Tetrahedron Letters 53 (2012) 1029–1032

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A route to selective functionalization of polyhydroxypyrrolidines

Carlos A. D. Sousa [a], Fabio Rizzo-Aguiar [a], M. Luísa C. Vale [a], Xerardo García-Mera [b], Olga Caamaño [b], José E. Rodríguez-Borges [a,*]

[a] Centro de Investigação em Química, Department of Chemistry and Biochemistry, Faculty of Science, University of Porto, Rua do Campo Alegre 687, 4169-007 Porto, Portugal
[b] Departamento de Química Orgánica, Facultade de Farmacia, Universidade de Santiago de Compostela, E-15782 Santiago de Compostela, Spain

ARTICLE INFO

Article history:
Received 2 November 2011
Revised 5 December 2011
Accepted 9 December 2011
Available online 16 December 2011

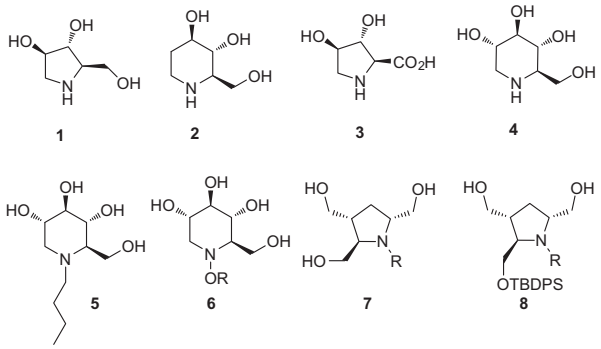
Keywords:
Polyhydroxypyrrolidines
Orthogonal protection
Selective functionalization
Azasugar

ABSTRACT

A route to selective functionalization of polyhydroxypyrrolidines is described. The method is based on orthogonal protection/deprotection along the process of synthesis of the referred pyrrolidines, which consist in hydroxylation of the double bond of 2-azabicyclo[2.2.1]hept-5-enes followed by its oxidative cleavage and in situ reduction of the intermediate dialdehyde. The synthesis of a novel *N*-hydroxypyrrolidine is also described.

Currently, the synthesis of iminosugars, also called azasugars, is an important and active field in synthetic organic chemistry.[1] Due to their structural resemblance to sugars and the consequent ability to act as glycosidase inhibitors,[2] these molecules (polyhydroxylated pyrrolidines/piperidines) often show potential in biological functions mediated by carbohydrates. In fact, these 'glycomimetics' have shown application in the control of diabetes,[3] Gaucher's disease,[4] cancer[3c,5] and viral infections (including influenza)[3c,6] or HIV.[7] In particular, DAB 1 (**1**), fagomine (**2**), and (2*S*,3*R*,4*R*)-3,4-dihydroxyproline (**3**) have been screened as potential inhibitors of HIV replication.[6d,e] 1-Deoxynojirimycin (**4**) has proved to be a powerful inhibitor of α-glycosidases[8]; and its *N*-alkylated form is used to treat Gaucher's disease (Migustat (**5**)).[4e] Some *O*-alkylated *N*-hydroxypiperidines (**6**) have also been described as active against glycosidases.[9]

In this context, we have previously reported the synthesis of polyhydroxymethylpyrrolidines **7** and **8**.[10] Herein we describe a route to the selective functionalization of the hydroxyl groups of this class of compounds, including novel polyhydroxymethyl *N*-hydroxypyrrolidines, whose synthesis is also described.



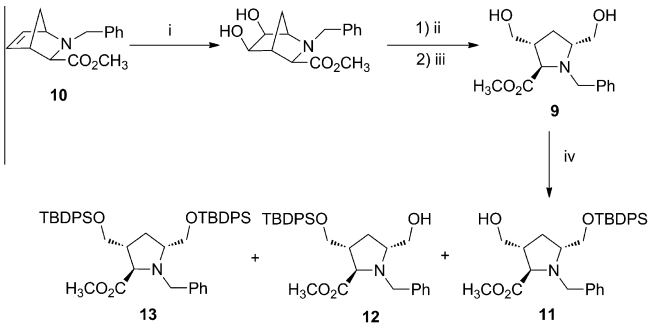
Selective protection of the hydroxyl groups of prolinate **9**, prepared from azabicycle **10** (*exo* isomer) by hydroxylation of the double bond and subsequent oxidative cleavage and in situ reduction of the intermediate dialdehyde,[10] using *tert*-butylchlorodiphenylsilane was attempted (Scheme 1). However, the addition of equimolar amounts of *tert*-butylchlorodiphenylsilane resulted in a mixture of monoprotected pyrrolidines **11** and **12** (yield = 45%; ratio 1:3) and diprotected pyrrolidine **13**.[11]

