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Reactivity of 1,2-cyclic sulfite xylosides towards nucleophiles

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ABSTRACT

1,2-Cyclic sulfite xylosides offer facile access to 1,2-oxazolines upon reaction with aromatic and alkyl nitriles under Lewis or Brönsted acid conditions. Additionally, hydrophobic ionic liquids facilitate acid-catalysed formations of such oxazolines and C- and O-linked xylosides, providing means to carry out fast reactions at room temperature, and this in yields comparable to reactions conducted in xylene at high temperature for extended reaction time.

1. Introduction

2-Oxazolines have been extensively studied[1] for many years and have found many synthetic applications, in particular, as protecting groups for carboxylic acids[2] and ligands in asymmetric catalysis.[3] They can also potentially act as precursors to stable 1-acyl-adenosine diphosphate ribose (acyl-ADPR) analogues, such as secondary amides of C-1 furanosides (Fig. 1), since such amides can be obtained by simple hydrolysis of the oxazoline precursor.[4]

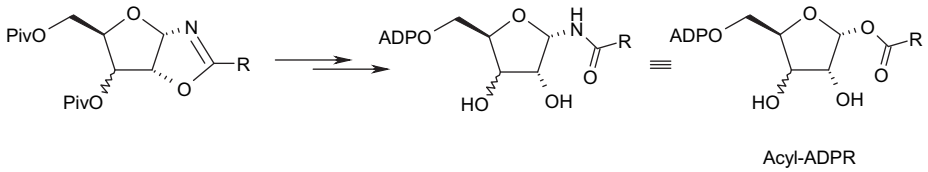

Figure 1. 2-Oxazoline precursors to secondary amides, acyl-adenosine diphosphate ribose analogues.

Two main synthetic methods have been developed to access oxazolines. The first is the Ritter reaction, which involves the reaction of a nitrile moiety with an epoxide in the presence of zinc chloride.[5] This methodology has been successfully applied to access a small number of 1,2-oxazolines derived from partially protected hexose derivatives. From such oxazolines, Danieshefsky described the synthesis of 1-amino sugars. The second consists of the condensation of an α-amino alcohol onto a carboxylic acid derivative.[6] Here, oxazoline-containing sugars have been synthesised from partially protected 1-amino sugars. While 1,2-anhydrofuranoside derivatives are too unstable reagents to be used to access oxazolines using the method developed by Danishefsky, 1-amino-furanoside derivatives are difficult to obtain in high yields and readily hydrolyse to their sugar parents in the presence of water. As previously mentioned one method of preparing oxazolines in a variation of the Ritter reaction uses an epoxide functionality as an alternative to 1,2-anhydrofuranoside deriviatives.[5] In an extension to this work, given that the reactivity of cyclic sulfite derivatives is often compared with that of epoxides,[7,8] a variation of the Ritter reaction using a furanoside incorporating this functionality, e.g., **1**, to obtain oxazoline derivatives of furanosides, **2a**–**e** (Scheme 1), has been examined. In addition, the reactivity of the 1,2-cyclic sulfite sugar diester **1** towards nucleophiles other than nitriles was investigated, to see whether C–C or C–O bond formation could be achieved under similar reaction conditions in the absence of a nucleophilic nitrogen (Scheme 1).

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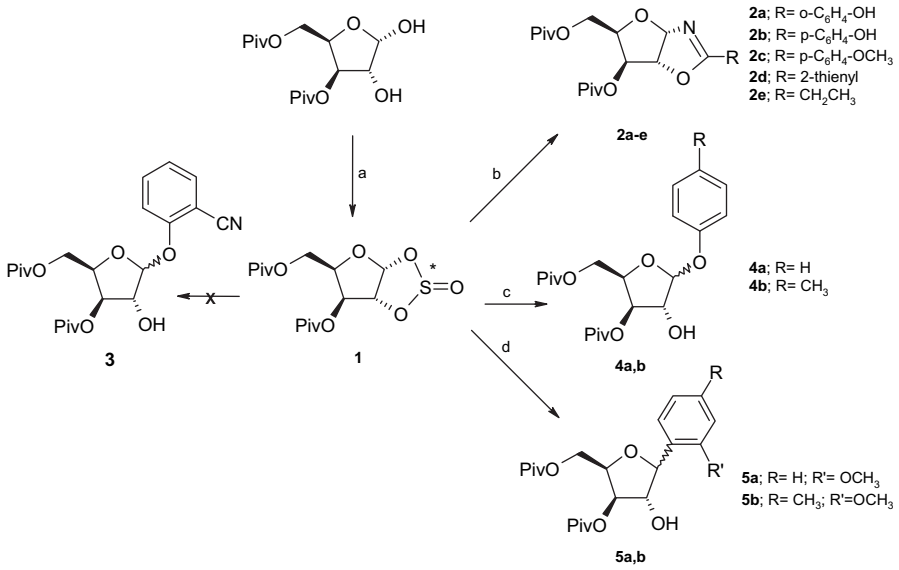


Scheme 1. Reaction scheme showing the reactivity of cyclic sulfites towards nucleophiles in the presence of acids.

