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The spirocyclopropyl moiety as a methyl surrogate in the structure of L-fucosidase and L-rhamnosidase inhibitors

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ABSTRACT

Nitrogen-in-the-ring analogues of L-fucose and L-rhamnose were prepared, which feature a spirocyclopropyl moiety in place of the methyl group of the natural sugar. The synthetic route involved a titanium-mediated aminocyclopropanation of a glyconitrile as the key step. Four new spirocyclopropyl iminosugar analogues were generated, which displayed some activity towards L-fucosidase and L-rhamnosidase.

1. Introduction

Fucose and rhamnose are the most abundant 6-deoxyhexoses found in nature. L-Fucose is commonly found in complex carbohydrates from all organisms. In bacterial cells it is a constituent of polysaccharides forming the cell wall.[1] In animal cells, L-fucose is a fundamental component of N- and O-linked glycoproteins or glycolipids, which play role in intercellular adhesion and recognition processes.[2] More specifically, L-fucose is present in ABH blood group antigens and in some Lewis-type oligosaccharides.[3] In sialyl Lewis^x, for instance, L-fucose plays a key role in the recognition by E-selectins present on endothelial cells, an event that mediates leukocytes' extravasation in tissues.[4] In addition, fucosylated oligosaccharides could be involved in the pathogenesis of many diseases.[5,6] L-Rhamnose is widely distributed in plants and bacteria as a component of the cell walls.[7] Rhamnosides are part of various natural bioactive compounds like cytotoxic saponins, plant glycoalkaloids and macrolides as well as terpenol or flavonoid glycosides.[7d,e] L-Rhamnose is also a fundamental component of the surface antigens of many microorganisms and has been identified as a structural element of bacterial virulence factors.[8]

The processing of L-fucose and L-rhamnose, that is, their transfer to or their trimming from a glycoconjugate, is mainly assumed by two classes of enzymes: glycosidases (EC 3.2.1) and glycosyltransferases (EC 2.4.1). Inhibition of these enzymes is an important task, not only to understand the biological functions of 6-deoxyhexoses, but also to develop new therapeutic agents.[9] Iminosugars, which feature the same hydroxyl configurations as the natural carbohydrate substrates, are generally found to interact strongly with the corresponding glyco-enzymes.[10] For instance, L-fuconojirimycin **1**,[11] its deoxy analogue DFJ **2**[12] or the pyrroline **3**[13] (Fig. 1) are potent inhibitors of fucosidase with K_i's in the low μM to the nM range.

Some pyrrolidine derivatives bearing aromatic substituents have also shown good inhibitory properties and good selectivity towards α-L-fucosidases.[14] An important exception to this rule is the lack of L-rhamnosidase inhibition by deoxyrhamnojirimycin (DRJ) **4**, the piperidine analogue of L-rhamnose.[15] By contrast, the C-5 epimer of **4** (compound **5**) displayed an astonishing strong effect on rhamnosidase. To rationalize these results, it was hypothesized that the methyl group at C-5 in the structures of iminosugars **4** or **5** appears to modulate the inhibition by modifying the conformation of the piperidine ring.[15] By analogy, we attempted to control the conformation of 6-deoxyhexoses mimics by introducing a constrained spirocyclopropyl moiety instead of the natural methyl substituent.

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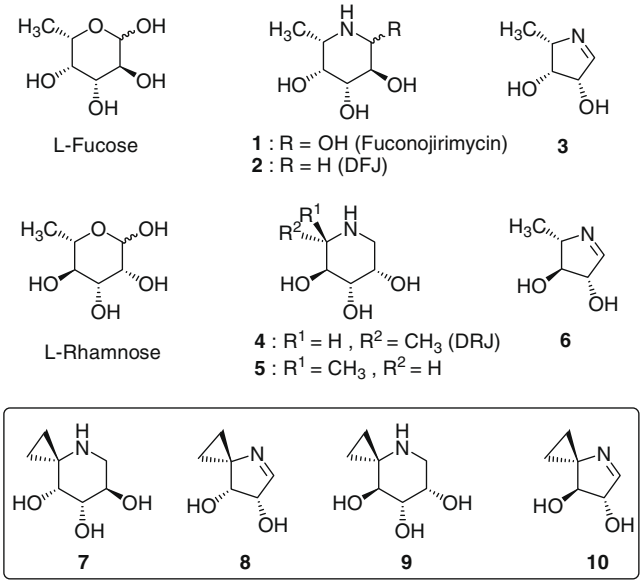


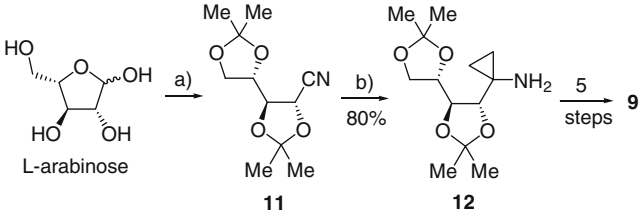
Figure 1. Structures of iminosugars **1**–**10**.

We reported in a preliminary communication the synthesis of spirocyclopropyl-DRJ **9**, using a titanium-mediated aminocyclopropanation of nitriles as the key reaction (Scheme 1).[16] Herein, we report the extension of the method to the preparation of new fucose and rhamnose analogues **7**, **8**, and **10** featuring such a spirocyclopropyl moiety, as well as their inhibition potencies towards glycosidases.

