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Sugar-based ethenyl ethers: stereoselective dipolar cycloadditions of nitrile oxides

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Abstract—Selected sugar-based ethenyl ethers have been employed in 1,3-dipolar cycloaddition with nitrile oxides. In the D-fructo series, high diastereoselectivity was observed as compared with the 3-epimeric D-psico series.

1. Introduction

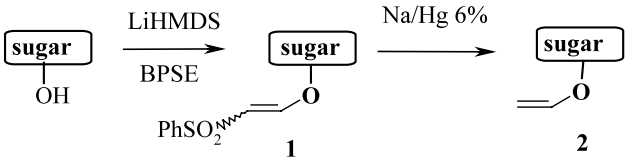
Carbohydrate-derived chiral auxiliaries are gaining greater importance and wider use, mainly as the result of their low cost and ready availability.[1] Among glycotemplates, the di-*O*-isopropylidene-D-fructopyrano skeleton is now renowned as a powerful chiral inducer.[2] Several D-fructose derivatives have been used as catalysts, in asymmetric epoxidation reactions with impressive results[3] and in the selective oxidation of diols.[4] They have also been developed as chiral auxiliaries, in Diels–Alder reactions,[5,6] aldol condensations and Michael additions,[7] stereoselective alkylations[8] and photochemical deconjugation reactions.[9] Our recently disclosed efficient route to sugar derived ethenyl ethers[10] prompted us to further explore their potential as new chiral auxiliaries. Some *O*-vinylated sugars have previously been examined as chiral intermediates in inverse-electron demand cycloaddition reactions with isoquinolinium salts,[11] or as precursors to enantiomerically pure cyclobutanols.[12] Herein we present the use of selected sugar-based ethenyl ethers as chiral dipolarophiles in the [3+2] cycloaddition with nitrile oxides.

2. Results and discussion

The ethenyl ethers **2** were readily generated from the corresponding carbohydrate precursors, 1,2:4,5-di-*O*-isopropylidene-D-fructopyranose, -D-psicopyranose and 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose in a two step sequence: Michael addition on bis-phenylsulfonylethylene (BPSE) followed by reductive desulfonylation (Scheme 1).[10]

Carbohydrate enol ethers **3**, **4** and **5** were selected with a view to pinpointing the importance of the proximity between the chiral template and the reacting group, and the influence of an epimeric situation between D-fructo and D-psico structures (Scheme 2).

We have investigated the chiral induction of our enol ethers in [3+2] dipolar cycloadditions with a selection of nitrile oxides (Scheme 3) prepared from the related oximes following the standard *N*-chlorosuccinimide-triethylamine procedure.[13] Cycloaddition of the nitrile oxides with chiral enol ethers **3**, **4** and **5** yielded the corresponding 4,5-dihydroisoxazoles in good yields. (Scheme 3 and Table 1). The sequence of reactions was performed as a one-pot process: the oxime was first transformed into the transient hydroximoyl chloride (NCS+pyridine in dry chloroform), then a solution of the enol ether and Et_3N in dry chloroform was added dropwise and the mixture heated under reflux for 2 h.



Scheme 1. Synthetic protocol for the preparation of ethenyl ethers **2**.

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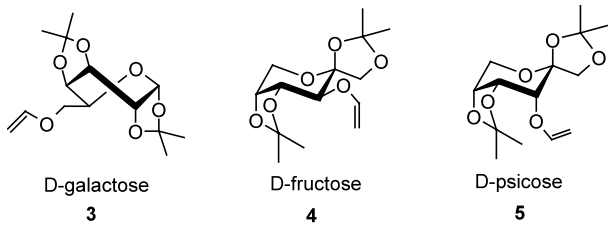
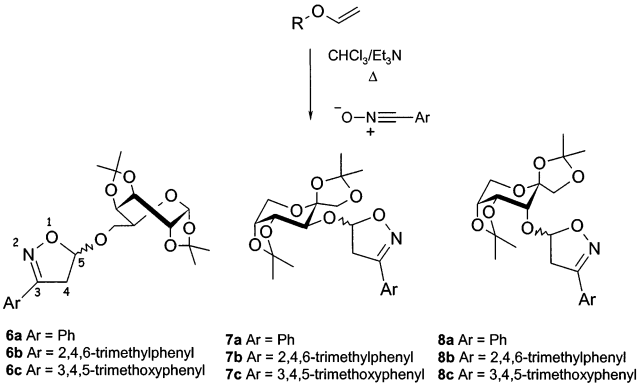


Scheme 2. Selected ethenyl ethers tested as chiral auxiliaries.



Scheme 3. [3+2] Cycloaddition process for the generation of 4,5-dihydroisoxazoles.

