Synthetic Access to the First Spirocyclopropyl Iminosugar

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Received 13 October 2005

Abstract: The synthesis of the first spirocyclopropyl iminosugar has been achieved in six steps and 13% overall yield from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose. The synthesis is based on an efficient two-step reaction involving the titanium-mediated aminocyclopropanation of 2,3,5-tri-*O*-benzyl-4-*O*-methanesulfonyl-D-arabinononitrile and the subsequent cyclization resulting from in situ nucleophilic attack of the so-formed amine. Addition of a Lewis acid during the cyclopropanation–cyclization sequence greatly improved the yields.

Key words: azasugars, glycosidases, metallacycle, nitriles, spiro compounds, titanium

Polyhydroxypyrrolidines, also termed iminosugars or azasugars, have been found to act as potent reversible glycosidase inhibitors.[1] As such, they represent important tools for the isolation and characterization of glycosidases as well as for the study of their mechanism of action.[2] Interestingly, iminosugars were also shown to induce notable biological effects and have been envisaged as anti-diabete, anti-retroviral or antitumour agents.[3] DMDP (**1**, 2,5-dideoxy-2,5-imino-D-mannitol) and its epimer **2** are representatives of this class of sugar mimics (Figure 1). Both compounds strongly inhibit α- and β-glucosidases and have been applied to the affinity purification of invertase.[4] DMDP also displayed some anti-HIV activity.[5] However, its high cytotoxicity has precluded its use as an effective antiviral drug. The development of new series of iminosugars might permit the identification of more potent and selective glycosidase inhibitors with improved biological profiles.

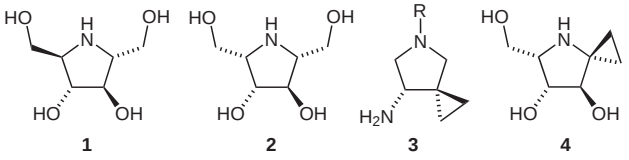
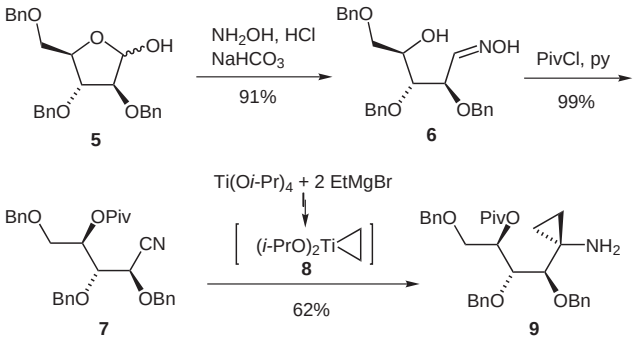


Figure 1

The spirocyclopropyl moiety is part of the structure of a number of bioactive molecules like sitafloxacin (DU-6859, **3**), a potent antibacterial agent.[6] The three-membered ring was identified as a prominent pharmacophore that induces essential binding interactions with the biological receptor. However, the introduction of a spirocyclopropyl group in the structure of iminosugars has not been achieved yet. To our minds, such compounds should have great potential due to conformational and electronic modifications in the structure of iminosugars, which might induce new and potent interactions in the binding site of glycosidases. We present here the synthesis of spirocyclopropyl polyhydroxypyrrolidine (**4**, Figure 1) based on a straightforward titanium-mediated transformation of a sugar-derived nitrile into the corresponding cyclopropylamine with concomitant cyclization.

The conversion of aromatic or aliphatic nitriles into primary cyclopropylamines can readily be achieved by using Grignard reagents, in the presence of titanium tetraisopropoxide.[7] The reactive intermediate involved in this transformation is assumed to be a titanacyclopropane. Recently, we described an application of this method to polyfunctionalized substrates such as sugar-derived nitriles.[8] A range of protecting groups like acetals, esters or ethers were shown to be well tolerated under the reaction conditions. Particularly, 2,3,5-tri-*O*-benzyl-4-*O*-pivaloyl-D-arabinononitrile (**7**), prepared in two steps from commercially available 2,3,5-tri-*O*-benzyl-D-arabinose (**5**), was smoothly transformed into the corresponding cyclopropylamine **9** by reaction with EtMgBr and Ti(O*i*-Pr)$_4$ (Scheme 1).



