Stereocontrolled synthesis of polyhydroxylated hexahydro-1*H*-cyclopent[*c*]isoxazoles by intramolecular oxime olefin cycloadditions: an approach to aminocyclopentitols

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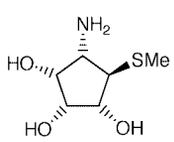
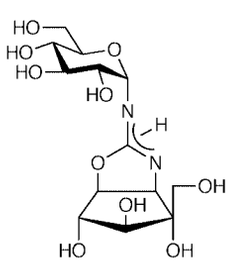
A series of alk-5-enyl aldehydes derived from various carbohydrates (D-glucose, D-mannose, D-galactose, D-glucal) can be transformed into the corresponding oximes. Thermolysis of these oximes results in the isolation of hexahydro-1*H*-cyclopent[*c*]isoxazoles in good yields *via* intramolecular oxime olefin cycloadditions. Modest to excellent levels of diastereocontrol are observed in these cycloaddition reactions depending on the precise nature of the oxime precursor. In the best case, D-glucose-derived oxime **4** produces hexahydro-1*H*-cyclopent[*c*]isoxazole **5** as the sole product in quantitative yield. When the oxime possesses a substituent (OBn or OBz) adjacent to the oxime carbon atom, it is observed that reactions show a preference to produce the diastereomeric cycloadduct in which this substituent is located in an *exo* orientation relative to the newly formed hexahydro-1*H*-cyclopent[*c*]isoxazole ring system. The role of the solvent polarity on the diastereochemical outcome of these reactions is briefly discussed. Unsuccessful efforts to extend this chemistry to oximes derived from alk-4-enyl aldehydes are also presented. Finally, it is demonstrated that the hexahydro-1*H*-cyclopent[*c*]isoxazoles can be transformed into stereochemically defined aminocyclopentitols.

Introduction

A number of biologically active natural products have been isolated and characterised which contain polyhydroxylated aminocyclopentane (aminocyclopentitol) motifs. Illustrative examples include the selective mannosidase inhibitor mannostatin A **1**,[1] and the very strong and specific trehalase inhibitor trehazolin **2**.[2] The biological activity of these and related structures has stimulated considerable interest in the synthesis of aminocyclopentitols, and while a number of elegant strategies have been devised,[3] new methods for the construction of aminocyclopentitols in a stereo- and enantiocontrolled fashion are still in demand.

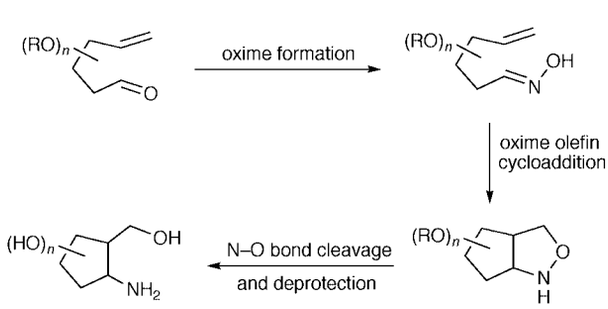


Mannostatin A **1**



Trehazolin **2**

We wished to examine whether intramolecular oxime olefin cycloaddition (IOOC) reactions could be used as the key step in an approach to stereochemically defined aminocyclopentitols bearing a hydroxymethyl substituent.[4] The first example of an IOOC reaction was reported by Oppolzer and Keller in 1970.[5] Additional examples of IOOC reactions have been reported by the groups of Wildman,[6] Grigg,[7] Heathcock[8] and Hassner,[9] among others.[10,11] Until very recently, no examples of these reactions had been reported in the field of carbohydrate chemistry.[4,11] Our general strategy to the target aminocyclopentitol system centres on conversion of a stereochemically defined, carbohydrate-derived alk-5-enyl aldehyde into the corresponding oxime, and subsequent thermally induced IOOC reaction to the hexahydro-1*H*-cyclopent[*c*]isoxazole skeleton (Scheme 1). In this key transformation, it is notable that two new stereogenic centres are created at the ring fusion. While previous studies on IOOC reactions indicated that good levels of stereocontrol can be accomplished in relatively simple systems, it was unclear at the outset of our studies whether good, predictable levels of stereocontrol could be accomplished in the more stereochemically complex scenarios depicted in Scheme 1. Further conversion of the resulting cycloadduct into the desired aminocyclopentitol was expected to be realised in a straightforward fashion by cleavage of the N–O bond and deprotection of the hydroxy groups (Scheme 1). In this paper, we present



Scheme 1

findings on the stereoselective IOOC reactions using a variety of carbohydrate-derived precursors, indicate what factors control the stereochemical outcome of these reactions, and demonstrate that the resultant cycloadducts can be transformed into aminocyclopentitols.

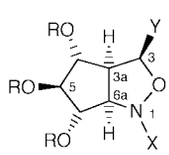
Results and discussion

Our investigations began using aldehyde **3**,[12] in which the three hydroxy groups along the backbone were protected as benzyl ethers. This compound was readily prepared from methyl

α-D-glucopyranoside in 5 steps using a Vasella fragmentation as the key step.[12a,13] Treatment of aldehyde **3** with hydroxylamine hydrochloride in warm ethanol in the presence of pyridine furnished oxime **4** as a 7:3 mixture of *E* and *Z* isomers as judged by ^{1}H NMR spectroscopy. Thermolysis of this oxime in toluene at 110 °C for 15 hours yielded **5** in quantitative yield as essentially a single stereoisomer. Identical results were obtained in this cycloaddition reaction using either geometrically pure *E*-**4** or a mixture of the *E*- and *Z*-isomer.

Next, we converted aldehyde **6**,[13,14] in which the three hydroxy groups along the backbone were protected as benzoyl esters, into oxime **7** and examined its IOOC reaction. In this instance, a 60% yield was observed for the conversion of this oxime into the diastereomerically pure 1*H*-cyclopent[*c*]-isoxazole **8** after column chromatography. ^{1}H NMR spectroscopic analysis of the crude reaction suggests that this reaction produces traces of another product (≤ 10%), possibly a diastereomeric cycloadduct, although our efforts to isolate and characterise this minor product were unsuccessful.

