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Stereoselective synthesis of deoxycarbaheptopyranose derivatives: 5a-carba-6-deoxy-α-DL-galacto-heptopyranose and 5a-carba-6-deoxy-α-DL-gulo-heptopyranose

Nurhan Horasan Kishali [a], Dilem Doğan [b], Ertan Şahin [a,†], Aslihan Gunel [c], Yunus Kara [a], Metin Balci [b,*]

[a] Department of Chemistry, Faculty of Sciences, Atatürk University, 25240 Erzurum, Turkey
[b] Department of Chemistry, Middle East Technical University,06531 Ankara, Turkey
[c] Department of Chemistry, Ahi Evran University, 40100 Kırşehir, Turkey

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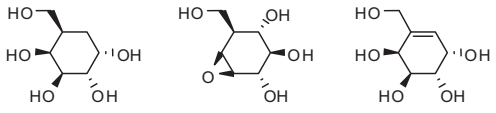
ABSTRACT

Two new deoxycarbaheptopyranoses, 5a-carba-6-deoxy-α-DL-galacto-heptopyranose and 5a-carba-6-deoxy-α-DL-gulo-heptopyranose were prepared starting from cyclohexa-1,4-diene. The addition of dichloroketene to cyclohexa-1,4-diene followed by the subsequent reductive elimination and Baeyer–Villiger oxidation in turn led to the formation of a bicyclic lactone. Reduction of the lactone moiety followed by acetylation gave a diacetate with *cis*-configuration. The introduction of additional acetate functionality into the molecule was achieved by singlet oxygen ene-reaction. The formed hydroperoxide was reduced and then acetylated. The triacetate was further functionalized either by direct *cis*-hydroxylation using OsO_4 or by epoxidation followed by a ring-opening reaction to give the title heptopyranose derivatives. One of the synthesized molecules, galacto-heptopyranose exhibited enzyme specific inhibition against α-glycosidase. On the other hand, they did not show any inhibition for α-amylase. However, both compounds, gulo-heptopyranose and galacto-heptopyranose increased the activity of α-amylase.

1. Introduction

Highly oxygenated cyclohexanes are often referred to as pseudosugars[1] or as carbasugars due to their resemblance of their structure to true sugars. In carbasugars the endocyclic oxygen atom is replaced by a methylene group.[2]



Carbapyranoses are rarely found in nature; however, as a substructure of other natural products they are widely distributed. Carba-α-D-galactopyranose **1**,[3] cyclophellitol,[2,4] and a conduritol derivative **3** (MK7607)[5] were isolated directly from natural sources. This type of compound is currently attracting interest among chemists as well as biochemists due to the interesting biological activities that they exhibit. As carbasugars are hydrolytically stable towards acid as well as enzymatic hydrolysis, several carbasugars have found application in the field of glycosidase inhibition.[6,7] Furthermore, it has been found that some carbasugars are nearly as sweet as D-fructose.[8,9] Consequently, the synthesis of carbasugars is of interest. McCasland et al. synthesized a series of carbasugars starting from 7-oxa-norbornene derivatives in 1966.[1,10] Since then, a number of methods have been developed for the preparation of carbapyranoses. After the pioneering work carried out by McCasland, oxa-norbornene derivatives were extensively used for the synthesis of carbasugars by Suami,[2] Ogawa,[11] Mehta,[12] and Hudlicky et al.[13]

The microbial oxidation of benzene derivatives to cyclohexadiene diols has also been prevalent in carbasugar synthesis.[14] Additional synthetic methods have been developed by other groups.[15–19] Recently, we described the synthesis of some carbasugars having two hydroxymethylene groups and showed that they act as glycosidase inhibitors.[20]

Wagner and Lundt[21] synthesized the first deoxycarbaheptopyranose **6** in several steps starting from tartaric acid **4**, which was

* Corresponding author. Tel.: +90 312 210 5140; fax: +90 312 210 3200; e-mail addresses: ertan@atauni.edu.tr (E. Şahin), mbalci@metu.edu.tr (M. Balci).
† Author to whom inquires concerning the X-ray structure should be directed. Tel.: +90 442 231 4380; fax: +90 442 236 0948.

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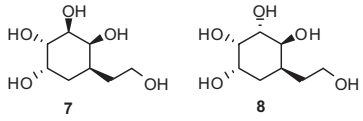
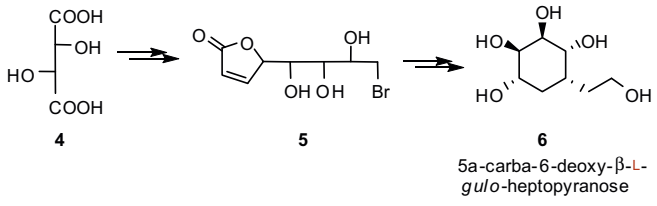
converted into the lactone **5** (Scheme 1). The key step was radical-induced carbocyclization of lactone derivative **5**, followed by reduction of the lactone moiety.



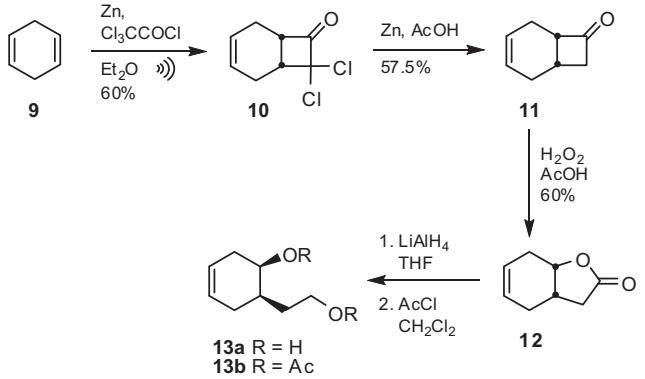
In the present paper, we describe the regio- and stereospecific synthesis of carbasugars **7** and **8** starting from the inexpensive, commercially available starting material cyclohexa-1,4-diene.



Scheme 1.

2. Results and discussion

The starting material, 8,8-dichlorobicyclo[4.2.0]oct-3-en-7-one (**10**)[22] was prepared by the addition of dichloroketene to cylohexa-1,4-diene in a yield of 60% (Scheme 2). The subsequent reductive elimination of the chlorine in **10** was accomplished without any complications by using zinc in refluxed acetic acid to yield **11** in 57.5% yield. The oxidation of the bicyclic ketone **11** of known stereochemistry with H_2O_2 acetic acid produced the lactone **12**.[23] To prevent the epoxidation of the double bond in **11**, the Baeyer–Villiger oxidation with H_2O_2 was used instead of *m*-chloroperbenzoic acid.

