Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 1969–1972

TETRAHEDRON: *ASYMMETRY*

Ring-opening reactions of iminosugar-derived aziridines: application to the general synthesis of α-1-*C*-substituted derivatives of fagomine

Jean-Yves Goujon,[a] David Gueyrard,[a] Philippe Compain,[a,*] Olivier R. Martin[a,*] and Naoki Asano[b]

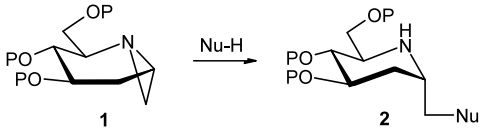
[a]*Institut de Chimie Organique et Analytique, CNRS-Université d'Orléans, rue de Chartres, BP 6759, 45067 Orléans, France*
[b]*Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa 920-1181, Japan*

Received 14 April 2003; accepted 29 April 2003

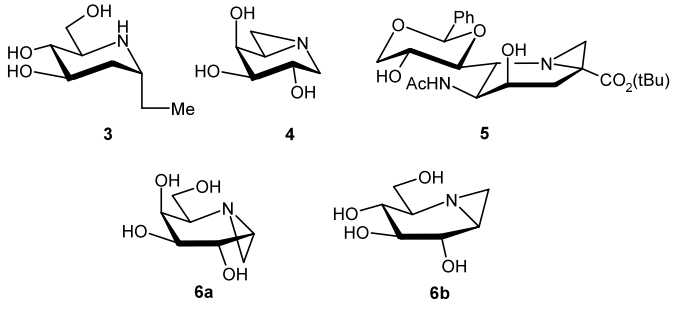
Abstract—A general approach to α-1-*C*-substituted derivatives of fagomine (2-deoxynojirimycin-α-*C*-glycosides) by ring-opening reactions of an aziridine with various heteroatomic nucleophiles, including thiol, amine, alcohol, carboxylate and phosphate, is reported. The nine-step reaction sequence proceeded in an overall yield of 14–28% from tri-*O*-benzyl-D-glucal. In the course of this study, the synthesis of α-1-*C*-ethyl-fagomine as well as of 1,*N*-anhydro derivatives of fagomine has been achieved for the first time.

Several classes of aziridine-containing natural products exhibit useful biological activity against a wide range of cancers or as antibiotic agents.[1] These properties are intimately associated with the chemical reactivity of the aziridine ring. Baeyer strain combined with the electronegativity of the nitrogen atom explain the ability of the three-membered saturated heterocycle to undergo ring-opening reactions under relatively mild conditions.[1] As a result, aziridines have a great value in organic synthesis as chemical intermediates. In order to take advantage of both the biological and synthetic properties of aziridines, we have designed a strategy for the preparation of iminosugar-derived aziridines **1** as potential irreversible inhibitors of glycosidases (P = H) and as advanced intermediates for the general synthesis of α-1-*C*-substituted derivatives of fagomine **2** of biological significance (P = protecting group) (Scheme 1).

Owing to their properties as inhibitors of carbohydrate-processing enzymes,[2] iminosugars promise a new generation of carbohydrate-based therapeutics for the control of various diseases[3] including cancer, viral infection and lysosomal storage disorders. In addition, fagomine was found recently to have potent antihyperglycemic effect in streptozotocin-induced diabetic mice and to enhance glucose-induced insulin secretion.[4] To our knowledge, only one example of a natural fagomine *C*-glycoside (compound **3**)[5] and four examples of iminosugar-derived aziridines having the 1-azabicyclo-[4.1.0]heptane skeleton have been reported to date: one independently by Ganem,[6a] compound **4**, and its enantiomer by Paulsen,[6b] one by Vasella,[7] compound **5**, and two by our group, compounds **6a**[8a] and **6b**[8b] (Scheme 2).



Scheme 1.

