Epimerisation of Carbohydrates and Cyclitols, 15[+]

Non-Classical Epimerisation of (1*S*,2*S*,3*S*,4*R*,5*R*)-1-*O*-Methylcyclohexane-1,2,3,4,5-pentol

Michael Frank,[a] Ralf Miethchen,*[a] and Helmut Reinke[a]

Keywords: Inositols / Epimerisation / Acetals / Carbohydrates

Methoxycyclitol **4** was acetalized in a non-classical one-pot procedure with chloral/dicyclohexylcarbodiimide forming the 4-*epi* derivative **6**. The stepwise deprotection of compound **6** is also described. Thus, decarbamoylation to the acetal **7** was achieved by heating **6** with methanolic sodium methoxide, and cleavage of the acid-stable trichloroethylidene moiety was realised in two steps via the corresponding ethylidene acetals **8** and **9**; the ethylidene function was removed with aqueous trifluoroacetic acid (compound **10** from **6** via **9**). Finally, the carbamoyl derivative **10** was converted into the tetra-*O*-acetyl product **12** via the tetrol **11**.

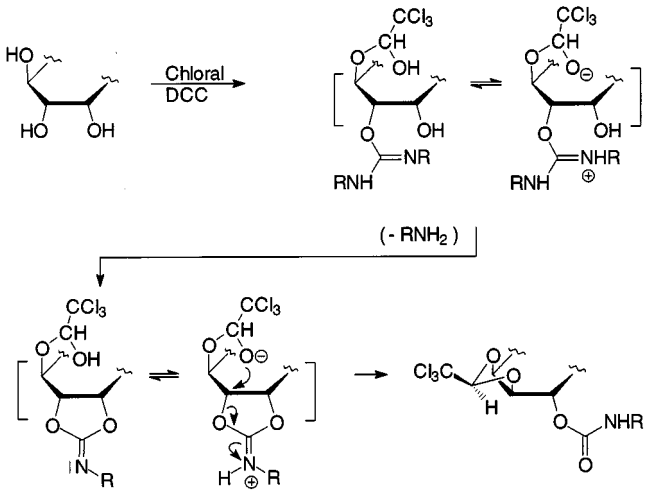
Introduction

Inositols and related polyhydroxycyclohexanes are often used as chiral auxiliaries in stereoselective syntheses.[2][3] The biological relevance of such compounds is well known.[4] Partially phosphorylated derivatives of those compounds have fundamental importance in biological systems, e.g. as second messengers.[5][6]

Because the succesful separation of inositol or polyhydroxycyclohexane derivatives from natural products is limited to only a few examples, various compounds of this type were prepared by chemical methods. Of the sixteen possible cyclohexanepentols only two have been found in nature.[7][8] Frequently, carbohydrates (or the widely available inositols) serve as convenient starting materials.

A facile one-pot method has been discovered for pyranose epimerisations using a non-conventional acetalation procedure with highly active carbonyl compounds in the presence of the co-reagent dicyclohexylcarbodiimide (DCC).[1,9−11] The most important requirement to satisfy is that the corresponding starting material shows a *cis*/*trans* sequence of three contiguous hydroxy groups. The mechanism of the reaction has been elaborated (see Scheme 1). In order to demonstrate the general character of this synthetic principle, the cyclitol derivative **4** has been epimerised by treatment with the reagent combination chloral/DCC. Moreover, some possibilities for the selective defunctionalisation of the 4-*epi* derivative generated from the cyclitol **4** have been indicated.

Starting material **4** was prepared by rearrangement of the 5,6-unsaturated glucopyranose derivative **1** induced by triisobutylaluminium[12] followed by debenzylation of the cyclohexane derivative formed, **2**[13] (see Scheme 2). It should be mentioned that the crude material of the tribenzyloxy derivative **2** contained the diastereomeric by-product **3** (about 8−9%) which was separated and characterised (see Experimental Section). Moreover, compound **3** was debenzylated by hydrogenation in the presence of Pd/C giving the all-*trans*-tetrol **5** (see Scheme 2). The analytical data of the two by-products **3** and **5** are given in the Experimental Section.