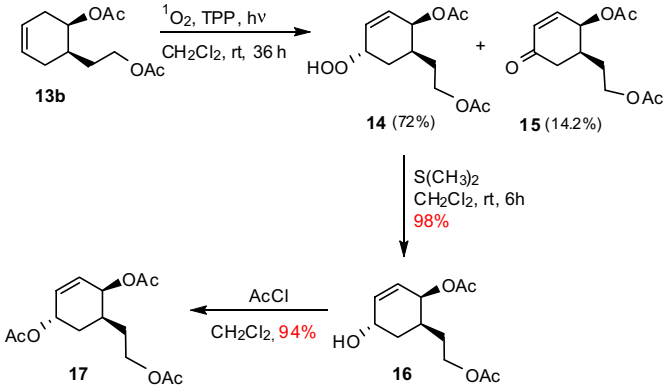


Scheme 2.

After the successful synthesis of lactone **12**, the next step was the reduction of the lactone to the corresponding diol by using the strong reducing agent, lithium aluminum hydride. The reduction was carried out in diethyl ether at 0 °C to give the diol **13a** in 90% yield, which was converted to diacetate **13b** with acetyl chloride in a nearly quantitative yield (Scheme 2).

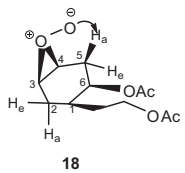
Since the reduction reaction took place at the carbonyl group, the configuration of the substituents, which were attached to the cyclohexene ring was retained.

For the introduction of an additional hydroxyl group into the molecule, cyclohexene derivative **13b** was submitted to a singlet oxygen ene-reaction. Tetraphenylporphyrin sensitized photo-oxygenation of **13b** in methylene chloride at room temperature produced two compounds **14** and **15**, in a ratio of 5.1:1 (Scheme 3). The structures of **14** and **15** were assigned based on ^1H and ^{13}C NMR spectra. Compound **14** showed the presence of a hydroperoxide group, whereas the other compound, **15**, did not. The hydroperoxide proton (−OO**H**) resonates as a broad singlet at 8.89 ppm. The most conspicuous features in the ^1H NMR spectrum of the hydroperoxide **14** were the presence of two double bond protons and the incorporation of hydroperoxide functionality in the molecule. Double resonance experiments clearly indicated that the HC=CH double bond was located between the carbon atoms bearing acetoxyl and hydroperoxide groups.

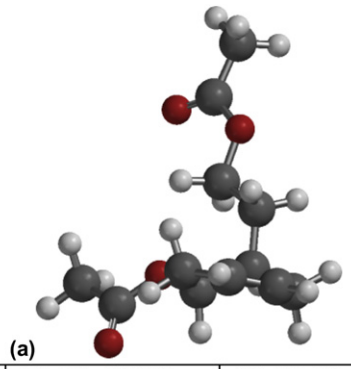


Scheme 3.

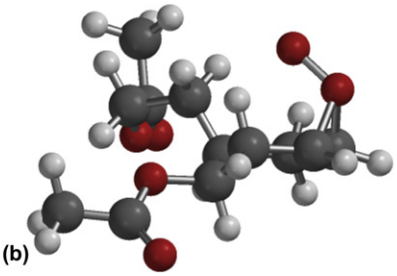
Furthermore, ^1H NMR analysis of the crude product suggested that the hydroperoxide was a single stereoisomer, although two stereoisomers could potentially be formed. The exact stereochemistry of the hydroperoxide functionality in **14** was later confirmed by single crystal X-ray analysis of the pentaacetate **21**. The regio- and stereoselective formation of the product **14** is remarkable. It is well established that singlet oxygen attacks the C=C double bond first in order to form perepoxide, which then rearranges to hydroperoxide.[24] The two faces of the double bond in **13b** are not symmetric; therefore, the double bond can be attacked from both sides. The configuration of the hydroperoxide in **14** shows an exclusively anti-attack. We assume that the repulsive interaction between the non-bonded electron pairs on the acetyl oxygen and singlet oxygen is responsible for the exclusively anti-attack.[25] In order to understand the regioselective formation of **14** we performed a restricted hybrid HF-DFT SCF calculation using the basis set 6-31G(d) as implemented in the Spartan08V111 package program. First we determined the most stable conformation of **14** as shown in Fig. 1.



The initially formed perepoxide **18** can abstract two different hydrogen atoms. The product **14** shows that the pendant oxygen exclusively abstracts the hydrogen atom connected to the C-5 carbon atom. For a cycloalkene[26] it was proposed that there is a correlation between the orientation of the allylic hydrogen in the ground state and its reactivity. The allylic hydrogens at the axial position are more reactive, because the orbital overlap between



	C2-C3-C4-H5a	C5-C4-C3-H2e
Dihedral angle	58°	34°



	C2-C3-C4-H5a	C5-C4-C3-H2e
Dihedral angle	72.1°	42.3°

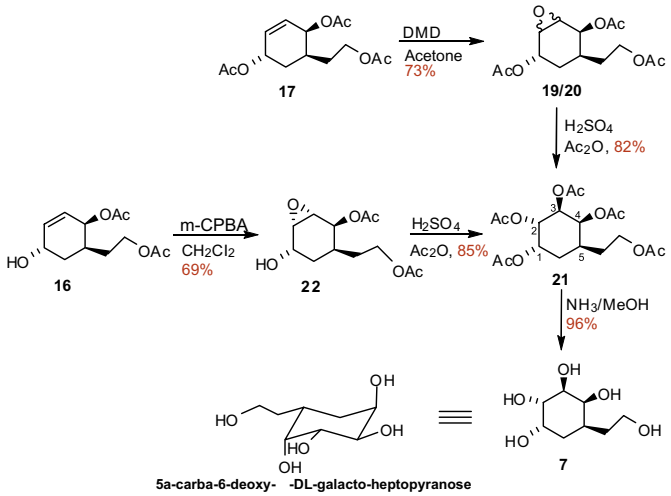
Fig. 1. a) Optimized geometry of the most stable conformation of **13b** (b) the formed perepoxide **18**.

oxygen and allylic hydrogens is optimum in such a conformation. Calculations clearly show that the H-5a has an axial orientation (Dihedral angle C2–C3–C4–H5a=72.1°), whereas the other allylic proton H-2e has an equatorial orientation (Fig. 1). Therefore, the findings support the regio- and stereoselectivity of this ene-reaction.

The exact position of the double bond in **15** was easily determined by double resonance experiments. This compound is a secondary product, that is, formed by the decomposition of **14**. It is well known that the hydroperoxides can undergo decomposition in the presence of bases and acids to give hydroxy ketones.[27]

The selective reduction of the peroxide functionality in **14** was achieved by using dimethyl sulfide[28] as a reductant to give the desired hydroxy diacetate **16**, which was converted to the triacetate **17** using acetyl chloride (Scheme 3).

