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APPLICATION OF SUGAR ALLYL TIN DERIVATIVES FOR THE PREPARATION OF HETEROCYCLIC COMPOUNDS[†]

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Abstract – Controlled fragmentation of sugar allyl tin, derivative of D-glucose, provided the eight carbon atom synthon: (2*R*,3*S*,4*R*)-tris(benzyloxy)oct-5,7-diene, which was used for the preparation of complex heterocyclic compounds. First step involved formation of the corresponding oxime, which underwent – under high pressure – the oxime/olefin cyclization (the alternative Diels-Alder product was not formed). Proper functionalization of the latter led to the tricyclic product.

1. INTRODUCTION

Application of sugars as starting materials for the preparation of complex optically pure products (chiron approach¹) is a well established method in synthetic organic chemistry. This approach is particularly useful in the synthesis of polyhydroxylated carbocyclic compounds which are regarded as sugar mimics.² Such compounds (which can be prepared by a number of methods including *e.g.*: Ferrier-II rearrangement,³ Sinaÿ ‘molecular scissors’,⁴ RCM cyclization of sugar olefins,⁵ and many others¹) possess interesting biological properties; because of their similarity to ‘normal’ sugars they efficiently block specific enzymes.⁶ Even more interesting are sugar analogs in which the ring oxygen atom is replaced by a nitrogen functionality (iminosugars).⁷

During the past years we have elaborated a convenient methodology for the preparation of enantiomerically pure carbo-bicyclic systems from sugar allyltins. The key-step consisted of a controlled

[†] Dedicated to Prof. Akira Suzuki on the occasion of his 80th birthday

fragmentation of these organometallics into isomerically pure (only *E* configuration across the internal double bond) dienoaldehydes, which – by proper functionalization – were converted either into bicyclo[4.4.0]decenes or bicyclo[4.3.0]nonenes (Figure 1).⁸

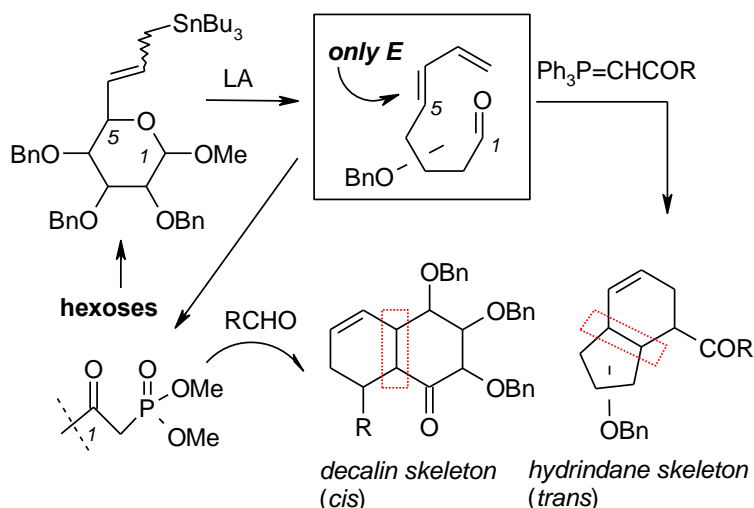


Figure 1. Convenient routes to precursors of highly oxygenated carbocyclic derivatives from sugar allyltins (ref. 8)

Such highly functionalized dienoaldehydes might also serve as precursors of heterocyclic derivatives. In the pioneering work by Herczegh, compound **1** was converted into the protected oxime **1a**, which then was used in the intramolecular Diels-Alder (IMDA) reaction leading to the corresponding bicycle (Figure 2).⁹ However, the methyl group protecting the oxygen atom made this derivative useless in the preparation of sugar mimetics. The drawback laid also in non-homogeneity of the starting diene **1**, which was prepared as a mixture of geometrical isomers across the internal double bond.⁹

