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Unexpected formation of a D-*chiro* inositol from a L-*chiro* precursor

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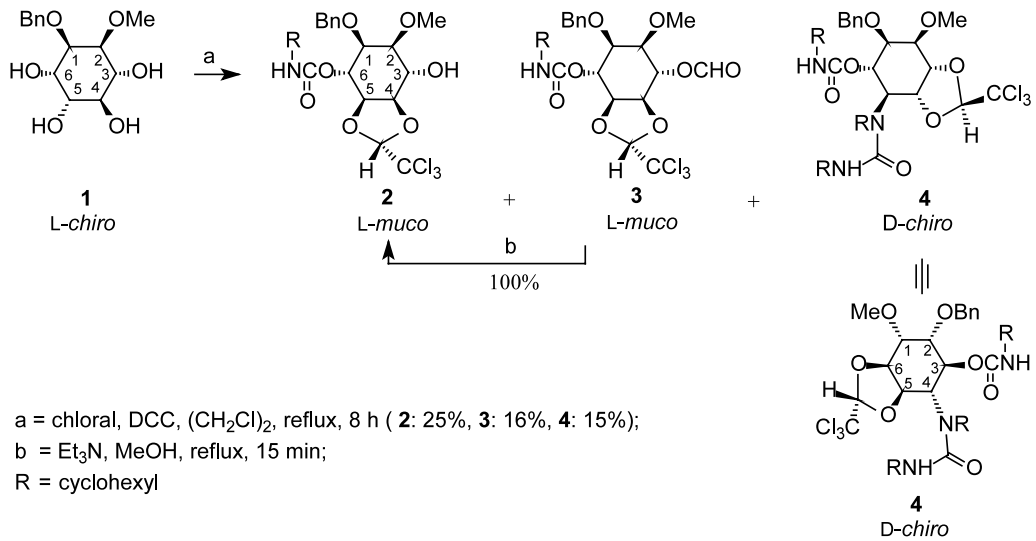
Abstract—In a one-step procedure, L-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol (**1**) was acetalized to the L-*muco*-inositol derivatives **2**, **3** and D-2-*O*-benzyl-3-*O*-cyclohexylcarbamoyl-4-(*N*,*N*′-dicyclohexylureido)-4-deoxy-1-*O*-methyl-5,6-*O*-trichloroethylidene-*chiro*-inositol (**4**). L-1-*O*-Benzyl-6-*O*-cyclohexylcarbamoyl-3-*O*-formyl-2-*O*-methyl-4,5-*O*-trichloroethylidene-*muco*-inositol (**3**) was quantitatively deformylated to L-1-*O*-benzyl-6-*O*-cyclohexylcarbamoyl-2-*O*-methyl-4,5-*O*-trichloroethylidene-*muco*-inositol (**2**) by boiling methanolic triethylamine.

The separation of inositol derivatives from natural sources is limited to a few representatives, so that various compounds of this type were prepared by chemical methods.[1–4] Some of the nine stereoisomeric inositols are only available in limited amounts, e.g. L-*muco* and D-*chiro* inositols. In 1994, a new epimerization method was reported for carbohydrates which used the reagent combination of chloral/DCC.[5] First attempts to apply this method to inositols containing five or six unprotected OH-groups (L-quebrachitol or *myo*-inositol) failed; however, the tetrahydroxy derivative (1*S*,2*S*,3*S*,4*R*,5*R*)-1-*O*-methylcyclohexane-1,2,3,4,5-pentol could be epimerized.[6]

Surprising results were just found starting with L-1-*O*-benzyl-2-*O*-methyl-*chiro*-inositol (**1**).[7–10] Refluxing of **1** in 1,2-dichloroethane with chloral/DCC for about 8 h yielded three products, the crystalline L-*muco*-inositol derivatives **2** (25%) and **3** (16%) and D-*chiro*-inositol derivative **4** (15%); Scheme 1. The latter is easily soluble



Scheme 1.

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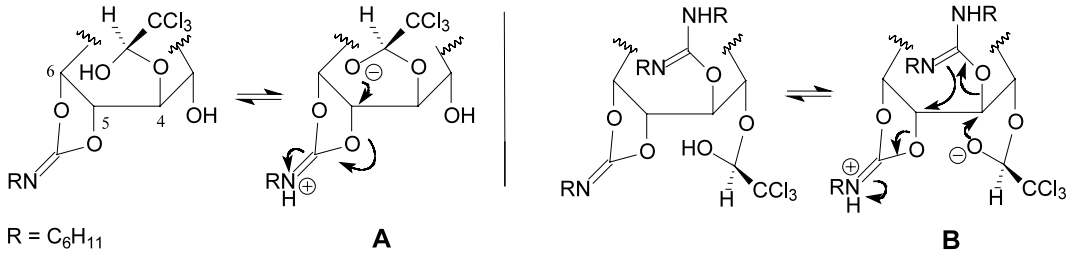

