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Regioselective Beckmann rearrangements of furanoside and pyranoside-derived oximes

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ABSTRACT

The Beckmann rearrangement is a useful reaction employed to provide access to amides from oxime substrates. Applied to cyclic structures, the Beckmann rearrangement leads to ring expansion and allows access to cyclic lactams. Our investigations focused upon the synthesis of glycoside-derived lactams from oxime precursors. In probing a range of conditions, we observed that 2,4,6-trichloro[1,3,5]triazine (TCT) was an effective and mild promoter of the rearrangement affording pyrano- and heptanoside lactam products with excellent regioselectivities.

1. Introduction

The Beckmann rearrangement, first discovered in 1886, involves the conversion of an oxime to an amide.[1] Since it results in the cleavage of a carbon–carbon bond and the formation of a carbon–nitrogen bond, the Beckmann rearrangement is a powerful method in the synthesis of lactams, which have evident therapeutic importance. Thus, lactam derivatives have been reported to be micromolar inhibitors of α- and β-glycosidase enzymes[2–4] and have also been used to synthesise peptide mimics[5,6] and ribofuranose systems.[7] The synthesis of some key pharmaceuticals involves a Beckmann rearrangement as an important step. For example an efficient method towards the synthesis of benzazepines, as reported by Cordero-Vargas et al.,[8] employed a Beckmann rearrangement in order to obtain an intermediate precursor to tolvaptan. Whilst Brønsted or Lewis acids are the archetypal catalysts in the Beckmann rearrangement,[9–19] these reagents can often lead to degradation of the starting materials, particularly under forcing reaction conditions. Cyanuric chloride (TCT, 2,4,6-trichloro[1,3,5]triazine)[20] has been reported to be a milder activator that also offers the advantage that it can be used on a large scale, without functionalisation of the oxime hydroxyl group.[21] Throughout the literature, in examples where Beckmann rearrangements occur, it is stated that the migrating group is that which is *trans* to the oxime hydroxyl group. Identification of which isomer of the oxime is the more stable, and hence present for the rearrangement, is the key for predicting the structure of the amide product.

With the growing interest in the potential use of functionalised medium-large sized rings as glycosidase inhibitors and monosaccharide mimics,[22] this programme has focused on investigating the feasibility of the Beckmann rearrangement of carbohydrate-derived oximes for furnishing functionalised lactam derivatives. Beckmann rearrangements on carbohydrate derivatives have previously been reported, for example by Dongare et al.,[23] using furanose derivatives, en-route to precursors to azythromycin and hydroxycyclic lactams. In addition, rearrangements of carbohydrate hydrazones have been reported by Tronchet et al.[24] allowing access to seven-membered aminolactams. Herein we have examined the Beckmann rearrangement of a wider range of furanoside and pyranoside substrates to more fully explore the potential of this approach for access to functionalised lactams.

2. Results and discussion

In order to probe the feasibility of using oximes derived from pyranosides and furanosides within the Beckmann rearrangement, ketones **1a**,[25] **2a**,[26] **3a**,[27] **4a**[28] and **5a**[29] were prepared according to the literature procedures as precursors to the oximes (Fig. 1). Ketones were specifically selected for study to probe the feasibility of using both pyranoside and furanoside derived oximes, as well as to allow the oxime functionality to be incorporated at differing positions within the glycopyranoside, in order to ultimately access different isomeric lactams. In addition, a range of protecting groups was incorporated within the substrates to probe the compatibility of the reagents required to effect the Beckmann rearrangement with the substrates themselves.

Due to the instability of the ketones **1a**, **2a**, **3a**, **4a** and **5a** to column chromatography, they were converted directly to their respective oximes **1b**, **2b**, **3b**, **4b** and **5b** (Fig. 2) by reaction with hydroxylamine hydrochloride and sodium acetate, and were purified by column chromatography prior to attempting the Beckmann

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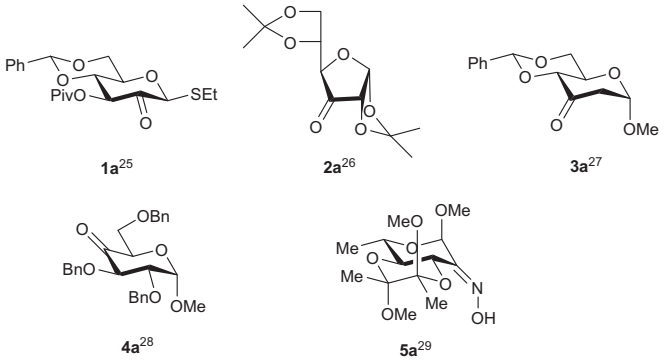
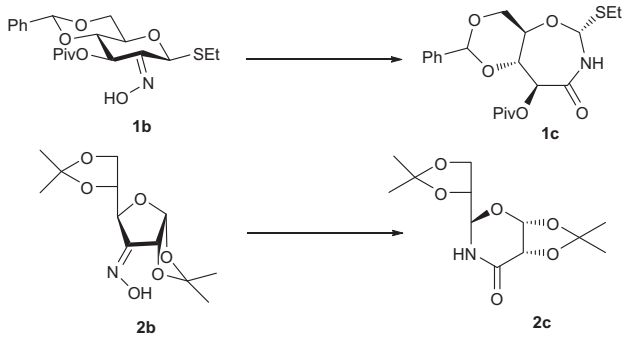


Figure 1.



Scheme 1. For reagents and conditions see Table 2.

rearrangement. Oximes were isolated in excellent synthetic yields as single isomers, whose configurations are as shown in Figure 2. Whilst the configurations of the oxime bonds for **1b**, **2b**, **3b**, **4b** and **5b** could not be deduced by NMR spectroscopic analysis at this stage of the programme, they could be deduced after the Beckmann rearrangements were subsequently performed, by considering the regioselectivity of the rearrangements (vide infra).