The gross chemical structures of 1*H*-cyclopent[*c*]isoxazoles **5** and **8** were determined using 1D- and 2D-NMR spectroscopy in conjunction with mass spectrometry. The relative stereochemical relationships within both these bicycles was elucidated using ^{1}H NMR vicinal coupling constants and selective NOE difference measurements. In the case of tribenzyl-substituted derivative **5**, significant NOE enhancements were observed between H-3a and H-6a (H-3a ⟶ H-6a {9.4%}; H-6a ⟶ H-3a {9.6%}) and between these ring-junction hydrogens and H-5 (H-3a ⟶ H-5 {2.2%}; H-6a ⟶ H-5 {2.8%}). Again, for tribenzoyl-substituted derivative **8**, NOE enhancements were observed between H-3a and H-6a (H-3a ⟶ H-6a {10.5%}; H-6a ⟶ H-3a {11.0%}) and between these ring-junction hydrogens and H-5 (H-3a ⟶ H-5 {3.8%}; H-5 ⟶ H-3a {2.3%}; H-6a ⟶ H-5 {4.6%}; H-5 ⟶ H-6a {2.8%}). Additional enhancements were measured for cycloadduct **8** between H-4 and H-6 (H-4 ⟶ H-6 {3.4%}; H-6 ⟶ H-4 {5.1%}). These experiments suggest that H-3a, H-5 and H-6a all reside on the *exo* face while H-4 and H-6 reside on the *endo* face of these bicycles. In addition, the vicinal coupling constants measured for **5** and **8** are in good agreement for those reported for **11** (Table 1) which was synthesised by Ferrier *et al.* and whose structure was unambiguously solved by X-ray crystallography.[15] Furthermore, the spectroscopic and physical data obtained for the 1*H*-cyclopent[*c*]isoxazole **5** is in close agreement with that reported by the group of Vasella (mp 108 °C {lit.,[12a] 104–106 °C}; $[\alpha]_D$ −3 (*c* 0.93, $CHCl_3$) {lit.,[12a] $[\alpha]_D$ −3.6 (*c* 0.9)†}, who synthesised it in a less direct fashion using an intramolecular nitrone olefin cycloaddition.

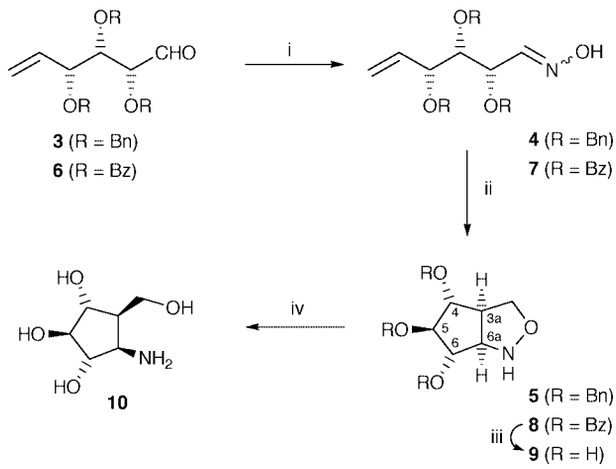


5 (R = Bn; X = H; Y = H)
8 (R = Bz; X = H; Y = H)
11 (R = Ac; X = Me; Y = SPh)

In the case of the 1*H*-cyclopent[*c*]isoxazole **8**, we have demonstrated that conversion to a stereochemically defined aminocyclopentitol can be accomplished in a straightforward fashion. Thus, cleavage of the benzoyl esters using methoxide yields triol **9**,[12a] which can be further converted into aminocyclopentitol **10** by cleavage of the N–O bond by catalytic hydrogenation (Scheme 2). No efforts have been made to effect such transformations using benzyl-protected 1*H*-cyclopent[*c*]-isoxazole **5**, as Vasella and co-workers have already successfully demonstrated that this material can be transformed into a variety of aminocyclopentitol and cyclopentene products.[12a]

Table 1 Vicinal coupling constants (in Hz) for 1*H*-cyclopent[*c*]isoxazoles **5**, **8** and **11**

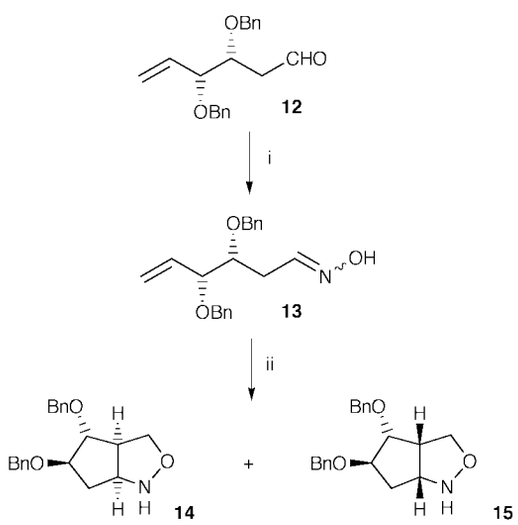
	5	**8**	**11**
$J_{3a,4}$	8.0	6.0	7.4
$J_{4,5}$	8.0	8.0	7.4
$J_{5,6}$	8.0	8.0	7.1
$J_{6,6a}$	6.5	6.0	3.8
$J_{6a,3a}$	10.0	9.5	9.1



3 (R = Bn)
6 (R = Bz)
4 (R = Bn)
7 (R = Bz)
10
5 (R = Bn)
8 (R = Bz)
9 (R = H)

Scheme 2 *Reagents, conditions and yields*: (i) $HONH_2$·HCl, pyridine, EtOH, 60 °C, 79% (for **3** ⟶ **4**); 85% (for **6** ⟶ **7**); (ii) toluene, 110 °C, 15 h, 100% (for **4** ⟶ **5**); 60% (for **7** ⟶ **8**); (iii) NaOMe, MeOH, rt, 60%; (iv) 10% Pd/C, H_2, MeOH, 91%.

To probe the remarkable diastereoselectivity observed in the conversion of oxime **4** into the 1*H*-cyclopent[*c*]isoxazole **5**, we decided to undertake a series of related oxime olefin cycloaddition reactions using substrates bearing different benzyl ether configurations along the backbone of the tethering chain. 2-Deoxy aldehyde **12**[13,16] was prepared from D-glucal again using the Vasella fragmentation protocol. Formation of the corresponding oxime **13** was straightforward and subsequent thermolysis produced the two inseparable diastereomeric adducts **14** and **15** in a 2:1 ratio (Scheme 3). Our inability to



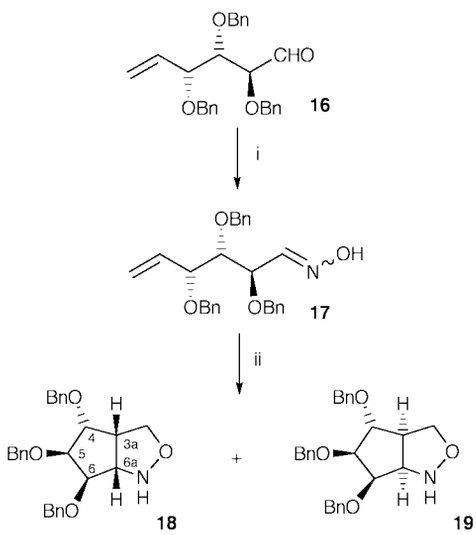
12
13
14
15

Scheme 3 *Reagents, conditions and yields*: (i) $HONH_2$·HCl, pyridine, EtOH, 60 °C, 93%; (ii) toluene, 110 °C, 36 h, 71%.

† $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}.

physically separate **14** and **15**, or to adequately resolve their ^{1}H NMR signals in a variety of deuterated solvents, meant that we have been unable to confidently assign which of these cycloadducts is produced as the major product. However, the most significant finding from this study is that the removal of the C-2 benzyl ether group from the oxime (**13** *cf.* **4**) has a very detrimental effect on the diastereoselectivity observed in the IOOC reaction. It is also of interest to note that the IOOC reaction of oxime **13** is significantly slower than that of oxime **4** (36 h *cf.* 15 h) although the origin of this rate difference is not entirely clear.