The absolute configuration of compounds **11** and **12** was unequivocally determined from crystallographic data of X-ray diffraction of the 3,5-dinitrobenzoylderivative of the isolated major monosilylated pyrrolidine **12** (Fig. 1).[11]

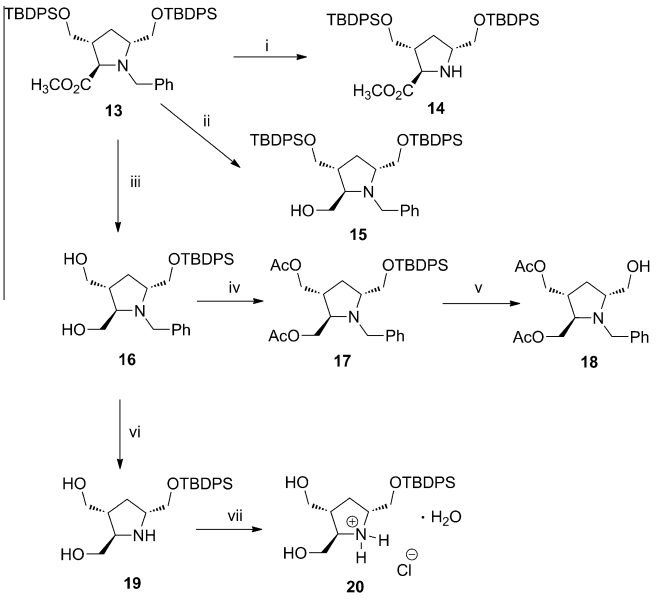
Although compounds **11** and **12** can be isolated by column chromatography, this method is not effective for the selective protection of the hydroxyl groups of compound **9**, particularly if we aim to

* Corresponding author. Tel.: +351 220402564; fax: +351 220402659.
E-mail address: jrborges@fc.up.pt (J.E. Rodríguez-Borges).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.037



Scheme 1. Reagents and conditions: (i) OsO_4/*N*-methylmorpholine *N*-oxide, dioxane/acetone/H_2O, rt, 12 h (90%); (ii) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, 30 min; (iii) $NaBH_4$, MeOH, 30 min (ii + iii, 84%); (iv) $ClSi^tBuPh_2$, Et_3N, DMAP, CH_2Cl_2, 12 h, 0 °C [**11**, 11%; **12**, 34%, **13**, 15%].



Scheme 2. Reagents and conditions: (i) H_2 6 bar, Pd/C 10%, HCl/MeOH, 10 days (74%); (ii) $BH_3{\cdot}SMe_2$ (5 M in Et_2O), 75 °C, 48 h (40%); (iii) $LiAlH_4$, Et_2O (89%); (iv) AcCl, Et_3N, DMAP, CH_2Cl_2, 24 h, 0 °C (70%); (v)TBAF/H_2O, acetone, 20 h (83%); (vi) $H_2/Pd(OH)_2$ 10% in MeOH, 40 h (70%); (vii) MeOH/H_2O/HCl/CH_2Cl_2 (slow evaporation).

obtain compound **11**. On the other hand, disilylated methyl prolinate **13** could readily be obtained in an 89% yield by using twice the equimolar amount of *tert*-butylchlorodiphenylsilane. Further application of a selective protection/deprotection methodology to compound **13**, yielded pyrrolidines **14**–**18** (Scheme 2), thus providing the possibility of regioselective functionalization at positions 1, 2, 3, and 5 of the (2*R*,3*R*,5*R*)-*tris*(hydroxymethyl)pyrrolidine.

N-debenzylation of **13** to afford **14** was accomplished by hydrogenolysis. Reduction of the ester group of **13** with borane dimethyl sulfide afforded compound **15**, whereas treatment of **13** with lithium aluminum hydride led to concomitant desilylation at position 3, yielding compound **16**. The structure of **16** was unequivocally established by X-ray crystallography of the monohydrated chloride **20** (Fig. 2).[12] *O*-acetylation of **16** followed by *O*-desilylation afforded compound **18**.

The *endo* stereoisomer of azabicycle **10** (**21**) was submitted to the same process of hydroxylation of the double bond described before, affording compound **22**; oxidative cleavage of **22** followed by in situ reduction of the intermediate dialdehyde afforded azabicycle **23** in a 13% overall yield (Scheme 3).[13] Subsequent protection of the hydroxyl group with *tert*-butylchlorodiphenylsilane, followed by *N*-debenzylation afforded compound **25**, which is suitable for *N*-functionalization.