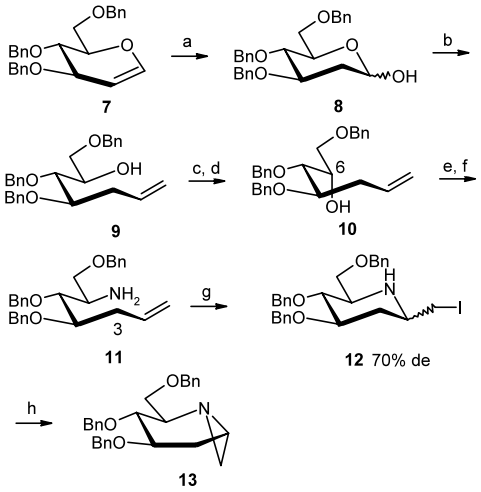


Scheme 2.

* Corresponding authors. Fax: +33 (0) 2 38 41 72 81; e-mail: philippe.compain@univ-orleans.fr; olivier.martin@univ-orleans.fr

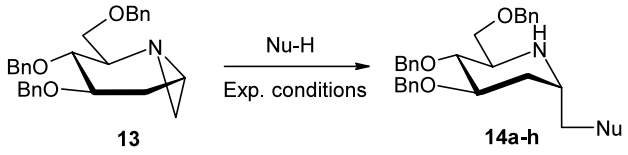
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00364-1

Herein, we report the first synthesis of a 1,*N*-anhydro derivative of fagomine **1**, its deprotection and its utilization as an advanced intermediate for the synthesis of α-1-*C*-substituted derivatives of fagomine **2** by way of regioselective opening reaction of the aziridine ring. The synthesis of the key intermediate **13** was performed in eight steps and 34% overall yield from tri-*O*-benzyl-D-glucal **7** (Scheme 3). Alkene **9**[9] was obtained in two steps by the conversion of **7** into the corresponding 2-deoxysugar **8** by a mild one-pot procedure,[10] followed by Wittig reaction. We then examined the introduction of the amino group at C6 of the D-*xylo* heptenitol **9** by way of a double Mitsunobu reaction. The configuration at C6 of **9** was inverted efficiently in 79% yield by reaction with *p*-nitrobenzoic acid in the presence of Ph_3P and DIAD,[8a] followed by debenzoylation under basic conditions to give the L-*arabino* heptenitol **10**. A second Mitsunobu reaction using phthalimide as nitrogen nucleophile afforded the expected D-*xylo* amino sugar **11** in 72% yield after removal of the phthalimido group. The amino-heptenitol **11** was then cyclized using NIS as the source of electrophile to produce the relatively unstable 1-*C*-iodomethyl derivatives of fagomine **12** with a good diastereoselectivity in favor of the α-diastereoisomer (70% de). The two epimers could be separated by flash chromatography, even though partial decomposition occurred.



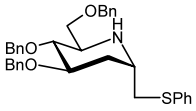
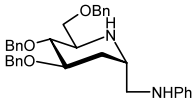
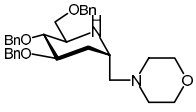
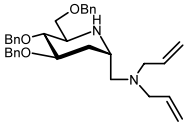
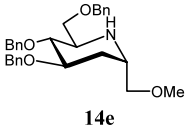
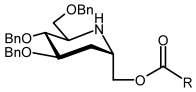
Scheme 3. *Reagents and conditions*: (a) (i) NIS (1.1 equiv.), CH_3CN/H_2O (95/5), 0°C, 15 mn; (ii) $Na_2S_2O_4$ (4 equiv.), $NaHCO_3$ (10 equiv.), DMF/H_2O (1/1), 5 h; (b) $Ph_3P^+CH_3Br^-$ (3.5 equiv.), *n*BuLi (3.3 equiv.), THF, 0°C to rt, 16 h, 81% (three steps); (c) PPh_3 (3 equiv.), *p*-nitrobenzoic acid (3 equiv.), DIAD (3 equiv.), toluene, 0°C to rt, 16 h; (d) Na (0.2 equiv.), MeOH, 1 h, 79% (two steps); (e) Phthalimide (3 equiv.), PPh_3 (3 equiv.), DIAD (3 equiv.), toluene, 0°C to rt, 16 h; (f) ethylenediamine (10 equiv.), EtOH, 80°C, 5 h, 72% (two steps); (g) NIS (1.2 equiv.), CH_2Cl_2, 1 h; (h) DBU (10 equiv.), THF, Δ, 6 h, 74% (two steps).

