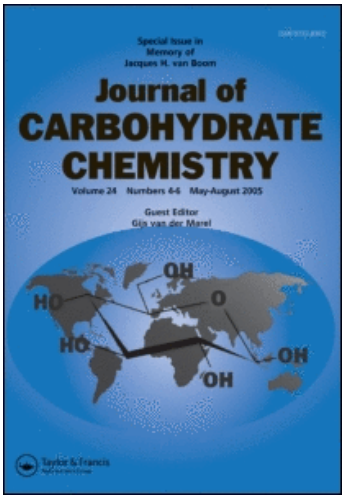

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STRATEGIES FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE MEDIUM-SIZED CARBOCYCLES FROM CARBOHYDRATES

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STRATEGIES FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE MEDIUM-SIZED CARBOCYCLES FROM CARBOHYDRATES

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ABSTRACT

A series of strategies (the Pauson–Khand reaction and the 1,3-dipolar cycloaddition reaction) have been analyzed in order to develop new and original synthetic protocols for the synthesis of enantiomerically pure medium-sized carbocycles. The intramolecular Pauson–Khand reaction on dideoxy-3,4:5,6-bis-*O*-(1-methylethylidene)-D/L-*glycero*-D-*gluco*-non-1-en-8-ynitol (**4**) is a low yielding, but highly stereoselective acyclic enyne precursor 1,2-procedure for the synthesis of bicyclo[5.3.0]decanones of type **5**. In the second approach (''the nitrone route''), the intramolecular nitrone cycloaddition of precursors **14** and **19** derived from D-mannose has afforded the corresponding 9-oxa-8-azabicyclo[5.3.0]decanes as a mixture of *trans* fused isomers, in a critically dependent reaction of a pre-existing isopropylidene group which entropically favors the approach of the reactive species; this is the first documented example of a 1,3-dipolar cycloaddition in 7-alkenyl nitrones.

Key Words: Carbohydrates; Medium-sized carbocycles; Carbocyclization; Pauson-Khand reaction; 1,3 Dipolar cycloaddition reaction; Nitrones

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INTRODUCTION

The synthesis of medium-sized rings, notably seven and eight-membered ring systems, has been usually hampered by entropic/enthalpic factors and transannular interactions between the methylene groups.[1a–1c] These are serious limiting factors which have usually resulted in low chemical yields of the desired products.[2a–2c] Although some solutions to this formidable challenge have been advanced using cycloaddition or annulation strategies,[3] the cyclization approach for the synthesis of these structures still remains a partially unsolved problem.[4a–4g] In view of these difficulties, we reasoned that chiral, highly functionalized precursors derived from carbohydrates could probably be excellent substrates in order to test the viability of these strategies for the preparation of chiral, densely functionalized medium-sized rings. In fact, it is now well recognized that carbohydrates form a large mass of readily available, enantiomerically pure, cheap starting materials with a plethora of stereocenters which can be easily modulated in suitable conformational and configurational terms for the synthesis of natural products.[5]

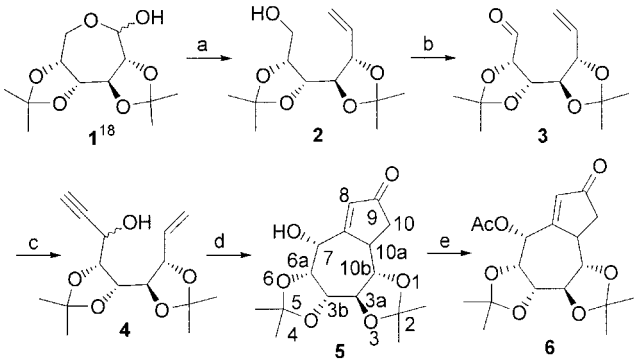
In this paper we want to disclose the full details of our recent efforts on the synthesis of seven-membered ring systems. We have particularly directed our attention to the Pauson–Khand (PK) reaction[6a–6c] and to the 1,3-dipolar cycloaddition (1,3-DC)[7] strategies. We have applied them to selected carbohydrate precursors in order to investigate their scope, synthetic potential and limitations for the synthesis of seven-membered ring systems. These synthetic efforts, due to the growing number of natural compounds of this type with attractive biological/pharmacological activity,[8] presumably will be useful for a rational design directed to the synthesis of some members of this family of molecules. A particularly important point in these reactions has been the stereochemical outcome in the formation of new stereocenters.

RESULTS AND DISCUSSION

The Pauson–Khand Approach

In order to test the viability of the PK reaction for the synthesis of [5.3.0]fused bicyclo decanones of type **5** in a single step, we prepared the conveniently substituted acyclic enyne precursor 1,2-dideoxy-3,4:5,6-bis-*O*-(1-methylethylidene)-D/L-*glycero*-D-*gluco*-non-1-en-8-ynitol (**4**) (Scheme 1).

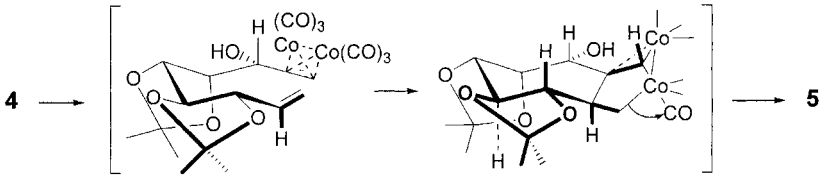
The 5,7-fused structural motif is found in the hydrazulene skeleton present in the guaianolide and pseudoguaianolide type of natural products.[9a,9b,10] Usual major strategies for the synthesis of bicyclo[5.3.0]decane structures rely on annulation strategies.[11a,11b] The PK approach for this purpose has been described, but until now the reported results have not been very encouraging. Thus, the intermolecular PK reaction of cycloheptene with differently substituted acetylenes has been studied, giving poor chemical yields of the desired products.[12] Schore has developed a method based on the fragmentation of the PK products resulting from the reaction of acetylenes with bicyclo [3.2.0]hept-6-enes.[13] More recently, in a study of the PK reaction of α,ω-allenynes Cazes has reported the synthesis of some 6,6(1*H*)azulenedicarboxylic acid derivatives.[14] Finally, others have described the intramolecular PK on 3-(prop-2-



Scheme 1. Pauson–Khand reaction on precursor **4**. Reagents: (a) $Ph_3P=CH_2$, THF, $-20°C$ (84%); (b) DMSO, DCC, CF_3CO_2H, rt, toluene (73%); (c) Ethynylmagnesium bromide, THF, 0°C (83%); (d) i. $Co_2(CO)_8$, ii. NMO. H_2O, CH_2Cl_2, rt (14%); (e) Ac_2O, Py, rt (90%).

ynylsulfanyl)cycloheptene with notable success; subsequent desulfuration gave the desired bicyclo[5.3.0]decane framework. Note that in this case the convenient and astute tactic needs a preformed cycloheptene ring template, a fact which limits the scope of this method.[15] In summary, to the best of our knowledge the intramolecular PK reaction of non-1-en-8-ynes has not been studied.[15b,15c] Prompted by this fact and desiring convenient precursors for the synthesis of the chiral, highly functionalized bicyclo[5.3.0]decanones present in most of the natural perhydroazulene class of sesquiterpenoids and in accordance with our project, we prepared compound **4** from the readily available starting material **1**,[16] derived from D-glucose, in a straightforward manner (Scheme 1). Compound **4** was isolated as an unseparable 3:2 mixture of *anti* and *syn* isomers in 83% yield. We have tentatively assigned the *anti* stereochemistry to the major isomer, in agreement with similar results from literature;[17a,17b] this assignment has been unequivocally demonstrated in the ''cyclic'' derivative (see below). The conventional protocol for the PK reaction applied to the mixture of isomers **4**, using chemical decomposition with *N-N*-oxide (NMO)[18] of the intermediate cobalt-complex, afforded a 14% yield of a single product **5**, which showed analytical and spectroscopic data in good agreement with those expected for the normal PK product. Additional proof was obtained from acetate **6**, prepared by standard conditions from alcohol **5** in 90% yield. From the structural point of view, particularly diagnostic were the vicinal coupling constants for protons H-10a and H-10b (10.1 Hz in **5**, and 10.4 Hz in **6**) (see Scheme. 1), a series of values which clearly point out that these protons are *trans*, showing that the PK reaction has taken place to give exclusively the *exo*[19] product. Regarding the stereochemistry at carbon C-7, a strong NOE effect between protons H-6a and H-7 (**5**: $J_{6a,7}=2.9$ Hz; **6**: $J_{6a,7}=2.4$ Hz) led us to conclude that the configuration at this carbon is *R*. This would imply that only the major *anti* isomer in product **4** has survived the PK reaction conditions, affording the only observed and isolated adduct. The other epimer probably was decomposed during the cobalt-complex intermediate transformation.

