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Note

Concentrated hydriodic acid in simultaneous deprotections of multifunctional inositols☆

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Abstract—L-1-Deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol was epimerized by chloral/DCC in boiling 1,2-dichloroethane yielding D-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-5,6-*O*-[(*R*/*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol. The latter and L-4-*O*-benzyl-3-*O*-cyclohexylcarbamoyl-5-*O*-methyl-1,2-*O*-(2,2,2-trichloroethylidene)-*muco*-inositol, L-4-*O*-benzyl-3-*O*-cyclohexylcarbamoyl-1,2-*O*-ethylidene-5-*O*-methyl-*muco*-inositol, D-1-*O*-cyclohexylcarbamoyl-2-deoxy-5,6-*O*-ethylidene-2-fluoro-3-*O*-methyl-*chiro*-inositol, as well as D-5-*O*-benzyl-4-*O*-cyclohexylcarbamoyl-3-deoxy-3-(*N*,*N*′-dicyclohexylureido)-6-*O*-methyl-1,2-*O*-(2,2,2-trichloroethylidene)-*chiro*-inositol were deprotected with boiling 57% aq hydrogen iodide. Ether, urethane and ethylidene acetal functions were simultaneously cleaved by the reagent, whereas the trichloroethylidene groups were still intact or were only removed in small quantities. Especially, the urea function of D-5-*O*-benzyl-4-*O*-cyclohexylcarbamoyl-3-deoxy-3-(*N*,*N*′-dicyclohexylureido)-6-*O*-methyl-1,2-*O*-(2,2,2-trichloroethylidene)-*chiro*-inositol was decomposed to a cyclohexylamino group. The hydrodechlorination of D-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-5,6-*O*-[(*R*/*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol using Raney-Nickel yielded a mixture of the corresponding 5,6-*O*-ethylidene- and 5,6-*O*-chloroethylidene derivatives. The three synthetic steps—hydrodehalogenation, HI-deprotection and peracylation- were combined without purification of the intermediates.

Keywords: Inositols; Fluoroinositols; Epimerization; Deprotection; Hydrogen iodide

The separation of inositol derivatives from natural sources is limited to a few representatives, so that various compounds of this type have to be prepared by chemical methods.[2–5] A new access to rare inositol derivatives from common diastereomers was opened by a convenient one-pot procedure using the chloral/DCC reagent combination.[1,6,7] This non-conventional acetalization/epimerization reaction yields epimerized inositol derivatives with useful protecting groups pattern (acetal, carbamoyl, ureido and formyl).

Scheme 1 shows two examples starting with L-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol (**1**)[6] and L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**4**).[1,8,†]

Recently, a review[10] was published about the non-conventional acetalizations/epimerizations of carbohydrates and inositols as well as about the possibilities for a stepwise deprotection of these manifold functionalized products. Simultaneous deprotections of such epimerized cyclitols were not investigated so far. In this paper, we report about the use of boiling 57% hydrogen

☆ Epimerization of carbohydrates and cyclitols, Part 20. For Part 19, see Ref. 1.

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† The numbering of the inositol derivatives based in this paper on the numbering of the corresponding simple member of a group of derivatives. Thus, D-2-deoxy-2-fluoro-*chiro*-inositol is the reference substance for the consistent numbering of the derivatives **5** and **14**–**18**; D-3-amino-3-deoxy-*chiro*-inositol is reference for **3**, **12** and **13** for the nomenclature of inositols, see Ref. 9.

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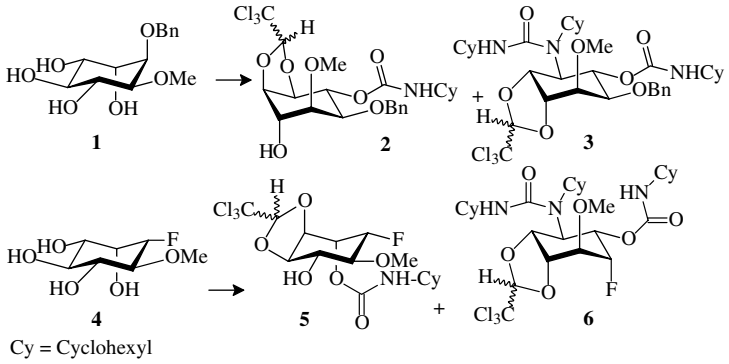
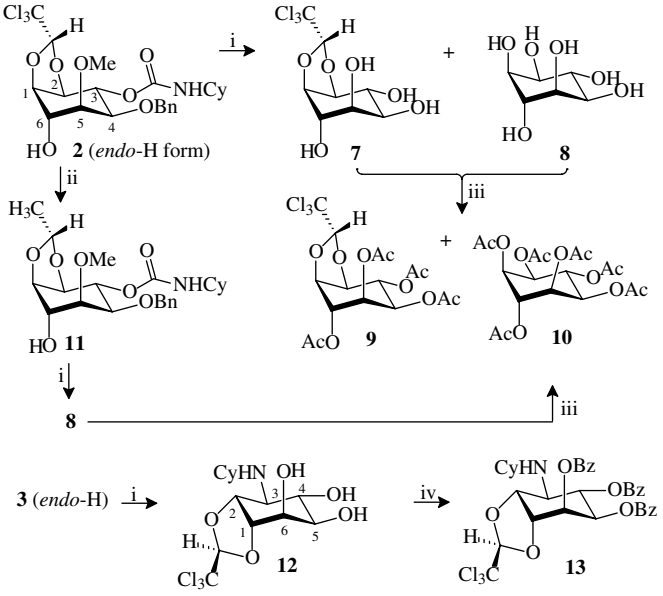


Scheme 1. Non-classical epimerization of L-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol (**1**)[6] and of L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**4**)[‡] with chloral/DCC yielding the single inverted major products **2** and **5** as well as the double inverted minor products **3** and **6**, respectively.