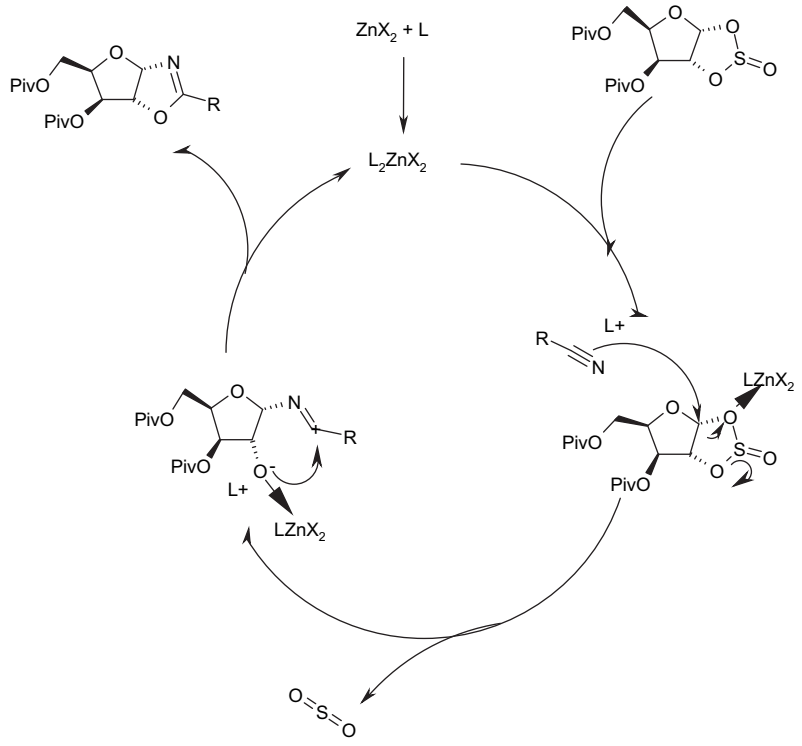
2. Results and discussion

Hardacre et al. have shown that ionic liquids provide facile access to 1,2-cyclic sulfite and sulfate diesters of furanosides.[9] These syntheses were achieved using immobilised morpholine as co-reagent. A suitably protected diol was converted to the cyclic sulfite by reaction with thionyl chloride in the presence of immobilized morpholine. The reaction can be performed in either anhydrous DCM under an atmosphere of argon, or in non-dried $[C_4mpyrr][NTf_2]$ in air. Whilst these reaction conditions both give very good yields of the cyclic sulfite **1**, for this work the DCM method was most commonly used. Initially, the stereo-controlled synthesis of the furanoside, **3**, was examined by reacting the xyloside 1,2-cyclic sulfite, **1**, with 2-hydroxybenzonitrile in the presence of a Lewis acid such as zinc chloride in xylene. Surprisingly, no O-addition products were detected; however, the 2-oxazoline, **2a**, was produced in moderate yields. Expanding this reaction to other nitrile-incorporating aromatics showed that only electron-rich nitriles reacted with **1** to yield the corresponding oxazolines. For example, the nitrile moieties of the *o*- and *p*-hydroxybenzonitriles (**2a** and **2b**, respectively) as well as those of 2-cyanothiophene (**2d**) and propionitrile (**2e**) were sufficiently nucleophilic when reacted in xylene to yield the respective oxazolines. When reacted with *p*-cyanoanisole the cyclic sulfite, **1**, reacted, albeit in low yield <5%, to give the 1,2-oxazoline derivative **2c**. It must be noted that, in the absence of a strongly nucleophilic nitrile group, due to the lack of activation by the *m*-hydroxyl group of *m*-hydroxybenzonitrile, reaction with this nitrile did not occur and both cyclic sulfite **1** and *m*-hydroxybenzonitrile were recovered.