As expected, condensation of 1,2:3,4-di-*O*-isopropylidene-6-*O*-vinyl-α-D-galactopyranose **3**[10b] with nitrile oxides yielded isoxazolines **6** without any diastereoselectivity (Table 1). This lack of chiral induction might certainly be due to the distance between the ethenyl ether and the chiral template. Recent literature results support the idea that chiral inductions are improved when the enol ether moiety comes closer to the sugar core.[12] In contrast, 1,2:4,5-di-*O*-isopropylidene-3-*O*-vinyl-β-D-fructopyranose **4** displays a closer proximity between the secondary ethenyl ether and the chiral template.[13] In that case, a very efficient chiral induction was observed, leading to higher diastereoselectivities up to 28:1 (in the case of **7b**). Epimeric 1,2;4,5-di-*O*-isopropylidene-3-*O*-vinyl-β-D-psicopyranose **5** displays a similar distance between the enol ether moiety and the chiral template, but surprisingly less efficient chiral induction was seen, even when the reactions were performed at room temperature.

Table 1. Yields of cycloaddition and epimeric ratio determined after purification except for **6** and **7a**

Compounds	Yield (%)	Epimeric ratio
6a	86	1:1
6b	98	1:1
6c	50	1:1
7a	73	10:1
7b	93	28:1
7c	70	11:1
8a	91	5:1
8b	97	2.7:1
8c	65	3:1

Determination of the configuration of the newly formed stereocenter in isoxazoles has been undertaken on conformational grounds. The conformations of vinyl ethers have long been studied.[14] Our starting assumption was that both D-fructopyranose and L-sorbopyranose-derived vinyl ethers assume a *syn* to *anti* conformation switch in the transition state.[15] Firstly, the high diastereoselectivity observed in cycloadditions involving the D-fructo vinyl ether **4** could be well explained by the steric hindrance generated on the *Si* face of the double bond in the *anti* conformation (Fig. 1). However, while accepting the first assumption that the *anti* conformation of vinyl ether is preferred at the transition state, in the *syn* conformation, again, the *Si* face of the double bond is hampered by the 4,5-*O*-isopropylidene group. As a preliminary conclusion, whatever the conformation of the vinyl ether, only the *Re* face is reasonably accessible to the nitrile oxide. Considering the major epimer, this hypothesis was confirmed by NOESY experiments on **7a**, **7b** and **7c** showing H-5i of isoxazole rings to be close to H-3, H-4 and to a methyl group of 4,5-*O*-isopropylidene of the sugar template (Fig. 1). In the minor epimer only interaction with H-3 of sugar ring was detected. The above prediction was reinforced by AM1 molecular modeling using ArgusLab 2.0 (Fig. 2). All of the results allow us conclude that the newly formed stereocenter has *R* configuration.

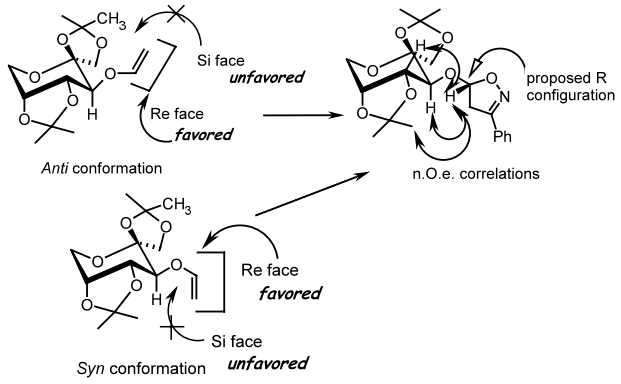


Figure 1. Face selectivity yielding the major epimer of 4,5-dihydroisoxazoles **7** during the cycloaddition process of the D-fructopyranose vinyl ether.

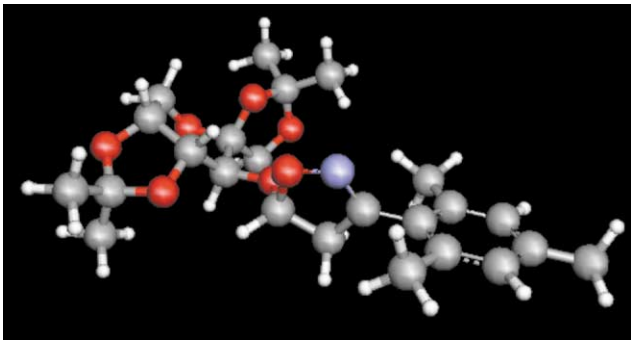


Figure 2. AM1 minimization results with **7b** major epimer.

The case of the D-psico vinyl ether **5** is divergent: whatever—*syn* or *anti*—the conformation, both faces are clearly accessible in both conformations. NOESY experiments failed to afford evidence for the configuration of the isoxazole stereocenter. Based on the favored *anti* conformation, the preferentially attacked face would be the *Re* face, resulting also in formation of the *R* isomer as the major epimer (Fig. 3).