Scheme 2. One-pot deprotection of cyclitol derivatives **2**, **3** and **11** by heating in 57% HI; (i) 57% HI, reflux, 2 h; (ii) Bu_3SnH/AIBN;[6] (iii) Ac_2O, pyridine, rt, 12 h; (iv) BzCl, pyridine, rt, 12 h; Cy = cyclohexyl.

iodide soln for simultaneous cleavages of several protecting groups. Concentrated hydriodic acid has been already proved successful for the L-quebrachitol demethylation.[11]

On refluxing of the inositol derivatives **2**,[6] **3**[6] and **11**[6] in concentrated hydriodic acid for 2 h, the methoxy, benzyloxy, carbamoyl and ethylidene groups were completely cleaved, whereas the trichloroethylidene group was only removed in parts (Scheme 2). Elongation of the reaction time from 2 to 16 h did not have appreciable influence on the product ratios. Thus, *muco*-inositol derivative **2** yielded a 5:1 mixture of 1,2-*O*-trichloroethylidene-*muco*-inositol (**7**) and *muco*-inositol (**8**). Because a direct column chromatographic separation of minor product **8** was difficult, the crude mixture of **7** and **8** was first peracetylated. The acetylated derivatives were then isolated in yields of 74% (**9**) and 15% (**10**). L-4-*O*-Benzyl-3-*O*-cyclohexylcarbamoyl-1,2-*O*-ethylidene-5-*O*-methyl-*muco*-inositol (**11**), prepared from **2** by hydrodechlorination with tributylstannane/AIBN,[6] was completely deprotected to *muco*-inositol (**8**) by boiling hydriodic acid. After acetylation of the latter and column chromatographic purification, the well-known 1,2,3,4,5,6-hexa-*O*-acetyl-*muco*-inositol (**10**) was obtained.[12–14]

Compared with the examples above, the isolation of aminoinositol **12**, generated from the doubly inverted epimerization product **3**,[6] by column chromatography was difficult. Therefore, the crude product was first perbenzoylated (peracetyl derivatives were not detectable by TLC), and the UV active derivative **13** was then separated by column chromatography (yield 45%). It is to mention that a part of compound **13** was debenzoylated in the course of the column chromatographic separation.

[‡] X-ray analysis reported in Ref. 1.

Fluorinated cyclitols are useful biological probes of phosphatidylinositol metabolism. Recently, Schedler and Baker[15] gave a topical overview about the fluoroinositols synthesized so far; see also Ref. 16. As recently reported in Ref. 1 and shown in Scheme 1, a further diastereomeric fluorocyclitol derivative (compound **5**) is accessible by one-pot epimerization of L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**4**). After the yield of compounds **5** could be significantly increased from 18%[1] to 61% (this paper) by use of a higher boiling solvent (1,2-dichloroethane instead of dichloromethane), the compound became important as precursor for further D-2-deoxy-2-fluoro-*chiro*-inositol derivatives.

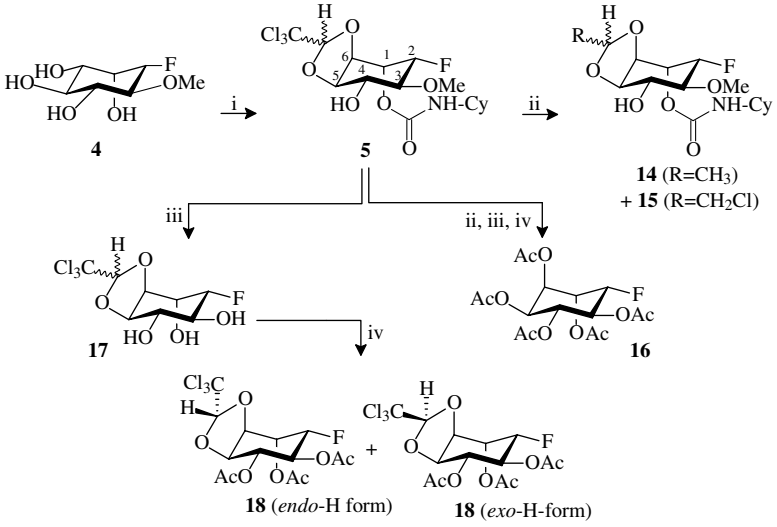
Compound **5** is a mixture of diastereomers, because the chiral C-atom of the acetal moiety is either (*S*)- or (*R*)-configurated. The endo-H diastereomer, D-5,6-*O*-[(*S*)-2,2,2-trichloroethylidene]-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-*chiro*-inositol, predominates in this mixture [(endo-H):(exo-H) ≈ 7.1:1]. Selected reactions of this diastereomeric mixture are shown in Scheme 3. Thus, it was treated with boiling concentrated hydriodic acid for 2 h. D-5,6-*O*-[(*S*)-2,2,2-Trichloroethylidene]-2-deoxy-2-fluoro-*chiro*-inositol (**17**) was formed and isolated (yield 64%). In a second experiment, the crude product obtained after the HI-deprotection of **5** was acetylated. Also in this case, only products were found with an intact trichloroethylidene group, that is, D-1,3,4-tri-*O*-acetyl-5,6-*O*-[(*S*)-2,2,2-trichloroethylidene]-2-deoxy-2-fluoro-*chiro*-inositol (**18**) in a yield of 76% and its exo-H diastereomer in a yield of 11%. This result shows that the trichloroethylidene group has to be first converted into an acid-unstable ethylidene group before a simultaneous total deprotection of the inositol derivative with hydriodic acid is possible.

Tributylstannane/AIBN[6,10,17] proved to be an unsuited reagent for the desired hydrodechlorination of **5**, because also fluoro-free products were formed, a consequence of competing hydrodefluorinations.[18,19] By contrast, Raney-Nickel did not cause hydrodefluorination, but it resulted from **5** a mixture of ethylidene acetal **14** and monochloroethylidene acetal **15** (ratio 1.3:1; estimated by NMR); for hydrodechlorinations of chloralacetals in the carbohydrate chemistry see also Ref. 20.