In what concerns *N*-hydroxypyrrolidines, only a few reports of multi-step syntheses were found in the literature.[14] *N*-hydroxypyrrolidines can be obtained by a similar methodology as described above, starting from the *exo* stereoisomer of the *N*-hydroxy-azabicycle **26** (Scheme 4).[15] After protection of the hydroxyl group of **26** using *tert*-butylchlorodiphenylsilane, the resulting bicycle **27** was submitted to di-hydroxylation followed by oxidative cleavage and in situ reduction, affording pyrrolidine **29**.

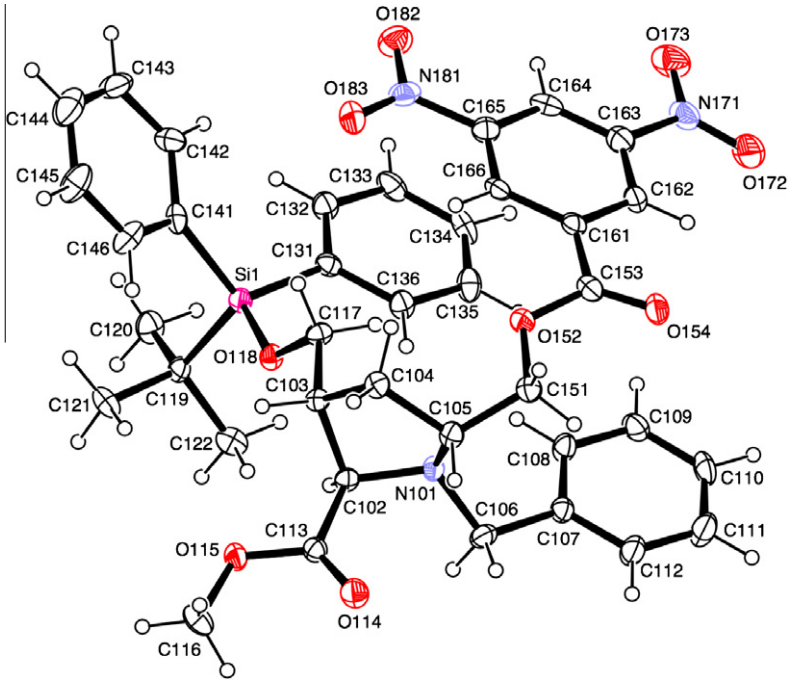


Figure 1. X-ray single crystal structure of the 1,3-dinitrobenzoyl derivative of **12**.

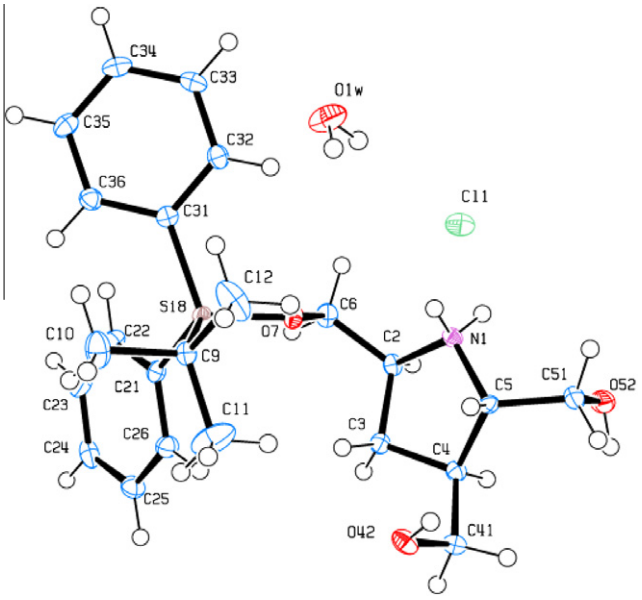
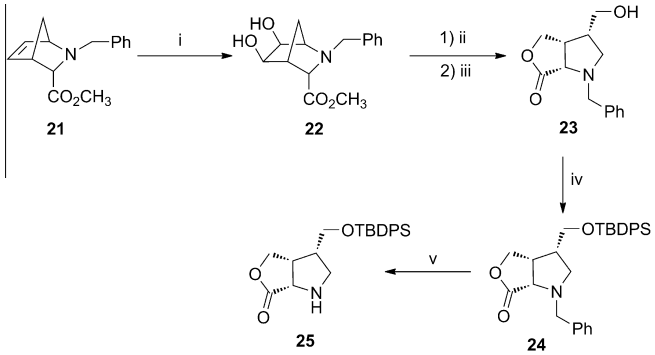
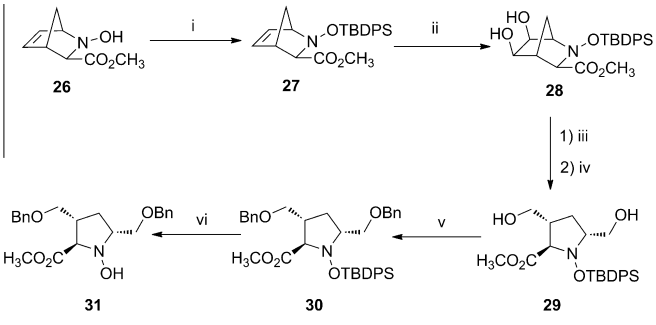


