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Diastereocontrol in the Intramolecular Cycloadditions of 2-Substituted-*erythro*-3,4-isopropylidenedioxyhex-5-enenitrile Oxides

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Abstract: The influence of the 2-substituent on the diastereoselectivity of the intramolecular cycloadditions in a series of 2-substituted-*erythro*-3,4-isopropylidene-dioxyhex-5-enenitrile oxides, generated *in situ* from selected sugar derivatives, was examined.

Keywords: *Carbohydrates; Nitrile oxides; Cycloadditions; Isoxazolines; Diastereoselection*

Since the isolation of the naturally occurring aminocyclopentitols *allosamidin*, *mannostatins A* and *B* and *trehazolin*, which show specific inhibition against *chitinase*, *α-D-mannosidase* and *trehalase*, respectively, intensive work has been made on their total synthesis and several new analogues have been prepared.[1] Furthermore, enantiomerically pure aminocyclopentitols are intermediates in the synthesis of carbocyclic nucleosides.[2] Some years ago, we reported the synthesis of cyclopentylamine **1** in enantiomerically pure form, precursor of carbocyclic nucleosides, such as *noraristeromycin* and *neplanocin A*[3,4] (Figure 1).

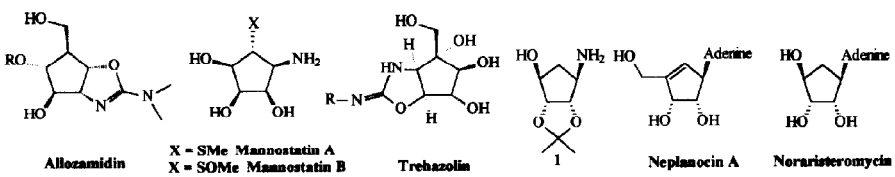

Figure 1

Our continuing interest in the synthesis of carbocycles from carbohydrates[5] prompted us to investigate the potential synthesis of new enantiomerically pure aminocyclopentitols by intramolecular nitrile oxide cycloadditions in suitable sugar derivatives and further ring opening of the resulting isoxazoline. There are two general ways in order to effect such a cleavage:[6] conversion to hydroxyketones, usually by Raney nickel hydrogenation, and reduction to aminoalcohols, usually by $LiAlH_4$. However, to the best of our knowledge only the first of them has been applied in the synthesis of cyclitols and aminocyclitols,[1,7] including the total syntheses of *allosamidin*[8] and *trehazolin*.[9] In order to check the possibility of preparing aminocyclopentitols with an exocyclic hydroxymethyl group by applying the $LiAlH_4$ method directly to fused isoxazolines, we

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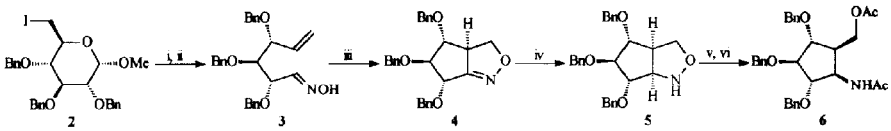
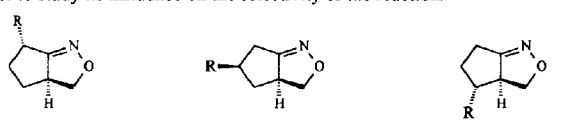
prepared cycloadduct **4** from *D*-glucose according to the general literature method (Scheme 1).[9] Different protective groups, however, were used to prevent deprotection or elimination in the subsequent reduction step. Compound **4** was prepared from **2** as a single diastereoisomer in three steps: ring opening according to Vasella's method,[10] conversion of the resulting aldehyde to oxime **3**[11] and oxidation with NaOCl. The overlapping proton signals in **4** did not allow us to determine by NMR methods whether the configuration of the new chiral center was identical to that observed when different protective groups were used.



Scheme 1 Reagents and conditions: i. Zn, EtOH 95%, reflux, 2 h, ii. $NH_2OH{\cdot}HCl$, MeONa or Na_2CO_3, MeOH, 20°C, 12 h. iii. NaOCl 5%, Et_3N, CH_2Cl_2, 0°C to 20°C, 8 h, 35% yield from **2**. iv. $NaBH_3CN$, AcOH(gl.), 0°C, 15 min, 96%. v. H_2, Raney Ni, $MeOH/H_2O$, 20°C, 2 h. vi. Ac_2O, pyridine, DMAP, 0°C to 20°C, 12 h, 95% yield from **5**.

After several unsuccessful attempts for N-O bond cleavage in **4** ($LiAlH_4$, Raney Ni, Pd/C and H_2, *etc.*), we applied an indirect method, that is hydrogenation of the C=N double bond with $NaBH_3CN$[12] to **5** and further N-O bond cleavage by H_2 over Raney Ni to give, after acetylation, the protected aminocyclopentitol **6**, in excellent overall yields. The hydrogenation of the C=N double bond of **4** was highly diastereoselective and only compound **5** was isolated, with spectral and analytical data identical to those reported in the literature,[10,11] confirming the configuration of the newly formed stereocenters in **4** and **5**. The successful and high yielding conversion of **4** to **6** shows a new way for the synthesis of aminocyclopentitols from sugars by applying the intramolecular nitrile oxide method.

From a synthetic point of view, the diastereocontrol induced by the polysubstitution of the sugar framework is an important feature in the intramolecular cycloadditions. The influence of only one substituent on the diastereoselectivity of the intramolecular cycloaddition process in hex-5-enenitrile oxides has been studied in detail and the general conclusion is that substituents at 2- or 4-positions favor the *exo*-cycloadducts, whereas the 3-substituents favor the *endo*-products (Figure 2).[6,13] However, the coexistence of more than one substituent on the carbon skeleton of hex-5-enenitrile oxide makes the application of these rules not so obvious. We focused our attention in the study of the diastereoselectivity of the intramolecular cycloadditions of 2-substituted-*erythro*-3,4-isopropylidenedioxyhex-5-enenitrile oxides, which vary in the nature of the 2-substituent and the relative configuration of the 2-chiral center. Both common methods for the generation of nitrile oxides,[14] namely oxidation of aldoximes and dehydration of primary nitroparaffins were used. All nitrile oxide precursors were prepared from *D*-ribose. In one case we prepared a precursor with a *cis*-disubstituted double bond, in order to study its influence on the selectivity of the reaction.

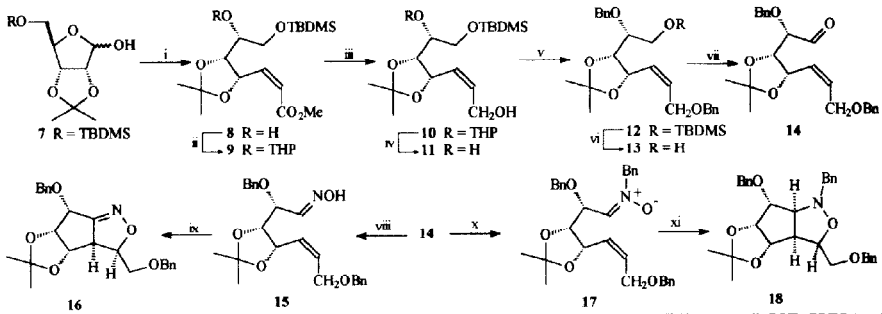


***Exo*-preference** ***Endo*-preference** ***Exo*-preference**

Figure 2

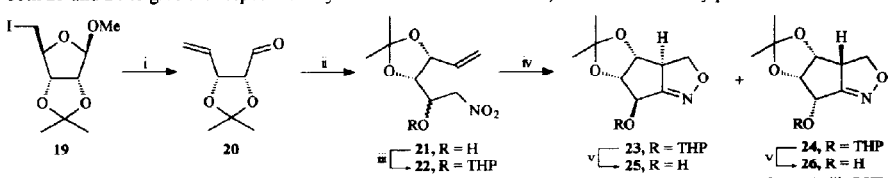
The oxime **15** (Scheme 2) was used as a nitrile oxide precursor, which under the conditions applied in the case of **3** gave the cycloadduct **16**, again as a single diastereomer in good overall yield. For comparison, the respective nitrone **17** gave cycloadduct **18** in 60% yield from **13**. The aldehyde **14**, precursor of the dipoles, was

prepared *in situ* from alcohol **13**, which in turn was prepared from *D*-ribose[5a] according to reaction sequences outlined in Scheme 2. Wittig olefination of the known ribose derivative **7**[15] gave the alkene **8** predominantly in the *Z*-form,[16] and further reduction of the ester group with DIBAL-H afforded compound **11** in poor yield (19%). For this reason the free hydroxyl group was protected and then the reduction proceeded smoothly to give after benzylation of both free hydroxyl groups[17] compound **12** in 52% yield from **9**. Finally, desilylation of the primary hydroxyl group led to the desired compound **13**; Swern oxidation of it gave the aldehyde **14**, which was further used without isolation.