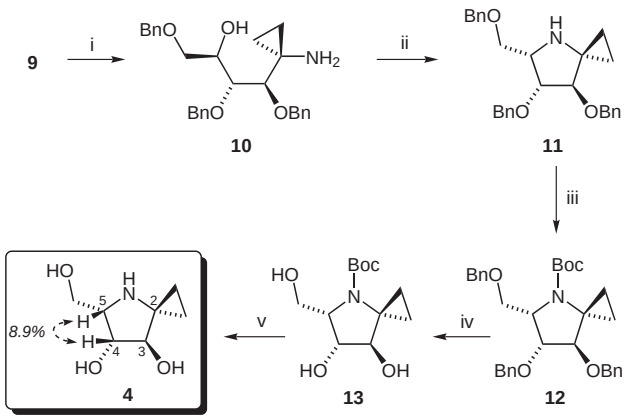
Scheme 1 Synthesis of sugar-derived cyclopropylamine **9**.[8]

In an initial approach we envisioned the synthesis of **4** by simple functional group transformations starting from the cyclopropylamine **9** (Scheme 2). To this purpose, the deprotection of the pivaloyl protecting group (MeONa/MeOH) was followed by mesylation of the free hydroxyl group (MsCl, pyridine). The corresponding mesylate was

SYNLETT 2006, No. 2, pp 0223–0226
Advanced online publication: 23.12.2005
DOI: 10.1055/s-2005-923582; Art ID: G33405ST

not isolated and underwent spontaneous intramolecular nucleophilic displacement with the primary amine to yield pyrrolidine **11** (42%) with inversion of the configuration at the C-5 stereocenter.[9]

We then focused on the deprotection conditions to afford **4**. Hydrogenolysis of benzyl-protected iminosugars is generally a difficult task, due to the presence of the nitrogen base which is known to inhibit the process.[10] Nevertheless, harsh conditions should be used to succeed, which are not compatible with the presence of a cyclopropyl moiety. Therefore, we performed debenzylation on the *N*-Boc protected derivative **12**. The reaction conditions used (2.8% Pd, 1 atm H_2, r.t., 16 h) led the cyclopropyl group unchanged and provided polyhydroxypyrrolidine **13** in 76% yield. Targeted iminosugar **4** was finally obtained in 66% yield after acidic removal of the remaining Boc protection (1 M HCl, 16 h) and purification on a Dowex 50 W-X8 resin (elution with 0.8 M NH_4OH). Compound **4** was isolated as a yellow foam and proved to be quite stable towards air and moisture. The structure of **4** was ascertained by spectral and analytical data.[11]

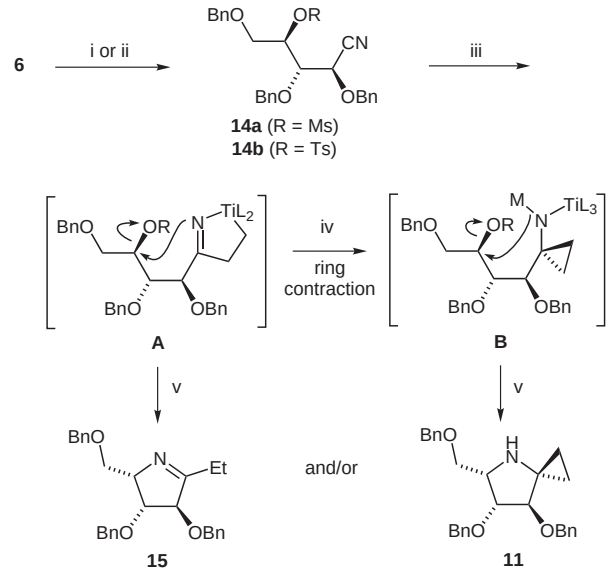


Scheme 2 *Reagents and conditions*: i) MeONa/MeOH, r.t., 48 h, 100%; ii) MsCl, pyridine, 0 °C, 1.5 h, 42%; iii) Boc_2O (2 equiv), Et_3N, THF, r.t., 88%; iv) H_2, 10% Pd/C (2.8% amount of Pd), MeOH, r.t., 16 h, 76%; v) 1 M HCl, r.t., 16 h, then Dowex 50 W-X8, 66%.