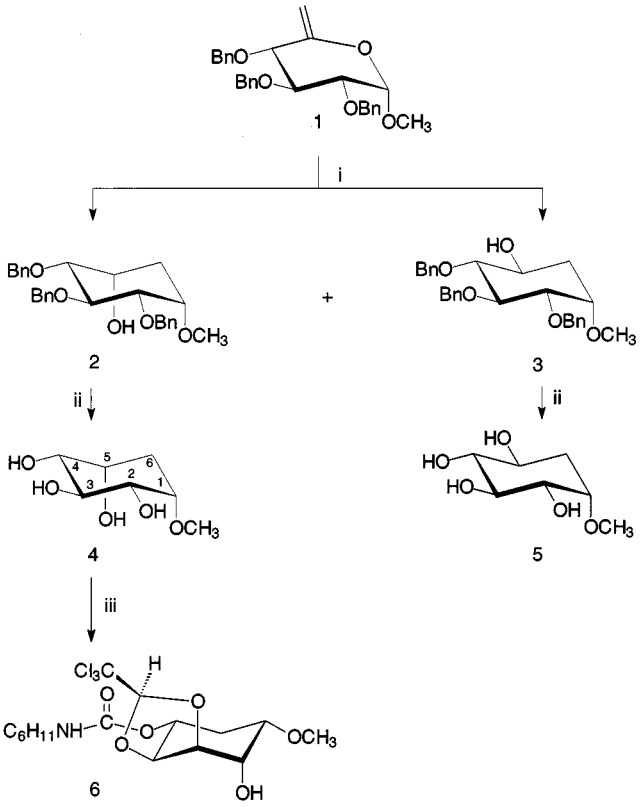
Scheme 1. Mechanism for the epimerisation

Substrate **4** shows, in contrast to compound **5**, the required *cis*/*trans* sequence of three contiguous hydroxy groups at C-3, -4 and -5 and adopts a $^4C_1$ conformation as confirmed by X-ray analysis (see Figure 1). As reported in previous papers,[1,9−11] the inversion of the configuration always takes place at the middle chiral carbon atom of such a triol unit. Thus, heating of the cyclitol **4** with chloral and DCC in 1,2-dichloroethane for 6 h generates the 4-*epi* derivative **6** in a yield of 70%. The cyclic acetal function bridges C-3 and -4, the carbamoyl group, which is simultaneously introduced, is arranged next to the acetal moiety in 5-position (see Scheme 2). Compound **6** may be used as substrate for regioselective reactions at the free OH group.

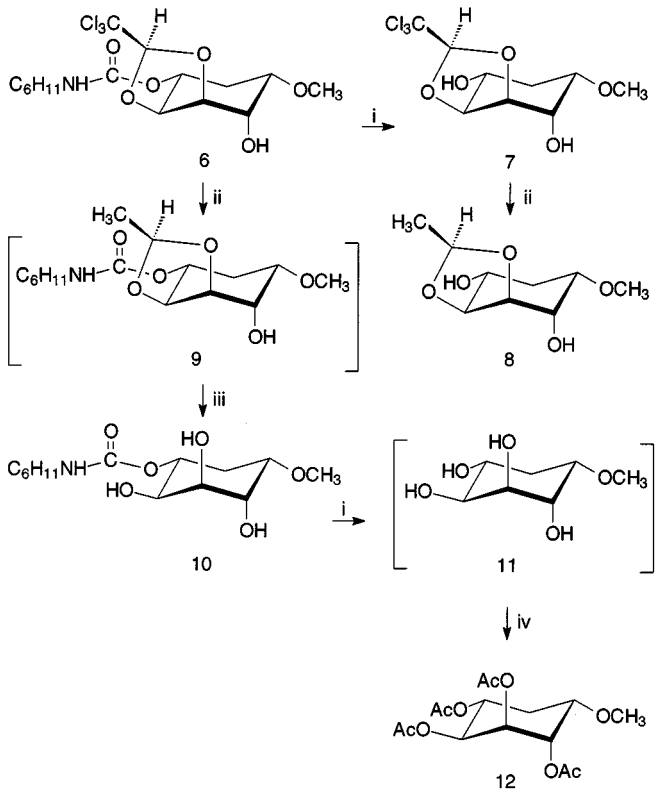
[+] Part 14: Ref.[1]

[a] Fachbereich Chemie, Universität Rostock,
Buchbinderstraße 9, D-18051 Rostock, Germany
Fax: (internat.) + 49(0)381/498-1819
E-mail: ralf.miethchen@chemie.uni-rostock.de

  1434−193X/99/0505−1259 $ 17.50+.50/0



Scheme 2. i: *i*Bu_3Al (toluene);[12] ii: H_2, Pd/C (MeOH/EtOAc); iii: DCC, chloral



Scheme 3. i: NaOMe/MeOH, reflux; ii: Bu_3SnH/AIBN (toluene, argon), reflux; iii: CF_3COOH (80%), r.t; iv: Ac_2O/pyridine, r.t.