The chromatographic properties of compounds **14** and **15** are very similar. The first fraction, obtained by recrystallization of the **14/15** mixture from cyclohexane/2-propanol (10:1) contained exclusively the endo-H diastereomers of **14** and **15**. This fraction allowed a NMR spectroscopic analysis of the two compounds.

For the HI-deprotection of **14/15**, the whole mixture was used. It was even possible to combine the hydrodechlorination, HI-deprotection and peracetylation procedures without column chromatographic purification of the intermediates. In this way, D-1,3,4,5,6-penta-*O*-acetyl-2-deoxy-2-fluoro-*chiro*-inositol (**16**) was obtained in 40% yield related to starting material **5** (Scheme 3). The synthesis of the parent compound D-2-deoxy-2-fluoro-*chiro*-inositol from the mixture of **14** and **15** was reported in a preliminary communication.[21]

The structures of the new compounds are supported by their NMR spectra; assignments of the signals based on two-dimensional $^{1}H,^{1}H$- and $^{13}C,^{1}H$-correlations spectra. Key signals attributable with confidence to a definite position were found out from typical correlations in the case of the fluorocyclitols (coupling of the ring protons and ring carbons with fluorine). On this basis the assignment of signals for the other ring atoms became possible. The atomic configurations of adjacent ring protons were assigned with the assistance of the Karplus relationship.[22] The spectra of **5**, **7**, **9**, **12**, **13**, **17**, **18** (endo-H form) and **18** (exo-H form) show the



Scheme 3. (i) = Chloral/DCC, $(CH_2Cl)_2$, reflux, 8 h; (ii) = Raney-Nickel/H_2, EtOH; (iii) = 57% HI, reflux, 2 h; (iv) = Ac_2O, pyridine, rt, 12 h.

characteristic signals of a trichloroethylidene group. The latter is characterized by the singlet of the acetal proton ($\delta \approx 5.28$–5.93) and by the C signals of the acetal moiety ($\delta_{CH} \approx 105.4$–$112.6$; $\delta_{CCl_3} \approx 96.0$–$105.6$).

The cyclic chloral acetals generated by a non-conventional epimerization reaction with chloral/DCC are mixtures of endo-H and exo-H diastereomers. The singlet of the acetal proton is a good marker to distinguish between the two diastereomeric forms, because the endo-H proton is always about 0.1–0.25 ppm downfield shifted compared to the corresponding exo-H signal.[10] In the case of the compound **5** the ratio of endo-H form to exo-H form, estimated by integration of the two acetal-H singlets, was about 7:1 (δ endo-H = 5.39, δ exo-H = 5.28). The corresponding singlets of **18** (endo-H form) and **18** (exo-H form) were found at δ 5.49 and δ 5.35, respectively.

The ethylidene groups of compounds **11**[6] and **14** (endo-H form) are characterized by a doublet for the methyl group at about 5.29–5.30 ppm and by a doublet of the methyl group at about 1.30–1.36 ppm. The corresponding signals of the chloroethylidene group of compound **15** (endo-H form) were found at 5.38 ppm (triplet); see also Ref. 6. In the case of the mixture from **14** and **15**, all signals of the two endo-H diastereomers could be exactly assigned. The crude mixture of **14** and **15** shows in the ^{19}F NMR spectrum as expected four singlets for the two endo-H (δ −199.9 and −202.4) and the two exo-H isomers (δ −198.1 and −199.2).

Whereas the chair conformation of aminoinositol **12** (Scheme 2) corresponds to the coupling constants of the compound, the benzoyl derivative **13** shows strong divergences in this point. The coupling constants of the ring protons indicate a boat or twisted boat conformation of **13**.

In conclusion, the simultaneous complete deprotection of non-classically epimerized inositols with a very different pattern of protecting groups was solved using boiling 57% HI. With that in hand, a rapid access was achieved to well-known (but rare) inositols and to new epimeric inositols (e.g., fluoroinositol diastereomers).

Refluxing of the inositols **2** (endo-H form), **3** (endo-H form), **5** and **11** in 57% hydrogen iodide resulted in simultaneous cleavage of the ether, urethane and ethylidene acetal protecting groups within 2 h. Additionally, a small percentage of the cyclic chloral acetal function was removed under this reaction conditions in the case of compound **2**. Prolongation of the reaction time from 2 to 16 h did not have an appreciable influence on the result. To achieve the simultaneous cleavage of all protecting groups by 57% hydrogen iodide, a preceding hydrodechlorination of the trichloroethylidene group of **2** and **5** was required.

N,*N*′-Dicyclohexylureido groups are decomposed by hydrogen iodide to cyclohexylamino groups as already observed in the reaction of **3** with acetic acid.[6]

1. Experimental

1.1. General

Melting points were measured using a polarizing microscope Leitz (Laborlux 12 Pol) equipped with a hot stage (Mettler FP 90). ^1H NMR and ^{13}C NMR spectra were recorded on Bruker spectrometers AC 250 (250.13 and 62.9 MHz, respectively), and AVANCE 500 (500.13 and 125.8 MHz, respectively). Calibration of spectra was carried out by means of solvent peaks. ($CDCl_3$: δ $^1H = 7.25$, δ $^{13}C = 77.0$; CD_3OD: δ $^1H = 3.30$, δ $^{13}C = 49.0$; $(CD_3)_2CO$: δ $^1H = 2.04$, δ $^{13}C = 29.8$; Me_2SO-d_6: δ $^1H = 2.5$, δ $^{13}C = 39.7$). ^{19}F NMR spectra were recorded at 235.2 MHz (spectrometer AC 250, δ ^{19}F values referenced to $CFCl_3$). Optical rotations were measured on a Polar LμP (IBZ Meßtechnik). LC–MS: LCQ Advantage, ESI-mode (Thermo Finnigan). Column chromatography: Particle size for silica gel 63–200 μm; thin layer chromatography (TLC): E. Merck Silica Gel 60 F_{254} foils; Chemicals: 57% aq HI (Riedel de Haën), zinc dust (E. Merck).

