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SYNTHESIS OF BRIDGED HEAD METHYL 3,4-*O*-(1',2'-DIMETHYL-CYCLOHEAXANE-1',2'-DIYL)-6,7-DIDEOXY-α-D-MANNOOCT-6-ENE-PYRANOSE-8,2-LACTONE FROM D-MANNOSE

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Abstract - The *vicinal* diequatorial diol at C-3 and C-4 of (**1**) was masked as cyclohexane diacetal derivative (**2**). Selective protection of C-2 as benzyl ether (**3a**) and Swern oxidation of the primary 6-OH gave the aldehyde derivative (**4**). Stereoselective *Wittig* condensation of **4** with Ph_3P=CH-CO_2Me followed by debenzylation and cyclization afforded the bridged α,β-unsaturated lactone derivative (**8**) in a moderate overall yield.

INTRODUCTION

As a consequence of the importance of the enantiomerically pure saturated and unsaturated γ- and δ-lactones,[1] the design and synthesis of structural and configurational variants of lacone-containing compounds continues to attract attention.[2,3] These investigations have shed light on the structure-activity relationships in such biologically active compounds. Furthermore, the lactone moieties are useful chiral building blocks for the synthesis of bioactive compounds[4] and materials with interesting technological properties.[5]

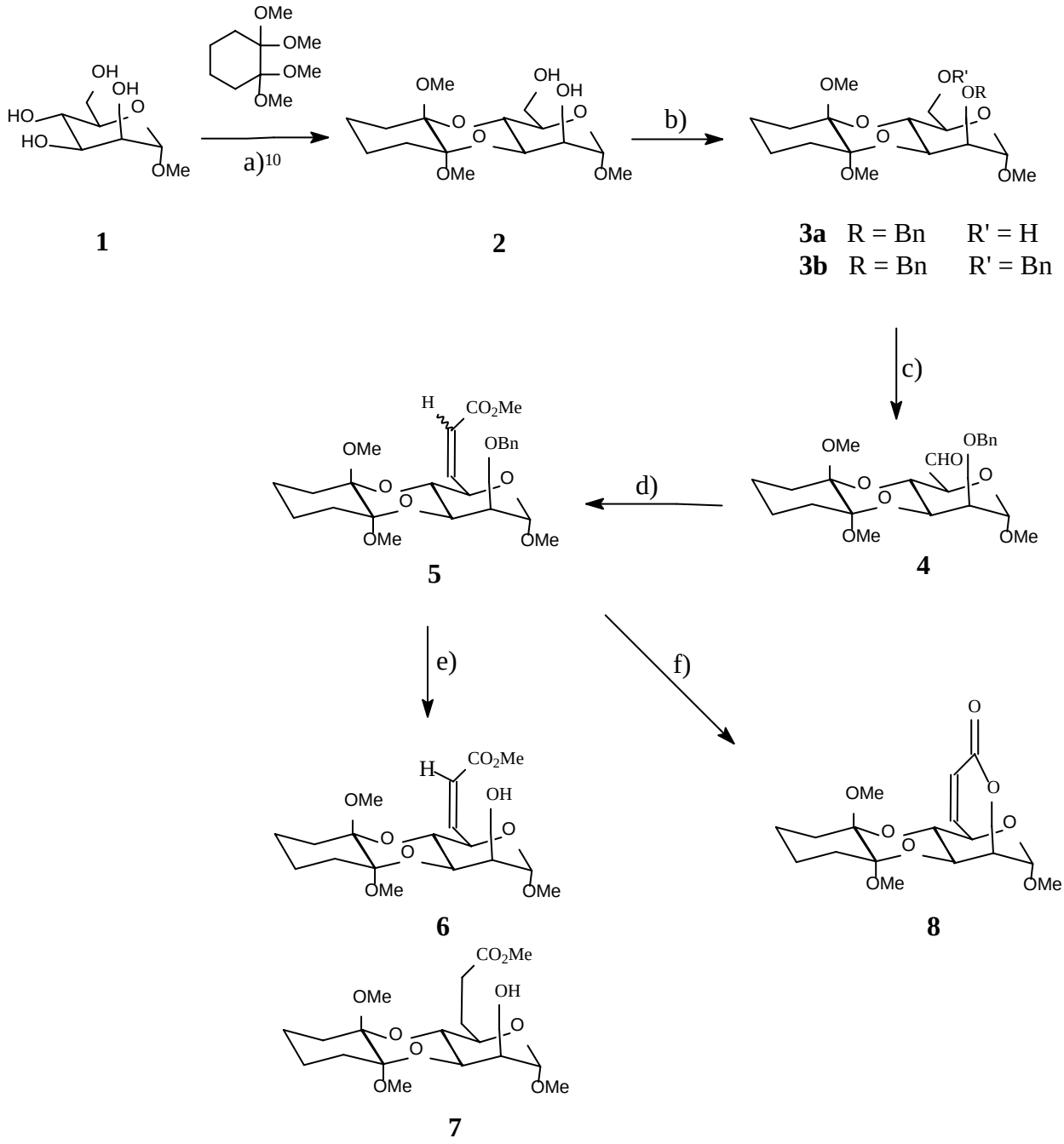
In continuation of our interest to obtain chiral α,β-unsaturated δ-lactones from the readily accessible carbohydrates, we recently reported the use of D-glucose to prepare the natural C_6-pyranoid unit of C_{12} eno-lactone natural products.[6] The synthesis of this unsaturated δ-lactone based on the direct lactonization of the corresponding δ-hydroxy-α,β-unsaturated ester, which was prepared *via* a olefination reaction of the chiral protected hydroxy aldehyde. The (*R*)-configuration of 4-OH of the sugar as well as the selective (*Z*)-olefination reaction were the key features in this synthesis. As an extension of this

