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Bioorganic & Medicinal Chemistry 14 (2006) 4047–4054
Bioorganic & Medicinal Chemistry

Spirocyclopropyl pyrrolidines as a new series of α-L-fucosidase inhibitors

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Received 14 December 2005; revised 24 January 2006; accepted 3 February 2006
Available online 20 February 2006

Abstract—Polyhydroxy 4-azaspiro[2.4]heptane derivatives (spirocyclopropyl iminosugars) were prepared in four to six steps from readily available protected aldoses. The key step of the reaction sequence involves a titanium-mediated aminocyclopropanation of glycononitriles with subsequent cyclization. Five new polyhydroxypyrrolidines so-obtained have been evaluated for their ability to inhibit 16 glycosidases. One of them exhibits selective inhibition of α-L-fucosidase from bovine kidney (K_i = 1.6 μM, competitive).

1. Introduction

Fucosyltransferases and α-L-fucosidases are involved in the processing of fucosylated glycoconjugates.[1–3] Owing to the great variety of physiological and pathological events relevant to fucose-containing oligosaccharides,[4–6] increasing attention has been drawn to the mode of action and inhibition of these enzymes. For instance, human α-1,3-fucosyltransferase, responsible for the production of sialyl Le^x,[7,8] is a potential target for the development of antiinflammatory agents.[9] On the other hand, high activity and aberrant distribution of α-fucosidases have been observed in cancer cells.[10,11] Consequently, fucosidases have been recognized as diagnostic markers for the early detection of colorectal and hepatocellular cancers. Moreover, α-fucosidase inhibitors have also been found to reduce HIV-infection, certainly by altering the glycosylation pattern of viral glycoproteins responsible for host cell surface binding.[12–14]

Much effort has been devoted towards the synthesis and biological evaluation of fucosyltransferase and fucosidase inhibitors. Nitrogen-containing fucose analogues such as 1,5-dideoxy-1,5-iminoalditols like deoxyfuconojirimycin **1**, or 1,4-dideoxy-1,4-iminoalditols **2**–**11** were shown to interfere with the fucose-processing enzymes (Fig. 1). It is usually postulated that these iminosugars compete with the natural substrate (a fucose glycoside or fucose-GDP) by mimicking its charge distribution and hydroxyl group topography at the transition state of the biocatalytic reaction.[15–17] Thus, deoxyfuconojirimycin **1** is the most potent inhibitor of α-L-fucosidase known so far (K_i = 5 nM).[18]

The five-membered-ring iminosugars featuring a methyl group at C-5 also displayed potent fucosidase inhibition properties (K_i = 8 nM for **4** and K_i = 10 nM for **2**; K_i in the micromolar range for other structures). A variety of configurations have been encountered in the pyrrolidine series (Fig. 1).[19–23] Moreover, Wong et al. have reported a synergistic inhibition of fucosyltransferase by iminosugar **7** in combination with GDP.[24] Other iminosugar-based fucosyltransferase inhibitors have been described since then.[25,26] Finally, the protected iminosugar **11** displayed a pronounced anti-HIV activity (50% reduction of virus yield in infected cells at 20 μM).[13]

We have recently explored the aminocyclopropanation of protected carbohydrates,[27] with the aim of synthesizing new cyclopropane-containing sugar analogues.[28]

Keywords: Azasugars; Glycosidases; Inhibition; Spiro compounds.
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doi:10.1016/j.bmc.2006.02.005

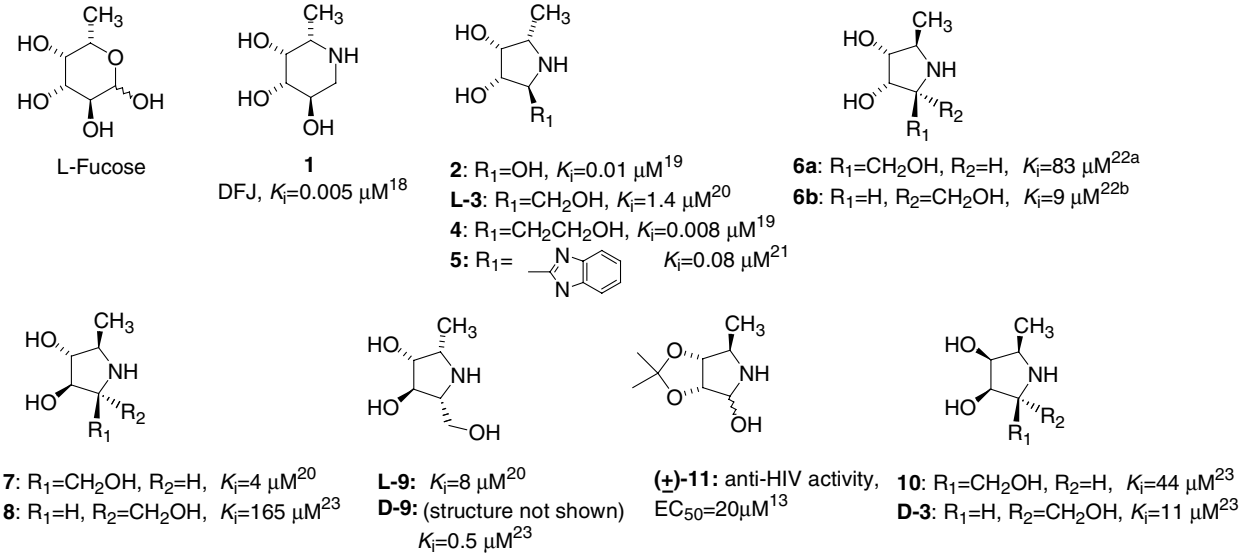


Figure 1. Structures of compounds **1**–**11** and their inhibitory activities on α-L-fucosidase from bovine kidney.

