Synthesis of 5-amino- and 5-hydroxy-3,3-difluoropiperidines†

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Received 8th June 2010, Accepted 5th July 2010
DOI: 10.1039/c0ob00231c

Synthetic routes toward new 5-amino- and 5-hydroxy-3,3-difluoropiperidines, which are of high interest as building blocks in medicinal chemistry, are described. The key step involves the *N*-halosuccinimide-induced cyclization of 2,2-difluoro-4-pentenylamines toward 5-halo-3,3-difluoropiperidines, which were used to synthesize 5-amino-3,3-difluoropiperidine. In a second strategy, iodolactonization of 2,2-difluoro-4-pentenoic acid gave the corresponding γ-lactone, which was transformed into 5-hydroxy-3,3-difluoropiperidine.

The introduction of a fluorine substituent in pharmaceutical and agrochemical compounds is a small modification in their chemical structure which can provoke highly advantageous changes in the chemical and biological properties of the compounds, including their lipophilicity, stability and bioavailability.[1] Among the wide range of organofluorinated compounds, substituted difluorinated piperidines have received a lot of attention in the patent literature as bifunctional building blocks for the use in structure–activity relationship studies of bioactive compounds.[2] Particularly in the case of 3,3-difluoropiperidines, the fluorine atoms at the β-position of the nitrogen of the piperidine ring dramatically lower the nucleophilicity and basicity of this nitrogen. Recently we published a new synthetic pathway toward valuable 4-substituted 3,3-difluoropiperidines consisting of a Cu-mediated 1,4-addition of ethyl bromodifluoroacetate to 3-substituted acrylonitriles followed by δ-lactamization and reduction.[3] However, this methodology could not be used for the synthesis of 5-substituted 3,3-difluoropiperidines because the 1,4-addition of ethyl bromodifluoroacetate to 2-substituted acrylonitriles turned out to be problematic. However, 5-substituted 3,3-difluorinated piperidines are promising compounds in medicinal chemistry and a general method for the synthesis of these compounds is clearly lacking in the literature. It should be noted that only one reference was found concerning 5-amino-3,3-difluoropiperidines and no literature data were found concerning the corresponding 3,3-difluoro-5-hydroxypiperidines bearing no further substituents at the piperidine ring. 5-Amino-3,3-difluoropiperidine **1** (Fig. 1) is known to be a PIM (proto-oncogene serine/threonine-protein)

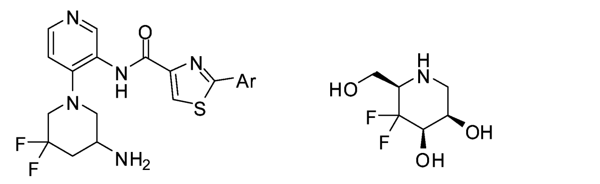

Fig. 1 Biologically active 5-amino- and 5-hydroxy-3,3-difluoropiperidines.

kinase inhibitor and has been designed for cancer treatment.[4] Matrix metalloprotease inhibitors[5] and excitatory amino acid receptor antagonists[6] are found among 5-acyl-3,3-difluoropiperidine derivatives, which are also promising compounds for the use in the treatment of nervous system disorders[7] and diseases depending on renin activity.[8] Substituted 5-hydroxy-3,3-difluoropiperidines, bearing additional functionalities at the piperidine ring (*e.g.* **2**) have been synthesized as azasugar derivatives and displayed β-glucosidase activities.[9]

5-Substituted 3,3-difluoropiperidines are generally prepared by deoxofluorination of the corresponding functionalized 3-piperidinones. Unfortunately, deoxofluorination reactions can suffer from the formation of rearranged or dehydrofluorinated products,[10] resulting in low yields of the targeted fluoroheterocycles. Therefore, the development of new strategies towards substituted difluoropiperidines, without the need for DAST or analogous deoxofluorination reagents, is of current interest. Recently, a 5-methyl-3,3-difluoropiperidine was synthesized *via* a cyclization/fluorination reaction of chlorinated diallylamines in superacid.[10]

In order to establish a generally applicable and efficient large scale synthesis of 5-substituted 3,3-difluoropiperidines, it was proposed to investigate the electrophile-induced cyclization of difluorinated *N*-alkenylamines **6** towards 5-halo-3,3-difluoropiperidines **8**, which were believed to be good precursors for 5-hydroxy- and 5-aminopiperidines.

