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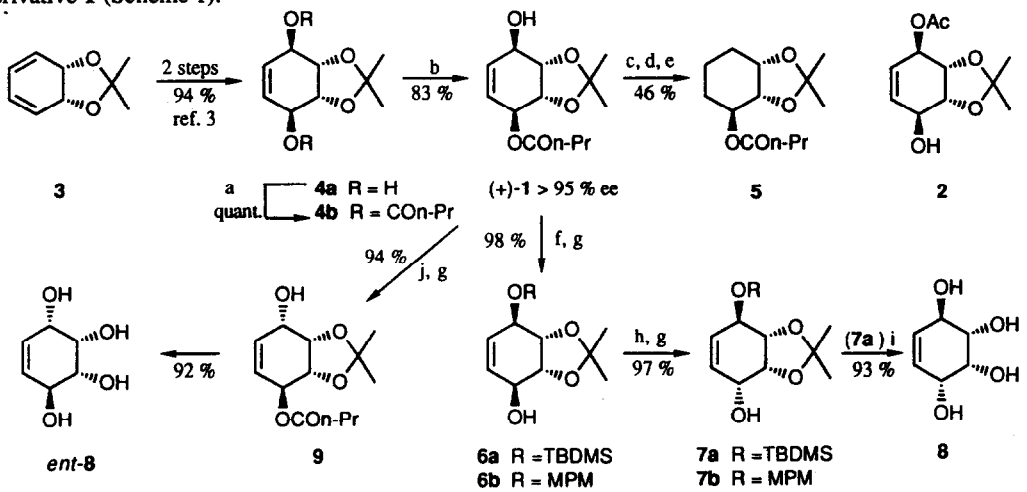
Cyclohexane Polyols : Enantioselective Synthesis of (+)-Fortamine and of Pseudosugars#

Liu Pingli, Maurits Vandewalle*

University of Gent, Department of Organic Chemistry, Laboratory for Organic Synthesis, Krijgslaan, 281 (S.4), B-9000 GENT (Belgium)

Abstract *: (1R,2S,3R,4S)-4-butyryloxy-2,3-isopropylidenedioxy-5-cyclohexen-1-ol (**1**) obtained upon enzymatic hydrolysis of the corresponding meso-dibutyrate **4b** is a fully functionalized homochiral building block for the synthesis of cyclohexane polyols. Applications are illustrated by the synthesis of (+)-fortamine (**10**) and of pseudosugars of the allo- (**65,68**), gulo- (**35,40**), manno- (**54,59**) and talo-series (**43,48**).*

In view of the recent interest in cyclohexane polyols[1] we have been developing methods for enantioselective formation of versatile homochiral building blocks[2]. As part of this ongoing programme we have recently reported the enantiotoposelective enzyme-catalyzed formation of the optically active meso-derivative **1** (Scheme 1).[2f]



(a) n-PrCOCl, NEt_3, DMAP, CH_2Cl_2, r.t., 48 h; (b) PGL, pH 7, 35°C, NaOH; (c) Rh/Al_2O_3 (5 %), H_2 (1 atm), EtOAc; (d) $Im_2C=S$, THF, reflux, 24 h; (e) Bu_3SnH, AIBN, PhH, reflux, 1 h; (f) **6a** : t-$BuPh_2SiCl$, imidazole, DMF, r.t., 5 h; **6b** : $MPMOC(=NH)CCl_3$, CSA, CH_2Cl_2, r.t., 24 h; (g) MeOH, $KHCO_3$, r.t.; (h) $PhCO_2H$, Ph_3P, DEAD, THF, r.t.; (i) Amberlyst-15, MeOH, r.t.; (j) p-NO_2-PhCOOH, Ph_3P, DEAD, THF, r.t.

Scheme 1

Dedicated to Professor Leon Ghosez on the occasion of his 60th birthday.

The substrate **4b** is a protected form of conduritol-A and was prepared from **3** by a modified procedure reported by Balci *et al.*.[3] Intermediate **3** is available either from 1,4-cyclohexadiene or from *cis*-cyclohexa-3,5-diene-1,2-diol obtainable by microbial oxidation of benzene[4]. Substrate **4b** was hydrolyzed by PGL, a recombinant *Fusarium solani pisi cutinase*[5] with >95 % ee as determined by ^{1}H NMR (500 MHz, $CDCl_3$) in the presence of Eu(hfc)$_3$ (no trace of the other enantiomer was observed). The absolute configuration was determined to be 1(R) by chemical correlation with **5**, the absolute configuration of which has been firmly established[2a]. During the course of our work, Johnson *et al.*,[6] have reported the enzyme-catalyzed esterification of **4a**, leading to **2** belonging to the enantiomeric series of **1**.

We presently want to fully report on some applications of the complete functionalized homochiral building block **1**. Evidently, due to the *meso*-nature, both enantiomers of any given target molecule are equally accessible (compare **1** and **6**). The 1,4-*trans* relative configuration is easily accessible by Mitsunobu inversion[7]. In the case of **9**, the reaction had to proceed *via* the p-nitrobenzoate, which was essential for subsequent selective hydrolysis.

Compounds **7** and **9** are precursors for (-)-conduritol C (**8**) and (+)-conduritol C (*ent*-**8**) respectively[6,8]. Next to conduritol C, applications in the area of aminocyclitols[9] and pseudosugars[10] were selected. Not only are the specific target molecules of interest, also intermediates with specific protected functions can be of importance for the synthesis of analogues, isomers and for other selected transformations.

(+)-Fortamine (10) (Scheme 2)

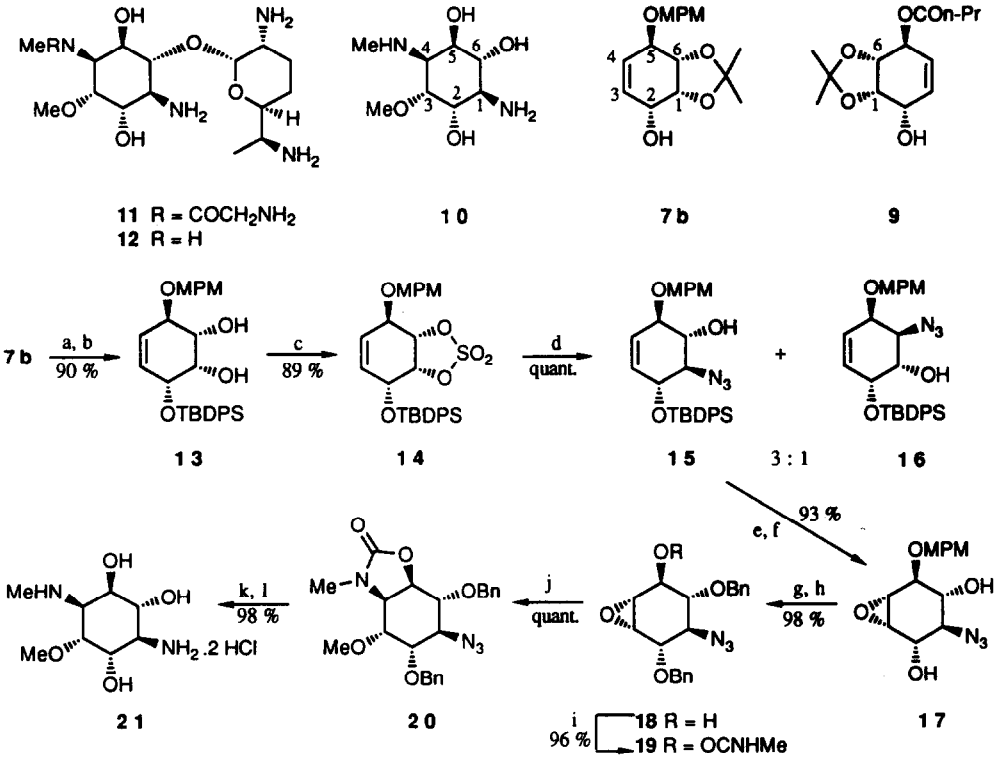
Amongst the diaminocyclitols (+)-fortamine **10** takes a special position; indeed the 1,4-relative position of the amino functions is a unique feature as normally the 1,3-disposition is observed. It is a component of fortimycin A (**11**) and B (**12**) which are 6-*epi*-purpurosamine glycosides of **10** or of its glycylamide[11]. Its unique structure and intrinsic properties make it an attractive target; next to several total syntheses of racemic **10**[12], one enantioselective route[13] has been described[14].

Our strategy centers around the introduction of the amino functions at C-1 and C-4 in **7b** (fortamine numbering). Upon comparing structures **7b** and **10**, it is obvious that the regioselectivity for substitution at C-1 (*versus* C-6) in **7b** will be critical. However, due to the "*meso*-nature" of **1**, also selective substitution in **9** at C-6 (C-4 in **10**) by a methylamine precursor, would open a viable approach. After exploring several alternatives a successful route was found in which the C-atoms of **7b** correspond to those of fortamine as indicated by the numbering of **7b** and **10**.