Scheme 2.

in light petroleum and numerous other organic solvents; however, it did not crystallize.[11]

Compound **3** is the 3-*O*-formyl derivative of L-*muco*-inositol derivative **2**. Boiling methanolic triethylamine allows a selective removal of formyl groups. By this procedure, compound **3** was quantitatively converted into **2** within 15 min (Scheme 1). The formation of **2** and **3** from **1** is in conformity with the mechanism of epimerizations described for *cis–trans* triol units of pyranoses.[5,6,12] That means, species **A** shown in Scheme 2 is the key intermediate; the configuration at the middle carbon atom (C-5) of the *cis–trans* triol unit (C-4/5/6) of **1** is inverted. As a consequence of imidocarbonate opening, the carbamoyl group must be located in the 6-position of the *muco*-derivatives **2** and **3**.

The formation of the inositol derivative **4** came as a surprise. Related to **1** the configuration at two C-atoms (C-4 and C-5) was inverted. We assume that compound **4** results from a reaction sequence via the key intermediate **B** which is formed from **A** (addition of 4-OH to DCC after hemiacetal displacement to 3-OH). Intermediate **B** allows a Tandem-sequence as marked by arrows in Scheme 2; the postulated C–N-bond formation is supported by results of Vowinkel and Gleichenhagen.[13] The configuration of **4** corresponds to a D-*chiro*-inositol derivative (compare formulas of **4** in Scheme 1). Therefore, the numbering of **4** was adapted corresponding to the rules.[14]

The structures of the compounds **2–4** are supported by NMR measurements; selected data of **2** and **4** see Ref. 15. The assignment of signals in the ^{1}H and ^{13}C NMR spectra was performed by recording DEPT and two-dimensional ^{1}H, ^{1}H and ^{13}C, ^{1}H correlation spectra. Thus, the signals for C-1 and C-2 could be confirmed by the correlation over three bonds to the proton signals OBn and OMe, respectively. On this basis the assignment of signals for the other ring atoms became possible. All spectra show the characteristic signals of a carbamoyl group and a trichloroethylidene group. The latter is characterized by the singlet of the acetal proton (**2**: $\delta = 5.39$, **3**: $\delta = 5.46$, **4**: $\delta = 5.45$) and by the C signals (δ_{CCl_3}98.9–99.7; δ_{CH}105.9–107.2) of the acetal moiety. The formyl group of **3** is characterized by the ^{1}H doublet $\delta = 8.14$, $J = 1.0$ Hz and the ^{13}C-signal $\delta = 160.2$. For compound **4**, the signal for C-4 is significantly shifted to higher field due to the *N*-substituent compared to the other ring-C-atom signals. In the ^{1}H spectrum of **4** recorded at room temperature some signals were displayed as broad signals which were sharpened at higher temperature indicating a dynamic process due to the flexibility of the molecule.[15]

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References

1. Posternak, T. *Les Cyclitols*; Hermann: Paris, 1962; English ed.; Holden-Day: San Francisco, 1965.
2. Hudlicky, T.; Cebulak, M. *Cyclitols and Their Derivatives. A Handbook of Physical, Spectral and Synthetic Data*; VCH Weinheim: New York, Cambridge, 1993.
3. Angyal, S. J.; Odier, L. *Carbohydr. Res.* **1980**, *80*, 203–206.
4. Takahashi, Y.; Nakayama, H.; Katagiri, K.; Ichikawa, K.; Ito, N.; Takita, T.; Takeuchi, T.; Miyake, T. *Tetrahedron Lett.* **2001**, *42*, 1053–1056.
5. Miethchen, R.; Rentsch, D. *Liebigs Ann. Chem.* **1994**, 1191–1197.
6. Frank, M.; Miethchen, R.; Reinke, H. *Eur. J. Org. Chem.* **1999**, 1259–1263 and references cited therein.
7. Compound **1** (mp 153–154°C; $[\alpha]_D^{24} = -54.2$ ($c = 1.0$, MeOH) was synthesized from L-quebrachitol via L-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol and L-1-*O*-benzyl-3,4:5,6-di-*O*-cyclohexylidene-2-*O*-methyl-*chiro*-inositol using well-known procedures.[8,9] Deacetalization was carried out with aqueous trifluoroacetic acid analogously to Ref. 10.
8. Angyal, S. J.; Irving, G. C.; Rutherford, D.; Tate, M. E. *J. Chem. Soc.* **1965**, 6662–6664.
9. Gero, S. D. *Tetrahedron Lett.* **1966**, *6*, 591–595.
10. Bath, S.; Billington, D. C.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Chem. Commun.* **1994**, *12*, 1495–1496.
11. A mixture of **1** (10 mmol), DCC (25 mmol) and chloral (35 mmol) in 1,2-dichloroethane (100 ml) was refluxed for 8 h. After addition of CH_2Cl_2 (150 ml) and 10% aq.