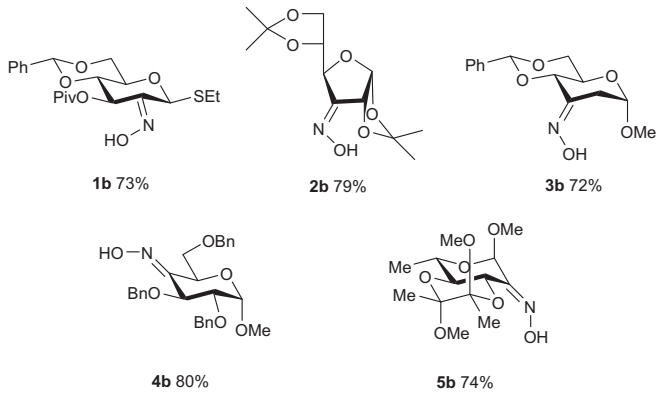


Figure 2.

A range of activators are available for the Beckmann rearrangement,[9–20] and, therefore, a range of activators and conditions were initially screened to probe their effectiveness for promoting rearrangement of one furanoside oxime **2b** and one pyranoside oxime **1b**. Optimum conditions from this initial screen were then applied to the wider range of oximes. The conditions used to optimise the Beckmann rearrangement are summarised within Table 1.

From the screening conditions the only activator that proved effective was TCT. This was, therefore, utilised to effect the Beckmann rearrangement of the wider range of oximes, as exemplified in Table 2. Where a rearrangement was successfully accomplished, the equivalents of TCT used, and reaction conditions employed, were altered in an attempt to optimise the yields further. The results portrayed in Table 2 represent the optimum results obtained.

For substrates **1b** and **2b**, the Beckmann rearrangement occurred with migration of the bond *trans*-to the oxime OH (i.e. the C-1,2 bond for **1b** and the C-3,4 bond for **2b**) to afford the lactam products **1c** and **2c** as single regioisomers in synthetically useful yields (Scheme 1). A thioethyl group was tolerated at C-1, to afford **1c** which is of potential use as a donor in subsequent glycosidation reactions. For oxime **2b**, the excellent regiocontrol was in contrast to that previously reported using a molybdenum catalyst, where the rearrangement resulted in a mixture of regioisomers, and the regioisomer **2c** was formed as the minor component.[23]

For substrates **3b**, **4b** and **5b** the rearrangements again proceeded to form in each case a single regioisomer of product, but in these cases elimination also occurred from the intermediate lactams introducing unsaturation within the products **3c**, **4c** and **5c**. Given the high degree of functionality, and the incorporation of stereogenic centres, within these products, the success of these rearrangements was particularly encouraging. Moreover, although the yield of formation of **3c** and **4c** was moderate, that for **5c** was excellent.

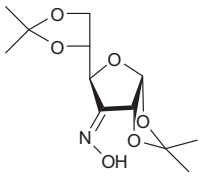
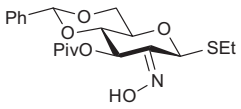
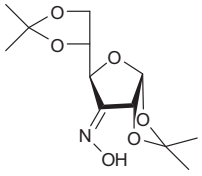
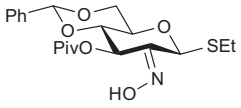
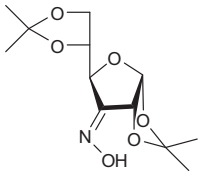
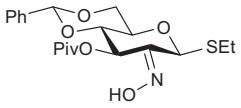
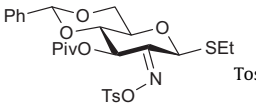
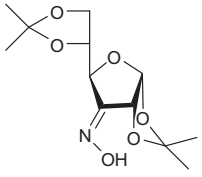
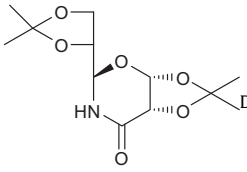
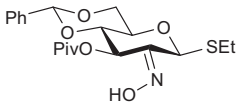
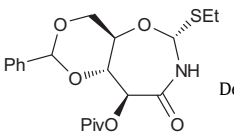
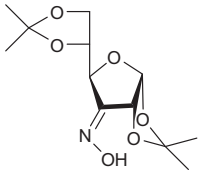
To account for the regioselectivities observed, migration was presumed to occur from the C-3,4 bond for oxime **3b**, the C-4,5 bond for oxime **4b** and the C-1,2 bond for oxime **5b**. Whilst the structures of **3c** and **5c** were unequivocally deduced from analysis of a range of spectroscopic data, the structure of **4c** was tentatively assigned as that shown in Scheme 2 via analysis of ^{1}H and ^{13}C NMR and IR spectroscopy; the material proved insufficiently stable for a complete set of spectroscopic data to be collected. Thus the ^{1}H NMR spectrum obtained for **4c** illustrated that the singlet peak resulting from the methoxy group in oxime **4b**, which was present at 3.44 ppm, was no longer present. Moreover, peaks were now present at 8.55 and 8.90 ppm and these could be accounted for by the formation of the imine and aldehyde functional groups, respectively, as proposed by structure **4c**. The corresponding carbons for these functional groups were present at 162.3 and 151 ppm, respectively. Finally, IR spectroscopic data showed stretches at 1774 and 1715 cm^{-1}, which could be accounted for by the α,β-unsaturated system and the aldehyde functional group, respectively.

The results summarised in Table 1 and Schemes 1 and 2 illustrate that oximes derived from a range of protected carbohydrate monomers have potential for access to functionalised six and seven-membered ring lactams. The oxime functionality has been incorporated at various positions within the carbohydrate framework, with good effect, and a range of protecting groups and anomeric groups have been tolerated within the reaction. In this way, access to a range of funtionalised lactams has been achieved in moderate to very good yield and the further manipulation of these to afford targets of interest for the inhibition of glycosidase enzymes is currently under investigation within our laboratories.