We envisioned to carry out the crucial nucleophilic substitution at C-1 on cyclic sulfate **14** because this involves less functional group interconversions than the chemoselective formation of a leaving group at C-1 and a protected C-6 oxy-function in diol **13** (Scheme 2). It is known that a cyclic 1,2-diol can be transformed directly to the sulfate upon treatment with sulfuryl chloride[15] instead of the usual 2-step procedure involving thionyl chloride[16]. Reaction of the cyclic sulfate **14** with lithium azide led in a moderate regioselectivity of 3:1 to the desired **15** as the major product; **15** and **16** are easily separated by column chromatography. This indicates a preference for the axial C-O bond of the cyclic sulfate to act as the leaving group.[17]

Stereoselective functionalization of the double bond in intermediate **15**, can be performed using the directing ability of allylic hydroxy functions. Deprotection of the 2-hydroxyl group and *syn*-epoxidation gave **17**. Protection of the two hydroxyl functions in **17** as benzyl ethers and cleavage of the MPM ether afforded the alcohol **18**, essential for the regioselective opening of the epoxide ring. The epoxy-urethane **19**, upon

treatment with NaH, underwent intramolecular displacement at C-4[18]; subsequent *in situ* methylation of the oxyanion gave **20** in virtually quantitative yield.



(a) TBDPSCl, imidazole, DMF, 45°C; (b) MeOH, PPTS, 45°C, 12 h; (c) SO_2Cl_2, Et_3N, CH_2Cl_2, r.t., 12 h; (d) LiN_3, DMF, 10°C, 24 h, then THF, H_2SO_4 (1 eq), H_2O (0.2 eq), r.t. 30 min then $NaHCO_3$ (s), r.t.; (e) TBAF, THF, r.t.; (f) mCPBA, CH_2Cl_2, r.t., 72 h; (g) NaH, BnBr, THF, r.t.; (h) DDQ, CH_2Cl_2/H_2O 20:1, r.t.; (i) Me-N=C=O, Et_3N, CH_2Cl_2, r.t., 24 h; (j) NaH, THF, r.t., 30 min then MeI, r.t.; (k) 5 % HCO_2H in EtOH, 10 % Pd/C, H_2, r.t.; (l) 6 N HCl, reflux.

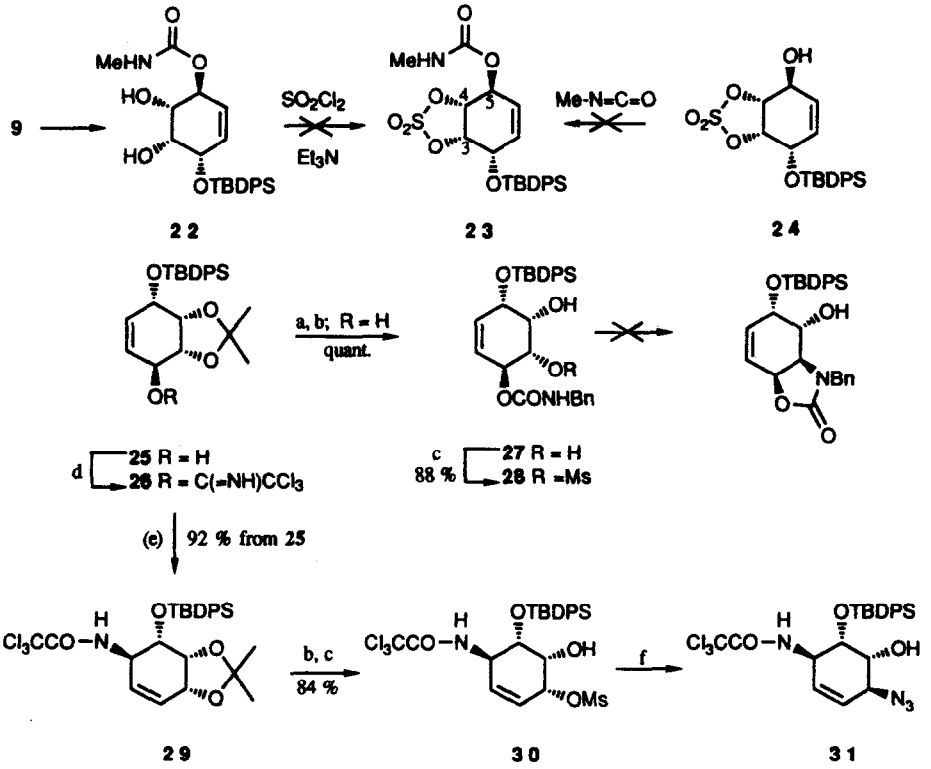
Scheme 2

Concomitant hydrogenolysis of the benzyl ethers during the hydrogenation of the azide in **20** was possible only when an acid solution was used. Finally, acid catalyzed hydrolysis of the oxazolidinone ring afforded (+)-fortamine dihydrochloride **21** which was purified on an Amberlyst IR-120 (H^+) column. Salt **21** exhibits $[\alpha]_D^{r.t.} = +3.96$ (c = 1.0, H_2O) and spectral data identical with those of (+)-fortamine dihydrochloride obtained from degradation of natural fortimicin B.[19]

Since fortamine dihydrochloride has been converted to the free form **10**[19] and since natural **10**, obtained from degradation of fortimicin A (**11**), has been converted back to **12**[20], our work also constitutes a formal synthesis of fortimicin B.

As mentioned above alternative approaches have been studied; we want to comment briefly on the results of some of them (Scheme 3). One of the alternatives, carried out in the enantiomeric series, (from **9**), aimed at complete regioselectivity by internal attack of the urethane on the cyclic sulfate in **23**. This strategy would have

introduced the C-4 methylamine substituent. However, both formation of the urethane of **24** and the formation of the cyclic sulfate from **22** failed. This is surprising as these reactions gave excellent results on analogous compounds such as respectively **18** and **13**.



(a) 4-$MeOC_4H_4N$=C=O, CH_2Cl_2, r.t., 5 h; (b) MeOH, PPTS, reflux, 3 h; (c) MsCl, Et_3N, CH_2Cl_2, 0°C, 30 min; (d) KH, $CNCCl_3$, THF, r.t., 1.5 h; (e) xylene, 140°C, 4 h; (f) NaN_3, DMF, 80°C.

Scheme 3

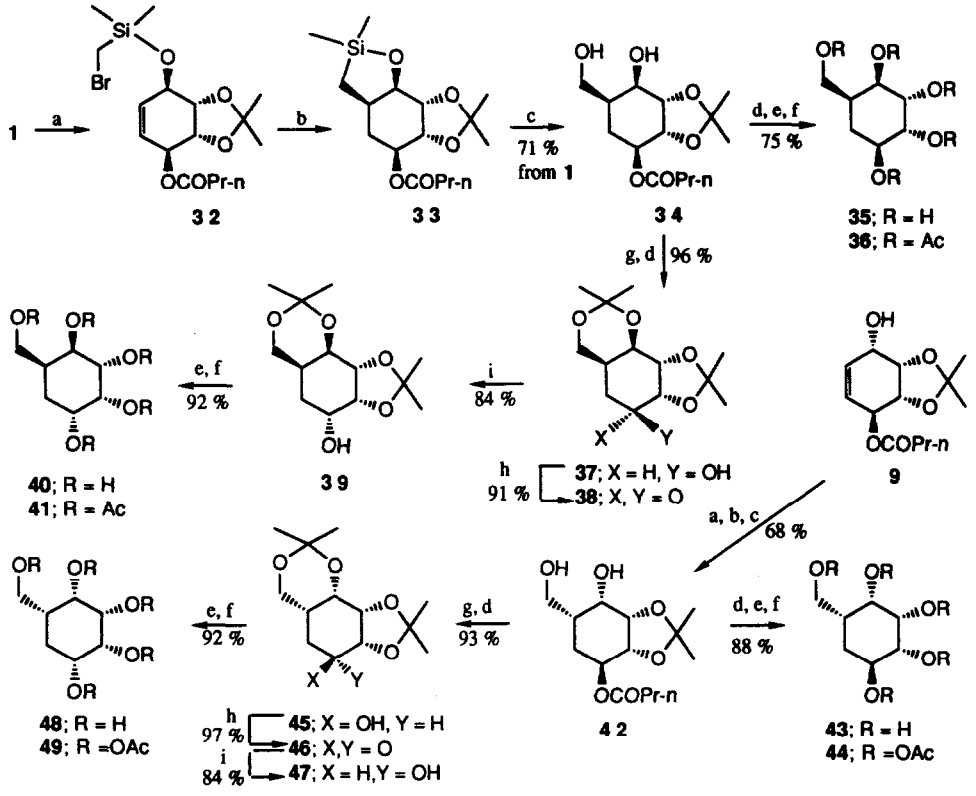
A close alternative involved the intramolecular displacement of a C-1 mesylate in **28**, available from **9**. The equatorial 4-hydroxyl group in **27** can selectively be mesylated. However the substitution, studied under a variety of conditions, different bases (t-BuOK, NaH, KH) or solvents (MeCN, THF, DMF, 1,4-dioxane, DME, HMPA), failed. Considering the successful transformation of epoxide **19**, this difference must be due to stereoelectronic constraints (colinearity of nucleophile and leaving group).

Another attractive alternative involved the Overman rearrangement[21] of trichloroimidate **26** which cleanly led to **29**. Hydrolysis of the acetal and selective mesylation gave **30**; it is noteworthy that the alternative cyclic sulfate formation of the intermediate α-diol failed (compare **13** and **22**). However, not surprisingly azide **31** was accompanied by the azide resulting from the SN_2' reaction (*ratio circa* 1:1).