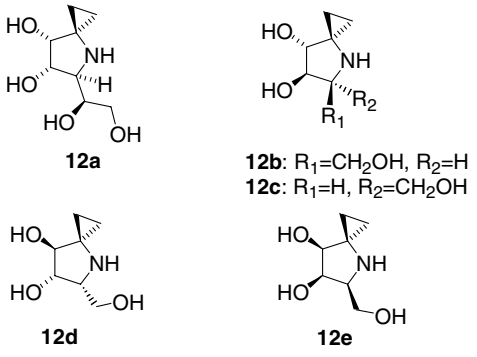


Figure 2. Structures of iminosugars **12a**–**e**.

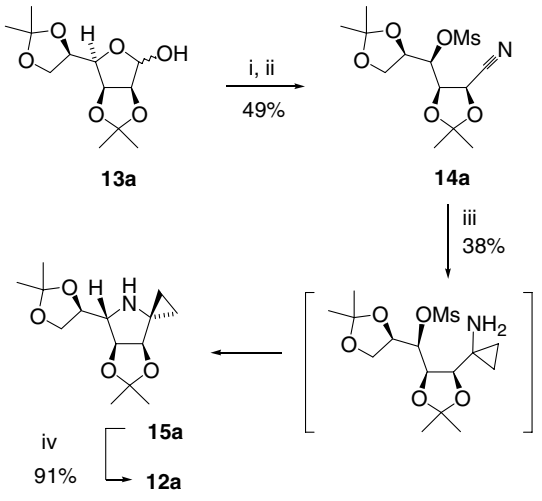
The replacement of the C-5 methyl group in structures like **2**–**11** by a spirocyclopropane ring could induce electronic and conformational modifications and consequently enhance the binding interactions towards the biological receptor. Accordingly, we describe herein the synthesis as well as the biological evaluation on α-L-fucosidase and other glycosidases of a series of spirocyclopropyliminosugars **12a**–**e** (Fig. 2).

2. Results and discussion

2.1. Chemistry

Titanium-mediated aminocyclopropanation of nitriles is a very convenient reaction that has been studied in our laboratories for several years.[29] Though highly reactive entities are involved in the process, we recently applied this transformation to functionalized substrates such as protected carbohydrates.[27] Our first trials to synthesize a spirocyclopropyl iminosugar based on this chemical transformation have also been reported in a previous communication.[28]

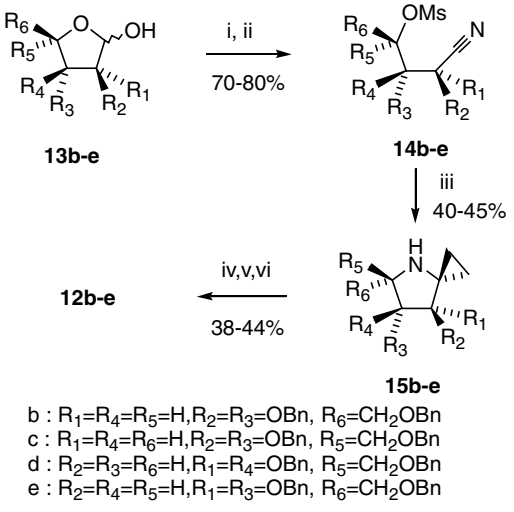
Since nitriles can easily be obtained from aldehydes, we envisioned the fully protected aldoses **13a**–**e** as starting materials for the synthesis of the targeted spirocyclopropyl iminosugars **12a**–**e**. As described in Scheme 1, the reaction of the commercially available D-mannose derivative **13a** with hydroxylamine hydrochloride in the presence of a base ($NaHCO_3$) afforded the corresponding aldoxime, which in turn was treated with an excess of methanesulfonyl chloride in pyridine. Dehydration occurred together with the mesylation of the C-5 free hydroxyl group to afford the nitrile **14a**[30] in acceptable yield (49%). Cyclopropanation of **14a** required the initial formation of the reactive organometallic species, resulting from the reaction of EtMgBr (2 equiv) with $Ti(O\text{-}^iPr)_4$. Under these conditions, a titanacyclopropane generated in situ reacted with the nitrile to form the corresponding cyclopropylamine.[29] The mechanism of this multistep transformation has been postulated in a previous communication[29a] and might be related to



Scheme 1. Synthesis of compound **12a**. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, $EtOH/H_2O$; (ii) MsCl, pyridine; (iii) EtMgBr (2.2 equiv), $Ti(O^iPr)_4$, −78 °C to rt, then $BF_3{\cdot}OEt_2$ (2 equiv), then H_2O; (iv) 1 M HCl, rt, then Dowex 50 W-X8.