Scheme 2 Reagents and conditions: i. $Ph_3P{=}CHCO_2Me$, $PhCO_2H$ (cat.), CH_2Cl_2, reflux, 36 h, 95%, *Z*:*E* ca. 11:1. ii. DHP, PPTS (cat.), CH_2Cl_2, 20°C, 24 h, 97%. iii. DIBAL-H, Et_2O, 0°C, 3 h. iv. $MgBr_2$, Et_2O, 20°C, 12 h. v. NaH, DMF, 0°C, 15 min, then BnCl, 0°C to 20°C, 14 h, 52% from **9**. vi. TBAF, THF, 0°C to 20°C, 90 min, 85%. vii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -55°C to 20°C. viii. $NH_2OH{\cdot}HCl$, MeONa or Na_2CO_3, MeOH, 20°C, 12 h. ix. NaOCl 5%, Et_3N, CH_2Cl_2, 0°C to 20°C, 8 h, 39% from **13**. x. BnNHOH·HCl, Na_2CO_3, EtOH 95%, 20°C, 12 h. xi. $CHCl_3$, reflux, 2 h, 60% from **13**.

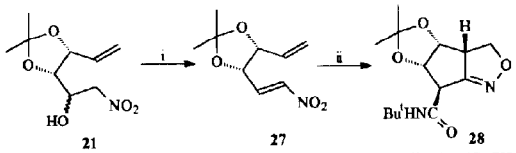
The inseparable mixture of diastereomeric primary nitro compounds **21** (Scheme 3), was prepared from the *D*-ribose derivative **19** in two steps, namely conversion of **19** to aldehyde **20** upon treatment with activated Zn in refluxing ethanol[3a] and further addition of nitromethane in a typical Henry reaction. The hydroxyl group in **21** was then protected as THP ether[17] and **22** were converted to the corresponding nitrile oxides by standard procedures. The intermediately formed nitrile oxides spontaneously added to the double bond to give products **23** and **24**, isolated chromatographically in 44 and 22% yield, respectively, as single cycloadducts from each C-2 diastereoisomer of **21**. To overcome potential problems in the assignement of the stereochemistry of the products raised by the presence of the stereogenic center in the THP group, this group was then removed from both **23** and **24** to give the respective bicyclic isoxazolines **25** and **26**, in enantiomerically pure form.



Scheme 3 Reagents and conditions: i. Zn, EtOH 95%, reflux, 2 h. ii. CH_3NO_2, EtONa, EtOH, 20°C, 24 h, 71% from **19**. iii. DHP, PPTS (cat.), CH_2Cl_2, 20°C, 24 h, 88%. iv. PhNCO, Et_3N, PhH, 72 h, 20°C, 66% (**23**:**24** 2:1). v. $MgBr_2$, Et_2O, 20°C, 12 h, 53% for **25** and 75% for **26**.

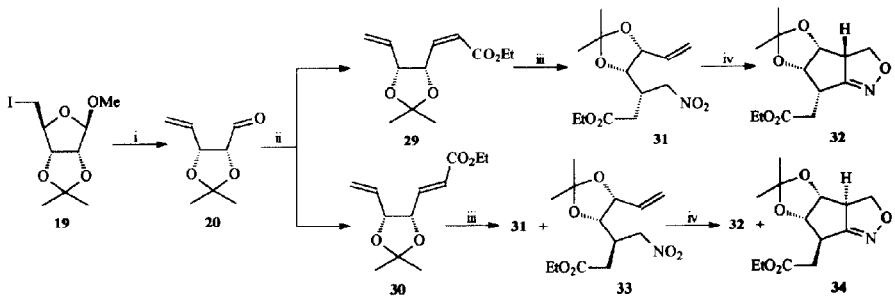
It is known that nitrile oxides can be prepared by adding isocyanides to the nitroalkenes, which can then be added to dipolarophiles.[18] Thus, addition of *tert*-butyl isocyanide to nitroalkene **27**, prepared from **21**

(Scheme 4) by standard procedures, afforded the fused isoxazoline **28** in enantiomerically pure form; no other stereoisomer was isolated.



Scheme 4 Reagents and conditions: i. Ac_2O, pyridine, DMAP, 0°C to 20°C, 48 h, 73%. ii. t-BuNC, CH_3CN, reflux, 6 h, 32%.

In the last example (Scheme 5), the nitrile oxide precursors **31** and **33** were prepared from **19** in three steps: conversion of **19** to the aldehyde **20**, further Wittig olefination with $Ph_3P{=}CHCO_2Et$ and finally Michael addition[19] of nitromethane. The *Z*-olefin **29** gave exclusively the nitrile oxide precursor **31**, whereas the *E*-isomer **30** afforded a *ca.* 5:1 inseparable mixture of **31** and **33**. At this stage, it was not easy to determine the configuration of the newly formed chiral center in **31** and **33**, a problem left to be solved after cyclisation. Both **31** and **31/33** were cyclised as in the case of **22**, to give in good yields **32** and mixture of **32** and **34**, respectively, which in the last case were easily separated chromatographically. The cycloaddition process was again highly distereoselective and only one product was isolated from each precursor.



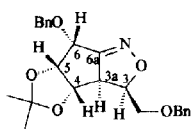
Scheme 5 Reagents and conditions. i. Zn, EtOH 95%, reflux, 2 h. ii. $Ph_3P{=}CHCO_2Et$, EtOH, 20°C, 24 h, 80% from **19** (**29**:**30** *ca.* 2:1). iii. CH_3NO_2, TBAF, THF, 20°C, 66% from **29** and 73% from **30** (**31**:**33** *ca.* 5:1), 24 h. iv. PhNCO, Et_3N, PhH, 72 h, 20°C, 72% from **31** and 79% from **31/33** (**32**:**34** *ca.* 5:1).

The configurations of the newly formed stereocenters in **16**, **18**, **25**, **26**, **28**, **32** and **34** were deduced from the ^{1}H-NMR coupling constants and the observed NOE enhancements. The proton spectral assignment was made by successive proton decouplings starting from an unequivocally assigned signal (Table 1). Several solvents ($CDCl_3$, C_6D_6 or their mixtures) were used in this process in order to differentiate as many signals as possible.

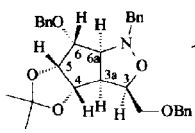
Thus, the 3a-H chemical shift in the ^{1}H-NMR spectrum of compound **16** appeared at δ 4.11 as a doublet of doublets with J = 11.6 and 2.1 Hz, which indicate *cis* and *trans* arrangements of the adjacent 3-H and 4-H, respectively. The large coupling constant was removed by double resonance at 3-H and the small one by irradiation at 4-H. The *cis* relative stereochemistry of 3a-H and 3-H was further confirmed by the large mutual NOE enhancements (19% of 3a-H upon saturation of 3-H and 18% of 3-H upon saturation of 3a-H). Although the *trans* disposition of 3a-H and 4-H was not supported by direct NOE experiments, because of the overlapping 4-H, 5-H and methylene signals, the rather moderate enhancement (7%) of 3a-H observed upon irradiation of the multiplet containing 4-H is compatible with that. The same stereochemistry was also

established for the analogous nitrone cycloadduct **18**. The 3a-H of compound **18** appeared at δ 3.10 as a triplet with J = 9.2 Hz, implying two *cis* connections with large almost equal coupling constants ($J_{3a,3}$ and $J_{3a,6a}$) and one *trans* connection with approximately zero coupling constant ($J_{3a,4}$). The so evidenced *trans* connectivity of 3a-H and 4-H is in accordance with the low NOE enhancements induced between them (3% of 3a-H on saturation of 4-H and 6% of 4-H upon saturation of 3a-H). The *cis* relative configuration of 3a-H and 6a-H was further supported by the large NOE enhancements observed between them (16% of 3a-H upon saturation of 6a-H and 8% of 6a-H on saturation of 3a-H). Unfortunatelly, no NOE data were available between 3a-H and 3-H, because of the overlapping of 3-H with other signals in all solvents tested. However, additional evidence for the proposed structure came from the high enhancement (16%) induced on 4-H upon saturation of 3-CH_2OBn. As molecular models showed, these two groups are in close proximity only when they both are on the concave side of an *exo* cycloadduct, as in structure **18**.