3. Conclusion

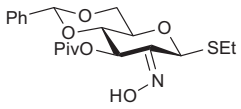
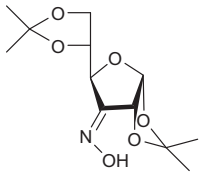
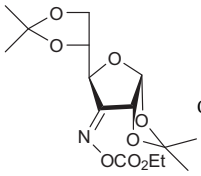
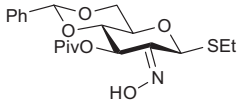
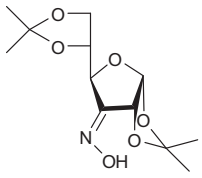
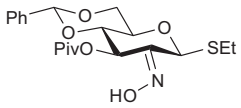
Oximes derived from pyranosides and furanosides have been prepared in excellent yields. The Beckmann rearrangement of these has then occurred with migration of the C–C bond *trans* to the oxime OH to afford lactams with excellent regioselectivities. The method has been effective for the rearrangement of oximes displaying a range of protecting groups and anomeric groups, and excellent compatibility of the protecting groups with the activator, TCT, has been observed. Whilst the yields are generally moderate, in some cases excellent conversion yields have been obtained, highlighting the synthetic value of this reaction.

Table 1

Substrate	Activation protocol	Result
 **2b**	*p*-TsOH or PPA, MeCN or DMF, rt to reflux	Decomposition
 **1b**	*p*-TsOH or PPA, MeCN or DMF, rt to reflux	Decomposition
 **2b**	P_2O_5 (1 or 2 equiv)/CF_3SO_3H (1 or 2 equiv), DMF, reflux	Decomposition
 **1b**	P_2O_5 (1 or 2 equiv)/CF_3SO_3H (1 or 2 equiv), DMF, reflux	Decomposition
 **2b**	*p*-TsCl, DMAP, pyr., rt then heat to 50 °C	Starting material returned in quantitative yield
 **1b**	*p*-TsCl, DMAP, pyr., rt then heat to 50 °C	 **6** Tosylated oxime **6** 82% plus oxime **1b**
 **2b**	TCT (1.2 equiv), DMF, rt o/n	 **2c** Desired product formed, 62%
 **1b**	TCT (1.2 equiv), DMF, rt o/n	 **1c** Desired product formed, 42%
 **2b**	NCS/PPh_3, DCM rt to reflux	Starting material returned in quantitative yield

(*continued on next page*)

Table 1 (*continued*)

Substrate	Activation protocol	Result
 **1b**	NCS/PPh_3, DCM rt to reflux	Starting material returned in quantitative yield
 **2b**	$ClCO_2Et$, pyr., DCM, 2.5 h then $BF_3{\cdot}OEt_2$, DCM, rt, 20 h	 **7** Oxime carbonate **7** formed in 54% yield but no rearrangement occurred
 **1b**	$ClCO_2Et$, pyr., DCM, 2.5 h then $BF_3{\cdot}OEt_2$, DCM, rt, 69 h	Decomposition
 **2b**	Microwave irradiation with or without $BiCl_3$ at temperatures ranging from 30 to 120 °C for up to 10 min	Starting material returned
 **1b**	Microwave irradiation with or without $BiCl_3$ at temperatures ranging from 30 to 120 °C for up to 10 min	Starting material returned

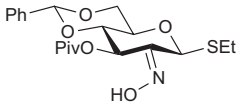
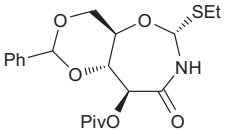
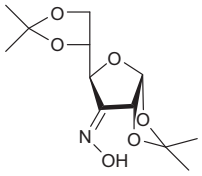
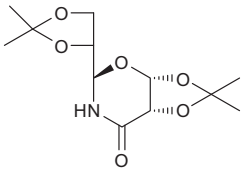
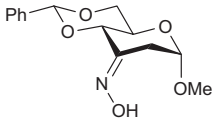
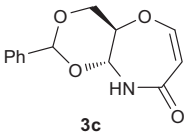
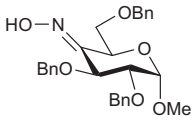
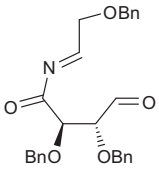
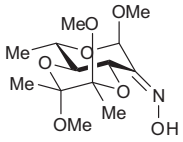
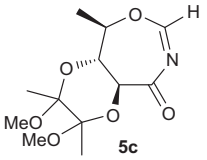
4. Experimental