In Scheme 2 we show a possible mechanism for this PK transformation. In agreement with the model proposed by Magnus,[20] the preferred intermediate complex should be in a chair-like conformation with most of the substituents in pseudoequatorial



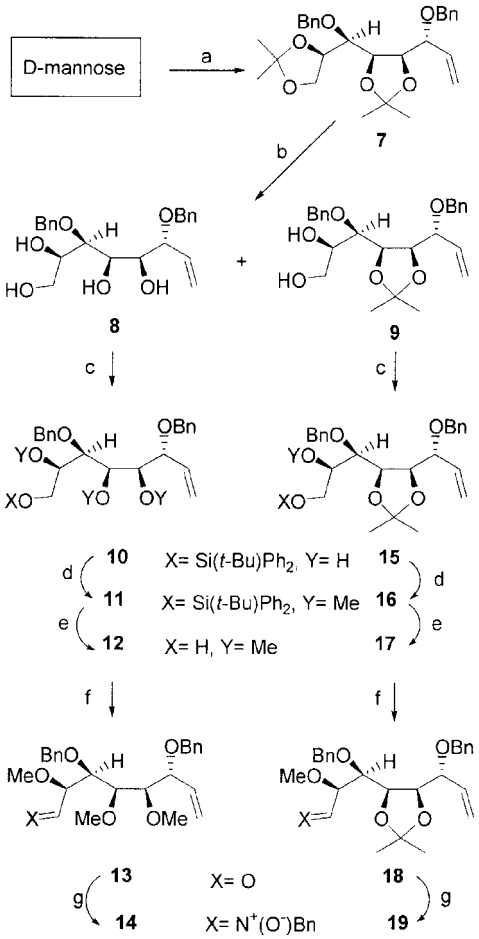
Scheme 2. Postulated transition state for the carbocyclization of the cobalt complex from precursor **4**.

orientations affording the observed *exo*-**5** product. In support of this model the observed coupling constant between protons H-2 and H-3 in compound **4**-*anti* is $J_{2,3} = 8.1$ Hz, a value which places these protons in a preferred *trans* 1,3-parallel arrangement. In summary, the first PK of a non-1-en 8-yne has been described, using a sugar derivative as starting material, giving highly stereospecific *exo* bicyclo[5.3.0]dodecanones in low yield. However, this is balanced by the simple access to the desired target molecules and the ready availability of the intermediates.

The Nitrone Route

The Intramolecular Olefin–Nitrone Cycloaddition (INC) reaction[21] is one of the best known and exploited 1,3-DC processes.[7] Since the pioneer work of LeBel[22] this reaction has been largely used for the synthesis of a variety of carbocyclic or heterocyclic systems in racemic or enantiomerically pure form. The majority of the described intramolecular 1,3-DC reactions are those in which the alkene part is linked to the carbon atom of the nitrone. In these cases bicyclic compounds of type [l.3.0] or [l.2.1] and containing isoxazolidine moieties have been observed. In this context the carbohydrate area[23] has been a particularly active domain, and different types of 5- or 6-alkenyl nitrones have been synthesized and submitted to 1,3-DC giving good yields of the resulting isoxazolidines, whose nature and stereoselectivity were dependent on the structure of the substrate.[24] However, in spite of these efforts, we were surprised to see that, at least to the best of our knowledge, 7-alkenyl nitrones have not yet been tested in the 1,3-DC.[25] This was very interesting for our purposes and prompted us to synthesize the INC precursors **14** and **19** (Scheme 3).[26]

These precursors have been obtained from D-mannose via the known di-*O*-benzyl derivative **7**[27] (Scheme 3). After acetal mediated acid hydrolysis, a mixture of the tetrol **8** and diol **9** was isolated. Both molecules were transformed following parallel synthetic sequences: 1) silylation at C-6; 2) *O*-protection at C2-, C-4 and C-5 (or at C-2 as *O*-methyl ethers); 3) desilylation; 4) oxidation; and 5) nitrone formation. All new compounds showed analytical and spectroscopic data in good agreement with these structures. With the desired precursors in our hands we checked the key INC reaction. Not surprisingly compound **14** was reluctant to undergo the 1,3-DC reaction, and it was recovered unchanged after heating a solution of this material in chlorobenzene for an extended period of time. We were pleased to see that precursor **19**, under the same conditions, afforded a mixture of isoxazoliodines **20** and **21** in 50% yield, as a 3:2 mixture of isomers (Scheme 4), which we were unable to separate. The spectroscopic

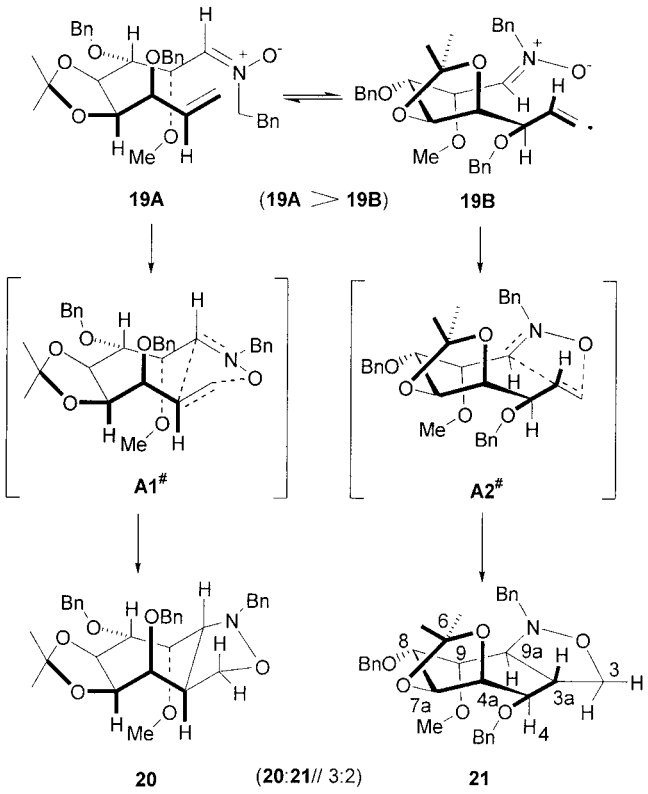


Scheme 3. Synthesis of precursors (**14** and **19**) for the INC reaction. Reagents: (a) Ref. [29]; (b) $AcOH/H_2O$ (4:1), rt (**8**: 78%; **9**: 20%); (c) $ClSi\textit{t}BuPh_2$, Py, DMAP, 0°C (for **8** to **10**: 83%), (for **9** to **15**: 99%); (d) NaH, IMe, Bu_4NI, THF, 0°C (for **10** to **11**: 60%), (for **15** to **16**: 74%); (e) Bu_4NF, THF, rt (for **11** to **12**: 93%; for **16** to **17**: 92%); (f) PCC, CH_2Cl_2, NaAcO, rt, molecular sieves (for **12** to **13**: 85%; for **17** to **18**: 93%); (g) $PhCH_2NHOH.HCl$, Py, CH_2Cl_2, reflux (for **13** to **14**: 74%; for **18** to **19**: 65%).

analysis of this mixture was difficult, as most of the signals were overlapping, and this fact complicated the structural determination. However, after a detailed ^1H and ^{13}C NMR analysis and complementary experiments (^1H-^1H COSY, HMQC, NOESY) it was soon evident that the reaction proceeded to give the corresponding bicyclic isoxazolidines as a mixture of only *trans* isomers at carbons C-3a and C-9a. In fact, the absence of any signal around 26.0 ppm in the ^{13}C NMR spectrum excluded the alternative compounds with a methylene in the bridge position. Conversely, we have found and identified specific and diagnostic signals for major isomer **20** [(δ) 44.5 (C-3a), 67.7 (C-9a); 3.80 (t, $J_{3,3a}=J_{3,3'}=7.4$ Hz, 1 H, H-3), 3.53 (dd, $J_{3,3'}=7.4$ Hz,

$J_{3',3a}$ = 10.7 Hz, 1 H, H-3′), 2.69 (dt, $J_{3,3a}$ = 7.4 Hz, $J_{3',3a}$ = $J_{9a,3a}$ = 10.7 Hz, 1 H, H-3a)] and for the minor isomer **21** [(δ) 42.4 (C-3a), 67.5 (C-9a); 4.07 (t, $J_{3,3'}$ = $J_{3a,3'}$ = 7.6 Hz, 1 H, H-3′), 3.68 (dd, $J_{3,3a}$ = 10.9 Hz, $J_{3,3'}$ = 7.6 Hz, 1 H, H-3), 3.62 (d, $J_{9,9a}$ = 10.1 Hz, 1 H, H-9), 3.14 (br t, $J_{9.,9a}$ = $J_{9a,3a}$ = 10.1 Hz, 1 H, H-9a)] that strongly support the absolute configuration at the newly formed stereocenters. These data (particularly the vicinal coupling constants of $J_{3a,9a}$) coupled to the absence of an NOE effect between the protons at the carbon atoms C-3a and C-9a, led us to tentatively conclude that compounds **20** and **21** are the *trans* isomers at these carbons.[28] An inspection of molecular models supported these assumptions.