the analogous Kulinkovitch and De Meijere reactions.[31] Titanium tetraisopropoxide (1 equiv) and EtMgBr (2 equiv) were added to an ethereal solution of **14a** at −78 °C and the resulting yellow solution was slowly warmed up to 0 °C. The addition of $BF_3{\cdot}OEt_2$ was required at this stage of the reaction to afford the targeted cyclopropylamine. As expected, cyclization occurred in situ, arising from the intramolecular nucleophilic displacement of the mesylate by the cyclopropylamine moiety. Protected azasugar **15a** was isolated in pure form in 38% yield, after neutralization of the reaction mixture and purification by column chromatography. Standard deprotection of the isopropylidene and subsequent purification by ion-exchange chromatography (Dowex 50WX-8, elution with 0.8 M NH_4OH) afforded azasugar **12a** as a white solid. According to previous observations,[28] the ring closure was assumed to occur with inversion of the configuration at the C-4 stereocenter of the D-mannose starting compound. Thus, azasugar **12a** might be regarded as an analogue of the potent α-L-fucosidase inhibitor **4** with a supplementary hydroxyl group on the side arm and a spiro cyclopropyl group in place of the L-configured methyl substituent. Other L-fucosidase inhibitors have been prepared following a related approach using also diacetonide D-mannose **13a**.[21]

The syntheses of spirocyclopropyl azasugars **12b–e** were performed by an analogous procedure, starting from 2,3,5-tri-*O*-benzylated furanoses **13b–e** (Scheme 2). Tri-*O*-benzyl-D-arabinose **13b** and its enantiomer **13d** are commercially available. Protected L-xylose **13c**[32] and D-ribose **13e**[33] were prepared according to previously published procedures via their methylglycofuranosides. Conversion to the corresponding glyconitriles **14b–e** was performed in two steps as above, by the reaction with hydroxylamine and the dehydration/mesylation process with an excess of methanesulfonyl chloride



Scheme 2. Synthesis of stereoisomers **12b–e**. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, $NaHCO_3$, $EtOH/H_2O$; (ii) MsCl, pyridine; (iii) EtMgBr (2.2 equiv), $Ti(O\text{-}^iPr)_4$, −78 °C to rt, then $BF_3{\cdot}OEt_2$ (2 equiv), then H_2O; (iv) Boc_2O (2 equiv), NEt_3, THF; (v) H_2, Pd/C, MeOH, rt; (vi) 1 M HCl, rt, then Dowex 50 W-X8.

(70–80% overall yield). The cyclopropanation/cyclization procedure was conducted in the presence of $Ti(O\text{-}^iPr)_4$/2 EtMgBr and $BF_3{\cdot}OEt_2$, which afforded the benzyl-protected azasugars **15b–e** (38–45% yield). The structures of the so-formed pyrrolidines were confirmed by HRMS and NMR experiments. In particular, the relatively high-field chemical shift of the C-5 methine carbon atoms at δ_C 58–64 indicated that they must be bonded to nitrogen (the ^{13}C NMR chemical shifts of the corresponding carbon atoms in furanoses **13b–e** are δ_C 75–80). The final step involved exhaustive debenzylation of pyrrolidines **15b–e**. This is usually a difficult task since the presence of nitrogen is known to inhibit the hydrogenolysis of *O*-benzyl-protecting groups. The introduction of HCl or AcOH in the reaction mixture as well as the use of black Pd or ammonium formate for hydrogen transfer allowed to overcome these drawbacks. However, the cyclopropyl group might also be transformed under these harsh reaction conditions. Nevertheless, debenzylation of **15b–e** was smoothly achieved after *N*-Boc protection of the cyclic secondary amine. Subsequent acidic removal of the urethane moiety followed by ion-exchange chromatography provided the targeted iminosugars **12b–e**. The process, as a whole, was successful and purification was not required in each individual step. Azasugars **12b–e** were isolated as very hygroscopic yellow solids and their structures were confirmed by spectral and analytical data.

2.2. Glycosidase-inhibition assays

Spirocyclopropyl azasugars **12a–e** have been evaluated for their inhibitory activities towards α-L-fucosidase from bovine kidney as well as fifteen other commercially available glycosidases (Table 1). Apart from a very weak inhibition (9% and 16%, respectively) towards β-galactosidases from bovine liver and *Aspergillus orizae*, pyrrolidine **12a** was a potent and selective inhibitor of α-L-fucosidase (96%). Kinetic analysis revealed a competitive inhibition pattern, with $K_i = 1.6\ \mu M$. Azasugar **12a** did not inhibit the other glycosidases at the maximum tested concentration of 1 mM: coffee beans and *Escherichia coli* α-galactosidase, *E. coli* β-galactosidase, yeast and rice α-glucosidases, *Aspergillus niger* and *rhizopus* mold amyloglucosidases, almonds β-glucosidase, and jack beans α-mannosidase, *Helix pomatia* β-mannosidase, *A. niger* β-xylosidase, jack beans and bovine kidney β-*N*-acetyl-glucosaminidase.