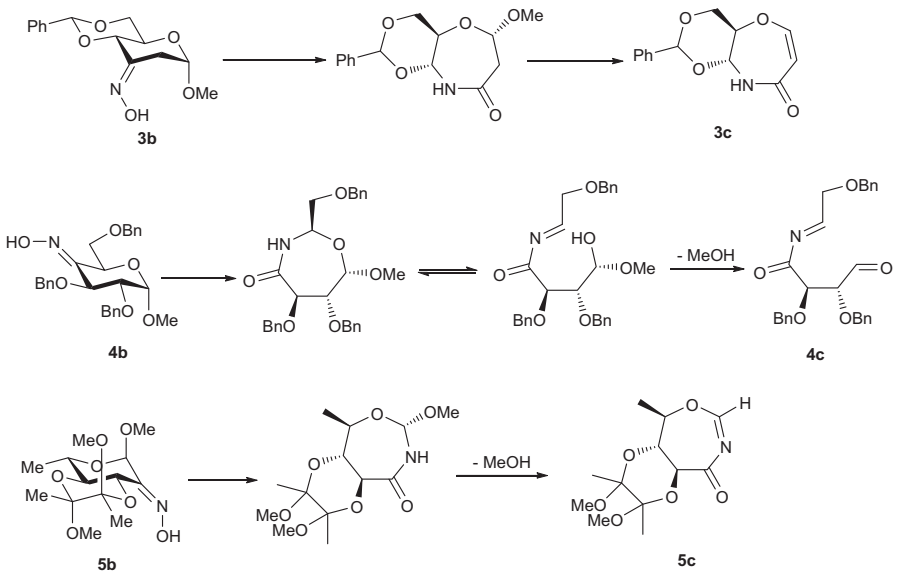
^{1}H NMR spectra were recorded in either chloroform-*d* or MeOH-*d* at 250 MHz on a Bruker DPX-250 FT-NMR spectrometer or at 400 MHz on a Bruker AMX-400 FT-NMR spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) using the following abbreviations: s (singlet); d (doublet); t (triplet); q (quartet); sxt (sextet); app. t (apparent triplet); m (multiplet); bs (broad singlet); bm (broad multiplet). Coupling constants (*J* values) are expressed in Hertz to the nearest 0.5 Hz. ^{13}C NMR spectra were recorded on the same spectrometers described above at 63 MHz or 100 MHz in chloroform-*d* or MeOH-*d*. Chemical shifts are reported in parts per million (ppm). Infrared spectra were recorded as thin films between sodium chloride plates on a Perkin–Elmer Paragon 1000 FT-IR spectrometer. The absorptions are stated in wavenumbers (cm^{-1}) and the abbreviations used to depict the degree of absorption are: w (weak); m (medium); s (strong); br (broad). Melting points were determined using an electrothermal digital heated metal block apparatus and are uncorrected. Mass spectrometry data were recorded using a Fisons VG Autospec mass spectrometer using chemical ionisation (C.I.). Molecular ions and fragment ions are reported as mass/charge (*m*/*z*) ratios. Optical rotation measurements were recorded using a Perkin–Elmer 341 polarimeter at the sodium D line (589 nm) in $CHCl_3$ or MeOH and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Thin layer chromatography (TLC) was performed on Merck aluminium backed plates coated with 0.2 mm Silica Gel 60 F_{254}. The spots were visualised using UV light (254 nm) or by spray-head development using an ethanol–sulfuric acid reagent (25:1 $EtOH/H_2SO_4$). Flash chromatography was carried out using Merck silica gel 60 (40–63 μm particle size) using head pressure by means of bellows. Beckmann rearrangement investigations under microwave conditions were performed using a CEM Discover 100 W microwave reactor. Anhydrous conditions for reactions were achieved using oven-dried glassware prior to use, anhydrous solvents and using an atmosphere of nitrogen or argon. Anhydrous solvents (acetonitrile, dichloromethane, diethyl ether, *N*,*N*-dimethylformamide, dimethyl sulfoxide, methanol and pyridine) were bought from Aldrich as sure-sealed bottles. Anhydrous THF was obtained by distillation over Na metal. All chemicals were obtained from Sigma–Aldrich, Acros, Fluka or Lancaster chemical suppliers.

4.1. Ethyl 2-deoxy-2-hydroxylimine-3-*O*-pivaloyl-4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside 1b[25]

Ketone **1a**[25] (2.77 g, 7.01 mmol) was solubilised in ethanol (10 mL). This was added to a solution of sodium acetate (1.73 g, 21.0 mmol) and hydroxylamine hydrochloride (1.46 g, 21.1 mmol) in water (10 mL) at 54 °C. The reaction mixture was stirred at approximately this temperature for a total of 2 h and then the reaction mixture was left to stir at room temperature overnight. The reaction mixture was washed with distilled water (30 mL) and extracted with DCM (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was then purified by column chromatography (5.5:1 hexane/ethyl acetate, with 1% NEt_3) to give pure **1b** as a white

Table 2

Oxime Substrate	Product	Activator	Conversion yield (%)
 **1b**	 **1c**	TCT (1.2 equiv), DMF, rt o/n	45
 **2b**	 **2c**	TCT (1.2 equiv), DMF, rt o/n	62
 **3b**	 **3c**	TCT (1.2 equiv), DMF, rt o/n	42
 **4b**	 **4c**	TCT (8.4 equiv), DMF, rt o/n	39
 **5b**	 **5c**	TCT (2.04 equiv), DMF, 50 °C, 2 h	78



Scheme 2. For reagents and conditions see Table 2.

foam (2.17 g, 73%). $[\alpha]_D^{20} = +88.4$ (*c* 1.0, $CHCl_3$) {lit.[25] $[\alpha]_D^{20} = +137.6$ (*c* 0.5, $CHCl_3$)}; IR (thin film): $\nu(cm^{-1})$: 3367 br (O–H), 3068 w, 2974 s (C–H), 2931 w, 2873 w, 2252 m, 1739 s (C=O), 1480 s, 1457 s, 1398 s, 1370 s, 1313 m (C–H), 1278 s, 1216 m, 1136 s, 1097 s (C–O), 1004 m (C=N), 913 s, 867 m, 799 w, 733 s, 698 s (Ar), 649 s (C–S); ^{1}H NMR ($CDCl_3$): δ 1.16 (9H, s, $(CH_3)_3CO$), 1.26 (3H, t, *J* 7.5, SCH_2CH_3), 2.60–2.77 (2H, m, SCH_2CH_3), 3.53–3.74 (2H, m, H-6, H-4), 4.27–4.34 (1H, m, H-6), 4.42–4.49 (1H, m,

H-5), 5.50 (1H, s, PhC*H*), 5.75 (1H, d, *J* 6.5, H-3), 6.24 (1H, s, H-1), 7.27–7.39 (5H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 15.09 (SCH_2CH_3), 21.48 (SCH_2CH_3), 26.84 ((CH_3)$_3$CCO), 39.23 (CH_3)$_3$CCO), 60.86 (C-5), 65.31 (C-6), 66.67 (C-3), 66.86, 69.89, 69.97, 70.55, 74.37 (C-1), 80.42 (C-4), 101.38 (PhCH), 126.40 (2 × Ar-C), 128.68 (2 × Ar-C), 129.39 (Ar-C), 137.41 (Ar-C), 151.24 (C-2), 152.35, 176.83 ((CH_3)$_3$CCO); *m*/*z* (CI): 409 ([M]$^+$, 8%), 38 (100), 307 (25), 242 (18), 149 (12). Found [M]$^+$, 409.1543 $C_{20}H_{27}O_6NS$ requires [M]$^+$, 409.1559.

