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D-2-Deoxy-2-fluoro-*chiro*-inositol—a new member of the deoxy fluoro inositol family

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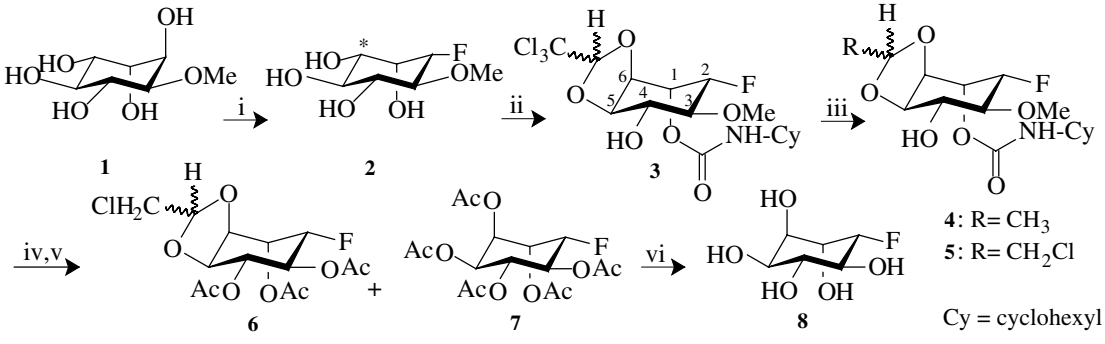
Dedicated to Professor Klaus Peseke on the occasion of his 65th birthday

Abstract—An efficient synthetic route to D-2-deoxy-2-fluoro-*chiro*-inositol has been developed with inversions of the C-1 and C-5 configuration of L-quebrachitol. The key steps of the route are two consecutive one pot epimerization procedures which do not require time-consuming protecting groups chemistry.

Biological activity and/or transport properties of organic compounds are influenced by fluorine and fluorinated moieties, respectively.[1,2] A number of diastereomeric deoxyfluoro inositols have been synthesized and evaluated as probes of the phosphatidylinositol pathway, most notably 5-deoxy-5-fluoro-*myo*-inositol, which is incorporated into the pathway at about 25% the level of *myo*-inositol itself.[3] The set of the six regioisomeric monodeoxy fluoro analogues of *myo*-inositol[3–14] as well as L-3-deoxy-3-fluoro-*chiro*-inositol,[15] 1-deoxy-1-fluoro-*scyllo*-,[9,16,17] 2-deoxy-2-fluoro-*scyllo*[14] and 2-deoxy-2-fluoro-*neo*-inositol [3] were synthesized so far. In this letter we report about an access to D-2-deoxy-2-fluoro-*chiro*-inositol (**8**) being a new member of the family of monofluoroinositols. The compound was synthesized from L-quebrachitol (**1**) by combination of efficient reaction steps as shown in Scheme 1. The essential points of the synthetic strategy are two epimerization procedures which evade a time-consuming protecting groups chemistry. The first regioselective epimerization occurs at fluorination of L-quebrachitol with diethylaminosulfur trifluoride (DAST) in dichloromethane.[12,18] This



Scheme 1. Synthesis of D-2-deoxy-2-fluoro-*chiro*-inositol (**8**) via non-classical epimerization of L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**2**).[7,12,18] Reagents and conditions: (i) DAST, CH_2Cl_2, rt, 4 h;[18] (ii) chloral, DCC, $(CH_2Cl)_2$, reflux, 6 h; (iii) Raney-Nickel/H_2, EtOH, rt, 16 h; (iv) 57% hydriodic acid, reflux, 2 h; (v) Ac_2O, pyridine, rt, 12 h; (vi) CsF/Al_2O_3, MeOH, rt, 10–12 h.[23]

Keywords: *chiro*-Inositols; L-Quebrachitol; Epimerization; Fluorination; Deoxy fluoro inositol.
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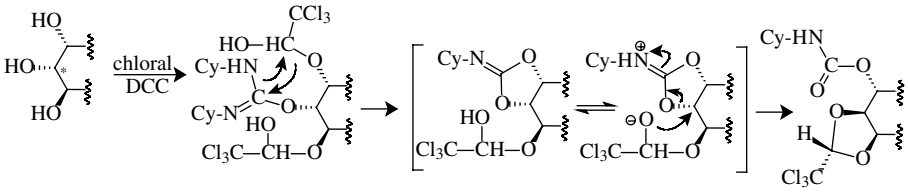

Scheme 2. Key steps of the non-classical epimerization of cyclic triols with *cis-trans* sequence of three vicinal OH-groups; Cy = cyclohexyl.

fluorination was originally reported by Kozikowski et al.[7] in 1989, first without use of any solvent and without characterization of **2**. However, the Kozikowski group modified later the protocol[12] and noted that *myo*-inositol derivative **2** is the sole product of the fluorination of L-quebrachitol with DAST. The structure of L-1-deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**2**)[19] was meanwhile also confirmed by X-ray analysis.[18]

L-1-Deoxy-1-fluoro-6-*O*-methyl-*myo*-inositol (**2**) meets the requirements for a non-classical acetalization/epimerization reaction with chloral/DCC,[20] because it shows a vicinal triol unit with *cis-trans* sequence (Scheme 1). The course of this epimerization reaction is simplistically shown in Scheme 2; for detailed explanations see review.[20]

Refluxing of **2** with chloral/DCC in 1,2-dichloroethane for 6–8 h gave D-1-*O*-cyclohexylcarbamoyl-2-deoxy-2-fluoro-3-*O*-methyl-5,6-*O*-[(*R*/*S*)-2,2,2-trichloroethylidene]-*chiro*-inositol (**3**). Consequently, the configuration at the marked C-atom of precursor **2** was inverted (Schemes 1 and 2). The yield of **3** was 61%.[21] Note that the numbering of the C-atoms is to change when a *myo*-inositol derivative was transformed into a D-*chiro*-inositol derivative (IUPAC rules for inositols[22]).