At first, suitable starting protected amines **6** were synthesized from the corresponding 2,2-difluoro-4-penten-1-ol **4**, which was prepared by reduction of 2,2-difluoro-4-pentenoic acid **3** (Scheme 1). This versatile synthetic building block is available from fluorinated precursors such as tetrafluoroethylene gas[11] or the commercially available and easily handled chlorodifluoroacetic acid.[12,13] The reduction of ethyl 2,2-difluoro-4-pentenoate to 2,2-difluoropent-4-en-1-ol **4** has been described before using $NaBH_4$.[14] However, to avoid the extra esterification step, it was decided to directly reduce 2,2-difluoro-4-pentenoic acid **3** using 3 equivalents of $LiAlH_4$ in diethyl ether. This sequence resulted in difluoroalcohol **4** in 80% yield and was performed on a 20 gram scale. Subsequently, 2,2-difluoropent-4-en-1-ol **4** was successfully tosylated toward compound **5a** in 64% yield by reaction of the

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† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for compounds **5a**, **6b–d**, **8–11** and **13–16** are available. See DOI: 10.1039/c0ob00231c

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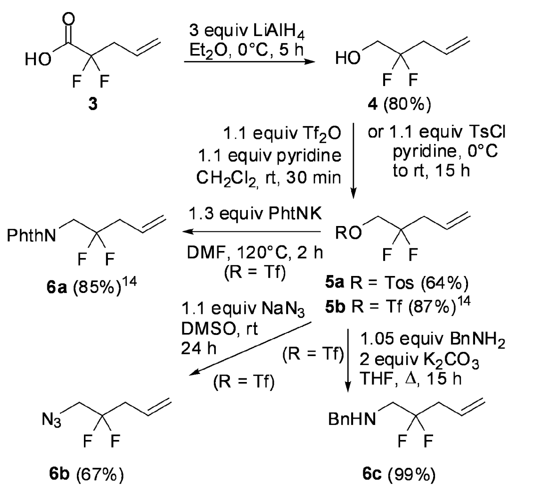
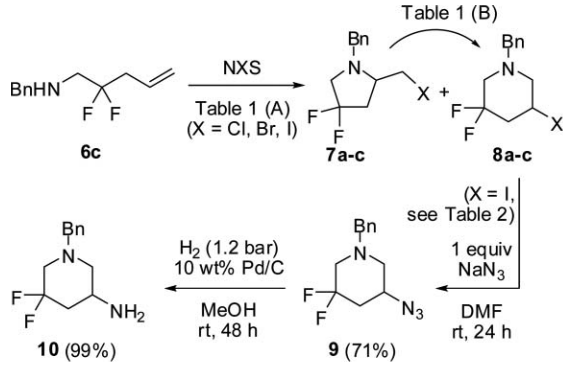


Scheme 1 Synthesis of fluorinated protected amines **6a–c**.



Scheme 2 Synthesis of 5-substituted difluoropiperidines **8–10**.

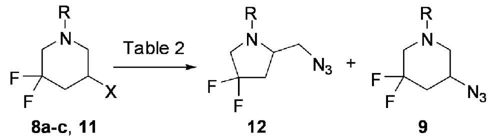
alcohol with tosyl chloride in pyridine. Unfortunately, tosylate **5a** could not be substituted by benzylamine or azide under various reaction conditions. Alternatively, triflation of 2,2-difluoropent-4-en-1-ol **4** *via* reaction with triflic anhydride yielded compound **5b**, which was directly transformed into the phthaloyl-protected amine **6a**.[14] Subsequently, reaction with 2 equiv. of $NH_2NH_2{\cdot}H_2O$ in ethanol at 50 °C gave the corresponding amine which was trapped as its HCl salt. Because the obtained ammonium salt could not be handled easily, it was decided to introduce the nitrogen *via* an azide substitution of triflate **5b**. Reaction of triflate **5b** with 1.1 equivalents of sodium azide in DMSO gave the new 5-azido-4,4-difluoropent-1-ene **6b** after 24 h at room temperature in 67% yield after distillation. Analogous to the synthesis of azide **6b**, the substitution of triflate **5b** with benzylamine in THF at reflux temperature proceeded very smoothly and yielded *N*-benzyl-2,2-difluoro-4-pentenamine **6c** in almost quantitative yield. Because of the ease of preparation of amine **6c**, even on a large scale, and the simple purification of **6c** *via* an acid–base extraction, the cyclization of *N*-halo difluoroamines using this substrate was investigated.

