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Synthesis of Optically Pure, Differentially Protected 1,4- and 1,6-Mannosyl-D-*myo*-Inositol Derivatives from 7-Oxabicyclo[2.2.1]heptan-2-one

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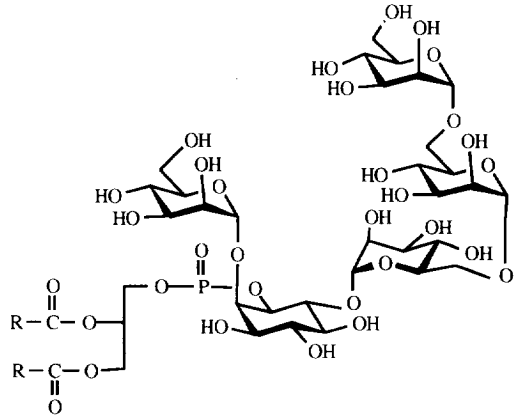
Dedicated to Prof. Félix Serratosa *in memoriam*

Abstract: Efficient procedures to prepare 4-*O*-mannosyl conduritol B derivatives from mannosyl oxanorbornanes are described. The osmium-catalyzed *cis*-dihydroxylation of the corresponding 1-*O*-acetates displays high π-facial selectivity *syn* to the acetate functionality to produce 1,4- and 1,6-mannosyl-D-*myo*-inositol derivatives.

Certain proteins are attached to cell surfaces by glycosylphosphatidyl inositols (GPI) anchors[1]. These anchored proteins shown a variety of biologycal functions including adhesion molecules, hydrolases, receptors and transmembrane signal inducers[2]. In the case of mannosyl-D-*myo*-inositols derivatives of these compounds are constituents of several GPI anchored proteins. For instance, in the glycolipids constituents of *Mycobacteria* the residue of *myo*-inositol appears glycosilated in the positons 2 and 6 by units of α-D mannopiranose[3] (Figure).

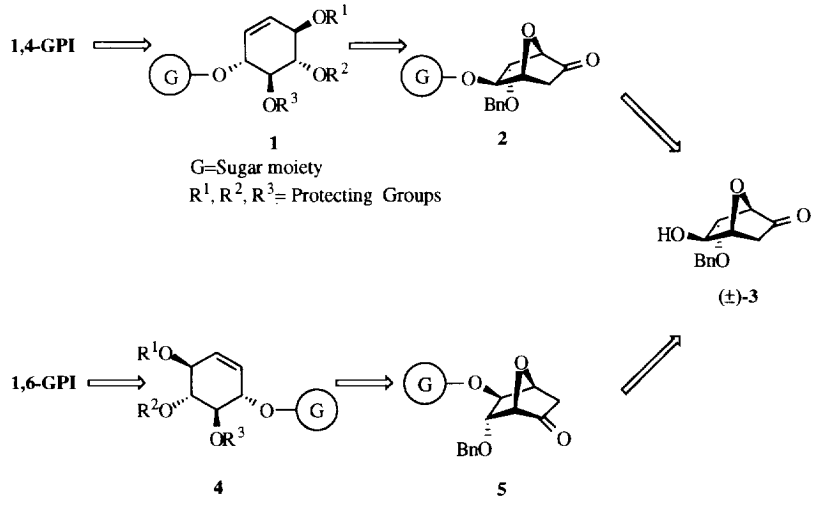


Figure

In a preliminary report[4] we have demonstrated that suitable protected precursors of 1,4- and 1,6-glucosyl-inositol derivatives can be prepared from glucosyl-conduritol B precursors **1** and **4**, which have been obtained from glucosyl-oxanorbornanes **2** and **5** by cleavage of the oxigen bridge[5]. In turn, these compounds have been derived from racemic ketone **3**[6] by glucosidation and separation of diastereomers. In this way in our

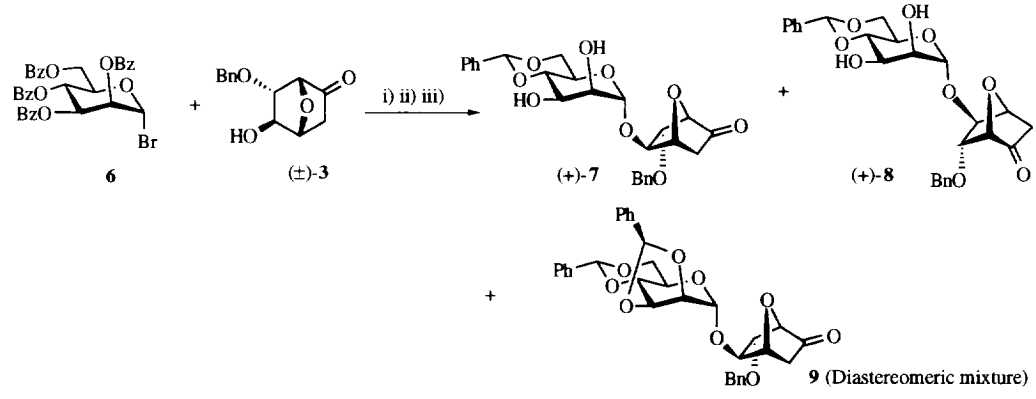
approach we take maximun advantage of the symmetry of *myo*-inositol and of the inherent chirality of the carbohydrate (Scheme 1).