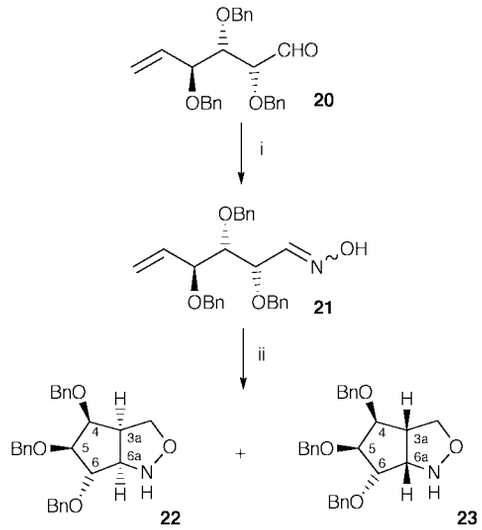
Further investigations into the role of the C-2 substituent on the stereoselectivity of the oxime cycloaddition have been undertaken using oxime **17**, which was prepared from D-mannose-derived aldehyde **16**,[16,17] using the same general approach (Scheme 4). Again, thermolysis yielded two diastereomeric cycloadducts **18** and **19** in a 4:1 ratio as judged by ^{1}H NMR analysis of the crude reaction mixture. Careful column chromatography allowed isolation of 1*H*-cyclopent[*c*]isoxazoles **18** and **19** in 64% and 12% yield, respectively.



Scheme 4 *Reagents, conditions and yields*: (i) $HONH_2$·HCl, pyridine, EtOH, 60 °C, 87%; (ii) toluene, 110 °C, 60 h, 64% (**18**), 12% (**19**).

The stereochemical outcome of this reaction was again resolved using NOE difference experiments. For major adduct **18**, large enhancements were observed between H-3a and H-6a (H-3a ⟶ H-6a {8.5%}; H-6a ⟶ H-3a {8.2%}); between H-3a and H-4 (H-3a ⟶ H-4 {11.4%}; H-4 ⟶ H-3a {8.7%}); and between H-5 and H-6 (H-5 ⟶ H-6 {8.2%}; H-6 ⟶ H-5 {8.4%}). Significantly smaller NOEs were observed between H-6 and H-6a (H-6 ⟶ H-6a {3.8%}; H-6a ⟶ H-6 {4.2%}).[18] From these NOE studies, we conclude that H-3a, H-4 and H-6a all reside on the *exo* face; while H-5 and H-6 reside on the *endo* face of bicycle **18**. In addition, a small vicinal coupling constant (1.5 Hz) is observed between H-6 and H-6a in this cycloadduct, suggesting that these two hydrogens are orientated at a dihedral angle close to 90°. This observation lends further support to this stereochemical assignment. Unfortunately, attempts to independently verify the stereochemistry of minor cycloadduct **19** by performing similar NOE experiments have not proven fruitful. In a variety of deuterated NMR solvents, too many of the signals remain coincident to allow meaningful NOE experiments to be performed.

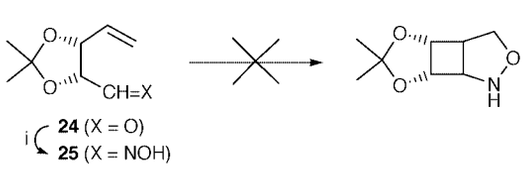
Using aldehyde **20**,[16,17] derived from D-galactose, we have investigated the role of the C-4 stereochemistry on the selectivity of these IOOC reactions. Conversion of this aldehyde into the corresponding oxime **21** proceeded in an uneventful fashion (Scheme 5). Subsequent thermolysis in refluxing toluene furnished 1*H*-cyclopent[*c*]isoxazoles **22** and **23** in 71% and 12% isolated yield after column chromatography.



Scheme 5 *Reagents, conditions and yields*: (i) $HONH_2$·HCl, pyridine, EtOH, 60 °C, 91%; (ii) toluene, 110 °C, 24 h, 71% (**22**), 12% (**23**).

NMR spectroscopy was used to elucidate the relative stereochemistry of the substituents within cycloadducts **22** and **23** although this was hampered by line broadening of the signals in their ^{1}H and ^{13}C NMR spectra. This problem was especially pronounced for the major adduct **22** for which the spectra had to be acquired at 80 °C ($Cl_2DCCDCl_2$). The most significant NOE enhancements were observed between H-3a and H-6a (H-3a ⟶ H-6a {10.3%}) and between H-3a and H-4 (H-3a ⟶ H-4 {9.4%}; H-4 ⟶ H-3a {8.4%}). For minor adduct **23**, large NOE enhancements were measured (60 °C in C_6D_6) between H-3a and H-6a (H-3a ⟶ H-6a {7.0%}; H-6a ⟶ H-3a {4.8%}); and between H-6a and H-6 (H-6a ⟶ H-6 {7.1%}; H-6 ⟶ H-6a {7.0%}). These comparative studies led us to conclude that both cycloadducts possess *cis*-fused bicyclic skeletons, and that major adduct **22** possesses H-4 *cis* to the ring junction hydrogens, whereas minor product **23** has H-6 *cis* to the ring junction hydrogens.

In an effort to produce functionalised cyclobutanes, we have attempted an IOOC reaction using a shorter linking tether between the oxime and the olefin reaction partners. Oxime **25** was produced from D-ribose-derived aldehyde **24**[19] in an identical fashion to that described earlier. In this case, the *E*- and *Z*-isomers of the oxime were readily separable. However, attempts to facilitate the IOOC reaction of (*E*)-**25** met with failure. Even in high boiling solvents (*o*-xylene or 1,2-dichlorobenzene) no reaction could be induced and the oxime was recovered unchanged (Scheme 6).

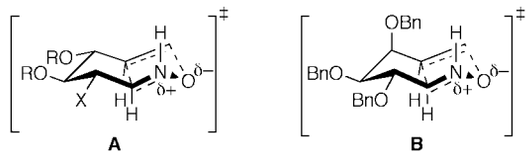


Scheme 6 *Reagents, conditions and yields*: (i) $HONH_2$·HCl, pyridine, EtOH, 60 °C, 82%.