1.2. D-1-*O*-Cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-5,6-*O*-[(*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol (5 endo-H) and D-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-5,6-*O*-[(*R*)-2,2,2-trichloroethylidene]-*chiro*-inositol (5 exo-H) by epimerization

To a suspension of L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**4**)[1] (1.0 g, 5.1 mmol) in $(CH_2Cl)_2$ (40 mL), DCC (3.16 g, 15.3 mmol) and chloral (1.7 mL, 17.8 mmol) were subsequently added with stirring at rt (argon atmosphere). Then the mixture was refluxed for 8 h. The work up procedure is analogous to that described in Ref. 1. The crystalline mixture of **5** (1.4 g, 61%, **5** (endo-H):**5** (exo-H) ≈ 7.1:1) and **6** (0.27 g, 8%) were separated by column chromatography (3:1 heptane/EtOAc). The pure diastereomer **5** (endo-H) could be obtained by fractionated crystallization from cyclohexane (mp 145–146 °C); Ref. 1 mp 145–146 °C. LC–MS [(M+H): *m*/*z* 452.0.

Compound **5** (endo-H): ^1H NMR (500 MHz, $CDCl_3$): δ 5.39 (s, 1H, $CHCCl_3$), 5.17 (ddd, 1H, $J_{1,F} \approx 21.8$, $J_{1,2} \approx 2.8$, $J_{1,6} \approx 6.0$ Hz, H-1), 4.76 (ddd, 1H, $J_{2,F} \approx 48.2$, $J_{1,2} \approx 2.8$, $J_{2,3} \approx 5.0$ Hz, H-2), 4.68 (m, 2H, H-6, NH), 4.56 (ddd, 1H, $J_{5,F} \approx 1.3$, $J_{4,5} \approx 8.5$, $J_{5,6} \approx 6.6$ Hz, H-5), 3.67 ('t', 1H, $J_{3,4} \approx 8.5$ Hz, H-4), 3.48 (s, 3H, OCH_3), 3.40 (ddd, 1H, $J_{3,F} \approx 15.7$, $J_{2,3} \approx 5.0$, $J_{3,4} \approx 8.5$ Hz, H-3) 3.40 (m, 1H, cyclohexyl–CH) 2.78 (br, 1H, OH), 1.88 (m, 2H, cyclohexyl–CH_2), 1.64 (m, 2H, cyclohexyl–CH_2), 1.53 (m, 1H, cyclohexyl–CH_2) 1.27 (m, 2H, cyclohexyl–CH_2), 1.09 (m, 3H, cyclohexyl–CH_2); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 153.8 (C(O)NH), 107.3 ($CHCCl_3$), 99.3

(CCl_3), 90.6 (d, $J_{C,F} \approx 199.0$ Hz, C-2), 81.0 (d, $J_{C,F} \approx 23.0$ Hz, C-3), 80.5 (C-5), 76.7 (d, $J_{C,F} \approx 7.0$ Hz, C-6), 72.0 (d, $J_{C,F} \approx 7.0$ Hz, C-4), 69.8 (d, $J_{C,F} \approx 18.0$ Hz, C-1), 59.4 (OCH_3), 50.3 (cyclohexyl–CH), 33.2 (2×), 25.4, 24.7 (2×) (5C, cyclohexyl–CH_2); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −202.7 (s).

Compound **5** (exo-H): acetal proton δ 5.28 (s).

1.3. Deprotection of epimerized inositol derivatives by hydrogen iodide soln[§]—general procedure

A soln of the corresponding inositol (1.0 mmol) in 57% aq HI-soln (2 mL) was refluxed for 2 h (Ar) and then concentrated under diminished pressure. The crude residue was purified by column chromatography.

1.3.1. 1,2-*O*-(2,2,2-Trichloroethylidene)-*muco*-inositol (7). The *muco*-inositol derivative **2** (endo-H)[6] (440 mg, 0.82 mmol) yielded after chromatographic purification (EtOAc) 152 mg (60%) of **7**, colourless crystals (diethyl ether), mp 111–113 °C; R_f 0.37 (5:1 $CHCl_3$–MeOH); ^1H NMR (250 MHz, CD_3OD): δ 5.87 (s, 1H, $CHCCl_3$), 4.88 (m, 2H, $J_{1,2} \approx 4.1$ Hz, H-1, H-2), 4.28 (m, 2H, H-3, H-6), 4.09 (dd, 2H, $J_{3,4} \approx 8.9$, $J_{4,5} \approx 2.9$ Hz, H-4, H-5); ^{13}C NMR (125.8 MHz, CD_3OD): δ 108.4 ($CHCCl_3$), 100.8 (CCl_3), 83.4 (C-1, C-2), 73.3 (C-3, C-6), 71.9 (C-4, C-5). Anal. Calcd for $C_8H_{11}Cl_3O_6$ (309.53): C, 31.04; H, 3.58. Found: C, 30.89; H, 3.40.