practical route, we wish to report herein the synthesis of bridged α,β-unsaturated lactone ring on the C-2 and C-6 positions of the D-mannose. The axial configuration of 2-OH in D-mannose invites speculation as to whether this property would encourage formation of such bridged ring structure. A bridged analogue of such α,β-unsaturated δ-lactone is also seen in *Fraser-Reid's* approach to part of the insect antifeedant azadirachtin.[7]

The structural and stereochemical features of such bridged lactone systems make them useful building block for further transformations, e.g., cycloadditions route for the construction of complex ring systems. In addition, the biological function[8] of mannose and its derivatives, that significantly depends on the nature of the substituents at various positions, would make a derivative of such polycyclic systems an interesting substrate for incorporation into combinatorial libraries and thus the synthesis of a new biologically active compound.

RESULTS AND DISCUSSIONS

The formation of a bridged lactone ring system on the C-2 and C-6 positions of D-mannose requires a selective protection of the hydroxyl groups at C-3 and C-4. Indeed, classical selective protection of these positions as their isopropylidene or benzylidene derivatives involves multistep protection and deprotection procedures.[9] A shortcut considered to achieve this goal was to apply cyclohexane-1,2-diacetal protective group, the efficient methodology developed by *Ley's* group for rapid selective protection[10] of the *vicinal* diequatorial diol of methyl α-D-mannopyranose (**1**) at positions 3 and 4. As shown in Scheme 1, the protecting agent 1,1,2,2-tetramethoxycyclohexane was prepared from commercially available cyclohexane-1,2-dione by boiling with methanol, trimethyl orthoformate and few drops of concentrated sulfuric acid. Treatment of methyl α-D-mannopyranose (**1**) with tetramethoxycyclohexane in boiling methanol in the presence of trimethyl orthoformate and catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) yielded the 3,4-diacetal derivative (**2**) as a pure crystalline product in 31% yield. Selective protection of the 2-OH[11] of compound (**2**) was achieved by reaction with benzyl bromide and sodium hydride in DMF to give 2-benzyl ether (**3a**) in 69% as a white foam. It is interesting to note that the 2,6-dibenzyl ether (**3b**) was isolated as a minor product (3%). Swern oxidation[12] of **3a** gave the aldehyde derivative (**4**) in excellent yield (97%). Although this aldehyde could be purified by rapid flash chromatography, it proved to be hygroscopic and it could be used directly in the next step. Thus the crude Swern oxidation product was dissolved in dry methanol and treated with 1.5



Key: a) *p*-TsOH, $CH(OMe)_3$, MeOH; b) BnBr, NaH, DMF; c) $(COCl)_2$, DMSO, CH_2Cl_2; d) $Ph_3P{=}CH\text{-}CO_2Me$, MeOH, *n*-BuLi; e) H_2, 10% Pd/C, CH_2Cl_2; f) $FeCl_3$, CH_2Cl_2.