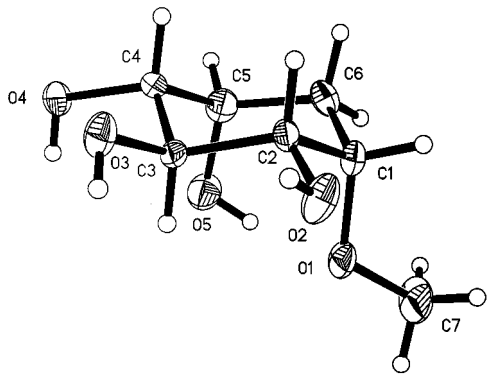


Figure 1. Molecular structure of compound **4** (probability 30%)

Scheme 3 shows how it is possible to selectively remove the protecting groups of **6**. Decarbamoylation was achieved by refluxing compound **6** with methanolic sodium methoxide (Zemplén reagent) to generate compound **7** with an intact trichloroethylidene function. Radical hydrogenation using Bu_3SnH/AIBN allows conversion of the trichloroethylidene group of **7** into an ethylidene group (compound **8**).[14]

In contrast to a trichloroethylidene function, an ethylidene acetal can easily be cleaved by treatment with aqueous trifluoroacetic acid. This possibility is demonstrated by the example of the ethylidene acetal **9**, generated from **6** by hydrogenation with Bu_3SnH/AIBN (Scheme 3). Crude product **9**, which is contaminated with trace amounts of a by-product (monochloroethylidene acetal), was treated with 80% trifluoroacetic acid at room temp. to cleave the ethylidene acetal with formation of the trihydroxy derivative **10**.[15] Compound **10** was decarbamoylated to tetrahydroxy derivative **11** by heating with methanolic sodium methoxide. Crude product **11** was subsequently peracetylated giving the 2,3,4,5-tetra-*O*-acetyl-1-*O*-methylcyclohexane-1,2,3,4,5-pentol (**12**).

The structures of compounds **6, 7, 8** and **10** are supported by their ^{1}H- and ^{13}C-NMR spectral data. The assignment of the signals has been unambiguously achieved by correlation experiments (H,H-COSY and C,H-COSY). The spectra of the product **6** show the characteristic signals of a carbamoyl and a chloral acetal function. The assignment of the 5-H signal of **6** (δ = 4.75) is additionally confirmed by the high-field shift of the signal of this proton after the decarbamoylation of **6** to **7** (δ = 3.96). As has been previously reported for numerous cyclic chloral acetals of carbohydrates[9,10,16] as well as for 4-*epi*-quinic acid and 4-*epi*-shikimic acid derivatives,[1] the singlet of the *endo*-H form of the acetal is characteristically shifted downfield in comparison with the corresponding signal of the *exo*-H form. The signals of the diastereomers of **6** are found at δ = 5.40 (*endo*-H form) and 5.29 (*exo*-H form). The integrals of these singlets were used to determine the ratio of the *endo*-H/*exo*-H diastereomers after column-chromatographic separation of **6** (*endo*-H/*exo*-H = 23:1).

After reductive conversion of **7** into the ethylidene derivative **8**, the corresponding acetal proton signal (**7**: δ = 5.36)

splits into a quadruplet (**8**: δ = 5.34, $J_{\text{acetal-H/methyl}} \approx 4.9$ Hz).

The coupling constants of the compounds **6**, **7**, **8**, **10**, and **12** indicate that they adopt a $^1C_4$ conformation in solution. For compound **7** the $^1C_4$ conformation was also confirmed by X-ray analysis (see Figure 2).

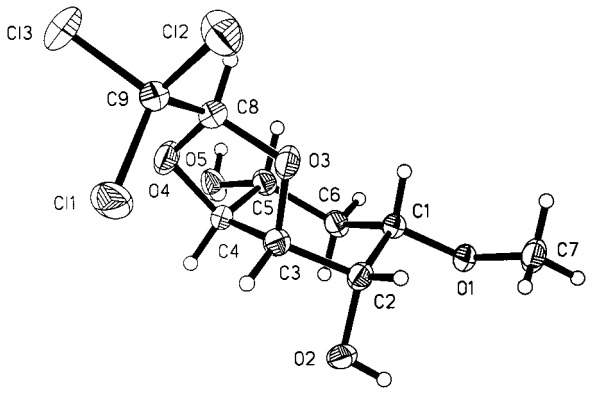


Figure 2. Molecular structure of compound **7** (probability 30%)