1.3.2. D-2-Deoxy-2-fluoro-5,6-*O*-[(*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol (17). D-5,6-*O*-[(*R*/*S*)-2,2,2-Trichloroethylidene]-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-*chiro*-inositol (**5**)[1] (740 mg, 1.65 mmol) yielded after chromatographic separation (30:1 $CHCl_3$–MeOH), 330 mg (64%) of **17**, colourless crystals (diethyl ether), mp 156–157 °C, R_f 0.32 (5:1 $CHCl_3$–MeOH), $[\alpha]_D^{22} + 66.2$ (*c* 0.66, MeOH), were isolated; **17** (endo-H form): ^1H NMR (250 MHz, CD_3OD): δ 5.52 (s, 1H, $CHCCl_3$), 4.61 (ddd, 1H, $J_{1,6} \approx 4.1$, $J_{5,6} \approx 5.7$ Hz, H-6), 4.50 (dd, 1H, $J_{4,5} \approx 8.0$ Hz, H-5), 4.44 (ddd, 1H, $J_{2,F} \approx 48.0$, $J_{1,2} \approx 3.0$, $J_{2,3} \approx 7.7$ Hz, H-2), 4.31 (ddd, 1H, $J_{1,F} \approx 14.2$ Hz, H-1), 3.86 (ddd, 1H, $J_{3,F} \approx 16.9$, $J_{3,4} \approx 9.2$ Hz, H-3), 3.54 (t, 1H, H-4); ^{13}C NMR (125.8 MHz, CD_3OD): δ 112.6 ($CHCCl_3$), 105.6 (CCl_3), 98.5 (d, $J_{C,F} \approx 180.0$ Hz, C-2), 88.1 (C-5), 85.3 (d, $J_{C,F} \approx 8.0$ Hz, C-6), 79.1 (d, $J_{C,F} \approx 8.0$ Hz, C-4), 76.2 (d, $J_{C,F} \approx 20.0$ Hz, C-3), 73.4 (d, $J_{C,F} \approx$ 18.0 Hz, C-1); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −202.8 (s). Anal. Calcd for $C_8H_{10}Cl_3FO_5$ (311.52): C, 30.84; H, 3.24. Found: C, 30.99; H, 3.26.

[§] Procedure corresponding to Angyal and Hoskinson;[11] HI was first distilled over zinc dust.

1.4. Deprotection of epimerized inositol derivatives by hydrogen iodide soln followed by acylation of the crude products—general procedure

A soln of the corresponding inositol (1.0 mmol) in 57% aq HI-soln (2 mL) was refluxed for 2 h (Ar) and then concentrated under diminished pressure. Then the crude residue was peracylated with Ac_2O (2 mL) and pyridine (5 mL) or with benzoylchloride/pyridine (only compound **3**, endo-H) for 12 h at rt. After concentration of the acylation mixture under diminished pressure, the corresponding crude product was three times co-distilled with 5 mL of toluene followed by column chromatographic separation.

1.4.1. 3,4,5,6-Tetra-*O*-acetyl-1,2-*O*-(2,2,2-trichloroethylidene)-*muco*-inositol (9) and 1,2,3,4,5,6-hexa-*O*-acetyl-*muco*-inositol (10). The L-4-*O*-benzyl-1,2-*O*-(2,2,2-trichloroethylidene)-3-*O*-cyclohexylcarbamoyl-5-*O*-methyl-*muco*-inositol (**2**, endo-H diastereomer)[6] (500 mg, 0.93 mmol) was successively deprotected to **7/8** and acetylated as described in the general procedure yielding the crude mixture of **9/10**. After column chromatographic separation (gradient: heptane/EtOAc 1:2 → heptane/EtOAc) 65 mg (16%) of **10**; colourless crystals (6:1 cyclohexane/EtOAc), mp 182–183 °C, R_f 0.26 (1:1 heptane/EtOAc) and 329 mg (74%) of **9**; colourless crystals (cyclohexane), mp 141–143 °C, R_f 0.29 (1:1 heptane/EtOAc) were isolated.

Compound **9**: ^1H NMR (500 MHz, $CDCl_3$): δ 5.51 (s, 1H, $CHCCl_3$), 5.50 (m, 2H, H-3, H-6), 5.23 (m, 2H, H-4, H-5), 4.62 (m, 2H, H-1, H-2), 2.12 (s, 6H, acetyl–CH_3), 2.08 (s, 6H, $2 \times CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.6, 169.1 ($2 \times C{=}O$), 106.1 ($CHCCl_3$), 98.5 (CCl_3), 78.4 (C-1, C-2), 68.1 (C-4, C-5), 67.2 (C-3, C-6), 20.7, 20.7 ($2 \times CH_3$). Anal. Calcd for $C_{16}H_{19}Cl_3O_{10}$ (477.68): C, 40.23; H, 4.01. Found: C, 40.49; H, 4.06.

Compound **10**: ^1H NMR (500 MHz, Me_2SO-d_6): δ 5.30–5.26 (br m, 2H, H-3, H-6), 5.19–5.16 (m, 4H, H-1, H-2, H-4, H-5), 2.08 (s, 6H, $2 \times CH_3$), 2.04 (s, 12H, $4 \times CH_3$); ^{13}C NMR (125.8 MHz, Me_2SO-d_6): δ 169.5 (C=O), 169.1 (C=O), 68.3 (C1, C2, C4, C5), 66.9 (C3, C6), 20.5 (CH_3). Anal. Calcd for $C_{18}H_{24}O_{12}$ (432.38): C, 50.00; H, 5.60. Found: C, 50.19; H, 5,56.

1.4.2. 1,2,3,4,5,6,-Hexa-*O*-acetyl-*muco*-inositol (10). A soln of the *muco*-inositol derivative **11**[6] (360 mg, 0.83 mmol) in 57% aq HI (2 mL) was refluxed for 2 h (Ar). After concentration of the mixture under diminished pressure, the residue was treated with Ac_2O (5 mL) and pyridine (2 mL) for 12 h at rt. Then, the mixture was poured on ice. After stirring for 30 min, compound **10** was extracted with ether. The crude product obtained by concentration of the combined ether phases was several times co-distilled with toluene before column chromatographic purification (R_f 0.25, 4:1

heptane/EtOAc). Yield: 165 mg (46%) of **10**; colourless crystals (6:1 cyclohexane/EtOAc), mp 182–183 °C (lit.[14] 179–180 °C) NMR data analogous to those described in paragraph 1.4.1.