A second set of experiments was devoted to an improvement of the synthetic pathway. We reasoned that the introduction of a leaving group (mesyl or tosyl) instead of the pivaloyl protecting group in the starting nitrile would shorten the reaction sequence. Indeed, cyclization might occur in situ during the cyclopropanation step, affording the key intermediate **11** in a more straightforward manner. To this purpose, the initial dehydration of oxime **6** was performed according to previously described procedures[12] either with methanesulfonyl chloride or toluenesulfonyl chloride in pyridine and produced nitrile **14a**[12] and **14b** in 76% and 35% yield, respectively (Scheme 3). Cyclopropanation of **14a** with EtMgBr (2 equiv) and Ti(O*i*-Pr)$_4$ (1 equiv) was carried out according to the previously optimized conditions (Et_2O, –78 °C to r.t. then 1 h at r.t.).[8] Mainly two compounds were isolated from the reaction mixture after hydrolytic work up, which were identified as the targeted pyrrolidine **11** (18%) in addition with the unexpected imine **15** which appeared as the major constituent (47%).

A cyclic titanium iminate has been postulated as intermediate in the aminocyclopropanation reaction, which is thought to undergo a ring contraction into the corresponding three-membered carbacycle.[7b,8] Accordingly, the competing formation of pyrrolidine **11** and imine **15** can be rationalized by an in situ nucleophilic displacement occurring either with the carbacycle **B** or the titanium iminate **A** (Scheme 3).

Though the key ring contraction occurs spontaneously at room temperature when α-alkoxy nitriles like **7** are used as substrates,[7b] the addition of a Lewis acid is required in other cases to afford acceptable yields of the corresponding cyclopropylamines. Accordingly, we investigated the influence of additional $BF_3{\cdot}OEt_2$ on the reaction outcome.



L = O*i*-Pr and/or OR
M = MgBr or BF_3^- (see text)

	15 Yield (%)	**11** Yield (%)
R = Ms (without $BF_3{\cdot}OEt_2$)	47%	18%
R = Ms (addition of $BF_3{\cdot}OEt_2$ after 60 min)	45%	17%
R = Ms (addition of $BF_3{\cdot}OEt_2$ after 10 min)	20%	42%
R = Ts (addition of $BF_3{\cdot}OEt_2$ after 60 min)	–	20%

Scheme 3 *Reagents and conditions*: i) MsCl (6 equiv) in pyridine, 0 °C to r.t., 3 h, 76%; ii) TsCl (6 equiv) in pyridine, 70 °C, 8 h, 35%; iii) EtMgBr (2.2 equiv), Ti(O*i*-Pr)$_4$, –78 °C to r.t.; iv) $BF_3{\cdot}OEt_2$ (2 equiv); v) H_2O.

The addition of $BF_3{\cdot}OEt_2$ to the reaction mixture after 60 minutes at room temperature did modify neither the yields nor the ratio of the products. In contrast, a rapid addition of the Lewis acid after 10 minutes at room temperature greatly improved the yield of the targeted pyrrolidine **11** (42%) at the expense of imine **15** (20%).[13] Coordination of $BF_3{\cdot}OEt_2$ to the nitrogen atom of the five-membered titanacycle **A** would induce a more efficient ring contraction into **B**, limiting the formation of the imine **15**.

Cyclopropanation of tosylate **14b** in the presence of $BF_3{\cdot}OEt_2$ gave **11** as the only reaction product. No trace of by-product **15** was observed in the crude reaction mixture by ^1H NMR. It was assumed that the nucleophilic displacement of the secondary tosyl leaving group in **A** was slow enough to permit the initial ring contraction into intermediate **B**. Unfortunately, the synthesis of substrate **14b** as well as its cyclopropanation were low yielding, which precluded the use of this compound on a preparative scale.

In short, two alternative routes were explored for the synthesis of protected azasugar **11** from the protected arabinose **5**. According to Scheme 1 and Scheme 2, **11** was obtained in 5 steps and 24% overall yield whereas only 3 steps (36% overall yield) were required via the mesylate **14a** (Scheme 3). This latter procedure was greatly improved by the time-controlled addition of $BF_3{\cdot}OEt_2$ during the aminocyclopropanation–cyclization step. Deprotection of azasugar **11** to target compound **4** was achieved in 44% overall yield via the *N*-Boc derivative **12**.

In summary, the first synthesis of a spiro cyclopropyl iminosugar was achieved in a few steps from a carbohydrate-derived nitrile. This synthetic approach seems to be general and constitutes a useful methodology for the synthesis of this new class of compounds. Work is in progress to extend this methodology to the synthesis of a series of azasugars in order to evaluate their biological properties.