Pseudo-sugars (Schemes 4 and 5)

Pseudo-sugars[22] are carbocyclic analogues of carbohydrates. 2,3,4,5-Tetrahydroxy-1-(hydroxymethyl)-cyclohexanes or 5a-carba-hexopyranoses, are thus related to hexopyranoses in which the ring oxygen has

been replaced by a methylene group. A number of them are found as components of important antibiotics[23]. The structural close resemblance to true-sugars endows them with interesting biological activities in the area of enzyme inhibitors, sweeteners and antibiotic, antiviral and anticancer therapy. The carba-hexopyranoses have attracted considerable synthetic efforts, which, to the best of our knowledge, has led to fifteen homochiral members[23,24].



(a) (bromomethyl)chlorodimethylsilane (1.1 eq), Et_3N (1.1 eq), DMAP (0.1 eq), CH_2Cl_2, 0°C, 2 h; (b) n-Bu_3SnH (1.5 eq), AIBN (0.1 eq), C_6H_6, reflux 5 h, then r.t., 5 h; (c) KF (2 eq), $KHCO_3$ (1 eq), H_2O_2 (35 %, 12 eq), THF/MeOH (1/1), 2.5 h, r.t., then Na_2SO_3 (12 eq), 0°C; (d) $KHCO_3$ (1 eq), MeOH, r.t.; (e) PTSA, MeOH, r.t.; (f) Ac_2O, r.t., 24 h; (g) 2,2-dimethoxypropane, DMF, PPTS, r.t., 24 h; (h) oxalylchloride (2 eq), DMSO (4 eq), Et_3N (5 eq), CH_2Cl_2, -78°C, 3 h; (i) $NaBH_4$, THF/MeOH (1:1), -78°C.

Scheme 4

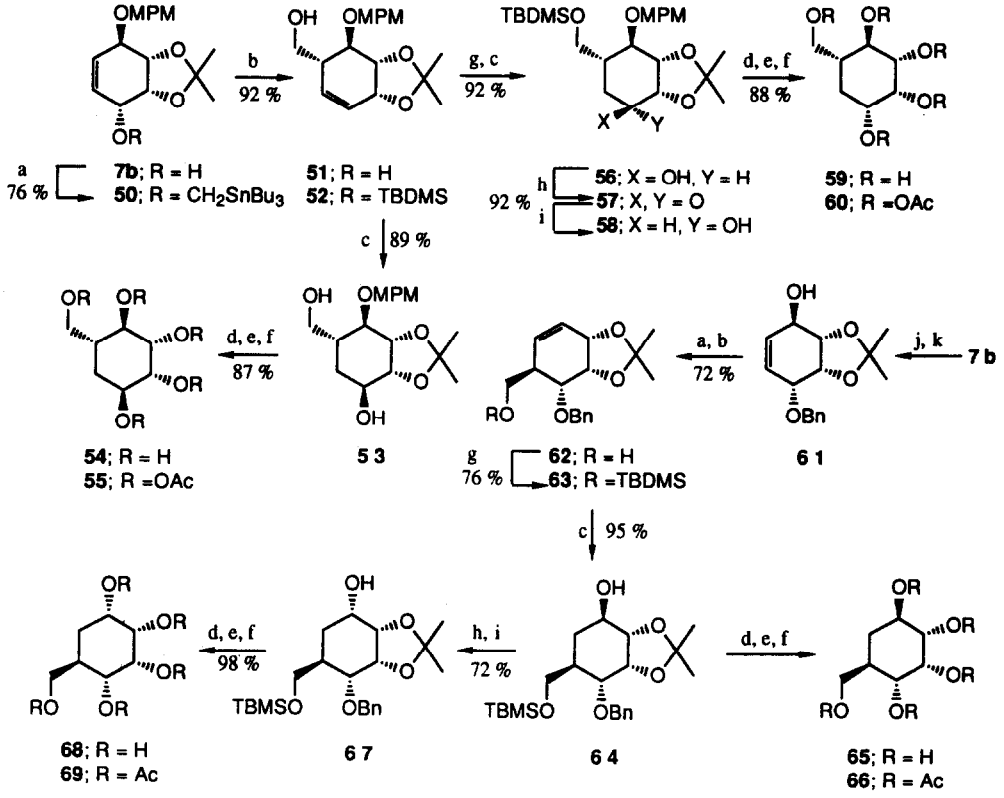
For the synthesis of these target molecules we need to introduce a functionalized 1-C-substituent on one of the sp^2-carbon atoms of **1**. As a consequence all D- and L-5a carba-hexoses, with a 2,3-*cis* substitution pattern (sugar numbering), can be obtained.

For the synthesis of 5a-carba-gulopyranoses **35** and **40** and 5a-carba-talopyranoses **43** and **48** the Stork radical cyclization is ideally suited[25]. Accordingly, the bromomethyl dimethyl silyl ether **32** was transformed into **33**. Ether **32** is rather unstable and had to be used directly after rapid filtration on celite and solvent evaporation. Oxidative cleavage of the carbon-silicon[26] bond in crude **33** led to **34**, a protected form of

5a-carba-β-L-gulopyranose **35**. Hydrolysis of **34** led to **35**, as a hygroscopic syrup, which was characterized as its penta-acetate **36**[10].

The α-anomer was obtained from **34**, *via* bis-acetonide **37**. Not surprisingly, Mitsunobu[7] inversion failed on this highly congested alcohol. Alternatively, an oxidation-reduction sequence led to **39**; Swern[27] oxidation gave a high yield, while methods based on PDC, PCC and Collins oxidation failed. The subsequent reduction of **38** afforded an easily separable mixture of **39** and **37** in 9:1 ratio. Hydrolysis of **39** led to 5a-carba-α-L-gulopyranose **40**, characterized as **41**[10].

For the synthesis of the 5a-carba D-talopyranoses, **43** and **48** the same reaction sequence can be used, starting from **9**. The Stork procedure gave the key intermediate **42** which was transformed into the penta-acetate **44**[10] of 5a-carba-α-D-talopyranose **43**. The β-anomer **48** and the penta-acetate **49**[10] were obtained *via* ketone **46**; here the reduction was completely diastereoselective.



(a) KH, ICH_2SnBu_3, THF, 0°C, r.t.; (b) n-BuLi, THF, -78°C; (c) BH_3, THF, -78°C, then H_2O_2, NaOH, 0°C; (d) Pd/C (10 %), MeOH, H_2 (1 atm.); (e) PTSA, MeOH, r.t.; (f) Ac_2O, py, r.t., 24 h; (g) TBDMS-Cl, imidazole, DMF; (h) oxalyl chloride, DMSO, Et_3N, -78°C; (i) $NaBH_4$, MeOH, 0°C; (j) NaH, THF, $INBu_4$, BnBr, r.t.; (k) DDQ, CH_2Cl_2/H_2O (5 %), 0°C → r.t.

Scheme 5

For the synthesis of the 5a-carba-mannopyranoses **54** and **59** and the 5a-carba-allopyranoses **65** and **68** the hydroxymethyl group was introduced *via* 2,3-Wittig rearrangement, subsequent to inversion of one of the

allylic oxy-substituent in **1**. Allylic alcohol **7b** was selected as the starting material. Formation of stannate **50** and [2,3]-sigmatropic shift, using Still's conditions[28] cleanly led to the cyclohexene **51**. Hydroboration and oxidative work-up[29] gave, next to 5 % of unidentified isomers, alcohol **53** which was transformed into 5a-carba-α-D-mannopyranose **54** and characterized as its penta-acetate **55**.

On the other hand, hydration of the double bond in **52**, allowed selective manipulation of the pseudo-anomeric hydroxyl group in **56**. This led to 5a-carba-β-D-mannopyranose **59** and its penta-acetate **60**[24b,c]. The 5a-carba-D-allopyranoses **65** and **68** were synthesized in essentially the same way after interchanging the destiny of the allylic oxy-groups in **7b**. The benzyl ether **61** now served as the starting material for Still's procedure. Hydration of the double bond in **63**, after protection of the primary hydroxyl group in **62**, led exclusively to **64**; full deprotection gave 5a-carba-β-D-allopyranose **65** and subsequently penta-acetate **66**[10]. On the other hand hydration of **62**, produced the expected secondary alcohol in 75 % yield next to 10 % isomeric material. The α-anomer **68** and it penta-acetate **69**[10] were obtained via **67** as described for **54** from **56**.

Except for the 5a-carba-mannopyranoses, the present study led, to the best of our knowledge, to the first reported synthesis of the 5a-carba-L-gulo (**35** and **40**), 5a-carba-D-talo- (**43** and **48**) and of the 5a-carba-D-allopyranoses (**65** and **68**). Moreover, because of the *meso*-nature of the common starting chiral building block **1** it is obvious that the respective enantiomers are also available.