In Scheme 4 we show a simple and possible rationale in order to explain the stereochemical outcome of this INC reaction. As shown, for the transition states leading to the carbocyclic products we propose a boat-like conformation, slightly preferred in terms of steric interactions, and a chair-like conformation with the alkene and the nitrone termini of the reaction in pseudoequatorial orientations to give the major and minor, **20** and **21** isomers, respectively. Note also that in this conformation the nitrone and the carbon of the dipolarophile are at convenient distance for the reaction to take place. In addition, and due to the forcing experimental conditions, we have assumed that only the *E* nitrone is operative in the reaction medium.[29] An interesting point also



Scheme 4. INC of nitrone **19** in chlorobenzene at 130°C.

to comment upon is the unsuccessful attempt to promote the INC in nitrone **14**. This is a nice example of the difficulties found in preparing seven-membered ring systems due to entropic factors. Compared with the success in nitrone **19**, it is clear that the presence of an *external* functional moiety, the isopropylidene group here, overrides other negative factors, and presumably influences the reacting partners by reducing the conformational freedom of the molecule. Examples of the benefit of the isopropylidene group, or other similar templates,[30] are known and have been used in our laboratory very recently.[31a–31c]

In summary, we have shown that the INC reaction of 7-alkenyl nitrone (**19**) derived from D-mannose is possible, gives a moderate yield of the expected 9-oxa-8-azabicyclo[5.3.0]decane derivatives as a mixture of *trans* fused isomers. In addition, we have found that this reaction is critically dependent on a pre-existing isopropylidene group that favors the approach of the termini of the reacting partners.

EXPERIMENTAL

General Methods. Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (Merck, 5539). Detection was done by UV (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% EtOH. Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups, and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck) and hexane/ethyl acetate mixtures as eluent unless otherwise stated. ^{1}H NMR spectra were recorded with a Varian VXR-300(400)S spectrometer, using tetramethylsilane as internal standard and ^{13}C NMR spectra were recorded with a Bruker WP-200-SY. Values with (*) can be interchanged. The MS spectra were recorded in a Hewlett Packard MDS 5973 or in a Hewlett Packard MSD 1100 (for the electrospray experiments, positive mode) spectrometer.

General Procedure (GP) for Grignard Addition. To a solution of the aldehyde in dry THF (1 M) under argon at 0°C, the Grignard reagent (4 equiv, 0.5 M in THF) was added, and the mixture was stirred for 1 h. Then, an aqueous saturated solution of ammonium chloride was added, and the mixture was extracted with ethyl acetate several times. The organic phase was washed with brine, dried, concentrated and the residue submitted to chromatography to give the corresponding alcohols as a mixture of *syn* amd *anti* products.

General Procedure (GP) for Oxidation with PCC. To a suspension of the alcohol sodium acetate (0.3 equiv), powdered molecular sieves and PCC (2 equiv) were added. The mixture was stirred at rt for 4 h. Then, the reaction was filtered over Celite, and the filtrate was concentrated. The residue was submitted to chromatography.

General Procedure (GP) for Silylation Reactions. The compound was dissolved in dry pyridine (0.12 M) and cooled to 0°C. Then 4-dimethylaminopyridine (0.1 equiv) and *t*-butyldiphenylsilyl chloride (1 equiv) were added under argon. The mixture was

stirred at rt for 24 h. The solvent was removed, the residue was taken up in ethyl acetate and washed with brine. The organic phase was dried, filtered and concentrated. The residue was submitted to chromatography.

General Procedure (GP) for Desilylation Reactions. The compound was dissolved in dry THF (0.14 M) and treated with tetrabutylammonium fluoride (3 equiv) at rt for 24 h. The solvent was evaporated, and the residue was submitted to chromatography.

General Procedure (GP) for the Synthesis of Nitrones. A 0.1 M solution of the aldehyde, *N*-benzylhydroxylamine hydrochloride (3.1 equiv) and pyridine (3.5 equiv) in CH_2Cl_2 was refluxed for 12 h. The solvent was eliminated, the residue was diluted with ethyl acetate, washed with brine, the organic phase was dried, filtered and concentrated, and the residue was submitted to chromatography.

General Procedure (GP) for Acetylation. The compound was treated with a mixture of acetic anhydride/pyridine (1/1, v/v) at rt overnight. The solvent was evaporated, and the residue was submitted to chromatography.

General Procedure (GP) for Acetal Hydrolysis. The compound was dissolved in a mixture of AcOH/H_2O (7:3) at rt until complete reaction (18–24 h). The solvent was evaporated, and the residue was submitted to chromatography.

General Procedure (GP) for *O*-alkylation (Benzylations or Methylation). The compound, dissolved in dry THF (0.2 M), under argon and at 0°C, was treated with sodium hydride (1.5 equiv, 60% dispersion in oil), a catalytic amount of tetrabutylammonium iodide and benzyl bromide or methyl iodide (1.1 equiv). After stirring at rt for 15 h, the reaction was complete, and some drops of AcOH were added. Then the mass was filtered over Celite. The filtrate was concentrated, diluted with water, extracted with CH_2Cl_2 several times and washed with brine. The organic layer was dried and filtered. The filtrate was concentrated and chromatographed.

1,2-Dideoxy-3,4:5,6-bis-(1-*O*-methylethylidene)-D-*gluco*-hept-1-enitol (2). To a suspension of hemiacetal **1**[16] (1.15 g, 4.41 mmol) and triphenylphosphonium bromide (4.91 g, 13.7 mmol, 2 equiv) in dry THF (7 mL), cooled at −20°C, under argon, *n*-BuLi (5.5 mL, 8.8 mmol, 1.6 M in hexane) was slowly added. The mixture was stirred at rt for 2 h and quenched with an aqueous saturated solution of ammonium chloride. Then, the mixture was diluted with methylene chloride, washed with an aqueous saturated solution of sodium bicarbonate, brine, dried, filtered and concentrated. The residue was submitted to flash chromatography (hexane/ethyl acetate: 7/3) to give compound **2** (960 mg, 84%): oil; $[\alpha]_D^{25}$ −12 (*c* 0.23, $CHCl_3$); IR (film) ν 3460 (OH), 2986, 2936 1380, 1216, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.79 (ddd, $J_{1,2}=17.3$ Hz, $J_{1',2}=10.1$ Hz, $J_{2,3}=7.6$ Hz, 1 H, H-2), 5.41 (dm, $J_{1,2}=17.3$ Hz, 1 H, H-1), 5.28 (dm, $J_{1',2}=10.1$ Hz, 1 H, H-1′), 4.45 (dd, $J_{3,4}=8.6$ Hz, $J_{2,3}=7.6$ Hz, 1 H, H-3), 4.23 (dt, $J_{6,7}=J_{6,7'}=5.2$ Hz, $J_{5,6}=6.7$ Hz, 1 H, H-6), 4.05 (dd, $J_{5,6}=6.7$ Hz, $J_{4,5}=1.7$ Hz, 1 H, H-5), 3.76 (t, $J_{6,7}=J_{7,OH}=5.2$ Hz, 2 H, H-7), 3.68 (dd, $J_{3,4}=8.6$ Hz, $J_{4,5}=1.7$ Hz, 1 H, H-4), 2.84 (t, $J_{7,OH}=5.2$ Hz, 1 H, OH), 1.50, 1.42 (2 s), 1.35 [4 s, $2\times OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4 (C-2), 120.1 (C-1), 109.8, 108.8

[2 C, 2 × O*C*$(CH_3)_2$O], 79.3 (C-3), 78.2 (C-6), 77.2 (C-4), 73.3 (C-5), 61.3 (C-7), 27.1, 26.8, 26.4, 25.5 [4 C, 2 × OC(*C*$H_3)_2$O]; MS (70 eV) *m/z* 243 ($M^+ - 15$, 12), 141 (5), 127 (21), 113 (10), 98 (36), 69 (52), 43 (100).

Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.30; H, 8.81.

6,7-Dideoxy-2,3:4,5-bis-(1-*O*-methylethylidene)-L-*manno*-hept-6-enose (3). To a solution of alcohol **2** (122 mg, 0.47 mmol), DMSO (0.8 mL, 11.0 mmol, 23.5 equiv), DCC (293 mg, 1.4 mmo, 3 equiv), pyridine (0.04 mL, 0.47 mL, 1 equiv) in dry toluene (1.6 mL, 0.3 M), trifluoroacetic acid (0.02 mL, 0.23 mmol, 0.5 equiv) was added. The mixture was stirred at rt for 1.5 h. Then, ethyl acetate was added, and the precipitated dicyclohexylurea was eliminated by filtration. The filtrate was washed with brine, dried, concentrated, and the residue was submitted to chromatography (hexane/ethyl acetate, 91/9) to give aldehyde **3** (84 mg, 73%) as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.64 (d, $J_{1,2}$ = 2.3 Hz, 1 H, H-1), 5.79 (ddd, $J_{6,7}$ = 17.4 Hz, $J_{6,7'}$ = 10.3 Hz, $J_{5,6}$ = 7.6 Hz, 1 H, H-6), 5.42 (dt, $J_{6,7}$ = 17.4 Hz, $J_{7,7'} = J_{7,5}$ = 1.1 Hz, 1 H, H-7), 5.28 (dt, $J_{6,7'}$ = 10.3 Hz, $J_{7,7'} = J_{7',5}$ = 1.1 Hz, 1 H, H-7′), 4.47 (dd, $J_{5,6}$ = 7.6 Hz, $J_{4,5}$ = 8.3 Hz, 1 H, H-5), 4.43 (dd, $J_{1,2}$ = 2.3 Hz, $J_{2,3}$ = 8.4 Hz, 1 H, H-2), 4.33 (dd, $J_{2,3}$ = 8.4 Hz, $J_{3,4}$ = 1.5 Hz, 1 H, H-3), 3.68 (dd, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 8.3 Hz, 1 H, H-4), 1.60, 1.40, 1.39, 1.36 [4 s, 2 × OC$(CH_3)_2$O]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.5 (C-1), 134.5 (C-6), 119.9 (C-7), 111.4, 109.7 [2 C, 2 × O*C*$(CH_3)_2$O], 81.0 (C-4)*, 78.5 (C-5)*, 77.9 (C-3)**, 75.2 (C-2)**, 27.2, 26.6, 26.5, 25.3 [4 C, 2 × OC(*C*$H_3)_2$O].

Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.77; H, 7.80.

1,2-Dideoxy-3,4:5,6-bis-(1-*O*-methylethylidene)-D/L-*glycero*-D-*gluco*-non-1-en-8-ynitol (4). Following the **GP** for Grignard addition, aldehyde **3** (110 mg, 0.43 mmol) was treated with ethynylmagnesium bromide (3.45 mL, 1.7 mmol, 4 equiv, 0.5 M in THF) to give **4** (101 mg, 83%), as an unseparable mixture of *anti* and *syn* isomers in 6 to 4 ratio, respectively, after chromatography (hexane/ethyl acetate, 3/1): oil; IR (film) ν 3428 (OH), 2988, 1382, 1219, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) (major isomer *anti*) δ 5.85 (ddd, $J_{1,2}$ = 17.4 Hz, $J_{1',2}$ = 10.4 Hz, $J_{2,3}$ = 8.1 Hz, 1 H, H-2), 5.45 (d, $J_{1,2}$ = 17.4 Hz, 1 H, H-1), 5.33 (dd, $J_{1',2}$ = 10.4 Hz, $J_{1,1'}$ = 0.6 Hz, 1 H, H-1′), 4.67 (ddd, $J_{6,7}$ = 6.0 Hz, $J_{7,9}$ = 2.2 Hz, $J_{7,OH}$ = 8.2 Hz, 1 H, H-7), 4.56 (t, $J_{2,3} = J_{3,4}$ = 8.1 Hz, 1 H, H-3), 4.24 (dd, $J_{5,6} = J_{6,7}$ = 6.0 Hz, 1 H, H-6), 4.16 (d, $J_{5,6}$ = 6.6 Hz, 1 H, H-5), 4.14 (d, $J_{3,4}$ = 8.1 Hz, 1 H, H-4), 4.03 (d, $J_{7,OH}$ = 8.2 Hz, 1 H, OH), 2.47 (d, $J_{7,9}$ = 2.2 Hz, 1 H, H-9), 1.57, 1.54, 1.48, 1.47 [4 s, 2×OC$(CH_3)_2$O]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.2 (C-2), 120.1 (C-1), 109.8, 109.0 [2 C, 2×O*C*$(CH_3)_2$O], 82.4 (C-8), 79.3 (C-1), 78.7 (C-7), 77.2 (C-4), 73.7 (C-6), 73.0 (C-5), 61.3 (C-7), 27.1, 26.7, 26.3, 25.4 [4 C, 2×OC(*C*$H_3)_2$O]; MS (70 eV) *m/z* 282 (M, 8), 149 (30), 105 (22), 91 (100), 57 (38).

Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.65; H, 7.81.

[3a*R*-(3aα,3bβ,6aβ,7β,10aα,10bβ)]-(3a,3b,6a,7,9,10a,10b)-Heptahydro-7-hydroxy-2,2,5,5,-tetramethylazuleno[4,5-d; 6,7-d]bis[1,3-dioxol]-9-one (5). To a solution of enyne **4** (100 mg, 0.35 mmol) in dry methylene chloride (14.2 mL, 0.025M), under argon, at rt, octacarbonyldicobalt (134 mg, 0.39 mmol, 1.1 equiv) was added. After 30 min, the mixture was cooled to 0°C and NMO. H_2O (303 mg, 2.2 mmol, 6.3 equiv) was added, and the mixture was stirred for 6 h. Then, the mixture was filtered over Celite, the filtrate was concentrated, and the residue was submitted to chromatography

(hexane/ethyl acetate, 65/35) to give **5** (20 mg, 14%): oil; $[\alpha]_D^{25}+20$ (*c* 0.17, $CHCl_3$); IR (film) ν 3436 (OH), 2932, 1718 (C=O), 1624 (C=C), 1374, 1214, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (s, 1 H, H-8), 5.01 (d, $J_{6a,7}=2.9$ Hz, 1 H, H-7), 4.58 (t, $J_{3a,3b}=J_{3a,10b}=8.9$ Hz, 1 H, H3a), 4.26 (t, $J_{3a,3b}=J_{6a,3b}=8.9$ Hz, 1 H, H3b), 4.14 (dd, $J_{6a,7}=2.9$ Hz, $J_{6a,3b}=8.9$ Hz, 1 H, H-6a), 3.39 (ddd, $J_{10a,10}=6.4$ Hz, $J_{10a,10b}=10.1$ Hz, $J_{10a,10'}=1.3$ Hz, 1 H, H-10a), 3.23 (dd, $J_{10a,10b}=10.1$ Hz, $J_{10b,3a}=9.0$ Hz, 1 H, H-10b), 2.71 (dd, $J_{10,10'}=19.4$ Hz, $J_{10a,10}=6.4$ Hz, 1 H, H-10), 2.73 (s, 1 H, OH), 2.45 (dd, $J_{10,10'}=19.4$ Hz, $J_{10a,10'}=1.3$ Hz, 1 H, H-10′), 1.59 (s), 1.46 (s), 1.40 (s), 1.39 (s) [$2\times OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3 (C-9), 172.7 (C-7a), 134.5 (C-8), 110.1, 109.9 [2 C, $2\times OC(CH_3)_2O$], 80.6 (C-10b), 78.8 (C-3a), 78.0 (C-6a), 77.3 (C-3b), 71.3 (C-7), 42.1 (C-10a), 40.2 (C-10), 29.8, 27.2, 26.5, 23.4 [4 C, $2\times OC(CH_3)_2O$]; MS (70 eV) *m/z* 310 (M^+, 10), 295 (M^+-15, 21), 194 (27), 124 (23), 110 (18), 43 (100).

Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.02; H, 7.40.

[3a*R*-(3aα,3bβ,6aβ,7β,10aα,10bβ)]-7-Acetoxy-(3a,3b,6a,7,9,10a,10b)-heptahydro-2,2,5,5,-tetramethylazuleno[4,5-d;6,7-d]bis[1,3-dioxol]-9-one (6). Compound **5** (20 mg, 0.064 mmol) was treated with Ac_2O/pyridine (1 mL, 1:1) at rt for 24 h. The solvents were removed and the residue was submitted to chromatography (hexane/ethyl acetate, 1/1) to give acetate **6** (19 mg, 90%): oil; $[\alpha]_D^{25}+21$ (*c* 0.44, $CHCl_3$); IR (film) ν 2986, 1748 ($O=CCH_3O$), 1719 (C=O), 1624 (C=C), 1373, 1225, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1 H, H-8), 6.06 (d, $J_{6a,7}=2.3$ Hz, 1 H, H-7), 4.38 (dd, $J_{3a,3b}=8.0$ Hz, $J_{3a,10b'}=9.0$ Hz, 1 H, H3a), 4.33 (t, $J_{3a,3b}=J_{6a,3b}=7.7$ Hz, 1 H, H3b), 4.19 (dd, $J_{6a,7}=2.3$ Hz, $J_{6a,3b}=7.7$ Hz, 1 H, H-6a), 3.32 (dd, $J_{10b,3a}=9.0$ Hz, $J_{10a,10b}=10.4$ Hz, 1 H, H-10b), 3.11 (ddd, $J_{10a,10b}=10.1$ Hz, $J_{10b,10A}=6.4$ Hz, $J_{10b,10B}=1.7$ Hz, 1 H, H-10a), 2.70 (dd, $J_{10A,10B}=19.4$ Hz, $J_{10a,10A}=6.4$ Hz, 1 H, H-10A), 2.45 (dd, $J_{10A,10B}=19.4$ Hz, $J_{10a,10B}=1.7$ Hz, 1 H, H-10B), 2.17 (s, 3 H, $OCOCH_3$), 1.49 (2s), 1.42 (s), 1.36 (s) [2 ×-$OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5 (C-9), 169.4 ($OCOCH_3$), 169.8 (C-7a), 135.4 (C-8), 110.7 [2 C, $2\times OC(CH_3)_2O$], 79.9 (C-10b), 79.4 (C-3a), 78.2 (C-3b), 77.4 (C-6a), 72.3 (C-7), 42.9 (C-10a), 40.1 (C-10), 27.3, 27.1, 26.6, 24.3 [4 C, $2\times OC(CH_3)_2O$], 21.1 ($OCOCH_3$); MS (70 eV) *m/z* 337 ($M^+ + 1$, 18), 310 (7), 177 (19), 149 (14), 43 (100).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19. Found: C, 64.67; H, 7.05.