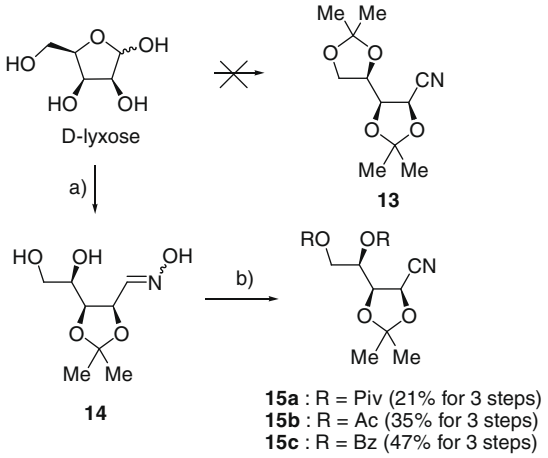
2. Results

2.1. Synthesis of spirocyclopropyl-DFJ 7

For the synthesis of compound **7**, we envisioned to follow a sequence of reactions similar to that used for the synthesis of **9**. The starting sugar is D-lyxose, which features the required hydroxyl distribution to reach the targeted L-fuco configuration of the final product. However, the synthesis of the key intermediate 2,3:4,5-di-*O*-isopropylidene-D-lyxononitrile **13** via the known dithioacetal[17] proved difficult and unsatisfactory yields were obtained when using literature protocols (Scheme 2). To overcome these difficulties, the preparation of a new fully protected lyxononitrile was attempted. We turned our attention to the elaboration of acyl derivatives **15a**–**c**, which could be readily obtained from D-lyxose. Additionally, compounds **15** feature an orthogonal protection pattern, which could simplify the last steps of the reaction sequence. Benzoyl or pivaloyl protecting groups were previously demonstrated to be compatible with selective and efficient cyclopropanation of the nitrile functionality.[18] Thus, synthesis of **15** started with



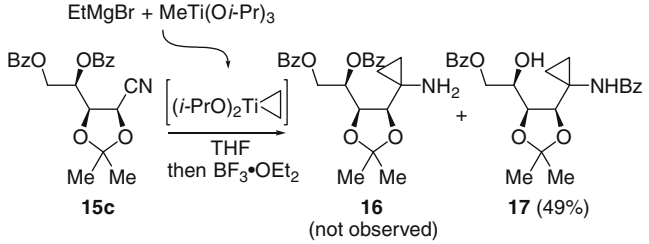
Scheme 1. Preparation of spirocyclopropyl-DRJ **9**. Reagents: (a) (i) HS–$(CH_2)_3$–SH, H^+, (ii) Me_2CO, H^+, (iii) MeI, $CaCO_3$, (iv) $H_2NOH{\cdot}HCl$, (v) MsCl, pyridine; (b) EtMgBr, MeTi(O*i*-Pr)$_3$, then $BF_3{\cdot}OEt_2$.



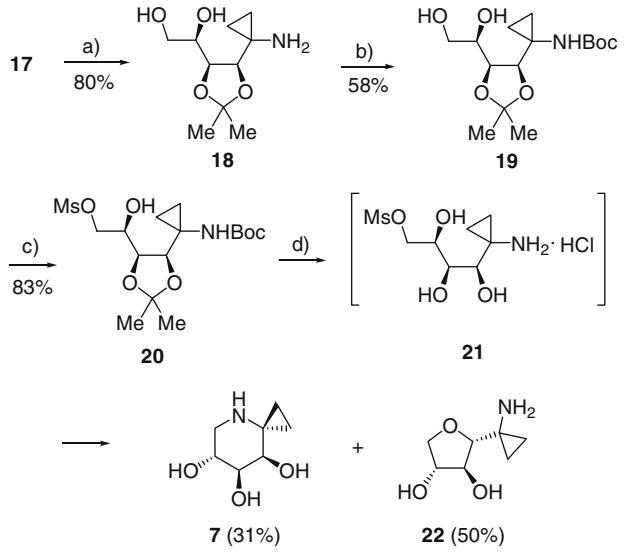
Scheme 2. Preparation of nitrile **13**. Reagents and conditions: (a) (i) Me_2CO, H_2SO_4, rt, (ii) $H_2NOH{\cdot}HCl$, MeONa, MeOH, rt; (b) RCl, pyridine, 70 °C.

the selective protection of D-lyxose as its 2,3-*O*-isopropylidene derivative using standard protocols,[19] followed by condensation with hydroxylamine to give the oxime intermediate **14** in a quantitative manner. We next envisioned to dehydrate the crude oxime **14** by treatment with an excess of acyl chloride, to obtain the corresponding nitrile and to protect simultaneously the free hydroxyl groups. Whereas the reaction of oxime **14** with pivaloyl chloride proved difficult and afforded the target compound **15a** in only 21% isolated yield, acetyl chloride was slightly more efficient and afforded **15b** in 35% yield. Best results were finally obtained with benzoyl chloride, giving the dibenzoyl nitrile derivative **15c** in 47% overall yield in three steps from D-lyxose.

However, cyclopropanation of **15c** with EtMgBr and MeTi(O*i*-Pr)$_3$ did not afford the expected primary amine **16** (Scheme 3). The *N*-benzoyl cyclopropylamine **17** was obtained instead as the major compound in 49% yield. Obviously, a selective migration of the C-4 *O*-benzoyl moiety to the so-formed primary amine has occurred during the reaction. Such an acyl transfer has recently been observed in the analogous reaction sequence applied to tetrabenzoyl-β-D-glucosyl cyanide.[16f] Nevertheless, compound **17** was isolated in preparative amount and was used as a key intermediate for the synthesis of spirocyclopropyl-DFJ **7**. The complete removal of the *N*- and *O*-benzoyl protecting groups was achieved under basic conditions in good yield (80%) to afford the partially protected amine **18** (Scheme 4). On the basis of what was experienced in the L-rhamno series,[16a] the direct cyclization of **18** to the corresponding piperidine was not attempted. *N*-Boc protection was conducted first to preclude side-reactions during the treatment with an activating agent. Thus, the primary amine **18** was treated with Boc_2O to give compound **19** in 58% yield. The primary alcohol was then selectively converted to the corresponding mesylate **20** by careful addition of MsCl at −20 °C in the presence of NEt_3. Simultaneous deprotection of the Boc and acetal protecting groups were carried



Scheme 3. Cyclopropanation of nitrile **15c**.