Reactions in xylene were carried out at 140 °C and in all cases took reaction times in excess of 16 h. Having established that ionic liquids provide a suitable medium for the stabilisation of cyclic sulfites allowing improved reaction yields, stability of the sulfite product and the use of simple reaction conditions (room temperature, in air), synthesis of the oxazolines was carried out in ILs. Reactions between cyclic sulfite **1** and aromatic nitriles in $[C_4mpyrr][NTf_2]$ were complete within 30–60 min at room temperature, and proceeded with yields comparable to those achieved in xylene. The IL $[C_4mpyrr][NTf_2]$ was chosen for its ability in facilitating 1,2-cyclic sulfite and sulfate diester formation and stabilisation in xyloside chemistry, and proved to be an excellent medium for nucleophilic substitution.[10] Here, the increased rate of reaction can be attributed to the activation of the $ZnCl_2$ catalyst by the ionic liquid. Xiao et al. proposed that the ionic liquid can complex to zinc chloride resulting in a intermediate, which can then interact with the sulfite oxygen more readily after the loss of one IL ligand as shown in Scheme 2.[11] This coordination then induces reaction at the anomeric carbon, loss of SO_2 and finally cyclisation to give the oxazoline. In xylene, this coordination with $ZnCl_2$ and the resulting C-1 xyloside activation only occurs at high temperatures. As well as an enhancement of the $ZnCl_2$ activity by $[C_4mpyrr][NTf_2]$, the formation of SO_2 as a by-product may also be facilitated by ILs' ability to absorb high concentrations of this species. Barrosse-Antle et al., while carrying out electroreduction of SO_2 in ionic liquids, showed that high concentrations of SO_2 could be achieved in a range of imidazolium ILs.[12] In forming the oxazolines, the IL may facilitate the quick removal of SO_2 from the reaction pathway due to its high affinity for SO_2. Xylene at room temperature can only achieve SO_2 concentrations of 0.3 mol % and therefore is unable to facilitate removal of SO_2 from the product in the same way as the IL unless heated.[13]

With Danishefsky's methodology, the stereochemistry at the C-1 position of the oxazoline is controlled by the stereochemistry, or lack thereof, of the epoxide prepared from a sugar glycal synthetic intermediate.[5] In contrast, the present procedure to access furanoside oxazolines can be achieved from partially protected sugars and is fully stereo-controlled via a cyclic sulfite intermediate. The methodology described here has the advantage that the stereochemistry at the C-1 position of the sugar of the oxazoline is directed by the stereochemistry imposed by the C-2 hydroxyl of the sugar.

The reactivity of the nitrile anion towards cyclic sulfite **1** in the presence of TfOH or $Zn(OTf)_2$ was also examined. The results were compared with those reported by Beaupere[14] who using NaCN in HMPA in the presence of $Yb(OTf)_3$ at 90 °C, described the first furanoside-C_1–CN bond formation from a glucofuranoside cyclic sulfite. Under our reaction conditions, the use of the cyanide salt only resulted in removal of the esters with no formation of C–C bonded products or oxazoline derivatives. Similarly, neither of these products could be isolated when using the benzyl protected parent of **1** to overcome the deprotection side-reaction.



Scheme 2. Mechanism of oxazoline formation in ILs.

The use of cyclic sulfite precursors for the preparation of O-linked furanosides has been little explored in the literature,[15] and to our knowledge no C-linked derivatives have been prepared in this manner. As such electron-rich aromatics lacking a nucleophilic nitrile moiety were examined in order to achieve stereo-controlled C–O or C–C bond formation in both xylene and $[C_4mpyrr][NTf_2]$. Only C–O bond containing products (**4a** and **4b**) with a 1:1 ratio of anomers were identified when phenolic aromatics were used whilst C–C bond containing products were solely isolated in the case of anisole reagents (**5a** and **5b**) also in a 1:1 ratio of anomers. Again, utilising the ionic liquid as solvent resulted in faster reaction times and allowed for room temperature conditions to be applied with yields comparable to those obtained for reactions conducted in xylene at 140 °C. This again was achieved by $ZnCl_2$ activation as described above. This behaviour can once again be attributed to the activation of the Lewis acid by the IL. Unlike with the oxazolines where the stereochemistry was dictated by the configuration at the C_2 position of the xyloside ring and the reversibility of the C–N bond formation, the cyclic sulfite does not provide any stereo-control over the nucleophilic attack of the latter aromatic reagents. In fact, the α/β product ratio was consistent with a true S_N1 mechanism whereupon acid-catalysis the cyclic sulfite ring opened at C-1 allowing for the nucleophile to come from either side of the molecule plane. It is thought that the steric hindrance introduced by the C-3 and C-5 esters has a major impact on the overall anomeric outcomes of these C–O and C–C bond formation.

These results indicate that while cyclic sulfites are potentially perfect reagents for stereo-controlled S_N2-type bond formation at the C-1 position of furanosides, in particular cyclic sulfite furanosides possessing (1*R*,2*R*)-configuration, the present conditions provide a suitable environment for true S_N1 mechanism, through which bond formation appears to be controlled by steric rather than electronic parameters. Investigations on the stereochemistry of the C–C bond formation through control of the stereochemistry at the C-3 position combined to the use of 'smaller' protecting groups are currently underway.

3. Conclusions

1,2-Cyclic sulfite xylosides have been shown to be highly versatile reagents to access to C–N, C–C and C–O containing nucleoside/glycoside analogues. Reactions in $[C_4mpyrr][NTf_2]$ resulted in an enhancement of the Lewis acids' catalytic role allowing for faster reaction and room temperature conditions.