It is known that *N*-alkenyl-*N*-chloroamines can be cyclized to pyrrolidines and piperidines *via* a Cu(I)-catalyzed radical cyclization,[15] *via* a catalytic hetero-Heck type reaction,[16] or *via* reaction with (Lewis) acids.[17,18] To evaluate this cyclization method, amine **6c** was treated with *N*-chlorosuccinimide in dichloromethane (Scheme 2, Table 1), and subsequently, 2 equivalents of $BF_3.OEt_2$ as a Lewis acid were added to the formed *N*-chloroamine **6d** in dichloromethane at −78 °C. This reaction resulted in an unsatisfactory 1 : 1 : 3 mixture of starting material, amine **6c** and pyrrolidine **7a** (X = Cl), respectively. However, when a catalytic amount (10 mol%) of tetrabutylammonium iodide (TBAI) was added after reaction of **6c** with NCS, cyclization proceeded smoothly to give a 18 : 82 mixture of fluorinated 5-chloromethylpyrrolidine **7a** and 5-chloropiperidine **8a** after heating for 15 h at 50 °C in $CHCl_3$ (Table 1).[19] A complete conversion towards piperidine **8a** was obtained after heating the obtained mixture during 60 h at 83 °C in dichloroethane in the presence of 1 equivalent of LiCl. Distinction between the isomeric pyrrolidine **7a** and piperidine **8a** was made by means of mass spectrometry. In the case of pyrrolidine **7a** the presence of an ion at *m*/*z* 196 accounted for the homolytic cleavage of a CH_2Cl-group. In contrast, the mass spectrum of **8a** did not show a *m*/*z* 196 fragment ion. In addition, in the ^1H NMR spectrum ($CDCl_3$) of 5-chloropiperidine **8a** the CHCl was assigned to the well-resolved t × t (11.3 Hz, 4.9 Hz) at δ 4.04 ppm typically for 5-halopiperidines, in comparison to the broad singlet of the NCH of 5-(halomethyl)pyrrolidines.[20] To evaluate the effect of the halogen, fluorinated amine **6c** was also treated with *N*-iodosuccinimide in dichloromethane at room temperature. A fast cyclization to 3,3-difluoro-5-iodopiperidine **8c** occurred without formation of the corresponding pyrrolidine. Also the reaction of amine **6c** with *N*-bromosuccinimide gave rise to a rapid formation of a 72 : 18 mixture of 5-bromomethylpyrrolidine **7b** and 5-bromopiperidine **8b**, respectively. The pyrrolidine intermediate **7b** was slowly, but completely converted into 1-benzyl-5-bromo-3,3-difluoropiperidine **8b** upon standing in acetone at room temperature and was isolated in 77% yield after flash chromatography. The three new fluorinated 5-halopiperidines **8a–c** (X = Cl, Br, I) show almost identical ^1H NMR spectra. However, in the ^{13}C NMR spectrum ($CDCl_3$) it is noted that the CHX peak

Table 1 Synthesis of 5-halogenated 3,3-difluoropiperidines **8a–c** from *N*-benzyl-2,2-difluoro-4-pentenamine **6c** (Scheme 2)

Entry	X	Reaction conditions A	Ratio **7** : **8**	Reaction conditions B	Difluoropiperidine **8** (isolated yield)
1	Cl	1) 1 equiv. NCS, CH_2Cl_2, 0 °C, 2 h (**6c** → **6d**) 2) 0.1 equiv. Bu_4NI, $CHCl_3$, 50 °C, 15 h (**6d** → **7a/8a**)	18 : 82	1 equiv. LiCl, $Cl(CH_2)_2Cl$, Δ, 60 h	**8a** (86%)
2	Br	1 equiv. NBS, CH_2Cl_2, rt, 2 h (**6c** → **7b/8b**)	72 : 28	acetone, rt, 72 h	**8b** (77%)
3	I	1 equiv. NIS, CH_2Cl_2, rt, 2 h (**6c** → **8c**)	0 : 100	(not applicable)	**8c** (82%)