4.2. (2*S*, 5*S*, 6*S*, 7*R*) 2-Thioethyl-5-*O*-pivaloyl-6,8-*O*-benzylidene-[1,3]oxazepan-4-one 1c

2,4,6-Trichloro[1,3,5]triazine (45.9 mg, 0.249 mmol) was solubilised in anhydrous DMF (0.5 mL) and the mixture was stirred for 30 min. Then ethyl 2-deoxy-2-hydroxylimine-3-*O*-pivaloyl-4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside **1b** (0.100 g, 0.244 mmol) in anhydrous DMF (1.5 mL) was added and the reaction stirred at rt under N_2 for 16 h. The solvent was removed azeotropically in vacuo using toluene. To the residue was added DCM (30 mL), H_2O (10 mL) and satd $NaHCO_3$ (15 mL). The two phases were separated and the aqueous phase re-extracted with DCM (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (100:4 v/v DCM/MeOH) to give pure oxazepan-4-one **1c** as a colourless oil (44.5 mg, 45%). $[\alpha]_D^{20} = +55.4$ (*c* 0.55, $CHCl_3$); IR (thin film): ν(cm^{-1}): 3348 br (N–H), 2974 m (C–H), 1740 s (C=O), 1648 m (C=O), 1594 m, 1480 m, 1456 m, 1370 m, 1282 m, 1178 m, 1154 m, 1098 s, 1077 m, 979 m, 752 m, 698 m; ^{1}H NMR ($CDCl_3$): δ 1.29 (9H, s, (CH_3)$_3$CO), 1.30–1.38 (3H, m, SCH_2CH_3), 2.71–2.78 (2H, m, SCH_2CH_3), 3.81 (1H, t, *J* 10.0, H-8), 3.97 (1H, app. t, *J* 10.0, H-6), 4.28–4.41 (2H, m, H-8, H-7), 5.58 (1H, s, PhC*H*), 5.86 (1H, d, *J* 9.5, H-5), 6.50 (1H, s, H-2), 7.33–7.39 (3H, m, Ar-H), 7.43 (2H, m, Ar-H), 8.50 (1H, s, NH); ^{13}C NMR ($CDCl_3$): δ 15.55 (SCH_2CH_3), 26.47 (SCH_2CH_3), 27.49 ((CH_3)$_3$CCO), 39.26 (CH_3)$_3$CCO), 64.35 (C-7), 68.96 (C-8), 69.06 (C-5), 76.20 (C-2), 79.84 (C-6), 101.58 (PhCH), 126.35 (Ar-C), 126.42 (Ar-C), 128.62 (2 × Ar-C), 129.43 (Ar-C), 137.34 (Ar-C), 163.93 (C-4), 177.52 ((CH_3)$_3$CCO); *m*/*z* (CI): 410 ([M+H]$^+$, 18%), 348 (100), 307 (44), 242 (41). Found [M+H]$^+$, 410.1625. $C_{20}H_{28}O_6NS$ requires [M+H]$^+$, 410.1637.

4.3. 1,2:5,6-Di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose oxime 2b[30]

Hydroxylamine·HCl (0.781 g, 11.2 mmol) and NaOH (0.420 g, 10.5 mmol) were dissolved in EtOH (25 mL) and the resulting NaCl filtered off. To this prepared solution was added ketone **2a** (0.4473 g, 1.73 mmol) and the reaction was stirred under N_2 at room temperature for 70 h. The reaction was then concentrated in vacuo. To the resulting white solid was added H_2O (6 mL) and DCM (30 mL). The two phases were separated and the aqueous phase re-extracted with DCM (5 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (3:2 v/v hexane/EtOAc) to yield pure oxime **2b** as a white solid (0.3760 g, 79%). Mp 97.2–101.0; (lit.[31] 103–104 °C); $[\alpha]_D^{20} = +173.3$ (*c* 0.9, $CHCl_3$) {lit.[31] $[\alpha]_D^{21} = +183$ (*c* 0.6, $CHCl_3$)}; IR (thin film): ν(cm^{-1}): 3370 br (OH), 2988 s (C–H), 2938 m (C–H), 1457 m (C–N), 1374 s (CH_3), 1215 s, 1158 s, 1071 s (C–O), 1023 s, 951 s, 877 s, 732 w; ^{1}H NMR ($CDCl_3$): δ 1.37 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.99–4.07 (2H, m, 2 × H-6), 4.29–4.36 (1H, m, H-5), 4.77 (1H, d, *J* 3.0, H-4), 5.29 (1H, d, *J* 4.5, H-2), 6.02 (1H, d, *J* 4.5, H-1); ^{13}C NMR ($CDCl_3$): δ 25.58 (*C*H$_3$), 26.40 (*C*H$_3$), 27.70 (*C*H$_3$), 27.92 (*C*H$_3$), 65.80 (C-6), 74.57 (C-2), 77.08 (C-5), 77.69 (C-4), 105.10 (C-1), 110.68 (*C*(CH_3)$_2$), 114.16 (*C*(CH_3)$_2$), 157.98 (C-3); *m*/*z* (CI): 274 ([M+H]$^+$, 100%), 258 (59), 216 (56), 140 (14), 101 (76). Found [M+H]$^+$, 274.1291. $C_{12}H_{20}NO_6$ requires [M+H]$^+$, 274.1291.

4.4. (2*R*, 5*S*, 6*S*, 7*R*) 5,6:7,8-Di-*O*-isopropylidene-[1,3]oxazinan-4-one 2c

2,4,6-Trichloro[1,3,5]triazine (0.224 g, 1.21 mmol) was solubilised in anhydrous DMF (0.8 mL). The complete disappearance of triazine was followed by TLC. Then a solution of 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose **2b** (0.318 g, 1.16 mmol) in anhydrous DMF (8 mL) was added and the reaction stirred under N_2 at rt for 44 h. The DMF was removed azeotropically using toluene and to the resulting residue were added H_2O (30 mL) and DCM (30 mL). The two phases were separated and the organic phase was washed successively with satd $NaHCO_3$ (20 mL), 1% HCl (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (2:1 v/v hexane/EtOAc) to yield pure **2c** as a yellow oil (0.197 g, 62%). $[\alpha]_D^{20} = +1.2$ (*c* 0.53, $CHCl_3$); IR (thin film): ν(cm^{-1}): 3384 br (N–H), 2940 m (C–H), 2506 m, 1736 w, 1654 w (C=O), 1457 w, 1377 w, 1255 w, 1164 w, 1074 s, 1035 s, 886 w; ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.53 (3H, s, CH_3), 4.01–4.14 (2H, m, 2 × H-8), 4.17–4.28 (1H, m, H-7), 4.54 (1H, d, *J* 3.5, H-5), 5.36 (1H, d, *J* 2.5, H-2), 5.90 (1H, d, *J* 3.5, H-6), 8.11 (1H, s, N*H*); ^{13}C NMR ($CDCl_3$): δ 25.56 (*C*H$_3$), 26.58 (*C*H$_3$), 27.08 (*C*H$_3$), 27.30 (*C*H$_3$), 67.73 (C-8), 72.62 (C-7), 76.20 (C-2), 83.56 (C-5), 105.44 (C-6), 109.90 (*C*(CH_3)$_2$), 112.84 (*C*(CH_3)$_2$), 159.96 (C-3).