Experimental Section

General: CC: Silica gel 60 (63−200 μm, Merck). − TLC: Silica gel foils 60 F_{254} (Merck), a solution of 1.0 g of vanillin in MeOH (250 mL), glacial acetic acid (25 mL), and concd. H_2SO_4 (10 mL) was used as spray reagent for TLC.[17] − NMR: Bruker AC 250 and ARX 400 equipment, ^{1}H and ^{13}C{^{1}H} NMR chemical shifts referenced to TMS. − M.p.: Polarizing microscope Leitz (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90). − Chemicals: Dicyclohexylcarbodiimide, chloral, AIBN and palladium on activated charcoal (Fluka). − Rotational photos of crystals were taken to check the quality of the material (**4** and **7**). The data collection was done in a routine ω-scan. The structures were solved by direct methods (Siemens SHELXTL, **1990**, Siemens Analytical X-ray Inst., Inc.) and refined by the full-matrix least-squares method of Siemens SHELXTL, Ver. 5.03. All non-hydrogen atoms were refined anisotropically, the hydrogen atoms put into theoretical positions and refined according to the riding model. Further data: **4**: STOE IPDS diffractometer with graphite-monochromated Mo-K_α radiation; temperature: 293(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic; space group: $C222_1$; unit cell dimensions: a = 6.9526(14) Å, b = 9.4526 (19) Å, c = 25.193 (5) Å; V = 1655.7 (6) Å^3; Z = 8; density (calculated): 1.430 Mg/m^3; absorption coefficient: 0.122 mm^{-1}; F(000) = 768; crystal size 0.42 × 0.4 × 0.07 mm; Θ range for data collection: 1.45−24.2°; index ranges: $-7 \le h \le 7$, $-9 \le k \le 9$, $-26 \le l \le 26$; reflections collected: 2513; independent reflections: 915 [R(int) = 0.0893]; data/restraints/parameters: 915/2/113; goodness-of-fit on F^2: 1.065; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0623; $wR2$ = 0.1652; R indices (all data): $R1$ = 0.0718, $wR2$ = 0.1606; absolute structure parameter: −3(4); largest diff. peak and hole: 0.276 and −0.259 e/Å^3. **7**: Siemens P4 four-circle diffractometer with graphite monochromator; temperature: 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: $P2_1$; unit cell dimensions: a = 6.036(1) Å, b = 10.020(1) Å, c = 10.872(2) Å, β = 94.0°; V = 655.9(2) Å^3; Z = 2; density (calculated): 1.557 Mg/m^3; absorption coefficient: 0.704 mm^{-1}; F(000): 316; crystal size: 0.84 × 0.56 × 0.4 mm; Θ range for data collection: 1.88 to 22.48°; index ranges: $-6 \le h \le 1$, $-10 \le k \le 1$, $-11 \le l \le 11$; reflections collected: 1373; independent reflections: 1036 [R(int) = 0.0198]; data/restraints/parameters: 1036/1/156; goodness-of-fit on F^2: 1.038; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0279, $wR2$ = 0.0725; R indices (all data): $R1$ = 0.0283, $wR2$ = 0.0729; absolute structure parameter: 0.05(9); largest diff. peak and hole: 0.178 and −0.215 e.Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-113632 (**4**) and -105279 (**7**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

(1*S*,2*S*,3*S*,4*R*,5*S*)-2,3,4-Tri-*O*-benzyl-1-*O*-methylcyclohexane-1,2,3,4,5-pentol (3): The by-product **3**, a diastereomer of derivative **2**,[12] could be chromatographically separated from the crude product **2** in a yield of 8.7%; (R_f = 0.23, heptane/ethyl acetate = 1:1); m.p. 84−86°C; $[\alpha]_D^{23}$ = +9.5 (c = 0.88, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.41−7.26 (m, 15 H, phenyl-H), 5.06−4.63 (3 dd, 6 H; 3 benzyl-CH_2), 3.92 (dd, 1 H, $J_{3,4} \approx 9.2$ Hz, 3-H), 3.83 (ddd, 1 H, $J_{5,6a} \approx 11.9$ Hz, $J_{5,6e} \approx 4.7$ Hz, 5-H), 3.64 (ddd, 1 H, $J_{1,2} \approx 3.0$ Hz, 1-H), 3.46 (dd, 1 H, $J_{2,3} \approx 9.6$ Hz, 2-H), 3.42 (s, 3 H, O−CH_3), 3.26 (dd, 1 H, $J_{4,5} \approx 9.2$ Hz, 4-H), 2.28 (ddd, 1 H, $J_{6a,6e} \approx 14.0$ Hz, $J_{1,6e} \approx 3.5$ Hz, 6e-H), 2.13 (br, 1 H, OH), 1.20 (ddd, 1 H, $J_{1,6a} \approx 1.3$ Hz, 6a-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 138.7, 138.4 (3 phenyl-C), 128.6, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 127.5 (phenyl-C), 86.4, 83.1, 81.8, 75.1, 67.9 (C-1−C-5), 75.7, 75.3, 72.7 (3 benzyl-CH_2), 57.4 (O−CH_3), 30.9 (C-6). − $C_{28}H_{32}O_5$ (448.55): calcd. C 74.98, H 7.19; found C 74.72, H 7.23.