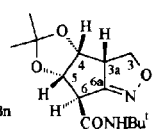
Table 1. *Selected ^{1}H-NMR assignments (ppm, Hz) of cycloadducts **16**, **18**, **25**, **26**, **28**, **32** and **34** prepared.*



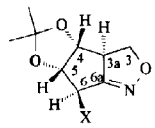
16



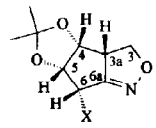
18



28



25. X = OH
34. X = CH_2CO_2Et



26. X = OH
32. X = CH_2CO_2Et

Compd	3-H	3a-H	4-H	5-H	6-H	$J_{3a,4}$	$J_{4,5}$	$J_{5,6}$
16	4.84	4.11	4.62	4.62	4.35	2.1	-	4.7
18	4.40	3.10	4.49	4.32	3.90	0	5.2	5.2
25	4.08, 4.74	4.08	4.45	4.74	4.60	2.4	6.8	3.6
26	4.40, 4.46	3.73	4.60	4.80	4.75	5.6	5.6	5.6
28	4.32, 4.49	4.11	4.67	5.26	3.40	5.5	5.5	0
32	4.27, 4.43	3.81	4.61	5.05	3.19	5.9	5.9	5.9
34	3.95, 4.70	3.95	4.47	4.70	3.26	4.0	6.8	3.5

The almost equal coupling constants $J_{3a,4} = J_{4,5} = J_{5,6}$ = 5.6 Hz in compound **26** are consistent with a *cis* disposition among these protons compared with the stereoisomer **25**, in which the smaller coupling constants ($J_{3a,4}$ = 2.4 Hz and $J_{5,6}$ = 3.6 Hz) indicate a *trans* relationship of these pairs of protons. For 3a-H and 4-H of **26** the *cis* connectivity was also corroborated by the considerable NOE enhancements (13% for 3a-H upon saturation of 4-H and 12% for 4-H upon saturation of 3a-H). No NOE evidence was possible for the other pairs in question because of the overlapping signals. However, the small NOE enhancement between 4-H and OH observed only in the isomer **25** further supports that in this case the OH and 4-H are on the same side of the ring.

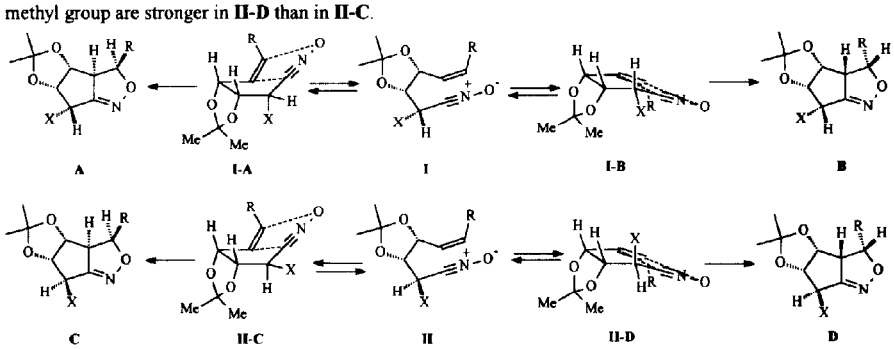
The value $J_{3a,4}$ = 5.5 Hz for compound **28** indicates a *cis* geometry for 3a-H and 4-H, which is also supported by large NOE enhancements (18% of 4-H upon saturation of 3a-H and 12% of 3a-H upon saturation of 4-H). The coupling constant $J_{5,6}$ has a value close to zero, which implies a *trans* relationship between 5-H

and 6-H. The induced NOE between 5-H and 6-H is significant but sufficiently smaller than that of 3a-H and 4-H (8% of 6-H upon saturation of 5-H and 7% of 5-H upon saturation of 6-H).

In compound **32** the values $J_{3a,4}$ = 5.9 Hz and $J_{5,6}$ = 5.9 Hz imply a *cis* relationship between them, which is in agreement with the considerable observed mutual NOE enhancements (16% and 11% of 3a-H and 4-H upon saturation of 4-H and 3a-H respectively, 16% and 13% of 6-H and 5-H upon saturation of 5-H and 6-H, respectively). Although NOE measurements were not obtainable in stereoisomer **34**, because of the overlapping of the signals, the smaller values of both coupling constants ($J_{3a,4}$ = 4.0 Hz and $J_{5,6}$ = 3.5 Hz) imply *trans* relationship of the corresponding protons.

It should be mentioned that the chemical shift of the two 3-H protons could be also used as a basis for differentiation of adducts **26**, **28** and **32** with *endo* stereochemistry from **25** and **34** with *exo* stereochemistry. In the former case, the chemical shifts of these protons show smaller differences and appear at δ 4.27-4.49, while in the last case, this difference is remarkably larger and one of the 3-H appears at δ 3.95-4.08 and the other at δ 4.70-4.74.

As already mentioned, with the exception of cycloadduct **4**, all intermediately formed hex-5-enenitrile oxides have a common feature in their structures (an acetonide group near the double bond) and substitution at α-carbon relative to nitrile oxide group (which varies in nature and relative configuration). In isoxazolines **23** (**25**), **24** (**26**), **32** and **34** the α-substituent lies in endo-position. The interpretation of the transition states of cycloadditions studied (Scheme 6, R = H) could explain the observed diastereoselectivity in these cases.[6,13,20] When the substituent X (OTHP, CH_2CO_2Et) has *erythro* relative configuration **I**, the almost linear nitrile oxide group and the restricted flexibility of carbon tether due to the acetonide group strongly favor the transition state **I-B**, because of the strong steric interactions between X and one methyl of the acetonide group in **I-A**. On the other hand, the *threo* substituent in **II** favors the transition state **II-C** against **II-D**, since now the substituent X is far from the acetonide group in both cases, while the steric interactions between the vinylic protons and the methyl group are stronger in **II-D** than in **II-C**.



Scheme 6

In contrast, isoxazoline **16** and isoxazolidine **18** have the 2-erythro-substituent in exo-positions. It is apparent here that the steric interactions between the R group (CH_2OBn) and the acetonide group in **I-B** make the **I-A** transition state preferred, which leads to the *exo*-adduct.[21] The *exo*-adduct **18** is additionally favored by the non-linear structure of nitrone **17**, which allows the transition state to adopt a geometry similar to **I-A**, which minimizes the interactions among the substituents, even in case of R = H.

The isoxazoline **28** has also the 2-threo-substituent in exo-position, in contrast to compounds **25** and **34**. It is likely here that the bulkiness of the *t*-butyl group together with the planar structure of the amidic H-N-C=O group brings the C-2 substituent into close proximity with the reacting groups in transition state **II-C**, favoring the transition state **II-D**, which in that case minimizes the steric interactions and leads to the formation of **28**.