4. Experimental

4.1. General

Two sets of parallel experiments using 1-butyl-1-methyl-pyrrolidinium bis{(trifluoromethyl)sulfonyl}imide ($[C_4mpyrr][NTf_2]$) and xylene were carried out. The ionic liquid $[C_4mpyrr][NTf_2]$ was prepared in house using standard literature methods[16] from 1-butyl-1-methyl-pyrrolidinium bromide. The bromide content of the ionic liquid was measured using ion chromatography and was below 5 ppm. The ionic liquid was used without drying and was found to have a water content of 0.03 wt % analysed via Karl Fischer Titration. Zinc chloride was purchased from Aldrich and dried under high vacuum before use. All the ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or 500 at 25 °C in $CDCl_3$ referenced to 0.00 ppm using TMS for the ^1H NMR and 77.00 ppm using $CDCl_3$ for the ^{13}C NMR unless otherwise stated. The O- and C-linked derivatives were obtained in a 1:1 anomeric ratio, unless otherwise stated only the α-anomer was isolated cleanly and characterised.

*4.1.1. 3,5-Di-O-pivaloyl-1,2-O-sulfinyl-D-xylofuranose (**1**).* To a solution of 1,2-dipivaloate xylofuranose (438 mg, 1.38 mmol) in freshly distilled dichloromethane were added morpholine resin (1.2 g, 3 equiv) (Stratospheres® PL-MPH) and a 1.3 M solution of thionyl chloride (1.16 ml, 1.52 mmol) in dry dichloromethane and the mixture stirred gently. The progression of the reaction was monitored by TLC (petroleum ether/EtOAc (7:3)). If needed, a further 0.3 equiv of thionyl chloride solution was added. After 2 h, the

mixture was filtered on a thin pad of silica and the resin rinsed with a large volume of dichloromethane. The filtrate was concentrated under reduced pressure to yield the expected compound (87%) as clear oil that crystallised with time and was stored at 4 °C. Mixture of two diastereoisomers at the sulfur centre was obtained in a 3:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.64 (d, 1H, J=3.9 Hz, H-1a), 6.49 (d, 1H, J=4.7 Hz, H-1b), 5.46 (d, 1H, J=3.8 Hz, H-3b), 5.39 (d, 1H, J=3.0 Hz, H-3a), 5.14 (d, 1H, J=3.9 Hz, H-2a), 5.00 (dt, 1H, J=3.8, 6.3 Hz, H-4b), 4.83 (d, 1H, J=4.8 Hz, H-2b), 4.44 (dt, 1H, J=3.1, 6.4 Hz, H-4a), 4.27 (m, 4H, H-5), 1.23 (s, 9H, Piv), 1.23 (s, 9H, Piv), 1.19 (s, 18H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.3, 177.2, 177.0 (C=O), 111.2 (C-1b), 109.2 (C-1a), 89.1 (C-2b), 85.5 (C-2a), 78.4 (C-4a), 78.0 (C-4b), 75.9 (C-3b), 74.8 (C-3a), 60.9, 60.6 (C-5), 39.5, 39.2 (Piv), 27.5, 27.4 (Piv); HRMS (ES) m/z ($M+NH_4^+$) calculated for $C_{15}H_{28}NO_8S$ 382.1530, found 382.1529. IR ν_{max} (thin film, $CHCl_3$) 2975, 1734, 1158 (S=O).

4.2. General synthetic procedure in organic solvents

The $ZnCl_2$ was introduced under argon in a two necked round bottomed flask and dried by heating under high vacuum. The $ZnCl_2$ was allowed to cool before use. A solution of cyano-arene (2.5 equiv), phenol (2.0 equiv) or arene (5 equiv) and cyclic sulfite xyloside (1 equiv), **1**, in xylene (100 mM sugar concentration) was then added under argon to the dried Lewis acid. The mixture in xylene was then heated at reflux under argon with stirring for 16 h. After cooling, ethyl acetate (5 cm^3) was added and the organic phase was neutralised with 1 M NaOH (5 cm^3). After rapid stirring to give an emulsion, the aqueous phase was then extracted twice with ethyl acetate and the combined organic fractions were then washed with a saturated. aq $NaHCO_3$ solution (5 cm^3) followed by a saturated aq NH_4Cl (5 cm^3) and brine (5 cm^3). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by silica chromatography using petroleum ether and diethyl ether mixtures as eluant. (For reaction yields see Tables 1 and 2).

Table 1
Yield comparison for oxazolines prepared from 1,2-cyclic sulfites as a function of the nitrile and solvent used. Xylene reflux, 16 h, or [C_4mpyrr][NTf_2] room temperature, 30–60 min all reactions with $ZnCl_2$ Lewis acid

Reagent	Solvent	Isolated yield (%)	Compound
o-CN-C_6H_4OH	Xylene	57	**2a**
	Ionic liquid	52	
m-CN–C_6H_4OH	Xylene	No reaction	—
	Ionic liquid	No reaction	
p-CN–C_6H_4OH	Xylene	77	**2b**
	Ionic liquid	68	
p-CN–$_6H_4OCH_3$	Xylene	<5	**2c**
	Ionic liquid	No reaction	
2-Thienyl	Xylene	34	**2d**
	Ionic Liquid	25	
CH_3CH_2CN	Xylene	50	**2e**
	Ionic liquid	60	