From our experimental results, it would appear that the asymmetric centre adjacent to the oxime carbon atom on the linking tether exerts the greatest influence on the stereochemical outcome of these reactions. In major cycloadducts **5**, **8**, **18** and **22**, the oxygen substituent at C-6 (cycloadduct numbering system) is positioned in an *exo* orientation relative to the bicyclic ring junction. Further evidence in support of the importance of this substituent is provided by the observation that low

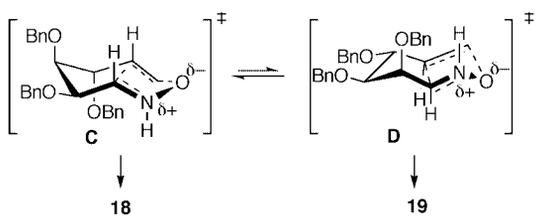
stereoselectivity is observed in the reaction of oxime **13** which only possesses a methylene group next to the oxime carbon atom. Interestingly, similar observations have been made by researchers studying the intramolecular nitrone olefin cycloaddition reactions of carbohydrate-derived substrates.[20]

To account for the stereochemical outcome of these reactions, we have analysed the most likely transition states leading to the observed products using scale models. For the conversion of D-glucose-derived oximes **4** and **7** into cycloadducts **5** and **8** respectively, we postulate that after initial 1,2-prototropic shift, these reactions proceed *via* transition state **A** in which the 1,3-dipole and olefin components adopt *exo* orientations and the oxygen substituents orientate themselves in pseudo-equatorial positions about the forming 5-membered ring (structure **A**, X = OR). For D-galactose-derived oxime **21**, a closely related transition state is proposed in which the C-4 substituent adopts a pseudo-axial orientation (transition state **B**).



Postulated transition states for IOOC cycloadditions involving D-glucose- and D-galactose-derived oximes.

To account for the stereochemical outcome in the D-mannose series, one must consider the relative merits of transition states **C** and **D**. We know from our experimental results that **18** is formed as the major product (*vide supra*). Hence, we suggest that transition state **C** must represent a lower-activation-energy pathway to product than transition state **D** (Scheme 7).



Scheme 7

Since, transition state **D** places fewer of the benzyl ether substituents in pseudo-axial orientations, we are drawn to the conclusion that polar effects are playing a key role in the stereochemical outcome of these IOOC reactions. Additional support for this hypothesis comes from our observations on the conversion of D-glucal-derived oxime **13** into cycloadducts **14** and **15**. If simple steric factors were controlling the outcome of this reaction, we might have expected to observe good levels of diastereocontrol in this transformation in favour of **14** by postulating the intermediacy of transition state **A** (X = H). Of course, this was not the case, and quite low levels of diastereoselectivity were observed (*vide supra*). Interestingly, we have observed that the diastereoselectivity observed in the conversion of oxime **21** into cycloadducts **22** and **23** is improved (**22**:**23** ≈ 10:1) by switching to a more polar solvent such as DMF (132 h, 110 °C). At the present time, the precise nature of the dipolar or stereoelectronic effects that are exerting a strong influence on the stereochemical outcome of these reactions remain unclear and work to unravel the subtleties of this reaction are ongoing.

In summary, we have demonstrated that intramolecular oxime olefin cycloaddition reactions of carbohydrate-derived precursors can be used to prepare polyhydroxylated hexahydro-1*H*-cyclopent[*c*]isoxazoles with good to excellent levels of stereocontrol which can be further transformed into aminocyclopentitols.

Experimental

General

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of nitrogen. Anhydrous solvents were prepared in accordance with standard protocols, or alternatively purchased from Aldrich in Sure/Seal™ bottles. IR spectra were recorded (4000–600 cm^{-1}) on a Nicolet Magna-550 FT-IR spectrometer with internal calibration. Spectra were recorded for samples as thin films or as KBr discs. NMR spectra were recorded on Bruker ACF-300 and DRX 400 spectrometers with either TMS or residual protic solvent as internal reference. NOE difference experiments were carried out using the Bruker microprogramme 'noemul' with presaturation to irradiate different frequencies within one multiplet. The preirradiation time was 4 s in total and average degree of saturation 80%. The numerical values of enhancements quoted were not corrected for incomplete saturation. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN elemental analyser. Mass spectra and accurate masses were recorded under EI^+ or CI^+ conditions on a VG Analytical ZAB-E instrument at the EPSRC Mass Spectrometry Centre, University College, Swansea or under EI^+ conditions on a Kratos Profile HV-3 mass spectrometer. Optical rotations were determined on the sodium D-line (589.3 nm) using an AA-1000 polarimeter. Light petroleum refers to the fraction with distillation range 40–60 °C.

General procedure for the synthesis of oximes

A stirred solution of requisite aldehyde, hydroxylamine hydrochloride (3 equiv.), pyridine (3 equiv.) and ethanol was heated at 60 °C for 45 min. On cooling, the ethanol was removed under reduced pressure and the residue taken up in diethyl ether and washed with water. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Purification of the oxime was accomplished by column chromatography.

2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*xylo*-hex-5-enose oxime 4

Treatment of aldehyde **3** (100 mg, 0.24 mmol) with hydroxylamine hydrochloride (50 mg, 0.72 mmol) and pyridine (58 µl, 0.72 mmol) in ethanol (0.5 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 4:1) provided oxime **4** (82 mg, 79%) as a colourless, oily, 7:3 mixture of *E* and *Z* isomers; ν_{max} (thin film)/cm^{-1} 3357 (OH), 3030, 2868, 1497, 1454, 1086, 1069, 1027, 934, 735, 697; δ_H (400 MHz; $CDCl_3$) 8.55 (0.3H, br s, OH_Z), 8.30 (0.7H, br s, OH_E), 7.46 (0.7H, d, $J_{1,2}$ 8.0, H-1_E), 7.37–7.27 (15H, m, ArH), 6.93 (0.3H, d, $J_{1,2}$ 6.0, H-1_Z), 5.82–5.77 (1H, m, H-5), 5.27–5.18 (2H, m, 2 × H-6), 4.87–4.54 (4.3H, m, 4 × CH_2Ph, H-2_Z), 4.45–4.32 (2H, m, 2 × CH_2Ph), 4.21 (0.3H, t, $J_{4,3} = J_{4,5}$ = 7.5, H-4_Z), 4.18–4.11 (1.4H, m, H-4_E, H-2_E), 3.79 (0.3H, dd, $J_{2,3}$ 3.0, $J_{4,3}$ 7.5, H-3_Z), 3.65 (0.7H, t, $J_{4,3} = J_{3,2}$ = 8.0, H-3_E); δ_C (100 MHz; $CDCl_3$) for major, *E*-isomer: 150.31 (C-1), 138.3 (C), 138.2 (C), 137.6 (C), 134.9 (C-5), 128.4 (CH), 128.34 (CH), 128.31 (CH), 128.2 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 119.2 (C-6), 82.7 (C-3), 81.1 (C-2), 76.6 (C-4), 75.0 (CH_2), 71.2 (CH_2), 70.9 (CH_2); *m*/*z* 431 (M^+), 414, 91 (Found: M^+, 431.2091. $C_{27}H_{29}NO_4$ requires *M*, 431.2096).