In this report we have applied this methodology for the syntesis of the differentially protected 1,4- and 1,6-mannosyl-D-*myo*-inositols.



Scheme 1

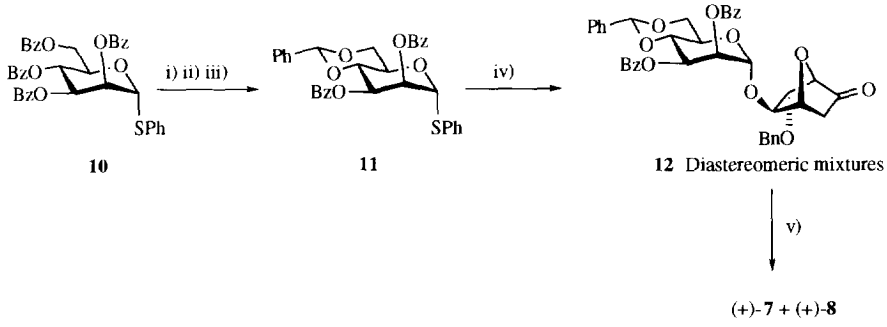
The reaction of ketone (±)-**3** with the mannosylbromide **6**[7] as a glycosyl donor, and in the previously reported conditions for the glucosyl analogue[4] affords a mixture of diastereomers **7** and **8** easily separable by column chromatography on silica gel. However is noteworthy that, together with the desired products **7** and **8**, the benzylidene derivative **9** (arising from the acetalation of the *syn* hydroxyl groups 2' and 3') were also isolated as a major product, being a diastereomeric mixture unseparable by column chomatography. These products are formed also in default of reagent, in different reaction conditions and in the presence of other coordinants solvents as DMF. In TLC it can be observed that these products appears before the consumption of the starting material (Scheme 2).



Key: i) $Hg(CN)_2$, $HgBr_2$, C_6H_6, Δ, 82%. ii) MeONa / MeOH. iii) $PhCH(OMe)_2$, p-TsOH.

Scheme 2

Although the formation of a second five membered cyclic acetal as byproduct in mannosides has been reported in well-defined conditions[8] and always in minor amounts, this compound could not be predictable as major component of the reaction mixture. After this result we have envisaged a more convergent approach to the compounds **7** and **8** incorporing the benzylidene moiety in the glycosyl donor. Then, and after considerable experimentation, glycosides **12** have been obtained in good yield starting from thioglycoside **11** using a modification of the Van Boom's activation conditions[9] (NBS in protic or Lewis acidic medium) used in several cases by Fraser-Reid[10]. Under the original conditions (NBS and HOTf -catalytic- or NBS and Et_3SiOTf -stechiometric-) we have obtained, respectively, decomposition of the reaction mixture or poor yield in glycosides. However, using catalytic amount of Et_3SiOTf (0.3 equiv) and low temperature, the reaction was almost instantaneous yielding glycosides **12**. Standard debenzylation and chromatographycal separation affords very good yields of glycosides (+)-**7** [$[\alpha]_D$ = +98.6° (*c* = 0.63, $CHCl_3$)] and (+)-**8** [$[\alpha]_D$ = +63.9° (*c* = 0.23, $CHCl_3$)] (Scheme 3).



10 **11** **12** Diastereomeric mixtures

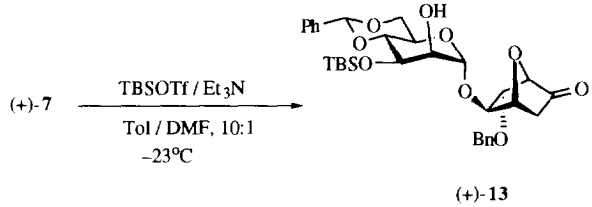
(+)-**7** + (+)-**8**

Key: i) MeONa, MeOH; ii) $PhCH(OMe)_2$, HBF_4, DMF, 0°C/rt; iii) BzCl, Et_3N, CH_2Cl_2; Overall yield (three steps) 45% iv) (±)-**3**, NBS, Et_3SiOTf, CH_2Cl_2, 0°C, 2 min 90%. v) MeONa, MeOH

Scheme 3

The structural determination of mannosyl derivatives (+)-**7** and (+)-**8** was performed by means of high resolution ^1H and ^{13}C NMR experiments, considering the coupling constants and the chemical shifts of the anomeric carbon in ^{13}C NMR toghether with selective homonuclear decoupling. On the other hand, the absolute configuration of (+)-**7** and (+)-**8** was secured by comparison using optically pure (-)-**3**[11]. In this case, optically pure (+)-**7** was obtained.