For further functionalization of the double bond, triacetate **17** was reacted with dimethyldioxirane[29] to give an isomeric mixture of epoxides **19**/**20** in a ratio of 2:1 (Scheme 4). The attempted separation of these isomers failed, therefore, the isomeric epoxide mixture **19**/**20** was submitted to a ring-opening reaction with sulfuric acid in acetic anhydride. Analysis of the reaction mixture indicated that only a single isomer, the pentatacetate **21**, was formed in 82% yield. In another experiment, the allylic alcohol **16** was reacted with *m*-chloroperbenzoic acid. Only a single epoxide isomer, **22**, was obtained according to the ^{1}H NMR spectrum of the crude product. It is well established that upon the treatment of cyclic allylic alcohols with *m*-CPBA the formation of epoxides occurs on the same side as the hydroxyl group.[30] The fact that a single isomer is formed during the epoxidation reaction strongly supports the participation of the hydroxyl group. Again, the attempted purification of the crude product failed due to the partial epoxide-ring opening during column chromatography. Therefore, the crude product **22** was submitted to acid-catalyzed ring-opening followed by acetylation to give **21** in 70% yield. The structure of **21** was found to be 5a-carba-6-deoxy-α-DL-galacto-heptopyranose based on the analysis of NMR spectroscopic data (COSY, HSQC, HMBC). The large coupling constant, J=11 Hz, between the axial protons H_2 and H_3 confirmed the trans-configuration at the new stereogenic centers. Finally, the structure **21** was further confirmed by single crystal analysis.



Scheme 4.

The results of this study confirmed unambiguously the proposed structure (Fig. 2a). The compound crystallizes in the monoclinic space group P21/c, with four molecules in the unit cell (Fig. 2b). Single crystal analysis, furthermore supported the trans-ring opening reaction as well as the stereochemistry of the singlet oxygen ene-reaction.

Deacetylation of pentaacetate **21** with ammonia in methanol afforded 5a-carba-6-deoxy-α-DL-galacto-heptopyranose **7** in high yield.

The triacetate **17** is an ideal compound for the synthesis of further heptopyranose derivatives. For that reason the double bond in **17** was *cis*-hydroxylated with OsO_4–NMO to give **23** (Scheme 5). After the acetylation of the reaction mixture, only a single isomer, **24**, was isolated in 67% yield. The two faces of the double bond in **17** are not symmetric and so the double bond can be attacked from both sides. We assume that OsO_4 approaches the double bond from the less congested side to form the diol **23**. It is likely that the non-bonded interactions between the substituents and OsO_4 are responsible for the exclusively anti-addition. The configuration of the pentaacetate **24** was confirmed by ^{1}H NMR spectroscopy. The most conspicuous feature in the ^{1}H NMR spectrum is the doublet of triplets arising from the alkoxy proton H-1 resonance at 5.24 ppm. The measured coupling constants J=4.5 and 3.7 Hz clearly indicated that the H-1 proton has an equatorial conformation and the acetate group attached to the carbon atom C-1 has an axial conformation. Otherwise, an axial proton attached to C1 would give a large coupling with the axial proton attached to the carbon atom C-6. Furthermore, the adjacent proton H-2 resonates as a broad triplet with a coupling constant of $J_{1,2}$=$J_{2,3}$=3.7 Hz. This small coupling indicates that the acetoxyl group attached to the C-2 carbon atom has an equatorial conformation. The fact that the acetate groups attached to the C-1 and C-2 carbon atoms has a *cis*-configuration strongly indicates that the OsO_4 approaches the molecule **17** from the anti-side of the double bond. The deacetylation of **24** with ammonia was carried out in methanol to give the free hexol **8** in a nearly quantitative yield.

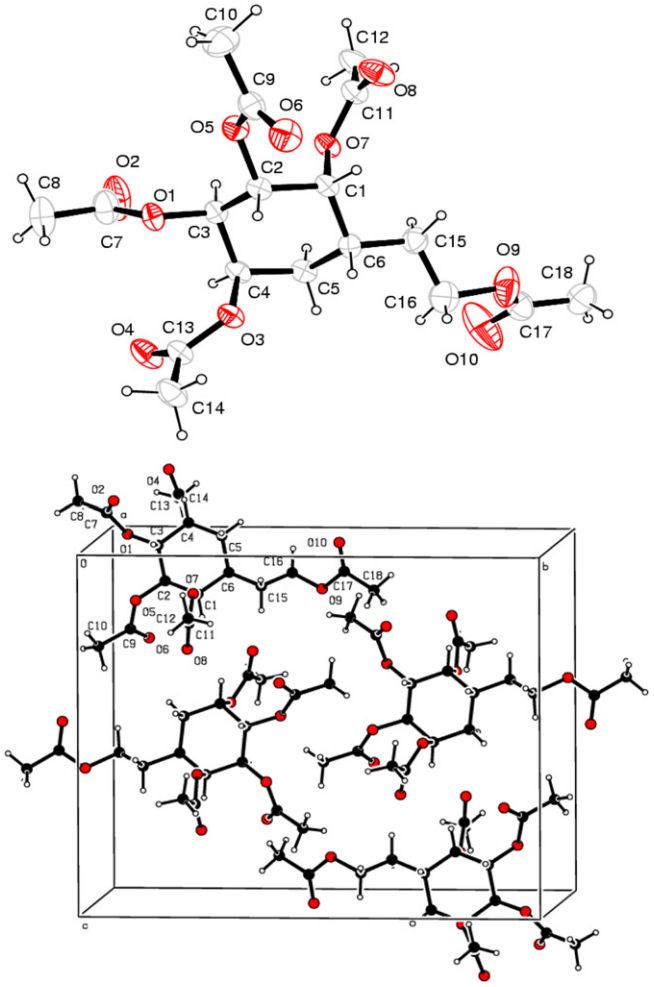


Fig. 2. a) The molecular structure of compound **21** showing the atom numbering scheme, thermal ellipsoids are drawn at the 40% probability level. (b) A packing diagram for **21**, viewed down the *c*-axis.

glucopyranoside was added to mixture and incubated at 25 °C for 5 min. Absorbance of the liberated *p*-nitrophenol was measured at 405 nm. For the control experiments, 50 μL phosphate buffer was used instead of a compound solution.

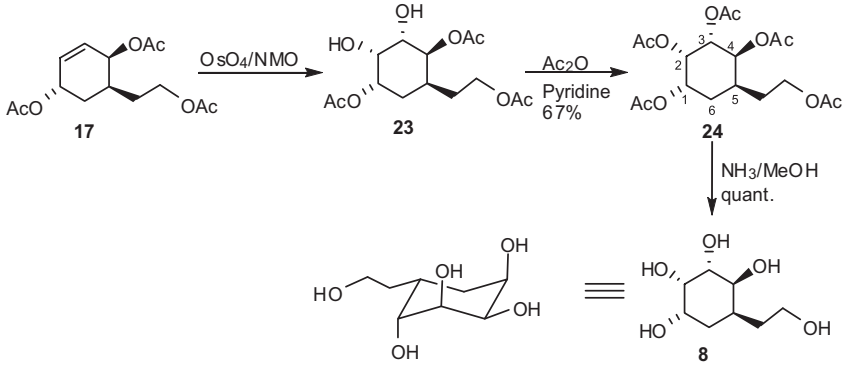
The pentol **8** did not show any inhibition for α-glucosidase. However, the inhibition rate was measured as 43.64% for pentol **7** in a 150 μM concentration (Table 1).