7,8-Dideoxy-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (8) and 7,8-dideoxy-4,5-*O*-(1-methylethylidene)-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (9). Following the **GP** for acetal acid hydrolysis compound **7** (27) (1.6 g, 3.4 mmol) afforded compounds **8** (1.0 g, 78%) and **9** (293 mg, 20%), after chromatography (hexane/ethyl acetate, 7/3). **8**: oil; $[\alpha]_D^{25}-3$ (*c* 3.2, $CHCl_3$); IR (film) ν 3500 – 3300, 1550, 1460, 1150, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 10 H, aromat.), 5.83 (ddd, $J_{7,8}=18.7$ Hz, $J_{7,8'}=10.7$ Hz, $J_{6,7}=7.9$ Hz, 1 H, H-7), 5.34 (dd, $J_{7,8}=18.7$ Hz, $J_{8,8'}=1.7$ Hz, 1 H, H-8), 5.30 (dd, $J_{7,8'}=10.7$ Hz, $J_{8,8'}=1.7$ Hz, 1 H, H8′), 4.63/4.56 (AB system, $J=11.3$ Hz, 2 H, $OCH_2C_6H_5$), 4.60/4.30 (AB system, $J=11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.02 (dd, $J_{6,7}=7.8$ Hz, $J_{5,6}=3.2$ Hz, 1 H, H-6), 3.78 – 3.71 (m, 4 H, H-2, H-3, H-4, H-5), 3.65 (br d, $J_{1,1'}=11.0$ Hz, 1 H, H-1), 3.52 (br dd, $J_{1,1'}=11.0$ Hz, $J_{1',2}=4.6$ Hz, 1 H, H-1′), 3.12 (br s, 3 H, OH), 2.89 (br s, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8 – 127.9 ($2\times OCH_2C_6H_5$), 133.9 (C-7), 120.9 (C-8),

81.9 (C-5), 77.4 (C-4), 73.8 (C-6), 72.9 ($OCH_2C_6H_5$), 71.9 (C-3), 71.3 (C-2), 70.5 ($OCH_2C_6H_5$), 63.6 (C-1); MS: Calcd for $C_{22}H_{28}O_6$ Na $(M+Na)^+$: 411.5. Found: 411.1.
9: oil; $[\alpha]_D^{25} - 9$ (*c* 0.2, $CHCl_3$); IR (film) ν 3500 – 3300, 1550, 1460, 1150, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 – 7.21 (m, 10 H, aromat.), 5.82 (ddd, $J_{7,8}=17.1$ Hz, $J_{7,8'}=10.2$ Hz, $J_{6,7}=7.9$ Hz, 1 H, H-7), 5.49 (dd, $J_{7,8}=10.2$ Hz, $J_{8,8'}=1.5$ Hz, 1 H, H-8), 5.35 (dd, $J_{7,8'}=17.1$ Hz, $J_{8,8'}=1.5$ Hz, 1 H, H8′), 4.62 (s, 2 H, $OCH_2C_6H_5$), 4.60/4.13 (AB system, $J=11.0$ Hz, 2 H, $OCH_2C_6H_5$), 4.39 (dd, $J_{3,4}=7.1$ Hz, $J_{4,5}=5.1$ Hz, 1 H, H-4), 4.17 (dd, $J_{1,1'}=10.0$ Hz, $J_{1,2}=4.7$ Hz, 1 H, H-1), 3.97 (br t, $J_{5,6}=J_{6,7}=7.9$ Hz, 1 H, H-6), 3.65 – 3.53 (m, 3 H, H-1′, H-3, H-5), 3.42 – 3.30 (m, 3 H, H-2, 2 × OH), 1.49, 1.38 [2 s, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3–127.7 ($2\times OCH_2C_6H_5$), 135.4 (C-7), 120.7 (C-8), 108.5 [$OC(CH_3)_2O$], 80.3 (C-5), 79.0 (C-4), 78.3 (C-6), 74.7 (C-3), 73.1 ($OCH_2C_6H_5$), 72.9 (C-2), 69.9 ($OCH_2C_6H_5$), 64.3 (C-1), 27.5, 25.7 [$OC(CH_3)_2O$]; MS: Calcd for $C_{25}H_{32}O_6$ Na $(M+Na)^+$: 451.5. Found: 451.2.

Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.77; H, 7.45.

7,8-Dideoxy-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (10). Following the **GP** for silylation reactions compound **8** (1.0 g, 2.64 mmol) gave product **10** (1.37 g, 83%) after chromatography (hexane/ethyl acetate, 7/3): oil; $[\alpha]_D^{25} + 6$ (*c* 0.11, $CHCl_3$); IR (film) ν 3600 – 3200, 3020, 2990, 1530, 1470, 1370, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.68/ 7.44 – 7.10 (m, 20 H, aromat.), 5.97 (ddd, $J_{7,8}=17.8$ Hz, $J_{7,8'}=10.6$ Hz, $J_{6,7}=8.0$ Hz, 1 H, H-7), 5.47 (dd, $J_{7,8}=10.6$ Hz, $J_{8,8'}=1.7$ Hz, 1 H, H-8), 5.43 (dd, $J_{7,8'}=17.8$ Hz, $J_{8,8'}=1.7$ Hz, 1 H, H8′), 4.67/4.43 (AB system, $J=11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.62 (s, 2 H, $OCH_2C_6H_5$), 4.15 (dd, $J_{6,7}=8.0$ Hz, $J_{5,6}=3.8$ Hz, 1 H, H-6), 3.99 (st, $J_{1,2}=J_{1',2}=J_{2,3}=J_{2,OH}=5.1$ Hz, 1 H, H-2), 3.95 – 3.85 (m, 4 H, H-1, H-3, H-4, H-5), 3.76 (dd, $J_{1,1'}=10.2$ Hz, $J_{1,2}=5.4$ Hz, 1 H, H-1′), 2.96 (d, $J_{2,OH}=5.1$ Hz, 1 H, OH), 2.85 (d, $J=7.2$ Hz, 1 H, OH), 2.53 (d, $J=2.9$ Hz, 1 H, OH), 1.11 [s, 9 H, $Si(C_6H_5)_2C(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2 – 127.7 [$2\times OCH_2C_6H_5$, $Si(C_6H_5)_2C(CH_3)_3$], 133.9 (C-7), 120.5 (C-8), 81.7 (C-5), 76.4 (C-4), 73.6 ($OCH_2C_6H_5$), 72.9 (C-6), 71.7 (C-3), 70.7 (C-2), 70.5 ($OCH_2C_6H_5$), 64.9 (C-1), 26.9 [$Si(C_6H_5)_2C(CH_3)_3$], 19.2 [$Si(C_6H_5)_2C(CH_3)_3$]; MS: Calcd for $C_{38}H_{46}O_6$ NaSi $(M+Na)^+$: 649.8. Found: 649.3.

Anal. Calcd for $C_{38}H_{46}O_6$: C, 76.22; H, 7.74. Found: C, 76.58; H, 7.48.

7,8-Dideoxy-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2,4,5-tri-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (11). Following the **GP** for *O*-methylation compound **10** (1.3 g, 2.18 mmol) afforded compound **11** (887 g, 60%) after chromatography (hexane/ethyl acetate: 95/5): oil; $[\alpha]_D^{25} - 14$ (*c* 0.36, $CHCl_3$); IR (film) ν 3020, 2900, 1400, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 – 7.58/ 7.36 – 7.12 (m, 20 H, aromat.), 5.94 (ddd, $J_{7,8}=17.3$ Hz, $J_{7,8'}=10.4$ Hz, $J_{6,7}=7.6$ Hz, 1 H, H-7), 5.32 (dd, $J_{7,8}=10.4$ Hz, $J_{8,8'}=1.9$ Hz, 1 H, H-8), 5.25 (dd, $J_{7,8'}=17.3$ Hz, $J_{8,8'}=1.9$ Hz, 1 H, H8′), 4.61/4.33 (AB system, $J=11.5$ Hz, 2 H, $OCH_2C_6H_5$), 4.56/4.52 (AB system, $J=6.6$ Hz, 2 H, $OCH_2C_6H_5$), 4.05 (dd, $J_{6,7}=7.8$ Hz, $J_{5,6}=2.3$ Hz, 1 H, H-6), 3.90 (dd, $J_{1,1'}=11.5$ Hz, $J_{1,2}=1.6$ Hz, 1 H, H-1), 3.89 (t, $J_{2,3}=J_{3,4}=2.1$ Hz, 1 H, H-3), 3.79 (dd, $J_{1,1'}=11.5$ Hz, $J_{1',2}=4.4$ Hz, 1 H, H-1′), 3.61 (dd, $J_{4,5'}=8.3$ Hz, $J_{5,6}=2.3$ Hz, 1 H, H-5), 3.41 (dd, $J_{4,5'}=8.3$ Hz, $J_{3,4}=2.1$ Hz, 1 H, H-4), 3.38 (s, 3 H, OCH_3), 3.36 – 3.32 (m, 1 H, H-2), 3.31 (s, 3 H, OCH_3), 3.20 (s, 3 H, OCH_3), 1.00 [s, 9 H, $Si(C_6H_5)_2C(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9 – 127.3 [$2\times OCH_2C_6H_5$,

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$Si(C_6H_5)_2C(CH_3)_3]$, 133.8 (C-7), 119.1 (C-8), 82.3 (C-5), 81.7 (2 C, C-2, C-4), 79.9 (C-6), 75.3 (C-3), 74.1 ($OCH_2C_6H_5$), 70.6 ($OCH_2C_6H_5$), 65.3 (C-1), 60.0, 59.1, 57.5 (3 C, $3 \times OCH_3$), 29.7 $[Si(C_6H_5)_2C(CH_3)_3]$, 19.3 $[Si(C_6H_5)_2C(CH_3)_3]$; MS: Calcd for $C_{41}H_{52}O_6$ NaSi $(M+Na)^+$: 691.9. Found: 691.3.