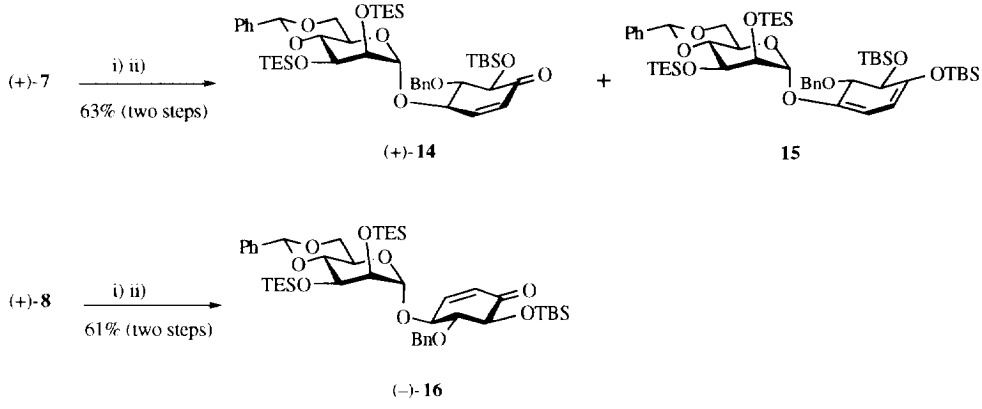
In order to achieve the opening of the oxigen bridge, which constitutes the next step in our synthetic approach, the protection of the free hydroxyl groups of (+)-**7** and (+)-**8** was necessary. This reaction was performed in first instance using standard conditions (TBSOTf/Et_3N), yielding almost exclusively the monosilylated products on the equatorial hydroxyl group. These compounds did not reacts subsequently to the disilylated one or to the ring opening compounds even in the presence of excess of reagents (Scheme 4).



(+)-**13**

Scheme 4

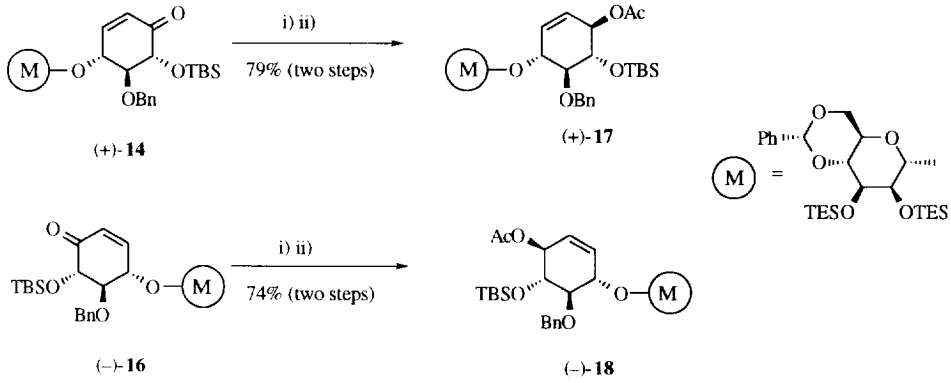
However, when triethylsilyl triflate was used in the same conditions, good yields of disilyl derivatives was obtained. The subsequent bridge cleavage of these compounds under standard conditions (TBSOTf, Et_3N, C_6H_6, rt)[5] affords compounds (+)-**14** [$[\alpha]_D$ = +91.0° (*c* = 0.75, $CHCl_3$)] and (-)-**16** [$[\alpha]_D$ = –45.8° (*c* = 0.6, $CHCl_3$)]. It is noteworthy that in the case of (+)-**7** we have observed the presence, in the reaction mixture, of the diene **15** arising from the enolization of the enone (+)-**14** and capture by the electrophile reagent (Scheme 5).



Key: i) TESOTf, Et_3N, Tol / DMF, 10:1, –23 °C. ii) TBSOTf, Et_3N, C_6H_6, rt.

Scheme 5

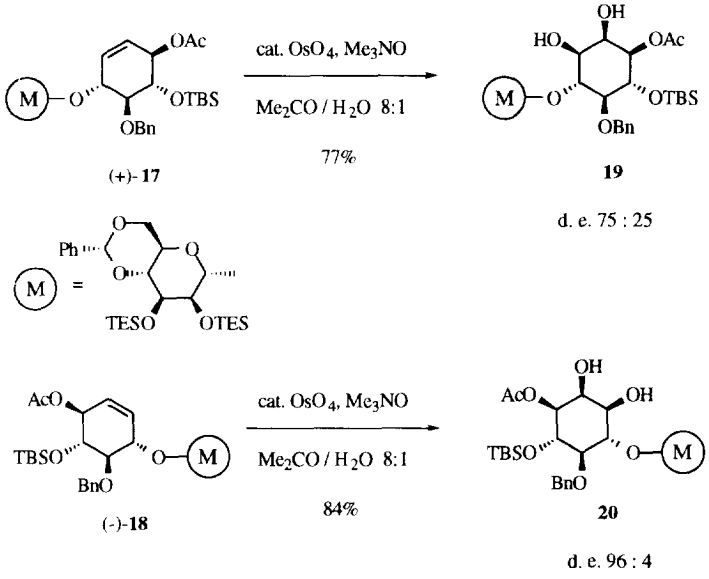
The two next steps were the reduction of the carbonyl group of the enones (+)-**14** and (-)-**16** and then the bis-hydroxylation of the resulting conduritol B derivatives. The reduction [(*t*-BuO)$_3$AlLiH, THF, 0ºC/rt] and acetylation of (+)-**14** gave the 4-mannosyl-conduritol B (+)-**17** [$[\alpha]_D$ = +64.0° (*c* = 0.68, $CHCl_3$)] with total regio- and stereoselectivity. On the other hand, the same reaction of (-)-**16** occurs also with total regio- and stereoselectivity, giving (-)-**18** [$[\alpha]_D$ = –57.2° (*c* = 0.46, $CHCl_3$)] but needing a larger reaction time (Scheme 6).