Finally, no change in the diastereoselectivity was observed on changing the structure of the nitrile oxide.

3. Conclusion

Selected sugar-based ethenyl ethers have been examined as chiral templates in cycloaddition processes involving several nitrile oxides. From these preliminary investigations it emerges that the 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyrano scaffold displays impressive properties in terms of stereoselective induction, whereas its epimeric β-D-psico counterpart is significantly less effective. Conformational observations for the D-fructo system infer that the high stereoselectivity attained in the optimal case results from the alternative blocked-face conformation, which produces the same epimer as the predominant product.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-250 instrument operating at 250 and 62.5 MHz, respectively, for solutions in $CDCl_3$ (internal TMS). The coupling constants (*J*) are reported in Hz and the chemical shifts (δ) in ppm downfield from TMS. Whenever appropriate, signal assignments were deduced by DEPT, COSY and HETCOR NMR experiments. Optical rotations were measured at 20°C using a Perkin–Elmer 141 digital polarimeter with a path length of 1 dm. Low resolution mass spectra (MS) were recorded by the ICOA Analytical Service on a Perkin–Elmer SCIEX API 300 (ion spray). HR-ESI-TOF-MS was performed on a Micromass LC TOF spectrometer. Analytical TLC was carried out on precoated silica gel 60F-254 plates (E. Merck) and developed by charring after a 5% H_2SO_4 ethanolic solution spray. Column chromatography was performed on silica gel SI 60 (43–60 μm) (E. Merck). The preparation of carbohydrate precursors **3**, **4** and **5** is described in a separate paper.[10b] ^{1}H and ^{13}C NMR resonances of cycloadducts are consistent with literature data.[16]

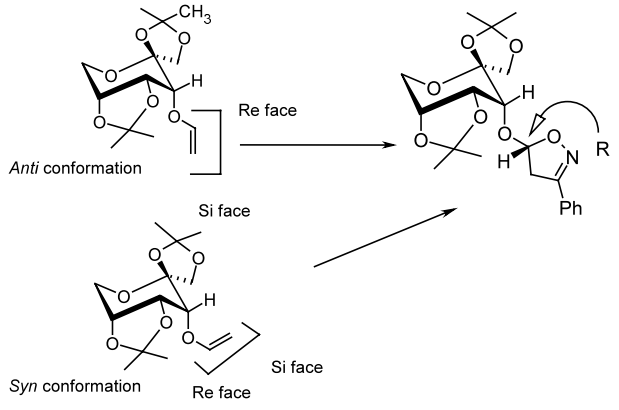


Figure 3. Face selectivity yielding the major epimer of 4,5-dihydroisoxazoles **8** in the case of the D-psicopyranose vinyl ether.

4.2. General procedure for the synthesis of isoxazoles

Typical methodology applied: the oxime (0.5 mmol) was dissolved in dry chloroform (1 mL), then *N*-chlorosuccinimide (0.55 mmol) and pyridine (two drops) were added. The mixture was stirred 2 h at room temperature. Solutions of the ethenyl ether (0.25 mmol) and Et_3N (0.37 mmol) in dry chloroform 0.5 mL) were added dropwise and the mixture was heated under reflux for 2 h. After removal of the solvent under reduced pressure, the diastereoisomeric isoxazoles were purified by column chromatography on silica gel.

4.3. (5*RS*)-[6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-pyranosyloxy)]-3-phenyl-4,5-dihydroisoxazoles, 6a

Column chromatography afforded (86% yield from **3**) a 1:1 mixture of **6a**, as a colorless gum: ^{1}H NMR δ 1.31 (s, iPrd), 1.32 (s, iPrd), 1.33 (s, iPrd), 1.44 (s, iPrd), 1.45 (s, iPrd), 1.50 (s, iPrd), 1.56 (s, iPrd), 3.28 (dd, J_{4ib-5i} = 2.3, $J_{4ia-4ib}$ = 17.4, H-4ib), 3.31 (dd, J_{4ib-5i} = 2.3, $J_{4ia-4ib}$ = 17.4, H-4ib), 3.40 (dd, J_{4ia-5i} = 5.9, H-4ia), 3.74–4.12 (m, H-4, H-5, H-6a, H-6b), 4.24–4.33 (m, H-2), 4.58 (dd, J_{2-3} = 2.6, J_{3-4} = 7.9, H-3), 4.61 (dd, J_{2-3} = 2.6, J_{3-4} = 7.9, H-3), 5.52 (d, J_{1-2} = 5.1, H-1), 5.55 (d, J_{1-2} = 4.9, H-1), 5.76 (dd, H-5i), 6.88 (s, H-Ar), 7.37–7.44 (m, H-Ar), 7.66–7.71 (m, H-Ar).^{13}C NMR δ 24.8, 24.9, 25.3, 26.4, 26.5 (iPrd), 42.2 (C-4i), 66.9, 68.3 (C-6), 66.0, 68.2, 70.7, 71.0, 71.1, 71.8 (C-2, C-3, C-4, C-5), 96.7, 96.8 (C-1), 104.1, 104.2 (C-5i), 109.1, 109.7, 109.8 (C_{IV}, iPrd), 129.4, 129.5 (C_{IV}-Ar), 127.3–130.7 (CH-Ar), 157.5, 157.6 (C_{IV}-C=N). MS *m*/*z* 406.5 [M+H]$^+$, 423.5 [M+NH_4]$^+$, 428.5 [M+Na]$^+$, 444.5 [M+K]$^+$. HRMS: $C_{21}H_{27}NO_7$: calcd 405.1787; found: 405.1782.