Table 1
Results of α-glucosidase inhibition assay

Compound	Inhibition[a] (%)	IC_{50} (μM)[d]
7	43.64±0.88[a,c,e]	200
8	NI[b]	—

[a] Four experiments are performed for all compound and triplicate in each experiment.
[b] NI: No Inhibition (The compound is added in 10–1000 μM range and did not observed inhibition).
[c] Inhibition by 150 μM compound.
[d] Concentration required for 50% inhibition of the enzyme activity under the assay conditions.
[e] $p<0.05$.

α-Amylase inhibition assay was performed according to Kim et al.[32] with slight modifications: 500 μL of α-amylase solution (obtained by dissolving α-amylase (0.5 mg/mL) in 20 mM phosphate buffer (pH 6.9) containing 6.7 mM sodium chloride) was mixed with a solution of **7** or **8**. The resulting mixture was incubated at 25 °C for 10 min. After preincubation, 500 μL of 1% starch solution in 20 mM phosphate buffer (pH 6.9) containing 6.7 mM sodium chloride was added to each tube. The reaction mixtures were then incubated at 25 °C for 10 min. The reaction was stopped by the addition of 1.0 mL of dinitrosalicylic acid reagent (1% 3,5-dinitrosalysilic acid in 0.5 M sodium hydroxide/2 M potassium hydroxide, 30% $NaKC_4H_4O_6$). The test tubes were then incubated at 85 °C (water bath) for 5 min, and then cooled to room temperature. Then 10 mL of distilled water was added to the reaction mixture; the absorbance was measured at 540 nm. For the control experiments, 500 μL phosphate buffer was used instead of the solution



5a-carba-6-deoxy-α-DL-gulo-heptopyranose

Scheme 5.

2.1. α-Glucosidase and α-amylase inhibition assay

α-Glucosidase inhibition assay was performed for compounds **7** and **8**. The test was carried out according to Kwon et al.[31]: 50 μL of sample solution (10–1000 μM) and 100 μL of 100 mM phosphate buffer (pH 6.9) containing an α-glucosidase solution (1.0 U/mL) were incubated at 25 °C for 10 min. After the incubation of enzyme and the test compounds, 50 μL 5-mM *p*-nitrophenyl-α-D-

containing the corresponding compounds. As a result of these experiments we noticed that compounds **7** and **8** did not show any inhibition for α-amylase. However, compounds **7** and **8** did increase the activity of α-amylase. α-Amylase inhibition activity was carried out in a range of 10–1000 μM (Table 2).

The compounds **7** and **8** increased the activity of α-amylase as well as the activity of α-glucosidase, which catalyzes the hydrolysis of the α-bond of large polysaccharides and glycogen.[33] Some vital

Table 2
Results of α-amylase inhibition assay

Concentration →	100 μM	200 μM	500 μM	1000 μM
Compounds*				
7	121.53±11.22[a]	140.75±1.54[a]	149.86±9.37[a]	182.37±14.64[a]
8	117.06±15.79[a]	116.96±3.30[a]	122.27±1.87[a]	152.89±38.38[a]

* Compounds did not show inhibition for α-amylase whereas these compounds were increased activity of α-amylase.
[a] $p<0.05$.

and genetic diseases are formed because of deficiency of alpha amylase and alpha glucosidase. These diseases are glycogen storage disease (Pompe's disease)[34] and Lafora's disease.[35] Also, deficiency of alpha amylase causes fatigue, sprue, hyoglycemia, depression, allergies, inflammation, cold hands and feet, and neck and shoulder aches. In light of these, amylase activators may use for treatment of these disease or disorders.

3. Conclusion

In summary, we developed a route for the synthesis of two different carboheptapyranoses **7** and **8** starting from readily available cyclohexa-1,4-diene. With the addition of dichloroketene to one of the double bonds in cyclohexa-1,4-diene, the stereochemistry at the carbon atoms C-4 and C-5 was controlled. The application of a singlet oxygen ene-reaction in turn defined the stereochemistry at the carbon atom C-1. The configuration of the other carbon atoms C-2 and C-3 were controlled by the epoxidation and *cis*-hydroxylation reactions. The variation of these methodologies may enable the possibility of the synthesis of other isomeric carboheptapyranoses.

4. Experimental section

4.1. General

Melting points are uncorrected. Infrared spectra were obtained from a solution ($CHCl_3$) in 0.1 mm cells or KBr pellets on an FT-IR Bruker Vertex 70 instrument. The ^1H and ^{13}C NMR spectra were recorded on a Bruker-Biospin (DPX-400) instrument. Apparent splitting is given in all cases. Column chromatography was performed on silica gel (60-mesh, Merck), TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates. Elemental analyses were carried out on a Leco-932 model CHNS analyzer. Baker's yeast α-glucosidase, *p*-nitrophenyl-α-D-glucopyranoside, K_2HPO_4, porcine pancreatic α-amylase were purchased from Sigma Chemical Co., soluble starch, 3,5-dinitro- salysilic acid, $NaKC_4H_4O_6\cdot 4H_2O$, sodium hydroxide, potasium hydroxide were purchased from Merck Co. inc.

4.2. 8,8-Dichlorobicyclo[4.2.0]oct-3-en-7-one (10)

A 500 mL two-neck round bottom flask was equipped with a nitrogen inlet and pressure-regulated dropping funnel. A solution of 1,4-cylohexadiene (5.0 g, 62.5 mmol) and Zn powder (8.15 g, 125 mmol) in dry ether (100 mL) of was immersed in an ultrasound bath where sonication was greatest to acquire maximum agitation. The water bath was cooled to 15 °C by adding pieces of ice periodically. A solution of trichloroacetyl chloride (22.7 g, 125 mmol) in dry ether (100 mL) was added dropwise within 2 h under sonication. Stirring of the reaction continued for an additional hour while the water bath temperature was maintained at 15 °C. When the reaction was complete, the solids were removed by simple filtration. The filtrate was extracted first with H_2O (2×100 mL) and then with saturated $NaHCO_3$ (2×100 mL). The organic solution was dried over Na_2SO_4 and the solvent was evaporated. The resulting mixture was purified by vacuum distillation at reduced pressure (7 mmHg). The first fraction (collected at 76 °C) was identified as the desired addition product **11**. Yellow liquid (7.164 g, 60%).[22] ^1H NMR (400 MHz, $CDCl_3$, ppm) δ 5.88–5.81 (2H, m, C*H*=C*H*), 4.03 (1H, ddd, *J* 10.6, 7.6, 2.4 Hz, O=CC*H*), 3.32 (1H, dt, *J* 7.6, 1.8 Hz, Cl_2CCH), 2.64–2.08 (4H, m, CH_2CH=CHCH_2).