Experimental Section

All reactions were carried out under argon atmosphere with magnetic stirring (unless otherwise specified). All solvents were purified or dried according to standard literature procedures. Solutions were dried on $MgSO_4$ and solvent evaporations were carried out in a Rotavapor at 16 mm Hg. Column chromatography was performed on SiO_2. HPLC separations were performed on a Knauer 64, a Waters 6000 A or a Kontron 420 delivery system with RI detection. Optical rotations were measured with a Perkin Elmer 421 polarimeter. IR spectra were recorded on a Perkin Elmer FTIR-1600 spectrometer, mass-spectra on a Finnigan 4000 or a HP-5988 spectrometer. The ^1H NMR spectra were recorded at 200 MHz (Varian-Gemini), 360 MHz or 500 MHz (WH-Brucker), the chemical shifts are expressed in ppm relative to TMS and coupling constants are in Hz. All solvents were purified or dried according to standard literature procedures. HRMS were performed on a Kratos MS-50 TC. Elemental analyses were carried out by ICHOR, Université Pierre et Marie Curie (Paris, France).

(1R,2S,3R,4S)-4-butyryloxy-2,3-isopropylidenedioxy-5-cyclohexen-1-ol (+)-1
To **4b** (5 g, 15.3 mmol) in 100 mL phosphate buffer (pH = 7) was added PGL (5 mg) at 30-35°C. A pH = 7 was maintained using pH-stat control. The reaction consumed 14.96 mL NaOH (1.0 M) and the automatic titration came to the end-level. Extraction with EtOAc, washing with brine drying, concentration and chromatography gave **1** (3.8 g, 96 %). No trace of *ent*-**1** could be detected by ^1H NMR (500 MHz, $CDCl_3$) in the presence of Eu(hfc)$_3$. $[\alpha]_D^{20}$ = +141.5 (c 1.1, $CHCl_3$); IR (film) : 3459, 2969, 2937, 1738, 1357, 1176, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 0.96 (t, J = 7.4 Hz, 3H), 1.37 (s, 3H), 1.47 (s, 3H), 1.68 (m, 2H), 2.36 (m, 2H), 2.29 (d, $J_{1,OH}$ = 5.0 Hz, -OH, 1H), 4.15 (dd, $J_{2,3}$ = 7.9, $J_{1,2}$ = 5.5 Hz, C_2-H), 4.24 (ddddd, $J_{1,OH}$ = 5.0, $J_{1,6}$ = 1.5, $J_{1,5}$ = 2.5, $J_{1,4}$ = 1.6 Hz, C_1-H), 4.30 (dd, $J_{2,3}$ = 7.9, $J_{3,4}$ = 5.2 Hz, C_3-H, 1H), 5.24 (dddd, $J_{3,4}$ = 5.2, $J_{4,5}$ = 2.5, $J_{4,6}$ = 2.5, $J_{1,4}$ = 1.6 Hz, C_4-H, 1H), 5.67 (ddd, $J_{5,6}$ = 10.0, $J_{1,6}$ = 2.5, $J_{4,6}$ = 2.5 Hz, C_6-H, 1H), 5.89 (ddd, $J_{5,6}$ = 10.0, $J_{4,5}$ = 2.5, $J_{1,5}$ = 2.5 Hz, C_5-H, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 172.91, 131.72, 127.48, 109.61, 78.80, 76.03, 72.05, 70.24, 36.17, 27.04, 24.83, 18.37, 13.62; Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found : C, 60.88; H, 7.80.

(1S,2S,3R,4S)-4-butyryloxy-2,3-isopropylidenedioxy-5-cyclohexen-1-ol (9)
To a solution of **1** (3.5 g, 13.65 mmol), Ph_3P (5.379, 20.48 mmol) and 4-nitrobenzoic acid (3.42 g, 20.48 mmol) in THF (50 ml) was added dropwise diethyl azodicarboxylate (3.61 g, 20.73 mmol). After stirring for 3 h at r.t. the mixture was filtered through silica gel (HOAc/hexane 1:1) and concentrated. The residue was taken up in MeOH (150 ml) and $KHCO_3$. After 4 h the solvent was replaced by EtOAc. Washing, drying, concentration and chromatography (EtOAc/hexane 1:3) gave **9** (3.35, 96 %). mp 81.5-82.5°C; $[\alpha]_D^{20}$ = +207.6 (c 1.4, $CHCl_3$); IR (KBr) : 3248, 2967, 2935, 1741, 1462, 1384, 1372, 1260, 1211, 1186, 1168,

1091, 1035, 982, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 0.93 (t, J = 7.4 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.62 (m, 2H), 225 (t, J = 7.3 Hz, 2H,), 2.58 (d, $J_{1,OH}$ = 8.9 Hz, -OH, 1H), 4.33 (dddd, $J_{1,OH}$ = 8.9, $J_{1,2}$ = 4.5, $J_{1,6}$ = 2.6, $J_{1,5}$ = 0.6 Hz, C_1-H, 1H), 4.43 (ddd, $J_{2,3}$ = 7.4, $J_{3,4}$ = 2.9, $J_{1,3}$ = 0.4 Hz, C_3-H, 1H), 4.58 (ddd, $J_{1,2}$ = 4.5, $J_{2,3}$ = 7.4, $J_{2,6}$ = 1.1 Hz, C_2-H, 1H), 5.26 (ddd, $J_{4,5}$ = 4.9, $J_{3,4}$ = 2.9, $J_{4,6}$ = 1.1 Hz, C_4-H, 1H), 6.03 (ddd, $J_{5,6}$ = 9.9, $J_{4,5}$ = 4.9, $J_{1,5}$ = 0.6 Hz, C_6-H, 1H), 5.98 (dddd, $J_{5,6}$ = 9.9, $J_{1,6}$ = 2.6, $J_{4,6}$ = 1.1, $J_{2,6}$ = 1.1 Hz, C_5-H, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 172.54, 135.92, 126.70, 109.45, 75.45, 75.38, 67.88, 65.15, 36.04, 26.12, 24.53, 18.46, 13.60; Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found : C, 60.79; H, 7.83.

+207.6 (c 1.4, $CHCl_3$); IR (KBr) : 3248, 2967, 2935, 1741, 1462, 1384, 1372, 1260, 1211, 1186, 1168, 1091, 1035, 982, 895 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 0.93 (t, J = 7.4 Hz, 3H), 1.32 (s, 3H), 1.40 (s, 3H), 1.62 (m, 2H), 225 (t, J = 7.3 Hz, 2H,), 2.58 (d, $J_{1,OH}$ = 8.9 Hz, -OH, 1H), 4.33 (dddd, $J_{1,OH}$ = 8.9, $J_{1,2}$ = 4.5, $J_{1,6}$ = 2.6, $J_{1,5}$ = 0.6 Hz, C_1-H, 1H), 4.43 (ddd, $J_{2,3}$ = 7.4, $J_{3,4}$ = 2.9, $J_{1,3}$ = 0.4 Hz, C_3-H, 1H), 4.58 (ddd, $J_{1,2}$ = 4.5, $J_{2,3}$ = 7.4, $J_{2,6}$ = 1.1 Hz, C_2-H, 1H), 5.26 (ddd, $J_{4,5}$ = 4.9, $J_{3,4}$ = 2.9, $J_{4,6}$ = 1.1 Hz, C_4-H, 1H), 6.03 (ddd, $J_{5,6}$ = 9.9, $J_{4,5}$ = 4.9, $J_{1,5}$ = 0.6 Hz, C_6-H, 1H), 5.98 (dddd, $J_{5,6}$ = 9.9, $J_{1,6}$ = 2.6, $J_{4,6}$ = 1.1, $J_{2,6}$ = 1.1 Hz, C_5-H, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 172.54, 135.92, 126.70, 109.45, 75.45, 75.38, 67.88, 65.15, 36.04, 26.12, 24.53, 18.46, 13.60; Anal. calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found : C, 60.79; H, 7.83.

(1S,2R,3S,4R)-2,3-isopropylidenedioxy-4-(4-methoxybenzyloxy)-5-cyclohexen-1-ol (6b)
A mixture of **1** (1.10 g, 4.29 mmol) 4-methoxybenzyl-2,2,2-trichloroacetimidate (1.82 g, 6.43 mmol) and CSA (100 mg) in CH_2Cl_2 (50 mL) was stirred for 48 h. EtOAc (100 mL) and H_2O (50 mL) were added. The water layer was extracted with EtOAc. The combined organic phase were concentrated and the residue was dissolved up in MeOH (30 mL) and K_2CO_3 (0.5 g) was added. After 4 h the solvent was evaporated and the residue was taken up in H_2O (50 mL) and extracted with EtOAc. The combined organic layers were dried and concentrated. Chromatography (EtOAc/hexane 1:3) gave **6b** (1.3 g, 98 %). $[\alpha]_D^{20}$ = -8.8 (c 1.2, $CHCl_3$); IR (film) : 3456, 2989, 2936, 2837, 1514, 1514, 1463, 1380, 1302, 1249, 1212, 1174, 1062, 1035, 776, 721, 697, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.36 (s, 3H), 1.43 (s, 3H), 2.74 (d, J = 6.8 Hz, OH, 1H), 3.80 s, 3H), 4.00 (m, 1H), 4.12 (m, 1H), 4.21 (dd, J = 7.7, 5.1 Hz, 1H), 4.39 (dd, J = 7.7, 4.1 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 5.94 (m, 1H), 5.99 (m, 1H), 6.88 (m, 2H), 7.28 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.60, 132.59, 130.03, 129.94, 129.84, 114.12, 109.32, 79.29, 77.96, 75.40, 71.43, 69.38, 55.58, 27.10, 24.93; Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found : C, 66.66; H, 7.44.