4.4. (5*RS*)-[6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-pyranosyloxy)]-3-mesityl-4,5-dihydroisoxazoles, 6b

Column chromatography afforded (98% yield from **3**) a 1:1 mixture of **6b**, as a colorless gum: ^{1}H NMR δ 1.33 (s, iPrd), 1.34 (s, iPrd), 1.46 (s, iPrd), 1.50 (s, iPrd), 1.57 (s, iPrd), 2.22 (s, Me), 2.28 (s, Me), 3.01 (dd, J_{4ib-5i} = 6.4, $J_{4ia-4ib}$ = 17.7, H-4ib), 3.27 (dd, J_{4ia-5i} = 6.4, H-4ia), 3.28 (dd, J_{4ia-5i} = 6.4, H-4ia), 3.74–4.18 (m, H-4, H-5, H-6a, H-6b), 4.25–4.34 (m, H-2), 4.61 (dd, J_{2-3} = 2.1, J_{3-4} = 7.8, H-3), 4.62 (dd, J_{2-3} = 2.1, J_{3-4} = 7.8, H-3), 5.33 (d, J_{1-2} = 5.3, H-1), 5.55 (d, J_{1-2} = 5.3, H-1), 5.69 (t, H-5i), 6.88 (s, H-Ar). ^{13}C NMR δ 19.9, 20.0, 21.5 (Me), 24.8, 25.4, 25.5, 26.3, 26.4, 26.5 (iPrd), 46.1, 46.2 (C-4i), 66.4, 67.7 (C-6), 66.1, 68.3, 70.9, 71.0, 71.1, 71.9 (C-2, C-3, C-4, C-5), 96.7, 96.8 (C-1), 103.1 (C-5i), 109.1,

109.6, 109.9 (C_{IV}, iPrd), 128.2, 128.7 (CH-Ar), 126.2, 126.3, 137.1, 139.2, 139.3 (C_{IV}-Ar), 158.8, 158.9 (C_{IV}-C=N). MS: m/z 448.5 $[M+H]^+$, 465.5 $[M+NH_4]^+$, 470.5 $[M+Na]^+$, 486.5 $[M+K]^+$. HRMS: $C_{24}H_{33}NO_7$: calcd 447.2257; found: 447.2249.

4.5. 5-[6-(1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-pyranosyloxy)]-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazoles, 6c

Column chromatography afforded (50% yield from **3**) a 1:1 mixture of **6c**, as a colorless gum: ^{1}H NMR δ 1.29 (s, iPrd), 1.31 (s, iPrd), 1.32 (s, iPrd), 1.42 (s, iPrd), 1.43 (s, iPrd), 1.49 (s, iPrd), 1.54 (s, iPrd), 3.26 (dd, $J_{4ib-5i}=2.1$, $J_{4ia-4ib}=18.1$, H-4ib), 3.29 (dd, $J_{4ib-5i}=2.1$, H-4ia), 3.37 (dd, $J_{4ia-5i}=5.7$, H-4ia), 3.86 (s, OMe), 3.71–4.09 (m, H-5, H-6a, H-6b), 4.18 (d, $J_{3-4}=7.5$, $J_{4-5}<0.5$, H-4), 4.25 (dd, $J_{3-4}=7.5$, $J_{4-5}=1.7$, H-4), 4.29 (dd, $J_{1-2}=5.1$, $J_{2-3}=2.5$, H-2), 4.31 (dd, $J_{1-2}=5.1$, $J_{2-3}=2.5$, H-2), 4.57 (dd, $J_{2-3}=2.5$, $J_{3-4}=7.5$, H-3), 4.60 (dd, $J_{2-3}=2.5$, $J_{3-4}=7.5$, H-3), 5.50 (d, $J_{1-2}=5.1$, H-1), 5.53 (d, $J_{1-2}=5.1$, H-1), 5.73 (dd, H-5′), 6.88 (s, H-Ar), 6.89 (s, H-Ar). ^{13}C NMR δ 24.8, 24.9, 25.3, 25.4, 26.3, 26.5 (iPrd), 42.2 (C-4i), 56.6, 56.7, 61.3 (OMe), 66.1, 66.9 (C-5), 68.1, 68.2 (C-6), 70.1, 70.7 (C-3), 70.9, 71.0 (C-2), 71.1, 71.7 (C-4), 96.7, 96.8 (C-1), 102.8 (C-5i), 104.1, 104.2, 104.3, 104.6, 104.7 (C-7, CH-Ar), 109.0, 109.1, 109.7, 109.8 (C_{IV}, iPrd), 124.8, 124.9, 140.3, 140.4, 153.7 (C_{IV}-Ar), 157.3, 157.4 (C_{IV}-C=N). MS: m/z 496.5 $[M+H]^+$, 513.5 $[M+NH_4]^+$, 518.5 $[M+Na]^+$, 534.5 $[M+K]^+$. HRMS: $C_{24}H_{33}NO_{10}$: calcd 495.2104; found: 495.2111.