4.3. Bicyclo[4.2.0]oct-3-en-7-one (11)

A solution of dichloroketone **10** (7.5 g, 39.3 mmol) in acetic acid (25 mL) was added dropwise to a suspension of Zn vigorously stirred (5.0 g, 76.9 mmol) in glacial acetic (50 mL) acid at room temperature. After the addition was complete, the temperature was raised to 70 °C and maintained at for 20 h. The reaction mixture was cooled to room temperature and stirred for an additional 8 h. To dissolve the formed Zn salts water was added. The resulting mixture was treated with diethyl ether, and the zinc residue was filtered. The ethereal layer was washed three times with water and a saturated solution of sodium carbonate to remove acetic acid, and dried over $MgSO_4$. The solvent was removed under vacuum. Chromatography of the residue on 30 g of silica gel eluting with ethyl acetate/hexane (1:9) afforded ketone **11** (2.75 g, 0.07 mol, 57.5%) as a colorless liquid.[22] ^1H NMR (400 MHz, $CDCl_3$) δ 5.90–5.81 (2H, m, C*H*=C*H*), 3.48–3.41 (1H, m, O=CC*H*), 3.22 (1H, ddd, *J* 17.8, 9.2, 3.8 Hz, O=CC*H*H), 2.83–2.77 (1H, m, CH_2CH), 2.55 (1H, ddd, *J*=17.8, 5.1, 3.1 Hz, O=CC*H*H), 2.42–2.01 (4H, m, CH_2CH=CHCH_2).

4.4. 3a,4,7,7a-Tetrahydro-1-benzofuran-2(3*H*)-one (12)

A solution of H_2O_2 (4.65 g, 30%) in acetic (2 mL) acid was added to a solution of bicyclo[4.2.0]oct-3-en-7-one (**11**) (5.0 g, 40.98 mmol) in CH_2Cl_2 (25 mL) and the resulting mixture was stirred for 6 h at room temperature. After completion of the reaction, the mixture was washed with water, saturated $NaHCO_3$, and then with brine. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure to give the known lactone **12**[23] as a colorless liquid (3.4 g, 60%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.88–5.81 (2H, m, C*H*=C*H*), 4.74 (1H, ddd, *J*=11.7, 6.0, 3.9 Hz, OC*H*) 2.74–1.91 (7H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 125.8, 124.0, 77.7, 36.8, 32.1, 27.4, 26.2. IR ($CHCl_3$, cm^{-1}): 3034, 2917, 2838, 1772, 1236, 1016.

4.5. 2-[*rel*-(1*S*,6*R*)-6-(Acetyloxy)cyclohex-3-en-1-yl]ethyl acetate (13b)

To a magnetically stirred slurry of $LiAlH_4$ (1.0 g, 26.3 mmol) in ether (180 mL) was added a solution of lactone **12** (3.0 g, 22 mmol) in ether (90 mL) dropwise at 0 °C over 3 h. The resulting mixture was then stirred at room temperature for an additional 3 h. The reaction mixture was cooled to 0 °C and cold water was added to destroy the unreacted $LiAlH_4$. The formed aluminum salt was filtered through silica gel (5 g). The organic layer was dried ($MgSO_4$). Removal of the solvent gave the diol **13a** (2.8 g, 89.7%). ^1H NMR (400 MHz, $CDCl_3$) δ 5.68–5.55 (m, 2H), 4.02–3.98 (m, 1H), 3.78–3.61 (m, 2H), 3.34–3.2 (br s, 2OH), 2.33–1.46 (m, 7H).

The above formed crude product **13a** was submitted without further purification to acetylation: a magnetically stirred solution of diol **13a** (2.8 g, 19.7 mmol) in CH_2Cl_2 (100 mL) was added acetyl chloride (8.25 g, 105 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 °C and then water (100 mL) was added. The organic phase was separated, washed with water and saturated $NaHCO_3$, and then dried (Na_2SO_4). Removal of the solvent under reduced pressure gave diacetate **13b** (4.28, 96%) as colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, br d, A-part of AB-system, *J*=9.9 Hz,=C*H*), 5.56

(1H, dm, *B*-part of AB-system, *J*=9.9 Hz,=C*H*), 5.10–5.14 (1H, m, AcOC*H*), 4.15 (1H, dt, A-part of AB-system, *J*=11.1, 6.5 Hz, AcOCH*H*),4.12 (1H, dt, *B*-part of AB-system, *J*=11.1, 6.6 Hz, AcOC*H*H), 2.39–2.10 (3H, m, C*HCH*$_2$CH$_2$), 2.05 (3H, s, Me), 2.03 (3H, s, Me), 2.05–1.51 (4H, m, CH_2CH=CHCH_2). ^{13}C NMR(100 MHz, $CDCl_3$, ppm) δ 170.5, 170.3, 125.3, 122.7, 69.9, 61.9, 32.6, 29.6, 29.5, 27.1, 20.7, 20.4. IR (KBr, cm^{-1}) 3029, 2933, 2856, 1739, 1443, 1374, 1247, 1042, 992, 846, 674, 673. Anal. Calcd for. $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.70; H, 8.24.

4.6. Photo-oxygenation of diacetate 13b

A stirred solution of diacetate **13b** (1.0 g, 4.4 mmol) in CH_2Cl_2 (150 mL) was added tetraphenylporphyrin (TPP, 50 mg). The resulting mixture was irradiated with a projection lamp (500 W) for 36 h at room temperature while oxygen was passed through the solution. Removal of the solvent (30 °C, 20 mmHg) and ^{1}H NMR spectroscopic analysis of the oily residue revealed that the conversion was approximately 95% and two products **14** and **15** were formed in a ratio of 5.1:1. Chromatography of the residue on silica gel (100 g) eluting with hexane/ethylacetate (70:30) gave as the first fraction *rel*-(1*S*,6*R*)-6-[2-(*acetyloxy*)*ethyl*]-4-*oxocyclohex*-2-*en*-1-*yl acetate* (15): pale yellow liquid, (142 mg, 14.2%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.91 (1H, dd, A-part of AB-system, *J*=10.0 Hz, 4.7 Hz, CH=C*H*CH), 6.02 (1H, d, *B*-part of AB-system, *J*=10.0 Hz, C*H*=CHCH), 5.42 (1H, t, *J*=3.9 Hz, C*H*OAc), 4.13–4.03 (2H, m, CH_2OAc), 2.57 (1H, dd, A-part of AB-system, *J*=16.8, 10.9 Hz, O=CCH_aH$_b$), 2.53–2.35 (3H, m, O=CCH$_a$$H_b$ and C*H*) 2.12 (3H, s, Me), 2.04 (3H, s, Me), 1.96 (1H, dq, *J*=14.4, 6.6 Hz, OCH$_2$CH_aH$_b$), 1.48 (1H, dq, *J*=14.4 and 6.4 Hz, OCH$_2$CH$_a$$H_b$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6 (C=O), 170.7 (OCO), 170.1 (OC=O), 144.1 (CH=CHCH), 131.6 (*C*H=CHCH), 67.4 (O*C*H), 61.6 (O*C*H$_2$), 39.4 (*C*H$_2$), 35.1 (*C*H$_2$), 29.1 (*C*H$_2$), 20.7 (*C*H$_3$), 20.6 (*C*H$_3$). ATR (cm^{-1}) 2958, 1733, 1684, 1369, 1213, 1023, 963, 892. Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.73; H, 6.95.