Scheme 1

molar equivalent of methoxycarbonylmethylenetriphenylphosphorane (Ph_3P=CH-CO_2Me, *Aldrich*) at –60°C→room temperature to give a mixture (75:25) of the (*Z/E*) α,β-unsaturated ester (**5**) in 31% yield. The two isomers were identified by the chemical shift and coupling constants of the olefinic protons [δ 7.52 ppm (dd, J = 7.3, 1.3 Hz) and δ 7.37 ppm (d, J = 7.3 Hz) for the *Z*-isomer of (**5**) and δ 7.65 (dd, J = 11.8, 1.3 Hz) and δ 7.64 (d, J = 11.8 Hz) for the *E*-isomer of **5**]. These assignment are corroborated by the ^{13}C NMR signals of C-6, C-7 and C=O carbons. Thus, for the *Z*-isomers these signals resonated respectively at δ 131.70, 130.78 and 165.17 ppm whereas for the *E*-isomer **5** at δ 131.91, 131.89 and 165.25 ppm respectively. Furthermore, the structure of **5** was fully characterized by spectroscopic and analytical means. The ^{1}H NMR spectrum of **5** showed a resonance at δ 4.66 ppm (d, J = 1.8 Hz) correspond to H-1. The $J_{1,2}$ value observed accords with *eq, eq* relationship. The H-3 and H-4 protons resonated at δ 4.24 ppm (dd, $J_{3,4}$ = 10.3, $J_{3,2}$ = 2.8 Hz) and δ 4.32 (dd, $J_{4,3}$ = $J_{4,5}$ = 10.3 Hz) respectively. The high ^3J values ($J_{3,4}$ = $J_{4,3}$ = $J_{4,5}$ = 10.3 Hz) indicated *ax, ax, ax* dispositions and accord with $^4C_1$ (D) conformation. Two doublets of AB system, reflect the isomers ratio, located at δ 4.97 ppm (d, J_{AB} = 11.8 Hz, 1H), δ 4.87 ppm (d, $J_{A'B'}$=12.1 Hz, minor isomer), and δ 4.63 (d, J_{AB} = 11.8 Hz, 1H) assigned for 2H of the benzyl group. The four methyl groups protons resonated at δ 3.30, 3.23, 3.22 and 3.16 ppm respectively. The benzylic aromatic protons showed a multiplet signals at δ 7.74-7.21 ppm whereas that belong to the 8H's of the cyclohexane ring H-3', H-4', H-5' and H-6' appeared at δ 1.82-1.64 ppm, δ 1.48-1.42 ppm and δ 1.42-1.26 ppm respectively.

Fortunately careful column chromatography could isolate a pure sample of *Z*-isomer of **5**. Cleavage of the benzyl protective group at position–2 was our next goal. Although several methods being available for this purpose,[13] it was expected that the common hydrogenolysis method could simultaneously reduce the double bond at position-6 to give the diacetal (**7**). Surprisingly, this was not the case, treatment of **5** with a catalytic amount of 10% Pd/C under a sphere of hydrogen gas for 12 h yielded only the desired diacetal (**6**) in high yield (90%). On the other hand debenzylation of **5** using anhydrous $FeCl_3$ in dry CH_2Cl_2[14] (0.1% solution) was next examined. In this case the benzyl group was removed with simultaneous intramolecular transestrification to give the desired lactone (**8**) directly in 48% yield, although it was expected that the acidic medium could cause acetal cleavage.

The structure of the bridged lactone (**8**) was fully characterized by spectral and analytical methods. ^{1}H NMR spectrum of **8** showed the persistence of the protons of the pyranoside ring with $^4C_1$(D)-conformation. A useful marker of the cyclization step was the disappearance of the ester methyl group

signal and there was no signal corresponds to the CO_2H proton. The ^{13}C NMR spectrum showed a signal at 165.0 ppm for the CO signal of the lactone ring; signals at δ 129.83, δ 128.33 ppm that can be attributed to the olefinic carbons at C-6 and C-7 respectively; signals at δ 99.09, δ 71.73, δ 66.71 and δ 64.36 that correspond to the pyranoside ring carbons. Signals belonging to the cyclohexane ring are resonate at δ 98.99 (C-1'), δ 98.65(C-2'), δ 26.92, δ 26.86, δ 21.32 and δ 21.33 ppm whereas that belong to the three OCH_3 carbons resonated at δ 61.34, δ 46.92 and δ 46.72 ppm, respectively.