(1*S*,2*S*,3*S*,4*R*,5*S*)-1-*O*-Methylcyclohexane-1,2,3,4,5-pentol (5): The benzyl derivative **3**[20] (260 mg, 0.58 mmol), dissolved in a mixture of methanol (10 mL) and ethyl acetate (10 mL), was debenzylated by hydrogenation under hydrogen in the presence of Pd/C. The reaction was complete after 24 h. Subsequently, the suspension was filtered through Celite. After washing the filter layer with methanol (2 × 10 mL), the combined filtrates were concentrated under reduced pressure and the residue was purified by column chromatography (R_f = 0.21, chloroform/methanol = 5:1); yield: 96 mg (93%); m.p. 76−78°C; $[\alpha]_D^{21}$ = +23.8 (c = 1.07, methanol). − ^{1}H NMR (250 MHz, CD_3OD): δ = 3.61 (ddd, 1 H, $J_{1,2} \approx 4.3$ Hz, 1-H), 3.56 (ddd, 1 H, $J_{5,6a} \approx 12.0$ Hz, $J_{5,6e} \approx 3.7$ Hz, 5-H), 3.50 (dd, 1 H, $J_{4,5} \approx 9.6$ Hz, 4-H), 3.39 (s, 3 H, O−CH_3), 3.37 (dd, 1 H, $J_{2,3} \approx 9.3$ Hz, 2-H), 3.14 (dd, 1 H, $J_{3,4} \approx 8.8$ Hz, 3-H), 2.24 (ddd, 1 H, $J_{6e,6a} \approx 14.0$ Hz, $J_{1,6e} \approx 4.7$ Hz, 6e-H), 1.30 (ddd, 1 H, $J_{1,6a} \approx 2.1$ Hz, 6a-H). ^{13}C NMR (100 MHz, CD_3OD): δ = 79.7, 79.3, 75.6, 74.7, 69.6 (C-1−C-5), 57.7 (O−CH_3), 32.9 (CH_2). − $C_7H_{14}O_5$ (178.18): calcd. C 47.19, H 7.92; found C 47.22, H 8.10.

(1*S*,2*S*,3*S*,4*R*,5*R*)-1-*O*-Methylcyclohexane-1,2,3,4,5-pentol (4): The benzyl derivative **2**[12] (1.0 g, 2.22 mmol), dissolved in a mixture of methanol (24 mL) and ethyl acetate (8 mL), was debenzylated by hydrogenation in the presence of Pd/C. After 24 h, the reaction mixture was worked up and purified as described for compound **5** (R_f = 0.24, chloroform/methanol = 5:1); yield: 380 mg (95.7%); m.p. 94−96°C (acetone); $[\alpha]_D^{23}$ = +2.3 (c = 0.95, MeOH). − ^{1}H NMR (250 MHz, CD_3OD): δ = 3.95−3.83 (m, 2 H, 3-H/5-H), 3.69−3.47 (m, 3 H, 1-H/2-H/4-H), 3.41 (s, 3 H, O−CH_3), 2.12 (ddd, 1 H, $J_{6a,6e} \approx 13.9$ Hz, $J_{1,6a} \approx 7.1$ Hz, $J_{5,6a} \approx 6.8$ Hz, 6a-H), 1.69 (ddd, 1 H, $J_{1,6e} \approx 3.4$ Hz, $J_{5,6e} \approx 3.8$ Hz 6e-H). − ^{13}C NMR (63 MHz, CD_3OD): δ = 80.2, 75.4, 73.7, 72.1, 70.3 (C-1−C-5), 57.8 (O−CH_3), 29.9 (CH_2). − $C_7H_{14}O_5$ (178.18): calcd. C 47.19, H 7.92; found C 47.05, H 7.98.

(1*S*,2*S*,3*R*,4*S*,5*R*)-5-*O*-(*N*-Cyclohexylcarbamoyl)-1-*O*-methyl-3,4-*O*-(2,2,2-trichloroethylidene)cyclohexane-1,2,3,4,5-pentol (6): 2.6 g

(17.7 mmol) of chloral and 2.6 g (12.6 mmol) of DCC were added to a solution of **4** (0.90 g, 5.1 mmol) in dry 1,2-dichloroethane (15 mL), and the mixture refluxed for 6 h. After cooling to room temp., aqueous acetic acid (15 mL, 10%) was added and the mixture shaken for 30 min. Then, the organic phase was separated and the aqueous phase was extracted with 1,2-dichloroethane (2 × 20 mL). The combined organic phases were neutralised with a satd. aqueous $NaHCO_3$ solution (25 mL), washed with water (25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The syrupy residue was purified by column chromatography (R_f = 0.16, toluene/ethyl acetate = 5:1). Compound **6** was isolated as a syrupy mixture of *endo*-H/*exo*-H diastereomers (23:1) in a yield of 1.53 g (70%). After re-chromatography, the pure *endo*-H form was obtained as amorphous solid; $[\alpha]_D^{25}$ = −55.6 (*c* = 1.20, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (s, 1 H, acetal-H), 4.75 (ddd, 1 H, $J_{5,6a} \approx$ 11.7 Hz, $J_{5,6e} \approx$ 4.3 Hz, 5-H), 4.74 (d, 1 H, $J_{NH,CH} \approx$ 7.9 Hz, N−H), 4.68 (dd, 1 H, $J_{3,4} \approx$ 5.4 Hz, 3-H), 4.54 (dd, 1 H, $J_{4,5} \approx$ 8.0 Hz, 4-H), 4.28 (dd, 1 H, $J_{2,3} \approx$ 3.4 Hz, 2-H), 3.57 (ddd, 1 H, $J_{1,2} \approx$ 3.0 Hz, $J_{1,6a} \approx$ 10.4 Hz, $J_{1,6e} \approx$ 7.2 Hz, 1-H), 3.50−3.41 (m, 1 H, C_6H_{11}−CH), 3.38 (s, 3 H, O−CH_3), 2.83 (br., 1 H, OH), 2.11 (ddd, 1 H, $J_{6a,6e} \approx$ 12.5 Hz, 6e-H), 1.76 (ddd, 1 H, 6a-H), 1.73−1.53 (m, 4 H, C_6H_{11}−CH_2), 1.39−1.05 (m, 6 H, C_6H_{11}−CH_2). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.7 (C=O), 105.8 (acetal-C), 99.1 (CCl_3), 79.3 (C-4), 78.9 (C-3), 75.7 (C-1), 70.0 (C-5), 68.9 (C-2), 56.8 (O−CH_3), 49.9 (C_6H_{11}−CH), 27.3 (C-6), 33.3, 25.4, 24.7 (5 C_6H_{11}−CH_2). − $C_{16}H_{24}Cl_3N_1O_6$ (432.73): calcd. C 44.41, H 5.59, N 3.24; found C 44.37, H 5.49, N 3.20.