In conclusion, we have shown in this study that the intramolecular cycloadditions in a series of 2-substituted-3*O*,4*O*-isopropylidene-*erythro*-3,4-dihydroxyhex-5-enenitrile oxides, generated *in situ* from selected sugar derivatives, are highly diastereoselective and only one cycloadduct was isolated in all reactions performed. Furthermore, the configuration of the 2-chiral center as well as the nature of the C-2 substituent are crucial and determine the selectivity of the reactions we studied. It was also demonstrated in one case that the fused isoxazoline ring thus generated could be converted to an aminocyclopentitol in two steps and high yield. In the light of these findings, our attempts are now focused in the total synthesis of aminocyclopentitols such as *trehazoline* and its analogues as well as in the synthesis of new carbocyclic nucleosides. Work in this direction is in progress.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. Microanalyses were performed on a Perkin-Elmer 2400-II Element analyzer and HRMS were obtained on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or IONSPEC FTMS spectrometer (MALDI) with DHB as matrix. The ^{1}H- and ^{13}C-NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane as internal standard.

(3aR,4R,5S,6S)-4,5,6-Tris(benzyloxy)-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole (4). To a solution of **2** (0.574 g, 1 mmol) in 95% EtOH (10 ml) activated Zn (0.654 g, 10 mmol)[10] was added and the mixture was refluxed with vigorous stirring under argon atmosphere until the complete disappearance of **2**. The mixture was cooled to room temperature, the solid was filtered off and the solvent was evaporated. The resulting aldehyde and $NH_2OH{\cdot}HCl$ (0.118 g, 1.7 mmol) were dissolved in absolute MeOH (10 ml), Na_2CO_3 (0.106 g, 1.7 mmol) or MeONa (0.081 g, 1.5 mmol) was added and the mixture was stirred at room temperature for 12 h, under argon atmosphere. The reaction mixture was then partitioned between CH_2Cl_2 (50 ml) and H_2O (25 ml), the organic layer was dried and the solvent was evaporated. The resulting oxime **3**[11] was dissolved in CH_2Cl_2 (10 ml), the solution cooled at 0 °C and commercial "bleach" (~5% NaOCl, 2 ml) and Et_3N (3 drops) were added. The mixture was stirred vigorously for 8 h and then CH_2Cl_2 (100 ml) and H_2O (40 ml) were added. The organic layer was separated, washed with brine (50 ml), dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on silica gel with EtOAc/hexane 1:7 as the eluent to give **4** as an oil (0.152 g, 35% from **2**): $[\alpha]_D$ +12.2 (*c* 0.6, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 3.66 (t, 1 H, *J* = 6.5 Hz), 3.83 (m, 1 H), 4.34-4.73 (m, 10H), 7.25-7.36 (m, 15H); ^{13}C-NMR($CDCl_3$) δ 55.9, 71.3, 72.4, 72.5, 74.2, 75.0, 84.8, 93.2, 127.3, 127.6, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 136.9, 137.5 (two peaks), 160.4; HRMS (FAB) calcd ($C_{27}H_{27}NO_4Na$) 452.1838 (M+Na), found 452.1830, σ 1.8 ppm.

(1R,5R,6R,7S,8S)-6,7,8-Tri-O-benzyl-3-oxa-2-azabicyclo[3.3.0]octane-6,7,8-triol (5). To a cold (0 °C) solution of **4** (0.212 g, 0.5 mmol) in glacial AcOH (2.5 ml) $NaBH_3CN$ (0.126 g, 2 mmol) was added and the mixture was stirred at 0 °C for 15 min. Then, CH_2Cl_2 (50 ml) and saturated aqueous $NaHCO_3$ (10 ml) were

added under vigorous stirring. When the gas release stopped, the organic layer was separated, washed with brine (20 ml), dried over Na_2SO_4, the solvent was evaporated and the residue was chromatographed on silica gel with EtOAc/hexane 1:3 as the eluent to give 0.208 g of **5** (96%): m.p. 104-106 °C, lit.[10,11] 104-106 and 108 °C; HRMS (FAB) calcd ($C_{27}H_{29}NO_4Na$) 454.1994 (M+Na), found 454.1984, σ 2.2 ppm.

(1R,2S,3S,4R,5R)-4-Acetamido-5-acetoxymethyl-1,2,3-tri-O-benzylcyclopentane-1,2,3-triol (6). Raney Ni was added to a solution of **5** (0.086 g, 0.2 mmol) in MeOH (2 ml) and the mixture was stirred under H_2 atmosphere at room temperature for 2 h. The catalyst was then filtered off, washed with THF (15 ml) and the combined organic layer was concentrated. The resulting oil was dissolved in dry pyridine (3 ml) and DMAP (0.010 g, 0.08 mmol) was added. The solution was cooled to 0 °C, acetic anhydride (0.09 ml) was added dropwise under argon atmosphere and was allowed to stir at room temperature for 12 h. Ice/water (10 ml) was then added, the mixture was extracted with CH_2Cl_2 (30 ml) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 ml) and brine (10 ml) and dried with Na_2SO_4. The solvent was then evaporated and the oil precipitated was crystallized upon addition of Et_2O/hexane to give **6** (0.099 g, 95%): m.p. 111-112 °C; $[\alpha]_D$ +63.5 (*c* 0.32, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.88 (s, 3 H), 1.97 (s, 3 H), 2.74 (m, 1 H), 3.71 (t, 1 H, *J* = 3.2 Hz), 3.78 (dd, 1 H, *J* = 7.3, 3.2 Hz), 3.97 (m, 1 H), 4.05 (dd, 1 H, *J* = 11.2, 4.7 Hz), 4.24 (dd, 1 H, *J* = 11.2, 6.3 Hz), 4.46 (d, 1 H, *J* = 10 Hz), 4.49 (d, 1 H, *J* = 10 Hz), 4.51 (d, 1 H, *J* = 11 Hz), 4.57 (d, 1 H, *J* = 11 Hz), 4.62 (d, 1 H, *J* = 12 Hz), 4.72 (d, 1 H, *J* = 12 Hz), 5.28 (s, 1H), 5.65 (d, 1 H, *J* = 8.2 Hz), 7.25-7.35 (m, 15 H); ^{13}C-NMR($CDCl_3$) δ 20.8, 23.3, 44.0, 53.0, 62.0, 71.3, 71.8, 72.1, 83.7, 84.5, 88.0, 127.75, 127.81, 127.9, 128.0, 128.36, 128.41, 128.48, 137.52, 137.85, 137.91, 169.6, 170.7. Anal. Calcd for $C_{31}H_{35}NO_6$: C, 71.93; H, 6.82; N, 2.71. Found: C, 72.00; H, 6.61; N, 3.00.

Methyl (4S,5S,6R)-(Z)-6-hydroxy-7-t-butyldimethylsilyloxy-4,5-isopropylidenedioxyhept-2-enoate (8). To a solution of 7[15] (2.98 g; 10 mmol), $PhCO_2H$ (0.056 g; 0.5 mmol) and Ph_3P=$CHCO_2Me$ (5.025 g; 18 mmol) were added and the mixture was refluxed under argon atmosphere for 36 h. The reaction mixture was then cooled and Et_2O was added until crystallization of Ph_3PO was started. The mixture was allowed to stand at room temperature for 20 h and the solid Ph_3PO was filtered off and washed with Et_2O. The combined filtrates were concentrated on a rotary evaporator and the residue was chromatographed on a column of silica gel using Et_2O/CH_2Cl_2/hexane (1:4:18) as the eluent to give 3.152 g of **8** and 0.285 g of its *E*-congener as oils. For **8**: $[\alpha]_D$ +70.6 (*c* 1, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.37 (s, 3 H), 1.47 (s, 3 H), 2.71 (d, 1 H, *J* = 4.3 Hz), 3.73 (s, 3H), 3.57-3.83 (m, 3 H), 4.26 (t, 1 H, *J* = 7.3 Hz), 5.77 (t, 1 H, *J* = 7.4 Hz), 5.99 (d, 1 H, *J* = 11.6 Hz), 6.31 (dd, 1 H, J = 11.6, 7.4 Hz); ^{13}C-NMR($CDCl_3$) δ −5.5, 18.3, 25.3, 25.8, 27.9, 51.5, 64.2, 69.9, 73.7, 77.9, 109.0, 121.7, 144.7, 166.4; HRMS (FAB) calcd ($C_{17}H_{32}O_6SiNa$) 383.1866 (M+Na), found 383.1869, σ 0.8 ppm.