Table 2
C–O and C–C bond formation products from reaction of 1,2-cyclic sulfites with phenols, arenes and Lewis acid in xylene and IL [C_4mpyrr][NTf_2]. Reaction in xylene at reflux and 16 h reaction time, or [C_4mpyrr][NTf_2] reaction at room temperature and 30–60 min all reactions with $ZnCl_2$ Lewis acid. In all cases α/β ratio was 1:1

Reagent	Conditions	Isolated yields (%)	Compound
C_6H_5OH	Xylene	77	**4a**
	Ionic liquid	71	
p-CH_3–C_6H_4OH	Xylene	61	**4b**
	Ionic liquid	63	
$C_6H_5OCH_3$	Xylene	62	**5a**
	Ionic liquid	66	
o-CH_3–$C_6H_4OCH_3$	Xylene	60	**5b**
	Ionic liquid	65	

4.3. General synthetic procedure in ([C_4mpyrr][NTf_2])

The $ZnCl_2$ was introduced under argon in a two necked round bottomed flask and dried by heating under high vacuum. The $ZnCl_2$ was allowed to cool before use. A solution of cyano-arene (2.5 equiv), phenol (2.0 equiv) or arene (5 equiv) and cyclic sulfite xyloside (1 equiv), **1**, in IL (100 mM sugar concentration) was then added under argon to the dried Lewis acid. The reaction mixture was then stirred at room temperature for 1 h. Ethyl acetate (5 cm^3) was then added and the organic phase was neutralized with 1 M NaOH (5 cm^3). After rapid stirring to give an emulsion the aqueous phase was then extracted twice with ethyl acetate and the combined organic fractions were then washed with a saturated aq $NaHCO_3$ solution (5 cm^3) followed by a saturated aq NH_4Cl (5 cm^3) and brine (5 cm^3). The organic phase was then dried over $MgSO_4$ and concentrated under reduced pressure. The product in IL was removed by addition of diethyl ether and decanting of the product. The organic phases were concentrated and purified by silica chromatography using petroleum ether and diethyl ether mixtures as eluant. (For reaction yields see Tables 1 and 2).

*4.3.1. 3,5-Di-O-pivaloyl-2′-o-hydroxyphenyl-α-D-xylofuranoso-[1,2-d]-Δ2′-oxazoline (**2a**).* Product isolated as a colourless oil as a single anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.62 (s, 1H, OH), 7.71 (dd, 1H, J=1.7, 7.9 Hz, Ph), 7.45 (m, 1H, Ph), 7.04 (dd, 1H, J=0.8, 8.5 Hz, Ph), 6.92 (mt, 1H, Ph), 6.37 (d, 1H, J=5.6 Hz, H-1), 5.40 (d, 1H, J=3.2 Hz, H-3), 4.83 (d, 1H, J=5.6 Hz, H-2), 4.29 (ABX, 2H, J=6.2, 6.5, 11.2 Hz, H-5), 4.07 (dt, 1H, J=3.3, 6.3 Hz), 1.26 (s, 9H, $(CH_3)_3C$), 1.17 (s, 9H, $(CH_3)_3C$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3 (C=O), 177.5 (C=O), 168.1 (Ph), 161.0 (C–CN), 135.2 (Ph), 129.1 (Ph), 119.4 (Ph), 117.6 (Ph), 109.4 (Ph), 99.9 (C-1), 84.3 (C-2), 75.8 (C-4), 75.4 (C-3), 61.0 (C-5), 39.5 ($(CH_3)_3C$), 39.1 ($(CH_3)_3C$), 27.5 ($(CH_3)_3C$), 27.5 ($(CH_3)_3C$); HRMS (ES) m/z ($M+H^+$) calculated for $C_{22}H_{30}NO_7$ 420.2022, found 420.2027. IR ν_{max} (thin film, $CHCl_3$) 2975, 1734, 1641, 1481, 1130. $[\alpha]_D^{20}$ +33 (c 0.65, $CHCl_3$).

*4.3.2. 3,5-Di-O-pivaloyl-2′-p-hydroxyphenyl-α-D-xylofuranoso-[1,2-d]-Δ2′-oxazoline (**2b**).* Product isolated as a colourless oil as a single anomer. ^{1}H NMR (300 MHz $CDCl_3$) δ 7.90 (d, 2H, J=8.7 Hz, Ph), 7.55 (d, 2H, J=8.7 Hz, Ph), 6.37 (d, 1H, J=5.7 Hz, H-1), 5.42 (d, 1H, J=3.2 Hz, H-3), 5.33 (s, 1H, OH), 4.90 (d, 1H, J=5.7 Hz, H-2), 4.33 (m, 2H, H-4, H-5), 4.15 (m, 1H, H-5), 1.28 (s, 9H, CH_3-Piv), 1.18 (s, 9H, CH_3-Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7 (C=O), 177.3 (C=O), 160.4 (C-CN), 138.2, 134.6, 131.7, 130.3, 129.3, 129.1, 128.7, 128.5, 128.4, 126.4 (Ph), 116.1 (Ph), 103.9 (C-1), 78.9 (C-3), 77.6 (C-2), 75.6 (C-4), 55.1 (C-5), 27.5 (Piv), 21.7 (Piv). HRMS (ES) m/z ($M+NH_4^+$) calculated for $C_{22}H_{33}N_2O_7$ 437.2281, found 437.2287. IR ν_{max} (thin film, $CHCl_3$) 2977, 1733, 1640, 1476, 1134. $[\alpha]_D^{20}$ +34 (c 0.55, $CHCl_3$).