In summary, bridged α,β-unsaturated lactone (**8**) has been synthesized by direct lactonization method,[15] in 5 steps, from D-mannose. The axial configuration of the OH group at C-2 and the stereoselective (*Z*)-olefination reaction at C-6 were the key features in this procedure.

EXPERIMENTAL

General methods. Unless otherwise indicated, all reactions were performed under nitrogen atmosphere. Silica gel for column chromatography refers to *Merk Kiselgel* 60, 70-230 mesh (gravity) and 230-400 mesh (flash). Melting points were determined on a *Reichert-Jung* thermometer apparatus and are uncorrected. Spectra were recorded as follows: ^1H NMR, *Varian unity* (400 MHz), deuteriochloroform solutions (*J* values are given in Hz and δ in ppm); ^{13}C NMR, *Varian unity* (100 MHz), deuteriochloroform solutions; MS spectra (electron impact), *VG Micromass 16F* spectrometer operating at 70 eV with an accelerating voltage of 4 kV and a variable source temperature. High resolution mass spectra were determined on a *KRATOS limited MS9/50* spectrometer. Optical rotations were measured on a *Perkin-Elmer 141* polarimeter for chloroform solutions at 20°C and $[\alpha]_D$ values are given in 10^{-1}deg.cm^{2}g^{-1}. Microanalysis were performed on a *Carlo E1ba EA 1108* instrument at the Department of Chemistry, University of Cape Town, South Africa and the Microanalytical Lab, University of Cairo, Cairo, Egypt. Silica gel for column chromatography refers to *Merck kiselgel 60*:70-230 mesh (gravity) and 230-400 mesh (flash).

1,1,2,2-Tetramethoxycyclohexane.[10] A solution of 2.5 g (22.3 mmol) of 1,2-cyclohexandione in a 10:20 mL (*v/v*) mixture of MeOH:$CH(OMe)_3$ (113 mmol) and 100 μL of concentrated sulfuric acid was refluxed for 5 h. The resulting black solution was neutralized with 400 mg of $NaHCO_3$. The solution was

then filtered over a Celite (5 g) and the column was washed with 5 mL of MeOH:$CH(OMe)_3$ (1:2) mixture. The solvent was removed under reduced pressure to give 4 g (88%) of crude product as a dark thick oil. It was contaminated by a small amount of unreacted cyclohexandione and it was used without further purification. It was purified by distillation (0.8 mmHg, 75°C) to give 1.5 g (33%) as a colorless oil. **^{1}H NMR**: δ 3.27 (s, 12H, 4x OCH_3), 1.70-1.64 (m, 4H, 2x H-3, 2x H-6), 1.41-1.37 (m, 4H, 2x H-4, 2x H-5). **^{13}C NMR**: δ 102.06 (C-1, C-2), 49.23 (OCH_3), 30.59 (C-3, C-6), 21.66 (C-4, C-5).

Methyl 3,4-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-α-D-mannopyranoside (2).[10] To a solution of 1.5 g (7.70 mmol) of methyl-α-D-mannopyranoside (**1**) and 2 g (9.8 mmol) of 1,1,2,2-tetramethoxycyclohexane in a 10:1 mL of MeOH:$CH(OMe)_3$ mixture was added *p*-TsOH (10 mg). The mixture was refluxed overnight (12 h) and then 50 mg of $NaHCO_3$ was added. The solvent was evaporated under vacuum and the crude product was purified by column chromatography using Et_2O:EtOH (10:1) as eluent to give 800 mg (31%) of **2** as a thick yellow oil, R_f 0.25. It was recrystallize from Et_2O to furnish **2** as a white needles, mp 168°C, $[\alpha]_D$ = + 191º (c 1 in $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O_8$: C, 53.89; H, 7.78. Found: C, 54.00; H, 7.60. **^{1}H NMR**: δ 4.72 (d, $J_{1,2}$=1.3 Hz, H-1), 4.26 (dd, 1H, $J_{4,3}$= 10.4, $J_{4,5}$=9.1 Hz, H-4), 4.15 (dd, 1H, $J_{3,4}$=10.4, $J_{3,2}$ =3.1 Hz, H-3), 3.95-3.90 (m, 1H, H-2), 3.84-3.74 (m, 3H, 2x H-6, H-5), 3.36 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.21 (s, 3H, OCH_3), 2.90 (br s, 1H, OH), 2.28 (br s, 1H, OH), 1.79-1.62 (m, 4H, H-3', H-6'), 1.55-1.45 (m, 2H, H-3', H-6'), 1.42-1.32 (m, 2H, H-4', H-5').**^{13}C NMR**: δ 101.12, 99.13, 98.74, 70.61, 69.98, 68.74, 63.78, 61.27, 54.83, 46.87, 46.75, 26.92, 21.26.