By contrast, the NIS-promoted cyclization of the *N*-benzyl-tetra-*O*-benzyl D-*gluco* analogue of **11**[11] is completely diastereoselective: this comparison confirms the important role of the 3-*O*-benzyl group in the stereochemical outcome of the cyclization of the latter heptenitol. To avoid degradation, the mixture of the two stereoisomers **12** was directly engaged, without purification, in the subsequent cyclization promoted by DBU. The aziridine **13** was obtained in 74% yield from **11** after purification by flash chromatography. Having the key bicyclic iminosugar **13** in hand, we first investigated ring-opening reactions of the aziridine with various heteroatomic nucleophiles including thiol, amine, alcohol, carboxylate and phosphate (Table 1 and Scheme 4).



Scheme 4. Ring-opening reactions of aziridine **13**.

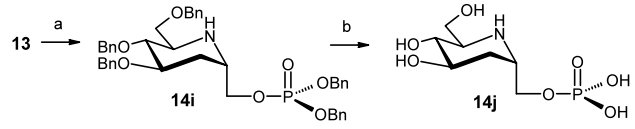
Table 1.

Entry	Exp. conditions	Product	yield[a]
1	PhSH (1.3 eq.); Et_3N (1.3 eq.), CH_2Cl_2, 3h	 **14a**	81%
2	$PhNH_2$ (2 eq.), $LiClO_4$ (0.1 eq.), CH_3CN, Δ, 2h	 **14b**	63%
3	Morpholine (1.3 eq.), $LiClO_4$ (0.1 eq.), CH_3CN, Δ, 2h	 **14c**	84%
4	Diallylamine (1.3 eq.), $LiClO_4$ (0.1 eq.), CH_3CN, Δ, 2h	 **14d**	81%
5	CSA (0.1 eq), MeOH, 16h	 **14e**	40%[b]
6	RCO_2H (1.3 eq.), CH_2Cl_2, 16h	 **14f** R = Ph	75%
7		**14g** R = propyl	82%
8		**14h** R= CH_2NHCbz	74%

[a] Yields determined after purification by flash chromatography.
[b] Not optimised.

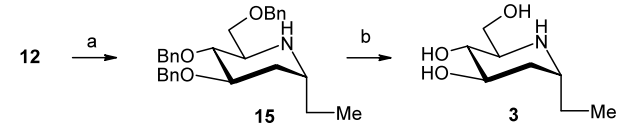
It is noteworthy that there has been few investigations on the ring-opening reactions of *N*-alkylated aziridines in comparison with aziridines *N*-activated by sub-

stituents such as sulfonyl, phosphoryl or carbonyl groups.[1] We were pleased to find that the corresponding ring-opening products **14** could be obtained in good yields and with a high degree of regioselectivity.[12] Bicyclic iminosugar **13** was readily opened with thiophenol in the presence of triethylamine at room temperature. In the presence of a catalytic amount of lithium perchlorate, aziridine **13** underwent cleavage by primary or secondary amines under the mild conditions recently developed by Yadav et al. for *N*-tosyl aziridine (Table 1, entries 2–4).[13] Aziridine **13** was opened by MeOH in the presence of camphorsulfonic acid (0.1 equiv.) to give **14e** in 40% yield (not optimized). Regioselective ring opening also occurred with various carboxylic acids in dichloromethane to provide the corresponding 2-deoxy-α-homonojirimycin derivatives **14f-h** in 74 to 82% yield (Table 1, entries 6–8).[7,14] The same experimental conditions using dibenzyl phosphate afforded protected iminosugar phosphate **14i** which was debenzylated with 10% Pd/C in MeOH/HCl 4N (20/1) to furnish the corresponding significant glycosyl phosphate mimetic **14j** in 85% yield (Scheme 5). To our knowledge, this is the first example of a ring-opening reaction of an *N*-alkylated aziridine by a phosphate.[15] Compound **14j** is a potential inhibitor of enzymes processing Glc-1-P and could be the precursor of novel UDP-Glc analogs as glycosyltransferase inhibitors.[2c,d]



Scheme 5. *Reagents and conditions*: (a) $(BnO)_2P(O)OH$ (1.3 equiv.), CH_2Cl_2, 16 h, 78%; (b) H_2, Pd/C, MeOH/HCl 4N cat., 24 h, 85%.