Key: i) (*t*-BuO)$_3$HAlLi, THF 0 °C/rt. ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

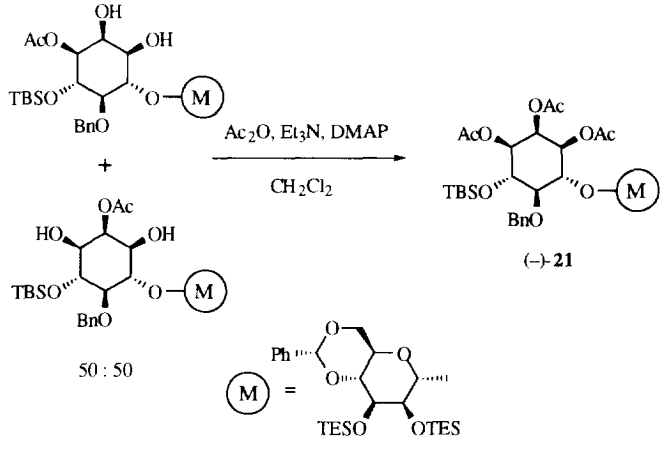
Scheme 6

The catalytic bishydroxylation of both mannosyl-conduritols B was achieved on the allylic acetyl derivatives in order to take advantage of the *syn* directing effect of the acetate moiety, previously observed in model compounds[12]. In both cases the major isomer was *anti* to the glycoside bond and *syn* to the acetate (Scheme 7).



Scheme 7

Unfortunately the large reaction time required for the formation of **20** produce the slowly migration of the acetate group to the position 2 (axial) in the major *myo*-inositol (*c. a.* 50%). Since both products are unseparables by chromatographic methods the characterization of the final products was performed by acetylation because both acetates affords the same triacetate (-)-**21** [$[\alpha]_D = -2.57°$ ($c = 0.70$, $CHCl_3$)] (Scheme 8).



Scheme 8

In conclusion, the results described herein establish an appropiated route to the synthesis of mannosyl-D-*myo*-inositol derivatives starting from racemic 7-oxanorbornenone, using the sugar moiety as chiral auxiliary group. The stereoselectivity control in the osmylation step, *syn* to an allylic acetate, constitutes a key step in the approach.

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Experimental.

General Methods. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran was distilled from sodium and benzophenone; benzene from sodium; toluene, DMF, HMPA, dichloromethane and triethylamine from calcium hydride; pyridine form KOH, acetone from $KMnO_4$. All other solvents were reagent grade. Commercial osmium tetroxide (2.5% wt. solution in *t*-BuOH) was purchased from Aldrich. Flash chromatography was performed using Merck 230-400 mesh silica gel. Analytical TLC was carried out on Merck (Kiesegel 60F-254) silica gel plates with detection by UV ligth, acidic vanillin solution or phosphomolybdic acid solution in ethanol. Melting points were determined on a Büchi 512 apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer 781 spectrometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on Brüker AC-250F or Varian VXR-300 instruments using $CDCl_3$ or methanol-d_4 as solvents with tetramethylsilane as an internal reference. The following abbreviations are used to describe peak patterns when appropiate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Elemental analyses were performed at the Universidad Complutense de Madrid.

Starting materials. Compounds (±)-**3** and (-)-**3** were prepared by previously described methods. See ref. 11.

Thiophenyl 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranoside 10. To a solution of 1,2,3,4,6-penta-O-benzoyl-α,β-D-mannopyranoside (5.4 g, 7.84 mmol) in anhidrous benzene were added PhSH (0.96 ml, 9.41 mmol) and $SnCl_4$ (0.64 ml, 5.49 mmol) at 0 °C. After 4 h at reflux the reaction was cooled, dissolved with EtOAc and washed with 5% aq $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 3:1) yielding **10** as a white solid (4.85 g, 90%). Data of **10**: R_f = 0.28 (hexane/EtOAc, 3:1). $[\alpha]_D$= +5.06° (*c*= 0.85, acetone). mp: 84 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 4.71 (AB system, 2 H, J = 12.2, 5.2, 2.3 Hz, H-6ax, H-6eq), 5.02 (ddd, 1 H, J = 9.9, 5.2, 2.3 Hz, H-5), 5.79 (d, 1 H, J = 1.4 Hz, H-1), 5.87 (dd, 1 H, J = 9.9, 3.1 Hz, H-3), 5.98 (dd, 1 H, J = 3.1, 1.4 Hz, H-2), 6.15 (t, 1 H, J = 9.9 Hz, H-4), 7.20-8.09 (m, 25 H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.1, 66.0, 67.1, 68.9, 69.9, 72.0, 86.1, 132.2, 132.7, 133.4, 133.5, 133.6, 165.2, 165.4, 165.5, 166.2. IR (KBr): 1740, 1610, 1590, 1460, 1320, 1290, 1270, 1180, 1100, 1080, 1040, 720, 690 cm^{-1}. Anal. calcd for $C_{40}H_{32}O_9S$: C, 69.75; H 4.68. Found: C, 69.40; H 4.55.