2,3,4-Tri-*O*-benzoyl-5,6-dideoxy-D-*xylo*-hex-5-enose oxime 7

Treatment of aldehyde **6** (532 mg, 1.16 mmol) with hydroxylamine hydrochloride (242 mg, 3.48 mmol) and pyridine (281 µl, 3.47 mmol) in ethanol (3 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 3:1) provided oxime **7** (470 mg, 85%) as a colourless, oily, 7:3 mixture of *E* and *Z* isomers; ν_{max} (thin

film)/cm^{-1} 3416 (OH), 3067, 1721 (C=O), 1603, 1449, 1260, 1101, 1065, 1019, 937, 707; δ_H (300 MHz; $CDCl_3$) 8.15–8.00 (7H, m, ArH, OH), 7.60–7.35 (9.7H, m, ArH, H-1$_E$), 6.79 (0.3H, d, $J_{1,2}$ 5.5, H-1$_Z$), 6.52 (0.3H, dd, $J_{1,2}$ 5.5, $J_{3,2}$ 4.0, H-2$_Z$), 6.13 (0.3H, dd, $J_{3,4}$ 7.0, $J_{3,2}$ 4.0, H-3$_Z$), 6.07 (0.7H, t, $J_{3,2} = J_{1,2} = 5.5$, H-2$_E$), 6.00–5.90 (2.7H, m, H-3$_E$, H-4, H-5), 5.53–5.32 (2H, m, 2 × H-6); *m*/*z* 473 (M^+), 334, 308, 281, 105 (Found: M^+, 473.1472. $C_{27}H_{23}NO_7$ requires *M*, 473.1474).

3,4-Di-*O*-benzyl-2,5,6-trideoxy-D-*threo*-hex-5-enose oxime 13

Treatment of aldehyde **12** (360 mg, 1.16 mmol) with hydroxylamine hydrochloride (242 mg, 3.48 mmol) and pyridine (281 µl, 3.48 mmol) in ethanol (3 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 2:1) provided oxime **13** (352 mg, 93%) as a colourless, oily, 50:50 mixture of *E* and *Z* isomers; ν_{max} (thin film)/cm^{-1} 3324, 3262 (OH), 3027, 2858, 1495, 1449, 1076, 927, 732, 691; δ_H (300 MHz; $CDCl_3$) 7.42 (0.5H, t, $J_{1,2} = J_{1,2'} = 6.0$, H-1$_E$), 7.38–7.25 (10H, m, ArH), 6.79 (0.5H, t, $J_{1,2} = J_{1,2'} = 5.0$, H-1$_Z$), 5.84 (1H, m, H-5), 5.40–5.30 (2H, m, 2 × H-6), 4.76–4.56 (3H, m, 3 × CH_2Ph), 4.44–4.37 (1H, m, CH_2Ph), 3.94 (1H, m, H-4), 3.75 (0.5H, m, H-3$_Z$), 3.68 (0.5H, m, H-3$_E$), 2.74–2.33 (2H, 2 × H-2); δ_C (75.4 MHz; $CDCl_3$) 149.7, 149.5, 138.27, 128.27, 138.22, 134.7, 134.6, 128.4, 128.0, 127.9, 127.8, 127.6, 119.6, 119.5, 82.1, 81.8, 78.9, 78.0, 73.1, 73.0, 70.7, 70.6, 31.2, 27.1, not all signals resolved; *m*/*z* 326 (M + H^+), 325, 202, 96 (Found: MH^+, 326.1760. $C_{20}H_{24}NO_3$ requires *m*/*z*, 326.1756).

2,3,4-Tri-*O*-benzyl-5,6-dideoxy-D-*lyxo*-hex-5-enose oxime 17

Treatment of aldehyde **16** (168 mg, 0.40 mmol) with hydroxylamine hydrochloride (84 mg, 1.21 mmol) and pyridine (98 µl, 1.24 mmol) in ethanol (0.8 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 4:1) provided oxime **17** (151 mg, 87%) as a colourless, oily, 80:20 mixture of *E* and *Z* isomers; ν_{max} (thin film)/cm^{-1} 3348, 3031, 2869, 1454, 1089, 1068, 697; δ_H (300 MHz; $CDCl_3$) 8.80 (0.2H, br s, OH$_Z$), 8.49 (0.8H, br s, OH$_E$), 7.42 (0.8H, d, $J_{1,2}$ 8.0, H-1$_E$), 7.37–7.16 (15H, m, ArH), 6.88 (0.2H, d, $J_{1,2}$ 7.0, H-1$_Z$), 5.86 (1H, m, H-5), 5.40–5.28 (2H, m, 2 × H-6), 5.02 (0.2H, dd, $J_{2,3}$ 4.0, $J_{1,2}$ 7.0, H-2$_Z$), 4.75–4.26 (6H, m, 6 × CH_2Ph), 4.22 (0.8H, dd, $J_{2,3}$ 5.0, $J_{1,2}$ 8.0, H-2$_E$), 4.07–3.98 (1H, m, H-4), 3.81–3.73 (1H, m, H-3); δ_C (75.4 MHz; $CDCl_3$) for major, *E*-isomer: 149.9 (C-1), 138.4 (C), 138.3 (C), 137.8 (C), 135.3 (C-5), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 119.2 (C-6), 82.6 (C-3), 80.6 (C-4), 76.6 (C-2), 74.8 (CH_2), 70.9 (CH_2), 70.8 (CH_2); *m*/*z* 449 (MNH_4^+), 432 (MH^+), 106 (Found: MH^+, 432.2178. $C_{27}H_{30}NO_4$ requires *m*/*z*, 432.2175).

2,3,4-Tri-*O*-benzyl-5,6-dideoxy-L-*arabino*-hex-5-enose oxime 21

Treatment of aldehyde **20** (265 mg, 0.64 mmol) with hydroxylamine hydrochloride (133 mg, 1.90 mmol) and pyridine (154 µl, 1.90 mmol) in ethanol (1.3 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 6:1) provided oxime **21** (250 mg, 91%) as a colourless, oily, 75:25 mixture of *E* and *Z* isomers; ν_{max} (thin film)/cm^{-1} 3359 (OH), 3032, 2868, 1495, 1455, 1065, 937, 738, 692; δ_H (300 MHz; $CDCl_3$) 7.42 (0.75H, d, $J_{1,2}$ 8.0, H-1$_E$), 7.36–7.22 (15H, m, ArH), 6.91 (0.25H, d, $J_{1,2}$ 6.0, H-1$_Z$), 5.99–5.84 (1H, m, H-5), 5.47–5.35 (2H, m, 2 × H-6), 5.07 (0.25H, dd, $J_{1,2}$ 6.0, $J_{3,2}$ 3.0, H-2$_Z$), 4.75–4.36 (5H, m, 5 × CH_2Ph), 4.25 (0.75H, dd, $J_{2,3}$ 5.0, $J_{1,2}$ 8.0, H-2$_E$), 4.22–4.11 (1.25H, m, CH_2Ph, H-4$_Z$), 4.06 (0.75H, dd, $J_{4,5}$ 7.5, $J_{3,4}$ 7.0, H-4$_E$), 3.80 (0.25H, dd, $J_{2,3}$ 3.0, $J_{4,3}$ 8.0, H-3$_Z$), 3.66 (0.75H, dd, $J_{4,3}$ 7.0, $J_{3,2}$ 5.0, H-3$_E$); *m*/*z* 431 (M^+), 340, 284, 208, 91 (Found: M^+, 431.2092. $C_{27}H_{29}NO_4$ requires *M*, 431.2096).