As the second fraction, the major product *rel*-(1*S*,6*S*)-6-[2-(*acetyloxy*)*ethyl*]-4-*hydroperoxycyclohex*-2-*en*-1-*yl acetate* (14) was isolated as viscous liquid (776 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (1H, br s, −OO*H*), 6.13 (1H, dd, A-part of AB-system, *J*=9.9, 5.2 Hz, CH=C*H*), 5.99 (1H, dd, *B*-part of AB-system, *J*=9.9, 4.7 Hz, C*H*=CH), 5.15 (1H, t, *J*=4.3 Hz, AcOC*H*), 4.55–4.51 (2H, m, −CH_2OAc), 4.0 (1H, dt, *J*=11.3, 5.2 Hz, HOOC*H*), 2.27 (1H, bd, *J*=14.3 Hz, C*H*), 2.08 (3H, s, C*H*$_3$), 2.05 (3H, s, C*H*$_3$), 2.0–2.08 (1H, CH_aH$_b$), 1.79 (1H, ddt, A-part of AB-system, *J*=14.5, 9.2 and 4.5 Hz, CH$_a$$H_b$), 1.66 (1H, ddd, *J*=14.4, 12.8 and 3.9 Hz, CHCH_aH$_b$), 1.57 (1H, ddt, *J*=14.4, 9.4, and 4.8 Hz, CHCH$_a$$H_b$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (O*C*=O), 170.6 (O*C*=O), 131.6 (*C*H=CH), 127.9 (CH=*C*H), 77.0 (HOO*C*H), 68.1 (O*C*H), 61.6 (O*C*H$_2$), 30.4 (*C*H$_2$) 29.2 (*C*H$_2$), 26.0 (*C*H$_2$), 21.0 (*C*H$_3$), 20.09 (*C*H$_3$). IR (KBr, cm^{-1}) 3403, 3029, 2960, 2933, 1736, 1439, 1381, 1254, 1035, 985, 765. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.71; H, 7.08.

4.7. *rel*-(1*S*,4*S*,6*S*)-6-[2-(Acetyloxy)ethyl]-4-hydroxycyclohex-2-en-1-yl acetate (16)

A solution of hydroperoxide **14** (500 mg, 1.94 mmol) in CH_2Cl_2 (25 mL) was added to magnetically stirred solution of Me_2S (309 mg, 5 mmol) in CH_2Cl_2 (25 mL) at room temperature. After the addition was complete (ca. 10 min), the mixture was stirred for 6 h and water (25 mL) was added. The organic phase was separated and dried over Na_2SO_4. Evaporation of solvent in vacuo and gave pure **16** (460 mg, 98%) as pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (1H, dd, A-part of AB-system, *J*=9.9, 4.2 Hz, C*H*=CH), 5.96 (1H, dd, *B*-part of AB-system, *J*=9.9, 4.6 Hz, CH=C*H*), 5.18 (1H, t, *J*=4.2 Hz, AcOC*H*), 4.25 (1H, q, *J*=3.9 Hz, OC*H*), 4.17–4.11 (2H, m, OCH_2), 2.58 (1H, br s, −O*H*), 2.25–2.17 (1H, m, CH$_2$C*H*CH$_2$), 2.05 (3H, s, C*H*$_3$), 2.04 (3H, s, C*H*$_3$), 1.88 (1H, dt, *J*=13.9 and 6.5 Hz, CHCH_aH$_b$CH), 1.82–1.71 (2H, m, C*H*$_2$), 1.59 (1H, ddt, *J*=13.9, 7.1, and 6.5 Hz, CHCH$_a$$H_b$CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (O*C*=O), 170.7 (O*C*=O), 133.1 (*C*H=CH), 127.5 (CH=*C*H), 67.9 (AcO*C*H), 63.3 (AcO*C*H$_2$), 62.4 (HO*C*H), 32.6 (*C*H$_2$), 29.8 (*C*H$_2$), 29.5 (*C*H$_2$), 20.9 (2C, *C*H$_3$). IR (KBr, cm^{-1}) 3391, 3037, 29.41, 2255, 1736, 1439, 1374, 1247, 1027, 977. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.23; H, 7.39.

4.8. *rel*-(1*S*,4*S*,5*S*)-4-(Acetyloxy)-5-[2-(acetyloxy)ethyl]cyclohex-2-en-1-yl acetate (17)

To a magnetically stirred solution of alcohol **16** (500 mg, 2.06 mmol) in CH_2Cl_2 (25 mL) was added acetyl chloride (400 mg, 5.1 mmol). The reaction mixture was stirred at room temperature for 6 h and then cooled to 0 °C. After addition of water (100 mL), the water phase was extracted with ether (3×30 mL). The combined organic extracts was washed with $NaHCO_3$ solution (2×10 mL) and water (2×5 mL), and then dried over Na_2SO_4. Removal of the solvent under reduced pressure gave triacetate **17** (550 mg, 94%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.10 (1H, dd, A-part of AB-system, *J*=9.9, 4.9 Hz, *H*C=CH), 6.00 (1H, dd, *B*-part of AB-system, *J*=9.9, 4.6 Hz, HC=C*H*), 5.30–5.27 (1H, m, O*CH*), 5.22 (1H, t, *J*=4.3 Hz, O*CH*), 4.16 (1H, dt, A-part of AB-system, *J*=11.1 and 6.8 Hz, OCH_aH$_b$), 4.13 (1H, dt, *B*-part of AB-system, *J*=11.1 and 6.5 Hz, OCH$_a$$H_b$), 2.19–2.13 (1H, m, CH$_2$C*H*CH$_2$), 2.06 (3H, s, C*H*$_3$), 2.05 (3H, s, C*H*$_3$), 2.04 (3H, s, C*H*$_3$), 1.95–1.88 (1H, m, C$H_aH_b$), 1.84–1.75 (2H, m, C$H_aH_b$ and CH$_a$$H_b$), 1.62 (1H, dq *J*=11.9 and 5.2 Hz, CH$_a$$H_b$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (OC=O), 170.5 (OC=O), 170.5 (OC=O), 129.8 (*C*H=CH), 129.2 (CH=*C*H), 67.3 (O*C*H), 66.1 (O*C*H), 62.3 (O*C*H$_2$), 30.5, 29.5, 29.4, 21.1 (*C*H$_3$), 20.9 (*C*H$_3$), 20.9 (*C*H$_3$). IR (KBr, cm^{-1}): 3029, 2952, 1739, 1447, 1374, 1247, 1027, 985, 919. Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.19; H, 7.34.