Methyl 2-*O*-benzyl-3,4-*O*-(1',2'dimethoxycyclohexane-1',2'-diyl)-α–D-mannopyranoside (3a) and methyl 2,6-di-*O*-benzyl-3,4-*O*-(1',2'-dimethylcyclohexane-1',2'-diyl)-α-D-mannopyranoside (3b). 612 mg (1.8 mmol) of 3,4-diacetal derivative (**2**) dissolved in 6 mL of DMF was stirred with NaH (77 mg, 2.0 mmol, 60% suspension in mineral oil). After 2 h benzyl bromide (235 μL, 2 mmol) was added and stirring was continued overnight (12 h). The reaction mixture was then poured into ice-cooled solution of saturated NH_4Cl (15 mL) and extracted with Et_2O (4x 20 mL). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated till dryness. The crude product was purified by column chromatography using Et_2O:hexane (1:1) as eluent to give 534 (69%) of pure **3a**, R_f 0.19, $[\alpha]_D$ = + 32º (c 0.5 in $CHCl_3$), as a white foam and 30 mg (3%) of pure **3b**, R_f 0.43, $[\alpha]_D$ = + 95º (c 0.5 in $CHCl_3$) as a colorless oil. Anal. Calcd for $C_{15}H_{26}O_8$ **(3a)**: C, 62.25; H, 7.54. Found: C, 61.93; H, 7.60. Anal. Calcd for $C_{29}H_{38}O_8$ **(3b)**: C, 67.70; H, 7.39. Found: C, 61.80; H, 7.50. The following spectral data were recorded: **3a**: **^{1}H NMR** δ 7.40-7.25 (m, 5H, aromatic H's), 4.97(d, J_{AB} = 11.5 Hz, 1H, $PhCH_2$), 4.66

(d, $J_{1,2}$ = 1.6 Hz, H-1), 4.63 (d, J_{AB} = 11.5 Hz, 1H, $PhCH_2$), 4.36 (dd, $J_{4,3}$ = 10.6, $J_{4,5}$ = 9.3 Hz, H-4), 4.21 (dd, $J_{3,4}$= 10.6, $J_{3,2}$ = 2.7 Hz, H-3), 3.84-3.75 (m, 3H, 2x H-6, H-5), 3.71 (dd, 1H, *J* = 2.7, 1.6 Hz, H-2), 3.30 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 2.20 (br s, 1H, OH), 1.84-1.64 (m, 4H, 2x H-3', 2x H-6'), 1.58-1.50 (m, 2H, H-4', H-5'), 1.48-1.38 (m, 2H, H-4', H-5'). **^{13}C NMR**; δ 138.58, 128.15, 128.07, 127.45, 100.68, 98.69, 98.40, 76.69, 76.07, 73.26, 71.12, 69.59, 64.59, 61.61, 54.60, 46.78, 46.67, 27.07, 26.96, 21.37, 21.31. **3b**: **^{1}H NMR**: 7.43-7.25 (m, 10H, aromatic H's), 4.96(d, J_{A1B1} = 11.9 Hz, 1H, $PhCH_2$), 4.68 (d, J_{A2B2} = 11.2 Hz, 1H, $PhCH_2$), 4.67 (d, 1H, $J_{1,2}$ = 1.4 Hz, H-1), 4.66 (d, J_{A1B1} = 11.9 Hz, 1H, $PhCH_2$), 4.48 (dd, $J_{4,5}$= $J_{4,3}$ = 11.7 Hz, 1H, H-4), 4.4 (d, J_{A2B2} = 11.2 Hz, 1H, $PhCH_2$), 4.32 (dd, $J_{3,4}$ = 10.3, $J_{3,2}$ = 2.5 Hz, 1H, H-3), 4.2 (dd, 1H, J = 7.8, 2.7 Hz, 1H, H-6), 3.95(m, 1H, H-6), 3.71(m, 1H, H-5), 3.32 (s, 3H, OCH_3), 3.23(s, 3H, OCH_3), 3.20 (s, 3H, OCH_3), 1.86-1.76 (m, 2H, 2x H-3'), 1.74-1.64 (m, 2H, H-6'), 1.62-1.50 (m, 2H, H-4', H-5'), 1.44-1.34 (m, 2H, H-4', H-5').