Thiophenyl 4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-α-D-mannopyranoside 11. To a solution of thiophenyl-4,6-*O*-benzylidene-α,α-D-mannopyranoside (1.9 g, 5.27 mmol) (previously obtained from **10**

(65%) after treatment with MeONa/MeOH, and subsequent reaction with α, α-dimetoxytoluene, $HBF_4{\cdot}EtO_2$ in DMF) in CH_2Cl_2 were added Et_3N (2.2 ml, 15.81mmol), Catalytic amounts of DMAP and BzCl (1.4 ml, 12.2 mmol) at room temperature. After 4 h the reaction was dissolved with CH_2Cl_2 and washed with HCl (5%), $NaHCO_3$ (5%), brine, dried ($MgSO_4$) and concentrated. The resulting residue was purified by chromatography (hexane/EtOAc, 5:1) yielding **11** as a white solid (2.4 g, 80%). Data of **11**: R_f= 0.28 (hexane/EtOAc, 3:1). $[\alpha]_D$= +5.06° (*c*= 0.85, acetone). pf: 84 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 4.71 (AB system, 2 H, *J* = 12.2, 5.2, 2.3 Hz, H-6ax, H-6eq), 5.02 (ddd, 1 H, *J* = 9.9, 5.2, 2.3 Hz, H-5), 5.79 (d, 1 H, *J* = 1.4 Hz, H-1), 5.87 (dd, 1 H, *J* = 9.9, 3.1 Hz, H-3), 5.98 (dd, 1 H, *J* = 3.1, 1.4 Hz, H-2), 6.15 (t, 1 H, *J* = 9.9 Hz, H-4), 7.20-8.09 (m, 25 H, H Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ 63.1, 66.0, 67.1, 68.9, 69.9, 72.0, 86.1 (C-anomérico), 132.2, 132.7, 133.4, 133.5, 133.6, 165.2, 165.4, 165.5, 166.2. IR (KBr): 1740, 1610, 1590, 1460, 1320, 1290, 1270, 1180, 1100, 1080, 1040, 720, 690 cm^{-1}. Anal. Calcd for $C_{40}H_{32}O_9S$: C, 69.75; H 4.68. Found: C, 69.40; H 4.55.

(+)-(1R,4R,5R,6R)- and (+)-(1S,4S,5S,6S)-6-*endo*-Benzyloxy-5-*exo*-(4,6-*O*-benzylidene-α-D-mannopyranosyloxy)-7-oxabicyclo[2.2.1]heptan-2-one, (+)-7 and (+)-8. To a solution of (±)-**3** (235 mg, 1 mmol) in CH_2Cl_2 with molecular sieves were added **11** (1.0 g, 1.75 mmol) and the resulting mixture was cooled at 0 °C. Then were added NBS (250 mg, 1.10 mmol), TESOTf (0.07 ml, 0.30 mmol). After 2 min were added Et_3N (1 ml), dissolved with EtOAc and filtered through silica gel. The solvents were evaporated and the resulting residue was purified by chromatography (hexane/EtOAc, 4:1) yielding a 50:50 mixture of glycosides as a white solid (635 mg, 91%). The treatment with MeONa/MeOH give quantitative yield of (+)-**7** and (+)-**8** that were separated by chromatography (hexane/EtOAc, 1:2). Data of (+)-**7**: R_f= 0.09 (hexane/EtOAc, 1:2). $[\alpha]_D$ = +98.6° (*c* = 0.63, $CHCl_3$). mp: 215-216 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.12 (d, 1 H, *J* = 17.7 Hz, H-3n), 2.51 (ddd, 1 H, *J* = 17.7, 6.7, 1.6 Hz, H-3x), 2.61 (ad, 1 H, *J* = 2.5 Hz, OH), 2.66 (d, 1 H, *J* = 1.7 Hz, OH), 3.78 (t, 1 H, *J* = 10.0 Hz, H-6'ax), 3.84 (td, 1 H, *J* = 9.0, 4.5 Hz, H-5'), 3.95 (t, 1 H, *J* = 9.0 Hz, H-4'), 4.09 (as, 1 H, H-5), 4.06-4.13 (m, 3 H, H-2', H-3', H-6), 4.18 (dd, 1 H, *J* = 9.0, 4.5 Hz, H-6'eq), 4.42 (d, 1 H, *J* = 5.6 Hz, H-1), 4.54 (AB system, 2 H, CH_2Ph), 4.76 (dd, 1 H, *J* = 6.7, 1.5 Hz, H-4), 5.01 (d, 1 H, *J* = 0.7 Hz, H-1'), 5.58 (s, 1 H, H-benzylidene), 7.25-7.52 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.0, 63.9, 68.6, 71.0, 72.7, 78.7, 79.5, 80.4, 82.8, 83.2, 99.5, 102.3, 126.3, 127.9, 128.2, 128.4, 128.6, 129.3, 136.7, 137.2, 206.4. IR (KBr): 3350, 3200, 2900, 2800, 1760, 1450, 1360, 1140, 1110, 1100, 1070, 1030, 1010, 990, 980, 770, 750, 700 cm^{-1}. Anal. Calcd for $C_{26}H_{28}O_9$: C, 64.45; H, 5.82. Found: C, 63.92; H, 5.97. Data of (+)-**8**: R_f= 0.15 (hexane/EtOAc, 1:2). $[\alpha]_D$ = +63.9° (*c* = 0.23, $CHCl_3$). mp: 79-80 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.13 (d, 1 H, *J* = 17.8 Hz, H-3n), 2.50 (ddd, 1 H, *J* = 17.8, 6.7, 1.6 Hz, H-3x), 2.76 (as, 2 H, 2 OH), 3.81 (t, 1 H, *J* = 10.0 Hz, H-6'ax), 3.85 (td, 1 H, *J* = 10.0, 3.3 Hz, H-5'), 3.95 (t, 1 H, *J* = 9.4 Hz, H-4'), 3.98 (s, 1 H, H-5), 3.99-4.02 (m, 2 H, H-2', H-6), 4.08 (dd, 1 H, *J* = 9.3, 3.5 Hz, H-3'), 4.25 (dd, 1 H, *J* = 9.3, 3.3 Hz, H-6'eq), 4.45 (d, 1 H, *J* = 5.4 Hz, H-1), 4.54 (AB system, 2 H, CH_2Ph), 4.78 (d, 1 H, *J* = 6.7 Hz, H-4), 4.90 (d, 1 H, *J* = 1.4 Hz, H-1'), 5.56 (s, 1 H, H-bencylidene), 7.20-7.50 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39.1, 63.7, 68.4, 68.5, 70.9, 72.7, 78.7, 80.3, 80.9, 82.5, 83.8, 99.5, 102.3, 126.2, 128.0, 128.2, 128.3, 128.5, 129.3, 136.5, 137.0, 206.7. Anal. Calcd for $C_{26}H_{28}O_9$: C, 64.45; H, 5.82. Found: C, 64.11; H, 6.05.