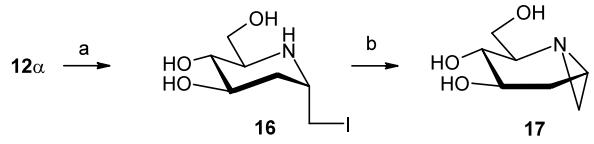
We then turned our attention to organometallic nucleophiles in order to synthesize *inter alia* α-1-*C*-ethyl-fagomine **3**, the only example of a fagomine *C*-glycoside recently isolated from *Adenophora triphylla* var. *japonica*.[5] The reaction of aziridine **13** with various organometallic reagents (MeLi, Me_2CuLi, $MeCeCl_2$) failed to give the desired product **15** under various experimental conditions. However, **15** could be obtained in 65% yield after purification by flash chromatography by the reaction of Me_2CuLi with the mixture of the two stereoisomers **12** (Scheme 6).[16]



Scheme 6. *Reagents and conditions*: (a) Me_2CuLi (1.1 equiv.), THF, −50°C to rt, 6 h, 65%; (b) H_2, Pd/C, EtOH, HCl 4N cat., 24 h, 88%.

Removal of the benzyl protecting groups in **15** provided the expected α-1-*C*-ethyl fagomine **3** in 88% yield.[17]

Finally, we investigated the deprotection of aziridine **13** in order to obtain the 1,*N*-anhydro derivative of fagomine **17**. Under usual debenzylation conditions, the reaction led to an untractable mixture of products (using Na/NH_3) or to the cleavage of the aziridine ring to give the α-1-*C*-methyl analogue of **15** in quantitative yield (using H_2, Pd/C). To overcome this difficulty, we first cleaved the benzyl groups at the stage of the α-1-*C*-iodomethyl derivative **12α** to generate **16**. The expected bicyclic iminosugar **17** was then obtained by intramolecular nucleophilic substitution promoted by K_2CO_3 in water (Scheme 7).[18]



Scheme 7. *Reagents and conditions*: (a) TMSI (8.5 equiv.), CH_2Cl_2, 0°C to rt, 16 h, 84%; (b) K_2CO_3 (1.8 equiv.), H_2O, 4 h, 90%.

In conclusion, ring-opening reactions of aziridine **13** with various heteroatomic nucleophiles provided a general approach to fagomine α-*C*-glycosides and related compounds. The nine-step reaction sequence proceeded in an overall yield of 14–28% from tri-*O*-benzyl-D-glucal **7**. In the course of this study, the first synthesis of α-1-*C*-ethyl-fagomine **16** has been achieved as well as that of 1,*N*-anhydro derivatives of fagomine. Investigations on the activity of the synthesized fagomine *C*-glycosides, especially as glycosidase and glycogen phosphorylase inhibitors, are in progress and will be reported in due course.

Acknowledgements

The authors express their gratitude to Yann Bilbille for assistance with synthetic work and to Kyoko Ikeda for optical activity and spectral data measurements. Financial support of this study by grants from CNRS and the association 'Vaincre les Maladies Lysosomales' is also gratefully acknowledged.

References

1. For recent reviews, see: (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247; (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.
2. (a) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999; (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (c) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077; (d) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541; (e) Schramm, V. L.; Tyler, P. C. *Curr. Top. Med. Chem.* **2003**, *3*, 525; (f) Lee, R. E.; Smith, M. D.; Pickering, L.; Fleet, G. W. J. *Tetrahedron Lett.* **1999**, *39*, 8689.
3. Iminosugars: Recent Insights Into Their Bioactivity and Potential As Therapeutic Agents in *Curr. Top. Med. Chem.*; Martin, O. R.; Compain, P., Eds.; Bentham, Neth., **2003**, *3*, issue 5.