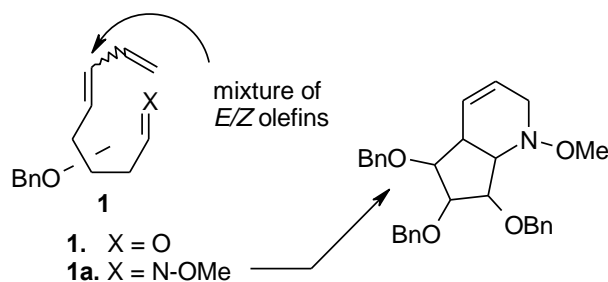


Figure 2. Herczegh approach to heterocyclic iminosugars

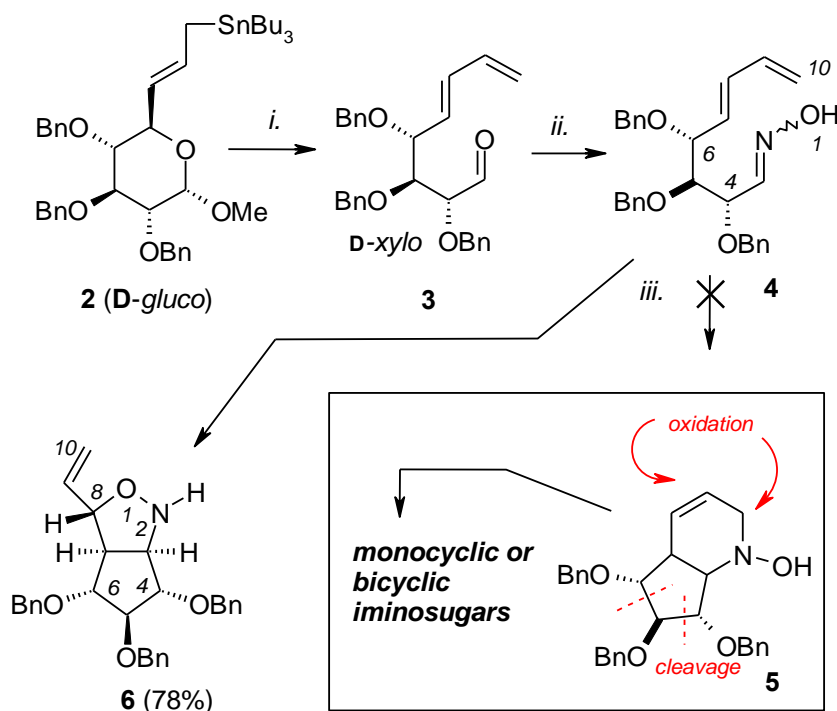
2. RESULTS AND DISCUSSION

Because of the synthetic potential of such bicyclic system we decided to investigate this reaction and prepare derivatives which might be conveniently transformed into sugar mimetics, either bicyclic or monocyclic.

2.1. Synthesis of heterocyclic derivatives from dienoaldehyde

The synthesis was initiated from the readily available in our laboratory dienoaldehyde **3** (with the *D*-xylo-configuration), originated from the *D*-gluco-configured allyltin **2**.⁸

Reaction of the aldehyde **3** with hydroxylamine under the standard conditions afforded the corresponding oxime **4** (obtained as a mixture of *syn-anti* stereoisomers; see Experimental), which was subjected to the IMDA reaction under high (10 kbar) pressure. This process, however, did not afford the desired product **5** (which could serve as a precursor of a wide variety of highly functionalized derivatives, by reactions shown in Scheme 1), but another bicycle identified as **6**, arising from the olefin/oxime cyclization¹⁰ (Scheme 1; for determination of the structure see chapter 2.2; Table 1 and Figure 4).[†] High selectivity observed in such process might be rather expected, since the substituents located at both stereogenic centers (at the C4 and C6) in the vicinity of the reaction centers are at the same side of the molecule. Similar trend was observed also for more simple derivatives.¹⁰



Scheme 1. *i*. ref. 8; *ii*. $\text{NH}_2\text{OH}\cdot\text{HCl}$, K_2CO_3 ; *iii*. 10 000 atm

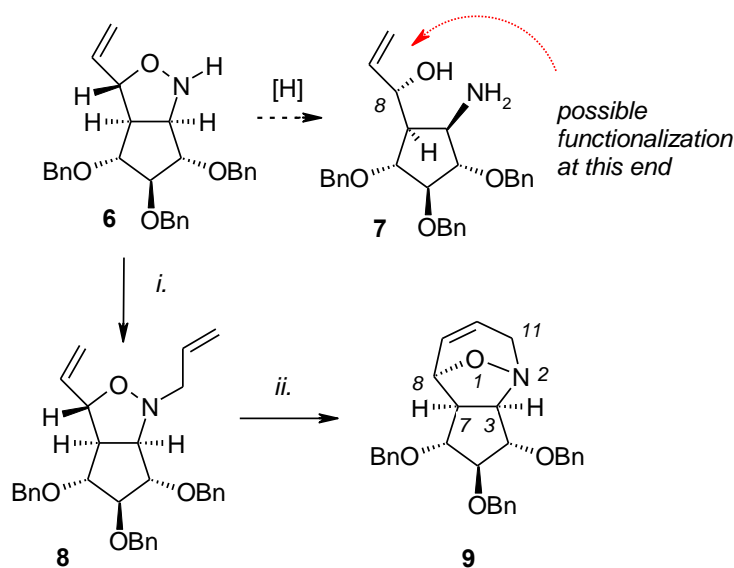
Compound **6** has a big potential as starting material in the preparation of complex molecules. The additional functionality, the vinyl group located at the C8 position (for numbering see Scheme 1), allows

[†] Oxime **4** underwent also cyclization to the same product **6** at normal pressure within several days (see Experimental)

for easy structural manipulations, which consequently should lead to a wide variety of mono- and bicyclic derivatives.

The most obvious choice of such functionalization, conversion of this compound into the cyclopentane **7** will not be discussed here despite its high synthetic potential (functionalization of the ‘*allylic alcohol end*’, *i.e.* the vinyl group located at the C8 position should provide a wide variety of mono-carbocyclic compounds). This transformation would involve cleavage of the N-O bond either by hydrogenation in the presence of metal catalysts (this method should be however avoided because of sensibility of the protecting groups) or by reduction with lithium aluminum hydride,¹¹ and will rather follow the route described for more simple sugar-derived bicyclic oxazolines.¹⁰

Taking, however, advantage from the presence of the vinyl unit in the molecule of **6**, we planned the synthesis of the tricyclic derivative **9** (Scheme 2).