Methyl (4S,5S,6R)-(Z)-6-(tetrahydropyran-2-yloxy)-7-t-butyldimethylsilyloxy-4,5-isopropylidenedioxyhept-2-enoate (9). To a solution of **8** (0.361 g; 1 mmol) in dry CH_2Cl_2 (10 ml) 3,4-dihydro-2*H*-pyran (0.084 g; 1 mmol) and PPTS (0.025 g; 0.1 mmol) were added and the mixture was stirred at room temperature under argon atmosphere for 24 h. Et_2O was then added (70 ml) and the organic phase was washed twice with brine (2x50 ml) and dried over Na_2SO_4. After evaporation of the solvent the residue was chromatographed on silica gel eluting with ethyl acetate/hexane 1:7 to give **9** (0.430 g; 97%) as a colorless oil (mixture of diastereoisomers): HRMS (FAB) calcd ($C_{22}H_{40}O_7SiNa$) 467.2441 (M+Na), found 467.2432, σ 1.9 ppm.

(2R,3S,4S)-(Z)-1-O-(t-Butyldimethylsilyl)-2,7-di-O-benzyl-4,5-O-isopropylidenehept-2-ene-1,2,3,4,7-pentol (12). To a stirred cold (0 °C) solution of **9** (2.225 g; 5 mmol) in dry Et_2O (50 ml), DIBALH 1M solution in hexanes (5 ml; 5 mmol) was added dropwise while the temperature was kept between –2 and +2 °C. MeOH

was then added (20 ml) to the cold solution and the mixture was stirred at 0 °C for 1 h. Et_2O was then added (200 ml) and the organic phase was washed with saturated aqueous potassium sodium tartrate (4x100 ml) and brine (2x50 ml) and dried over Na_2SO_4. The solvent was then evaporated to give 1.777 g of **10** in satisfactory purity, which was used in the next step without further purification. A solution of the above compound in dry Et_2O (100 ml) was added to a solution of $MgBr_2$ (15 mmol) in C_6H_6/Et_2O and the mixture was stirred vigorously at room temperature for 12 h under argon atmosphere. CH_2Cl_2 (300 ml) was subsequently added, the solution was washed with brine (2x50 ml) and dried over Na_2SO_4 to give after evaporation of the solvent **11** as a colorless oil, which was used in the next step without further purification: HRMS (FAB) cald ($C_{16}H_{32}O_5SiNa$) 355.1917 (M+Na), found 355.1927, σ=2.8 ppm. The above-obtained oil was dried *in vacuo*, dissolved in dry DMF (100 ml) and the solution was cooled to 0 °C. NaH 95% (1.265 g; 50 mmol) was added to this solution and the resulting suspension was vigorously stirred at 0 °C for 15 min and then $PhCH_2Cl$ (15 ml; 100 mmol) was added dropwise. The mixture was then allowed to warm at room temperature and stirred for 14 h. EtOH was subsequently added (CAUTION: hydrogen evolution!) at 0 °C and after 1 h the mixture was dissolved in CH_2Cl_2 (250 ml) and washed with water (4x100 ml). The organic layer was dried (Na_2SO_4), the solvent was evaporated in a rotavapor and the less volatile DMF and $PhCH_2Cl$ (excess) were distilled *in vacuo* (5-10 mmHg) at temperature <45 °C. The resulting red-brown residue was chromatographed on a column of silica gel eluted with hexane initially and then EtOAc/hexane 1:30 to give **12** as a colorless oil (1.340 g, 52% from **9**): $[\alpha]_D$ –30.2 (*c* 0.64, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 0.066 (s, 3 H), 0.069 (s, 3 H), 0.91 (s, 9 H), 1.33 (s 3 H), 1.46 (s, 3 H), 3.55 (ddd, 1 H, ΣJ = 17.3 Hz), 3.76 (dd, 1 H, J = 11.2, 5.2 Hz), 3.92 (ddd, 1 H, J = 12.1, 4.6, 1.5 Hz), 3.97 (dd, 1 H, J = 12.1, 2.2 Hz), 4.13 (ddd, 1 H, J = 11.2, 6.8, 1.3 Hz), 4.21 (dd, 1 H, J = 8.5, 6.3 Hz), 4.36 (d, 1 H, J = 11.1 Hz), 4.39 (d, 1 H, J = 11.1 Hz), 4.41 (d, 1 H, J = 11.3 Hz), 4.81 (d, 1 H, J = 11.3 Hz), 4.90 (dd, 1 H, J = 9.2 6.2 Hz), 5.68 (m, 1 H), 5.81 (m, 1 H), 7.22-7.33 (m, 10 H); ^{13}C-NMR($CDCl_3$) δ –5.4, 18.3, 25.4, 25.9, 28.0, 63.5, 65.9, 72.0, 72.2, 73.5, 76.5, 78.4, 108.6, 127.4, 127.5, 127.6, 127.8, 128.2, 128.25, 128.33, 130.5, 138.1, 138.7; HRMS (FAB) calcd ($C_{30}H_{44}O_5SiNa$) 535.2856 (M+Na), found 535.2836, σ 3.1 ppm.

(2R,3S,4S)-(Z)-2,7-Di-O-benzyl-4,5-O-isopropylidenehept-2-ene-1,2,3,4,7-pentol (13). Method A: To a cold (0 °C) solution of **12** (0.513 g; 1 mmol) in THF (10 ml) tetrabutylammonium fluoride (TBAF·$3H_2O$, 0.631 g; 2 mmol) was added and the mixture was allowed to warm at room temperature. The mixture was stirred for 90 min, CH_2Cl_2 (100 ml) was added and the solution was washed with water (2x50 ml) and dried (Na_2SO_4), the solvent was evaporated in a rotavapor and the residue was chromatographed on silica gel with EtOAc/hexane 1:4 as the eluent to give **13** as a colorless oil (0.340 g; 85%): $[\alpha]_D$ –7.6 (*c* 3, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.33 (s, 3 H), 1.45 (s, 3 H), 2.37 (br, 1 H), 3.51 (m, 1 H), 3.71-3.88 (m, 2 H), 3.95 (ddd, 1 H, J = 12.9, 5.1, 1.6 Hz), 4.12 (ddd, 1 H, J = 13.0, 6.9, 1.4 Hz), 4.24 (dt, 1 H, J = 6.4, 1.9 Hz), 4.37 (d, 1 H, J = 11.8 Hz), 4.39 (d, 1 H, J = 11.8 Hz), 4.42 (d, 1 H, J = 11.2 Hz), 4.56 (d, 1 H, J = 11.2 Hz), 4.95 (dd, 1 H, J = 8.1, 6.5 Hz), 5.66 (t, 1 H, J = 10.6 Hz), 5.77-5.89 (m, 1H), 7.22-7.33 (m, 10 H); ^{13}C-NMR($CDCl_3$) δ 25.0, 27.6, 61.1, 65.6, 71.2, 72.1, 73.4, 77.2, 77.4, 108.5, 127.38, 127.42, 127.5, 127.6, 127.7, 128.15, 128.18, 130.4, 137.7, 137.8; HRMS (FAB) calcd ($C_{24}H_{30}O_5Na$) 421.1991 (M+Na), found 421.1997, σ 1.4 ppm. Method B: To solution of **12** (0.513 g; 1 mmol) in THF (4 ml), water (4 ml) and acetic acid (12 ml) were added and the mixture was stirred at room temperature for 35 h. CH_2Cl_2 (100 ml) was subsequently added and the solution was washed repeatedly with saturated aqueous $NaHCO_3$ (CAUTION: CO_2 evolution!) and brine (50 ml) and dried over Na_2SO4. The solvent was then evaporated and the product was obtained as in Method A (0.312 g; 78%).