The four stereoisomers **12b–e** are much weaker inhibitors of α-L-fucosidase than analogue **12a** but, despite their marked differences in their absolute configurations, **12b–e** display very similar affinities towards this enzyme (41–55% inhibition at 1 mM). They also inhibit β-galactosidase from bovine liver (24–73%) to a larger extent than **12a**. Surprisingly, the D-*arabino* configurated azasugar **12c** is a moderate inhibitor of amyloglucosidases from *A. niger* ($IC_{50} = 100\ \mu M$) and *rhizopus* mold ($IC_{50} = 47\ \mu M$) but is completely inactive towards other α-glucosidases. This behaviour is very similar to that observed for polyhydroxylated pyrrolizidines like casuarine or analogues.[34] Stereoisomers **12d**,**e** are weak inhibitors of rice α-glucosidase (11% and 45%,

Table 1. Inhibition data of compounds **12a**–**e** towards α-L-fucosidase from bovine kidney

Enzyme	**12a**	**12b**	**12c**	**12d**	**12e**
α-L-Fucosidase					
Bovine kidney	97% IC_{50} = 13 μM K_i = 1.6 μM[a]	49%	50%	41%	55%
β-Galactosidase					
Bovine liver	9%	24%	73%	65%	49%
Aspergillus orizae	16%	—[b]	—	—	—
α-Glucosidase					
Rice	—	—	—	11%	45%
Amyloglucosidase					
Aspergillus Niger	—	—	82%(IC_{50} = 100 μM)	—	—
Rhizopus mold	—	—	84%(IC_{50} = 47 μM)	—	—
β-Glucosidase					
Almonds	—	—	—	—	30%

Inhibition values are expressed as % of inhibition at 1 mM concentration.
[a] Competitive.
[b] No inhibition detected at 1 mM.

respectively), whereas **12b** had no effect on α-glucosidases. In addition, a 30% inhibition of β-glucosidase from almonds was observed for compound **12e**. Stereoisomers **12b**–**e** did not inhibit the other glycosidases at 1 mM.

In contrast to 1-deoxyfuconojirimycin **1**, the structural analogues or epimers of which showed reduced inhibitory activities towards α-L-fucosidase, a variety of configurations are tolerated for polyhydroxypyrrolidines (Fig. 1). This phenomenon has been attributed to the sterically less demanding character of the five-membered half-chair-like inhibitors when compared to six-membered chair-like azasugars. Accordingly, polyhydroxypyrrolidines from either the L-series (compounds **2**–**5**, L-**9**) or the D-series (**6**–**8**, D-**9** and **10**) exhibit fucosidase inhibition in the micromolar range. Nevertheless, the most active isomers possess the all-*cis* orientation of the substituents at positions 3, 4, and 5. Our results are in agreement with this latter observation, since **12a** is the most potent inhibitor among the tested spirocyclopropyl iminosugars. The presence of a spirocyclopropyl substituent, which could mimic the methyl group in either the L- or D-series, seems detrimental for binding to fucosidase. This is particularly obvious when comparing the kinetic values of epimers **8** and L-**9** with their cyclopropyl-bearing analogue **12c**. This result could be attributed either to disfavourable interactions in the binding site or to the inadequate conformation of the pyrrolidine ring induced by the spirocyclopropyl substituent. The synthesis and biological evaluation of a *gem*-dimethyl analogue might permit us to answer this question.

3. Conclusion

Efficient syntheses of new iminosugars containing spirocyclopropyl groups are disclosed. One of them, (5*S*,6*R*,7*S*)-6,7-dihydroxy-5-[(1*S*)-1,2-dihydroxyethyl]-4-azaspiro[2.4]heptane **12a**, which shares with L-fucose the same configuration at C-2, C-3, C-4, exhibits potent inhibition of α-L-fucosidase from bovine kidney (K_i = 1.6 μM, competitive). Though **12a** is a weaker α-L-fucosidase inhibitor than analogues **2**, L-**3** or **4** that have a methyl group instead of the cyclopropyl group, it is an attractive lead according to the observed enzyme selectivity. Furthermore, the more pronounced hydrophobic character of the spirocyclopropyl iminosugars makes them valuable models for their biological evaluation as anti-HIV or anti-cancer agents.

4. Experimental

4.1. Chemistry

4.1.1. General information. 2,3:5,6-Di-*O*-isopropylidene-α-D-mannofuranose was purchased from Acros. 2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose and 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose were obtained from Sigma. All reactions were performed under argon. Diethyl ether was distilled from sodium/benzophenone ketyl before use. $Ti(O\text{-}^iPr)_4$ was used as received. Grignard reagents were titrated in THF by menthol in the presence of orthophenanthroline. Merck silica gel F254 (0.2 mm) was used for TLC plates, detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid or an aqueous solution of $KMnO_4$ (2%)/Na_2CO_3 (4%), followed by heating. Flash column chromatography was performed over silica gel Merck 9385 (40–63 μm) Kieselgel 60. NMR spectra were recorded on a Bruker AC 250 spectrometer (250 MHz for ^1H, 62.5 MHz for ^{13}C). Chemical shifts are expressed in parts per million using TMS as internal standard. Coupling constants are in hertz and splitting pattern abbreviations are: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter in the specified solvents. High-resolution mass spectra (HRMS) were performed on Q-TOF Micro micromass positive ESI (CV = 30 V).