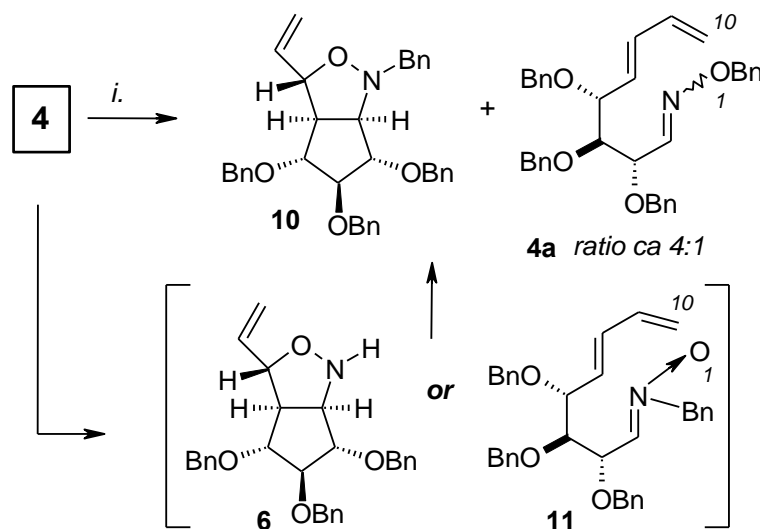
Scheme 2. *i.* All-Br, CH₃CN, K₂CO₃, 65%;
ii. Grubbs' I cat. CH₂Cl₂, reflux, 8h, 97%

First step involved allylation of **6** at the nitrogen atom, which was performed under the standard conditions. The resulting diolefin **8** was then subjected to the ring closing metathesis reaction (RCM)¹² which afforded the target compound **9** in 97% yield. The first generation Grubbs' catalyst was highly effective in this cyclization. The advanced NMR studies fully confirmed the structure of the product (see chapter 2.2)

The desired IMDA product (of type **5**) might be, eventually, prepared from the *O*-protected oxime

(analogously to the Herczegh procedure), so we decided to protect this oxime with benzyl group. It is known that alkylation of oximes under neutral or weakly basic conditions provides the *N*-alkylated products, while alkylation under strong basic conditions (involving the oxime anions) affords the *O*-protected derivatives.¹³

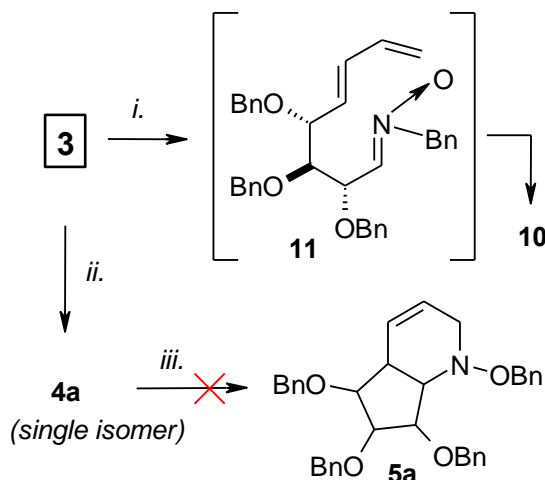
We have treated the oxime **4** with benzyl chloride in basic media (EtOH, EtONa) in order to protect the hydroxyl group; the results are shown in Scheme 3. After the reaction two products were isolated. First one, cyclic (formed in low yield), was identified as *N*-benzylated oxazoline **10**, with the same, as in **6**, configuration at the three newly created stereogenic centers (see chapter 2.2 and Experimental). Second product, acyclic, was identified as *O*-protected oxime **4a** (mixture of two geometrical isomers in the 4:1 ratio); the alternative structure, nitron **11** (arising from alkylation of the nitrogen atom in **4**) should be excluded on the basis of the NMR data (for determination of the structure see chapter 2.2, Table 1 and Figure 3). Formation of the *O*-protected oxime **4a** might be expected based on the literature data, but formation of cyclic product **10** (especially, that it was formed in low yield) raised a question: if this compound was a product of simple alkylation of **6** (formed *via* oxime/olefin cyclization) or (more likely) was obtained *via* 1,3-dipolar cycloaddition of nitron **11**.



Scheme 3. *i.* BnCl, EtOH, EtONa

To distinguish between these two pathways, the nitron **11** was prepared on independent route from dienoaldehyde **3** under the standard conditions (Scheme 4). However, it could not be isolated, because underwent spontaneous cyclization providing the benzylated oxazoline **10**; the intramolecular 1,3-dipolar

cycloaddition was therefore very fast.



Scheme 4. *i.* Bn-NH-OH , CH_2Cl_2 , MgSO_4 , 65%;
ii. $\text{H}_2\text{N-OBn}$, MeOH , 72%, NaOAc , *iii.* 10 kbar

This observation allowed us to rationalize the results of the reaction of oxime **4** with benzyl chloride under strongly basic conditions. Alkylation of oxime occurred at both atoms: the oxygen – providing the protected oxime **4a** and nitrogen, which furnished the nitron spontaneously undergoing cyclization. As expected¹³ the *O*-alkylation was the major pathway in this reaction.