Methyl-2-*O*-benzyl-3,4-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-6-aldehydo-α-D-manno-pyranoside (4). A solution of dry DMSO (116 μL, 1.6 mmol) in CH_2Cl_2 (3 mL) was dropwise added to a solution of oxalyl chloride (693 μL, 1.4 mmol) in CH_2Cl_2 (10 mL) at –60°C (internal temperature). After stirring for 12 min, a solution of the diacetal (**3a**) (534 mg, 1.24 mmol) in CH_2Cl_2 (4 mL) was dropwise added. The mixture was stirred at –60°C for 30 min and treated with Et_3N (530 μL, 1.2 mmol). After 1 h the cooling bath was removed. Water (10 mL) was added and the mixture was allowed to reach rt. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2x 10 mL) and the combined organic extracts were washed with sat. aqueous NH_4Cl, water and dried over $MgSO_4$. Evaporation of the solvent afforded crude aldehyde (**4**) (520 mg, 97%) which was a single spot on TLC. The crude material was used in the next step. A purer sample (white solid, hygroscopic, mp 102°C (Et_2O) was obtained by flash chromatography (EtOAc/hexane 1:5), R_f 0.22. Anal. Calcd for $C_{22}H_{30}O_8.H_2O$: C, 59.72; H, 7.23. Found: C, 59.32; H, 6.96. **EI-MS**: 392(M^+ - OCH_3)(5), 143(7), 127(5), 111(4), 99(9), 91(100), 81, 67, 55, 41, 28. **^{1}H NMR**: 7.43-7.25 (m, 5H, aromatic H's), 4.98 (d, J_{AB} = 11.5 Hz, 1H, $PhCH_2$), 4.66 (d, $J_{1,2}$ = 1.4 Hz, 1H, H-1), 4.63 (d, J_{AB} = 11.5 Hz, 1H, $PhCH_2$), 4.37 (dd, $J_{4,3}$ = 10.4, $J_{4,5}$ = 9.0 Hz,1H, H-4), 4.22 (dd, $J_{3,4}$ = 10.4, $J_{3,2}$ = 2.6 Hz, 1H, H-3), 3.82-3.70 (m, 2H, H-2, H-5), 3.30 (s, 3H, OCH_3), 3.23 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 1.82-1.64 (m, 4H, H-3', H-6'), 1.48-1.42 (m, 2H, H-4', H-5'), 1.42-1.26 (m, 2H, H-4', H-5'). **^{13}C NMR**: δ 176.60, 138.53, 128.16, 128.10, 127.48, 100.68, 98.70, 98.41, 76.09, 73.29, 71.10, 69.57, 64.57, 61.59, 54.62, 46.78, 46.69, 27.07, 26.95, 21.37, 21.30.