4.6. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranosyloxy)]-3-phenyl-4,5-dihydroisoxazoles 7a

Column chromatography afforded (73% yield from **4**) both epimers of **7a** in a 10:1 ratio (determined from crude product), the major isomer being the only product isolated as a colorless gum: *major*: $[\alpha]_D$ +5 (c 2.6, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.22 (s, 3H, iPrd), 1.39 (s, 3H, iPrd), 1.44 (s, 3H, iPrd), 1.62 (s, 3H, iPrd), 3.27 (d, 1H, $J_{4ib-5i}<0.5$, $J_{4ia-4ib}=17.2$, H-4ib), 3.41 (dd, 1H, $J_{4ia-5i}=6.1$, H-4ia), 3.93–4.20 (m, 6H, H-1a, H-1b, H-3, H-5, H-6a, H-6b), 4.34 (dd, 1H, $J_{3-4}=5.9$, $J_{4-5}=7.2$, H-4), 6.15 (d, 1H, H-5i), 7.41–7.45 (m, 2H, H-Ar), 7.65–7.68 (m, 3H, H-Ar).^{13}C NMR (67.5 MHz, $CDCl_3$) δ 27.5, 28.3, 29.1, 30.3 (4×iPrd), 43.8 (C-4i), 60.2 (C-6), 71.7 (C-1), 73.3, 73.7, (C-3, C-5), 77.9 (C-4), 102.7 (C-5i), 103.6 (C-2), 109.3, 112.0 (2×C_{IV}, iPrd), 127.3, 129.1, 134.5 (5×CH-Ar), 130.2 (C_{IV}-Ar), 168.5 (C_{IV}-C=N).MS (IS): m/z 423.5 $[M+NH_4]^+$, 428.5 $[M+Na]^+$, 444.5 $[M+K]^+$. HRMS: $C_{21}H_{27}NO_7$: calcd 405.1787; found: 405.1790.

4.7. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranosyloxy)]-3-mesityl-4,5-dihydroisoxazole, 7b

Column chromatography afforded (93% yield from **4**) both epimers of **7b** in a 28:1 ratio (determined from crude product), as colorless gums: *major*: $[\alpha]_D$ +142 (c 1.5, $CHCl_3$). ^{1}H NMR δ 1.36 (s, 3H, iPrd), 1.39 (s, 3H, iPrd), 1.47 (s, 3H, iPrd), 1.64 (s, 3H, iPrd), 2.23 (s, 6H, Me), 2.28 (s, 3H, Me), 3.04 (dd, 1H, $J_{4ib-5i}<0.5$, $J_{4ia-4ib}=17.9$, H-4ib), 3.28 (dd, 1H, $J_{4ia-5i}=6.2$, H-4ia), 3.97 (d, 1H, $J_{1a-1b}=9.8$, H-1b), 4.03–4.11 (m, 3H, H-3, H-6), 4.16–4.23 (m, 2H, H-5, H-1a), 4.36 (dd, 1H, $J_{3-4}=7.9$, $J_{4-5}=5.3$, H-4), 6.20 (d, 1H, H-5i), 6.88 (s, 2H, H-Ar). ^{13}C NMR δ 20.2, 21.5 (3×Me), 26.6, 26.8, 26.9, 28.7 (4×iPrd), 46.2 (C-4i), 60.6 (C-6), 72.2 (C-1), 73.3, 74.4, 78.1 (C-3, C-4, C–5), 101.9 (C-5i), 104.9 (C-2), 109.7, 112.3 (2×C_{IV}, iPrd), 128.8 (2×CH-Ar), 125.6, 137.1, 139.3 (4×C_{IV}-Ar), 159.1 (C_{IV}-C=N). MS: m/z 448.5 $[M+H]^+$, 470.5 $[M+Na]^+$, 486.5 $[M+K]^+$. HRMS: $C_{24}H_{33}NO_7$: calcd 447.2257; found: 447.2247.