1.4.3. D-4,5,6-Tri-*O*-benzoyl-3-cyclohexylamino-3-deoxy-1,2-*O*-(2,2,2-trichloroethylidene)-*chiro*-inositol (13). D-5-*O*-Benzyl-4-*O*-cyclohexylcarbamoyl-3-deoxy-3-(*N*,*N*′-dicyclohexylureido)-6-*O*-methyl-1,2-*O*-trichloroethylidene-*chiro*-inositol (3 endo-H)[6] (400 mg, 0.54 mmol) was deprotected to D-1,2-*O*-(2,2,2-trichloroethylidene)-3-cyclohexylamino-3-deoxy-*chiro*-inositol (**12**)[¶] as described in the general procedures 1.3. The crude product **13** was dissolved in CH_2Cl_2–pyridine (7 mL, 1:1) and then benzoyl chloride (0.31 mL, 2.7 mmol) was added with cooling. After the mixture was allowed to react for 12 h at rt, the colourless precipitate was removed by filtration and washed with CH_2Cl_2 (15 mL). The combined filtrates were subsequently washed with water (10 mL), satd aq $NaHCO_3$ soln (10 mL) and 5%-$NaHSO_4$ soln (10 mL), dried (Na_2SO_4) and concentrated under diminished pressure. Compound **13** (167 mg, 44%) was separated by column chromatography (15:1→1:1 heptane/EtOAc). Colourless needles (*i*-PrOH), mp 161–162 °C, R_f 0.28 (1:1 heptane/EtOAc), $[\alpha]_D^{23}$ +118.3 (*c* 0.50, $CHCl_3$).

Compound **12**: ^{1}H NMR (500 MHz, CD_3OD): δ 5.58 (s, 1H, $CHCCl_3$), 4.69 (dd, 1H, $J_{1,2} \approx 5.5$, $J_{2,3} \approx 8.2$ Hz, H-2), 4.62 (dd, 1H, $J_{1,2} \approx 5.5$, $J_{1,6} \approx 3.5$ Hz, H-1), 4.18 ('t', 1H, $J_{1,6} \approx 3.5$, $J_{5,6} \approx 3.1$ Hz, H-6), 3.71 (dd, 1H, $J_{3,4} \approx 9.5$, $J_{4,5} \approx 8.7$ Hz, H-4), 3.65 (dd, 1H, $J_{4,5} \approx 8.7$, $J_{5,6} \approx 3.1$ Hz, H-5), 3.13 (dd, 1H, $J_{2,3} \approx 8.2$, $J_{3,4} \approx 9.5$ Hz, H-3), 3.10 (m, 1H, CH), 2.20–1.10 (m, 10H, cyclohexyl–CH_2); ^{13}C NMR (125.8 MHz, CD_3OD): δ 107.7 (*C*$HCCl_3$), 100.7 (CCl_3), 81.7 (C-2), 81.3 (C-1), 73.1 (C-5), 70.3 (C-4), 70.0 (C-6), 59.3 (C-3), 56.7 (cyclohexyl–CH), 33.6, 32.4, 26.8, 26.2, 26.0 (cyclohexyl–CH_2). LC–MS: *m*/*z* 390.1.

Compound **13**: ^{1}H NMR (500 MHz, Me_2SO-d_6): δ 8.02 (m, 2H, *o*-Ph), 7.92 (m, 2H, *o*-Ph), 7.75–7.69 (m, 3H, *o*-Ph, *p*-Ph), 7.63–7.51 (m, 4H, 2 × *p*-Ph, *m*-Ph), 7.48 (m, 2H, *m*-Ph), 7.37 (m, 2H, *m*-Ph), 5.93 (s, 1H, C*H*CCl_3), 5.93 (m, 1H, H-6), 5.66–5.60 (m, 2H, H-1, H-2), 4.96 (dd, 1H, $J_{3,4} \approx 6.5$, $J_{4,5} \approx 5.5$ Hz, H-4), 4.76 (dd, 1H, $J_{5,6} \approx 4.0$ Hz, H-5), 3.50 (br m, 1H, H-3), 2.72 (br m, 1H, cyclohexyl–CH), 1.93–0.81 (m, 10H, cyclohexyl–CH_2); ^{13}C NMR (125.8 MHz, Me_2SO-d_6): δ 165.5 (COC_6H_5), 164.9 (COC_6H_5), 164.7 (COC_6H_5), 134.2 (*i*-Ph), 133.9 (*i*-Ph), 133.6 (*i*-Ph); 129.7, 129.5, 129.4, 129.2, 129.2, 129.1, 128.9, 128.9, 128.7 (Ph–C); 105.4 (*C*$HCCl_3$), 99.2 (CCl_3), 82.3 (C-4), 76.3 (C-5); 71.6, 70.7 (C-1, C-2); 68.1 (C-6), 55.9 (C-3), 54.9 (cyclohexyl–CH); 33.7, 33.4 (2,2′-cyclohexyl–CH_2); 25.8 (4-cyclohexyl–CH_2); 24.4, 24.4 (3,3′-cyclohexyl–CH_2). IR (Nujol): NH band 3425.5 cm^{-1}. LC–MS *m*/*z* 703.1. Anal. Calcd for $C_{35}H_{34}Cl_3NO_8$ (703.02): C, 59.80; H, 4.88; N, 2.00. Found C, 60.20; H, 4.92; N, 1.85.