4.5. Methyl 4,6-*O*-benzylidene-2-deoxy-α-D-erythro-hexopyranoside-3-ulose oxime 3b[32]

A solution of hydroxylamine·HCl (52.1 mg, 0.764 mmol) and NaOAc (56.3 mg, 0.686 mmol) in distilled H_2O (0.5 mL) was heated to 54 °C. To this was added methyl 4,6-*O*-benzylidene-2-deoxy-α-D-erythro-hexopyranosid-3-ulose **3a** (60.1 mg, 0.227 mmol) in ethanol (4.5 mL) and the reaction heated at 54 °C for 7.5 h. The ethanol was removed in vacuo and to the residue was added DCM (20 mL) and H_2O (20 mL). The two phases were separated and the aqueous phase was re-extracted with DCM (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (7:1 v/v DCM/EtOAc + 1% NEt_3) to yield pure oxime **3b** as a white solid (45.9 mg, 72%). Mp 208.6–209.7 (lit.[33] 208 °C); $[\alpha]_D^{20} = +86.8$ (*c* 0.5, $CHCl_3$) (lit.[33] $[\alpha]_D^{23} = +202$ (*c* 1.0, $CHCl_3$)); IR (thin film): ν(cm^{-1}): 3243 m (O–H), 2906 m (C–H), 2361 m, 2343 m, 1452 w, 1403 w, 1379 w, 1278 w, 1210 m, 1128 s, 1094 s, 1054 s, 988 s, 915 m, 852 w, 748 m, 697 m, 643 m; ^{1}H NMR ($CDCl_3$): δ 2.25 (1H, dd, *J* 4.5, 15.0, H-2, eq.), 3.37 (3H, s, OCH_3), 3.57 (1H, d, *J* 15.0, H-2, ax.), 3.84 (1H, t, *J* 10.0, H-6), 3.99–4.13 (1H, m, H-5), 4.23 (1H, d, *J* 9.5, H-4), 4.31 (1H, dd, *J* 4.5, 10.0, H-6), 4.92 (1H, d, *J* 4.5, H-1), 5.62 (1H, s, PhC*H*), 7.32–7.38 (3H, m, Ar-H), 7.40–7.52 (2H, m, Ar-H), 8.77 (1H, br s, NO*H*); ^{13}C NMR ($CDCl_3$): δ 30.64 (C-2), 55.30 (O*C*H$_3$), 65.17 (C-5), 69.85 (C-6), 78.42 (C-4), 98.95 (C-1), 102.62 (PhCH), 126.78 (2 × Ar-C), 128.67 (2 × Ar-C), 129.51 (Ar-C), 137.31 (Ar-C), 149.59 (C-3); *m*/*z* (CI): 280 ([M+H]$^+$, 11%), 247 (24), 181 (12), 149 (100). Found [M+H]$^+$, 280.1174. $C_{14}H_{18}NO_5$ requires [M+H]$^+$, 280.1185.

4.6. (2*R*, 3*R*) 3,8-*O*-Benzylidene-[1,4]oxazepin-4-one 3c

2,4,6-Trichloro[1,3,5]triazine (31.0 mg, 0.168 mmol) was added to anhydrous DMF (0.5 mL). After the formation of a white solid, the reaction was monitored by TLC until complete disappearance of the triazine starting material. Then a solution of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-erythro-hexopyranoside-3-ulose oxime

3b (45.9 mg, 0.164 mmol) in anhydrous DMF (1 mL) was added and the reaction was stirred under N_2 at rt for 20 h. The DMF was azeotropically removed in vacuo using toluene. Next, DCM (20 mL) and H_2O (7 mL) were added to the residue and the two phases separated. The organic phase was washed successively with satd $NaHCO_3$ (7 mL), 1% HCl (7 mL) and then with brine (7 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (3:2 v/v hexane/EtOAc) to yield pure rearranged product **3c** as a white solid (16 mg, 42%). Mp 180.7–183.3; $[\alpha]_D^{20} = +49.9$ (*c* 0.3, $CHCl_3$); IR (thin film): $\nu(cm^{-1})$: 3170 s (N–H), 3055 m, 2891 s (C–H), 2252 w, 1645 m (C=O), 1603 s, 1469 m, 1452 m, 1407 m, 1379 m, 1262 s, 1229 s, 1137 s, 1096 s, 1059 m, 1030 m, 987 s, 923 m, 784 m, 751 s, 731 s, 714 s, 696 s, 642 s, 502 m; ^{1}H NMR ($CDCl_3$): δ 3.94 (1H, t, *J* 10.5, H-8), 4.13 (1H, sxt, *J* 4.8, H-2), 4.45 (1H, dd, *J* 4.8, 10.5, H-8), 4.55 (1H, d, *J* 11.0, H-3), 5.66 (1H, s, PhC*H*), 6.00 (1H, d, *J* 6.0, H-6), 6.71 (1H, d, *J* 6.0, H-7), 7.32–7.41 (3H, m, Ar-H), 7.48–7.54 (2H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 68.67 (C-8), 71.73 (C-2), 74.60 (C-3), 94.72 (C-6), 102.25 (Ph*C*H), 126. 73 (2 × Ar-C), 128.70 (2 × Ar-C), 129.62 (Ar-C), 137.01 (Ar-C), 146.26 (C-5), 151.23 (C-7); *m*/*z* (CI): 247 ([M]$^+$, 100%), 181 (69), 131 (55). Found [M]$^+$, 247.0856. $C_{13}H_{13}O_4N$ requires [M]$^+$, 247.0845.