(+)-(4*R*,5*S*,6*R*)-5-benzyloxy-4-(4,6-*O*-benzylidene-2,3-bis-*O*- triethyl-silyl-α-*D*-manno-piranosyloxy)-6-(*tert*-butyldimethylsiliyloxy)-cyclohex-2-en-1-one, (+)-14. To a cold solution (-23 °C) of (+)-**7** (50 mg, 0.10mmol), toluene/DMF (10/1) (15 ml/mmol), freshly distilled Et_3N (0.06 ml, 0.40mmol) and TESOTf (0.09 ml, 0.40 mmol) were added under an argon atmosphere and the mixture stirred for 1 h at -23°C. The resultant solution was diluted with EtOAc, and K_2CO_3 (5 mg) was added. The mixture was washed with 5% aq $NaHCO_3$ and dried over $MgSO_4$. Filtration and concentration under reduce pressure gave an oil that was purified by chromatography on silica gel (hexane/EtOAc, 5:1). To a solution of the product in dry benzene (5 ml) were added Et_3N (0.03 ml, 0.27 mmol) and TBDMSOTf (0.03 ml, 0.18 mmol). The mixture was stirred at room temperature for 20 h, diluted with EtOAc, washed with 5% aq $NaHCO_3$, brine,

dried over $MgSO_4$ and filtered. Concentration under reduced pressure gave a crude product which was purified by column chromatography on silica gel (hexane:EtOAc, 10:1) to give (+)-**14** (47 mg, 63 %, two steps) as a transparent oil and diene **15** (15mg). Data of (+)-**14**: R_f = 0.46 (hexane/EtOAc, 5:1). $[\alpha]_D$ = +91.0° (*c* = 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ –0.03 (s, 3 H, MeSi), 0.13 (s, 3 H, MeSi), 0.45 (q, 6 H, CH_2Si), 0.62 (m, 6 H, CH_2Si), 0.88 (s, 9 H, *t*-BuSi), 0.96 (t, 9 H, CH_3CH_2Si), 3.73 (t, 1 H, *J* = 9.2 Hz, H-6'ax), 3.78 (dd, 1 H, *J* = 10.5, 8.5 Hz, H-5), 3.84-3.89 (m, 2 H, H-2', H-4'), 3.91-3.99 (m, 2 H, H-3', H-5'), 4.16 (dd, 1 H, *J* = 10.2, 4.5 Hz, H-6'eq), 4.38 (d, 1 H, *J* = 10.5 Hz, H-6), 4.63 (dt, 1 H, *J* = 8.4, 1.8 Hz, H-4), 4.90 (AB system, 2 H, CH_2Ph), 4.94 (d, 1 H, *J* = 1.2 Hz, H-1'), 5.43 (s, 1 H, H-benzylidene), 6.10 (dd, 1 H, *J* = 10.5, 2.4 Hz, H-2), 6.77 (dd, 1 H, *J* = 10.8, 2.1 Hz, H-3), 7.10-7.40 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ –5.0, –4.7, –4.6, 4.8, 4.9, 6.8, 6.9, 18.5, 25.7, 65.1, 68.6, 69.8, 73.7, 73.8, 75.6, 78.8, 84.1, 98.4, 102.3), 126.6, 127.0, 127.2, 127.8, 128.3, 128.3, 128.7, 135.5, 137.6, 144.0, 197.1.