Methyl 2-*O*-benzyl-3,4-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-7-methoxycarbonyl-6,7-dideoxy-α-D-mannohept-6-enopyranoside (5). Butyllithium (300 μL, 2.5 M in hexane) was added slowly to a solution of Ph_3P=CH-CO_2Me (670 mg, 2.0 mmol) in dry MeOH (8.0 mL) at –20°C. The resulting solution was cooled to –60°C and treated rapidly with a solution of crude aldehyde (**4**) in dry MeOH (10 mL). The mixture was allowed to warm up to rt for 12 h. Then the solvent was evaporated without heating to give a residue which was dissolved in 3 mL of CH_2Cl_2 and added to the top of a column of silica gel and flash-chromatographed using ether/hexane 1:1, R_f 0.21, to give 180 mg (31%) of **5** as a mixture of two possible stereoisomers, separable, as a thick colorless oil, $[\alpha]_D$ = +87° (c, 0.5 in $CHCl_3$). Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.76; H, 7.11. Found: C, 62.29; H, 7.34. **CI-MS**: 447 (M^+ - OCH_3)(3), 393 (8), 280 (9), 279 (43), 259 (47), 239 (7), 201 (8), 143 (7), 142 (11), 141 (11), 136 (9), 127 (35), 105 (9), 99 (21), 91 (100), 77 (8), 67 (16). **EI-MS**: 277 (27), 215 (2), 201 (4), 105 (11), 91 (38), 85 (11), 83 (150, 77(17), 59 (150, 55 (18), 45(22), 43(100). **^{1}H NMR**: δ 7.65 (dd, $J_{6,7}$ = 11.8, 1.3 Hz, 1H, H-6, *E*-isomer), 7.66 (d, $J_{7,6}$ = 11.8 Hz, H-7, *E*-isomer), 7.52 (dd, $J_{6,7}$ = 7.3, 1.3 Hz, 1H, H-6, *Z*-isomer), 7.37 (d, $J_{6,7}$ = 7.3Hz, H-7, *Z*-isomer), 7.74-7.21 (m, 5H, aromatic H's), 4.97 (d, J_{AB} = 11.8 Hz, 1H, $PhCH_2$), 4.87 (d, $J_{A'B'}$ = 12.1 Hz, 1H, $PhCH_2$), 4.66 (d, $J_{1,2}$ = 1.1 Hz, H-1), 4.63 (d, J_{AB} = 11.8 Hz, 1H, $PhCH_2$), 4.32 (dd, $J_{4,3}$ = $J_{4,5}$ = 10.3 Hz, 1H, H-4), 4.24 (dd, $J_{3,4}$ = 10.3, $J_{3,2}$ = 2.8 Hz, 1H, H-3), 3.82-3.70 (m, 2H, H-2, H-5), 3.3 (s, 3H, CO_2CH_3), 3.23(s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.16 (s, 3H, OCH_3), 1.80-1.56 (m, 4H, 2x H-3', 2x H-6'), 1.54-1.44 (m, 2H, H-4', H-5'), 1.40-1.30 (m, 2H, H-4', H-5'). **^{13}C NMR**: Major (*Z*-isomer); δ 165.17, 138.23, 132.07, 131.97, 128.15, 128.08, 127.46, 100.69, 98.70, 98.40, 76.06, 73.26, 71.07, 69.57, 64.63, 61.66, 54.61, 46.78, 46.67, 27.06, 26.95, 21.37, 21.30. Minor (*E*-isomer); δ 165.24, 138.36, 131.91, 131.89, 131.59, 131.70, 130.78, 130.69, 128.61, 128.50, 128.50, 128.38, 100.20, 98.74, 98.41, 72.96, 69.45, 68.69, 54.83, 46.83, 28.95, 24.08, 23.93, 23.40. Pure *Z*-isomer , colorless thick oil, showed the following spectral data; **^{1}H-NMR**: δ 7.44 (ddd, $J_{6,7}$= 8.2, $J_{6,5}$ = 7.6, 1.5 Hz, 1H, H-6), 7.42 (d, $J_{7,6}$ = 8.2 Hz, 1H, H-7), 7.35-7.25 (m, 5H, aromatic H's), 4.98 (d, J_{AB} = 11.7 Hz, 1H, $PhCH_2$), 4.66 (d, $J_{1,2}$= 1.8 Hz, 1H, H-1), 4.63 (d, J_{AB} = 11.7 Hz, 1H, $PhCH_2$), 4.37 (dd, $J_{4,3}$ = 10.5, $J_{4,5}$ = 9.5 Hz, 1H, H-4), 4.22 (dd, $J_{3,4}$ = 10.5, $J_{3,2}$ = 2.8 Hz, 1H, H-3), 3.78 (dd, $J_{5,4}$= 9.4, $J_{5,6}$ = 7.6 Hz, 1H, H-5), 3.71 (dd, $J_{2,3}$ = 2.8, $J_{2,1}$ = 1.8 Hz, 1H, H-2), 3.30 (s, 3H, CO_2CH_3), 3.23 (s, 3H, OCH_3), 3.22 (s, 3H, OCH_3), 3.15 (s, 3H, OCH_3), 1.83-1.70 (m, 4H, 2x H-3', 2x H-6'), 1.54-1.50 (m, 2H, H-4', H-5'), 1.44-1.35 (m, 2H, H-4', H-5').