minor: $[\alpha]_D$ −153 (c 0.34, $CHCl_3$). ^{1}H NMR δ 1.37 (s, 3H, iPrd), 1.42 (s, 3H, iPrd), 1.51 (s, 3H, iPrd), 1.54 (s, 3H, iPrd), 2.21 (s, 6H, Me), 2.29 (s, 3H, Me), 3.00 (d, 1H, $J_{4ia-4ib}=17.9$, H-4ib), 3.32 (dd, 1H, $J_{4ia-5i}=6.4$, H-4ia), 3.87–4.21 (m, 6H, H-1a, H-1b, H-3, H-5, H-6a, H-6b), 4.51 (dd, 1H, $J_{3-4}=6.0$, $J_{4-5}=6.0$, H-4), 5.91 (d, 1H, H-5i), 6.89 (s, 2H, H-Ar). MS: m/z 448.5 $[M+H]^+$, 470.5 $[M+Na]^+$.

4.8. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-fructopyranosyloxy)]-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazoles, 7c

Column chromatography afforded (70% yield from **4**) a 10:1 mixture of **7c**, as a colorless gum: *major*: $[\alpha]_D$ +4 (c 2.6, $CHCl_3$). ^{1}H NMR δ 1.25 (s, 3H, iPrd), 1.39 (s, 3H, iPrd), 1.46 (s, 3H, iPrd), 1.63 (s, 3H, iPrd), 3.26 (d, 1H, $J_{4ib-5i}<0.5$ Hz, $J_{4ia-4ib}=17.0$ Hz, H-4ib), 3.42 (dd, 1H, $J_{4ia-5i}=4.9$ Hz, H-4ia), 3.89–4.33 (m, 16H, H-1a, H-1b, H-3, H-4, H-5, H-6a, H-6b, OMe), 6.15 (d, 1H, H-5i), 6.91 (s, 2H, H-Ar). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 26.1, 27.4, 28.6, 29.9 (4×iPrd), 42.2 (C-4i), 56.6 (OMe), 60.2 (C-6), 61.2 (OMe), 71.7 (C-1), 73.2, 74.3, 77.9 (C-3, C-4, C-5), 102.3 (C-2), 102.8 (C-5i), 104.2, 104.6 (2×CH-Ar), 109.6, 110.6 (2×C_{IV}, iPrd), 122.8, 138.7, 151.9 (4×C_{IV}-Ar), 156.0 (C_{IV}-C=N). MS (IS): m/z 496.5 $[M+H]^+$, 518.5 $[M+Na]^+$, 534.5 $[M+K]$.

minor: $[\alpha]_D$ −0.75 (c 0.2, $CHCl_3$). ^{1}H NMR δ 1.30 (s, 3H, iPrd), 1.40 (s, 3H, iPrd), 1.47 (s, 3H, iPrd), 1.63 (s, 3H, iPrd), 3.44 (d, 1H, $J_{4ia-4ib}=17.6$, H-4ib), 3.60 (dd, 1H, $J_{4ia-5i}=5.7$, H-4ia), 3.40–4.36 (m, 16H, H-1a, H-1b, H-3, H-4, H-5, H-6a, H-6b, OMe), 6.13 (d, 1H, H-5i), 6.91 (s, 2H, H-Ar). MS (IS): m/z 496.5 $[M+H]^+$, 518.5 $[M+Na]^+$. HRMS: $C_{24}H_{33}NO_{10}$: calcd 495.2104; found: 495.2098.

4.9. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-psicopyranosyloxy)]-3-phenyl-4,5-dihydroisoxazoles, 8a