To obtain the desired IMDA product we have prepared the *O*-benzylated oxime **4a** on independent route by reaction of **3** with *O*-benzylated hydroxylamine. However, this compound did not undergo [4+2] cyclization even under high (10 kbar) pressure (Scheme 4). This result was very surprising, since under thermal conditions reported by Herczegh, the *O*-methyl derivative proceeded smoothly (see Figure 2). We do not have any explanation for this phenomenon, because the cyclization reactions are usually highly accelerated by high pressure.¹⁴

2.2. Determination of the structure of oxazoline **6** and benzylated oxime **4a** and tricycle **9**

The structures of the products: oxime **4a** (isolated from the experiment shown in Scheme 4) and oxazoline **6** were established by advanced NMR experiments (Table 1; Figures 3 and 4). Assignment of the ^1H and ^{13}C NMR chemical shift was made based on the ^1H NOESY and ^1H TOCSY selective experiments, as well as on results of ^1H - ^{13}C HSQC and HMBC correlations. Additionally, ^1H - ^{15}N HMBC sequence was employed to distinguish different types of nitrogen atoms (oxime/nitron and amine). Results of the assignment are collected in Table 1. For oxazoline structure the NMR experiments were

performed in C₆D₆ solution at 328K in order to receive a good ¹H NMR signals separation.

Table 1. The ¹H ¹³C and ¹⁵N NMR resonances of **4a**^a and **6**

	oxime 4a (CDCl ₃ /299K)	Oxazoline 6 (C ₆ D ₆ /328K)
H3/C3 ^b	7.51/149.6	3.35/66.6
H4/C4	4.13/76.4	3.89/85.5
H5/C5	3.59/82.8	3.93/86.3
H6/C6	4.21/80.7	3.68/84.8
H7/C7	5.53/130.3	2.50/53.7
H8/C8	6.18/134.6	4.15/85.3
H9/C9	6.26/136.3	5.36/135.6
H10/C10	5.09 (<i>cis</i>), 5.15 (<i>trans</i>)/118.0	4.86 (<i>cis</i>), 4.95 (<i>trans</i>)/115.9
N2	+3.5	-223.1

^a The spectra were recorded for the (isolated) main isomer of **4a**

^b For numbering of the skeleton see Figure 3 and 4

The ¹⁵N gradient selected HMBC experiment performed for **4a** revealed the nitrogen signal at δ+3.5 ppm (correlated with protons H4 and H3 as well as methylene protons of benzyl group). This ¹⁵N NMR chemical shift pointed unambiguously at the oxime structure (typical data are in range: +30 to -60 ppm) and excluded the nitron one (typical δ: -75 to -110 ppm).¹⁵

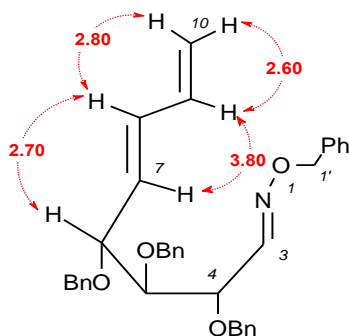


Figure 3. The nOe values observed for oxime **4a**

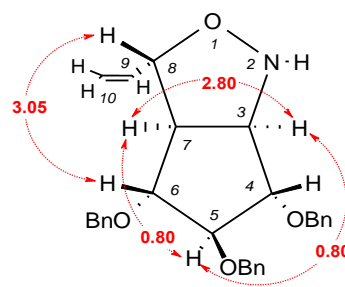


Figure 4. The nOe values observed for oxazoline **6**

The structure of **4a** was evaluated also on the basis of the ¹H NOESY selective experiments. NOE effects (presented in Figure 3) confirmed the (expected)⁸ *trans* geometry across the internal C=C double bond and indicated the *s-trans* conformation of the diene.

Determination of the structure of oxazoline **6** was also evident from the NMR spectra. Cyclization of oxime **4** led to the bicyclic system in which new single bonds: C3-C7 and C8-O1 were created, which was fully confirmed by significant changes in the ^1H and especially in ^{13}C chemical shifts (Table 1). The ^{13}C NMR signals of the C3, C7, and C8 atoms (involved in the double bond) in oxime **4** are in typical (ca. 130-150 ppm) field, whereas – after cyclization – are shifted to much higher field (ca. 50-90 ppm). The oxime type nitrogen signal (N2) was converted into the amine type; the ^{15}N NMR shielding strongly increased (+3.5 \rightarrow -223 ppm). Analysis of the ^1H NOESY selective experiments taken on H3, H6, H7, and H8 protons provided the NOE effects presented in Figure 4, which indicated that protons in pairs: H3-H7, as well as, H6-H8 are in *cis*-relationship. Weak NOE effects observed at H3 and H7 after irradiation of the H5 also pointed at the *cis* relationship between H3, H5, and H7 protons.