Figure 2. X-ray single crystal structure of **20**.



Scheme 3. Reagents and conditions: (i) OsO_4/*N*-methylmorpholine *N*-oxide, dioxane/acetone/H_2O, rt, 7 h (32%); (ii) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, 2 h; (iii) $NaBH_4$, MeOH, 2H (ii + iii, 42%); (iv) $ClSi^tBuPh_2$, Et_3N, DMAP, CH_2Cl_2, 12 h, 0 °C (57%); (v) H_2 6 bar, Pd/C 10%, HCl/MeOH, 24 h (85%).



Scheme 4. Reagents and conditions: (i) $ClSi^tBuPh_2$, Et_3N, DMAP, CH_2Cl_2, 12 h, 0 °C (92%); (ii) OsO_4/*N*-methylmorpholine *N*-oxide, dioxane/acetone/H_2O, rt, 18 h (90%); (iii) $NaIO_4/SiO_2$, CH_2Cl_2/H_2O, 3h; (iv) $NaBH_4$, MeOH, 5 h (iii + iv, 62%); (v) $BnOC(NH)CCl_3$, CF_3SO_3H, CH_2Cl_2, 1.5 h, rt (99%); (vi) TBAF/H_2O, acetone, 24 h, rt (75%).

Di-benzylation of the hydroxyl groups and subsequent desilylation afforded *N*-hydroxypyrrolidine **31**.

Attempts to perform the same reactions with the *endo* isomer of **28** (oxidative cleavage of the C_5–C_6 bond followed by in situ reduction of the intermediate dialdehyde) led to degradation of the starting material with recovery of traces of bicyclic compounds, pointing to the occurrence of undesired rearrangements similar to those illustrated in Scheme 3 for compound **22**.

All new compounds presented in this work were fully characterized by ^1H and ^{13}C NMR and mass spectrometry.

In conclusion, an efficient and straightforward orthogonal protection/deprotection methodology, allowing selective introduction of functional groups in polyhydroxymethylpyrrolidines, whose synthesis revealed to be effective and simple, has been developed.

Acknowledgments

The authors thank to Fundação para a Ciência e Tecnologia (FCT) for financial support given to *Faculdade de Ciências da Universidade do Porto* (project PTDC/QUI/67407/2006) and through the re-equipment program REDE/1517/RMN/2005 and CONC-REEQ/275/QUI. C.A.D.S. and F.R.A. thank for Grants SFRH/BD/31526/2006 and SFRH/BD/45545/2008, respectively.

Supplementary data

Supplementary data (NMR data, NMR spectra and mass spectroscopy data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.037.