(*E*)-2,3-*O*-Isopropylidene-4,5-dideoxy-D-*erythro*-pent-5-enose oxime (*E*)-25 and (*Z*)-2,3-*O*-isopropylidene-4,5-dideoxy-D-*erythro*-pent-5-enose oxime (*Z*)-25

Treatment of aldehyde **24** (280 mg, 1.79 mmol) with hydroxylamine hydrochloride (374 mg, 5.38 mmol) and pyridine (435 µl, 5.38 mmol) in ethanol (4 ml) according to the general procedure above and subsequent column chromatography (light petroleum–ethyl acetate; 6:1) provided *less polar* oxime (*Z*)-**25** (77 mg, 25%) as a white solid, mp 98 °C; ν_{max} (KBr)/cm^{-1} 3236 (OH), 3097, 1456, 1386, 1373, 1306, 1256, 1217, 1156; δ_H (300 MHz; $CDCl_3$) 7.86 (1H, br d, OH), 6.82 (1H, d, $J_{1,2}$ 5.0, H-1), 5.77 (1H, m, H-4), 5.42–5.18 (2H, m, 2 × H-5), 5.31 (1H, dd, $J_{1,2}$ 5.0, $J_{3,2}$ 7.0, H-2), 4.83 (1H, m, H-3), 1.55 (3H, s, CH_3), 1.41 (3H, s, CH_3); δ_C (75.4 MHz; $CDCl_3$) 150.4, 133.2, 118.2, 109.6, 78.5, 72.7, 27.6, 25.2; *m*/*z* 172 (MH^+), 156, 115, 98 (Found: MH^+, 172.0972. $C_8H_{14}NO_3$ requires *m*/*z*, 172.0974); and *more polar* oxime (*E*)-**25** (174 mg, 57%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3385 (OH), 1375, 1218, 1053; δ_H (300 MHz; $CDCl_3$) 7.79 (1H, br s, OH), 7.31 (1H, d, $J_{1,2}$ 8.0, H-1), 5.76 (1H, m, H-4), 5.47–5.28 (2H, m, 2 × H-5), 4.76 (1H, m, H-3), 4.69 (1H, dd, $J_{1,2}$ 8.0, $J_{3,2}$ 7.0, H-2), 1.54 (3H, s, CH_3), 1.42 (3H, s, CH_3); δ_C (75.4 MHz; $CDCl_3$) 149.0, 132.2, 119.4, 110.0, 79.1, 75.9, 27.9, 25.4; *m*/*z* 172 (MH^+), 156, 114, 98 (Found: MH^+, 172.0975).

(3a*R*,4*R*,5*S*,6*S*,6a*R*)-4,5,6-Tribenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 5[12a]

A stirred solution of oxime **4** (87 mg, 0.20 mmol) in dry toluene (3 ml) under nitrogen was heated at reflux for 15 h. On cooling, the solvent was removed *in vacuo* to give **5** (87 mg, 100%) as a white solid, mp 108 °C (from diethyl ether–hexane) (lit.,[12a] 104–106 °C), $[\alpha]_D$ −3 (*c* 0.93, $CHCl_3$) {lit.,[12a] $[\alpha]_D$ −3.6 (*c* 0.9)}; ν_{max} (KBr)/cm^{-1} 3206 (NH), 3028, 2874, 1497, 1453, 1360, 1117, 1094, 1069, 1029; δ_H (400 MHz; C_6D_6) 7.46–7.12 (15H, m, ArH), 4.99 (1H, d, *J* 12.0, CH_2Ph), 4.90 (1H, d, *J* 12.0, CH_2Ph), 4.88 (1H, d, *J* 12.0, CH_2Ph), 4.76 (1H, d, *J* 12.0, CH_2Ph), 4.59 (1H, d, *J* 12.0, CH_2Ph), 4.52 (1H, br s, NH), 4.47 (1H, d, *J* 12.0, CH_2Ph), 4.07 (1H, t, $J_{5,4} = J_{5,6} = 8.0$, H-5), 4.00 (1H, dd, $J_{5,6}$ 8.0, $J_{6a,6}$ 6.5, H-6), 3.70 (1H, t, $J_{4,5} = J_{4,3a} = 8.0$, H-4), 3.65 (1H, d, $J_{3,3'}$ 8.5, H-3), 3.35 (1H, dd, $J_{6a,3a}$ 10.0, $J_{6a,6}$ 6.5, H-6a), 2.87 (1H, m, H′-3), 2.49 (1H, m, H-3a); δ_C (100 MHz; C_6D_6) 139.3 (C), 139.1 (C), 138.9 (C), 128.3 (CH), 128.27 (CH), 128.24 (CH), 127.74 (CH), 127.68 (CH), 127.63 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 86.1 (C-5 and -6), 85.3 (C-4), 75.4 (C-3), 72.4 (CH_2), 72.0 (CH_2), 71.8 (CH_2), 66.5 (C-6a), 49.7 (C-3a); *m*/*z* 431 (M^+), 340, 218, 91 (Found: M^+, 431.2103; C, 75.16; H, 6.72; N, 3.22%. Calc. for $C_{27}H_{29}NO_4$ *M*, 431.2097; C, 75.15; H, 6.77; N, 3.24%).

(3a*R*,4*R*,5*S*,6*S*,6a*R*)-4,5,6-Tribenzoyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 8

A stirred solution of oxime **7** (456 mg, 0.96 mmol) in dry toluene (16 ml) under nitrogen was heated at reflux for 15 h. On cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography (light petroleum–ethyl acetate; 1:1) to provide bicycle **8** (273 mg, 60%) as a white solid, mp 207–209 °C (from toluene); $[\alpha]_D^{22}$ −29 (*c* 1.09, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3242 (NH), 1721 (C=O), 1265, 1106, 702; δ_H (400 MHz; $CDCl_3$) 8.15–7.95 (6H, m, ArH), 7.60–7.30 (9H, m, ArH), 6.00 (1H, t, $J_{5,4} = J_{5,6} = 8.0$, H-5), 5.62–5.35 (2H, m, NH, H-6), 5.34 (1H, dd, $J_{4,5}$ 8.0, $J_{4,3a}$ 6.0, H-4), 4.63 (1H, d, $J_{3,3'}$ 9.0, H-3), 4.25 (1H, dd, $J_{6a,3a}$ 9.5, $J_{6a,6}$ 6.0, H-6a), 3.69 (1H, m, H′-3), 3.21 (1H, m, H-3a); δ_C (100 MHz; $CDCl_3$) 166.2 (C), 165.6 (C), 133.5 (CH), 133.3 (CH), 133.26 (CH), 129.9 (CH), 129.87 (CH), 129.84 (CH), 129.5 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 79.2 (C-4), 78.7 (C-6), 76.8 (C-5), 75.8 (C-3), 66.0 (C-6a), 50.7 (C-3a), not all carbons resolved; *m*/*z* 473 (M^+), 105, 77 (Found: M^+, 473.1472; C, 68.35; H, 4.77; N, 2.69%. $C_{27}H_{23}NO_7$ requires *M*, 473.1475; C, 68.49; H, 4.90; N, 2.96%).