Configuration of the *N*-benzyl-bicycle **10** (formed in the reaction of oxime **4** with benzyl chloride; see Scheme 3) was identical with the oxazoline **6** which was proven by simple benzylation of the latter under the standard conditions (see Experimental).

Assignment of the structure of compound **9** was obvious from the spectral data. The mass of the molecular ion of **9** differed by 28D from the ion of the starting material (di-olefin **8**), which strongly suggested elimination of ethylene molecule and pointed at the structure **9**. This was fully confirmed by the NMR data in which only two olefinic signals were seen (see Experimental). Although the configuration at the ring junctions was already known (it was the same as in starting **6**) it was additionally supported by the NOE values shown in Figure 5.

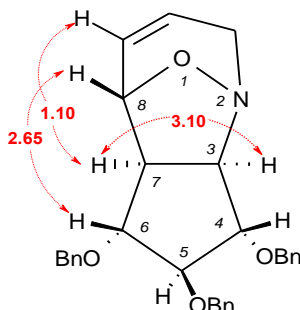


Figure 5. The NOE values observed for **9**

3. CONCLUSION

Sugar allyltin derivatives are convenient starting materials for the preparation of highly functionalized

dienoaldehydes, which '*normally*' are used for the preparation of carbobicyclic systems. However, besides this '*traditional*' application, they might be also applied in the synthesis of heterocyclic derivatives. We have shown, that intramolecular cyclization of the oxime, obtained from the corresponding dienoaldehyde derived from sugar allyltin, proceeds efficiently and highly stereoselectively under high pressure to produce the bicyclic 1H-cyclopent[c]isoxazole. Even more effective is cyclization of the corresponding nitron obtained from the dienoaldehyde. Additional functionality (the vinyl group), present in the bicyclic structure of the product of oxime/olefin cyclization, allowed us to prepare the tricyclic compound by simple allylation of the nitrogen atom in this isoxazole followed by ring closing metathesis. Such derivatives (bicyclic and tricyclic) have a big synthetic potential for the preparation of highly functionalized sugar mimics. The oxime/olefin cyclization is much faster than the intramolecular Diels-Alder process, which was not observed even under high pressure.

4. EXPERIMENTAL

4.1. General

The NMR spectra of all compounds were measured in CDCl₃ solutions (unless otherwise stated) with following spectrometers: Bruker DRX 500 (at temperature 303 K) equipped with a TBI 500SB H-C/BB-D-05 Z-G probehead, Varian-NMR-vnmrs500 (at temperature 298 K) equipped with a PFG Auto XDB (¹H-¹⁹F/¹⁵N-³¹P 5 mm) probehead, and Varian-NMR-vnmrs600 (at temperature 299 K) equipped with a PFG Auto XID (¹H/¹⁵N-³¹P 5 mm) indirect probehead. For diene/oxime structure benzene-D₆ were chosen to receive a best ¹H NMR signal separation needed in process of configuration determination. Standard experimental conditions and standard Bruker and Varian programs were used. To assign the structures under consideration following 1D and 2D experiments were employed: the ¹H selective NOESY, ¹H selective TOCSY, COSY, ¹H-¹³C gradient selected HSQC and HMBC with adiabatic pulses optimized for ¹J(C-H) = 146 Hz and ⁿJ(C-H) = 8 Hz. Additionally, the ¹H-¹⁵N gradient selected HMBC optimized for ⁿJ(N-H) = 5 Hz were used to distinguish different types of nitrogen atom in molecules of oxazoline/oxime/nitron.

The ¹H and ¹³C NMR spectral data are given relative to the TMS signal at 0.0 ppm. Nitromethane (δ = 0.0 ppm) was used as an external standard for the ¹⁵N NMR spectra. Concentration of all solutions used for

measurements was about 20-30 mg of compounds in 0.6 cm³ of solvent.

The relative configurations of the protons were determined based on ¹H selective NOESY experiments using standard Varian (ChemPack 4.1) sequence. The ¹H and ¹³C NMR signals of benzyl groups occurring at the typical δ values were omitted for simplicity.

Mass spectra were recorded with an ESI/MS Mariner (PerSeptive Biosystem) mass spectrometer. Optical rotations were measured with a Digital Jasco polarimeter DIP-360 (λ = 589 nm) for solutions in CHCl₃ (c = 1) at room temperature.

Column chromatography was performed on silica gel (Merck, 70-230 or 230-400 mesh). Methylene chloride was distilled from CaH₂ and THF from potassium prior to use. Organic solutions were dried over anhydrous magnesium sulfate.

2,3,4-Tri-*O*-benzyl-5,6,7,8-tetradecoxy-D-xylo-oct-5(*E*),7-dienose oxime 4

To a solution of the dienoaldehyde **3**^{8,16} (1.70 g, 3.8 mmol) in EtOH / pyridine mixture (70 mL; 6:1 v/v), hydroxylamine hydrochloride (300 mg, 4.5 mmol, 1.2 equiv.) was added and the mixture was stirred for 3 h at room temperature. After that time TLC (hexane – EtOAc, 3:1) showed disappearance of the starting material and formation of two more polar products. The solution was concentrated and the residue partitioned between EtOAc and 5% aq. HCl (20 mL both). The organic phase was separated, washed with water, brine, dried and concentrated and the product was purified by column chromatography (hexane – EtOAc, 10:1) to afford a mixture of *syn/anti* oximes **4** (535mg, 1.15mmol; 30%) and oxazoline **6** (1.135 g; 2.48 mmol, 65%).