Acknowledgment

The authors thank the 'Ministère de l'Enseignement Supérieur et de la Recherche' for a doctoral fellowship (C.L.) and the Université de Reims-Champagne-Ardenne (BQR program 2004) for a financial support.

References and Notes

(1) (a) Asano, N.; Kato, A.; Miyauchi, M.; Kizy, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625. (b) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280. (c) Wrodnigg, T. M.; Withers, S. G.; Stütz, A. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1063. (d) 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. (e) Behr, J.-B.; Guillerm, G. *Tetrahedron: Asymmetry* **2003**, 111. (f) Tschamber, T.; Gessier, F.; Dubost, E.; Newsome, J.; Tarnus, C.; Kohler, J.; Neuburger, M.; Streith, J. *Bioorg. Med. Chem.* **2003**, *11*, 3559. (g) Carmona, A. T.; Popowycz, F.; Gerber-Lemaire, S.; Rodriguez-Garcia, E.; Schütz, C.; Vogel, P.; Robina, I. *Bioorg. Med. Chem.* **2003**, *11*, 4897. (h) Behr, J.-B.; Chevrier, C.; Defoin, A.; Tarnus, C.; Streith, J. *Tetrahedron* **2003**, *59*, 543. (i) Chevrier, C.; LeNouen, D.; Neuburger, M.; Defoin, A.; Tarnus, C. *Tetrahedron Lett.* **2004**, *45*, 5363. (j) Wrodnigg, T. M.; Diness, F.; Gruber, C.; Häusler, H.; Lundt, I.; Rupitz, K.; Steiner, A. J.; Stütz, A. E.; Tarling, C. A.; Withers, S. G.; Wölfler, H. *Bioorg. Med. Chem.* **2004**, *12*, 3485. (k) Lysek, R.; Vogel, P. *Helv. Chim. Acta* **2004**, *87*, 3167. (l) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349. (m) Asano, N.; Ikeda, K.; Yu, L.; Kato, A.; Takebayashi, K.; Adachi, I.; Kato, I.; Ouchi, H.; Takahata, H.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2005**, *16*, 223. (n) Kim, J. H.; Curtis-Long, M. J.; Seo, W. D.; Lee, J. H.; Lee, B. W.; Yoon, Y. J.; Kang, K. Y.; Park, K. H. *Bioorg. Med. Chem.* **2005**, *15*, 4282. (o) Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Diez, R.; Galvez, J. A. *Synlett* **2005**, 1734.

(2) *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, **1999**.

(3) (a) Mehta, A.; Zitzmann, N.; Rudd, P.; Block, T.; Dwek, R. *FEBS Lett.* **1998**, *430*, 17. (b) *Iminosugars: Recent Insights into their Bioactivity and Potential as Therapeutic Agents*, Martin, O. R., Compain, P., Eds. *Curr. Top. Med. Chem.* **2003**, *3*. (c) Fiaux, H.; Popowycz, F.; Favre, S.; Schütz, C.; Vogel, P.; Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *J. Med. Chem.* **2005**, *48*, 4237. (d) Kim, J. H.; Curtis-Long, M. J.; Seo, W. D.; Ryu, Y. B.; Yang, M. S.; Park, K. H. *J. Org. Chem.* **2005**, *70*, 4082.

(4) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stütz, A. E. *Carbohydr. Res.* **1993**, *250*, 67.

(5) 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.

(6) (a) Bogdanovitch, T.; Esel, D.; Kelly, L. M.; Bozdogan, B.; Credito, K.; Lin, G.; Smith, K.; Ednie, L. M.; Hoellman, D. B.; Appelbaum, P. C. *Antimicrob. Agents Chemother.* **2005**, *49*, 3325. (b) Dhople, A. M.; Namba, K. *J. Chemother.* **2003**, *15*, 47.

(7) (a) Bertus, P.; Szymoniak, J. *Chem. Commun.* **2001**, 1792. (b) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2002**, *67*, 3965. (c) Bertus, P.; Szymoniak, J. *Synlett* **2003**, 265. (d) Laroche, C.; Bertus, P.; Szymoniak, J. *Tetrahedron Lett.* **2003**, *44*, 2485. (e) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2003**, *68*, 7133. (f) Laroche, C.; Harakat, D.; Bertus, P.; Szymoniak, J. *Org. Biomol. Chem.* **2005**, *3*, 3482. (g) Gensini, M.; Kozhushkov, S. I.; Yufit, D. S.; Howard, J. A. K.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2002**, 2499.