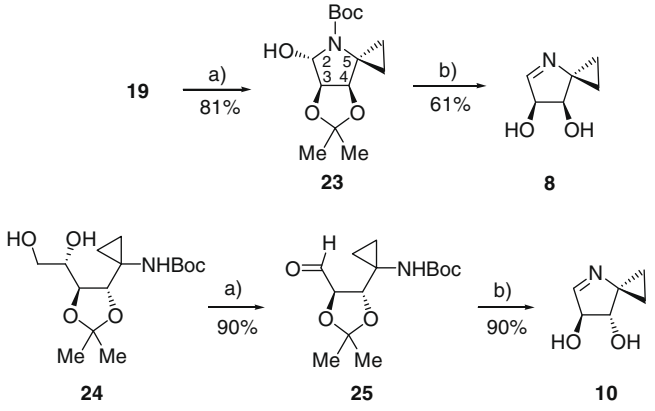


Scheme 4. Preparation of spirocyclopropyl-DFJ **7**. Reagents and conditions: (a) NaOH, EtOH–H_2O, 80 °C, 24 h; (b) Boc_2O, Et_3N, THF, 50 °C, 24 h; (c) MsCl, Et_3N, CH_2Cl_2, −20 °C; (d) HCl 2 N, MeOH, 50 °C, 2 h then K_2CO_3.

out with diluted hydrochloric acid. The so-obtained ammonium salt **21** was next treated with a base to induce the required intramolecular nucleophilic displacement to afford piperidine **7**. However, treatment of **21** with ammonia afforded the *C*-cyclopropylamine furanoid **22** as the only cyclization product. Such a cycloetherification process has been frequently observed as an unexpected side-reaction with activated 1,4-diols, due to kinetically favored formation of the five-membered cycle over the six-membered one.[20] Investigation of the reaction conditions (nature of the base, temperature) to produce **7** were conducted. Finally, preparation of iminosugar **7** was best achieved by treatment of **21** with K_2CO_3 at 0 °C (31% yield from **20**). Both products **7** and **22** were easily separated by flash chromatography over silica gel and the targeted 5-spirocyclopropyl-deoxyfuconojirimycin **7** was further purified by ion-exchange chromatography on Dowex 50WX-8 resin (elution with 0.8 M NH_4OH).

2.2. Synthesis of pyrrolines 8 and 10

The reaction sequence applied to the preparation of pyrroline **8** is depicted in Scheme 5. First, oxidative cleavage of the previously prepared diol **19** with silica-supported $NaIO_4$ afforded the corresponding aldehyde, which spontaneously cyclized to give hemiaminal **23**. Compound **23** proved stable at room temperature and was purified by silica gel chromatography (EtOAc/petroleum ether, 9/1, v/v; 81% isolated yield). According to the ^1H and ^{13}C NMR spectra ($CDCl_3$), **23** appeared as a single anomer. The configuration at the C-2 stereocenter was attributed according to the $J_{2,3}$ coupling constant ($J_{2,3}$ ca. 0 Hz), which is characteristic of a *trans* relationship between both hydrogen atoms for this series of compounds.[21] Deprotection of **23** under acidic conditions (1 M HCl) and purification by ion-exchange chromatography afforded pyrroline **8** in 61% yield.



Scheme 5. Synthesis of pyrrolines **8** and **10**. Reagents and conditions: (a) $NaIO_4$–SiO_2, CH_2Cl_2, rt; (b) 1 M HCl, EtOH, then ion-exchange chromatography.

A similar sequence of reactions then allowed access to the epimeric pyrroline **10** which features the rhamnose-like configuration. Oxidative cleavage of the diol **24**, which was prepared according to the literature protocol,[16a] gave the corresponding aldehyde **25** in 90% yield. The *trans* configured isopropylidene protecting group in compound **25** probably hampers the spontaneous cyclization at this stage. Nevertheless, complete deprotection of **25** (1 M HCl) followed by ion-exchange chromatography afforded the expected pyrroline **10** in 90% isolated yield.

2.3. Enzymatic assays

Iminosugars **7**–**10** were assayed against α-L-fucosidase, naringinase (α-L-rhamnosidase) and a panel of 12 other glycosidases (Table 1). Spirocyclopropyl-DFJ **7** was a potent and very specific inhibitor of α-L-fucosidase (K_i = 18 μM) whereas spirocyclopropyl-DRJ **9** was slightly active against α-L-rhamnosidase (72% inhibition at 1 mM).

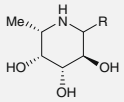
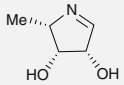
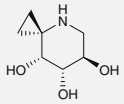
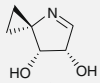
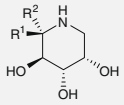
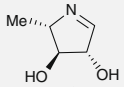
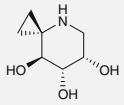
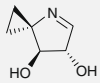
Surprisingly, the *fuco*-configured pyrroline **8** was a weak inhibitor of α-L-fucosidase (76% inhibition at 1 mM) but displayed a strong affinity for the rhamnosidase (K_i = 57 μM). In contrast, the *rhamno*-designed pyrroline **10** did slightly inhibit both the fucosidase (19% inhibition at 1 mM) and the rhamnosidase (72% inhibition at 1 mM). Concerning the other glycosidases tested, compounds **7**–**10** were inactive at the tested concentration of 1 mM towards coffee beans α-galactosidase, *Escherichia coli* and *Aspergillus oryzae* β-galactosidase, yeast and rice α-glucosidase, *Aspergillus niger* amyloglucosidase, almonds β-glucosidase, Jack beans α-mannosidase, snail β-mannosidase, *A. niger* β-xylosidase, Jack beans and bovine kidney β-*N*-acetyl-glucosaminidase.

3. Discussion

We designed spirocyclopropyl iminosugars as glycosidase inhibitors because these bicyclic structures show all properties necessary, that is, (i) an intramolecular nitrogen atom that may be protonated to mimic the oxocarbenium intermediate, (ii) hydroxyl repartition analogous to that of the natural substrate, and (iii) an additional group that could induce favorable interactions in the active site of the enzyme. Indeed, a large hydrophobic pocket surrounds the methyl substituent of fucose in its binding site, as observed in crystal structures extracted from the protein data bank. The cyclopropyl substituent could easily enter this site and favorably interfere with the respective amino acids. Furthermore, we anticipated that the presence of the small spirocyclic moiety would induce conformational modifications in compounds **7**–**10**, which could promote novel and more potent binding interactions. To further explore the SAR within this family of compounds, their inhibition potencies were compared with known inhibitors from the literature (Table 1).

