SYNTHESIS AND CHEMISTRY OF HIGHLY FLUORINATED OXEPANE-2,7-DIOLS

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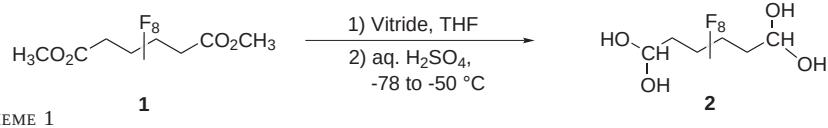
In memory of Professor Miloš Hudlický.

Reduction of dimethyl perfluoroadipate with Vitride yielded the title compounds, which were also prepared by dehydration of 1*H*,6*H*-perfluorohexane-1,1,6,6-tetrol. The configurations of the oxepanediols were assigned based on the crystal structure of the bis(*tert*-butyldiphenylsilyl) ether of the *cis* stereoisomer. Treatment with ethanolic HCl ring-opened the diols to 1*H*,6*H*-1,6-diethoxyperfluorohexane-1,6-diol, and dehydration with P_4O_{10} gave perfluorohexanedial.

Keywords: Reductions; Cyclizations; Hemiacetals; Aldehydes; Oxepanes; Fluorinated compounds; X-Ray diffraction.

Greenwald and Evans reported that reduction of dimethyl perfluoroadipate (**1**) with Vitride, sodium bis(2-methoxyethoxy)aluminum hydride, followed by an aqueous acid workup yields the tetrol **2** [1] (Scheme 1).

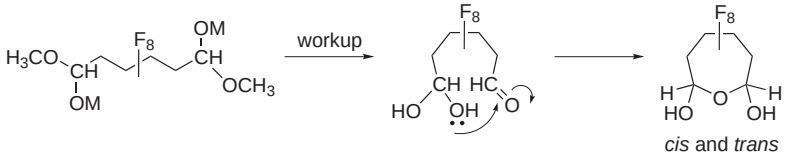


1 **2**

SCHEME 1

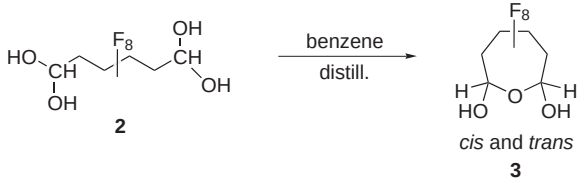
We confirmed this result, but obtained an entirely different product on some occasions following nominally the same procedure[2]. The ^{19}F NMR spectrum (CD_3CN) of the crystalline tetrol consisted simply of two singlets of equal area (δ –122.2, –127.8). That of the new product comprised six doublets and a singlet. Relative areas revealed that two compounds were present in the ratio ~2.5 : 1. The major one was responsible for an AX pattern (–119.6, –132.9, J = 277, 4 F) and an AB quartet (–124.3, –129.7, J = 289, 4 F); the minor one gave rise to an AX pattern (–116.5, –135.1, J = 265,

4 F) and a singlet (–127.6, 4 F). The inequivalence of geminal fluorines apparent from the AB and AX patterns pointed to cyclic structures, *viz*. *cis*- and *trans*-2*H*,7*H*-perfluorooxepane-2,7-diol (**3**), presumably formed as shown in Scheme 2.



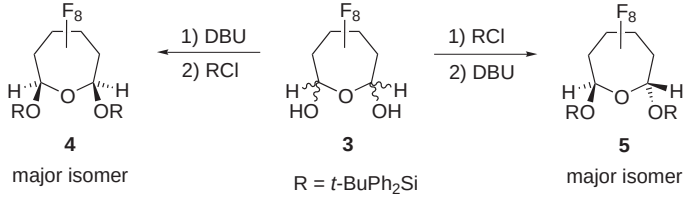
SCHEME 2

Five- and six-membered-ring diols are produced when perfluorosuccinic and perfluoroglutaric diesters, respectively, are reduced as above, but formation of cyclic diols in the present case was unexpected[3]. Simple distillation of benzene from a mixture of tetrol **2** with that solvent suffices to effect clean dehydration, providing an alternative route to oxepane **3** (Scheme 3).



SCHEME 3

Diol **3** was derivatized in acetonitrile with *tert*-butyldiphenylsilyl chloride under two sets of conditions, with very different results (Scheme 4). When DBU was introduced prior to slow addition of the silylating agent, *cis*-acetal **4** was obtained.

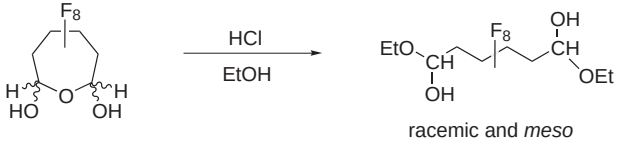


SCHEME 4

Its stereochemistry was revealed by X-ray crystal structure determination (ORTEP, Fig. 1)[4]. When the order of addition was reversed, the *trans*-acetal **5** was the heavily dominant product. Addition of DBU to the diol was found to sharply increase the ratio of the minor to the major stereoisomer; thus, acetal **4** was derived from the minor isomer, which must have

the *cis* configuration. It is surprising that the fluorines at C4 and C5 in *cis*-**3** are isochronous in CD_3CN; in derivative **4** they differ in chemical shift by 2.1 ppm.