Anal. Calcd for $C_{41}H_{52}O_6$: C, 76.84; H, 8.18. Found: C, 76.77; H, 8.06.

7,8-Dideoxy-2,4,5-tri-*O*-methyl-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (12). Following the **GP** for desilylation reactions compound **11** (790 mg, 1.2 mmol) gave product **12** (470 g, 93%) after chromatography (hexane/ethyl acetate, 85/15): oil; $[\alpha]_D^{25} - 2$ (*c* 0.11, $CHCl_3$); IR (film) ν 3600 – 3200, 3010, 2990, 1460, 1090 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.17 (m, 10 H, aromat.), 5.89 (ddd, $J_{7,8} = 17.7$ Hz, $J_{7,8'} = 10.5$ Hz, $J_{6,7} = 7.6$ Hz, 1 H, H-7), 5.32 (dd, $J_{7,8} = 10.5$ Hz, $J_{8,8'} = 1.7$ Hz, 1 H, H-8), 5.26 (dd, $J_{7,8'} = 17.7$ Hz, $J_{8,8'} = 1.7$ Hz, 1 H, H8′), 4.63/4.59 (AB system, $J = 11.5$ Hz, 2 H, $OCH_2C_6H_5$), 4.55/4.32 (AB system, $J = 11.8$ Hz, 2 H, $OCH_2C_6H_5$), 4.05 (dd, $J_{6,7} = 7.9$ Hz, $J_{5,6} = 2.8$ Hz, 1 H, H-6), 3.85 (dd, $J_{2,3} = 3.1$ Hz, $J_{3,4} = 6.6$ Hz, 1 H, H-3), 3.81 (br d, $J_{1,1'} = 4.8$ Hz, 1 H, H-1), 3.69 – 3.65 (m, 1 H, H-1′), 3.55 (dd, $J_{4,5'} = 7.8$ Hz, $J_{5,6} = 2.8$ Hz, 1 H, H-5), 3.37 (s, 3 H, OCH_3), 3.36 (s, 3 H, OCH_3), 3.35 – 3.27 (m, 2 H, H-2, H-4), 3.27 (s, 3 H, OCH_3), 2.05 (br d, $J = 5.4$ Hz, 1 H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3 – 127.2 ($2 \times OCH_2C_6H_5$), 134.6 (C-7), 119.1 (C-8), 81.9 (C-5), 81.0, 80.6 (2 C, C-2, C-4), 79.7 (C-6), 77.1 (C-3), 74.1 ($OCH_2C_6H_5$), 70.2 ($OCH_2C_6H_5$), 59.9 (OCH_3), 59.0 (C-1), 58.8, 56.3 (2 C, $2 \times OCH_3$); MS: Calcd for $C_{25}H_{34}O_6$ Na $(M+Na)^+$: 453.6. Found: 453.5.

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.68; H, 7.85.

1,7,8-Trideoxy-2,4,5-tri-*O*-methyl-1-[oxido(phenylmethyl)imino]3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (14). Following the **GP** for oxidation via PCC compound **12** (110 mg, 0.25 mmol) afforded **13** (93 mg, 85%) after chromatography (hexane/ethyl acetate, 75/25), ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 (d, $J_{1,2} = 2.0$ Hz, 1 H, H-1), 7.35 – 7.24 (m, 10 H, aromat.), 5.95 (ddd, $J_{7,8} = 17.1$ Hz, $J_{7,8'} = 10.2$ Hz, $J_{6,7} = 7.6$ Hz, 1 H, H-7), 5.42 (dd, $J_{7,8} = 10.2$ Hz, $J_{8,8'} = 1.9$ Hz, 1 H, H-8), 5.34 (dd, $J_{7,8'} = 17.1$ Hz, $J_{8,8'} = 1.9$ Hz, 1 H, H8′), 4.65 (s, 2 H, $OCH_2C_6H_5$), 4.63/4.38 (AB system, $J = 11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.11 (dd, $J_{6,7} = 7.6$ Hz, $J_{5,6} = 3.9$ Hz, 1 H, H-6), 4.07 (t, $J_{2,3} = J_{3,4} = 4.0$ Hz, 1 H, H-3), 3.81 (dd, $J_{2,3} = 4.3$ Hz, $J_{1,2} = 2.0$ Hz, 1 H, H-2), 3.63 (dd, $J_{4,5} = 7.0$ Hz, $J_{3,4} = 4.0$ Hz, H-4), 3.50 (dd, $J_{4,5} = 7.0$ Hz, $J_{5,6} = 3.9$ Hz, H-5), 3.44 (s, 6 H, $2 \times OCH3$), 3.43 (s, 3 H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7 (C-1), 138.4 – 127.7 ($2 \times OCH_2C_6H_5$), 134.9 (C-7), 119.4 (C-8), 86.1 (C-2), 82.3 (C-3), 80.7 (C-4), 80.5 (C-5), 79.7 (C-6), 74.2 ($OCH_2C_6H_5$), 70.5 ($OCH_2C_6H_5$), 60.4 (OCH_3), 59.0 (OCH_3), 58.1 (OCH_3). Following the **GP** for the synthesis of nitrones this aldehyde (82 mg, 0.19 mmol) gave nitrone (**14**) (75 mg, 74%) after chromatography (hexane/ethyl acetate, 6/4): oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.23 (m, 15 H, aromat.), 6.89 (d, $J_{1,2} = 7.6$ Hz, 1 H, H-1), 5.88 (ddd, $J_{7,8} = 17.5$ Hz, $J_{7,8'} = 10.1$ Hz, $J_{6,7} = 7.6$ Hz, 1 H, H-7), 5.35 (dd, $J_{7,8} = 10.1$ Hz, $J_{8,8'} = 1.7$ Hz, 1 H, H-8), 5.28 (dd, $J_{7,8'} = 17.5$ Hz, $J_{8,8'} = 1.7$ Hz, 1 H, H8′), 4.86 – 4.80 (m, 3 H, H-2, $N(O)CH_2C_6H_5$), 4.73/4.64 (AB system, $J = 11.5$ Hz, 2 H, $OCH_2C_6H_5$), 4.58/4.35 (AB system, $J = 11.6$ Hz, 2 H, $OCH_2C_6H_5$), 4.09 – 4.02 (m, 2 H, H-6, H-3), 3.56 (dd, $J_{3,4} = 3.9$ Hz, $J_{4,5} = 6.8$ Hz, 1 H, H-4), 3.31 (s, 3 H, OCH_3) , 3.30 – 3.25 (m, 1 H, H-5), 3.29 (s, 3 H, OCH3), 3.26 (s, 3 H, OCH_3).

Anal. Calcd for $C_{32}H_{39}NO_6$: C, 72.02; H, 7.37; N, 2.62. Found: C, 72.24; H, 7.45; N, 2.77.