4.7. Methyl 2,3,6-tri-*O*-benzyl-α-D-*xylo*-pyranoside-4-ulose oxime 4b

At first, NaOAc (537 mg, 6.55 mmol) was solubilised in distilled water (20 mL) and hydroxylamine hydrochloride (457 mg, 6.57 mmol) was added. The contents were heated to 54 °C and **4a** (1.01 g, 2.18 mmol) in EtOH (20 mL) was added. The solution was stirred under argon for 2 h at 77 °C, then at room temperature overnight. The contents were then partitioned between water (40 mL) and CH_2Cl_2 (40 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (5:1 toluene/EtOAc) yielded **4b** as a colourless oil (834 mg, 80%).$[\alpha]_D^{20} = +59.7$ (*c* 1.04, $CHCl_3$); ν_{max} (NaCl disc/cm^{-1}) 3366 (br s, OH), 3030 (m, CH), 2916 (s, CH), 1497 (s, C=C (arom)), 1454 (s, C=C (arom)), 1200 (s, C=N), 1123 (s, C–O), 1071 (s, C–O), 737 (s, CH (arom)), 698 (s, CH (arom)); δ_H (400 MHz, $CDCl_3$): 3.44 (3H, s, OCH_3), 3.70 (1H, dd, *J* 10.5, 3.0, C(6)H), 3.80 (1H, dd, *J* 10.5, 8.0, C(6′)H), 3.87 (1H, t, *J* 3.5, C(2)H), 4.12 (1H, d, *J* 3.5, C(3)H), 4.31 (1H, d, *J* 12.0, OCH_2Ph), 4.54 (1H, d, *J* 11.5, OCH_2Ph), 4.59–4.64 (4H, m, OCH_2Ph), 4.87 (1H, d, *J* 4.0, C(1)H), 5.26 (1H, dd, *J* 8.0, 2.5, C(5)H), 7.21–7.34 (15H, m, Ph), 8.82 (1H, s, NO*H*); δ_C (101 MHz, $CDCl_3$): 56.5 (OCH_3), 67.1 (C5), 69.2 (C6), 70.1 (OCH_2Ph), 72.0 (OCH_2Ph), 73.1 (OCH_2Ph), 76.6 (C3), 78.8 (C2), 96.9 (C1), 127.5–128.3 (ArC), 137.4–138.0 (ArC), 152.9 (C=NOH); *m*/*z* (CI) 478 ([M+H]$^+$, 77%), 477 ([M]$^+$, 6%), 446 (100), 400 (36). Found [M]$^+$ 477.2172, $C_{28}H_{31}NO_6$ requires 477.2151.

4.8. (2′*S*,3′*S*)-Methyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-L-*lyxo*-hexopyranoside-2-ulose oxime 5b

At first, $NH_2OH{\cdot}HCl$ (400 mg, 5.75 mmol) was added to NaOH (92.2 mg, 2.30 mmol) in EtOH (10 mL). Distilled water (2 mL) was then added followed by **5a** (275 mg, 0.897 mmol). The reaction was stirred at room temperature for 20 h, then it was partitioned between water (30 mL) and CH_2Cl_2 (30 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 30 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo to yield crude **5b** as a colourless solid (215 mg, 74%) which was used without further purification. $[\alpha]_D^{20} = -212.9$ (*c* 1.03, $CHCl_3$); ν_{max} (NaCl disc/cm^{-1}) 3291 (br m, OH), 2944 (s, CH), 1450 (m, C=N), 1376 (s, CH_3), 1141 (s, C–O), 1111 (s, C–O), 1037 (s, C–O); δ_H (250 MHz, $CDCl_3$): 1.22 (3H, d, *J* 6.5, C(6)H), 1.24 (3H, s, CH_3), 1.29 (3H, s, CH_3), 3.17 (3H, s, OCH_3), 3.21 (3H, s, OCH_3), 3.36 (3H, s, OCH_3), 3.40 (1H, app. t, *J* 10.0, C(4)H), 3.87–3.98 (1H, m, C(5)H), 4.59 (1H, d, *J* 10.0, C(3)H), 5.72 (1H, s, C(1)H), 8.31 (1H, br. s, N=OH); δ_C (63 MHz, $CDCl_3$): 16.8 (CH_3), 18.0 (CH_3), 18.1 (CH_3), 48.1 (OCH_3), 48.8 (OCH_3), 55.4 (OCH_3), 66.6 (C5), 67.6 (C3), 74.1 (C4), 91.5 (C1), 100.1 (C), 100.4 (C), 150.9 (C2); *m*/*z* (ESI) 328 ([M+Na]$^+$, 100%). Found [M+Na]$^+$ 328.1361, $C_{13}H_{23}N_1Na_1O_7$ requires 328.1367.

4.9. (2′*S*,3′*S*,7*R*)-Methyl 2,3-*O*-(2′,3′-dimethoxybutane-2′,3′-diyl)-[1,3]-oxazepin-4-one 5c