*4.3.3. 3,5-Di-O-pivaloyl-2′-p-methoxyphenyl-α-D-xylofuranoso-[1,2-d]-Δ2′-oxazoline (**2c**).* Product isolated as a colourless oil as a single anomer: ^{1}H NMR (300 MHz $CDCl_3$) δ: 7.90 (d, 2H, J=8.5 Hz, Ph), 6.86 (d, 2H, J=8.5 Hz, Ph), 6.25 (d, 1H, J=5.6 Hz, H-1), 5.30 (d, 1H, J=3.2 Hz, H-3), 4.74 (d, 1H, J=5.6 Hz, H-2), 4.17 (t, 1H, J=4.6 Hz, H-5a), 4.08–3.97 (m, 2H, H-4, H-5b), 3.97 (s, 3H, Ph-OCH_3), 1.17 (s, 9H, CH_3), 1.10 (s, 9H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ176.9, 176.1 (C=O), 165.6 (Ph-OMe), 162.1 (C–CN), 129.9 (Ph), 112.9 (Ph), 99.8 (C-1), 83.6 (C-2), 74.6 (C-3), 74.0 (C-4), 59.7 (C-5), 54.4 ($PhCH_3$) 26.1 (2×Piv); HRMS (ES) m/z ($M+H^+$) calculated for $C_{23}H_{32}NO_7$ 434.2179, found 434.2179. IR ν_{max} (thin film, $CHCl_3$) 2973, 1733, 1641, 1477, 1129. $[\alpha]_D^{20}$ +37 (c 0.5, $CHCl_3$).

*4.3.4. 3,5-Di-O-pivaloyl-2′-thiophenyl-α-D-xylofuranoso-[1,2-d]-Δ2′-oxazoline (**2d**).* Product isolated as a pale yellow oil as a single anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, 1H, J=0.8 Hz, 3.7 Hz, Ph), 7.57 (dd, 1H, J=0.8, 5.0 Hz, Ph), 7.13 (dd, 1H, J=3.8, 5.0 Hz, Ph),

6.31 (d, 1H, *J*=5.6 Hz, H-1), 5.39 (d, 1H, *J*=3.3 Hz, H-3), 4.83 (d, 1H, *J*=5.6 Hz, H-2), 4.29 (ABX, 2H, *J*=11.2, 3.88, 6.56 Hz, H-5), 4.11 (ddd, 1H, *J*=2.8, 6.1, 9.8 Hz, H-4), 1.24 (s, 9H, Piv), 1.17 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 177.5 (C=O), 162.7 (C–CN), 132.8, 132.3 (Ph), 128.3 (Ph), 101.4 (C-1), 85.4 (C-3), 75.6 (C-2, C-4), 61.1 (C-5), 39.5, 39.1 (Piv), 27.6, 27.5, 27.5 (Piv); HRMS (ES) *m/z* ($M+H^+$) calculated for $C_{20}H_{28}NO_6S$ 410.1637, found 410.1623. IR ν_{max} (thin film, $CHCl_3$) 2978, 1733, 1637, 1528, 1426, 1273, 1146. $[\alpha]_D^{20}$ +12 (*c* 0.12, $CHCl_3$).

*4.3.5. 3,5-Di-O-pivaloyl-2′-ethyl-α-D-xylofuranoso-[1,2-d]-Δ2′-oxazoline (**2e**).* Product isolated as a colourless oil as a single anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 (d, 1H, *J*=5.7 Hz, H-1), 5.19 (d, 1H, *J*=3.4 Hz, H-3), 4.56 (d, 1H, *J*=5.7 Hz, H-2), 4.21 (dd, 1H, *J*=6.4, 11.3 Hz, H-5), 4.17 (dd, 1H, *J*=6.4, 11.3 Hz, H-5′), 3.93 (ddd, 1H, *J*=3.4, 6.4, 11.3 Hz, H-4), 2.32 (m, 2H, CH_2CH_3), 1.16 (t, 3H, *J*=7.6 Hz, CH_2CH_3), 1.15 (s, 9H, Piv), 1.12 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.1, 175.1 (C=O), 170.8 (C–CN), 98.7 (C-1), 82.5 (C-2), 73.3 (C-3), 720.9 (C-4), 58.9 (C-5), 37.1, 37.0 (Piv), 25.2, 25.1 (Piv), 19.5 ($\mathbf{C}H_2CH_3$), 8.3 ($CH_2\mathbf{C}H_3$). HRMS (ES) *m/z* ($M+H^+$) calculated for $C_{18}H_{30}NO_6$ 356.2073, found 356.2086. IR ν_{max} (thin film, $CHCl_3$) 2975, 1735, 1641. $[\alpha]_D^{20}$ +9 (*c* 1, $CHCl_3$).