4.9. Epoxidation of 16 with *m*-CPBA

To a stirred solution of **16** (200 mg, 0.83 mmol) in CH_2Cl_2 (8 mL) was added *m*-CPBA 60% (310 mg, 1.66 mmol). The reaction mixture was stirred overnight, the solid matter was removed by filtration, and the filtrate was washed with saturated $NaHCO_3$ (2×50 mL), and water (50 mL), and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave epoxide **22** (148 mg, 69%, yellow liquid). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (1H, br s, AcOC*H*), 4.2 (br s, 1H), 4.16–4.05 (4H, m, O*H*, HOC*H*, and OCH_2), 3.45–3.38 (2H, m, epoxide), 2.17 (3H, s, C*H*$_3$), 2.04 (3H, s, C*H*$_3$), 2.08–2.02 (5H, m, C*H*, and 2CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) 171.0 (O*C*=O), 170.3 (O*C*=O), 68.9 (AcO*C*H), 63.1 (O*C*H$_2$), 62.0 (HO*C*H), 54.7 (epoxide), 54.2 (O*C*H), 31.5, 30.9, 26.6, 20.9 (*C*H$_3$), 20.8 (*C*H$_3$). IR (KBr, cm^{-1}) 3469, 2938, 1734, 1438, 1359, 1250, 1047; HRMS (CI, Na): MNa$^+$, found 265.1059. $C_{12}H_{18}NaO_5$ requires 265.1052.

4.10. Epoxidation of 17 with dimethyldioxirane (DMD)

Dimethyldioxirane was prepared from acetone using potassium monoperoxysulfate as described by Adam et al.[29] To a magnetically stirred solution of DMD (1.05 mmol, 0.07 M) in acetone (100 mL) was added triacetate **17** (300 mg, 1.06 mmol) and stirred for 2 h at −5 °C then for 2 h at room temperature. Evaporation of the solvent afforded a mixture of epoxides **19** and **20** in a ratio of 3:2. Purification of the residue on neutral Al_2O_3 (50 g) eluting with ethyl acetate/*n*-hexane (1:9) gave an epoxide mixture (231 mg, 73%) in a ratio of 2:1. 5-(*Acetyloxy*)-3-[2-(*acetyloxy*)*ethyl*]-7-*oxabicyclo*[4.1.0]*hept*-2-*yl acetate* (19/20).^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (2H, br t, *J*=3.2 Hz, AcOC*H*), 5.23–5.12 (1H, m, AcOC*H*), 5.10–5.05 (1H, m, AcOC*H*), 4.18–4.00 (2H, t, OCH_2), 3.54 (1H, dd, *J*=3.9 and 3.5 Hz, epoxide), 3.47 (1H, t, *J*=3.8 Hz, epoxide), 3.3 (1H, dd, *J*=3.5

and 2.4 Hz, epoxide), 3.22–3.19 (1H, m, epoxide), 2.14 (3H, s, CH_3), 2.13 (3H, s, CH_3), 2.12 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.04 (3H, s, CH_3), 1.85–1.4 (5H, m, CH and CH_2). IR (KBr, cm^{-1}) 3064, 2960, 2856, 1739, 1439, 1374, 1247, 1046, 1035, 908, 738. Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 56.18; H, 6.68.

4.11. 1,2,3,4,7-Penta-*O*-acetyl-6-deoxy-5a-carba-α-DL-galacto-heptopyranose (21)

To a stirred solution of **19**/**20** (200 mg, 0.77 mmol) in Ac_2O (2 mL) was added a catalytic amount of concentrated H_2SO_4 (20 mg). The reaction mixture was stirred for 3 h at room temperature. The mixture was cooled to 0 °C and water (20 mL) was added followed by stirring for 1 h. The reaction mixture was extracted with ether (3×50 mL). The combined organic extracts were washed with $NaHCO_3$ solution (15 mL) and water (15 mL), and then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the pentaacetate **21** (220 mg, 82.1%) as a white crystalline solid. Mp 116.7–117.5 °C from Et_2O/*n*-hexane. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48–5.46 (2H, m, OCH), 5.22 (1H, dd, A-part of AB-system, J=10.9 and 2.7 Hz, OCH), 5.18 (1H, dd, *B*-part of AB-system, J=10.9 and 2.9 Hz, OCH), 4.09–4.05 (2H, m, OCH_2), 2.24–2.13 (1H, m, CH), 2.12 (3H, s, CH_3), 2.11 (3H, s, CH_3), 2.05 (3H, s, CH_3), 2.00 (3H, s, CH_3), 1.98 (3H, s, CH_3), 1.8–1.77 (2H, m, CH_2), 1.64 (1H, dq, J=14.2 and 7.0 Hz, CH_aH$_b$), 1.51 (dq, J=14.2, 6.8 Hz, CH$_a$H$_b$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (O*C*=O), 170.8 (O*C*=O), 170.2 (O*C*=O), (2C), 170.0 (O*C*=O), 71.0 (AcO*C*H), 69.9 (AcO*C*H), 69.3 (AcO*C*H), 68.6 (AcO*C*H), 61.8 (AcO*C*H$_2$), 30.9, 30.0, 29.8, 21.0 (*C*H$_3$), 20.9 (*C*H$_3$), 20.7 (*C*H$_3$) (3C). IR (KBr, cm^{-1}): 2974, 2948, 1751, 1455, 1391, 1249, 1172, 1069, 1017, 940, 863. Anal. Calcd for. $C_{18}H_{26}O_{10}$: C, 53.73; H, 6.51. Found: C, 53.50; H, 6.67.

4.12. 5a-Carba-6-deoxy-α-DL-galacto-heptopyranose (7)

Pentaacetate **21** (100 mg, 0.25 mmol) was dissolved in abs methanol (20 mL). While dry NH_3 gas was passed through the solution, the mixture was stirred for 4 h at room temperature. Evaporation of the solvent and the formed acetamide gave the pentol **7**; (46 mg) in a yield of 96% (viscous liquid). ^{1}H NMR (400 MHz, D_2O) δ 4.21–4.14 (1H, m, OCH), 4.07–4.06 (1H, m, OCH), 3.95–3.91 (1H, OCH), 3.73–3.61 (3H, m, OCH and OCH_2), 2.17–1.6 (5H, m, CH and CH_2). ^{13}C NMR (100 MHz, D_2O) δ 72.2 (O*C*H), 71.8 (O*C*H), 71.3 (O*C*H), 69.4 (O*C*H), 59.2 (O*C*H$_2$), 34.1 (*C*H), 31.2 (O*C*H$_2$), 30.7 (O*C*H$_2$). IR (KBr, cm^{-1}): 3391, 2953, 1734, 1688, 1494. Anal. Calcd for $C_8H_{16}O_5$: C, 49.99; H, 8.39. Found: C, 50.40; H, 8.57.