At first, TCT (123 mg, 0.669 mmol) was stirred in anhydrous DMF (0.5 mL) for 2.5 h. A solution of **5b** (108 mg, 0.334 mmol) in anhydrous DMF (1.5 mL) was added and the reaction was heated to 45–50 °C for 2 h. The solution was stirred for 21 h at room temperature and then the contents were partitioned between CH_2Cl_2 (20 mL) and water (20 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash column chromatography on silica gel (2:1 Petroleum ether (40–60°)/Et_2O) allowed the isolation of **5c** as a colourless syrup (71.6 mg, 78%). $[\alpha]_D^{20} = -362$ (*c* 0.87, $CHCl_3$); ν_{max} (NaCl disc/cm^{-1}) 2950 (s, CH), 1731 (s, C=O), 1453 (s, C=N), 1379 (s, CH_3), 1177 (s, C–O), 1146 (s, C–N), 1036 (s, C–O); δ_H (250 MHz, $CDCl_3$): 1.21 (3H, s, CH_3), 1.26 (3H, s, CH_3), 1.34 (3H, d, *J* 6.5, OCH_3), 3.20 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.92 (1H, dd, *J* 10.0, 5.0, C(6)H), 4.44 (1H, d, *J* 10.0, C(5)H), 5.09 (1H, quin, *J* 5.0, C(7)H), 8.01 (1H, s, C(2)H); δ_C (63 MHz, $CDCl_3$): 16.5 (C8), 17.4 (CH_3), 17.7 (CH_3), 48.7 (OCH_3), 49.2 (OCH_3), 59.6 (C5), 69.4 (C7), 70.4 (C6), 99.6 (C), 99.8 (C), 116.3 (C4), 160.5 (C2); *m*/*z* (ESI) 296 ([M+Na]$^+$, 100%). Found [M+Na]$^+$ 296.1089, $C_{12}H_{19}N_1NaO_6$ requires 296.1105.

4.10. Ethyl 2-deoxy-2-hydroxylimine tosyl-3-*O*-pivaloyl-4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside 6

Ethyl 2-deoxy-2-hydroxylimine-3-*O*-pivaloyl-4,6-*O*-benzylidene-1-thio-α-D-glucopyranoside **1b** (97.0 mg, 0.237 mmol) was solubilised in anhydrous pyridine (0.8 mL). *p*-Toluenesulfonyl chloride (0.116 g, 0.608 mmol) and DMAP (1.8 mg, 0.015 mmol) were added and the reaction stirred under N_2 at rt for 20 h. The pyridine was azeotropically removed in vacuo using toluene. The crude product was purified by column chromatography (100:1 v/v DCM/EtOAc) to yield pure tosylated oxime **6** as a white foam (0.1096 g, 82%). $[\alpha]_D^{20} = +1.9$ (*c* 0.1, MeOH); IR (thin film): $\nu(cm^{-1})$: 2924 s (C–H), 2856 s (C–H), 1720 w (C=O), 1462 m, 1403 w, 1377 w, 1174 m, 1126 m, 1034 m, 1012 m, 684 m; ^{1}H NMR ($CDCl_3$): δ 1.20 (9H, s, (CH_3)$_3$CO), 1.33 (3H, t, *J* 7.5, SCH_2CH_3), 2.44 (1H, s, CH_3), 2.65–2.77 (2H, m, SCH_2CH_3), 3.82–3.93 (2H, m, H-6, H-4), 4.27–4.35 (2H, m, H-6, H-5), 5.55 (1H, s, PhC*H*), 5.72 (1H, d, *J* 9.5, H-3), 6.30 (1H, s, H-1), 7.30–7.44 (7H, m, Ar-H), 7.75–7.79 (2H, m, Ar-H); ^{13}C NMR ($CDCl_3$): δ 15.45 (SCH_2CH_3), 22.15 (CH_3), 26.66 (SCH_2CH_3), 27.40 ((CH_3)$_3$CCO), 39.14 (CH_3)$_3$CCO), 64.33 (C-5), 68.63 (C-3), 68.66 (C-6), 76.94 (C-1), 79.35 (C-4), 101.57 (PhCH), 126.28 (2 × Ar-C), 128.64 (2 × Ar-C), 129.22 (2 × Ar-C), 129.49 (Ar-C), 130.05 (2 × Ar-C), 132.32 (Ar-C), 137.06 (Ar-C), 145.90 (Ar-C), 158.57 (C-2), 176.81 ((CH_3)$_3$C*C*O).

4.11. 1,2:5,6-Di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-(*O*-ethyl methanoate)ulose 7

1,2:5,6-Di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose **2b** (0.688 g, 2.52 mmol) was solubilised in anhydrous DCM (10 mL). To this was added anhydrous pyridine (0.20 mL, 2.52 mmol) followed by the dropwise addition of ethyl chloroformate (0.24 mL,

2.52 mmol). The reaction was stirred at rt under N_2 for 3.5 h. TLC analysis showed the reaction to be complete. The reaction was diluted with DCM (30 mL) and H_2O (35 mL). The two phases were separated and the aqueous phase was re-extracted with DCM (3×35 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (3:2 v/v hexane/EtOAc) to yield pure oxime carbonate **7** as a white sticky solid (0.4718 g, 54%). $[\alpha]_D^{20} = +192.0$ (*c* 1.0, $CHCl_3$); IR (thin film): $\nu(cm^{-1})$: 2989 m (C–H), 1784 s (C=O), 1458 w, 1373 m, 1236 s, 1158 m, 1066 m, 1027 m, 927 w, 854 m, 776 w, 740 w; ^1H NMR ($CDCl_3$): δ 1.35 (3H, s, CH_2CH_3), 1.40 (3H, s, CH_3), 1.44 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.95–4.04 (2H, m, $2 \times$ H-6), 4.35 (2H, q, *J* 1.5, 7.0, CH_2CH_3), 4.39–4.47 (1H, m, H-5), 4.97 (1H, dd, *J* 1.5, 2.5, H-4), 5.23 (1H, dd, *J* 1.0, 4.5, H-2), 6.04 (1H, dd, *J* 2.5, 4.5, H-1); ^{13}C NMR ($CDCl_3$): δ 14.65 (CH_2CH_3), 25.67 (CH_3), 26.33 (CH_3), 27.78 (CH_3), 28.08 (CH_3), 64.74 (C-6), 65.72 (CH_2CH_3), 76.47 (C-2), 77.94 (C-5), 78.29 (C-4), 105.26 (C-1), 110.52 ($C(CH_3)_2$), 114.88 ($C(CH_3)_2$), 153.61 (C-3), 165.67 (C=O); *m*/*z* (CI) 346 ($[M+H]^+$, 20%), 331 (13), 330 (82), 256 (14), 198 (100), 126 (40). Found $[M+H]^+$, 346.1492. $C_{15}H_{23}NO_8$ requires $[M+H]^+$, 346.1502.

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