(3R,3aR,4S,5S,6R)-3-Benzyloxymethyl-6-benzyloxy-4,5-isopropylidenedioxy-3a,4,5,6,-tetrahydro-3H-cyclopent[c]isoxazole (16). A solution of dry DMSO (0.220 g; 2.8 mmol) in dry CH_2Cl_2 (0.8 ml) was added to

a solution of $(COCl)_2$ (0.14 ml; 1.5 mmol) in dry CH_2Cl_2 (3 ml) which had been cooled to –60 to –55 °C, under argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min before a solution of **13** (0.398 g; 1 mmol) in dry CH_2Cl_2 (1.2 ml) was added carefully during a period of 5 min, while the temperature was kept to –60 to –55 °C. The stirring was continued for 15 min and then Et_3N (0.85 ml; 6 mmol) was added at the same temperature. After another 10 min stirring at low temperature the mixture was allowed to warm to room temperature. CH_2Cl_2 (50 ml) was subsequently added and the solution was washed with saturated aqueous NaCl (2x30 ml). The organic layer was dried over Na_2SO_4, the solvent was removed on a rotary evaporator and the resulting aldehyde **14**, without further purification was dissolved in absolute MeOH (10 ml) and NH_2OH·HCl (0.118 g; 1.7 mmol) and Na_2CO_3 (0.106 g; 1.7 mmol) or MeONa (0.081 g; 1.5 mmol) were added. The mixture was stirred at room temperature for 12 h under argon atmosphere and then was partitioned between CH_2Cl_2 (50 ml) and H_2O (25 ml). The organic layer was concentrated and the residue was chromatographed on a column of silica gel with ethyl acetate/hexane as the eluent to give oxime **15** as mixture of (*Z,E*)-isomers.The oxime was then dissolved in CH_2Cl_2 (10 ml) and cooled to 0 °C. Aqueous 5% NaOCl (2 ml) and Et_3N (3 drops) were added and the mixture was vigorously stirred for 8 h. CH_2Cl_2 (100 ml) and H_2O (40 ml)were subsequently added, the organic layer was separated, washed with saturated aqueous NaCl (50 ml) and dried over Na_2SO_4. The solvent was then evaporated and the residue was chromatographed on a column of silica gel with ethyl acetate/hexane as the eluent to give **16** as a colorless oil: $[\alpha]_D$ –101.4 (*c* 0.64, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.32 (s, 3 H), 1.54 (s, 3 H), 3.58 (dd, 1 H, *J* = 11.1, 2.7 Hz), 3.64 (dd, 1 H, *J* = 11.1, 3.7 Hz), 4.11 (dd, 1 H, *J* = 11.6, 2.1 Hz), 4.35 (d, 1 H, *J* = 4.7 Hz), 4.44 (d, 1 H, *J* = 11.8 Hz), 4.58 (d, 1 H, *J* = 11.8 Hz), 4.62 (m, 2 H), 4.64 (d, 1 H, *J* = 12.2 Hz), 4.66 (d, 1 H, *J* = 12.2 Hz), 4.84 (dt, 1 H, *J* = 11,5, 3.4 Hz), 7.25-7.37 (m, 10 H); ^{13}C-NMR($CDCl_3$) δ 25.8, 26.1, 56.3, 69.2, 71.1, 71.7, 73.7, 76.6, 81.0, 82.8, 114.0, 127.6, 127.7, 127.9, 128.0, 128.5, 137.3, 137.4, 164.3; HRMS (FAB) calcd ($C_{24}H_{27}NO_5Na$) 432.1787 (M+Na), found 432.1775, σ 2.8 ppm.

(1S,4R,5R,6S,7S,8R)-N-Benzyl-8-O-benzyl-4-benzyloxymethyl-6,7-O-isopropylidene-2-aza-3-oxa-bicyclo[3.3.0]octane-6,7,8-triol (18). To a solution of aldehyde **14** in EtOH (15 ml), prepared from **13** (0.398 g; 1 mmol) according to the procedure described in the former paragraph, Na_2CO_3 (0.500 g; 4.7 mmol) and BnNHOH·HCl (0.176 g; 1.1 mmol) were added and the mixture was stirred at room temperature for 12 h under argon atmosphere. CH_2Cl_2 (100 ml) was subsequently added and the solution was washed with saturated aqueous NaCl (2x50 ml) and dried over Na_2SO_4. The solvent was then evaporated and the residue was chromatographed on silica gel with ethyl acetate/hexane 1:5 first as the eluent to remove the reaction byproducts and ethyl acetate then to elute nitrone **17**, which without characterization was dissolved in dry $CHCl_3$ (10 ml) and the solution was refluxed for 2 h. The solvent was subsequently evaporated and the residue was chromatographed on silica gel with EtOAc/hexane 1:5 to give isoxazolidine **18** (0.300 g, 60% from **13**) as an oil: $[\alpha]_D$ +4.4 (*c* 2.5, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.24 (s, 3 H), 1.48 (s, 3 H), 3.10 (t, 1 H, *J* = 9.2 Hz), 3.55 (dd, 1 H, *J* = 11.0, 3.4 Hz), 3.63 (dd, 1 H, *J* = 11.0, 3.8 Hz), 3.70 (d, 1 H, *J* = 13.0 Hz), 3.90 (m, 1 H), 3.99 (d, 1 H, *J* = 13 Hz), 4.03 (t, 1 H, Σ*J* = 15.5 Hz), 4.32 (t, 1 H, *J* = 5.2 Hz), 4.34-4.47 (m, 3 H), 4.49 (d, 1 H, *J* = 5.2 Hz), 4.61 (d, 1 H, *J* = 12.1 Hz), 4.71 (d, 1 H, *J* = 12.1 Hz), 7.20-7.39 (m, 15 H); ^{13}C-NMR($CDCl_3$) δ 24.3, 26.9, 51.5, 60.7, 67.5, 71.9, 73.6, 74.2, 75.5, 78.4, 79.5, 80.6, 110.6, 127.28, 127.31, 127.7, 127.96, 128.02, 128.3, 128.9, 136.9, 137.4, 138.4; HRMS (FAB) calcd ($C_{31}H_{35}NO_5Na$) 524.2413 (M+Na), found 524.2424, σ 2.1 ppm.

(2R,3R,4R)-3,4-O-Isopropylidene-1-nitrohex-5-ene-2,3,4-triol and *(2S,3R,4R)-3,4-O-Isopropylidene-1-nitrohex-1-ene-2,3,4-triol (21).* To a solution of **19**[3a] (7.6 g; 24.2 mmol) in absolute EtOH (80 ml), activated Zn (15.7 g; 242 mmol) was added and the mixture was refluxed with vigorous stirring under argon atmosphere,

until the complete consuming of **19** (ca. 2 h). Sometimes it was necessary to add a drop of AcOH to initiate the reaction. The mixture was cooled at room temperature and the solid was filtered off. In a separate flask, Na (0.56 g; 24.2 mmol) was dissolved in absolute EtOH (50 ml) in an ice-bath (CAUTION: hydrogen evolution!) and the resulting solution together with CH_3NO_2 (4.43 g; 72.6 mmol) were added to the above prepared solution of aldehyde **20**. The mixture was stirred at room temperature for 24 h, then decanted into an equal volume of H_2O and neutralized with hydrochloric acid. The solution was subsequently extracted with CH_2Cl_2 (2 x 100 ml), the organic layer was dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on silica gel with EtOAc/hexane 1:10 as the eluent to give the mixture of diastereoisomeric alditols **21** (3.728 g; 71%) as a colorless oil: $[\alpha]_D$ –24.8 (*c* 2.7, $CHCl_3$); ^{13}C-NMR($CDCl_3$) δ 25.1, 27.5, 67.7, 77.7, 78.0, 78.6, 109.4, 118.8, 132.6 (for one isomer) and 24.7, 26.8, 67.7, 77.3, 78.5, 78.8, 109.5, 120.6, 133.0 (for the other isomer); HRMS (FAB) calcd ($C_9H_{15}NO_5Na$) 240.0848 (M+Na), found 240.0843, σ 2.1 ppm.