4.1.2. Representative procedure for the preparation of glyconononitriles: 2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-D-arabinononitrile (14b). To a stirred solution of NH_2O-H·HCl (6.40 g, 92 mmol) in EtOH (70 mL) and H_2O (70 mL) was added $NaHCO_3$ (6.70 g, 80 mmol) by small

portions. After 15 min at rt, the protected aldose **13b** (8.40 g, 20 mmol) was slowly added and the resulting mixture was reacted for 2 h at rt. The mixture was extracted with Et_2O (3× 50 mL), dried ($MgSO_4$), filtered and evaporated to give the corresponding oxime, which was used as crude material in the next step.

A solution of the so-obtained oxime (1.46 g, 3.36 mmol) in pyridine (5 mL) was slowly added to a cold (0 °C) solution of MsCl (1.72 mL, 22.4 mmol) in pyridine (5 mL). The mixture was warmed to rt and left to react for 3 h. The reaction was quenched with cold water (30 mL) and the resulting solution was extracted with EtOAc (2× 50 mL). The organic phases were combined, dried ($MgSO_4$) and evaporated to give **14b** (1.27 g, 76%) as a colourless oil after purification by silica gel column chromatography (petroleum ether/EtOAc 70:30). $[\alpha]_D^{20}$ −21 (*c* 5.5, $CHCl_3$) (lit.[30] $[\alpha]_D^{20}$ −25 (*c* 1.0, $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, 15H), 5.10 (m, 1H), 4.84 (d, 1H, J = 11.1 Hz), 4.82 (d, 1H, J = 11.1 Hz), 4.71 (d, 1H, J = 11.1 Hz), 4.59 (d, 1H, J = 11.1 Hz), 4.56 (s, 2H), 4.41 (d, 1H, J = 4.2 Hz), 4.10 (dd, 1H, J = 5.6, 4.2 Hz), 3.93 (dd, 1H, J = 11.2, 3.3 Hz), 3.79 (dd, 1H, J = 11.2, 6.1 Hz), 3.00 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.2 (C_q), 136.5 (C_q), 135.2 (C_q), 128.6–127.9 (CH), 116.5 (C_q), 78.8 (CH), 77.3 (CH), 75.0 (CH_2), 73.5 (CH_2), 73.1 (CH_2), 68.0 (CH_2), 67.4 (CH), 38.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_6SNa$ 518.1613 $(M+Na)^+$, found 518.1625.

4.1.3. 2,3:5,6-Di-*O*-isopropylidene-4-*O*-methanesulfonyl-D-mannononitrile (14a). The nitrile **14a** (934 mg, 49% over two steps) was prepared from **13a** (1.47 g, 5.65 mmol) using the procedure described for **14b**. $[\alpha]_D^{20}$ +48 (*c* 0.76, $CHCl_3$) (lit.[30] $[\alpha]_D^{20}$ +52 (*c* 1.0, $CHCl_3$)); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.92 (d, 1H, J = 5.0 Hz), 4.80 (t, 1H, J = 9 Hz), 4.31–4.22 (m, 2H), 4.16–4.02 (m, 2H), 3.12 (s, 3H), 1.55 (s, 3H), 1.48 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 117.0 (C_q), 112.4 (C_q), 112.0 (C_q), 81.2 (CH), 78.2 (CH), 74.5 (CH), 68.1 (CH_2), 67.0 (CH), 39.3 (CH_3), 27.3 (CH_3), 26.6 (CH_3), 26.0 (CH_3), 25.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{13}H_{22}NO_7S$ 336.1117 $(M+H)^+$, found 336.1119.

4.1.4. 2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-L-xylononitrile (14c). The nitrile **14c** (874 mg, 80% over two steps) was prepared from **13c** (925 mg, 2.20 mmol) using the procedure described for **14b**. $[\alpha]_D^{20}$ −39 (*c* 0.6, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.12 (m, 15H), 4.85 (q, 1H, J = 4.7 Hz), 4.76 (d, 1H, J = 11.2 Hz), 4.71 (d, 1H, J = 11.2 Hz), 4.60 (d, 1H, J = 11.1 Hz), 4.38 (d, 1H, J = 11.1 Hz), 4.37 (d, 1H, J = 11.1 Hz), 4.28 (d, 1H, J = 11.1 Hz), 4.18 (d, 1H, J = 4.5 Hz), 3.95 (t, 1H, J = 4.6 Hz), 3.64 (dd, 1H, J = 10.9, 4.4 Hz), 3.48 (dd, 1H, J = 10.9, 5.4 Hz), 2.98 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.5 (C_q), 137.0 (C_q), 135.3 (C_q), 128.4–129.2 (CH), 116.6 (C_q), 79.2 (CH), 77.5 (CH), 75.9 (CH_2), 73.9 (CH_2), 73.2 (CH_2), 68.6 (CH_2), 67.5 (CH), 38.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_6SNa$ 518.1613 $(M+Na)^+$, found 518.1594.

4.1.5. 2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-L-arabinononitrile (14d). The nitrile **14d** (1.27 g, 70% over two steps) was prepared from **13d** (1.55 g, 3.69 mmol) using the procedure described for **14b**. $[\alpha]_D^{20}$ +21 (*c* 1.58, $CHCl_3$) (lit.[30] $[\alpha]_D^{20}$ +24 (*c* 1.45, $CHCl_3$)); ^{1}H NMR and ^{13}C NMR spectra as for the enantiomer **14b**; HRMS (ESI) *m/z* calcd for $C_{27}H_{30}NO_6S$ 496.1794 $(M+H)^+$, found 496.1784.