Table 2 Optimization of the synthesis of 3-azidopiperidine **9**



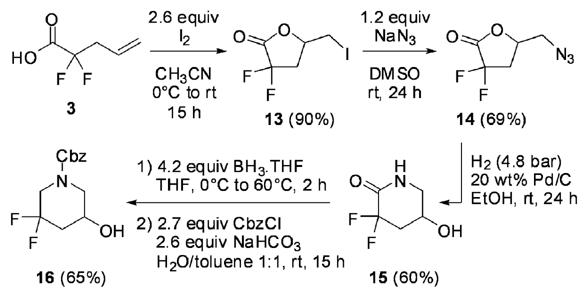
	X	R	Reaction conditions	Conversion	12 : 9
11	Cl	Boc	NaN_3, rt to 100 °C, DMF or DMSO	0%	/
8a	Cl	Bn	2 equiv. NaN_3, DMSO, 100 °C, 15 h	100%	14 : 86
8b	Br	Bn	1.1 equiv. NaN_3, DMF, rt, 24 h	29%	6 : 94
8b	Br	Bn	1.1 equiv. NaN_3, DMF, 70 °C, 15 h	100%	10 : 90
8c	I	Bn	1 equiv. NaN_3, DMF, rt, 24 h	100%	7 : 93(71)[a]

[a] Isolated yield of 3-azidopiperidine **9** in parentheses.

(determined by DEPT-135 analysis) is clearly shifted upfield from the chlorine (50.3 ppm), over the bromine (40.1 ppm), to the iodine derivative (15.4 ppm), which is another structural evidence of the 6-membered ring structure.

New 5-halogenated 3,3-difluoropiperidines **8** can thus be prepared on a large scale and form good substrates for further functionalization reactions toward 5-substituted 3,3-difluoropiperidines. In particular, 5-amino-3,3-difluoropiperidine is an interesting target molecule for the use as bifunctional building block for incorporation in bioactive compounds. It is known that piperidines having a leaving group at the 3-position react with nucleophiles *via* intramolecular substitution of the leaving group by nitrogen and subsequent opening of the bicyclic aziridinium ion at the more substituted carbon by the nucleophile to give 3-functionalized piperidines, which are sometimes accompanied by small amounts of the corresponding pyrrolidines bearing a CH_2Nu substituent at the 5-position.[21] Indeed, when 5-halopiperidines **8a–c** were reacted with sodium azide as a nucleophile in DMSO or DMF, 5-azido-3,3-difluoropiperidine **9** was formed accompanied by small amounts (about 6–14%) of the 5-azidomethylpyrrolidine isomer **12** (Table 2). The best results were obtained by treating 5-iodo-3,3-difluoropiperidine **8c** with NaN_3 in DMF at rt during 24 h, resulting in complete conversion towards **12** and **9** in a ratio of 7 : 93, respectively. 5-Azido-3,3-difluoropiperidine **9** was separated from the pyrrolidine isomer *via* flash chromatography and was isolated in 71% yield. Catalytic hydrogenation of 5-azido-3,3-difluoropiperidine **9** at atmospheric pressure gave 5-amino-3,3-difluoropiperidine **10** in almost quantitative yield without removal of the *N*-benzyl group (Scheme 2). Analogous reactions of 3,3-difluoro-5-iodopiperidine **8c** with nucleophiles such as ammonia, sodium hydroxide, sodium acetate or potassium cyanide in methanol or DMF gave complex mixtures. In order to avoid the neighbouring group participation of the piperidine nitrogen during the nucleophilic substitution reactions, 5-chloro-3,3-difluoropiperidine **8a** was converted to 1-Boc-5-chloro-3,3-difluoropiperidine **11** *via* standard methods in almost quantitative yield.[22] However, when 1-Boc-5-chloropiperidine **11** was reacted with sodium azide under various reaction conditions, only tetrahydropyridine derivatives were observed, probably because of the enhanced acidity of the protons at the α-position of the piperidine nitrogen of **11** in comparison to the 1-benzylderivative **8a**.