1.4.4. D-1-*O*-Cyclohexylcarbamoyl-2-deoxy-5,6-*O*-ethylidene-2-fluoro-3-*O*-methyl-*chiro*-inositol (14) and D-5,6-*O*-(2-chloroethylidene)-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-*chiro*-inositol (15). To a stirred soln of **5** (650 mg, 1.44 mmol) in EtOH (10 mL) Raney-Ni (1.0 g) was added (H_2-atmosphere). After the suspension was stirred for 8 h at rt, triethylamine (1 mL) was added and stirring was continued for 8 h. Then the mixture was filtered through Kieselguhr, and the filtrate was concentrated under diminished pressure. After column chromatographic purification (1:1 heptane/EtOAc), 445 mg of a crystalline mixture of the ethylidene acetals **14** and the chloroethylidene acetal (**15**) were isolated (**14**:**15** ≈ 1.3:1); R_f 0.20 (1:3 heptane/EtOAc). Recrystallization of this four component fraction from 10:1 cyclohexane/*i*-PrOH gave a mixture of the endo-H isomers of **14** and **15**, colourless fine needles, which were 'felted'. One of the compounds melts at 152–154 °C, the other at 161–163 °C (polarizing microscope). The two exo-H isomers of **14** and **15**, enriched in the filtrate, were detected by LC–MS [(M+H): *m*/*z* 348 and 382, respectively]. Their ^{19}F NMR singlets were found at δ −198.1 and −199.2.

Compound **14** (endo-H): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.29 (q, 1H, $J \approx 5.0$ Hz, C*H*CH_3), 5.29 (m, 1H, H-1), 4.80 (ddd, 1H, $J_{2,F} \approx 48.2$, $J_{1,2} \approx 3.0$, $J_{2,3} \approx 6.0$ Hz, H-2), 4.72 (d, 1H, $J \approx 8.0$ Hz, NH), 4.40–4.26 (m, H-5, H-6), 3.69 ('t', 1H, $J_{3,4} \approx J_{4,5} \approx 8.5$ Hz, H-4), 3.56 (s, 3H, OCH_3), 3.55–3.40 (m, 2H, H-3, cyclohexyl–CH), 2.68 (br, 1H, OH), 1.96–1.11 (m, 10H, cyclohexyl–CH_2), 1.36 (d, 1H, $J \approx 5.0$ Hz, C*H*$_3$CH); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 154.1 (C(O)NH), 100.8 (*C*HCH_3), 90.9 (d, $J_{C,F} \approx 182.2$ Hz, C-2), 81.6 (d, $J_{C,F} \approx 23.8$ Hz, C-3), 78.2 (C-5), 75.1 (d, $J_{C,F} \approx 6.5$ Hz, C-6), 71.4 (d, $J_{C,F} \approx 7.5$ Hz, C-4), 69.5 (d, $J_{C,F}$ 17.5 Hz, C-1), 59.6 (OCH_3), 50.3 (cyclohexyl–CH), 33.2 (2×), 25.4, 24.7 (2×) (cyclohexyl–CH_2), 20.1 (CH*C*H_3); ^{19}F{^{1}H} NMR (235 MHz, $CDCl_3$): δ −199.9 (s). LC–MS (M+H): *m*/*z* 348.

Compound **15** (endo-H): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (t, 1H, $J \approx 4.0$ Hz, $ClCH_2CH$), 5.18 (ddd, 1H, $J_{F,H} \approx 22.5$, $J_{1,2} \approx 3.0$, $J_{1,6} \approx 6.3$ Hz, H-1), 4.81 (ddd, 1H, $J_{2,F} \approx 48.5$, $J_{1,2} \approx 3.0$, $J_{2,3} \approx 5.0$ Hz, H-2), 4.72 (d, 1H, $J \approx 8.0$ Hz, NH), 4.40–4.26 (m, 2H, H-5, H-6), 3.73 ('t', 1H, $J_{3,4} \approx J_{4,5} \approx 8.5$ Hz, H-4), 3.54 (s, 3H, OCH_3), 3.55–3.40 (m, 4H, H-3, cyclohexyl–CH, $CHCH_2Cl$), 2.68 (br, 1H, OH), 1.96–1.11 (m, 10H,

[¶] After neutralization of the crude product mixture with methanolic Et_3N, a column chromatographic separation of compound **12** was attempted. However, **12** could only be accumulated but not be isolated in pure form. The contaminated solid of **12** obtained was investigated by LC–MS. Besides the major product **12** (molar mass 390) a second product (molar mass 497), which likewise contains a 2,2,2-trichloroethylidene group, was detected.

cyclohexyl–CH_2); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 153.9 (C(O)NH), 102.1 ($CHCH_2Cl$), 90.8 (d, $J_{C,F} \approx 183.4$ Hz, C-2), 81.0 (d, $J_{C,F} \approx 21.2$ Hz, C-3), 79.0 (C-5), 74.0 (d, $J_{C,F} \approx 6.5$ Hz, C-6), 70.7 (d, $J_{C,F} \approx 7.5$ Hz, C-4), 69.5 (d, $J_{C,F} \approx 17.5$ Hz, C-1), 59.2 (OCH_3), 50.2 (cyclohexyl–CH), 44.6 (CH_2Cl), 33.2 (2×), 25.4, 24.7 (2×) (5C, cyclohexyl–CH_2); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −202.4 (s). LC–MS (M+H): *m*/*z* 382.

1.4.5. D-1,3,4,5,6-Penta-*O*-acetyl-2-deoxy-2-fluoro-*chiro*-inositol (16). To a stirred soln of **5** (3.40 mg, 0.75 mmol) in EtOH (5 mL) Raney-Ni (0.5 g) was added (H_2-atmosphere). After the suspension was stirred for 8 h at rt, triethylamine (1 mL) was added and stirring was continued for 8 h. Then the mixture was filtered through Kieselguhr, and the filtrate was concentrated under diminished pressure. The residue (316 mg) was refluxed for 2 h in 57% aq HI-soln (2 mL). The soln was then concentrated under diminished pressure followed by acetylation of the residue and isolation of compound **16** as described for compound **10** (R_f 0.18, 1:1 heptane/EtOAc). Yield of **16**: 117 mg (40% related to **5**); colourless syrup, $[\alpha]_D^{22}$ +27.0 (*c* 0.86, $CHCl_3$).