(1R,2R,3S,4R)-2,3-isopropylidenedioxy-4-(4-methoxybenzyloxy)-5-cyclohexen-1-ol (7b)
From **6b** (1.20 g, 3.91 mmol) as described for **9** from **1**. Yield of **7b** was 1.16 g, 97 %. mp 55-56°C; $[\alpha]_D^{20}$ = -113.6 (c 1.6, $CHCl_3$); IR (KBr) : 3450, 2898, 2910, 1613, 1514, 1381, 1249, 1073, 1034, 894, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.37 (s, 3H), 1.43 (s, 3H), 2.53 (d, J = 7.0 Hz, -OH, 1H), 3.80 (s, 3H), 4.18 (dd, J = 3.2, 3.2 Hz, 1H), 4.42 (m, 1H), 4.44 (dd, J = 6.5, 3.2 Hz, 1H), 4.47 (dd, J = 7.6, 4.2 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 6.03 (m, 2H), 7.25 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.51, 133.81, 130.43, 129.75, 114.09, 109.48, 77.51, 75.81, 73.49, 70.91, 65.21, 66.68, 26.52, 24.72; Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found : C, 66.67; H, 7.23.

(1R,2R,3S,4R)-1-(t-butyldiphenylsilyloxy)-4-(4-methoxybenzyloxy)-2,3-sulfuryldioxy-5-cyclohexene (14)
A mixture of **13** (1.05 g, 2.08 mmol), DMAP (30 mg) and Et_3N (3 mL) in anhydrous CH_2Cl_2 (20 mL) was treated dropwise with SO_2Cl_2 (3.14 mL, 3.14 mmol, 1M solution in CH_2Cl_2) at r.t.. After 4 h, Et_3N (2 mL) and SO_2Cl_2 (2 mL, 2.0 mmol, 1.0 M solution in CH_2Cl_2) were added at r.t. and stirring was continued for 12 h. The mixture was poured into EtOAc (100 mL) and saturated aqueous $NaHCO_3$ (50 mL); the water phase was extracted with EtOAc. The combined organic phases were dried, filtered, concentrated. Flash chromatography (EtOAc/hexane 2:8) afforded **14** (1.04 g, 89 %) as a colorless oil. $[\alpha]_D$ = -84.1 (c 1.2, $CHCl_3$); IR (film) : 2932, 1613, 1514, 1392, 1251, 1122, 1113, 1034, 824, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.05 (s, 9H), 3.81 (s, 3H), 4.52 (d, J = 11.4 Hz, 1H), 4.56 (dd, J = 4.7, 3.5 Hz, 1H), 4.59 (d, J = 11.4 Hz, 1H), 4.65 (ddd, J = 4.3, 3.0, 1.9 Hz, 1H), 4.75 (dd, J = 7.9, 4.3 Hz, 1H), 5.67 (ddd, J = 9.9, 4.7, 1.9 Hz, 1H), 5.90 (dd, J = 9.9, 3.0 Hz, 1H), 6.88 (m, 2H), 7.22 (m, 2H), 7.40 (m, 6H), 7.63 (m, 2H), 6.59 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.83, 136.25, 136.18, 133.38, 132.52, 131.84, 131.11, 130.41, 130.36, 130.06, 129.04, 128.12, 128.06, 114.29, 81.118, 79.92, 72.72, 71.65, 64.79, 55.60, 27.05, 19.41.

(1R,2R,3R,4R)-3-Azido-1-(4-methoxybenzyloxy)-4-(t-butyldiphenylsilyloxy)-5-cyclohexen-2-ol (15)
A mixture of **14** (0.90 g, 1.58 mmol) and lithium azide (0.16 g, 3.26 mmol) in dry DMP (10 mL) was stirred at 5-10°C for 24 h. The solvent was evaporated (0.01 mm Hg) at 50°C. The residue was dissolved in THF (20 mL) and H_2SO_4 (86 µL, 1.60 mmol) and H_2O (29 µL, 1.60 mmol) were added followed, after 30 min by $KHCO_3$ (solid, 0.32 g, 3.2 mmol). Stirring for 1 h, filtration through a silica gel pat (EtOAc/hexane 1:1), solvent evaporation and flash chromatography (EtOAc/hexane 15:85) afforded **15** (0.62 g, 72 %) next to **16** (0.21 g, 25 %). $[\alpha]_D$ = -102.5 (c 1.8, $CHCl_3$); IR (film) : 2111, 1612, 1513, 1469, 1427, 1387, 1302, 1250, 1110, 1055, 822, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.08 (s, 9H), 2.54 (d, J = 2.4 Hz, OH), 3.53 (ddd, J = 10.0, 4.4, 2.4 Hz, 1H), 3.56 (dd, J = 10.0, 5.7 Hz), 1H), 4.02 (m, 1H), 4.18 (m, 1H), 4.55 (d, J = 11.4 Hz), 1H), 4.60 (d, J = 11.4 Hz, 1H), 5.36 (ddd, J = 10.4, 2.10, 2.10, 1H), 5.50 (ddd, J = 10.4, 2.0, 2.0 Hz), 1H), 6.58 (m, 2H), 7.23 (m, 2H), 7.42 (m, 6H), 7.69 (m, 4H); MS : 528 (M^+ -1), 472 (M^+ -C_4H_9), 444, 338, 199, 121.

(1S,2S,3R,4S,5S,6S)-2-Azido-5,6-epoxy-4-(4-methoxybenzyloxy)-cyclohexan-1,3-diol (17)
A mixture of **15** (0.45 g, 0.85 mmol) and Bu_4NF (1.7 mL, 1.7 mmol, 1.0 M in THF) in THF (5 mL) was stirred at r.t. for 2 h. The flash chromatography (EtOAc/hexane 3:7) gave the alcohol as colorless crystalline solid (quant.).
A mixture of the allylic alcohol (150 mg, 0.51 mmol) and MCPBA (355 mg, 75 %, 1.54 mmol) in CH_2Cl_2 (10 mL) was stirred at r.t. for 3 days. The mixture was diluted with EtOAc, washed with 10 % Na_2SO_3 and the water phase was extracted with EtOAc; The combined organic layers were dried, filtered and concentrated. Flash chromatography (EtOAc/hexane 3:7) afforded **17** (147 mg, 95 %) as colorless crystalline solid. mp 106-107°C; $[\alpha]_D$ = -131.1 (c 0.8, $CHCl_3$); IR (KBr) : 3665, 3010, 2885, 2834, 2117, 1616, 1514, 1466, 1220, 1367, 1300, 1299, 1248, 1170, 1101, 1032, 992, 938, 849, 812 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 2.38 (s (b), 1H, OH), 2.52 (d, J = 2.3 Hz, 1H), 3.24 (d, J = 3.8 Hz), 1H), 3.31 (dd, J = 10.9, 8.9 Hz, 1H), 3.40 (m, 2H), 3.68 (dd, J = 8.0, 0.5 Hz, 1H), 3.81 (s, 3H), 3.87 (m, 1H), 4.64 (d, J = 11.3 Hz, 1H), 4.74 (d, J = 11.3 Hz, 1H), 6.91 (m, 2H), 7.30 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.60, 129.72, 129.19, 114.09, 77.90, 93.92, 72.82, 71.20, 63.88, 55.87, 55.29, 53.99; Anal. calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.67. Found : C, 54.68; H, 5.44; N, 13.65.

(1S,2R,3R,4S,5S,6S)-3-Azido-2,4-dibenzyloxy-5,6-epoxycyclohexanol-1 (18)
A solution of **17** (120 mg, 0.39 mmol) in dry THF (2 mL) was added to a mixture of benzyl bromide (267 mg, 1.56 mmol), NaH (62 mg, 1.56 mmol), and Bu_4NI (50 mg) in dry THF (5 mL) at 0°C. After stirring at r.t. for 3 h, the mixture was poured in saturated aq. NH_4Cl solution (20 mL) and extracted with EtOAc. The organic layer was washed with brine, dried, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and water (1 mL), DDQ (266 mg, 1.17 mmol) was added in one portion at 0°C. After stirring at r.t. for 3 h, EtOAc (50 mL) was added and the solution was washed with 10 % Na_2SO_3. The water phase was extracted with EtOAc, and the combined organic layers were washed with $NaHCO_3$ solution and brine, dried, filtered and concentrated. Flash chromatography (EtOAc/hexane 3:7) afforded **18** (139 mg, 98 %) as a colorless crystalline solid. mp 73-74°C; $[\alpha]_D$ = -76.0 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) : 2.04 (d, $J_{1,OH}$ = 2.0 Hz, OH, 1H), 3.08 (dd, J = 10.9, 8.0 Hz, 1H), 3.12 (d, J = 3.8 Hz, 1H), 3.34 (ddd, J = 3.8, 1.8, 0.5 Hz, 1H), 3.55 (dd, J = 10.9, 9.1 Hz, 1H), 3.71 (dd, J = 9.1, 1.8 Hz, 1H), 3.93 (ddd, J = 8.0, 2.0, 0.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.79 (d, J = 11.9 Hz, 1H), 4.84 (d, J = 11.9 Hz, 1H), 4.95 (d, J = 11.5 Hz, 1H), 7.40 (m, 10H); ^{13}C NMR (200 MHz, $CDCl_3$) : 138.12, 137.93, 129.12, 128.92, 128.84, 126.61,128.51, 128.33, 82.80, 78.08, 75.33, 72.81, 71.14, 62.67, 55.71, 54.23; Anal. calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found : C, 63.36; H, 5.77; N, 11.62.