Concerning the six-membered iminosugars, fuconojirimycin **1**, the accurate copy of fucose with nitrogen in the ring, is one of the most potent inhibitor of α-L-fucosidase known so far with K_i = 1 nM. Its 1-deoxy analogue DFJ **2** retains strong inhibition

Table 1
Inhibitory activities of compounds **7**–**10** and structurally related analogues from the literature[a,b]

Compound	α-L-Fucosidase (bovine kidney)	α-L-Rhamnosidase (*Penicillium decumbens*)
	**1** (R = OH) (0.001 μM)[11] **2** (R = H) (0.003 μM)[11]	ND ND
 **3**	(0.010 μM)[13]	ND
 **7**	83% (18 μM)	NI
 **8**	76%	87% (57 μM)
	**4** (R^1 = H, R^2 = CH_3) NI[c,22] **5** (R^1 = CH_3, R^2 = H) ND	NI[c,22] (1.0 μM)[15]
 **6**	ND	(0.14 μM)[21a]
 **9**	NI	72%
 **10**	19%	72%

[a] Percentage of inhibition at 1 mM concentration, K_i (in brackets), NI = no inhibition at 1 mM concentration of inhibitor, ND = not determined.
[b] All the inhibition are competitive.
[c] Lysosomal α-L-fucosidase.

(K_i = 3 nM) despite the loss of one hydroxyl function. The replacement of the methyl substituent by the spirocycle in the structure of DFJ reduces the potential for inhibiting α-L-fucosidase by ca. four orders of magnitude (K_i = 18 μM). Interestingly, the same structural modification, when applied to DRJ **4** (0% inhibition of rhamnosidase at 1 mM), allows to recover some activity (72% inhibition at 1 mM for compound **9**). However, spirocyclopropyl-DRJ **9** is still a weaker inhibitor of rhamnosidase than *epi*-DRJ **5** (99% inhibition at 1 mM, K_i = 1.0 μM).

In contrast to piperidine iminosugars, where epimers often show a total loss of their inhibitory potencies, a variety of configurations is tolerated with polyhydroxypyrrolidines, which can be interpreted in terms of lower steric demand.[23] This is illustrated in Figure 2 with pyrrolidine-type rhamnosidase inhibitors **26**–**29**, the best of which display various configurations and substitution patterns. In the present work, both spirocyclopropyl-pyrrolines **8** and **10** display inhibition potencies against α-L-rhamnosidase. Surprisingly, the *fuco* configured **8** is a potent inhibitor of α-L-rhamnosidase, even more active than the *rhamno*-designed **10**. However, pyrrolines **8** or **10** do not inhibit naringinase as effectively as the methyl analogue **6** (K_i = 0.14 μM) or as the pyrrolidines **26**–**29**.[24] Here again, the spirocyclopropyl substituent seems to be detrimental.

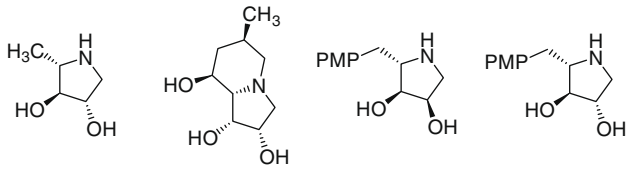


Figure 2. Structures of rhamnosidase inhibitors **26**–**29**.[24]

In the fucose series, SAR studies have demonstrated that the most active pyrrolidine structures retain the natural all-*cis* orientation of the substituents at positions C-3, C-4, and C-5 of the five-membered ring as found in **3**.[25] In agreement with these results, the *fuco* configured **8** was active against α-L-fucosidase whereas its *rhamno* counterpart was not.

4. Conclusion

Synthesis of unprecedented spirocyclopropyl-piperidines and -pyrrolines in the L-fuco and L-rhamno series was achieved from glyconononitriles by using Ti-mediated aminocyclopropanation as the key step. Thus, piperidine analogues of DRJ and DFJ with a spirocyclopropyl moiety in the place of the methyl group were prepared, respectively, from L-arabinose in 11 steps and 20% overall yield and from D-lyxose in eight steps and 3% overall yield. Spirocyclopropyl-DFJ displayed a potent and specific inhibition towards L-fucosidase (K_i = 18 μM), however lower than the corresponding methyl derivative (K_i = 3 nM). In the L-rhamno series, spirocyclopropyl DRJ exhibited some inhibition towards L-rhamnosidase. Preparation of new pyrroline analogues was also achieved. The L-fuco-designed pyrroline showed an unexpected inhibition of L-rhamnosidase (K_i = 57 μM). However, our results suggest that the replacement of the methyl substituent by a spirocyclopropyl group reduces the inhibitory potency towards the corresponding enzymes.

5. Experimental

5.1. General

All reactions were performed under argon. The solvents were dried and distilled prior to use. Silica Gel 60 F_{254} (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 M 9385 (40–63 μm) Kieselgel 60. NMR spectra were recorded on a 250 MHz or a 500 MHz spectrometer (250 MHz or 500 MHz for ^{1}H, 62.8 MHz or 125 MHz for ^{13}C, as indicated). Chemical shifts are expressed in parts per million (ppm) using TMS as internal standard. IR spectra were recorded with an IR^{TM} plus MIDAC spectrophotometer and are expressed in cm^{-1}. Optical rotations were determined at 20 °C 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).

5.2. Chemistry

5.2.1. 4,5-Di-*O*-benzoyl-2,3-*O*-isopropylidene-D-lyxononitrile 15c

To a suspension of D-lyxose (4.60 g, 30.6 mmol) in acetone (50 mL) was added concentrated H_2SO_4 (130 μL, 2.45 mmol). The mixture was stirred at room temperature for 12 h and the solution was basified by adding K_2CO_3. After filtration of the precipitate, the

filtrate was concentrated under reduced pressure to give 2,3-*O*-isopropylidene-D-lyxofuranose (5.80 g, quant.) as a pure 30/70 mixture of anomers α and β (white foam).

R_f (α/β) = 0.50 and 0.60 (100% EtOAc).