(3aS,4R,5R,6R)-6-(Tetrahydropyran-2-yloxy)-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole ***(23)*** and *(3aR,4R,5R,6S)-6-(tetrahydropyran-2-yloxy)-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole* ***(24)***. A solution of **21** (1.97 g; 9.1 mmol), 3,4-dihydro-2*H*-pyran (0.92 g; 10.9 mmol) and pyridinium *p*-toluenesulfonate (PPTS, 0.228 g; 0.91 mmol) in dry CH_2Cl_2 (90 ml) was stirred at room temperature for 24 h. The reaction progress was followed by TLC. CH_2Cl_2 (200 ml) was then added and the solution was washed with brine (2 x 150 ml) and dried over Na_2SO_4. Evaporation of the solvent followed by elution through a chromatography column with EtOAc/hexane 1:7 yielded **22** (2.39 g; 88%) as a mixture of four diastereoisomers, which was used in the next step without complete characterization. A solution of the above compound **22**, PhNCO (2.94 g; 24.7 mmol) and Et_3N (10 drops) in toluene (40 ml) was stirred at room temperature for 5 days and then decanted into an equal volume of H_2O. The stirring was continued for 1 h and the organic layer was separated and dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on a column of silica gel, eluted with EtOAc/CH_2Cl_2 to give first isoxazoline **23** (1.00 g; 44%), followed by its epimer **24** (0.50 g; 22%). For **23**: m.p. 115-117 °C; $[\alpha]_D$ –42.5 (*c* 1.83, $CHCl_3$); HRMS (FAB) calcd ($C_{14}H_{21}NO_5Na$) 306.1317 (M+Na), found 306.1311, σ 2.0 ppm. For **24**: m.p. 117-118°C; $[\alpha]_D$ +145.1 (*c* 1.86, $CHCl_3$); HRMS (FAB) calcd ($C_{14}H_{21}NO_5Na$) 306.1317 (M+Na), found 306.1312, σ 1.6 ppm.

(3aS,4R,5R,6R)-6-Hydroxy-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole ***(25)***. A solution of $MgBr_2$ was prepared by reaction of activated Mg (0.117 g; 4.85 mmol) with $BrCH_2CH_2Br$ (0.902 g; 4.85 mmol) in dry Et_2O (10 ml) (CAUTION: gas evolution!). This solution was added to a solution of **23** (0.441 g; 1.56 mmol) and the mixture was stirred at room temperature for 18 h and then decanted to H_2O (20 ml). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 40 ml) and the combined organic solution was dried (Na_2SO_4), the solvent was evaporated and compound **25** was isolated by chromatographing the residue in silica gel using EtOAc/hexane 1:1 as the eluent (0.165 g; 53%): oil; $[\alpha]_D$ –55.4 (*c* 1.7, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.40 (s, 3 H), 1.59 (s, 3 H), 2.94 (d, 1 H, *J* = 1.5 Hz), 4.08 (m, 2 H), 4.45 (dd, 1 H, *J* = 6.8, 2.4 Hz), 4.60 (dd, 1 H, *J* = 3.6, 1.5 Hz), 4.74 (m, 2 H); ^{13}C-NMR($CDCl_3$) δ 24.6, 25.9, 55.6, 62.7, 73.9, 80.6, 81.4, 114.5, 164.6; HRMS (FAB) calcd ($C_9H_{14}NO_5$) 200.0923 (M+H), found 200.0928, σ 2.5 ppm.

(3aR,4R,5R,6S)-6-Hydroxy-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent[c]isoxazole ***(26)***. As in the case of **25**, compound **26** (0.263 g; 75%) was prepared from **24** (0.500 g; 1.76 mmol): m.p. 137-139 °C; $[\alpha]_D$ +198.6 (*c* 1, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.38 (s, 3 H), 1.50 (s, 3 H), 2.70 (d, 1 H, *J* = 10.2 Hz), 3.73 (dt, 1 H, *J* = 10.8, 5.6 Hz), 4.40 (dd, 1 H, *J* = 10.8, 8.3 Hz), 4.46 (dd, 1 H, *J* = 10.8, 8.3 Hz), 4.60 (dd as t, 1 H, *J* = 5.6 Hz), 4.75 (dd, 1 H, *J* = 10.2, 5.6 Hz), 4.80 (dd as t, 1 H, *J* = 5.6 Hz); ^{13}C-NMR($CDCl_3$) δ 24.6, 26.0, 52.2,

67.4, 69.3, 74.2, 81.3, 111.8, 165.3; HRMS (FAB) calcd ($C_9H_{14}NO_5$) 200.0923 (M+H), found 200.0928, σ 2.5 ppm.

(3S,4R)-(E)-3,4-O-Isopropylidene-1-nitrohexa-1,5-diene-3,4-diol (27). To a stirred solution of nitroalditols **21** (1.642.g; 7.56 mmol) in dry CH_2Cl_2 (40 ml), acetic acid anhydride (4.3 ml) and dry pyridine (2.5 ml) were added at 0 °C. The reaction mixture was allowed to warm at room temperature and the stirring was continued for 48 h. The solution was then washed successively with aqueous 5% HCl (2x50 ml), saturated aqueous $NaHCO_3$ (2x100 ml) and H_2O (100 ml) and dried over Na_2SO_4. Compound **27** (1.100 g; 73%) was isolated as an oil by evaporating the solvent and chromatographing the residue in silica gel with EtOAc/hexane 1:12 as the eluent: $[\alpha]_D$ –48.2 (*c* 1.21, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.42 (s, 3 H), 1.56 (s, 3 H), 4.81 (t, 1 H, *J* = 7.3 Hz), 4.91 (dd, 1 H, *J* = 7.3, 3.8 Hz), 5.32 (d, 1 H, *J* = 10.1 Hz), 5.42 (d, 1 H, *J* = 17.0 Hz), 5.69 (ddd, 1 H, *J* = 17.0, 10.1, 7.3 Hz), 7.10 (dd, 1 H, *J* = 13.3, 3.8 Hz), 7.15 (d, 1 H, *J* = 13.3 Hz); ^{13}C-NMR($CDCl_3$) δ 24.9, 27.4, 74.7, 79.2, 110.0, 119.7, 132.7, 138.1, 140.3; HRMS (FAB) calcd ($C_9H_{14}NO_5$) 200.0923 (M+H), found 200.0927, σ 2.0 ppm.

(3aR,4R,5S,6R)-6-t-Butylaminocarbonyl-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent-[c]isoxazole (28). A solution of **27** (0.792 g; 4 mmol) and *t*-BuNC (0.830 g; 10 mmol) in CH_3CN (10 ml) was refluxed for 6 h. The solvent was then evaporated and the residue was chromatographed on silica gel with EtOAc/hexane 1:2 as the eluent to give several reaction by-products at first, not containing the isoxazoline ring (NMR check) and then compound **28** (0.350 g; 32%): m.p. 159-161 °C; $[\alpha]_D$ +124.2 (*c* 1.33, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.33 (s, 3 H), 1.34 (s, 9 H), 1.44 (s, 3 H), 3.40 (s, 1 H), 4.11 (dt, 1 H, *J* = 11.2, 5.5 Hz), 4.32 (dd, 1 H, *J* = 11.2, 7.9 Hz), 4.49 (dd, 1 H, *J* = 11.2, 7.9 Hz), 4.67 (t, 1 H, *J* = 5.5 Hz), 5.26 (d, 1 H, *J* = 5.5 Hz), 6.16 (s, 1 H); ^{13}C-NMR($CDCl_3$) δ 24.7, 26.6, 28.5, 49.8, 51.6, 56.3, 69.7, 75.4, 87.5, 111.1, 165.1, 166.7; HRMS (MALDI-FTMS) calcd ($C_{14}H_{22}N_2O_4Na$) 305.1477 (M+Na), found 305.1489, σ 3.9 ppm.