(1S,2R,3R,4S,5S,6S)-3-Azido-2,4-dibenzyloxy-5,6-epoxy-1-(N-methylcarbonyl)cyclohexane (19)
A mixture of **18** (100 mg, 0.27 mmol), methyl isocyanate (200 µL) and Et_3N (20 µL) in CH_2Cl_2 (10 mL) was stirred at r.t. for 48 h. Solvent evaporation and HPLC (EtOAc/CH_2Cl_2 5:95) gave **19** (111 mg, 96 %) as colorless crystalline solid. mp 176-177°C; $[\alpha]_D$ = -123.6 (c 0.8, $CHCl_3$); IR (KBr) : 3413, 3314, 3089, 3034, 2119, 1696, 1558, 1348, 1258, 1145, 1087, 1030, 973, 848, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 2.72 (d, J = 4.9 Hz, 3H), 3.10 (d, J = 3.7 Hz, 1H), 3.29 (m, 1H), 3.31 (dd, J = 10.6, 7.8 Hz, 1H), 3.61 (dd, J = 10.5, 10.5 Hz, 1H), 3.68 (m, 12H), 4.34 (m, 1H), 4.57 (d, J = 11.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.75 (d, J = 11.9 Hz, 1H), 4.80 (d, J = 11.9 Hz, 1H), 4.86 (d, J = 7.8 Hz, 1H), 7;35 (m, 10H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.60, 129.72, 129.19, 114.09, 77.90, 93.92, 72.82, 71.20, 63.88, 55.87, 55.29, 53.99; Anal. calcd. for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found : C, 62.27; H, 5.61; N, 13.27.

(1R,2R,3S,4S,5R,6R)-4-Azido-3,4-dibenzyloxy-2-methoxy-9-methyl-8-oxo-9-aza-7-oxa-bicyclo(4,3,0)-nonane (20)

A mixture of **19** (100 mg, 0.23 mmol), in dry anhydrous THF (5 mL) was treated with NaH (25 mg) at r.t. After 2.5 h, iodomethane MeI (100 µL) was added and stirring was continued for 1 h. The mixture was poured into sat. NH_4Cl solution (10 mL) and extracted with EtOAc. The organic phase was dried, filtered and concentrated. Preparative HPLC (EtOAc/CH_2Cl_2 2;98) gave **20** (103 mg, quant.) as a slightly yellow oil. $[\alpha]_D$ = -35.2 (c 1.0, $CHCl_3$);

IR (film) : 2920, 2110, 1770, 1456, 1424, 1394, 1358, 1265, 1098, 1024, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 2.71 (s, 3H), 3.36 (dd, J = 7.1, 2.1 Hz, 1H), 3.37 (s, 3H), 3.51 (dd, J = 7.0, 4.8 Hz, 1H), 3.52 (dd, J = 6.7, 4.5 Hz, 1H), 3.84 (dd, J = 8.7, 5.5 Hz, 1H), 3.88 (dd, J = 8;6, 5.8 Hz, 1H), 4.59 (d, J = 12.1 Hz, 1H), 4.68 (dd, J = 8;6, 8.6 Hz, 1H), 4.70 (d, J = 10.9 Hz, 1H), 4.78 (d, J = 12.1 Hz, 1H), 4.93 (d, J = 10.9 Hz, 1H), 7.38 (m, 10H); MS : 409 (M^+ -N_2-1), 319, 290, 273, 190, 135, 91.

(+)-Fortamine dihydrochloride (21)

A solution of **20** (50 mg; 0.12 mmol) in MeOH (10 mL) and formic acid (1 mL) was stirred with 10 % Pd/C (25 mg) under H_2 (1 atm) at r.t. for 6 h. After filtration and evaporation the residue was dissolved in HCl (3 mL; 6N) and refluxed for 12 h. The solvent was evaporated and the residue was passed through a column of Amberlyst IR-120 (H^+) resin (eluted with water, then 5 % aq. NH_3 solution). The eluent was concentrated and the residue was treated with HCl (1N). The solution was concentrated giving **21** (31.2 mg, quant.) as a slightly yellow solid. $[\alpha]_D$ = +3.97 (c 1.0, H_2O); lit.[18] $[\alpha]_D$ = +4.0 (c 0.8, H_2O); ^1H NMR (500 MHz, D_2O) : 2.87 (s, 3H), 3.54 (dd, J = 8.0, 8.0 Hz, 1H), 3.75 (dd, J = 5.8, 4.6 Hz, 1H), 3.87 (dd, J = 8.1, 8.1 Hz), 4.01 (dd, J = 6.0, 3.1 Hz, 1H), 4.20 (dd, j = 8.0, 4.6 Hz, 1H), 4.23 (dd, J = 8.0, 3.0 Hz, 1H).

(1S,2R,3S,4R,5S)-5-Butyryloxy-3,4-isopropylidenedioxy-1-hydroxymethylcyclohexan-2-ol (34)

To a solution of **1** (1.00 g, 3.9 mmol), Et_3N (0.43 g, 4.2 mmol), and 4-dimethylaminopyridine (45 mg, 0.37 mmol) in dry CH_2Cl_2 (50 mL), (bromomethyl)dimethylchlorosilane (0.8 g, 4.2 mmol) was added dropwise at 0°C. After 2 h at r.t. the mixture was diluted with dry hexane (100 mL), filtered through celite (EtOAc/hexane 1:3), concentrated and dried in high vacum for 2 h. The residue was dissolved in dry benzene (60 mL), tributyltin hydride (1.7 g, 5.8 mmol) and AIBN (32 mg, 0.2 mmol) in benzene (10 mL) were injected by a mechanical syringe pump during 5 h under gentle reflux. After 5 h reflux the solvent was evaporated and a mixture of the residue, $KHCO_3$ (0.4 g, 3.9 mmol), KF (0.46 g, 7.8 mmol) in MeOH and THF (30 mL 1:1) was treated dropwise with 35 % H_2O_2 (4 mL, 47.6 mmol) at 0°C. After 2.5 h at r.t. H_2O (15 mL) was added, followed by Na_2SO_3 (6.0 g, 47.6 mmol) at 0°C. The organic solvents were removed at r.t. Extraction with Et_2O, drying, filtration, concentration and chromatography (EtOAc/hexane 1:1) afforded **34** (0.81 g, 71 %) as colorless crystalline solid. mp 81-82°C; $[\alpha]_D$ = +93.5 (c 2.5, $CHCl_3$); IR (KBr) : 3454, 2940, 1738, 1455, 1383, 1242, 1222, 1186, 1074, 1005, 861, 784, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 0.94 (t, J = 7.39 Hz, 3H), 1.35 (s, 3H), 1.49 (s, 3H), 1.63 (m, 3H), 1.82 (m, 1H), 2.03 (m, 1H), 2.1 (m, 1H), 2.45 (t (b), 1H, -OH), 3.45 (d, J = 2.3 Hz -OH, 1H), 3.80 (m, 1H), 3.91 (m, 1H), 4.20 (dd, J = 8.4, 5.4 Hz), 4.21 (m, 1H), 4.35 (m, 1H), 4.94 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 173.75, 109.64, 78.65, 76.83, 74.91, 70.05, 65.72, 37.00, 36.66, 28.28, 26.58, 25.50, 18.71, 13.87; Anal. calcd. for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found : C, 58.12; H, 8.37.

(1S,2R,3S,4R,5S)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-β-L-gulopyranose penta-acetate) (36)

A mixture of **34** (50 mg, 0.17 mmol) and K_2CO_3 (23 mg, 0.17 mmol) in MeOH (2 mL) was stirred at 45°C for 4 h. The solvent was evaporated and the residue was filtered through silica gel (MeOH/CH_2Cl_2 1:1). The filtrate was concentrated and treated with PTSA (20 mg) in MeOH (2 mL) overnight. The solvent was evaporated and the residue treated with acetic anhydride (1 mL) in pyridine (1;5 mL) for 24 h. Solvent evaporation and flash column chromatography (EtOAc/hexane 1:1) gave **36** (50 mg, 75 %) as colorless crystalline solid.