$[\alpha]_D^{20}$ = +16 (*c* 0.328, H_2O); lit.: $[\alpha]_D^{21}$ = +18 (*c* 0.10, H_2O).[19b]

^{1}H NMR (250 MHz, CD_3OD): δ = 5.19 (br s, 0.7H, H1), 4.98 (br s, 0.3H, H1), 4.74 (m, 1H, H2), 4.57 (m, 0.3H, H3), 4.50 (m, 0.7H, H3), 4.30–4.00 (m, 0.9H, H4, H5), 3.85–3.65 (m, 2.1H, H4, H5), 1.45 (s, 0.9H, CH_3), 1.37 (s, 2.1H, CH_3), 1.31 (s, 0.9H, CH_3), 1.26 (s, 2.1H, CH_3) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 113.9 ($C(CH_3)_2$), 108.0 (0.3C1), 102.6 (0.7C1), 87.6, 82.0, 81.6 (0.7C2, 0.7C3, 0.7C4), 86.8, 82.4, 79.8 (0.3C2, 0.3C3, 0.3C4), 66.7 (0.3C5), 61.6 (0.7C5), 26.8 (1.4CH_3), 25.3 (0.6CH_3) ppm.

To a solution of hydroxylamine hydrochloride (1.33 g, 19.2 mmol) in MeOH (10 mL) was added a suspension of sodium methoxide (1.17 g, 21.6 mmol) in MeOH (5 mL). The mixture was stirred at room temperature for 5 min then at 0 °C for 10 min. The precipitate was filtered and a solution of 2,3-*O*-isopropylidene-D-lyxofuranose (1.52 g, 7.99 mmol) in MeOH (5 mL) was added to the filtrate. The mixture was refluxed for 2 h then concentrated under reduced pressure. The crude oxime was then dissolved in pyridine (20 mL) and the solution cooled to 0 °C. Benzoyl chloride (9.27 mL, 79.9 mmol) was slowly added and the mixture was stirred at 70 °C for 72 h. Cold water (30 mL) was added dropwise and the aqueous phase was extracted with EtOAc (4 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/petroleum ether) yielded nitrile **15c** (1.49 g, 47% for the three steps) as white crystalline plates.

R_f = 0.35 (20% EtOAc/petroleum ether).

$[\alpha^{20}_{Hg(436)}]$ = +3 (*c* 0.5, $CHCl_3$); mp = 136 °C.

IR (KBr): *ν* = 3090, 3002, 2988, 2942, 1720, 1451, 1266, 1061 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.20–8.00 (m, 4H, Ar-H), 7.55–7.40 (m, 6H, Ar-H), 5.83 (dt, *J* = 5.0, *J* = 5.0, *J* = 6.2 Hz, 1H, H4), 4.98 (d, *J* = 5.6 Hz, 1H, H2), 4.70 (d, *J* = 5.0 Hz, 2H, H5), 4.61 (dd, *J* = 5.6, *J* = 6.2 Hz, 1H, H3), 1.64 (s, 3H, CH_3), 1.42 (s, 3H, CH_3) ppm.

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 165.8 (C=O), 165.6 (C=O), 133.6 (1 Ar-C), 133.5 (1 Ar-C), 130.1, 129.9, 129.5, 128.7, 128.6 (10 Ar-C), 116.2 (C1), 113.1 ($C(CH_3)_2$), 76.4 (C3), 70.1 (C4), 65.3 (C2), 62.9 (C5), 26.9 (CH_3), 25.8 (CH_3) ppm.

HRMS (ESI): *m/z* calcd for $C_{22}H_{21}NO_6Na$ $[M+Na]^+$: 418.1267; found: 418.1277.

Anal. Calcd for $C_{22}H_{21}NO_6$: C, 66.83; H, 5.35; N, 3.54. Found: C, 66.89; H, 5.25; N, 3.48.

5.2.2. (1*R*)-1-*C*-[1-(*N*-Benzoyl)-aminocyclopropyl]-4-*O*-benzoyl-1,2-*O*-isopropylidene-D-threitol 17

To a solution of nitrile **15c** (455 mg, 1.15 mmol) in dry THF (10 mL) under N_2 atmosphere was added a solution of MeTi(O*i*-Pr)$_3$ (414 μL, 1.73 mmol). The yellow solution was stirred at room temperature for 10 min and ethylmagnesium bromide (1.05 mL, 1.65 M in THF, 1.73 mmol) was added dropwise over a period of 15 min. After 1 h, $BF_3{\cdot}OEt_2$ (291 μL, 2.30 mmol) was added and the solution was stirred at room temperature for further 1 h. Water (10 mL) then 1 M aqueous solution of HCl (1 mL) were added. The mixture was then basified with 3 M aqueous NaOH solution and the aqueous phase was extracted with EtOAc (3 × 10 mL). Combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a crude brown oil. Purification by flash chromatography (50% EtOAc/petroleum ether) afforded **17** (240 mg, 49% yield) as a yellow oil.

R_f = 0.30 (50% EtOAc/petroleum ether).

$[\alpha]_D^{20}$ = +2 (*c* 0.482, $CHCl_3$).

IR (KBr): *ν* = 3355, 3065, 2985, 2934, 1721, 1655, 1487, 1453, 1277 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2H, Ar-H), 7.65–7.54 (m, 2H, Ar-H), 7.40–7.25 (m, 6H, Ar-H), 4.52–4.35 (m, 3H, H3, H4a, H4b), 4.18 (d, *J* = 7.4 Hz, 1H, H2), 4.0 (d, *J* = 7.4 Hz, 1H, H1), 1.29 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.20 (m, 1H, CH_2), 1.08 (m, 1H, CH_2), 0.90–0.75 (m, 2H, CH_2) ppm.

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 167.9 (C=O), 166.8 (C=O), 133.4 (1 Ar-C), 131.3 (1 Ar-C), 129.8, 129.7, 128.5, 127.0 (10 Ar-C), 108.6 ($C(CH_3)_2$), 80.2 (C1), 76.4 (C2), 67.6 (C4), 67.4 (C3), 32.0 (*C*–NH), 26.5 (CH_3), 24.3 (CH_3), 12.9 (CH_2), 10.6 (CH_2) ppm.