7,8-Dideoxy-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-4,5-*O*-(1-methylethylidene)-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (15). Following the **GP** for silylation reactions compound **9** (167 mg, 0.39 mmol) afforded compound **15** (260 mg, 99%) after chromatography (hexane/ethyl acetate, 4/1): oil; $[\alpha]_D^{25} + 16$ (*c* 0.11, $CHCl_3$); IR (film) ν 3500 – 3300, 2990, 1450, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.71/ 7.48 – 7.26 (m, 20 H, aromat.), 5.85 (ddd, $J_{7,8} = 17.2$ Hz, $J_{7,8'} = 10.3$ Hz, $J_{6,7} = 7.9$ Hz, 1 H, H-7), 5.48 (dd, $J_{7,8} = 10.3$ Hz, $J_{8,8'} = 1.6$ Hz, 1 H, H-8), 5.33 (dd, $J_{7,8'} = 17.2$ Hz, $J_{8,8'} = 1.6$ Hz, 1 H, H8′), 4.63/4.36 (AB system, $J = 11.8$ Hz, 2 H, $OCH_2C_6H_5$), 4.55 (dd, $J_{4,5} = 5.7$ Hz, $J_{3,4} = 4.6$ Hz, 1 H, H-4), 4.56/4.26 (AB system, $J = 11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.21 (dd, $J_{5,6} = 8.8$ Hz, $J_{4,5} = 5.7$ Hz, 1 H, H-5), 4.11 (t, $J_{5,6'} = J_{6,7} = 8.4$ Hz, 1 H, H-6), 4.08 – 4.02 (m, 1 H, H-2), 3.92 (dd, $J_{1,1'} = 10.5$ Hz, $J_{1,2} = 4.6$ Hz, 1 H, H-1), 3.73 (dd, $J_{1,1'} = 10.5$ Hz, $J_{1',2} = 6.2$ Hz, 1 H, H-1′), 3.72 (t, $J_{2,3} = J_{3,4} = 4.6$ Hz, 1 H, H-3), 1.50, 1.38 [2 s, $OC(CH_3)_2O$], 1.13 [s, 9 H, $Si(C_6H_5)_2C(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 – 127.0 [2 × $OCH_2C_6H_5$, $Si(C_6H_5)_2C(CH_3)_3$], 135.8 (C-7), 119.8 (C-8), 108.2 [$OC(CH_3)_2O$], 82.9 (C-5), 78.7 (C-4), 78.1 (C-6), 77.1 (C-3), 72.9 (C-2), 72.0 ($OCH_2C_6H_5$), 68.7 ($OCH_2C_6H_5$), 62.5(C-1), 26.6, 26.0, 25.1 [$OC(CH_3)_2O$], 25.1 [$Si(C_6H_5)_2C(CH_3)_3$], 11.9 [$Si(C_6H_5)_2C(CH_3)_3$]; MS: Calcd for $C_{41}H_{50}O_6NaSi$ $(M + Na)^+$: 689.9. Found: 690.1.

Anal. Calcd for $C_{41}H_{50}O_6$: C, 77.08; H, 7.89. Found: C, 77.37; H, 7.76.

7,8-Dideoxy-1-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2-*O*-methyl-4,5-*O*-(1-methylethylidene)-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (16). Following the **GP** for *O*-methylations compound **15** (260 mg, 0.39 mmol) afforded compound **16** (197 mg, 74%) after chromatography (hexane/ethyl acetate, 93/7): oil; $[\alpha]_D^{25} - 13$ (*c* 0.2, $CHCl_3$); IR (film) ν 3010, 2900, 1410, 1350, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 – 7.69/ 7.47 – 7.21 (m, 20 H, aromat.), 5.89 (ddd, $J_{7,8} = 17.2$ Hz, $J_{7,8'} = 10.3$ Hz, $J_{6,7} = 7.5$ Hz, 1 H, H-7), 5.42 (dd, $J_{7,8} = 10.3$ Hz, $J_{8,8'} = 1.5$ Hz, 1 H, H-8), 5.30 (dd, $J_{7,8'} = 17.2$ Hz, $J_{8,8'} = 1.5$ Hz, 1 H, H8′), 4.68/4.29 (AB system, $J = 11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.60/4.54 (AB system, $J = 5.0$ Hz, 2 H, $OCH_2C_6H_5$), 4.42 (d, $J_{3,4} = 5.6$ Hz, 1 H, H-4), 4.22 (dd, $J_{5,6} = 6.6$ Hz, $J_{6,7} = 7.4$ Hz, 1 H, H-6), 4.06 (dd, $J_{1,1''} = 11.1$ Hz, $J_{1,2} = 3.2$ Hz, 1 H, H-1), 4.05 (d, $J_{5,6} = 6.7$ Hz, 1 H, H-5), 3.90 (t, $J_{2,3} = J_{3,4} = 5.6$ Hz, 1 H, H-3), 3.81 (dd, $J_{1,1'} = 11.1$ Hz, $J_{1',2} = 5.1$ Hz, 1 H, H-1′), 3.41 (ddd, $J_{1,2} = 3.2$ Hz, $J_{1',2} = 5.1$ Hz, $J_{2,3} = 5.6$ Hz 1 H, H-2), 3.27 (s, 3 H, OCH_3), 1.44, 1.35 [2 s, $OC(CH_3)_2O$], 1.08 [s, 9 H, $Si(C_6H_5)_2C(CH_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7-127.1 [2 × $OCH_2C_6H_5$, $Si(C_6H_5)_2C(CH_3)_3$], 135.8 (C-7), 120.0 (C-8), 108.6 [$OC(CH_3)_2O$], 83.8 (C-2), 78.9 (C-4), 78.7 (C-5), 78.5 (C-6), 76.9 (C-3), 73.3 ($OCH_2C_6H_5$), 69.5 ($OCH_2C_6H_5$), 62.7 (C-1), 57.5 (OCH_3), 26.9 [$Si(C_6H_5)_2C(CH_3)_3$], 26.5, 25.5 [$OC(CH_3)_2O$], 12.3 [$Si(C_6H_5)_2C(CH_3)_3$]; MS: Calcd for $C_{42}H_{52}O_6Na$ $(M + Na)^+$: 663.9. Found: 664.9.

Anal. Calcd for $C_{42}H_{52}O_6$: C, 78.71; H, 8.18. Found: C, 78.66; H, 8.42.

7,8-Dideoxy-2-*O*-methyl-4,5-*O*-(1-methylethylidene)-3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (17). Following the **GP** for desilylation reactions compound **16** (187 mg, 0.27 mmol) afforded compound **17** (112 mg, 92%) after

chromatography (hexane/ethyl acetate, 75/25): oil; $[\alpha]_D^{25} + 9$ (*c* 0.24, $CHCl_3$); IR (film) ν 3500 – 3100, 2900, 1470, 1360, 1200 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 – 7.21 (m, 10 H, aromat.), 5.80 (ddd, $J_{7,8} = 17.4$ Hz, $J_{7,8'} = 10.3$ Hz, $J_{6,7} = 8.1$ Hz, 1 H, H-7), 5.41 (dd, $J_{7,8} = 10.3$ Hz, $J_{8,8'} = 1.0$ Hz, 1 H, H-8), 5.25 (dd, $J_{7,8'} = 17.4$ Hz, $J_{8,8'} = 1.0$ Hz, 1 H, H8′), 4.71/4.27 (AB system, $J = 12.2$ Hz, 2 H, $OCH_2C_6H_5$), 4.53/4.20 (AB system, $J = 11.6$ Hz, 2 H, $OCH_2C_6H_5$), 4.28 (dd, $J_{3,4} = 3.3$ Hz, $J_{4,5} = 6.3$ Hz, 1 H, H-4), 4.17 (dd, $J_{4,5} = 6.3$ Hz, $J_{5,6} = 8.3$ Hz, 1 H, H-5), 3.97 (t, $J_{5,6} = J_{6,7} = 8.2$ Hz, 1 H, H-6), 3.89 (dd, $J_{1,1'} = 12.0$ Hz, $J_{1,2} = 5.1$ Hz, 1 H, H-1), 3.85 (t, $J_{2,3} = J_{3,4} = 3.3$ Hz, 1 H, H-3), 3.69 (dd, $J_{1,1'} = 12.0$ Hz, $J_{1',2} = 3.9$ Hz, 1 H, H-1′), 3.33 – 3.31 (m, 1 H, H-2), 3.32 (s, 3 H, OCH_3), 1.47, 1.33 [2 s, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7 – 127.2 ($2 \times OCH_2C_6H_5$), 135.8 (C-7), 120.7 (C-8), 109.3 [$OC(CH_3)_2O$], 84.4 (C-2), 78.5 (3 C, C-4, C-5, C-6), 67.2 (C-3), 72.9 ($OCH_2C_6H_5$), 69.4 ($OCH_2C_6H_5$), 59.9 (C-1), 57.7 (OCH_3), 26.5, 25.5 [$OC(CH_3)_2O$]; MS (70 eV) *m*/*z* 367 (6), 277 (5), 181 (21), 169 (49), 91 (100), 75 (18).

Anal. Calcd for $C_{26}H_{34}O_6$: C, 77.59; H, 8.51. Found: C, 7.44; H, 8.34.