4. (a) Nojima, H.; Kimura, I.; Fu-Jin, C.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397; (b) Taniguchi, S.; Asano, N.; Tomino, F.; Miwa, I. *Horm. Metab. Res.* **1998**, *30*, 679.
5. Asano, N.; Nishida, M.; Miyauchi, M.; Ikeda, K.; Yamamoto, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Phytochemistry* **2000**, *53*, 379.
6. (a) Tong, M. K.; Ganem, B. *J. Am. Chem. Soc.* **1988**, *110*, 312; (b) Paulsen, H.; Matzke, M.; Orthen, B.; Nuck, R.; Reutter, W. *Liebigs Ann. Chem.* **1990**, *10*, 953.
7. Bernet, B.; Bulusu Murty, A. R. C.; Vasella, A. *Helv. Chim. Acta* **1990**, *73*, 940.
8. (a) Martin, O. R.; Xie, F.; Liu, L. *Tetrahedron Lett.* **1995**, *36*, 4027; (b) Martin, O. R.; Saavedra, O. *Tetrahedron Lett.* **1995**, *36*, 799.
9. (a) Désiré, J.; Dransfield, P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, 1329; (b) Tius, M. A.; Busch-Petersen, J. *Tetrahedron Lett.* **1994**, *35*, 5181.
10. Costantino, V.; Imperatore, C.; Fattorusso, E.; Mangoni, A. *Tetrahedron Lett.* **2000**, *41*, 9177.
11. (a) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991; (b) Boschetti, A.; Nicotra, F.; Panza, L.; Russo, G. *J. Org. Chem.* **1988**, *53*, 4181.
12. The alternative regioisomer could not be detected by NMR spectroscopy.
13. Yadav, J. S.; Subba Reddy, B. V.; Parimala, G.; Venkatram Reddy, P. *Synthesis* **2002**, *16*, 2383.
14. No migration of the acyl group to the endocyclic nitrogen occurred as it was unambiguously established by IR and NMR spectral data.
15. For an example of opening of an *N*-activated aziridine by a phosphate, see: Misiura, K.; Kinas, R. W.; Stec, W. J.; Kusnierczyk, H.; Radzikowski, C.; Sonoda, A. *J. Med. Chem.* **1988**, *31*, 226.
16. Jefford, C. W.; Wang, J. *Tetrahedron Lett.* **1993**, *34*, 1111.
17. Spectral properties of synthetic **3** are in good agreement with the reported data for the natural product.[5] Selected data: ^{13}C NMR (62.9 MHz, D_2O-TSP) for synthetic α-1-*C*-ethyl-fagomine: δ 13.1, 26.1, 37.5, 55.2, 57.4, 64.9, 72.4, 76.6 {lit.[5] ^{13}C NMR (100 MHz, D_2O-TSP): δ 13.1, 26.1, 37.1, 55.4, 57.8, 64.5, 72.2, 76.2}. $[\alpha]_D^{20}$ +42.3 (*c* 0.4, H_2O); {lit.[5] $[\alpha]_D^{20}$ +45.7 (*c* 0.7, H_2O)}; HRMS (CI) *m*/*z* 176.1281 $[M+H]^+$ ($C_8H_{18}NO_3$ requires 176.1286).
18. Selected data for bicyclic iminosugar **17**: ^{1}H NMR (500 MHz, D_2O-TSP): δ 1.66 (br d, 1H), 1.97 (ddd, 1H, J=6.0, 9.6, 14.2 Hz), 2.02 (br d, 1H), 2.23 (m, 1H), 2.44 (ddd, 1H, J=2.3, 3.5, 14.2 Hz), 2.57 (ddd, 1H, J=3.2, 6.0, 9.6 Hz), 3.34 (dd, 1H, J=8.7, 9.6 Hz), 3.76 (dd, 1H, J=6.0, 11.5 Hz), 3.89 (dd, 1H, J=3.2, 11.5 Hz); ^{13}C NMR (125 MHz, D_2O-TSP) δ 32.1, 34.9, 36.8, 66.4, 69.5, 71.3, 74.7; $[\alpha]_D^{20}$ +57.7 (c=0.4, H_2O); HRMS (CI) *m*/*z* 160.0976 $[M+H]^+$ ($C_7H_{14}NO_3$ requires 160.0973).