Column chromatography afforded (55% yield from **5**), both epimers of **8a** in a 3:1 ratio, as a colorless gum: *major*: $[\alpha]_D$ +53 (c 2.9, $CHCl_3$). ^{1}H δ 1.28 (s, 6H, iPrd), 1.40 (d, 6H, iPrd), 3.38–3.50 (m, 2H, $J_{4ia-4ib}=5.1$ Hz, H-4i), 3.70–3.90 (m, 2H, $J_{6a-6b}=11.5$ Hz, H-6), 3.92 (d, 1H, $J_{1a-1b}=9.3$ Hz, H-1a), 4.15 (d, 1H, $J_{3-4}=2.2$ Hz, H-3), 4.30 (d, 1H, H-5), 4.38 (d, 1H, H-1b), 4.55 (dd, 1H, $J_{4-5}=7.8$ Hz, H-4), 5.95 (dd, 1H $J_{5i-4i}=5.1$ Hz, H-5i,), 7.35–7.45 (m, 3H, H-Ar), 7.63–7.7 (m, 2H, H-Ar). ^{13}C NMR δ 23.4, 24.2, 24.7 and 25.3 (4×iPrd), 40.4 (C-4i), 61.6 (C-6), 70.3 (C-1), 72.6, 72.7 and 73.0 (C-3, C-4 and C-5), 102.5 (C-5i), 104.3(C-2), 107.6 (C_{IV} iPrd), 108.7 (C_{IV} iPrd), 124.8, 125.5, 127.3 and 129.1

(CH-Ar), 142 (C_{IV}Ar), 156 ($C_{C=N}$). MS: m/z 423.5 $[M+NH_4]^+$, 428 $[M+Na]^+$, 444.5 $[M+K]^+$. HRMS: $C_{21}H_{27}NO_7$: calcd 405.1787; found: 405.1779.

minor: $[\alpha]_D$ −34 (c 0.07, $CHCl_3$). ^{1}H NMR δ 1.3 (d, 6H, iPrd), 1.4 (d, 6H, iPrd), 3.4–3.47 (m, 2H, H-4i), 3.88 (d, 1H, $J_{1a-1b}=9.3$ Hz, H-1a), 3.95 (dd, 2H, $J_{6a-6b}=4.4$ Hz, H-6), 4.08–4.14 (m, 2H, H-3, H-5), 4.17 (d, 1H, H-1b), 4.54 (dd, 1H, $J_{4-5}=7.1$ Hz, $J_{4-3}=2.9$ Hz, H-4), 5.91 (dd, 1H, $J_{5i-4i}=4.9$ Hz, H-5i), 7.35–7.48 (m, 3H, H-Ar), 7.60–7.70 (m, 2H, H-Ar). MS: m/z 428 $[M+Na]^+$.

4.10. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-psicopyrano-syloxy)]-3-mesityl-4,5-dihydroisoxazoles, 8b

Column chromatography afforded (75% yield from **5**), both epimers of **8b** in a 3:1 ratio, as a colorless gum: *major*: $[\alpha]_D$ +75 (c 2.3, $CHCl_3$). ^{1}H NMR δ 1.29 (s, 3H, iPrd), 1.43 (s, 3H, iPrd), 1.46 (s, 3H, iPrd), 1.49 (s, 3H, iPrd), 2.24 (s, 6H, CH_3), 2.29 (s, 3H, CH_3), 3.07 (d, 1H, $J_{4ia-4ib}=17.6$ Hz, H-4ia), 3.32 (dd, 1H, $J_{4ib-5i}=5.9$ Hz, H-4ib), 3.69 (d, 1H, $J_{6a-6b}=13.2$ Hz, H-6a), 3.81 (dd, 1H, $J_{6b-5}=1.5$ Hz, H_{6b}), 3.89 (d, 1H, $J_{1a-1b}=9.3$ Hz, H-1a), 4.25 (d, 1H, $J_{3-4}=2.2$ Hz, H-3), 4.31 (d, 1H, $J_{5-4}=7.6$ Hz, H-5), 4.35 (d, 1H, H-1b), 4.48 (dd, 1H, H-4), 5.85 (d, 1H, H-5i), 6.85 (s, 2H, 2H-Ar). ^{13}C NMR δ 20.1 and 21.5 ($3CH_3$), 25.2, 26.1, 26.7 and 27.1 (4×iPrd), 46.3 (C-4i), 63.5 (C-6), 72.0 (C-1), 73.1 (C-3), 74.6 (C-4 and C-5), 102.8 (C-5i), 106.0 (C-2), 109.3 (C_{IV} iPrd), 110.2 (C_{IV} iPrd), 125.9 (CH-Ar), 128.9 (CH-Ar), 137.1, 139.4 (C_{IV} Ar), 159.4 ($C_{C=N}$). MS: m/z 471.5 $[MH+Na]^+$. HRMS: $C_{24}H_{33}NO_7$: calcd 447.2257; found: 447.2248.