4.13. 1,2,3,4,7-Penta-*O*-acetyl-6-deoxy-5a-carba-α-gulo-heptopyranose (24)

To a stirred solution of triacetate **17** (171.6 mg, 0 0.61 mmol) in acetone/H_2O (2 mL, 1:1) were added NMO (91 mg, 0.77 mmol) and OsO_4 (2.0 mg, 0.008 mmol) at 0 °C. The resulting mixture was stirred vigorously under nitrogen at room temperature for 24 h. During the stirring the reaction mixture became homogeneous. Sodium hydrogensulfite (0.01 g) and florisil (0.5 g) slurried in water (2 mL) were added, the slurry was stirred for 10 min and the mixture was filtered through a pad of Celite (0.5 g) in a 50 mL sintered-glass funnel. The Celite cake was washed with acetone (3×10 mL). The filtrate was neutralized to pH 7 with H_2SO_4. The organic layer was removed in vacuo. The pH of the resulting aqueous solution was adjusted to pH 5 with sulfuric acid, and the diol was separated from *N*-methylmorpholine hydrosulfate by extraction with ethyl acetate (4×20 mL). The combined ethyl acetate extracts were washed with 5 mL of 25% NaCl solution and three times with water and dried (Na_2SO_4). Evaporation of the solvent gave **23**, which was submitted to acetylation.

To a magnetically stirred solution of diol **23** (120 mg, 0.38 mmol) in pyridine (1 mL) was added Ac_2O (0.16 g, 1.6 mmol). The reaction mixture was stirred at room temperature for 6 h. The mixture was cooled to 0 °C and 1 M HCl solution (25 mL) added, and the mixture was extracted with ether (3×25 mL). The combined organic extracts were washed with $NaHCO_3$ solution (25 mL) and water (10 mL), and then dried (Na_2SO_4). Removal of the solvent under reduced pressure and recrystallization of the product from ethyl acetate/*n*-hexane gave **24** (112.6 mg, 66.6%, as colorless solid, mp 138.0–138.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 5.24 (1H, t, J=3.0 Hz, AcOCH), 5.14 (1H, t, J=3.4 Hz, AcOCH), 5.08 (1H, t, J=3.7 Hz, AcOCH) 5.02 (1H, dt J=4.5 and 3.0 Hz, AcOCH), 4.05 (1H, dt, A-part of AB-system, J=12.6 and 6.2 Hz, AcOCH_aH$_b$), 4.01 (1H, dt, *B*-part of AB-system, J=12.6 and 6.4 Hz, AcOCH$_a$H$_b$), 2.11–2.05 (1H, m, CH), 2.02 (6H, s, 2×CH_3), 2.0 (3H, s, CH_3), 1.97 (3H, s, CH_3), 1.95 (3, H, s, CH_3), 1.91–1.83 (1H, m, CH_aH$_b$), 1.78–1.49 (3H, m, CH$_a$H$_b$) and (CH_aH$_b$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (O*C*=O), 170.1 (O*C*=O), 169.8 (O*C*=O), 169.5 (O*C*=O), 169.4 (O*C*=O), 69.7 (O*C*H), 68.9 (O*C*H), 68.7 (O*C*H), 68.4 (O*C*H), 62.0 (O*C*H$_2$), 31.2 (*C*H), 29.8 (*C*H$_2$), 26.8 (*C*H$_2$), 21.0 (*C*H$_3$), 20.9 (*C*H$_3$), 20.8 (*C*H$_3$), 20.7 (*C*H$_3$), 20.6 (*C*H$_3$). (KBr, cm^{-1}) 2960, 1747, 1439, 1374, 1239, 1042, 611. Anal. Calcd for $C_{18}H_{26}O_{10}$: C, 53.73; H, 6.51. Found: C, 53.48; H, 6.34.

4.14. 5a-Carba-6-deoxy-α-L-talo-heptopyranose (8)

Pentaacetate **24** (80 mg, 0.2 mmol) was dissolved in abs methanol (25 mL). While dry NH_3 gas was passed through solution, the mixture was stirred for 4 days at room temperature. When the reaction was complete the solvent was removed by rotary evaporator to give the pentol **8** in quantitative yield (38 mg, viscous oil). ^{1}H NMR (400 MHz, D_2O) δ 3.96–3.91 (1H, m, OCH), 3.81–3.78 (1H, m, OCH), 3.74–3.70 (2H, m, OCH), 3.1–3.51 (2H, m, OCH_2), 1.88–1.80 (1H, m, CH), 1.71–1.59 (2H, m, CH_2), 1.48 (1H, qui, J=7.2 Hz, CH_aH$_b$), 1.41 (1H, dt, J=14.4 and 4.0 Hz, CH$_a$H$_b$). ^{13}C NMR (100 MHz, D_2O, ppm): 73.4 (O*C*H), 72.9 (O*C*H), 69.3 (O*C*H), 68.4 (O*C*H), 59.4 (O*C*H$_2$), 33.1 (*C*H), 31.2 (*C*H$_2$), 26.9 (*C*H$_2$). IR (KBr, cm^{-1}): 3354, 2932, 1665, 1561. HRMS Calcd for $C_8H_{16}O_5Na$: 215.0895; Found 215.0890.

4.15. Crystallography

For the crystal structure determination, the single-crystal of the compound **21** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer (equipped with a two-dimensional area IP detector). The graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega$=5° for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Crystal Clear (Rigaku/MSC Inc., 2005) software.[36] The structures were solved by direct methods using SHELXS-97 and refined by a full-matrix least-squares procedure using the program SHELXL-97.[37] H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for 21: $C_{18}H_{26}O_{10}$, crystal system, space group: monoclinic, *P*21/c; unit cell dimensions: a=7.9834(5), b=18.1820(8), c=14.4307(8) Å, α=90 β=95.053(3), γ=90; volume: 2086.5(2) Å^3; Z=4; calculated density: 1.28 mg/m^3; absorption coefficient: 0.105 mm^{-1}; F(000): 856; θ range for data collection 2.2–30.4°; refinement method: full-matrix least-square on F^2; data/parameters: 2257/258; goodness-of-fit on F^2: 1.055; final R indices [$I>2\sigma(I)$]: R_1=0.089, wR_2=0.142; R indices (all data): R_1=0.140, wR_2=0.240; largest diff. peak and hole:

0.842 and −0.269 e $Å^{-3}$; Crystallographic data were deposited in CSD under CCDC registration number 768082.

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Supplementary data

These data include the ^{1}H and ^{13}C NMR spectra of eleven compounds. Supplementary data related to this article can be found online version, at doi:10.1016/j.tet.2010.11.102.

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