References and notes

1. (a) Compain, P.; Martin, O. R. *Iminosugars: From Synthesis to Therapeutic Applications*; Chichester: Wiley, 2007; (b) Cipolia, L.; Fernandes, M. R.; Gregori, M.; Airoldi, C.; Nicotra, F. *Carbohydr. Res.* **2007**, *342*, 1813–1830; (c) Liao, W.; Ibrahem, I.; Cordova, A. *Chem. Commun.* **2006**, 674–676; (d) McDonnell, C.; Cronin, L.; O'Brien, J. L.; Murphy, P. V. *J. Org. Chem.* **2004**, *69*, 3565–3568; (e) Cipolla, L.; Ferla, B.; Nicotra, F. *Curr. Top. Med. Chem.* **2003**, *3*, 485–511; (f) Draper, J. A.; Britton, R. *Org. Lett.* **2010**, *12*, 4034–4037.
2. (a) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856–4865. and references cited therein; (b) Robinson, K. M.; Rhinehart, B. L.; Ducep, J. B.; Danzin, C. *Drugs Future* **1992**, *17*(8), 705–720; (c) Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875–1881.
3. (a) Ichikawa, Y.; Igarashi, Y.; Ichikawa, M.; Suhara, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3007–3018; (b) Anzeveno, P. B.; Creemer, L. J.; Daniel, J. K.; King, C.-H.; Liu, P. S. *J. Org. Chem.* **1989**, *54*, 2539–2542; (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (d) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265–295.
4. (a) Dwek, R. A.; Butters, T. D.; Platt, F. M.; Zitzmann, N. *Nat. Rev. Drug Disc.* **2002**, *1*, 65–75; (b) Cox, T.; Lachmann, R.; Hollack, C.; Aerts, J.; van Welly, S.; Hrebicek, M.; Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. *Lancet* **2000**, *355*, 1481–1485; (c) Kolter, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 1955–1959; (d) Spreitzer, H. *Österreichische Apotheker-zeitung* **2009**, *63*, 736; (e) Van Giersbergen, P. L. M.; Dingemanse, J. *J. Clin. Pharmacol.* **2007**, *47*, 1277–1282.
5. (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215–5222; (b) Spearman, M. A.; Jamieson, J. C.; Wright, J. A. *Exp. Cell Res.* **1987**, *168*, 116–126; (c) Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 5546–5556; (d) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267–8271; (e) Fleet, G. W. J.; Nash, R. J.; Fellows, L. E.; Parekh, R. J.; Rademacher, T. W. *Chem. Lett.* **1986**, *15*, 1051–1054.
6. (a) Fleet, G. W. J.; Witty, D. R. *Tetrahedron: Asymmetry* **1990**, *1*, 119–136; (b) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 9229–9233; (c) Bickley, J. F.; Gilchrist, T. L.; Mendoça, R. *Arkivoc* **2002**, 192–204; (d) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F. X.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128–132; (e) Tyms, A. S.; Berrie, E. M.; Ryder, T. A.; Nash, R. J.; Hegarty, M. P.; Taylor, D. L.; Mobberley, M. A.; Davis, J. M.; Bell, E. A.; Jeffries, D. J.; Taylor-Robinson, D.; Fellows, L. E. *Lancet* **1987**, 1025–1026; (f) McDowell, W.; Schwarz, R. T. *Biochimie* **1988**, *70*, 1535–1549.
7. Greimel, P.; Spreitz, J.; Stutz, A. E.; Wrodmiggm, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513–523.
8. Hughes, A. B.; Rudge, A. J. *J. Nat. Prod. Rep.* **1994**, *11*, 135–162.
9. Sun, L.; Li, P.; Landry, D. W.; Zhao, K. *Tetrahedron Lett.* **1996**, *37*, 1547–1550.
10. (a) Alves, M. J.; García-Mera, X.; Vale, M. L. C.; Santos, T. P.; Aguiar, F. R.; Rodríguez-Borges, J. E. *Tetrahedron Lett.* **2006**, *47*, 7595–7597; (b) Rodríguez-Borges, J. E.; Vale, M. L. C.; Aguiar, F. R.; Alves, M. J.; García-Mera, X. *Synthesis* **2008**, *6*, 971–977; (c) Ferreira da Costa, J.; Caamaño, O.; Fernández, F.; García-

Mera, X.; Midón, P.; Rodríguez-Borges, J. E. *Tetrahedron* **2010**, *66*, 6797–6805.
11. (a) Santos, T. P.; Borges, J. E.; Vale, M. L.; García-Mera, X. *Novel homoisoazanucleosides with potential biological activity*, in *19th IUPAC Conference on Physical Organic Chemistry*, 13–18 July 2008, Santiago de Compostela, Spain; (b) The crystallographic data for the corresponding 3,5-dinitrobenzoylderivative of **12** have been deposited at the Cambridge Crystallography Data Centre as supplementary publication number CCDC240023. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ, UK.
12. The crystallographic data for the compound **20** have been deposited at the Cambridge Crystallography Data Centre as supplementary publication number UKCCDC805275. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2, 1EZ.
13. The low yield observed results from two main reasons: (1) *endo* adducts similar to **21** are usually more sensible to reaction conditions than their *exo* isomers; (2) oxidative cleavage and in situ reduction of *endo* adducts similar to **22** may result in material degradation and/or intramolecular rearrangements.
14. (a) Humphrey, A. J.; Parsons, S. F.; Smith, M. E. B.; Turner, N. J. *Tetrahedron Lett.* **2000**, *41*, 4481–4485; (b) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235–4238; (c) Owotoki, W.; Geffken, D.; Kurz, T. *Aust. J. Chem.* **2006**, *59*, 283–288.
15. Sousa, C. A. D.; Vale, M. L. C.; Rodríguez-Borges, J. E.; García-Mera, X.; Rodríguez-Otero, J. *Tetrahedron Lett.* **2008**, *49*, 5777–5781.