The next synthetic step was the hydrodechlorination of the acid-stable chloral acetal unit with H_2/Raney nickel in ethanol. It resulted a 1.3:1 mixture of ethylidene derivative **4** and chloroethylidene derivative **5**.[23] After refluxing of this mixture in 57% hydriodic acid, the intensive dark-colored crude product obtained was peracetylated before it was column chromatographically prepurified. The main fraction contained both, chloroethylidene derivative **6** and pentaacetyl derivative **7**. This mixture was treated with aluminia supported caesium fluoride in methanolic suspension at room temperature overnight.[23,24] Target compound **8** was obtained in a yield of 75% related to **3**.

The structures of the new products are supported by LC–MS data and NMR spectra; the NMR data of the compounds **4**, **5**, **7** and **8** are given in Ref. 23. Moreover, an X-ray analysis confirms configuration and conformation of target compound **8**.

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23. D-2-Deoxy-2-fluoro-*chiro*-inositol (**8**):
(1): To a stirred solution of **3**[18,21] (304 mg, 0.67 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 reduced pressure. After column chromatographic purification (1:1 heptane/EtOAc), 208 mg of a crystalline 1.3:1 mixture of **4** and **5** was obtained.
4 (*endo*-H form): ^{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, 2H, 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, 3H, $J \approx 5.0$ Hz, CH_3CH); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 154.1 (C(O)NH), 100.8 ($CHCH_3$), 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, $J_{C,F} \approx 17.5$ Hz, C-1), 59.6 (OCH_3), 50.3 (cyclohexyl–CH), 33.2 (2×), 25.4, 24.7 (2×) (cyclohexyl–CH_2), 20.1 ($CHCH_3$); ^{19}F{1H} NMR (235 MHz, $CDCl_3$): δ −199.9 (s). LC–MS (M+H): m/z = 348.

5 (*endo*-H form): ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.38 (t, 1H, $J \approx 4.0$ Hz, $ClCH_2CH$), 5.18 (ddd, 1H, $J_{1,F} \approx 22.5$, $J_{1,2} \approx 3.0$, $J_{1,6} \approx 6.3$ 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, cyclohexyl–CH_2); ^{13}C NMR (125.7 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.

(2): The 1.3:1 mixture of **4** and **5** (208 mg) was refluxed in 2 mL of 57% aqueous HI for 2 h. After concentration of the solution under reduced pressure, the residue was peracetylated with acetic acid anhydride/pyridine at rt (8 h). Then it was again concentrated. Compounds **6** (R_f = 0.27, 2:1 heptane/EtOAc) and **7** (R_f = 0.37, 2:1 heptane/EtOAc) were column chromatographically separated as mixed fraction (200 mg); LC–MS (**6**: [M+H]: m/z 393; **7**: [M]: m/z 368.4). **7**: ^{1}H 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, $5 \times CH_3$). ^{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), 71.7 (d, $J_{C,F} \approx 21.0$ Hz, C-3), 70.4 (s, C-5), 70.4 (d, $J_{C,F} \approx 10.2$ Hz, C-4), 68.8 (d, $J_{C,F} \approx 17.7$ Hz, C-1), 68.1 (d, $J_{C,F} \approx 6.7$ Hz, C-6), 20.5 (CH_3); ^{19}F{^{1}H} 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.

(3): To a stirred suspension of aluminia supported caesium fluoride[24] (150 mg, c = 1.533 mmol CsF/g support, 1/15 mol equiv fluoride per acetyl group) in MeOH (10 mL), the mixture of **6** and **7** (200 mg) was added and stirring was continued at rt overnight. After filtration and evaporation of the solvent, the residue was column chromatographically ($CHCl_3$/MeOH 20:1 → 5:1) purified. 92 mg (75%) of **8** related to **3** were isolated. The colourless crystals were recrystallized from acetone/MeOH (10:1), R_f 0.48 ($CHCl_3$/MeOH 1:1); $[\alpha]_D^{21}$ +46.2 (c 0.66, MeOH); LC–MS [M]: m/z 182. On heating compound **8** loses from 163–164 °C and up water by polycondensation; the polycondensate melts finally at 212–213 °C. ^{1}H NMR (250 MHz, CD_3OD): δ 4.52 (ddd, 1H, $J_{2,F} \approx 48.8$, $J_{1,2} \approx 3.3$, $J_{2,3} \approx 9.5$ Hz, H-2), 4.11 (ddd, 1H, $J_{1,F} \approx 6.9$, $J_{1,6} \approx 4.0$ Hz, H-1), 3.93 (ddd, 1H, $J_{6,F} \approx 4.4$, $J_{5,6} \approx 3.3$ Hz, H-6), 3.82 (ddd, 1H, $J_{3,F} \approx 12.3$, $J_{3,4} \approx 9.4$ Hz, H-3), 3.71 (dd, 1H, $J_{4,5} \approx 9.7$ Hz, H-5), 3.55 (dd, 1H, H-4); ^{13}C NMR (62.9 MHz, CD_3OD): δ 94.2 (d, $J_{C,F} \approx 179.0$ Hz, C-2), 74.2 (d, $J_{C,F} \approx 11.0$ Hz, C-4), 73.4 (d, $J_{C,F} \approx 8.4$ Hz, C-6), 72.8 (d, $J_{C,F} \approx 18.2$ Hz, C-3), 72.2 (s, C-5), 71.6 (d, $J_{C,F} \approx 17.1$ Hz, C-1); ^{19}F{^{1}H} NMR (235 MHz, CD_3OD): δ −206.5.

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