AcOH (200 ml), the mixture was shaken to destroy excess DCC. Precipitated urea was removed, the organic phase was concentrated and the crude product was treated with 50 ml of acetone (further urea remains). After concentration of the filtrate **2** (R_f=0.11), **3** (R_f=0.40) and **4** (R_f=0.28) were isolated by column chromatography (heptane/EtOAc 2:1 v/v). The syrupy product **2** (25%) crystallized from heptane; mp 124–124.5°C, $[\alpha]_D^{29}=-13$ (c=1.34, $CHCl_3$); **3** (16%) crystallized from light petroleum/diethyl ether (2:1 v/v) mp 142–143°C, $[\alpha]_D^{29}=-8$ (c=1.37, $CHCl_3$) and the syrupy product **4** (15%) gave only an amorphous solid after concentration of its light petroleum solution under reduced pressure (melting range 85–90°C), $[\alpha]_D^{22}=+7$ (c=1.07, $CHCl_3$).

12. Miethchen, R.; Rentsch, D.; Frank, M. *J. Carbohydr. Chem.* **1996**, *15*, 15–31.
13. Vowinkel, E.; Gleichenhagen, P. *Tetrahedron Lett.* **1974**, 139–142.
14. Angyal, S. J.; Anderson, L.; Cahn, R. S.; Dawson, R. M. C.; Hoffmann-Ostenhof, O.; Klyne, W.; Posternak, T., *Nomenclature of Cyclitols*, *Recommendations* **1973**, *Pure Appl. Chem. 37*, **1974**, 285–297.
15. Compound **2**: ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=5.52 (dd, 1H, $J_{1,6}$~3.7 Hz, $J_{5,6}$~2.0 Hz, H-6), 5.39 (s, 1H, C$\underline{H}$-CCl_3), 4.79 and 4.59 (d, J~12.0 Hz, C$\underline{H}_2$-Ph), 4.67 (d, 1H, $J_{NH,CH}$~8.0 Hz, NH), 4.58 (dd, 1H, H-5), 4.54 (dd, 1H, $J_{3,4}$~$J_{4,5}$~6.3 Hz, H-4), 4.16 (dd, 1H, $J_{2,3}$~9.8 Hz, $J_{3,4}$~6.3 Hz, H-3), 3.93 (ddd, 1H, $J_{1,6}$~3.7 Hz, $J_{1,2}$~2.6 Hz, $^4J_{1,5}$~1.0 Hz, H-1), 3.30 (s, 3H, OMe), 3.22 (dd, 1H, $J_{2,3}$~9.8 Hz, $J_{1,2}$~2.6 Hz, H-2), 2.88 (br, 1H, OH), 2.00–1.05 (m, 10H, cyclohexyl-CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=153.5 (C(O)NH), 105.9 (C$\underline{H}$-CCl_3), 99.2 (CCl_3), 81.7 (C-4), 78.9 (C-2), 77.8 (C-5), 72.4 (C-1), 71.8 (C$\underline{H}_2$-Ph), 68.6 (C-3), 67.0 (C-6), 57.5 (OMe).
Compound **4** ^{1}H NMR (300.13 MHz, $CDCl_3$, 55°C) δ=5.30 (dd, 1H, $J_{3,4}$~8.2 Hz, $J_{2,3}$~3.5 Hz, H-3), 5.45 (s, 1H, C$\underline{H}$-CCl_3), 5.14 (dd, 1H, $J_{5,6}$~6.7 Hz, $J_{4,5}$~9.8 Hz, H-5), 4.80 and 4.71 (d, J~12.0 Hz, C$\underline{H}_2$-Ph), 4.79 (dd, 1H, $J_{1,6}$~5.5 Hz, $J_{5,6}$~6.7 Hz, H-6), (d, 1H, J~12.0 Hz, C$\underline{H}_2$-Ph), 4.89 (br, 1H, H-4), 4.54 (d, 1H, J~7.5 Hz, NH), 4.41 (d, 1H, J~7.5 Hz, NH), 3.79 (dd, 1H, $J_{2,3}$~3.5 Hz, $J_{1,2}$~2.0 Hz, H-2), 3.70 (dd, 1H, $J_{1,6}$~5.5 Hz, $J_{1,2}$~2.0 Hz, H-1), 3.44 (s, 3H, OMe); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ=156.7 (NHC(O)N), 154.4 (NHC(O)O), 107.2 (C$\underline{H}$-CCl_3), 99.7 (CCl_3), 80.3 (C-6), 78.8 (C-1), 77.6 (C-2), 76.9 (C-5), 72.1 (CH_2-Ph), 70.7 (C-3), 58.0 (OMe), 56.3 (C-4); IR (Nujol): 1631 cm^{-1} (C=O, urea moiety), 1722 cm^{-1} (C=O, carbamoyl moiety), 3330 cm^{-1}, 3381 cm^{-1} (NH).