(8) Laroche, C.; Behr, J.-B.; Szymoniak, J.; Bertus, P.; Plantier-Royon, R. *Eur. J. Org. Chem.* **2005**, 5084.

(9) The *cis*-relationship between the H-4 and H-5 hydrogen atoms was confirmed by NOE experiments on the final product **4**. The irradiation of H-4 resulted in a NOE (8.9%) on H-5 (Scheme 2).

(10) (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley and Sons: New York, **2001**. (b) Bronislaw, P.; Bartsch, C. *J. Org. Chem.* **1984**, *49*, 4076. (c) Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981.

(11) Selected data for compound **4**: $[\alpha]_D^{20}$ +45 (*c* 0.16, H_2O). ^1H NMR (250 MHz, D_2O): δ = 0.55 (m, 1 H, CH_2CH_2), 0.68 (m, 3 H, CH_2CH_2), 3.37 (ddd, 1 H, *J* = 4.7 Hz, *J* = 6.6 Hz, *J* = 6.6 Hz, H-5), 3.53 (dd, 1 H, *J* = 6.6 Hz, *J* = 11.2 Hz, CH_2OH), 3.60 (d, 1 H, *J* = 1.6 Hz, H-3), 3.66 (dd, 1 H, *J* = 6.6 Hz, *J* = 11.2 Hz, CH_2OH), 4.10 (dd, 1 H, *J* = 1.6 Hz, *J* = 4.7 Hz, H-4). ^{13}C NMR (62.5 MHz, D_2O): δ = 6.1, 12.2, 45.1, 60.5, 61.3, 78.2, 81.9. HRMS-ESI: *m/z* calcd for $C_7H_{13}NO_3 + H^+$: 160.0974; found: 160.0975.

(12) Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 699.

(13) **Typical Procedure for the Cyclopropanation of Nitrile 14a.**

A solution of ethylmagnesium bromide (2.2 mmol, 1 to 2 M in Et_2O) was added at –78 °C under argon to a solution of nitrile **14a** (0.49 g, 1 mmol) and Ti(O*i*-Pr)$_4$ (0.33 mL, 1.1 mmol) in Et_2O (25 mL). The yellow solution was stirred for 10 min, and warmed for ca. 1 h to 0 °C. The orange reaction mixture was warmed directly to r.t. (water bath) and after 10 min, $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added. After stirring for 1 h, 1 N HCl (3 mL) and Et_2O (15 mL) were added. The resulting two clear phases were neutralized with 10% aq NaOH (10 mL) and the mixture was extracted with Et_2O (2×30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (Et_2O–Et_3N, 98:2) giving **15** (86 mg, 20%) and **11** (182 mg, 42%).

Imine **15**: R_f = 0.58 (Et_2O–Et_3N, 98:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.10 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 2.30–2.50 (m, 2 H, CH_2CH_3), 3.73 (d, 2 H, *J* = 4.0 Hz, CH_2OBn). 4.21 (m, 2 H), 4.47–4.62 (m, 7 H), 7.20–7.40 (m, 15 H, Ar-H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 10.5, 25.2, 68.7, 70.6, 73.0, 73.1, 73.8, 84.5, 88.4, 127.8–128.9, 138.4, 138.5, 139.0, 179.7.

Cyclopropylamine **11**: R_f = 0.10 (Et_2O–Et_3N, 98:2). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.55–0.72 (m, 3 H, cyclopropyl-H), 0.92 (m, 1 H, cyclopropyl-H), 3.60–3.72 (m, 4 H, H-3, H-5, H-6$_{a,b}$), 4.11 (dd, 1 H, *J* = 1.6 Hz, *J* = 4.3 Hz, H-4), 4.40 (d, 1 H, J_{AB} = 12.0 Hz, CH_2Ph), 4.50–4.60 (m, 5 H, -CH_2Ph), 7.20–7.40 (m, 15 H, Ar-H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 8.3, 12.6, 44.6, 60.2, 69.2, 71.7, 72.1, 73.5, 84.7, 86.8, 127.58–128.54, 138.4, 138.4, 138.5. HRMS-ESI: *m/z* calcd for $C_{28}H_{31}NO_3 + H^+$: 430.2382; found: 430.2375.