*4.3.6. 1-O-Phenyl-3,5-di-O-pivaloyl-α-D-xylofuranose (**4a**).* Product isolated as a yellow oil as a 1:1 anomeric mixture. α-Anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, 2H, *J*=7.3, 8.7 Hz, Ph), 7.10 (d, 2H, *J*=7.7 Hz, Ph), 7.07 (dd, 1H, *J*=7.3, 5.2 Hz, Ph), 5.70 (d, 1H, *J*=4.6 Hz, H-1), 5.38 (dd, 1H, *J*=5.7, 6.4 Hz, H-3), 4.69 (dt, 1H, *J*=4.5, 6.5 Hz, H-4), 4.46 (dt, 1H, *J*=5.3, 7.6 Hz, H-2), 4.23 (dd, 1H, *J*=4.3, 12.1 Hz, H-5a), 4.10 (dd, 1H, *J*=4.8, 12.1 Hz, H-5b), 2.94 (d, 1H, *J*=7.9 Hz, OH), 1.25 (s, 9H, Piv), 1.22 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5 (C=O), 178.4 (C=O), 156.6 (CØ), 130.0, 129.8, 123.5, 117.5, 116.7 (Ph), 99.7 (C-1), 77.9 (C-3), 76.8 (C-2), 75.8 (C-4), 52.1 (C-5), 27.6, 27.5, 27.4 (Piv). HRMS (EI) *m/z* (M^+) calculated for $C_{21}H_{30}O_7$ 394.1992, found 394.1976. IR ν_{max} (thin film, $CHCl_3$) 3401, 2923, 1731, 1640, 1451. $[\alpha]_D^{20}$ −13 (*c* 0.2, $CHCl_3$).

*4.3.7. 1-O-p-Methyl phenyl-3,5-di-O-pivaloyl-α-D-xylofuranose (**4b**).* Product isolated as a pale yellow oil as a 1:1 anomeric mixture. α-Anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, 2H, *J*=14.5 Hz, Ph), 6.98 (d, 2H, *J*=14.0 Hz, Ph), 5.64 (d, 1H, *J*=8.0 Hz, H-1), 5.38 (dd, 1H, *J*=3.5, 6.0 Hz, H-3), 4.69 (dt, 1H, *J*=8.5, 16.5 Hz, H-4), 4.43 (dt, 1H, *J*=8.5, 12.0 Hz, H-2), 4.23–4.05 (m, 2H, H-5a,b), 2.94 (d, 1H, *J*=13.0 Hz, OH), 2.16 (s, 3H, CH_3), 1.25 (s, 9H, Piv), 1.20 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.4 (C=O), 178.5 (C=O), 168.3 (CØ), 154.4 (CØ), 132.9, 130.4, 128.3, 117.5 (Ph), 100.0 (C-1), 78.0 (C-3), 76.6 (C-2), 75.7 (C-4), 62.1 (C-5), 39.3 (CH_3), 27.7, 27.6, 27.5, 27.4 (Piv); HRMS (ES^-) *m/z* ($M-H^+$) calculated for $C_{22}H_{31}O_7$ 407.2070, found 407.2087. IR ν_{max} (thin film, $CHCl_3$) 3412, 2925, 1733, 1635, 1456. $[\alpha]_D^{20}$ −14 (*c* 1, $CHCl_3$).