4.1.6. 2,3,5-Tri-*O*-benzyl-4-*O*-methanesulfonyl-D-ribononitrile (14e). The nitrile **14e** (1.25 g, 73% over two steps) was prepared from **13e** (1.45 g, 3.45 mmol) using the procedure described for **14b**. $[\alpha]_D^{20}$ +57 (*c* 2.2, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40–7.25 (m, 15H), 5.07 (m, 1H), 4.90 (d, 1H, J = 11.0 Hz), 4.82 (d, 1H, J = 11.0 Hz), 4.72 (d, 1H, J = 11.0 Hz), 4.50 (m, 4H), 4.13 (m, 1H), 3.70 (m, 2H), 3.12 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.6 (C_q), 136.9 (C_q), 135.5 (C_q), 129.2–128.3 (CH), 116.7 (C_q), 79.9 (CH), 78.1 (CH), 75.1 (CH_2), 73.9 (CH_2), 73.1 (CH_2), 68.8 (CH_2), 68.6 (CH), 39.1 (CH_3); HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_6SNa$ 518.1613 $(M+Na)^+$, found 518.1612.

4.1.7. Representative procedure for the Ti-mediated cyclopropanation of glyconononitriles: (5*S*,6*R*,7*S*)-6,7-dibenzyloxy-5-benzyloxymethyl-4-azaspiro[2.4]heptane (15e). A solution of titrated ethylmagnesium bromide (2.2 mmol, 1–2 M in diethyl ether) was added at −78 °C under argon to a solution of nitrile **14e** (496 mg, 1 mmol) and $Ti(O\text{-}^iPr)_4$ (330 μL, 1.1 mmol) in Et_2O (25 mL). The yellow solution was warmed for ca. 1 h to 0 °C. The orange reaction mixture was warmed directly to room temperature (water bath) and after 10 min, $BF_3{\cdot}OEt_2$ (0.25 mL, 2 mmol) was added. The solution was stirred for 1 h at rt and 1 N HCl (3 mL) and ether (15 mL) were then added. The resulting two clear phases were neutralized with 10% aq NaOH (10 mL) and the mixture was extracted with diethyl ether (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/NEt_3 98:2) giving **15e** (182 mg, 45%) as a colourless oil. $[\alpha]_D^{20}$ −34 (*c* 4.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.14 (m, 15H), 4.62 (d, 1 H, J = 12.0 Hz), 4.55–4.39 (m, 5H), 4.14 (dd, 1H, J = 5.8, 4.4 Hz), 3.74–3.61 (m, 2H), 3.56–3.45 (m, 2H), 2.41 (br s, NH), 0.98–0.85 (m, 1H), 0.68–0.50 (m, 2H), 0.26 (ddd, 1H, J = 10.2, 5.4, 3.3 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.6 (C_q), 138.4 (C_q), 138.3 (C_q), 128.4–128.3 (CH), 127.7–127.4 (CH), 82.2 (CH), 80.3 (CH), 73.2 (CH_2), 73.0 (CH_2), 72.0 (CH_2), 70.3 (CH_2), 58.6 (CH), 42.8 (C_q), 11.9 (CH_2), 8.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{28}H_{32}NO_3$ 430.2382 $(M+H)^+$, found 430.2377.

4.1.8. (5*S*,6*R*,7*S*)-6,7-Di-*O*-isopropylidene-6,7-dihydroxy-5-[(1*S*)-1,2-di-*O*-isopropylidene-1,2-dihydroxyethyl]-4-azaspiro[2.4]heptane (15a). The cyclopropane **15a** (127 mg, 38%) was prepared from **14a** (420 mg, 1.25 mmol) using the procedure described for **15e**. $[\alpha]_D^{20}$ +36 (*c* 1.15, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.45 (d, 1H, J = 5.6 Hz), 4.15–3.98 (m, 3H), 3.63 (t, 1H, J = 7.1 Hz), 3.18 (br d, 1H, J = 7.9 Hz), 2.81 (br s, NH), 1.44 (s, 3H), 1.36 (s, 3H), 1.28 (s, 3H), 1.23 (s,

3H), 0.91–0.52 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 111.3 (C_q), 109.3 (C_q), 86.9 (CH), 84.5 (CH), 75.1 (CH), 68.2 (CH), 67.0 (CH_2), 45.0 (C_q), 26.6 (CH_3), 26.4 (CH_3), 25.3 (CH_3), 24.2 (CH_3), 15.5 (CH_2), 5.6 (CH_2); HRMS (ESI) *m/z* calcd for $C_{14}H_{24}NO_4$ 270.1705 $(M+H)^+$, found 270.1702.