Data for **4**: HRMS: m/z calcd for: C₂₉H₃₁NO₄ [M+Na⁺]: 480.21453; found: 480.2155. ¹H NMR (500 MHz) for the main isomer: δ : 3.57 (dd, J = 5.9, 4.5 Hz, 1H, H-5), 4.12 (dd, J = 7.7, 4.5 Hz, 1H, H-4), 4.18 (dd, J = 7.1, 6.3 Hz, 1H, H-6), 5.15 (m, 2H, H-10), 5.54 (dd, J = 15.2, 7.8 Hz, 1H, H-7), 6.23 (m, 2H, H-8 and H-9), 7.46 (d, J = 7.8 Hz, 1H, H-3); ¹³C NMR (125 MHz) δ : 76.52, 80.34, 82.74 (C-4, C-5, C-6), 118.05 (C-10), 130.32, 134.68, 136.18 (C-7, C-8, C-9), 150.05, (C-3). ¹H NMR (500 MHz) for the minor isomer (selected signals): δ : 3.80 (dd, J = 7.3, 3.2 Hz, 1H, H-5), 4.3 (m, 1H, H-6), 4.40 (m, 1H, H-10), 6.92 (d, J = 6.1 Hz, 1H, H-3); ¹³C NMR (125 MHz) δ : 71.7, 81.2, 81.7 (C-4, C-5, C-6).

When the mixture of *syn/anti* oximes **4** was left for three days the NMR spectra showed only cyclic

product **6**.

2,3,4-Tri-*O*-benzyl-5,6,7,8-tetradeoxy-D-xylo-oct-5(*E*),7-dienose *O*-benzyl-oxime **4a**

To a solution of the dienoaldehyde **3** (515 mg, 1.1 mmol) in MeOH (50 mL), *O*-benzyl-hydroxylamine (200 mg, 1.3 mmol, 1.2 equiv.) and sodium acetate (115 mg, 1.3 mmol, 1.2 equiv.) were added and the mixture was stirred till disappearance of the starting material (8 h; TLC monitoring in hexane – EtOAc, 3:1). Methanol was removed in vacuum, and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic solution was separated, washed with water, brine, dried and concentrated, and the crude product was purified by column chromatography to afford single stereoisomeric oxime **4a** (442 mg, 0.81 mmol, 72%). $[\alpha] +51.1$; HRMS: m/z calcd for: $C_{36}H_{37}NO_4$ $[M+Na^+]$: 570.26148; found: 570.26203. NMR (500 MHz; see also Table 1) δ : 3.59 (dd, $J = 6.2, 4.3$ Hz, 1H, H-5), 4.13 (dd, $J = 7.9, 4.3$ Hz, 1H, H-4), 4.21 (m, 1H, H-6), 5.09-5.15 (m, 2H, H-10), 5.53 (dd, $J = 15.3, 7.8$ Hz, 1H, H-7), 6.18 (m, 1H, H-8); 6.26 (m, 1H, H-9); ^{13}C NMR (125 MHz): 76.4 (C-4), 80.7 (C-6), 118.0 (C-10), 82.8 (C-5), 130.3 (C-7), 134.6 (C-8), 136.3 (C-9), 149.6 (C-3).

(7*R*,6*R*,5*S*,4*S*,3*R*,8*R*)-8-*C*-Vinyl-4,5,6-tri-*O*-benzyl-hexahydro-1*H*-cyclopent[*c*]isoxazole **6**

To a solution of the dienoaldehyde **3** (370 mg, 0.84 mmol) in EtOH / pyridine mixture (35 mL; 6:1 v/v), hydroxylamine hydrochloride (70 mg, 1.00 mmol, 1.2 equiv.) was added and the mixture was stirred for 3 h at room temperature. Then it was worked-up as above, but the crude product was immediately without any purification dissolved in a mixture toluene/benzene (2 mL, 4:1 v/v), placed in a high pressure apparatus¹⁷ and kept for three days at 10 kbar. Then it was allowed to reach the normal pressure, the solvent was removed in vacuum, and the crude product was isolated by column chromatography (hexane – EtOAc, 9:1) to afford derivative **6** as an oil. Yield: 298 mg (78%). $[\alpha] -60.2$; HRMS: m/z calcd for $C_{29}H_{31}NO_4$ $[M+Na^+]$: 480.21453; found: 480.21407. 1H NMR (500 MHz) δ : 2.84 (ddd, $J = 9.6, 6.9, 2.0$ Hz, 1H, H-7), 3.78 (m, 1H, H-6), 3.83 (m, 1H, H-3), 3.90 (m, 1H, H-4), 3.96 (m, 1H, H-5), 4.38 (m, 1H, H-8), 4.59-4.83 (3x2H, O-CH₂Ph), 5.24 (m, 1H, H-10a), 5.26 (m, 1H, H-10b), 5.72 (ddd, $J = 16.3, 10.7, 4.5$ Hz, 1H, H-9); ^{13}C NMR (125 MHz) δ : 53.6 (C-7), 66.7 (C-3), 72.2, 72.3, 72.7 (3 x O-CH₂Ph), 84.4 (C-6), 85.3 (C-4), 85.8 (C-8), 86.5 (C-5), 117.6 (C-10), 134.7 (C-9). 1H NMR (500 MHz, C₆D₆) δ : 2.50