(1R,2S,6R,7S,9S)-7-Hydroxy-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo[7.4.0.0^{2,6}] tridecane (37)

A mixture of **34** (0.5 g, 1.7 mmol), 2,2-dimethoxypropane (10 mL), and pyridinium p-toluenesulfonate (30 mg) in DMF (10 mL) was stirred for 24 h. The mixture was diluted with Et_2O (100 mL) washed with brine, concentrated and treated overnight with K_2CO_3 (0.27 g, 1.9 mmol) in MeOH (10 mL). The solvent was evaporated and EtOAc (50 mL) and brine (30 mL) were added and the water phase was extracted with EtOAc. The combined organic layers were dried, filtered and concentrated to afford **37** (0.45 g, 96 %) as a colorless crystalline solid.mp 78-80°C; $[\alpha]_D$ = +57.9 (c 1.0, $CHCl_3$); IR (KBr) : 3454, 2990, 2941, 1380, 1243, 1065, 1021, 981, 894 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.34 (s, 3H), 1.37 (s, 3H), 1.44 (s, 3H), 1.46

(s, 3H), 1.46 (ddd, J = 13.0, 4.5, 4.5 Hz, 1H), 1.70 (m, 1H), 2.07 (dd, J = 24.1, 11.4 MHz, 1H), 2.78 (b (s), -OH, 1H), 3.61 (d, J = 11.9 Hz, 1H), 3.75 (m, 1H), 4.02 (dd, J = 6.7, 6.2 Hz, 1H), 4.07 (dd, J = 7.2, 2.2 Hz, 1H), 4;10 (dd, J = 11.9, 2.9 Hz, 1H), 4.31 (s (b), 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 108.84, 99.38, 79.62, 77.69, 72.01, 68.14, 64.24, 31.00, 29.87, 29.18, 28.30, 26.18, 18.88; MS : 243 (M^+ -CH_3), 185,125, 95, 59, 43; Anal. calcd. for $C_{13}H_{22}N_3O_5$: C, 60.45; H, 8.58. Found : C, 60.13; H, 8.37.

(1R,2S,6R,7R,9S)-7-Hydroxy-4,4,12,12-tetramethyl-3,5,11,13-tetraoxatricyclo[7.4.0.0^{2,6}] tridecane (39)

DMSO (270 µL, 3.76 mmol) was added dropwise to a stirred solution of oxalyl chloride (165 µL, 1.88 mmol) in anhydrous CH_2Cl_2 (6 mL) at -78°C. After 5 min, a solution of **37** (241 mg, 0.93 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred at -78°C for 3.5 h. Et_3N (130 µL, 4.65 mmol) was added and the mixture was warmed to -10°C over 2 h and then quenched with water (1 mL). The mixture was diluted with Et_2O (50 mL), washed with brine, dried, filtered, concentrated and flash chromatographed (EtOAc/hexane 15:85) affording **38** (218 mg, 91 %) as a colorless crystalline solid.

To a solution of **38** (50 mg, 0.19 mmol) in THF (2 mL) and MeOH (1 mL), $NaBH_4$ (11 mg, 0.29 mmol) was added at -78°C. After 4 h, the mixture was slowly warmed to 0°C and poured in EtOAc and H_2O (15 mL each). After extraction with EtOAc, the combined organic layers were dried, filtered, concentrated and purified by preparative HPLC to afford **39** (42.2 mg, 84 %) as colorless crystalline solid next to **37** (5 mg, 10 %). mp 78-79°C; $[\alpha]_D$ = +36.4 (c 1.0, $CHCl_3$); IR (KBr) : 3440, 2990, 2939, 1638, 1618, 1383, 1267, 1211, 1084, 1056, 856 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.36 (s, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.49 (s, 3H), 1.76 (m, 1H), 1;97 (m, 2H), 2;08 (d, J = 6.1 Hz, -OH, 1H) 3.59 (dd, J = 11.8, 1.7 Hz, 1H), 4.07 (dd, J = 11.8, 2.9 Hz, 1H), 4.20 (m, 3H), 4.30 (dd, J = 6.8, 4.0 Hz, 1H); Anal. calcd. for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found : C, 60.06; H, 8.30.

(1S,2R,3S,4R,5R)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-α-L-gulopyranose penta-acetate) (41)

A mixture of **39** (15 mg, 0.058 mmol) and PTSA (5 mg) in MeOH (1.5 mL) was stirred at 45°C for 5 h. The solvent was evaporated in vacuo, and the residue was treated with Ac_2O (1 mL) in pyridine (1.5 mL) for 24 h. The solvent evaporation, and HPLC purification (50 % EtOAc in hexane) gave **41** (18 mg, 92 %) as colorless syrup[10].

(1R,2S,3S,4R,5S)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-α-D-talopyranose penta-acetate) (44)

From **9** as described for **36** from **1**[10].

(1R,2S,3S,4R,5R)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-β-D-talopyranose penta-acetate) (49)

From **9** as described for **41** from **1**[10].

(1R,2S,3S,4R)-2,3-isopropylidenedioxy-4-p-methoxybenzyloxy-1-(tributylstannylmethyl-oxy)-5-cyclohexene (50)

To a suspension of KH (0.7 g) in THF (30 mL) was added a solution of **7b** (1.00 g, 3.26 mmol) in THF (30 mL) at 0°C. After 30 min at r.t. n-Bu_3SnCH_2I (1.70 g, 3.92 mmol) was added dropwise at 0°C. After stirring at r.t. for 3 h, the mixture was poured in saturated NH_4Cl (20 mL) extracted with Et_2O, washed with brine, dried, filtered and concentrated. Flash chromatography (Et_2O/hexane 1:9)) afforded **50** (1.64 g, 76 %) as a colorless oil, next to **7b** (0.15 g, 15 %). ^1H NMR (500 MHz, $CDCl_3$) : 0.88 (m, 15H), 1.28 (m, 6H), 1.34 (s, 3H), 1.38 (s, 3H), 1.49 (m, 6H), 3.80 (s, 3H), 3.89 (m, 2H, -$SnCH_2O$-), 4.01 (m, 1H), 4.06 (dd, J = 4.6, 2.7 Hz, 1H), 4.42 (ddd, J = 7.3, 2.6, 0.6 Hz, 1H), 4.46 (d, J = 11.3 Hz, 1H), 4.50 (d, J = 11.3 Hz, 1H), 4.62 (ddd, J = 7.3, 3.8, 1.1 Hz, 1H), 5.98 (dddd, J = 9.9, 4.6, 1.8, 0.6 Hz, 1H), 6.08 (ddd, J = 9.9, 2.9, 1.1 Hz, 1H), 6.85-6.88 (m, 2H), 7.24-7.26 (m, 2H).

(1R,2S,3R,4S)-4-Hydroxymethyl-1,2-isopropylidenedioxy-3-p-methoxybenzyloxy-5-cyclohexene (51)

To a solution of **50** (1.50 g, 2.26 mmol) in THF (20 mL) was added dropwise butyllithium (1.54 mL, 2.42 mmol, 1.6 M in hexane) at -78°C. After 2.5 h, the reaction was quenched with water at -78°C. The mixture was warmed to r.t. and poured in EtOAc (100 mL) and brine (30 mL); the water phase was extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated. Flash chromatography EtOAc/hexane 1:3) afforded **51** (0.67 g, 92 %) as colorless oil. $[\alpha]_D$ = +24.9 (c 1.9, $CHCl_3$); IR (film) : 3443, 2935, 1613, 1513, 1460,1379, 1248, 1170, 1083, 1036, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 42 (s, 3H), 1.56 (s, 3H), 2.26 (dd, J = 7.0, 2.3 Hz, -CH_2OH, 1H), 2.32 (m, 1H), 3.51 (dd, J =

8.8, 8.8 Hz, 1H), 3.70 (m, 2H), 3.80 (s, 3H), 4.28 (dd, J = 8.3, 6.7 Hz, 1H), 4.62 (d, J = 11.1 Hz, 1H), 4.56 (dddd, J = 6.7, 4.8, 3.2, 1.3 Hz, 1H), 5.68 (m, 1H), 5.90 (ddd, J = 9.9, 3.2,3.2 Hz, 1H), 6.89 (m, 2H), 7.32 (m, 2H).

(1S,2R,3S,4R,5R)-5-Hydroxymethyl-2,3-isopropylidenedioxy-4-p-methoxybenzyloxy-1-cyclohexanol (53)

To a solution of **51** (80 mg, 0.25 mmol) in THF (2 mL) was added dropwise BH_3-THF (1.0 mL, 1.0 M solution in THF, 1.0 mmol) at -78°C. The mixture was slowly warmed to r.t. and stirred for 1.5 h. The mixture was cooled to 0°C and water was carefully added followed by dropwise addition of H_2O_2 (35 %, 0.2 mL) and NaOH solution (0.13 mL, 0.1 M). The reaction was warmed to r.t. and stirred for 1.5 h. EtOAc (25 mL) and brine (15 mL) were added and water phase was extracted with EtOAc. The combined organic layers were dried, filtered, concentrated and purified by preparative HPLC ($MeOH/CH_2Cl_2$ 2:98) affording **53** (75 mg, 89 %) as colorless oil. $[\alpha]_D$ = +32.2 (c 0.9, $CHCl_3$);
IR (film) : 3438, 2935, 1612, 1514, 1378, 1247, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.38 (s, 3H), 1.51 (s, 3H), 1.64 (m, 2H), 2.07 (m, 1H), 2.32 (d, J = 4.4 Hz, -OH, 1H), 2.54 (m (t), $-CH_2OH$), 3.56 (dd, J = 9;2, 6.3 Hz, 1H), 3.57 (m, 1H), 3.80 (s, 3H), 4.02 (m, 1H), 4.16 (dd, J = 6.3, 4.1 Hz, 2H), 4.34 (dd, J = 6.3, 6.3 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 4.81 (d, J = 11.3 Hz, 1H), 6.88 (m, 2H), 7;28 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.63, 130.26, 130.04, 114.18, 109.30, 80.82, 79.66, 78.81, 72.52, 67.55, 55.23, 55.56, 36.49, 29.23, 28.03, 25.93; MS : 338 (M^+), 289, 176, 137, 121, 77, 43.

