,3-dioxo-hexahydropyrido-[1,2-*c*][1,3]diazepine carboxylates, a new bicyclic skeleton which allows further functionalisation.

The authors thank the BOF (Bijzonder Onderzoeksfonds Universiteit Gent, Research Fund of Ghent University) for financial support of this research.

Notes and references

1 W. B. Wright, H. J. Brabander, E. N. Greenblatt, I. P. Day and R. A. Hardy, *J. Med. Chem.*, 1978, **21**, 1087.
2 G. De Martino, S. Massa and F. Corelli, *Eur. J. Med. Chem.-Chim. Ther.*, 1983, **18**, 347.
3 G. B. Jones, C. L. Davey, T. C. Jenkins, A. Kamal, G. Kneale, S. Neidle, G. D. Webster and D. E. Thurston, *Anti-cancer Drug Des.*, 1990, **5**, 249.
4 G. M. Karp, M. C. Manfredi, M. A. Guaciaro, C. L. Ortlip, P. Marc and I. T. Szamosi, *J. Agric. Food Chem.*, 1997, **45**, 493.
5 S. Wattanasin, J. Kallen, S. Myers, Q. Guo, M. Sabio, C. Ehrhardt, R. Albert, U. Hommel, G. Weckbecker, K. Welzenbach and G. Weitz-Schmidt, *Bioorg. Med. Chem. Lett.*, 2005, 1217.
6 P. Y. Lam, P. K. Jadhav, C. J. Eyermann, C. N. Hodge, Y. Ru, L. T. Bacheler, J. L. Meek, M. J. Otto, M. M. Rayner, Y. N. Wong, C. H. Chang, P. C. Wever, D. A. Jackson, T. R. Sharpe and S. Erickson-Vittanen, *Science*, 1994, **263**, 380.
7 For a recent discussion on privileged skeletons for HIV-protease inhibitors see: E. Specker, J. Böttcher, H. Lilie, A. Heine, A. Schoop, G. Müller, N. Griebenow and G. Klebe, *Angew. Chem., Int. Ed.*, 2005, **44**, 2.
8 L. Wang and R. S. Hosmane, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 2893.
9 C. V. Stevens, N. Dieltiens and D. D. Claeys, *Org. Lett.*, 2005, **7**, 1117.
10 N. Dieltiens, C. V. Stevens, D. De Vos, B. Allaert, R. Drozdzak and F. Verpoort, *Tetrahedron Lett.*, 2004, **45**, 8995; N. Dieltiens, C. V. Stevens, B. Allaert and F. Verpoort, *ARKIVOC*, 2005, **I**, 92. For a recent review on RCM see: A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3012. Recent articles concerning the use of RCM for the synthesis of azaheterocycles: T. J. Donohoe, A. J. Orr, K. Gosby and M. Bingham, *Eur. J. Org. Chem.*, 2005, **10**, 1969; S. Varray, R. Lazaro, J. Martinez and F. Lamaty, *Eur. J. Org. Chem.*, 2002, **14**, 2308. For a recent review on the use of RCM for the synthesis of azaheterocycles see: A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199.
11 S. Ballaz, A. Barber, A. Fortuño, J. Del Rio, M. Martin-Martinez, I. Gomez-Monterrey, R. Herranz, R. Gonzalez-Muñiz and M. T. Garcia-Lopez, *Br. J. Pharmacol.*, 1997, **121**, 759; M. Latorre, J. M. Bartolomé-Nebreda, M. T. Garcia-Lopez, R. Gonzalez-Muñiz, R. Herranz, J. Del Rio and E. Cenarruzabeitia, *Pharmacology*, 2004, **72**, 68; P. Munoz-Ruiz, M. T. Garcia-Lopez, E. Cenarruzabeitia, J. Del Rio, M. Dufresne, M. Foucaud, D. Fourmy and R. Herranz, *J. Med. Chem.*, 2004, **47**, 5318 (and references cited therein).
12 F. Herold, J. Kleps, I. Wolska and G. Nowak, *Il Farmaco*, 2002, **57**, 959.
13 E. L. Ellsworth, H. D. H. Showalter, K. M. Hutchings and D. Q. Nguyen, *PCT Int. Appl.*, 2002, CAN 138:14071.
14 K. W. Fowler and R. J. Chorvat, *US Pat.*, 1987, CAN 107:176063.
15 M. Schaefer and K. Drauz, *Ger. Offen.*, 1994, CAN 120:270444.
16 D. E. Ryono and C. Q. Sun, *Eur. Pat. Appl.*, 1996, CAN 126:131476.
17 G. Guillena, I. Mico, C. Najera, J. Ezquerra and C. Pedregal, *An. Quim., Int. Ed.*, 1996, **92**, 362.
18 The fragmentation of pyroglutamates under basic conditions has been observed by us before: N. Dieltiens, C. V. Stevens, K. G. R. Masschelein and T. Rammeloo, *Tetrahedron*, 2005, **61**, 6749.
19 For the first report on RCM on substrates with a vinylic chloride see: W. Chao and S. Weinreb, *Org. Lett.*, 2003, **5**, 2505.