(1*S*,2*S*,3*R*,4*S*,5*R*)-1-*O*-Methyl-3,4-*O*-(2,2,2-trichloroethylidene)-cyclohexane-1,2,3,4,5-pentol (7): 0.68 g (1.57 mmol) of **6**, dissolved in anhydrous methanol (15 mL)/sodium methoxide (0.5 g, 9.5 mmol), was decarbamoylated by heating the solution under reflux for 8 h. Subsequently, the reaction mixture was cooled and neutralised with an acidic ion exchanger (Amberlite IR-120). After evaporation of the solvent under reduced pressure and column chromatographic purification (R_f = 0.22, toluene/ethyl acetate = 2:1), 483 mg (85.3%) of the colourless crystalline compound **7** was obtained; m.p. 114−115°C (heptane/diethyl ether = 25:1, v/v), $[\alpha]_D^{25}$ = +16.2 (*c* = 1.51, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.36 (s, 1 H, acetal-H), 4.69 (dd, 1 H, $J_{3,4} \approx$ 5.4 Hz, 3-H), 4.63 (dd, 1 H, $J_{4,5} \approx$ 5.0 Hz, 4-H), 3.98 (dd, 1 H, $J_{2,3} \approx$ 5.4 Hz, 2-H), 3.96 (dd, 1 H, $J_{5,6a} \approx$ 6.7 Hz, 5-H), 3.64 (ddd, 1 H, $J_{1,2} \approx$ 3.0 Hz, $J_{1,6a} \approx$ 7.1 Hz, $J_{1,6e} \approx$ 4.0 Hz, 1-H), (s, 3 H, O−CH_3), 1.99 (dd, 1 H, $J_{6a,6e} \approx$ 13.3 Hz, 6a-H), 1.96 (ddd, 1 H, 6e-H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 106.2 (acetal-C), 99.4 (CCl_3), 81.4 (C-4), 79.9 (C-3), 77.9 (C-1), 69.1 (C-2), 67.7 (C-5), 57.9 (OCH_3), 29.1 (C-6). − $C_9H_{13}Cl_3O_5$ (307.56): calcd. C 35.15, H 4.26; found C 35.28, H 4.33.

(1*S*,2*S*,3*R*,4*S*,5*R*)-3,4-*O*-Ethylidene-1-*O*-methylcyclohexane-1,2,3,4,5-pentol (8): A solution of **7** (485 mg, 1.58 mmol), Bu_3SnH (1.61 g, 5.53 mmol) and AIBN (35 mg) in dry toluene (20 mL) was refluxed for 12 h under argon. After cooling, the solution was shaken with a satd. aqueous KF solution (30 mL) for 30 min and the precipitated Bu_3SnF removed by filtration. Then the organic phase was separated, washed with water (2 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by column chromatography (R_f = 0.24, ethyl acetate/toluene = 2:1) giving 285 mg (89%) of **8** as colourless syrup; $[\alpha]_D^{25}$ = +48.0 (*c* = 1.05, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.34 [q, 1 H, *J*(acetal-H,acetal-CH_3) ≈ 4.9 Hz, acetal-H], 4.24 (dd, 1 H, $J_{3,4} \approx$ 5.2 Hz, 3-H), 4.16 (dd, 1 H, $J_{4,5} \approx$ 5.2 Hz, 4-H), 3.92 (dd, 1 H, $J_{2,3} \approx$ 5.3 Hz, 2-H), 3.87 (dd, 1 H, $J_{5,6} \approx$ 7.3 Hz, 5-H), 3.60 (ddd, 1 H, $J_{1,2} \approx$ 3.1 Hz, $J_{1,6a} \approx$ 7.2 Hz, $J_{1,6e} \approx$ 4.0 Hz, 1-H), 3.43 (s, 3 H, O−CH_3), 1.95 (dd, 1 H, $J_{6a,6e} \approx$ 14.0 Hz, 6a-H), 1.90 (ddd, 1 H, 6e-H), 1.31 (d, 1 H, acetal-CH_3). − ^{13}C NMR (62.9 MHz, $CDCl_3$): **δ** = 100.9 (acetal-C), 79.3 (C-4), 78.4 (C-3), 77.4 (C-1), 68.8 (C-2), 67.6 (C-5), 57.7 (O−CH_3), 29.3 (C-6), 21.2 (acetal-CH_3). − $C_9H_{16}O_5$ (204.22): calcd. C 52.93, H 7.90; found C 52.79, H 7.76.