(ddd, $J = 9.3, 6.9, 1.6$ Hz, 1H, H-7), 3.35 (dd, $J = 9.3, 6.1$ Hz, 1H, H-3), 3.68 (m, 1H, H-6), 3.89 (m, 1H, H-4), 3.93 (m, 1H, H-5), 4.15 (d, $J = 11.8$ Hz, 1H, H-8), 4.86 (ddd, $J = 10.6, 1.6, 1.2$ Hz, 1H, H-10a), 4.95 (ddd, $J = 17.5, 1.6, 1.2$ Hz, 1H, H-10b), 5.36 (ddd, $J = 17.5, 10.6, 4.5$ Hz, 1H, H-9); ^{13}C NMR (125 MHz, C_6D_6) δ : 53.7 (C-7), 66.6 (C-3), 72.2, 72.3, 72.7 (3x O-CH₂Ph); 84.8 (C-6); 85.3 (C-8); 85.5 (C-4); 86.3 (C-5); 115.9 (C-10); 135.6 (C-9). Anal. Calcd for: $\text{C}_{29}\text{H}_{31}\text{NO}_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 75.88; H, 6.87; N, 3.09.

N*-Allyl-(7*R*,6*R*,5*S*,4*S*,3*R*,8*R*)-8-*C*-Vinyl-4,5,6-tri-*O*-benzyl-hexahydro-1*H*-cyclopent[*c*]isoxazole **8*

To a solution of oxazoline **6** (175 mg, 0.38 mmol) in MeCN (20 mL) containing potassium carbonate (150 mg), allyl bromide (0.3 mL, 3.8 mmol, 10 equiv.) was added and the mixture was boiled under reflux for 24 h. TLC analysis (hexane – EtOAc, 3:1) indicated disappearance of the starting material and formation of new less polar product. The mixture was partitioned between EtOAc (20 mL) and water (20 mL), the organic phase was separated, and the aqueous one extracted with EtOAc (20 mL). Combined organic solutions were washed with water, brine, dried, and concentrated, and the product was isolated by column chromatography (hexane – EtOAc, 3:1) to afford compound **8** (125 mg, 0.25 mmol, 65%). $[\alpha]_D^{25} +7.0$; HRMS: m/z calcd for: $\text{C}_{32}\text{H}_{35}\text{NO}_4$ $[\text{M}+\text{Na}^+]$: 520.24583; found: 520.24612. ^1H NMR (500 MHz) † δ : 2.81 (m, 1H, H-7), 3.95 (m, 1H, H-3), 5.15-5.26 (m, 4H, H-10 and H-13), 5.84-5.98 (m, 2H, H-9 and H-12); ^{13}C NMR (125 MHz) δ : 55.38 (C-7), 61.34 (C-11), 72.87 (C-3), 118.38, 118.57 (C-10, C-13), 133.75, 136.80 (C-9, C-2). Anal. Calcd for: $\text{C}_{32}\text{H}_{35}\text{NO}_4$: C, 77.24; H, 7.09; N, 2.81. Found: C, 77.29; H, 7.10; N, 2.82.

Synthesis of tricyclic derivative **9 by RCM reaction**

To a solution of the diolefin **8** (22.5 mg, 0.045 mmol) in CH_2Cl_2 (15 mL) under an argon atmosphere, the first generation Grubbs' catalyst (4 mg) was added and the mixture was boiled under reflux for 8 hours. After this time TLC (hexane – EtOAc, 3:1) indicated disappearance of the starting material and formation of new more polar product. The mixture was cooled to room temp., the solvent was removed in vacuum, and the residue was purified by column chromatography (hexane – EtOAc 10:1) to afford pure **9** as an oil

† For numbering of the skeleton of **8** and **9** see Scheme 2.

(21 mg, 0.044 mmol, 97%). HRMS: m/z calcd for: $C_{30}H_{31}NO_4$ $[M+Na^+]$: 492.21453; found: 492.21539. NMR (600 MHz) δ : 2.90 (ddd, $J = 18.6, 3.6, 1.9$ Hz, 2H, H-11), 3.04 (~t, $J = 8.4$, 1H, H-7), 3.45 (m, 1H, H-3), 3.69 (~t, $J = 8.0$, 1H, H-6), 3.86 (m, 1H, H-4), 3.88 (m, 1H, H-5), 4.01 (d, $J = 4.8$ Hz, 1H, H-8), 5.44 (ddd, $J = 10.0, 3.3, 1.9$ Hz, 1H, H-10), 5.95 (m, 1H, H-9); ^{13}C NMR (150 MHz): 56.23 (C-11), 60.90 (C-7), 82.69, 86.25, 87.55 (C-4, C-5, C-6), 120.91 (C-10), 130.32 (C-9).