(3a*R*,4*R*,5*R*,6a*S*)-4,5-Dibenzyloxyhexahydro-1*H*-cyclopent-[*c*]isoxazole 14 and (3a*S*,4*R*,5*R*,6a*R*)-4,5-dibenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 15

A stirred solution of oxime **13** (87 mg, 0.27 mmol) in dry toluene (4 ml) under nitrogen was heated at reflux for 36 h. On cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography (light petroleum–ethyl acetate; 1:2) to give an inseparable 2:1 mixture of bicycles **14** and **15** (67 mg, 71%) as a colourless oil; stereochemistry of major adduct could not be determined; ν_{max} (thin film)/cm^{-1} 3216, 2929, 2858, 1449, 1357, 1096, 691; δ_H (400 MHz; C_6D_6; 80 °C) 7.45–7.10 (10H, m, ArH), 4.62–4.40 (4.33H, m, 4 × CH_2Ph, H-3$_{min}$), 4.13 (0.33H, dt, $J_{5,4} = J_{5,6} = 7.0$, $J_{5,6'}$ 9.0, H-5$_{min}$), 3.85 (0.66H, dt, $J_{5,4} = J_{5,6'}$ 6.0, $J_{5,6}$ 7.0, H-5$_{maj}$), 3.81–3.75 (1H, m, H-4), 3.72 (0.66H, dd, $J_{3,3'}$ 8.5, $J_{3,3a}$ 4.0, H-3$_{maj}$), 3.62–3.46 (1.32H, m, H-3$_{maj}$, H-6a$_{maj}$), 3.40 (0.33H, m, $J_{6a,3a} = J_{6a,6} = 9.0$, $J_{6a,6'}$ 2.0, H-6a$_{min}$), 3.13 (0.33H, t, $J_{3',3a} = J_{3',3} = 8.0$, H′-3$_{min}$), 2.65–2.61 (1H, m, H-3a), 2.20–2.08 (1H, m, H-6), 1.78 (0.66H, m, H′-6$_{maj}$), 1.71 (0.33H, dt, $J_{6,6'}$ 14.0, $J_{5,6'} = J_{6a,6'} = 9.0$, H′-6$_{min}$); δ_C (100 MHz; C_6D_6; 30 °C) 139.4 (C), 139.0 (C), 138.9 (C), 138.8 (C), 128.36 (CH), 128.33 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.49 (CH), 127.46 (CH), 127.25 (CH), 127.19 (CH), 127.16 (CH), 88.0 (C-4$_{maj}$), 84.0 (C-4$_{min}$), 83.6 (C-5$_{maj}$), 82.0 (C-5$_{min}$), 75.7 (C-3$_{maj}$), 71.96 (CH_2), 71.86 (CH_2), 71.7 (CH_2), 71.5 (C-3$_{min}$), 71.1 (CH_2), 62.1 (C-6a$_{maj}$), 60.4 (C-6a$_{min}$), 53.2 (C-3a$_{maj}$), 48.5 (C-3a$_{min}$), 36.2 (C-6$_{min}$), 34.3 (C-6$_{maj}$); *m*/*z* 326 (MH$^+$), 106 (Found: MH$^+$, 326.1757. $C_{20}H_{24}NO_3$ requires *m*/*z*, 326.1756).

(3a*S*,4*R*,5*S*,6*R*,6a*S*)-4,5,6-Tribenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 18 and (3a*R*,4*R*,5*S*,6*R*,6a*R*)-4,5,6-tribenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 19

A stirred solution of oxime **17** (410 mg, 0.95 mmol) in dry toluene (14 ml) under nitrogen was heated at reflux for 60 h. On cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography (toluene–acetone; 10:1 ⟶ 5:1) to give *less polar* bicycle **18** (263 mg, 64%) as a colourless oil; $[\alpha]_D^{23}$ −18 (*c* 0.76, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3219 (NH), 3063, 3030, 2863, 1496, 1453, 1366, 1135, 1072, 1027, 735, 697; δ_H (400 MHz; C_6D_6) 7.45–7.10 (15H, m, ArH), 4.70 (1H, br s, NH), 4.65 (1H, d, *J* 12.0, CH_2Ph), 4.64 (1H, d, *J* 12.0, CH_2Ph), 4.59 (1H, d, *J* 12.0, CH_2Ph), 4.55 (3H, m, H-3, 2 × CH_2Ph), 4.46 (1H, d, *J* 12.0, CH_2Ph), 4.35 (1H, t, $J_{4,5} = J_{4,3a} = 8.0$, H-4), 4.11 (1H, dd, $J_{5,4}$ 8.0, $J_{5,6}$ 4.5, H-5), 3.98 (1H, dd, $J_{5,6}$ 4.5, $J_{6a,6}$ 1.5, H-6), 3.49 (1H, br d, $J_{6a,3a}$ 8.0, H-6a), 2.93 (1H, dd, $J_{3',3a}$ 7.5, $J_{3,3'}$ 8.5, H′-3), 2.74 (1H, m, H-3a); δ_C (100 MHz; C_6D_6) 139.3 (C), 139.1 (C), 139.0 (C), 128.33 (CH), 128.30 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.4 (CH), 127.3 (CH), 83.8 (C-5), 81.9 (C-6), 81.3 (C-4), 72.38 (CH_2), 72.35 (CH_2), 72.26 (CH_2), 71.0 (C-3), 66.1 (C-6a), 46.8 (C-3a); *m*/*z* 431 (M$^+$), 346, 91 (Found: M$^+$, 431.2091. $C_{27}H_{29}NO_4$ requires *M*, 431.2097); and *more polar* bicycle **19** (50 mg, 12%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3231 (NH), 3062, 3032, 2924, 2863, 1495, 1449, 1357, 1091, 738, 691; δ_H (400 MHz; C_6D_6) 7.50–7.10 (15H, m, ArH), 4.78 (1H, m, CH_2Ph), 4.62–4.49 (3H, m, 3 × CH_2Ph), 4.30 (2H, m, 2 × CH_2Ph), 4.07–3.96 (2H, m, H-3, H-4), 3.93–3.81 (3H, m, H-5, H-6, H-6a), 3.55 (1H, m, H-3), 2.80 (1H, m, H-3a); δ_C (100 MHz; C_6D_6) 138.6 (C), 138.5 (C), 129.1 (CH), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.7 (CH), 127.5 (CH), 125.4 (CH), 84.9 (C-6), 83.9 (C-5), 77.9 (C-4), 75.1 (C-3), 72.9 (CH_2), 72.7 (CH_2), 71.7 (CH_2), 64.3 (C-6a), 53.2 (C-3a), not all aromatic signals resolved; *m*/*z* 431 (M$^+$), 401, 91 (Found: M$^+$, 431.1727)