4.1.9. (5*S*,6*R*,7*R*)-6,7-Dibenzyloxy-5-benzyloxymethyl-4-azaspiro[2.4]heptane (15b). The cyclopropane **15b** (146 mg, 42%) was prepared from **14b** (400 mg, 0.81 mmol) using the procedure described for **15e**. $[\alpha]_D^{20}$ +22 (*c* 3.4, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.21 (m, 15H), 4.59–4.49 (m, 5H), 4.37 (d, 1H, *J* = 12.1 Hz), 4.10 (dd, 1H, *J* = 4.2, 1.6 Hz), 3.75–3.59 (m, 4H), 1.81 (br s, NH), 0.96–0.55 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.2 (C_q), 128.3–128.2 (CH), 127.7–127.3 (CH), 86.5 (CH), 84.5 (CH), 73.3 (CH_2), 71.9 (CH_2), 71.4 (CH_2), 69.0 (CH_2), 60.0 (CH), 44.3 (C_q), 12.4 (CH_2), 8.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{28}H_{32}NO_3$ 430.2382 $(M+H)^+$, found 430.2375.

4.1.10. (5*R*,6*R*,7*R*)-6,7-Dibenzyloxy-5-benzyloxymethyl-4-azaspiro[2.4]heptane (15c). The cyclopropane **15c** (270 mg, 40%) was prepared from **14c** (776 mg, 1.57 mmol) using the procedure described for **15e**. $[\alpha]_D^{20}$ +52 (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.25 (m, 15H), 4.57–4.51 (m, 5H), 4.45 (d, 1H, *J* = 11.9 Hz), 4.04 (dd, 1H, *J* = 4.7, 1.6 Hz), 3.66–3.55 (m, 3H), 3.35 (q, 1H, *J* = 4.9 Hz), 2.51 (br s, NH), 0.95–0.66 (m, 3H), 0.62–0.52 (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.3 (C_q), 138.2 (C_q), 128.4–128.3 (CH), 127.7–127.5 (CH), 88.5 (CH), 87.5 (CH), 73.2 (CH_2), 71.9 (CH_2), 70.9 (CH_2), 70.0 (CH_2), 63.9 (CH), 44.9 (C_q), 12.5 (CH_2), 7.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_{28}H_{32}NO_3$ 430.2382 $(M+H)^+$, found 430.2387.

4.1.11. (5*R*,6*S*,7*S*)-6,7-Dibenzyloxy-5-benzyloxymethyl-4-azaspiro[2.4]heptane (15d). The cyclopropane **15d** (172 mg, 40%) was prepared from **14d** (500 mg, 1.01 mmol) using the procedure described for **15e**. $[\alpha]_D^{20}$ −24 (*c* 2.1, $CHCl_3$); ^{1}H NMR and ^{13}C NMR spectra as for the enantiomer **15b**; HRMS (ESI) *m/z* calcd for $C_{28}H_{32}NO_3$ 430.2382 $(M+H)^+$, found 430.2375.

4.1.12. (5*S*,6*R*,7*S*)-6,7-Dihydroxy-5-[(1*S*)-1,2-dihydroxyethyl]-4-azaspiro[2.4]heptane (12a). The diacetonide **15a** (127 mg, 0.47 mmol) was treated with a 1 M HCl solution (2 mL) overnight. Evaporation of the water gave a crude material, which was subjected to ion-exchange chromatography on a Dowex 50WX-8 resin (H^+ form). Elution with 0.8 M NH_4OH permitted us to isolate pure **12a** (81 mg, 91%) as a white solid, after lyophilization of the corresponding fractions. $[\alpha]_D^{20}$ +3.3 (*c* 0.8, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 4.03 (dd, 1H, *J* = 8.1, 4.9 Hz, H-6), 3.63 (dt, 1H, *J* = 7.4, 4.2 Hz, H-1′), 3.47 (d, 1H, *J* = 4.9 Hz, H-7), 3.45 (dd, 1H, *J* = 11.5, 4.2 Hz, H-2′a), 3.23 (dd, 1H, *J* = 11.5, 7.4 Hz, H-2′b), 2.96 (dd, 1H, *J* = 8.1, 4.2 Hz, H-5), 0.73–0.42 (m, 4H); ^{13}C NMR (62.5 MHz, D_2O) δ 75.9 (CH), 73.5 (CH), 71.0 (CH), 64.0 (CH_2), 63.2 (CH), 44.6 (C_q), 11.1 (CH_2), 6.9 (CH_2); HRMS (ESI) *m/z* calcd for $C_8H_{16}NO_4$ 190.1079 $(M+H)^+$, found 190.1085.