Ethyl (4S,5R)-(Z)-4,5-isopropylidenedioxyhepta-2,6-dienoate (29) and *Ethyl (4S,5R)-(E)-4,5-isopropylidenedioxyhepta-2,6-dienoate (30)* To a solution of **19**[3a] (5.0 g; 15.9 mmol) in absolute EtOH (60 ml) activated Zn (10.3 g; 159 mmol) was added and the mixture was refluxed with vigorous stirring under argon atmosphere, until complete consumption of **19** (*ca.* 2 h). Sometimes it was necessary to add a drop of AcOH to initiate the reaction. The mixture was cooled at room temperature, the solid was filtered off and $Ph_3P{=}CHCO_2Et$ (7.680 g; 22 mmol) and $PhCO_2H$ (0.04 g) were added and the resulting mixture was stirred at room temperature for 24 h. The solvent was then evaporated and the mixture chromatographed on silica gel with EtOAc/hexane 1:20 as the eluent to give the *Z*-isomer **29** at first (1.908 g; 53%) followed by the *E*-isomer **30** (0.972 g; 27%) as colorless oils. For **29**: $[\alpha]_D$ +178 (*c* 3.9, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.28 (t, 3 H, *J* = 7.1 Hz), 1.41 (s, 3 H), 1.54 (s, 3 H), 4.16 (q, 2 H, *J* = 7.1 Hz), 4.87 (t, 1 H, *J* = 6.6 Hz), 5.15 (d, 1 H, *J* = 10.3 Hz), 5.28 (d, 1 H, *J* = 17 Hz), 5.61-5.72 (m, 2 H), 5.89 (d, 1 H, *J* = 11.7 Hz), 6.18(dd, 1 H, J = 11.7, 7.4 Hz); ^{13}C-NMR($CDCl_3$) δ 14.1, 25.0, 27.7, 60.2, 75.6, 79.5, 109.0, 117.6, 121.3, 133.9, 146.3, 165.4. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.55; H, 7.92.For **30**: $[\alpha]_D$ -23.3 (*c* 5.5, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.29 (t, 3 H, *J* = 7.1 Hz), 1.42 (s, 3 H), 1.56 (s, 3 H), 4.21 (q, 2 H, *J* = 7.1 Hz), 4.71 (dd as t, 1 H, *J* = 7.4 Hz), 4.78 (dd as t, 1 H, *J* = 5.6 Hz), 5.27 (d, 1 H, *J* = 10.3 Hz), 5.37 (d, 1 H, *J* = 17.2 Hz), 5.70 (ddd, 1 H, *J* = 17.2, 10.3, 7.4 Hz), 6.07 (d, 1 H, *J* = 15.6 Hz), 6.18(dd, 1 H, J = 15.6, 5.4 Hz); ^{13}C-NMR($CDCl_3$) δ 14.1, 25.3, 27.7, 60.4, 77.4, 79.7, 109.5, 119.1, 122.6, 133.4, 143.5, 165.9. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.78; H, 8.10.

Ethyl (3S,4S,5R)-3-nitromethyl-4,5-isopropylidenedioxyhept-6-enoate (31). To a stirred solution of **29** (0.339 g; 1.5 mmol) and CH_3NO_2 (0.091 g; 1.5 mmol) in THF (3 ml) was added TBAF $3H_2O$ (0.020 g) at room

temperature and the resulting orange solution was stirred for 24 h and then decanted into H_2O (20 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The organic layer was dried (Na_2SO_4) the solvent was evaporated and the residue was purified by column chromatography on silica gel with EtOAc/hexane 1:9 as the eluent to give **31** (0.285 g; 66%) as a colorless oil: $[\alpha]_D$ –6.5 (*c* 2.2, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.26 (t, 1 H, *J* = 7.1 Hz), 1.35 (s, 3 H), 1.47 (s, 3 H), 2.48 (d, 2 H, *J* = 6.1 Hz), 2.78 (m, 1 H), 4.15 (q, 2 H, *J* = 7.1 Hz), 4.24 (t, 1 H, *J* = 7.0 Hz), 4.54-4.74 (m, 3 H), 5.36 (d, 1 H, *J* = 10.3 Hz), 5.43 (d, 1 H, *J* = 17.2 Hz), 5.93 (ddd, 1 H, *J* = 17.2, 10.3, 7.4 Hz); ^{13}C-NMR($CDCl_3$) δ 13.9, 24.9, 27.2, 32.9, 34.2, 60.8, 75.4, 76.8, 78.7, 108.7, 119.7, 132.8, 170.7; HRMS (FAB) calcd ($C_{13}H_{22}NO_6$) 288.1447 (M+H), found 288.1455, σ 2.8 ppm.

Ethyl (3R,4S,5R)-3-nitromethylhept-4,5-isopropylidenedioxyhept-6-enoate (33). By the same procedure from **30** (0.678 g; 3 mmol), there was obtained an inseparable mixture of **31** and **33** (0.625 g; 73%) in *ca.* 5:1 ratio (by ^{1}H-NMR). For **33** (from the mixture): ^{13}C-NMR($CDCl_3$) δ 14.0, 24.9, 27.1, 32.4, 34.5, 60.7, 75.7, 76.3, 78.7, 108.6, 119.9, 132.8, 171.4.

(3aR,4R,5S,6S)-6-Ethoxycarbonylmethyl-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent-[c]isoxazole (32). A solution of **31** (0.268 g; 1.07 mmol), PhNCO (0.507 g; 4.26 mmol) and Et_3N (2 drops) in benzene (5 ml) was stirred at room temperature for 3 days and then decanted to an equal volume of H_2O. The stirring was continued for 1 h and the organic layer was separated and dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on a column of silica gel, eluted with EtOAc/hexane 1:4 to give isoxazoline **32** (0.180 g; 72%) as an oil: $[\alpha]_D$ +66.8 (*c* 2.53, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.27 (t, 3 H, *J* = 7.1 Hz), 1.31 (s, 3 H), 1.42 (s, 3 H), 2.75 (dd, 1 H, *J* = 17.3, 8.8 Hz), 2.82 (dd, 1 H, *J* = 17.3, 5.5 Hz), 3.19 (ddd, 1 H, Σ*J* = 20.2 Hz), 3.81 (dt, 1 H, *J* = 11.0, 5.9 Hz), 4.17 (m, 2 H), 4.27 (dd, 1 H, *J* = 11.0, 8.0 Hz), 4.43 (dd, 1 H, *J* = 11.0, 8.0 Hz), 4.61 (dd as t, 1 H, J = 5.9 Hz), 5.05 (dd as t, 1 H, *J* = 5.9 Hz); ^{13}C-NMR($CDCl_3$) δ 13.9, 24.3, 25.8, 29.4, 36.2, 55.4, 60.4, 68.9, 74.6, 83.9, 110.5, 166.1, 171.7; HRMS (MALDI-FTMS) calcd ($C_{13}H_{19}NO_5Na$) 292.1161 (M+Na), found 292.1154, σ 2.4 ppm.

(3aR,4R,5S,6R)-6-Ethoxycarbonylmethyl-4,5-isopropylidenedioxy-3a,4,5,6-tetrahydro-3H-cyclopent-[c]isoxazole (34). A solution of the mixture **31/33** (0.865 g; 3.02 mmol) prepared as above from **30**, PhNCO (1.053 g; 9 mmol) and Et_3N (3 drops) in toluene (00 ml) was stirred at room temperature for 3 days and then decanted into an equal volume of H_2O. The stirring was continued for 1 h and the organic layer was separated and dried (Na_2SO_4), the solvent was evaporated and the residue was chromatographed on a column of silica gel, eluted with EtOAc/hexane 1:4 to give first the isoxazoline **34** (0.105 g; 13%), followed by its epimer **32** (0.535 g; 66%). For **34**: $[\alpha]_D$ –7.3 (*c* 0.22, $CHCl_3$); ^{1}H-NMR($CDCl_3$) δ 1.27 (t, 3 H, *J* = 7.1 Hz), 1.32 (s, 3 H), 1.54 (s, 3 H), 2.81 (dd, 1 H, *J* = 17.1, 6.2 Hz), 2.85 (dd, 1 H, *J* = 17.1, 6.2 Hz), 3.26 (dt, 1 H, *J* = 6.2, 3.5 Hz), 3.95 (m, 2 H), 4.17 (q, 2 H, *J* = 7.1 Hz), 4.47 (dd, 1 H, *J* = 6.8, 4.0 Hz), 4.70 (m, 2 H); ^{13}C-NMR($CDCl_3$) δ 14.1, 25.0, 27.4, 33.7, 39.0, 59.4, 60.9, 74.1, 80.5, 87.7, 113.2, 167.1, 171.0; HRMS (FAB) calcd ($C_{13}H_{20}NO_5$) 270.1341 (M+H), found 270.1350, σ 3.3 ppm.

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