HRMS (ESI) calcd for $C_{24}H_{28}NO_6$ $[M+H]^+$: 426.1917; found: 426.1914.

5.2.3. (1*R*)-1-*C*-(1-Aminocyclopropyl)-1,2-*O*-isopropylidene-D-threitol 18

Cyclopropylamine **17** (140 mg, 0.33 mmol) was dissolved in a 4:1 mixture of ethanol and water (10 mL) and aqueous 3 M NaOH solution (3 mL) was added. The mixture was stirred at 80 °C for 24 h then solvents were evaporated under reduced pressure. The residue was taken up in a 7:3 mixture EtOAc/MeOH then filtered through a pad of silica gel. Concentration of the filtrate gave an orange oil which was purified by flash chromatography (30% MeOH/EtOAc) to yield compound **18** (57 mg, 80%; pale yellow oil).

R_f = 0.20 (30% MeOH/EtOAc).

$[\alpha]_D^{20}$ = −25 (*c* 0.488, MeOH).

IR (KBr): *ν* = 3417, 1593, 1386 cm^{-1}.

^{1}H NMR (250 MHz, CD_3OD): δ = 4.28 (d, *J* = 8.0 Hz, 1H, H2), 3.96 (t, *J* = 6.7 Hz, 1H, H3), 3.66 (d, *J* = 8.0 Hz, 1H, H1), 3.60 (d, *J* = 6.7 Hz, 2H, H4), 1.52 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 0.84 (m, 1H, CH_2), 0.76–0.58 (m, 3H, CH_2) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 109.5 ($C(CH_3)_2$), 82.3 (C1), 77.3 (C2), 70.7 (C3), 64.6 (C4), 33.7 (*C*–NH_2), 26.4 (CH_3), 24.0 (CH_3), 12.4 (CH_2), 8.2 (CH_2) ppm.

HRMS (ESI) calcd for $C_{10}H_{19}NO_4Na$ $[M+Na]^+$: 240.1212. found: 240.1214.

5.2.4. (1*R*)-1-*C*-[1-(*N*-*tert*-Butyloxycarbonyl)aminocyclopropyl]-1,2-*O*-isopropylidene-D-threitol 19

To a solution of the aminodiol **18** (82 mg, 0.38 mmol) in THF (2 mL) at room temperature was added Et_3N (58 μL, 0.42 mmol). At 0 °C, a solution of Boc_2O (83 mg, 0.38 mmol) in THF (1 mL) was added dropwise and the mixture was stirred at 50 °C for 24 h. Water (3 mL) was then added and the resulting aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic fractions were dried over anhydrous $MgSO_4$ and filtered. After removing of the solvent under reduced pressure, the residue was purified by flash chromatography (80% EtOAc/petroleum ether) to give the diol **19** (70 mg, 58%) as a colorless oil.

R_f = 0.28 (80% EtOAc/petroleum ether).

$[\alpha]_D^{20}$ = −6 (*c* 0.450, $CHCl_3$).

IR (film): *ν* = 3372, 2980, 2932, 1699, 1168 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.91 (br s, 1H, N*H*), 4.13 (m, 1H, H2), 4.08 (m, 1H, H3), 3.87 (d, *J* = 7.1 Hz, 1H, H1), 3.76 (dd, *J* = 6.3, *J* = 11.2 Hz, 1H, H4a), 3.67 (dd, *J* = 4.6, *J* = 11.2 Hz, 1H, H4b), 3.00 (br s, 1H, O*H*), 1.48 (s, 3H, C(CH_3)$_2$), 1.41 (s, 9H, C(CH_3)$_3$), 1.32 (s, 3H, C(CH_3)$_2$), 0.93 (m, 1H, CH_2), 0.86–0.65 (m, 3H, CH_2) ppm.

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 156.1 (C=O), 108.2 ($C(CH_3)_2$), 80.3 (C1), 78.9 ($C(CH_3)_3$), 76.4 (C2), 68.7 (C3), 65.8 (C4), 31.7 (*C*–NH), 28.3 (C(CH_3)$_3$), 26.3 (CH_3), 24.1 (CH_3), 13.2 (CH_2), 10.4 (CH_2) ppm.

HRMS (ESI) calcd for $C_{15}H_{27}NO_6Na$ $[M+Na]^+$: 340.1736; found: 340.1732.

Anal. Calcd for $[C_{15}H_{27}NO_6 + 1/3H_2O]$: C, 55.71; H, 8.62; N, 4.33. Found: C, 55.69; H, 8.75; N, 4.26.

5.2.5. (1*R*)-1-*C*-[1-(*N*-*tert*-Butyloxycarbonyl)aminocyclopropyl]-1,2-*O*-isopropylidene-4-*O*-methanesulfonyl-D-threitol 20

To a solution of diol **19** (60 mg, 0.19 mmol) and Et_3N (48 μL, 0.34 mmol) in CH_2Cl_2 (2 mL) at −20 °C was slowly added MsCl (15 μL, 0.19 mmol). The solution was stirred 15 min at −20 °C. Water (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic fractions were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give a crude yellow residue. Purification by flash chromatography (50% EtOAc/petroleum ether) afforded **20** (50 mg, 83%) as white crystals and recovered starting material **19** (12 mg).

R_f = 0.36 (50% EtOAc/petroleum ether).

$[\alpha]_D^{20}$ = −4 (*c* 0.582, $CHCl_3$); mp = 159 °C.

IR (KBr): 3362, 3266, 2979, 2929, 1696, 1518, 1374, 1182 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 5.60 (br s, 1H, N*H*), 4.40–4.22 (m, 3H, H3, H4a, H4b), 4.17 (d, *J* = 7.5 Hz, 1H, H2), 4.02 (d, *J* = 7.5 Hz, 1H, H1), 3.09 (s, 3H, C*H*$_3$S), 2.95 (d, *J* = 6.3 Hz, 1H, O*H*), 1.49 (s, 3H, C*H*$_3$), 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.33 (s, 3H, C*H*$_3$), 1.13 (m, 1H, C*H*$_2$), 0.98 (m, 1H, CH_2), 0.90–0.75 (m, 2H, CH_2).