1,7,8-Trideoxy-2-*O*-methyl-1-[oxido(phenylmethyl)imino]3,6-bis-*O*-(phenylmethyl)-D-*glycero*-D-*manno*-oct-7-enitol (19). Following the **GP** for oxidations via PCC compound **17** (100 mg, 0.22 mmol) afforded compound **18** (93 mg, 93%) after chromatography (hexane/ethyl acetate, 4/1) {oil; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (d, $J_{1,2} = 0.6$ Hz, 1 H, H-1), 7.33 – 7.26 (m, 10 H, aromat.), 5.80 (ddd, $J_{7,8} = 17.8$ Hz, $J_{7,8'} = 10.3$ Hz, $J_{6,7} = 8.3$ Hz, 1 H, H-7), 5.44 (dd, $J_{7,8} = 10.3$ Hz, $J_{8,8'} = 1.6$ Hz, 1 H, H-8), 5.41 (dd, $J_{7,8'} = 17.8$ Hz, $J_{8,8'} = 1.6$ Hz, 1 H, H8′), 4.70/4.26 (AB system, $J = 12.1$ Hz, 2 H, $OCH_2C_6H_5$), 4.52/4.13 (AB system, $J = 11.5$ Hz, 2 H, $OCH_2C_6H_5$), 4.40 (dd, $J_{3,4} = 3.7$ Hz, $J_{4,5} = 5.9$ Hz, 1 H, H-4), 4.19 (dd, $J_{4,5} = 5.9$ Hz, $J_{5,6} = 9.1$ Hz, 1 H, H-5), 3.91 (t, $J_{5,6} = J_{6,7} = 8.9$ Hz, 1 H, H-6), 3.91 – 3.89 (m, 2 H, H-2, H-3), 3.30 (s, 3 H, OCH_3), 1.45, 1.37 [2 s, $OC(CH_3)_2O$]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0 (CHO), 138.7 – 127.3 ($2 \times OCH_2C_6H_5$), 135.7 (C-7), 120.8 (C-8), 109.6 [$OC(CH_3)_2O$], 88.6 (C-2), 79.6, 78.5, 78.3 (2 C) (4 C, C-3, C-4, C-5, C-6), 67.2 (C-3), 72.5 ($OCH_2C_6H_5$), 69.4 ($OCH_2C_6H_5$), 58.5 (OCH_3), 26.5, 25.5 [$OC(CH_3)_2O$]}. Following the **GP** for the synthesis of nitrones this crude aldehyde (50 mg, 0.11 mmol) afforded compound (**19**) (38 mg, 65%) after chromatography (hexane/ethyl acetate, 1:1) as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 15 H, aromat.), 6.89 (d, $J_{1,2} = 7.3$ Hz, 1 H, H-1), 5.79 (ddd, $J_{7,8} = 17.2$ Hz, $J_{7,8'} = 10.3$ Hz, $J_{6,7} = 7.9$ Hz, 1 H, H-7), 5.41 (dd, $J_{7,8} = 10.3$ Hz, $J_{8,8'} = 1.5$ Hz, 1 H, H-8), 5.27 (dd, $J_{7,8'} = 17.2$ Hz, $J_{8,8'} = 1.5$ Hz, 1 H, H8′), 4.85 [s, 2 H, $N(O)CH_2C_6H_5$], 4.84 (dd, $J_{1,2} = 7.3$ Hz, $J_{2,3} = 1.9$ Hz, 1 H, H-2), 4.80/4.62 (AB system, $J = 12.4$ Hz, 2 H, $OCH_2C_6H_5$), 4.56/4.14 (AB system, $J = 11.2$ Hz, 2 H, $OCH_2C_6H_5$), 4.22 (dd, $J_{5,6} = 8.8$ Hz, $J_{4,5} = 5.4$ Hz, 1 H, H-5), 4.11 (dd, $J_{4,5} = 5.4$ Hz, $J_{3,4} = 6.9$ Hz, 1 H, H-4), 3.98 (dd, $J_{3,4} = 6.9$ Hz, $J_{2,3} = 1.9$ Hz, 1 H, H-3), 3.83 (t, $J_{5,6} = J_{6,7} = 8.6$ Hz, 1 H, H-6), 3.02 (s, 3 H, OCH_3), 1.41, 1.26 [2 s, $OC(CH_3)_2O$].

Anal. Calcd for $C_{33}H_{39}NO_6$: C, 72.64; H, 7.20; N, 2.57. Found: C, 72.54; H, 7.34; N, 2.64.

(3a*S*,4*R*,4a*R*,7a*S*,8*R*,9*R*,9a*S*)-Octahydro-9-methoxy-6,6-dimethyl-4,8-bis(phenylmethyl)-1H[1,3]-dioxolo[4,5]cyclohept[1,2-c]isoxazole (20) and (3a*R*,4*R*,4a*R*,7a*S*,8*R*,9*R*,9a*R*)-octahydro-9-methoxy-6,6-dimethyl-4,8-bis(phenylmethyl)-1*H*[1,3]-dioxolo[4,5]cyclohept[1,2-c]isoxazole (21). Nitrone **19** (38 mg, 0.075 mmol) was dissolved in chlorobenzene (3 mL), and the solution was warmed at reflux for 20 h.

The solvent was removed, and the residue was submitted to chromatography (hexane/ethyl acetate, 75/25) to give adducts **20** and **21** (19 mg, 50%) as an unseparable mixture of isomers in a 6 to 4 ratio, respectively: oil; IR (film) ν 2900, 1560, 1480, 1120, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) {(major isomer **20**) δ 7.33 – 7.16 (m, 15 H, aromat.), 5.03/4.47 (AB system, $J = 11.7$ Hz, 2 H, $OCH_2C_6H_5$), 4.76/4.52 (AB system, $J = 12.3$ Hz, 2 H, $OCH_2C_6H_5$), 4.60 (t, $J_{8,7a} = J_{4a,7a} = 8.3$ Hz, 1 H, H-7a), 4.51 (d, $J_{4,4a} = 2.3$ Hz, 1 H, H-4), 4.19 (dd, $J_{4,4a} = 2.3$ Hz, $J_{4a,7a} = 8.3$ Hz, 1 H, H-4a), 3.89 (d, $J_{7a,8} = 8.3$ Hz, 1 H, H-8), 3.86 (s, 2 H, $NCH_2C_6H_5$), 3.80 (t, $J_{3,3a} = J_{3,3'} = 7.4$ Hz, 1 H, H-3), 3.53 (dd, $J_{3,3'} = 7.4$ Hz, $J_{3',3a} = 10.7$ Hz, 1 H, H-3′), 3.50 (s, 3 H, OCH_3), 3.44 (br s, 1 H, H-9), 3.05 – 2.70 (m, 1 H, H-9a), 2.69 (dt, $J_{3,3a} = 7.4$ Hz, $J_{3',3a} = J_{9a,3a} = 10.7$ Hz, 1 H, H-3a), 1.43, 1.30 [2 s, $OC(CH_3)_2O$]} {(minor isomer **21**) δ 7.33 – 7.16 (m, 15 H, aromat.), 4.89/4.61 (AB system, $J = 11.5$ Hz, 2 H, $OCH_2C_6H_5$), 4.63/4.42 (AB system, $J = 12.0$ Hz, 2 H, $OCH_2C_6H_5$), 4.46 (dd, $J_{8,7a} = 8.3$ Hz, $J_{4a,7a} = 5.4$ Hz, 1 H, H-7a), 4.14 (d, $J_{7a,4a} = 5.4$ Hz, 1 H, H-4a), 4.07 (t, $J_{3,3'} = J_{3a,3'} = 7.6$ Hz, 1 H, H-3′), 3.90 – 3.87 (m, 2 H, H-4, H-8), 3.84 (s, 2 H, $NCH_2C_6H_5$), 3.68 (dd, $J_{3,3a} = 10.9$ Hz, $J_{3,3'} = 7.6$ Hz, 1 H, H-3), 3.62 (d, $J_{9,9a} = 10.1$ Hz, 1 H, H-9), 3.46 (s, 3 H, OCH_3), 3.14 (br t, $J_{9,9a} = J_{9a,3a} = 10.1$ Hz, 1 H, H-9a), 3.05 – 2.70 (m, 1 H, H-3a), 1.47, 1.30 [2 s, $OC(CH_3)_2O$]}; ^{13}C NMR (75 MHz, $CDCl_3$) {(major isomer **20**) δ 138.7 – 127.4 ($2 \times OCH_2C_6H_5$), 107.5 [$OC(CH_3)_2O$], 79.7 (C-4a), 78.7 (C-9), 78.0 (C-7a), 75.8 ($OCH_2C_6H_5$), 74.7, 74.6 (C-8, C-4),72.8 ($OCH_{2C_6}H_5$), 67.7 (C-9a), 67.0 (C-3), 62.3 ($NCH_2C_6H_5$), 61.1 (OCH_3), 44.5 (C-3a), 26.4, 23.7 [$OC(CH_3)_2O$]} {(minor isomer **21**) δ 138.5 – 126.9 ($2 \times OCH_2C_6H_5$), 108.6 [$OC(CH_3)_2O$], 82.4 (C-9), 81.1 (C-4), 77.8 (C-4a), 76.1 (C-8), 74.1 ($OCH_2C_6H_5$), 73.6 (C-7a), 71.7 ($OCH_2C_6H_5$), 68.4 (C-3), 67.5 (C-9a), 64.7 ($NCH_2C_6H_5$), 58.1 (OCH_3), 42.4 (C-3a), 25.9, 23.3 [$OC(CH_3)_2O$]}; MS *m/z* 545 (M^+, 21), 530 ($M^+ - 15$, 5), 284 (64), 188 (8), 91 (100).

Anal. Calcd for $C_{33}H_{39}NO_6$: C, 72.64; H, 7.20; N, 2.57. Found: C, 72.75; H, 7.55; N, 2.45.

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