(-)-(4*S*,5*R*,6*S*)-5-benzyloxy-4-(4,6-*O*-benzylidene-2,3-bis-*O*- triethylsilyl-α-*D*-manno-piranosyloxy)-6-(*tert*-butyldimethylsilyloxy)-cyclohex-2-en-1-one, (-)-16. From (+)-**8** (60 mg, 0.12 mmol) and following the same procedure as before, (-)-**16** (61 mg, 61 %, two steps) was obtained as a transparent oil. Data of (-)-**16**: R_f = 0.43 (hexane/EtOAc, 5:1). $[\alpha]_D$ = –45.8° (*c* = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ –0.02 (s, 3 H, MeSi), 0.14 (s, 3 H, MeSi), 0.52-0.55 (m, 12 H, -CH_2Si), 0.81-0.86 (t, 18 H, CH_3CH_2Si), 0.88 (s, 9 H, *t*-BuSi), 3.77-3.88 (m, 4 H, H-2', H-5', H-5, H-6'ax), 3.95 (t, 1 H, *J* = 8.1 Hz, H-4'), 3.99 (dd, 1 H, *J* = 9.1, 3.3 Hz, H-3'), 4.19 (dd, 1 H, *J* = 10.5, 5.1 Hz, H-6'eq), 4.22 (d, 1 H, *J* = 10.5 Hz, H-6), 4.49 (dt, 1 H, *J* = 8.4, 2.4 Hz, H-4), 4.86 (AB system, 2 H, CH_2Ph), 4.99 (d, 1 H, *J* = 1.8 Hz, H-1'), 5.52 (s, 1 H, H-benzylidene), 6.04 (dd, 1 H, *J* = 10.2, 2.3 Hz, H-2), 6.84 (dd, 1 H, *J* = 10.2, 1.5 Hz, H-3), 7.29-7.40 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ –5.2, –4.6, 4.8, 4.9, 6.8, 18.5, 25.8, 65.5, 68.7, 69.6, 73.6, 75.3, 78.9, 79.0,.79.4, 85.1, 102.3, 104.8, 126.3, 126.7, 127.3, 128.0, 128.1, 128.2, 129.0, 137.4, 138, 147.7, 197.0.

(+)-1L-1-*O*-Acetyl-3-*O*-benzyl-4-*O*-[4,6-*O*-benzylidene-2,3-bis-*O*-[(*tert*-butyl)-di-methyl-silyl]-α-D-mannopyranosyl]-2-*O*-[(*tert*-butyl)dimethylsilyl] conduritol B, (+)-17. To a stirred cold (0°C) solution of (+)-**14** (73 mg, 0.088 mmol) in dry THF (4 ml), $LiAl(O\text{-}t\text{-}Bu)_3H$ (81mg, 0.354 mmol) was added. After 18 h at room temperature, the reaction was quenched with HCl 0.5 N and the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. The organic solvents were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 ml); Ac_2O (0.03 ml), Et_3N (0.02 ml) and DMAP (3 mg) were added and the mixture stirred for 1 h at room temperature, diluted with CH_2Cl_2 and washed with water and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 5:1) affording (+)-**17** (61 mg, 79%, two steps) as a transparent oil. Data of (+)-**17**: R_f = 0.41 (hexane/EtOAc, 5:1). $[\alpha]_D$ = +64.0° (*c* = 0.68, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ –0.12 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi), 0.39 (q, 6 H, *J* = 7.8 Hz, CH_3CH_2Si), 0.61 (m, 6 H, CH_3CH_2Si), 0.74 (t, 9 H, *J* = 7.5 Hz, CH_3CH_2Si), 0.79 (s, 9 H, *t*-BuSi), 0.95 (t, 9 H, *J* = 7.8 Hz, CH_3CH_2Si), 2.07 (s, 3 H, MeCO), 3.50 (dd, 1 H, *J* = 9.5, 7.6 Hz, H-3), 3.53 (dd, 1 H, *J* = 10.5, 8.1 Hz, H-3), 3.59 (t, 1 H, *J* = 9.9 Hz, H-6'ax), 3.72 (t, 1 H, *J* = 9.6 4.5 Hz, H-5'), 3.72 (t, 1 H, *J* = 9.6 Hz, H-6'ax), 3.83-3.95 (m, 5 H, H-2, H-2', H-3', H-4', H-5'), 4.15 (dd, 1 H, *J* = 9.6, 4.2 Hz, H-6'eq), 4.15 (dd, 1 H, *J* = 9.6, 4.2 Hz, H-6'eq), 4.42 (dq, 1 H, *J* = 7.8, 2.4 Hz, H-4), 4.83 (d, 1 H, *J* = 7.8 Hz, CH_2Ph), 4.88 (d, 1 H, *J* = 1.5 Hz, H-1'), 4.95 (d, 1 H, *J* = 7.8, 2.4 Hz, H-1), 5.41 (s, 1 H, H-benzylidene), 5.61 (dt, 1 H, *J* = 10.5, 2.1 Hz, H-5), 5.76 (dt, 1 H, *J* = 10.5, 1.8 Hz, H-6), 7.30-7.40 (m, 10 H, H-Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.8, –4.1, 4.7, 4.9, 6.7, 6.9, 18.0, 21.3, 25.7, 65.0, 68.7, 69.8, 73.7, 73.8, 74.4, 75.5, 76.1, 78.5, 82.3, 98.0, 102.3, 125.7, 126.4, 126.6, 126.9, 127.2, 127.7, 128.1, 128.7, 137.6, 138.1, 170.5.