*4.3.8. 1-o-Methoxyphenyl-3,5-di-O-pivaloyl-α-D-xylofuranose and 1-o-methoxyphenyl-3,5-di-O-pivaloyl-β-D-xylofuranose (**5a**).* Product isolated as a colourless oil as an inseparable 1:1 anomeric mixture. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, *J*=12.4 Hz, Ph), 6.37 (d, 2H, *J*=14.5 Hz, Ph), 7.24 (t, 1H, *J*=13.2 Hz, Ph), 6.99 (t, 1H, *J*=12.5 Hz, Ph), 6.91 (d, 2H, *J*=15.8 Hz, Ph), 6.90 (dt, 1H, *J*=7.9 Hz, Ph), 5.18 (dd, 1H, *J*=1.2, 3.9 Hz, H-2α), 5.13 (d, 1H, *J*=3.3 Hz, H-1α), 5.07 (dd, 1H, *J*=2.7, 5.1 Hz, H-3β), 4.72 (d, 1H, *J*=5.7 Hz, H-1β), 4.62 (dt, 1H, *J*=10.2, 6.0 Hz, H-4α), 4.53 (dd, 1H, *J*=5.7, 11.4 Hz, H-4β), 4.43–4.37 (m, 5H, H-5α,β, H-3β), 4.04 (dd, 1H, *J*=5.7, 2.7 Hz, H-2β), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.12 (d, 1H, *J*=4.7 Hz, OH), 2.84 (d, 1H, *J*=4.4 Hz, OH), 1.21 (s, 9H, Piv), 1.20 (s, 9H, Piv), 1.19 (s, 9H, Piv), 1.18 (s, 9H, Piv); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.3 ($C\text{Ø}OCH_3$), 179.3 (C=O), 178.5 (C=O), 178.0 (C=O), 159.8 (CØ), 156.3 (CØ), 128.8, 127.6, 126.3, 121.2, 114.2, 110.3 (Ph), 85.4 (C-1α), 84.2 (C-2α), 83.7 (C-3α), 82.7 (C-1β), 81.9 (C-2β), 79.6 (C-4α), 77.8 (C-4β), 77.7 (C-3β), 62.4 (C-5α), 55.9 (OCH_3), 55.7 (OCH_3), 27.5, 27.3, 27.2, 27.1 (Piv); HRMS (ES) *m/z* ($M+Na^+$) calculated for $C_{22}H_{32}O_7Na$ 431.2046, found 431.2045. IR ν_{max} (thin film, $CHCl_3$) 3415, 2926, 1733, 1635, 1481, 1153.

*4.3.9. 1-(o-Methoxy-p-methyl)-phenyl-3,5-O-pivaloyl-α-D-xylofuranose and 1-(o-methoxy-p-methyl)-phenyl-3,5-O-pivaloyl-β-D-xylofuranose (**5b**).* Product isolated as a colourless oil as a 1:1 anomeric mixture. α-Anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, 1H, *J*=2.0 Hz, Ph), 7.08 (dd, 1H, *J*=2.5, 8.5 Hz, Ph), 6.76(d, 1H, *J*=8.5 Hz, Ph), 5.44 (d, 1H, *J*=3.5 Hz, H-1), 5.35 (dd, 1H, *J*=1.2, 3.5 Hz, H-3), 4.69 (dt, 1H, *J*=3.5, 6.5 Hz, H-4), 4.23–4.35 (m, 2H, H-5a, H-2), 4.24 (dd, 1H, *J*=6.5, 11.0 Hz, H-5b), 3.77 (s, 3H, OCH_3), 3.14 (d, 1H, *J*=4.7 Hz, OH), 2.30 (s, 3H, $PhCH_3$), 1.21 (s, 9H, 3×CH_3), 1.19 (s, 9H, 3×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5 (C=O), 177.5 (C=O), 154.1 (OPh), 130.6, 129.7, 128.7, 124.0, 110.4 (Ph), 79.9 (C-1), 78.2 (C-3), 76.9 (C-4), 75.9 (C-2), 62.2 (C-5), 55.9 (OCH_3), 39.4, 39.2, 27.6, 27.5, 27.1 (Piv), 21.1 (CH_3). HRMS (CI) *m/z* ($M+NH_4^+$) calculated for $C_{23}H_{38}NO_7$ 440.2648, found 440.2660. IR ν_{max} (thin film, $CHCl_3$) 3409, 2973, 1725, 1643, 1215, 1128. $[\alpha]_D^{20}$ −12 (*c* 0.25, $CHCl_3$). β-Anomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, 1H, *J*=2.5 Hz, Ph), 7.02 (dd, 1H, *J*=2.0, 8.0 Hz, Ph), 6.75 (d, 1H, *J*=8.5 Hz, Ph), 5.15 (dd, 1H, *J*=2.0, 4.5 Hz, H-3), 5.08 (d, 1H, *J*=3.5 Hz, H-1), 4.58 (dt, 1H, *J*=4.5, 6.0 Hz, H-4), 4.40 (m, 2H, H-5), 4.06 (dd, 1H, *J*=1.5, 3.0 Hz, H-2), 3.82 (s, 3H, OCH_3), 2.85 (s, 1H, OH), 2.28 (s, 3H, CH_3), 1.18 (s, 9H, 3×CH_3), 1.10 (s, 9H, 3×CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5 (C=O), 178.0 (C=O), 154.3 ($C\text{Ø}CH_3$), 129.0, 127.9, 126.9, 110.4 (Ph), 83.4 (C-1), 82.7 (C-2), 79.7 (C-3), 77.8 (C-4), 62.2 (C-5), 56.1 (OCH_3), 39.2, 39.1 (Piv), 27.6, 27.2 (Piv), 21.0 (CH_3); HRMS (CI) *m/z* ($M+H^+$) calculated for $C_{23}H_{35}O_7$ 423.2382, found 423.2376. IR ν_{max} (thin film, $CHCl_3$) 3401, 2975, 1722, 1643, 1454, 1216, 1130. $[\alpha]_D^{20}$ −25 (*c* 0.15, $CHCl_3$).

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