(3a*R*,4*S*,5*S*,6*S*,6a*R*)-4,5,6-Tribenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 22 and (3a*S*,4*S*,5*S*,6*S*,6a*S*)-4,5,6-tribenzyloxyhexahydro-1*H*-cyclopent[*c*]isoxazole 23

A stirred solution of oxime **21** (234 mg, 0.54 mmol) in dry toluene (8 ml) under nitrogen was heated at reflux for 24 h. On cooling, the solvent was removed *in vacuo* and the residue purified by column chromatography (light petroleum–ethyl acetate; 2:1) to give *less polar* bicycle **22** (167 mg, 71%) as a white solid mp 114 °C; $[\alpha]_D^{20}$ +5 (*c* 1.04, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3160 (NH), 2924, 2853, 1495, 1444, 1347, 1152, 1091, 1024, 840, 735, 692; δ_H (400 MHz; $Cl_2DCCDCl_2$; 80 °C) 7.40–7.33 (15H, m, ArH), 4.83 (1H, d, *J* 11.9, CH_2Ph), 4.76–4.72 (3H, m, CH_2Ph), 4.65 (1H, d, *J* 12.0, CH_2Ph), 4.62 (1H, d, *J* 11.9, CH_2Ph), 4.25 (1H, dd, $J_{3,3'}$ 8.1, $J_{3,3a}$ 5.1, H-3), 4.13 (1H, dd, $J_{4,5}$ 4.1, $J_{3a,4}$ 6.7, H-4), 4.03 (1H, br t, $J_{4,5} = J_{5,6} \approx 4.1$, H-5), 3.99–3.95 (1H, dd, $J_{6,6a}$ 3.2, $J_{5,6}$ 5.0, H-6), 3.80 (1H, t, $J_{3,3'} = J_{3',3a} = 8.1$, H′-3), 3.76 (1H, dd, $J_{6a,3a}$ 8.6, $J_{6a,6}$ 3.2, H-6a), 3.20 (1H, m, H-3a); δ_C (100 MHz; $Cl_2DCCDCl_2$; 80 °C) 138.6 (C), 138.5 (C), 138.4 (C), 128.5 (CH), 127.7 (CH), 127.65 (CH), 127.6 (CH), 85.2 (C-5), 83.4 (C-6), 78.4 (C-4), 73.4 (CH_2), 72.9 (CH_2), 72.2 (CH_2), 71.2 (C-3), 69.3 (C-6a), 48.6 (C-3a), not all aromatic carbons resolved; *m*/*z* 431 (M$^+$), 397, 369, 242, 91 (Found: M$^+$, 431.2106; C, 75.13; H, 6.77; N, 3.12%. $C_{27}H_{29}NO_4$ requires *M*, 431.2097; C, 75.15; H, 6.77; N, 3.24%); and *more polar* bicycle **23** (27 mg, 12%) as a colourless oil; ν_{max} (thin film)/cm^{-1} 3221 (NH), 3062, 3037, 2868, 1501, 1449, 1357, 1209, 1132, 732, 697; δ_H (400 MHz; C_6D_6; 60 °C) 7.45–7.10 (15H, m, ArH), 4.69 (1H, d, *J* 12.0, CH_2Ph), 4.68 (1H, d, *J* 12.0, CH_2Ph), 4.62 (2H, m, *J* 12.0, 2 × CH_2Ph), 4.56 (1H, d, *J* 12.0, CH_2Ph), 4.49 (1H, d, *J* 12.0, CH_2Ph), 4.30 (1H, dd, $J_{5,6}$ 8.0, $J_{6,6a}$ 6.7, H-6), 4.06 (1H, dd, $J_{4,5}$ 4.0, $J_{5,6}$ 8.0, H-5), 3.74 (1H, dd, $J_{3a,6a}$ 8.0, $J_{6,6a}$ 6.7, H-6a), 3.59 (1H, dd, $J_{4,5}$ 4.0, $J_{3a,4}$ 1.9, H-4), 3.50 (1H, br t, H-3), 3.35 (1H, dd, $J_{3,3'}$ 8.8, $J_{3',3a}$ 2.9, H′-3), 2.85 (1H, m, H-3a); δ_C (100 MHz; C_6D_6; 30 °C) 139.3 (C), 139.1 (C), 138.9 (C), 128.3 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 127.4 (CH), 84.0 (C-5), 81.4 (C-6), 80.5 (br, C-4), 74.0 (br, C-3), 72.4 (2 × CH_2), 72.1 (CH_2), 61.0 (C-6a), 51.1 (C-3a), not all aromatic carbons resolved; *m*/*z* 431 (M$^+$), 217, 91 (Found: M$^+$, 431.2092. $C_{27}H_{29}NO_4$ requires *M*, 431.2097).

(3a*R*,4*R*,5*S*,6*S*,6a*R*)-4,5,6-Trihydroxyhexahydro-1*H*-cyclopent[*c*]isoxazole 9[12a]

A solution of sodium methoxide (produced from fresh sodium shavings) in methanol (3 ml) was added to bicycle **8** (146 mg, 0.31 mmol) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 1 h, then neutralised with Dowex 50 (H$^+$) resin, filtered, and concentrated *in vacuo*. Column chromatography (CH_2Cl_2–MeOH; 1:1 containing 2% of 32% aq. ammonia) provided triol **9** (30 mg, 60%) as a white solid; $[\alpha]_D^{20}$ −60 (*c* 0.50, MeOH) {lit.,[12a] $[\alpha]_D$ −58.3 (*c* 1.2, MeOH)}; δ_H (300 MHz; CD_3OD) 3.97 (1H, d, *J* 9.0), 3.61–3.37 (5H, m), 2.55 (1H, m); δ_C (75.4 MHz; CD_3OD) 81.2, 79.7, 79.3, 75.8, 67.4, 51.9; *m*/*z* 161 (M$^+$), 122, 100, 70 (Found: M$^+$, 161.0687. Calc. for $C_6H_{11}NO_4$: *M*, 161.0688).

(1*R*,2*S*,3*S*,4*R*,5*R*)-1-Amino-2,3,4-trihydroxy-5-(hydroxymethyl)cyclopentane 10[12a]

A solution of bicycle **9** (25 mg, 0.15 mmol) in MeOH (2.5 ml) was hydrogenated in the presence of 10% Pd on carbon (spatula tip) at room temperature under one atmospheric pressure of hydrogen overnight. The catalyst was removed by filtration through Celite and the filtrate concentrated *in vacuo* to give cyclopentane **10** (23 mg, 91%) as a white solid; $[\alpha]_D^{20}$ +2 (*c* 0.44, MeOH); δ_H (300 MHz; D_2O) 3.78 (3H, m), 3.70 (1H, t, *J* 8.0), 3.60 (1H, t, *J* 8.0), 3.30 (1H, dd, *J* 8.0, *J* 10.0), 2.15 (1H, m); δ_C (75.4 MHz; D_2O) 79.7, 79.4, 74.1, 58.5, 53.3, 44.8; *m*/*z* 163 (M$^+$), 122, 105, 73.

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Paper 9/05706D