Because the previous strategy was not applicable to synthesize 3,3-difluoro-5-hydroxypiperidines, which are of significant interest as building blocks in medicinal chemistry, another synthetic methodology was evaluated. For this purpose, the easily accessible 2,2-difluoro-4-pentenoic acid **3** was cyclized using a iodolactonization reaction in acetonitrile toward α,α-difluoro-γ-iodomethyl-γ-butyrolactone **13** in 90% yield (Scheme 3). The iodine substituent was then displaced by azide in DMSO to give the fluorinated γ-azidomethyl-γ-lactone **14** in 69% yield. Reduction of **14** by catalytic hydrogenation (H_2, Pd/C) led to the intermediate amine, which underwent a smooth rearrangement towards 3,3-difluoro-5-hydroxy-2-piperidinone **15**. However, due to the high polarity of lactam **15**, only 60% could be recovered after flash chromatography and crystallization. Finally, 2-piperidinone **15** was successfully reduced using $BH_3 \cdot THF$ and the obtained 3,3-difluor-5-hydroxypiperidine was trapped as the benzyloxycarbonyl derivative **16** in 65% overall yield.[23]



Scheme 3 Synthesis of 3,3-difluoro-5-hydroxypiperidine **16**.

In conclusion, straightforward synthetic pathways toward 5-amino- and 5-hydroxy-3,3-difluoropiperidines were developed, starting from 2,2-difluoro-4-pentenoic acid. Cyclization of *N*-benzyl-*N*-(2,2-difluoro-4-pentenyl)amine using NIS yielded a new 5-iodo-3,3-difluoropiperidine in high yield. This piperidine was subsequently used for the efficient synthesis of 5-amino-3,3-difluoropiperidine. Alternatively, iodocyclization of the starting difluoropentenoic acid gave the corresponding γ-lactone, which proved to be a good starting material for the synthesis of 5-hydroxy-3,3-difluoropiperidine. The synthesized 5-substituted difluoropiperidines were obtained on large scale and are of high interest as building block for medicinal chemistry.

Acknowledgements

The authors are indebted to the Research Foundation – Flanders (FWO-Flanders), Ghent University (GOA, BOF) and Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica NV, for financial support.

Notes and references

1 (*a*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*b*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359.

2 For examples, see; (*a*) M. G. Stanton, J. Hubbs, D. Sloman, C. Hamblett, P. Andrade, M. Angagawc, G. Bi, R. M. Black, J. Crispino, J. C. Cruz, E. Fan, G. Farris, B. L. Hughes, C. M. Kenific, R. E. Middleton, G. Nikov, P. Sajonz, S. Shah, N. Shomer, A. A. Szewczak,

F. Tanga, M. T. Tudge, M. Shearman, B. Munoz, *Bioorg. Med. Chem. Lett.* 2010, **20**, 755; (*b*) S. Ninkovic, J. F. Braganza, M. R. Collins, J. C. Kath, H. Li, D. T. Richter PCT Int. Appl. WO 2010016005, 2010; (*c*) S. Ninkovic, J. F. Braganza, M. R. Collins, J. C. Kath, H. Li and D. T. Richter, *Chem. Abstr.*, 2010, **152**, 262750.

3 R. Surmont, G. Verniest, J. W. Thuring, G. Macdonald, F. Deroose and N. De Kimpe, *J. Org. Chem.*, 2010, **75**, 929.

4 M. Burger, J. Lan, M. Lindvall, G. Nishiguchi, M. Tetalman PCT Int. Appl. WO 2009109576, 2009; M. Burger, J. Lan, M. Lindvall, G. Nishiguchi and M. Tetalman, *Chem. Abstr.*, 2009, **151**, 358734.

5 Y. Li, J. Zhou, D. Burns, W. Yao PCT Int. Appl. WO 2005037826, 2005; Y. Li, J. Zhou, D. Burns and W. Yao, *Chem. Abstr.*, 2005, **142**, 430307.

6 S. A. Filla, K. J. Hudziak, B. M. Mathes, P. L. OrnsteinPCT Int. Appl. WO 2002053555, 2002; S. A. Filla, K. J. Hudziak, B. M. Mathes and P. L. Ornstein, *Chem. Abstr.*, 2002, **137**, 78866.

7 S. Gagliardi, E. Le Poul, L. Lingard, G. Palombi, S. M. Poli, J.-P. Rocher PCT Int. Appl. WO 2006123257, 2006; S. Gagliardi, E. Le Poul, L. Lingard, G. Palombi, S. M. Poli and J.-P. Rocher, *Chem. Abstr.*, 2006, **145**, 505460.

8 K. Masuya, F. Yokokawa, O. Irie, A. Nihonyanagi, A. Toyao, T. Ehara, K. Konishi, T. Kanazawa, M. Suzuki PCT Int. Appl. 2006, WO 200609476, 2006; K. Masuya, F. Yokokawa, O. Irie, A. Nihonyanagi, A. Toyao, T. Ehara, K. Konishi, T. Kanazawa and M. Suzuki, *Chem. Abstr.*, 2006, **145**, 335938.