Methyl-3,4-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-7-methoxycarbonyl-6,7-dideoxy-α-D-manno-hept-6-enopyranoside (6).100 mg (0.2 mmol) of a pure *Z*-isomer of **5** was dissolved in 10 mL of EtOAc

and stirred with 30 mg of 10% Pd/C under a balloon of H_2 gas for 12 h. The solution was then filtered and the insoluble residue was washed with EtOAc (2x 10 mL). The combined filtrate was evaporated and the residue was chromatographed over silica gel using EtOAc/hexane (1:4) as eluent to give 90 mg (90%) of pure **6** as a colorless oil. R_f 0.25, $[\alpha]_D$ = + 103º (c 0.5 in $CHCl_3$). Anal. Calcd for $C_{18}H_{28}O_9.H_2O$: C, 50.94; H, 7.54. Found: C, 50.60; H, 7.40. **EI-MS**: 422 (M^+-CO_2CH_3) (10%), 143 (12), 111 (11), 105 (100), 99 (11), 91 (21), 83 (21), 55 (11), 43 (10). **^{1}H NMR**: δ 7.57 (dd, $J_{6,7}$ = 8.4, $J_{6,5}$= 3.35 Hz, H-6), 7.45 (dd, $J_{7,6}$= 8.4, 2.0 Hz, 1H, H-7), 4.84 (d, $J_{1,2}$= 1.3 Hz, 1H, H-1), 4.48 (dd, $J_{4,3}$= 10.4, $J_{4,5}$ = 9.1 Hz, 1H, H-4), 4.4 (dd, $J_{3,4}$= 10.5, $J_{3,2}$= 2.9 Hz, 1H, H-3), 3.88-3.80 (m, 2H, H-2, H-5), 3.39 (s, 3H, CO_2CH_3), 3.31 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 1.96 (br s, 1H, OH), 1.80-1.60 (m, 4H, 2x H-3', 2x H-6'), 1.58-1.42 (m, 2H, H-4', H-5'), 1.40-1.30 (m, 2H, H-4', H-5'). **^{13}C-NMR**: δ 166.96, 129.88, 128.22, 99.12, 98.90, 98.59, 71.51, 70.70, 66.30, 65.77, 64.36, 65.77, 64.36, 61.33, 55.03, 46.92, 26.84, 26.61, 21.11, 21.02.

Methyl-3,4-*O*-(1',2'-dimethoxycyclohexane-1',2'-diyl)-6,7-dideoxy-α-D-mannooct-6-enopyranose-8,2-lactone (**8**). To a solution of 100 mg (0.2 mmol) of a pure *Z*-isomer of **5** in 100 mL of CH_2Cl_2, anhydrous $FeCl_3$ (33 mg, 0.2 mmol) was added. After a few minutes the color of the reaction changed to brown and the TLC showed an identical spot as **6**. The flask was fitted with a condenser and the reaction mixture was heated at 80°C for 3 h then 5 mL of H_2O was added. The mixture was cooled to rt and diluted with CH_2Cl_2 (100 mL) and it was allowed to stir for further 5 min. The mixture was extracted with CH_2Cl_2 and the combined organic phase was dried over $MgSO_4$ and evaporated till dryness to give 89 mg of crude **8**. It was purified by flash chromatography using (EtOAc/hexane 1:10) as eluent to afford 36 mg (R_f 0.15, 48%) of pure **8** as a colorless oil, $[\alpha]_D$ (Na/Hg) = +111° (c 0.5 in $CHCl_3$). Anal. Calcd for $C_{17}H_{24}O_8$: C, 57.30; H, 6.74. Found: C, 58.00; H, 6.97. **EI-MS**: 325 (M^+-OCH_3) (2), 293 (M^+-2x OCH_3) (5), 149 (49), 143 (4), 127 (10), 111 (8), 105 (4), 97 (13), 90 (75), 85(26), 83 (21), 71 (51), 57 (93), 43 (100). **^{1}H-NMR**: δ 7.52 (dd, $J_{7,8}$= 7.8, $J_{7,6}$=3.1 Hz, 1H, H-7), 7.46 (d, $J_{8,7}$= 7.8 Hz, 1H, H-8), 4.83 (d, $J_{2,3}$= 1.5 Hz, 1H, H-2), 4.60 (dd, $J_{5,6}$= 9.4, $J_{5,4}$ = 9.4 Hz, 1H, H-5), 4.0 (dd, $J_{4,5}$= 9.4, $J_{4,3}$ = 3.1 Hz, 1H, H-4), 3.9-3.8 (m, 2H, H-6, H-3), 3.28 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 1.80-1.60 (m, 4H, 2x H-3', 2x H-6'), 1.60-1.40 (m, 4H, 2x H-4', 2x H-5'). **^{13}C-NMR**: δ 165.0, 133.06, 129.83, 128.33, 99.09, 89.99, 98.65, 71.57, 70.73, 66.71, 64.36, 61.34, 46.92, 46.72, 26.92, 26.86, 21.32, 21.23.

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