(1*S*,2*S*,3*R*,4*S*,5*R*)-5-*O*-(*N*-Cyclohexylcarbamoyl)-1-*O*-methylcyclohexane-1,2,3,4,5-pentol (10): A solution of **6** (212 mg, 0.49 mmol), Bu_3SnH (0.5 g, 1.72 mmol) and AIBN (20 mg) in dry toluene (20 mL) was hydrodehalogenated as described for compound **8**. The syrupy crude product **9** was deacetalized by treatment with 80% aqueous trifluoroacetic acid (10 mL) under stirring (6 h at room temp.). After evaporation of the solvents under reduced pressure, the residue was purified by column chromatography (R_f = 0.13, toluene/ethyl acetate = 1:5). The overall yield (two steps) of crystalline colourless product **10** was 117 mg (79%); m.p. 129−130.5°C (methanol); $[\alpha]_D^{25}$ = −35.4 (*c* = 0.25, MeOH). − ^{1}H NMR (250 MHz, CD_3OD): δ = 4.69 (m, 5-H), 4.47 (br., 1 H, N−H), 3.98 (ddd, 1 H, $J_{2,3} \approx$ 2.7 Hz, $J_{2,6e} \approx$ 1.2 Hz, 2-H), 3.88 (dd, 1 H, $J_{3,4} \approx$ 4.6 Hz, 3-H), 3.72 (dd, 1 H, $J_{4,5} \approx$ 9.5 Hz, 4-H), 3.55 (ddd, 1 H, $J_{1,6a} \approx$ 11.2 Hz, $J_{1,6e} \approx$ 4.5 Hz, 1-H), 3.30 (s, 3 H, O−CH_3), 3.28−3.22 (m, 1 H, cyclohexyl-C−H), 2.01 (dddd, 1 H, $J_{5,6e} \approx$ 4.6 Hz, $J_{6a,6e} \approx$ 11.9 Hz, 6e-H), 1.89−176 (m, 2 H, cyclohexyl-CH_2), 1.75−1.62 (m, 3 H, cyclohexyl-CH_2), 1.56 (m, 1 H, 6a-H), 1.38−1.02 (m, 5 H, cyclohexyl-CH_2). − ^{13}C NMR (63 MHz, CD_3OD): δ = 158.1 (C=O), 77.0 (C-1), 73.5 (C-3), 72.9 (C-5), 71.7 (C-4), 70.5 (C-2), 56.7 (O−CH_3), 51.2 (cyclohexyl-C−H), 34.1 (cyclohexyl-CH_2), 30.3 (C-6), 26.6, 26.6, 26.1, 26.1 (4 cyclohexyl-CH_2). − $C_{14}H_{26}NO_6$ (303.35): calcd. C 55.43, H 8.31, N 4.62; found C 55.21, H 8.21, N 4.56.