9 R.-W. Wang, X.-L. Qiu, M. Bols, F. Ortega-Caballero and F. L. Qing, *J. Med. Chem.*, 2006, **49**, 2989.

10 E. Vardelle, A. Martin-Mingot, M.-P. Jouannetaud, C. Bachmann, J. Marrot and S. Thibaudeau, *J. Org. Chem.*, 2009, **74**, 6025.

11 (*a*) J. F. Normant, O. Reboul, R. Sauvêtre, H. Deshayes, D. Masure and J. Villieras, *Bull. Soc. Chim. Fr.*, 1974, 2072; (*b*) M. Kolb, F. Gerhart and J.-P. François, *Synthesis*, 1988, 469.

12 H. Greuter, R. W. Lang and A. J. Romann, *Tetrahedron Lett.*, 1988, **29**, 3291.

13 F. Xu, B. Simmons, J. Armstrong III and J. Murry, *J. Org. Chem.*, 2005, **70**, 6105.

14 D. A. Kendrick, C. Danzin and M. Kolb, *J. Med. Chem.*, 1989, **32**, 170.

15 (*a*) R. Göttlich, *Synthesis*, 2000, 1561; (*b*) G. Heuger, S. Kalsow and R. Göttlich, *Eur. J. Org. Chem.*, 2002, 1848; (*c*) M. Noack and R. Göttlich, *Chem. Commun.*, 2002, 536.

16 J. Helaju and R. Göttlich, *Chem. Commun.*, 2002, 720.

17 (*a*) F. Minisci, *Synthesis*, 1973, 1; (*b*) L. Stella, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 337; (*c*) M. Hemmerling, A. Sjöholm and P. Somfai, *Tetrahedron: Asymmetry*, 1999, **10**, 4091; (*d*) A. Sjöholm, M. Hemmerling, N. Pradeille and P. Somfai, *J. Chem. Soc., Perkin Trans. 1*, 2001, 891.

18 M. Noack, S. Kalsow and R. Göttlich, *Synlett*, 2004, 1110.

19 (*a*) R. Göttlich and M. Noack, *Tetrahedron Lett.*, 2001, **42**, 7771; (*b*) M. Noack and R. Göttlich, *Eur. J. Org. Chem.*, 2002, 3171.

20 (*a*) K. Abbaspour Tehrani, K. Van Syngel, M. Boelens, J. Contreras, N. De Kimpe and D. W. Knight, *Tetrahedron Lett.*, 2000, **41**, 2507; (*b*) N. De Kimpe and M. Boelens, *J. Chem. Soc., Chem. Commun.*, 1993, 916; (*c*) N. De Kimpe, M. Boelens, J. Piqueur and J. Baele, *Tetrahedron Lett.*, 1994, **35**, 1925.

21 (*a*) D. Black and J. E. Doyle, *Adv. Heterocycl. Chem.*, 1981, **27**, 1; (*b*) R. H. Reitsema, *J. Am. Chem. Soc.*, 1949, **71**, 2041; (*c*) C. F. Hammer and J. D. Weber, *Tetrahedron*, 1981, **37**, 2173; (*d*) J. Cossy, C. Dumas, P. Michel and D. Gomez Pardo, *Tetrahedron Lett.*, 1995, **36**, 549; (*e*) N. De Kimpe and M. Boelens, *Tetrahedron Lett.*, 1996, **37**, 3171; (*f*) E. Rosas Alonso, K. Abbaspour Tehrani, M. Boelens, D. W. Knight, V. Yu and N. De Kimpe, *Tetrahedron Lett.*, 2001, **42**, 3921; (*g*) C. V. Stevens, M. Peristeropoulou and N. De Kimpe, *Tetrahedron*, 2001, **57**, 7865.

22 V. D. Vitnik, M. D. Ivanovic, Z. J. Vitnik, J. B. Dordevic, Z. S. Zizak, Z. D. Juranic and I. O. Juranic, *Synth. Commun.*, 2009, **39**, 1457.

23 (*a*) N. Nuh and C. M. Thompson, *Tetrahedron*, 1995, **51**, 5935; (*b*) A. Gross, D. R. Borcherdin, D. Friedrich and J. S. Sabol, *Tetrahedron Lett.*, 2001, **42**, 1631.