(-)-1D-1-*O*-Acetyl-3-*O*-benzyl-4-*O*-[4,6-*O*-benzylidene-2,3-bis-*O*-[(*tert*-butyl)-di-methyl-silyl]-α-D-mannopyranosyl]-2-*O*-[(*tert*-butyl)dimethylsilyl] conduritol B, (-)-18. From (-)-**16**

(32 mg, 0.039 mmol) and following the same procedure as before, (-)-**18** (25 mg, 74 %, two steps) was obtained as a transparent oil. Data of (-)-**18**: R_f= 0.47 (hexane/EtOAc, 5:1). $[\alpha]_D$ = –57.2° (*c* = 0.46, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ –0.08 (s, 3 H, MeSi), 0.04 (s, 3 H, MeSi), 0.50-0.55 (m, 12 H, CH_3CH_2Si), 0.78-0.85 (m,18 H, CH_3CH_2Si), 0.81 (s, 9 H, *t*-BuSi), 2.07 (s, 3 H, MeCO), 3.57 (dd, 1 H, *J* = 10.2, 7.8 Hz, H-3), 3.78-3.93 (m, 5 H, H-2, H-2', H-6'ax, H-4'), 3.97 (dd, 1 H, *J* = 9.3, 2.7 Hz, H-3'), 4.15 (da, 1 H, *J* = 7.2 Hz, H-6'eq), 4.28 (dq, 1 H, *J* = 7.8, 2.1 Hz, H-4), 4.81 (AB system, 2 H, CH_2Ph), 4.88 (d, 1 H, *J* = 1.5 Hz, H-1), 5.33 (dq, 1 H, *J* = 8.1, 2.4 Hz, H-1), 5.49 (s, 1 H, H-benzylidene), 5.52 (dt, 1 H, *J* = 10.5, 2.1 Hz, H-5), 5.74 (dt, 1 H, *J* = 10.5, 2.2 Hz, H-6), 7.28-7.43 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.8, –4.1, 4.8, 4.8, 6.8, 18.0, 21.3, 25,7, 65.1, 68.7, 69.7, 73.8, 75.1, 77.2, 77.4, 79.0, 81.1, 83.1, 102.2, 104.4, 126.3, 126.4, 126.7, 127.1, 128.0, 128.1, 128.9, 129.7, 137.6, 138.4, 170.5.

(–)-1,2,3-Tri-*O*-acetyl-5-*O*-benzyl-6-*O*-(4,6-*O*-benzylidene-2,3-bis-*O*-triethylsilyl-α -*D*-mannopyranosyl)-4-*O*-*tert*-butyldimethylsilyl *D*-*myo*-inositol, (–)-21. To a solution of (-)-**18** (30 mg, 0.034 mmol) and Me_3NO (2 equiv), in an 8:1 mixture of acetone:water, was added 0.05 equiv of 2.5 wt % solution of OsO_4 in *t*-BuOH. The reaction was stirred at room temperature for 24 h and was quenched with a few drops of 10% aqueous solution of sodium bisulfite. The mixture was concentrated in *vacuo* and the crude was suspended in MeOH and filtered through a short column of silica gel. The crude was purified by column chromatography on silica gel (hexane/EtOAc, 5:1). The product showed a mixture of the two bis-hydroxylated diastereomers in a ratio 96:4 (determined by integration of the well resolved signals for benzylidene protons). Due to the migration of the acetyl group to the position 2 (*c. a.* 50 %), was achieved the total acetylation with excess of Ac_2O, Et_3N and DMAP in CH_2Cl_2. Column chromatography on silica gel (hexane/EtOAc, 10:1) affording (-)-**21** (23 mg, 77 %, two steps). Data of (-)-**21**: R_f= (hexane/EtOAc, 5:1). $[\alpha]_D$ = –2.57° (*c* = 0.70, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ –0.20 (s, 3 H, MeSi), 0.05 (s, 3 H, MeSi), 0.33-0.50 (m, 12 H, CH_3CH_2Si), 0.73-0.81 (m, 18 H, CH_3CH_2Si), 0.78 (s, 9 H, *t*-BuSi), 2.01 (s, 3 H, MeCO), 2.11 (s, 3 H, MeCO), 2.14 (s, 3 H, MeCO), 3.48 (dt, 1 H, *J* = 9.9, 8.7 Hz, H-5), 3.79 (m, 2 H, H-6'ax, H-2'), 3.84 (m, 2 H, H-4', H-3'), 3.90 (m, 1 H, H-5'), 4.03 (ta, 1 H, *J* = 9.6 Hz, H-4), 4.17 (dd, 1 H, *J* = 9.9, 4.2 Hz, H-6'eq), 4.21 (ta, 1 H, *J* = 9.9 Hz, H-6), 4.84 (dd, 1 H, *J* = 9.9, 2.7 Hz, H-3), 4.88 (AB system, 2 H, CH_2Ph), 5.02 (dd, 1 H, *J* = 10.2, 3.0 Hz, H-1), 5.09 (d, 1 H, *J* = 1.8 Hz, H-1'), 5.47 (s, 1 H, H-benzylidene), 7.28-7.37 (m, 10 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ –4.5, –4.1, 4.8, 4.9, 6.7, 17.9, 20.6, 20.9, 22.7, 25.6, 64.8, 68.9, 69.2, 69.7, 71.6, 73.9, 74.2, 75.0, 77.0, 79.0, 83.8, 102.0, 102.5, 125.0, 125.5, 126.3, 126.7, 126.9, 128.0, 128.2, 128.9, 137.6, 138.0, 169.7, 169.7, 169.8. IR (CCl_4): 2960, 2920, 2880, 2860, 1760, 1450, 1420, 1370, 1250, 1220, 1140, 1090, 1040, 1010, 920, 780, 760, 690 cm^{-1}.

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