^1H NMR (500 MHz, $CDCl_3$): δ 5.52–5.46 (m, 2H, H-3, H-1), 5.41 ('q', $J_{6,F} \approx J_{1,6} \approx J_{5,6} \approx 3.5$ Hz, 1H, H-6), 5.36 ('t', 1H, $J_{4,F} \approx J_{3,4} \approx J_{4,5} \approx 10.2$ Hz, H-4), 5.21 (dd, 1H, $J_{4,5} \approx 10.2$, $J_{5,6} \approx 3.5$ Hz, H-5), 4.97 (ddd, 1H, $J_{2,F} \approx 46.4$, $J_{1,2} \approx 3.5$, $J_{2,3} \approx 9.8$ Hz, H-2), 2.18, 2.15, 2.06, 2.01, 1.95 (s, 15H, 5 × CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 171.4, 171.4, 171.4, 170.7, 170.5 (5 × C═O), 88.9 (d, $J_{C,F} \approx 188.6$ Hz, C-2), 70.4 (s, C-5), 68.1 (d, $J_{C,F} \approx 6.7$ Hz, C-6), 70.4 (d, $J_{C,F} \approx 10.2$ Hz, C-4), 71.7 (d, $J_{C,F} \approx 21.0$ Hz, C-3), 68.8 (d, $J_{C,F} \approx 17.7$ Hz, C-1), 20.5 (CH_3); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −207.5. Anal. Calcd for $C_{16}H_{21}FO_{10}$ (392.34): C, 48.98; H, 5.40. Found: C, 49.23; H, 5.57.

1.4.6. D-1,3,4-Tri-*O*-acetyl-2-deoxy-2-fluoro-5,6-*O*-[(*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol (18 endo-H) and D-1,3,4-tri-*O*-acetyl-2-deoxy-2-fluoro-5,6-*O*-[(*R*)-2,2,2-trichloroethylidene]-*chiro*-inositol (18 exo-H). The diastereomeric fluoroinositols **5**[1] (500 mg, 1.11 mmol) were deprotected by HI to crude product **17a**,**b** and then latter acetylated to **18** as described in the general procedures 1.3 and 1.4. The acetyl derivatives were separated by column chromatography (gradient: heptane/EtOAc 5:1 → heptane/EtOAc 1:1) yielding 370 mg (76%) of **18** (endo-H); colourless amorphous solid (cyclohexane), mp 47–49 °C, R_f 0.26 (1:1 heptane/EtOAc), and 55 mg (11%) of **18** (exo-H); colourless amorphous solid, R_f 0.23 (1:1 heptane/EtOAc).

Compound **18** (endo-H form): ^1H NMR (500 MHz, $CDCl_3$): δ 5.59 (ddd, 1H, $J_{1,F} \approx 18.2$, $J_{1,2} \approx 2.8$, $J_{1,6} \approx 4.0$ Hz, H-1), 5.49 (s, 1H, $CHCCl_3$), 5.33 (ddd, 1H, $J_{3,F} \approx 12.5$, $J_{2,3} \approx 6.3$, $J_{3,4} \approx 8.5$ Hz, H-3), 5.22 (m, 1H, H-4), 4.81 (ddd, 1H, $J_{2,F} \approx 47.0$, $J_{1,2} \approx 2.8$, $J_{2,3} \approx 6.3$ Hz, H-2), 4.75–4.72 (m, 2H, H-5, H-6), 2.17, 2.12, 2.09 (3s, 9H, 3 × CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.8, 169.6, 169.3 (3 × C═O), 106.9 ($CHCCl_3$), 98.6 (CCl_3), 88.5 (d, $J_{C,F} \approx 186.0$ Hz, C-2), 78.5 (s, C-5), 76.5 (d, $J_{C,F} \approx 7.2$ Hz, C-6), 70.3 (d, $J_{C,F} \approx 5.5$ Hz, C-4), 69.9 (d, $J_{C,F} \approx 25.5$ Hz, C-3), 68.5 (d, $J_{C,F} \approx 17.5$ Hz, C-1), 20.7, 20.7, 20.6 (3 × CH_3); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −203.5. Anal. Calcd for $C_{14}H_{16}Cl_3FO_8$ (437.63): C, 38.42; H, 3.69. Found: C, 38.77; H, 3.53.

Compound **18** (exo-H form): ^1H NMR (500 MHz, $CDCl_3$): δ 5.61 (ddd, 1H, $J_{1,F} \approx 21.8$, $J_{1,2} \approx 2.5$, $J_{1,6} \approx 5.0$ Hz, H-1), 5.55 ('q', 1H, $J_{4,F} \approx J_{4,5} \approx 7.5$, $J_{3,4} \approx 8.0$ Hz, H-4), 5.35 (s, 1H, $CHCCl_3$), 5.31 (ddd, 1H, $J_{3,F} \approx 12.5$, $J_{2,3} \approx 5.5$, $J_{3,4} \approx 8.0$ Hz, H-3), 4.90 (ddd, 1H, $J_{2,F} \approx 47.2$, $J_{1,2} \approx 2.5$, $J_{2,3} \approx 5.5$ Hz, H-2), 4.64–4.58 (m, 2H, H-5, H-6), 2.20, 2.11, 2.10 (3s, 9H, 3 × CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.7, 169.5, 169.2 (3 × C═O), 107.2 ($CHCCl_3$), 96.0 (CCl_3), 88.9 (d, $J_{C,F} \approx 185.2$ Hz, C-2), 76.9 (s, C-5), 76.88 (d, $J_{C,F} \approx 7.3$ Hz, C-6), 72.5 (d, $J_{C,F} \approx 4.6$ Hz, C-4), 70.8 (d, $J_{C,F} \approx 26.8$ Hz, C-3), 69.3 (d, $J_{C,F} \approx 18.2$ Hz, C-1), 20.70, 20.65, 20.58 (3s, 3 × CH_3); $^{19}F\{^1H\}$ NMR (235 MHz, $CDCl_3$): δ −201.7.

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