(1R,2R,3S,4R,5S)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-α-D-mannopyranose penta-acetate) (55)

A mixture of **53** (50 mg) and 10 % Pd/C (10 mg) in MeOH (1.5 mL) was stirred under H_2 (1 atm) for 12 h. The catalyst was filtered off, and PTSA (10 mg) was added. After stirring for 6 h, the solvent was evaporated. The residue was treated with Ac_2O in pyridine for 24 h. After usual work-up, the residue was purified by preparative HPLC (EtOAc/hexane 1:1) to afford **55** (50 mg, 87 %) as a colorless crystalline solid. mp 89-91°C; $[\alpha]_D$ = +35.5 (c 1.4, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) : 1.88 (m, 2H), 1.96 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.10 (s, 3H), 2.12 (s, 1H), 2.23 (m, 1H), 3.93 (dd, J = 11.4, 3.9 Hz, 1H), 4.09 (dd, J = 11.4, 5.6 Hz, 1H), 5.01 (dd, J = 6.7, 3.1 Hz, 1H), 5.18 (m, 1H), 5.20 (m, 1H), 5.29 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) : 171.01, 170.30, 170.24, 169.58, 71.07, 69.58, 69.27, 68.53, 63.97, 35.81, 27.72, 21.31, 21.13, 21.05, 21.01, 20.93; Anal. calcd. for $C_{17}H_{24}O_{10}$: C, 53.57; H, 6.23. Found : C, 52.64; H, 6.18.

(1S,2R,3S,4R,5R)-5-(t-Butyldimethylsiloxy)methyl-2,3-isopropylidenedioxy-4-p-methoxybenzyloxy-1-cyclohexanol (56)

A mixture of **52** (200 mg, 0.62 mmol), t-butylchlorodimethylsilane (113 mg, 0.74 mmol), imidazole (101 mg, 1.48 mmol) in dry DMF (2 mL) was stirred for 3 h. Et_2O and water (40 mL each) were added. The organic layer was washed with brine, dried, filtered and concentrated to afford a crude residue.
To a solution of this residue in THF (10 mL), BH_3-THF (5 mL, 5 mmol, 1.0 M solution in THF) was added dropwise at -78°C. Stirring was continued for 2 h at r.t. The excess borane was destroyed as described for **53**. Work-up gave **56** (260 mg, 92 % overall yield) as a colorless oil. $[\alpha]_D$ = +8.9 (c 1.9, $CHCl_3$); IR (film) : 3445, 1614, 1515, 1379, 1252, 1066, 976, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 0.05 (s, 6H), 0.90 (s, 9H), 1.36 (s, 3H), 1.49 (s, 3H), 1.74 (m, 2H), 1.99 (m, 2H), 2.33 (d, J = 5.7 Hz, 1H), 3.56 (dd, J = 9.7, 4.7 Hz), 3.66 (dd, J = 8.0, 6.1 Hz, 1H), 3.71 (dd, J = 9.7, 4.9 Hz, 1H), 3.80 (s, 3H), 3.99 (m, 1H), 4.16 (dd, J = 6.3, 3.9 Hz, 1H), 4.34 (dd, J = 6.3, 6.3 Hz, 1H), 4.53 (d, J = 1.1 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 6.86 (m, 2H), 2.28 (m, 2H).; ^{13}C NMR (200 MHz, $CDCl_3$) : 159.43, 130.85, 129.72, 114.03, 109.95, 79.42, 78.89, 77.02, 72.72, 68.03, 63.90, 55.54, 37.17, 29.03, 27.84, 26.21,25.76, 18.55, -5.09, -5.16.; MS : 437 (M^+ -CH_3), 316, 258, 251, 183, 121.

(1R,2R,3S,4R,5R)-5-t-(Butyldimethylsiloxy)methyl-2,3-isopropylidenedioxy-4-p-methoxybenzyloxy-1-cyclohexanol (58)

From **56** as described for **39** from **37**. $[\alpha]_D$ = +12.9 (c 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) : 0.041 (s, 3H), 0.045 (s, 3H), 0.89 (s, 9H), 1.40 (s, 3H), 1.54 (s, 3H), 1.56 (m, 1H), 1.70 (dd, J = 23.8, 11.5 Hz, 1H), 1.80 (ddd, J = 12.9, 9.0, 4.6 Hz, 1H), 2.08 (d, J = 8.6 Hz, 1H), 3.56 (dd, J = 10.1, 6.6 Hz, 1H), 3.61 (dd, J = 9K6, 3.4 Hz, 1H), 3.68 (dd, J = 9.6, 5.0 Hz, 1H), 3.80 (s, 3H), 3.93 (m, 1H), 4.20 (dd, J = 6.0, 5.9 Hz, 1H), 4.35 (dd, J = 5.0, 5.0 Hz, 1H), 4.48 (d, J = 11.0 Hz, 1H), 4.79 (d, J = 11.0 Hz, 1H), 6.85 (m, 2H), 7.28 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) : 159.36, 131.26, 129.70, 109.57, 82.00, 78.53, 72.91, 68.41, 68.28, 63.63, 55.54, 40.20, 30.45, 28.07, 26.41, 26.19, 18.53, -5.11, -5.18.

(1R,2R,3S,4R,5S)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-β-D-mannopyranose penta-acetate) (60)
From **58** as described for **55** from **53**. mp 117-118°C; $[\alpha]_D$ = +2.9 (c 1.1, $CHCl_3$); ^1H NMR (500 MHz, C_6D_6) : 1.41 (m, 1H), 1.68-1.67 (m, 1H), 1.63 (s, 3H), 1.66 (s, 3H), 1.67 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 1.88 (m, 1H), 3.75 (dd, J = 11.4, 3.4 Hz, 1H), 4.08 (dd, J = 11.4, 5.2 Hz), 4.77 (ddd, J = 12.2, 4.8, 2.6 Hz, 1H), 5.05 (dd, J = 10.2, 2.8 Hz, 1H), 5.47 (dd, J = 10.7, 10.6 Hz, 1H), 5.88 (m, 1H); ^{13}C NMR (360 MHz, C_6D_6) : 169.89, 169.66, 169.61, 169.34, 169.06, 72.16, 70.22, 69.02, 68.95, 63.26, 36.94, 27.64, 20.29, 20.22, 20.19, 20.14.

(1R,2S,3R,4R)-4-Benzyloxy-1-hydroxy-2,3-isopropylidenedioxy-5-cyclohexene (61)
A mixture of **7b** (0.80 g, 2.61 mmol), Bu_4NI (100 mg, 0.27 mmol) and NaH (0.20 g) in THF (15 mL) was treated with benzyl bromide (0.67 g, 3.90 mmol). After 3 h, the mixture was poured into saturated NH_4Cl (50 mL) with Et_2O, dried, filtered, concentrated. Chromatography (EtOAc/hexane 2:8) afforded the benzyl ether (1.02 g, 98 %) as a colorless oil.
A solution of this ether (1.0 g, 2.52 mmol in CH_2Cl_2 (40 mL) and H_2O (2 mL) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzyoquinone (1.8 g, 7.93 mmol) at 0°C. After 4 h at r.t. the mixture was diluted with EtOAc and washed with 10 % Na_2SO_3 solution. $NaHCO_3$ solution and brine, dried, filtered and concentrated. Flash chromatography (EtOAc/hexane 35:65) afforded **61** (0.63 g, 91 %) as colorless oil. $[\alpha]_D$ = -75.7 (c 1.1, $CHCl_3$); IR (film) : 3443, 2915, 1451, 1254, 1092, 795 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) : 1.36 (s, 3H), 1.42 (s, 3H), 1.89 (d, J = 3.6 Hz, 1H), 4.30 (ddd, j = 4.2, 2.9, 1.6 Hz, 1H), 4.33 (ddd, J = 7.3, 2.9, 0.5 Hz, 1H), 4.36 ((m, 1H), 4.60 (ddd, J = 7.3, 4.0, 1.0 Hz, 1H), 4.69 (d, J = 12.8 Hz, 1H), 4.72 (d, J = 12.8 Hz, 1H), 6.02 (dddd, J = 9.9, 4.4, 1.4, 0.7 Hz, 1H), 6.08 (ddd, J = 9.9, 2.9, 1.0 Hz, 1H), 7.34 (m, 5H); ^{13}C NMR (200 MHz, $CDCl_3$) : 138.45, 132.95, 130.90, 128.64, 128.01, 127.92, 109.81, 79.14, 75.72, 71.93, 71.63, 67.67; 26.57, 24.99; MS : 261 (M^+ -CH_3), 188, 176, 109, 91.

(1R,2R,3R,4S,5R)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (5a-carba-β-D-allopyranose penta-acetate) (66)
From **61** as described for **55** from **7b**[10].

(1R,2R,3R,4S,5S)-2,3,4,5-Tetra-acetoxy-1-(acetoxymethyl)-cyclohexane (69) (5a-carba-α-D-allopyranose penta-acetate) (69)
From **63** as described for **60** from **56**[10].

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