minor: $[\alpha]_D$ −315 (c 0.96, $CHCl_3$). ^{1}H NMR δ 1.37 (s, 3H, iPrd), 1.40 (s, 3H, iPrd), 1.47 (s, 3H, iPrd), 1.51 (s, 3H, iPrd), 2.23 (s, 6H, $2CH_3$), 2.28 (s, 3H, CH_3), 3.15 (dd, 1H, $J_{4ia-4ib}=7.9$ Hz, $J_{4ia-5i}=1.5$ Hz, H-4ia), 3.31 (dd, 1H, $J_{4ib-5i}=6.1$ Hz, H-4ib), 3.87–4.02 (m, 3H, H-6, H-1a), 4.17 (d, 1H, $J_{3-4}=3.7$ Hz, H-3), 4.26 (dd, 2H, $J_{1a-1b}=9.3$ Hz, H-1b, H-3), 4.61 (dd, 1H, $J_{4-5}=7.1$ Hz, H-4), 5.96 (dd, 1H, H-5i), 6.89 (s, 2H, 2H-Ar). ^{13}C NMR δ 18.2 and 19.6 ($3CH_3$), 23.3, 24.2, 24.8 and 25.3 (4×iPrd), 44.4 (C-4i), 61.7 (C-6), 70.2 (C-1), 71.3 and 72.7 (C-3, C-4 and C-5), 101.0 (C-2), 104.2 (C-5i), 107.5 (C_{IV} iPrd), 108.4 (C_{IV} iPrd), 124.0 (CH-Ar), 127.0 (CH-Ar), 135.2 and 137.5 (C_{IV} Ar), 157.6 ($C_{C=N}$). MS: m/z 471.5 $[MH+Na]^+$; 486 $[M+K]^+$; 504 $[M+K+NH_4]^+$.

4.11. (5*RS*)-5-[3-(1,2:4,5-Di-*O*-isopropylidene-β-D-psicopyranosyloxy)]-3-(3,4,5-trimethoxyphenyl)-4,5-dihydroisoxazoles, 8c

Column chromatography afforded (65% yield from **5**), both epimers of **8c** in a 3:1 ratio, as a colorless gum: *major*: $[\alpha]_D$ +50 (c 3.1, $CHCl_3$). ^{1}H NMR δ 1.31 (s, 3H, iPrd), 1.47 (s, 6H, 2×iPrd), 1.51 (s, 3H, iPrd), 3.3–3.5 (m, 2H, H-4i), 3.7 (d, 1H, $J_{6a-6b}=12.7$ Hz, H-6a), 3.81 (dd, 1H, $J_{6b-5}=1.5$ Hz, H-6b), 3.89–3.92 (m, 10H, H-1a, OCH_3), 4.20 (d, 1H, $J_{3-4}=2.4$ Hz, H-3), 4.34 (d, 1H, $J_{5-4}=7.8$ Hz, H-5), 4.42 (d, 1H, $J_{1a-1b}=9.3$ Hz, H-1b), 4.56 (dd, 1H, H-4), 6.00 (dd, 1H, $J_{4ia-5i}=5.3$ Hz, $J_{4ib-5i}=2.8$ Hz, H-5i), 6.85 (s, 2H, 2H-Ar). ^{13}C NMR δ 25.2, 25.9, 26.6 and 27.2 (4×iPrd), 42.3 (C-4i), 56.7 (OCH_3), 61.3 (C-6), 72.1 (C-1), 74.4 (C-3), 74.5 (C-4), 74.7 (C-5), 104.4 (C-5i), 104.7 (2CH-Ar), 106.1 (C2), 109.3, (C_{IV} iPrd), 110.5 (C_{IV} iPrd), 124.5, 126.3, 140.5 and 153.7 (C_{IV}-Ar), 157.6 ($C_{C=N}$). MS: m/z 496.5 $[M+H]^+$, 518.5 $[M+Na]^+$, 534 $[M+K]^+$; 542 $[MH+2Na]^+$, 550.5 $[MH+3NH_4]^+$. $C_{24}H_{33}NO_{10}$: calcd 495.2104; found: 495.2095.

minor: $[\alpha]_D$ −155 (c 1.3, $CHCl_3$).). ^{1}H NMR δ 1.38 (s, 3H, iPrd), 1.39 (s, 3H, iPrd), 1.47 (s, 3H, iPrd), 1.57 (s, 3H, iPrd), 3.31–3.48 (m, 2H, H-4i), 3.89–3.96 (m, 10H, H-1a, OCH_3), 4.00–4.04 (m, 2H, H-6), 4.10 (d, 1H, $J_{3-4}=4.2$ Hz, H-3), 4.17 (d, 1H, $J_{1a-1b}=9.3$ Hz, H_{1b}), 4.20–4.25 (m, 1H, H-5), 4.56 (dd, 1H, $J_{4-5}=6.8$ Hz, H-4), 5.98 (dd, 1H, $J_{5i-4ia}=5.4$ Hz, $J_{5i-4ib}=2.0$ Hz, H-5i), 6.90 (s, 2H, H-Ar). MS: m/z 496.5 $[M+H]^+$, 518.5 $[M+Na]^+$, 534 $[M+K]^+$.

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