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 156.2 (C=O), 108.7 (*C*(CH$_3$)$_2$), 79.7 (C1), 79.5 (*C*(CH$_3$)$_3$), 75.7 (C2), 71.4 (C4), 67.0 (C3), 37.8 (*C*H$_3$S), 31.8 (*C*–NH), 28.5 (C(*C*H$_3$)$_3$), 26.5 (CH$_3$), 24.3 (CH$_3$), 13.5 (CH_2), 10.9 (CH_2).

HRMS (ESI): *m/z* calcd for $C_{16}H_{29}NO_8NaS$ $[M+Na]^+$: 418.1512; found: 418.1514.

Anal. Calcd for $C_{16}H_{29}NO_8S$: C, 48.59; H, 7.39; N, 3.54. Found: C, 49.00; H, 7.52; N, 3.39.

5.2.6. 5-*C*-Spirocyclopropyl-(5-demethyl-1-deoxy)-L-fuconojirimycin 7

A 2 M HCl solution (1 mL) was added to a solution of **20** (40 mg, 0.10 mmol) in MeOH (1 mL) and the mixture was stirred 30 min at room temperature. After evaporation of the solvents, water (2 mL) and K_2CO_3 were added (pH 12). The solution was stirred at room temperature for 30 min and concentrated under reduced pressure. The residue was taken up in MeOH, the precipitate was filtered and the filtrate was concentrated under reduced pressure to give a crude 1/1 mixture of cyclopropylamine **22** and iminosugar **7** as mesylate salts. The two products were separated by flash chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH/H_2O: 6/4/0.5/0.5) and each compound was purified on Dowex 50WX-8 (H^+ form) by eluting with a 3% NH_4OH solution.

Spirocyclopropyl iminosugar **7** (5 mg, 31% for the two steps, colorless foam).

R_f = 0.40 (CH_2Cl_2/MeOH/NH_4OH/H_2O: 6/4/0.5/0.5).

$[\alpha]_D^{20}$ = +12 (*c* 0.10, MeOH).

IR (KBr): ν = 3363, 2926, 1212, 1040 cm^{-1}.

^1H NMR (250 MHz, CD_3OD): δ = 3.73 (ddd, *J* = 5.1, *J* = 9.1, *J* = 10.6 Hz, 1H, H2), 3.45 (dd, *J* = 2.6, *J* = 9.1 Hz, 1H, H3), 3.12 (br s, 1H, H4), 2.94 (dd, *J* = 5.1, *J* = 13.1 Hz, 1H, H1a), 2.39 (dd, *J* = 10.6, *J* = 13.1 Hz, 1H, H1b), 0.65–0.51 (m, 3H, CH_2), 0.44 (m, 1H, CH_2) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 76.7 (C4), 76.2 (C3), 69.9 (C2), 50.2 (C1), 41.2 (C5), 11.7 (CH_2), 11.0 (CH_2) ppm.

HRMS (ESI): *m/z* calcd for $C_7H_{14}NO_3$ $[M+H]^+$: 160.0974; found: 160.0972.

5.2.7. (2*R*,3*R*,4*R*)-2-(1-Aminocyclopropyl)-3,4-dihydroxytetrahydrofurane 22 (8 mg, 50% for the two steps, colorless foam)

R_f = 0.45 (CH_2Cl_2/MeOH/NH_4OH/H_2O: 6/4/0.5/0.5).

$[\alpha]_D^{20}$ = +7 (*c* 0.24, H_2O). IR (film): ν = 3355, 2922, 1605, 1072, 1046 cm^{-1}.

^1H NMR (250 MHz, CD_3OD): δ = 4.06 (br s, 1H, H3), 3.97 (br s, 1H, H4), 3.89 (dd, *J* = 3.5, *J* = 9.5 Hz, 1H, H5a), 3.81 (d, *J* = 9.5 Hz, 1H, H5b), 3.11 (d, *J* = 2.9 Hz, 1H, H2), 0.73–0.55 (m, 4H, CH_2) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 93.8 (C2), 80.9 (C3), 78.5 (C4), 75.1 (C5), 35.2 (*C*–NH_2), 14.4 (CH_2), 10.7 (CH_2) ppm.

MS (ESI): *m/z* = 160.1 $[M+H^+]$. HRMS (ESI): *m/z* calcd for $C_7H_{14}NO_3$ $[M+H]^+$: 160.0974; found: 160.0979.

5.2.8. (2*R*,3*R*,4*R*)-*N*-*tert*-Butyloxycarbonyl-3,4-*O*-isopropylidene-5-spirocyclopropyl-2,3,4-trihydroxypyrrolidine 23

$NaIO_4/SiO_2$ (0.5 g) was slowly added to a solution of diol **19** (70 mg, 0.22 mmol) in CH_2Cl_2 (10 mL) and the suspension was stirred 30 min at room temperature. Silica gel was filtered (elution: 100% EtOAc) and the solution was concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/petroleum ether) gave pyrrolidine **23** (51 mg, 81%) as a colorless oil.

R_f = 0.45 (20% EtOAc/petroleum ether).

$[\alpha]_D^{20}$ = +93 (*c* 1.02, $CHCl_3$).

IR (film): ν = 3440, 2980, 2936, 1674, 1393 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 5.53 (br s, 1H, H2), 4.55 (d, *J* = 6.0 Hz, 1H, H3 or H4), 4.27 (d, *J* = 6.0 Hz, 1H, H3 or H4), 1.45 (s, 3H, C*H*$_3$), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.30 (s, 3H, C*H*$_3$), 1.06 (s, 1H, CH_2), 0.90–0.70 (m, 3H, CH_2) ppm.

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 154.0 (C=O), 111.8 (*C*(CH$_3$)$_2$), 87.8 (C2), 85.9, 82.5 (C3, C4), 81.1 (*C*(CH$_3$)$_3$), 46.0 (C5), 28.4 (C(*C*H$_3$)$_3$), 26.9 (C(*C*H$_3$)$_2$), 25.6 (C(*C*H$_3$)$_2$), 12.0 (CH_2), 6.2 (CH_2) ppm.