4.1.13. Representative procedure for the deprotection of compounds 15b–e: (5*S*,6*R*,7*R*)-6,7-dihydroxy-5-hydroxymethyl-4-azaspiro[2.4]heptane (12b). A solution of **15b** (160 mg, 0.37 mmol), Boc_2O (220 mg, 1 mmol) and NEt_3 (0.23 mL) in THF (5 mL) was stirred for 5 h at rt. Water (5 mL) was then added and the solution was extracted with EtOAc (2× 10 mL). The combined organic phases were dried and evaporated. The Boc derivative was purified before debenzylation by silica gel chromatography (petroleum ether/EtOAc 80:20). The fractions with R_f = 0.5 were dissolved in MeOH (3 mL) and palladium 10% on charcoal (72 mg) was added. Hydrogenolysis was performed overnight and the reaction mixture was filtered on a Celite pad and evaporated. Purification by column chromatography (petroleum ether/EtOAc 10:90) gave the *N*-Boc pyrrolidine as a white solid (73 mg, 76% from **15b**). The compound was then treated overnight with 1 M HCl. Evaporation of the solvents gave a crude material, which was subjected to ion-exchange chromatography (Dowex 50WX-8 resin). Elution with 0.8 M NH_4OH permitted to isolate pure **12b** (26 mg, 44% from **15b**) as a yellowish hygroscopic solid, after lyophilization of the corresponding fractions. $[\alpha]_D^{20}$ +40 (*c* 0.16, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 4.10 (dd, 1H, *J* = 4.6, 1.6 Hz, H-6), 3.66 (dd, 1H, *J* = 11.2, 6.6 Hz, H-1′a), 3.60 (d, 1H, *J* = 1.6 Hz, H-7), 3.53 (dd, 1H, *J* = 11.2, 6.6 Hz, H-1′b), 3.36 (td, 1H, *J* = 6.6, 4.7 Hz, H-5), 0.72–0.50 (m, 4H); ^{13}C NMR (62.5 MHz, D_2O) δ 81.8 (CH), 78.2 (CH), 61.3 (CH), 60.5 (CH_2), 45.0 (C_q), 12.2 (CH_2), 6.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_7H_{14}NO_3$ 160.0974 $(M+H)^+$, found 160.0975.

4.1.14. (5*R*,6*R*,7*R*)-6,7-Dihydroxy-5-hydroxymethyl-4-azaspiro[2.4]heptane (12c). The cyclopropane **12c** (30 mg, 38% over three steps) was prepared from **15c** (215 mg, 0.50 mmol) using the procedure described for **12b**. $[\alpha]_D^{20}$ +58 (*c* 0.52, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 3.95 (dd, 1H, *J* = 5.4, 3.1 Hz, H-6), 3.77 (d, 1H, *J* = 3.1 Hz, H-7), 3.70 (t, 2H, *J* = 5.1 Hz, H-1′a,b), 3.09 (dt, 1H, *J* = 5.4, 5.1 Hz, H-5), 0.83–0.62 (m, 4H); ^{13}C NMR (62.5 MHz, D_2O) δ 82.1 (CH), 80.6 (CH), 65.4 (CH), 61.6 (CH_2), 44.8 (C_q), 11.5 (CH_2), 5.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_7H_{14}NO_3$ 160.0974 $(M+H)^+$, found 160.0977.

4.1.15. (5*R*,6*S*,7*S*)-6,7-Dihydroxy-5-hydroxymethyl-4-azaspiro[2.4]heptane (12d). The cyclopropane **12d** (34 mg, 45% over three steps) was prepared from **15d** (205 mg, 0.48 mmol) using the procedure described for **12b**. $[\alpha]_D^{20}$ −36 (*c* 0.52, H_2O); ^{1}H NMR and ^{13}C NMR spectra as for the enantiomer **12b**; HRMS (ESI) *m/z* calcd for $C_7H_{14}NO_3$ 160.0974 $(M+H)^+$, found 160.0972.

4.1.16. (5*S*,6*R*,7*S*)-6,7-Dihydroxy-5-hydroxymethyl-4-azaspiro[2.4]heptane (12e). The cyclopropane **12e** (38 mg, 38% over three steps) was prepared from **15e** (273 mg, 0.64 mmol) using the procedure described for **12b**. $[\alpha]_D^{20}$ −47 (*c* 0.74, H_2O); ^{1}H NMR (250 MHz, D_2O) δ 4.40 (dd, 1 H, *J* = 5.9, 4.7 Hz, H-6), 3.91 (d, 1 H, *J* = 4.7 Hz, H-7), 3.75 (dd, 1 H, *J* = 11.4, 5.9 Hz, H-1′a), 3.66 (dd, 1 H, *J* = 11.4, 5.9 Hz, H-1′b), 3.35 (q, 1 H, *J* = 5.9 Hz, H-5), 0.90-0.50 (m, 4H); ^{13}C NMR

(62.5 MHz, D_2O) δ 75.4 (CH), 72.9 (CH), 60.4 (CH_2), 60.3 (CH), 43.6 (C_q), 10.1 (CH_2), 7.0 (CH_2); HRMS (ESI) *m/z* calcd for $C_7H_{14}NO_3$ 160.0974 $(M+H)^+$, found 160.0969.

4.2. Enzymatic assays

The experiments were performed essentially as previously described.[35] Briefly, 0.01–0.5 U/mL of enzyme (1 U = 1 mol of glycoside hydrolyzed/min), preincubated for 5 min at 20 °C with the inhibitor, and increasing concentrations of aqueous solution of the appropriate *p*-nitrophenyl glycoside substrates buffered to the optimum pH of the enzyme were incubated for 20 min at 37 °C (45 °C for the amyloglucosidases). The reaction was stopped by the addition of a 2.5 volumes of 0.2 M sodium borate buffer, pH 9.8. The *p*-nitrophenolate formed was quantified at 410 nM, and IC_{50} value was calculated. Double-reciprocal (Lineweaver–Burk) plots were used to determine the inhibition characteristics.

Acknowledgments

The authors thank M. Choumane (undergraduate student) for her help concerning technical aspects of this work and the 'Ministère de l'Enseignement Supérieur et de la Recherche' for a doctoral fellowship (C.L.)

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