(1*S*,2*S*,3*R*,4*S*,5*R*)-2,3,4,5-Tetra-*O*-acetyl-1-*O*-methylcyclohexane-1,2,3,4,5-pentol (12): A solution of compound **10** (100 mg, 0.33 mmol) in 1% methanolic sodium methoxide (15 mL) was heated for 15 h under reflux. When the reaction was finished (TLC control: $CHCl_3$/MeOH = 5:1, R_f = 0.22), the mixture was cooled down, neutralised with an acidic ion exchanger (Amberlite IR 120), filtered, and the filtration residue was washed with methanol (2 × 10 mL). The combined methanolic solutions were concentrated under reduced pressure and the crude product **11** obtained treated with a mixture of acetic anhydride (5 mL) and pyridine (5 mL) under stirring (room temp., 24 h). After evaporation of the solvents under reduced pressure, the residue was co-distilled with toluene (2 × 10 mL) giving the syrupy tetra-*O*-acetyl derivative **12**, which was purified by column chromatography (R_f = 0.20, toluene/ethyl acetate = 3:1). Yield: 94 mg (82%, related to **10**), colourless crystals, m.p. 109−110°C (toluene); $[\alpha]_D^{23}$ = −5.90 (*c* = 1.15, $CHCl_3$). − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.37 (dd, 1 H, $J_{3,4} \approx$ 4.9 Hz, 3-H), 5.28 (ddd, 1 H, $J_{2,3} \approx$ 3.2 Hz, $J_{2,6e} \approx$ 1.4 Hz, 2-H), 5.17 (dd, 1 H, $J_{4,5} \approx$ 9.6 Hz, 4-H), 5.07 (ddd, 1 H, $J_{5,6e} \approx$ 4.6 Hz, $J_{5,6a} \approx$ 10.6 Hz, 5-H), 3.62 (ddd, 1 H, $J_{1,2} \approx$ 3.0 Hz, $J_{1,6a} \approx$ 11.2 Hz, $J_{1,6e} \approx$ 4.3 Hz, 1-H), 3.30 (s, 3 H, O−CH_3), 2.20 (dddd, 1 H, $J_{6a,6e} \approx$ 12.5 Hz, 6e-H), 2.11, 2.07, 2.02, 1.96 (4 s, 4 × 3 H, 4 C(O)CH_3), 1.85 (ddd, 1 H, 6a-H). − ^{13}C NMR (63 MHz, $CDCl_3$): δ = 170.1, 169.8, 169.4, 169.0 (4 *C*(O)CH_3), 73.8, 70.2, 67.9, 67.8, 67.3 (C-1, C-2, C-3, C-4, C-5), 57.2 (O−CH_3), 29.8 (C-6), 20.9, 20.8, 20.7, 20.6 [4 C(O)*C*H_3]. − $C_{15}H_{22}O_9$ (346.33): calcd. C 52.02, H 6.40; found C 52.25, H 6.46.

Acknowledgments

The authors are grateful to Dr. Rhett Kempe (Institut für Organische Katalyseforschung e.V., Rostock) for recording the X-ray data

of compound **4**. We also thank the Fonds der Chemischen Industrie for financial support of our research.

[1] M. Frank, R. Miethchen, *Carbohydr. Res.* **1998**, *313*, 49−53.
[2] N. Chida, T. Tobe, M. Suwama, M. Ohtsuka, S. Ogawa, *J. Chem. Soc., Chem. Commun*. **1990**, 994−995.
[3] T. Akiyama, H. Nishimoto, T. Kuwata, S. Ozaki, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 180−188.
[4] [4a] T. Posternak, *Les Cyclitols*, Hermann, Paris, **1962**; engl. ed.: Holden-Day, San Francisco, **1965**. − [4b] T. Hudlicky, M. Cebulak, *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral, and Synthetic Data*, VCH, Weinheim, New York, Cambridge, **1993**.
[5] D. C. Billington, *Chem. Soc. Rev.* **1989**, *18*, 83−122.
[6] D. C. Billington, *The Inositol Phosphates − Chemical Synthesis and Biological Significance*, VCH Weinheim, **1993**.
[7] S. J. Angyal, L. Odier, *Carbohydr. Res.* **1982**, *101*, 209−219.
[8] G. E. McCasland, *Adv. Carbohydr. Chem.* **1965**, *20*, 11−65.
[9] R. Miethchen, D. Rentsch, *Liebigs Ann.Chem.* **1994**, 1191−1197.
[10] R. Miethchen, D. Rentsch, M. Frank, *J. Carbohydr. Chem.* **1996**, *15*, 15−31.
[11] C. Zur, A. O. Miller, R. Miethchen, *J. Fluorine Chem.* **1998**, *90*, 67−76.
[12] S. K. Das, J.-M. Mallet, P. Sinaÿ; *Angew. Chem.* **1997**, *109*, 513−516.; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 493−496.
[13] Precursor **1** was synthesised from methyl α-D-glucopyranoside via methyl 6-chloro-6-deoxy-2,3,4,-tri-*O*-benzyl-α-D-glucopyranoside and subsequent dehydrohalogenation with NaH at 50°C as reported by Evans et al.[18], and Lezellier et al.[19], respectively.
[14] R. Miethchen, D. Rentsch, *Carbohydr. Res.* **1996**, *293*, 139−145.
[15] The chloroethylidene group of the by-product is not cleaved under these conditions; the chromatographic purification of **10** is very easy.
[16] R. Miethchen, D. Rentsch, *J. Prakt. Chem./Chem.-Ztg*. **1995**, *337*, 422−423.
[17] J. S. Metthews, *Biochim. Biophys. Acta* **1963**, *69*, 163.
[18] M. E. Evans, L. Long jr., F. W. Parrish, *J. Org. Chem.* **1968**, *33*, 1074−1076.
[19] P. Lezellier, R. Ralainirina, D. Beaupère, R. Uzan, *Tetrahedron Lett.* **1994**, *35,* 4555−4558.
[20] Separated as a by-product of **2** using the procedure reported by P. Sinaÿ et al.[12]

Received November 10, 1998
[O98507]