HRMS (ESI) calcd for $C_{14}H_{23}NO_5$ Na $[M+Na]^+$: 308.1474; found: 308.1477.

Anal. Calcd for $[C_{14}H_{23}NO_5 + 1/4H_2O]$: C, 58.01; H, 8.17; N, 4.83. Found: C, 58.16; H, 8.14; N, 4.82.

5.2.9. (3*S*,4*R*)-3,4-Dihydroxy-5-spirocyclopropyl-Δ-pyrroline 8

A 1 M HCl solution (1 mL) was added to a solution of **23** (38 mg, 0.13 mmol) in EtOH (0.3 mL) and the mixture was stirred 2 h at room temperature. Solvents were evaporated under reduced pressure to give the corresponding iminosugar as a single anomer. Purification on Dowex 50WX-8 (H^+ form) by elution with a 3% aqueous solution of NH_4OH afforded imine **8** as a pure compound (10 mg, 61%, yellow oil) after lyophilization.

$[\alpha]_D^{20}$ = +104 (*c* 0.096, MeOH).

IR (film): ν = 3371, 2924, 2854, 1562, 1068 cm^{-1}.

^1H NMR (250 MHz, CD_3OD): δ = 7.47 (s, 1H, H2), 4.77 (d, *J* = 6.1 Hz, 1H, H3), 3.74 (d, *J* = 6.1 Hz, 1H, H4), 1.20–0.80 (m, 4H, CH_2) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 169.5 (C2), 79.4 (C3), 74.2 (C4), 60.5 (C5), 12.6 (CH_2), 10.0 (CH_2) ppm.

HRMS (ESI) calcd for $C_6H_{10}NO_2$ $[M+H]^+$: 128.0712; found: 128.0714.

5.2.10. (3*S*)-3-*C*-[(*N*-*tert*-Butyloxycarbonyl)-1-aminocyclopropyl]-2,3-*O*-isopropylidene-D-glyceraldehyde 25

$NaIO_4/SiO_2$ (0.83 g) was slowly added to a solution of diol **24** (114 mg, 0.36 mmol) in CH_2Cl_2 (10 mL) and the suspension was stirred 1 h at room temperature. SiO_2 was filtered (elution: 100% EtOAc) and the solution was concentrated under reduced pressure. Purification by flash chromatography (40% EtOAc/petroleum ether) gave aldehyde **25** (92 mg, 90%) as white crystals.

R_f = 0.33 (40% EtOAc/petroleum ether).

$[\alpha]_D^{20}$ = −25 (*c* 1.2, $CHCl_3$); mp = 135 °C.

IR (KBr): ν = 3364, 2988, 2934, 2836, 1729, 1700, 1512, 1168 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 9.76 (s, 1H, H1), 5.10 (br s, 1H, N*H*), 4.61 (d, *J* = 6.3 Hz, 1H, H2), 3.74 (d, *J* = 6.3 Hz, 1H, H3), 1.45 (s, 3H, C(C*H*$_3$)$_2$), 1.39 (s, 9H, C(C*H*$_3$)$_3$), 1.30 (s, 3H, C*H*$_3$), 1.05–0.90 (m, 2H, CH_2), 0.90–0.75 (m, 2H, CH_2) ppm.

^{13}C NMR (62.8 MHz, $CDCl_3$): δ = 201.0 (C1), 155.9 (C=O), 110.8 (*C*(CH$_3$)$_2$), 82.9, 81.2 (C2, C3), 79.8 (*C*(CH$_3$)$_3$), 33.2 (*C*–NH), 28.4 (C(*C*H$_3$)$_3$), 26.8 (C(*C*H$_3$)$_2$), 26.2 (C(*C*H$_3$)$_2$), 12.7 (CH_2), 11.4 (CH_2) ppm.

HRMS (ESI) calcd for $C_{14}H_{24}NO_5$ $[M+H]^+$: 286.1654; found: 286.1652.

Anal. Calcd for $[C_{14}H_{23}NO_5 + 1/2H_2O]$: C, 57.13; H, 8.22; N, 4.76. Found: C, 57.27; H, 7.92; N, 4.77.

5.2.11. (3*S*,4*S*)-3,4-Dihydroxy-5-spirocyclopropyl-Δ-pyrroline 10

A 1 M HCl solution (3 mL) was added to a solution of **25** (115 mg, 0.40 mmol) in EtOH (1 mL) and the mixture was stirred for 2 h at room temperature. Solvents were evaporated under reduced pressure to give the corresponding iminosugar as a 50:50 mixture of anomers. Purification on Dowex 50WX-8 (H^+ form) by elution with a 3% aqueous solution of NH_4OH afforded imine **10** as a pure compound (45 mg, 90%, yellow oil).

$[\alpha]_D^{20}$ = +23 (*c* 0.574, MeOH).

IR (KBr): ν = 3403, 1652, 1024 cm^{-1}.

^1H NMR (250 MHz, CD_3OD): δ = 7.44 (s, 1H, H2), 4.55 (d, *J* = 3.3 Hz, 1H, H3), 3.80 (d, *J* = 3.3 Hz, 1H, H4), 1.25–1.02 (m, 2H, CH_2), 0.90–0.72 (m, 2H, CH_2) ppm.

^{13}C NMR (62.8 MHz, CD_3OD): δ = 168.2 (C2), 86.0 (C3), 80.7 (C4), 59.3 (C5), 13.8 (CH_2), 9.1 (CH_2) ppm.

HRMS (ESI) calcd for $C_6H_{10}NO_2$ $[M+H]^+$: 128.0712; found: 128.0715.

5.3. Glycosidase inhibition

The enzymatic assays were performed as follows: 0.01–0.5 unit/mL of enzyme (1 unit = 1 mol of glycoside hydrolyzed/min), pre-incubated for 10 min at 20 °C with the inhibitor, and increasing concentration 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.[26] The reaction was stopped by the addition of 100 μL of 0.3 M sodium borate buffer pH 9.8. The *p*-nitrophenolate formed was quantified at 405 nm, and IC_{50} values were calculated. Double-reciprocal (Lineweaver–Burk) plots were used to determine the inhibition characteristics of active compounds.

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