***N*-Benzyl-(7*R*,6*R*,5*S*,4*S*,3*R*,8*R*)-8-*C*-vinyl-4,5,6-tri-*O*-benzyl-hexahydro-1*H*-cyclopent[*c*]isoxazole 10**

The bicyclic derivative **6** (75 mg, 0.16 mmol) was dissolved in MeCN (25 mL) to which potassium carbonate (100 mg) and benzyl bromide (0.2 mL, 1.6 mmol) were added and the mixture was boiled under reflux for 6 h. After that time TLC (hexane – EtOAc, 3:1) indicated disappearance of the starting material and formation of less polar product. Solvent was removed in vacuum and the residue partitioned between water (5 mL) and EtOAc (10 mL). The organic phase was separated, washed with water, brine, dried and concentrated, and the product was purified by column chromatography (hexane – EtOAc, 10:1) to afford **10** (65 mg, 0.12 mmol, 75%). $[\alpha]_D -6.5$; HRMS: m/z calcd for: $C_{36}H_{37}NO_4$ $[M+Na^+]$: 570.26148; found: 570.26203. NMR (500 MHz) δ : 2.81 (m, 1H, H-7), 3.60 (dd, $J = 9.3, 5.6$ Hz, 1H, H-3), 4.10 (m, 1H, H-6), 4.22 (m, 1H, H-4), 4.31 (t, $J = 6.6$ Hz, 1H, H-5), 4.46 (m, 1H, H-8), 5.20 (d, $J = 10.3$ Hz, 1H, H-10a), 5.30 (d, $J = 17.1$ Hz, 1H, H-10b), 5.90 (ddd, $J = 17.1, 10.3, 7.3$ Hz, 1H, H-9); ^{13}C NMR (125 MHz) δ : 55.9 (C-7), 73.4 (C-3), 83.9 (C-4), 85.3 (C-8), 85.9 (C-6), 90.1 (C-5), 117.4 (C-10), 137.5 (C-9).

Reaction of the oxime **4 with benzyl chloride**

To a solution of oxime **4** (48 mg, 0.11 mmol) in EtOH (10 mL) containing EtONa (100 mg) benzyl chloride (0.15 mL, 0.13 mmol) was added and the mixture was stirred at room temp. for 2 h. Then it was concentrated under reduced pressure and the residue was partitioned between water (15 mL) and EtOAc (15 mL). The organic phase was separated, washed with water, dried and concentrated, and the residue was purified by column chromatography (hexane – EtOAc, 4:1) to afford benzylated oxazoline **10** (10 mg, 0.018 mmol, 16%; identical in all respect with the compound prepared by benzylation of **6**) and the mixture of geometrical isomers of oxime **4a** (34 mg, 0.062 mmol, 56%) in the ratio 4:1 (detected by integration of signals H5 occurring at δ : 3.55 and 3.76 ppm).

In the NMR spectra of this mixture, the signals of the major stereoisomer were consistent with analogous data recorded for pure *N*-benzylated oxime obtained from reaction of **3** with BnO-NH₂. Selected signals for the minor isomer: ¹H NMR (500 MHz) δ: 3.75 (dd, *J* = 7.6, 2.9 Hz, 1H, H-7), 4.20 (m, 1H, H-8), 5.47 (m, 1H, H-1), 6.14 (m, 1H, H-2), 6.22 (m, 1H, H-9), 6.90 (d, *J* = 5.8, 1H, H-3); ¹³C NMR (125 MHz) δ: 72.2, 81.1, 81.6 (C-4, C-5, C-6), 118.0 (C-10), 130.3, 134.7, 136.3 (C-7, C-8, C-9), 152.3 (C-3).

Reaction of the dienoaldehyde **3** with *N*-benzyl-hydroxylamine

To a solution of the dienoaldehyde **3** (240 mg, 0.54 mmol) in CH₂Cl₂ (50 mL), *N*-benzyl-hydroxylamine (103 mg, 0.65 mmol, 1.2 equiv.) and magnesium sulfate (500 mg.) were added, and the mixture was stirred till disappearance of the starting material (10 h; TLC monitoring in hexane – EtOAc, 3:1). Solvent was removed in vacuum, and the residue partitioned between EtOAc (50 mL) and water (50 mL). The organic solution was separated, washed with water, brine, dried and concentrated, and the crude product was purified by column chromatography (hexane – ethyl acetate, 10:1) to afford only the bicyclic derivative **10** (identical in all respect with **10** prepared from **6** (193 mg, 0.42 mmol, 78%).

Attempts of cyclization of **4a** under high pressure

The *O*-protected oxime **4a** (one isomer obtained in the reaction of **3** was dissolved in a mixture toluene/benzene (2 mL, 4:1 v/v), placed in a high pressure apparatus, and kept for three days at 10 kbar. After this time no product was formed; only unreacted oxime was recovered (TLC and NMR analysis).

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