Ethanolic HCl ring-opened diol **3** giving dihemiacetal **6** in 95% yield based on starting diester[5] (Scheme 5). Presumably a mixture of racemic and *meso* forms, **6** nonetheless melts sharply and the two stereoisomers are indistinguishable by ^{19}F NMR. The spectrum (CD_3CN) consisted of a singlet (–122.0, 4 F) and an AB quartet (–123.7, –129.2, J = 277, 4 F). Since C2 and C7 are chiral carbons, the geminal fluorines at C3 and C6 are anisochronous, but the more distant ones at C4 and C5 are uninfluenced by the stereocenters. In the ^1H NMR spectrum (CD_3CN), the protons at the chiral centers appear as a doublet of doublets, as they are coupled unequally to the vicinal fluorines; the methylene hydrogens appear as a 16-line subsplit AB quartet, reflecting their inequivalence.



3 **6**

SCHEME 5

Even at reflux in the reaction with oxepane **3**, ethanolic HCl gives only dihemiacetal **6** unaccompanied by bis(diethylacetal). This is understandable as a consequence of the many fluorines that are present. Interconversion

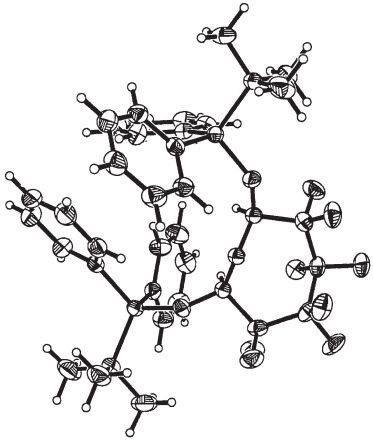
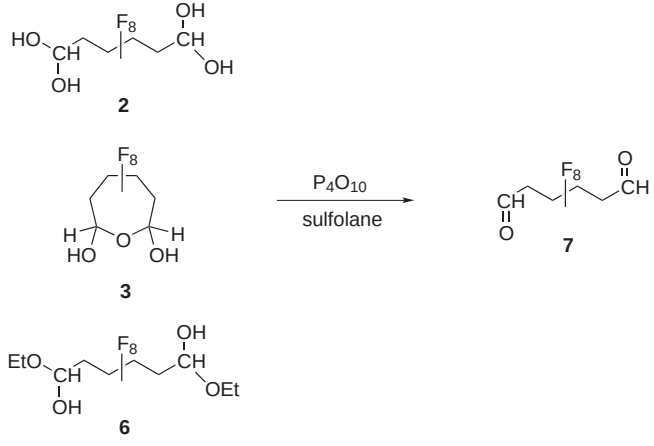


FIG. 1
ORTEP drawing of the *cis*-2,7-Bis(*tert*-butyldiphenylsiloxy)-2*H*,7*H*-perfluorooxepane (**4**)

among hemiacetals or between a geminal diol and a hemiacetal can take place *via* the corresponding aldehyde without the intervention of a carbocation intermediate, but formation of an acetal requires such an intermediate. The electron-withdrawing fluorines in dihemiacetal **6** powerfully oppose the generation of a positive charge at C2 and C7.

Interestingly, in water the ^{19}F NMR spectrum of dihemiacetal **6** comprises just two resonances of equal area (δ –121.0, –123.1), so even the fluorines neighboring to the chiral centers are in equivalent environments in this solvent. The compound is only slightly soluble in water, but it dissolves completely over the course of several hours at room temperature as a result of hydrolysis to tetrol **2**.

Heating on a steam bath with P_4O_{10} in sulfolane transformed tetrol **2**, diol **3**, and dihemiacetal **6** into dialdehyde **7**[6] [^{19}F NMR (CD_3CN): –122.7 (s, 4 F), –124.9 (s, 4 F)] (Scheme 6). Limiting the amount of P_4O_{10} in the reaction with tetrol **2** resulted in only partial dehydration, thus offering yet another method for preparing diol **3**. As in the ester reduction and earlier tetrol dehydration, the *trans*/*cis* ratio was ~2.5 : 1, presumably reflecting equilibration of the stereoisomeric mixture.



SCHEME 6

EXPERIMENTAL

All ^1H (300 MHz) and ^{19}F (282.2 MHz) spectra were recorded on a Varian Unity Plus 300 spectrometer. The former were referenced to TMS *via* residual protiated solvent and the latter to internal $CFCl_3$ (upfield negative). Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Melting points were performed on a Thomas Hoover Uni-melt apparatus and are uncorrected. Flash column chromatography was carried out on EM Reagent silica gel 60 (230–400 mesh) with hexane/ether as eluting solvent. Ether and THF were distilled from

sodium and benzophenone. Dimethyl perfluoroadipate was obtained from Synquest Laboratories, Inc. Other reagents were obtained primarily from Acros Organics and were used without further purification unless otherwise noted. Elemental analysis was performed at Atlantic Microlab Inc., Norcross GA, U.S.A.

cis- and *trans*-2*H*,7*H*-Perfluorooxepane-2,7-diol (**3**)

Dimethyl perfluoroadipate (10.06 g, 0.0316 mol) was added to dry tetrahydrofuran, (THF, 90 ml) in a 500 ml three-neck, round-bottom flask fitted with a thermometer, gas adapter, mechanical stirrer, and a dropping funnel. The reaction was run under nitrogen atmosphere *via* a Firestone valve. The mixture was cooled to –70 °C in a dry ice/isopropyl alcohol bath, and the dropping funnel was charged with Vitride (13.6 ml, 70% solution in toluene, 3.5 mol l^{-1}) in 10 ml of THF. The reducing agent was added slowly to the flask with vigorous stirring and with care to keep the temperature of the reaction at –70 °C. That temperature was maintained for 2.5 h after the addition.

Sulfuric acid (100 ml, 20% v/v), chilled to <5 °C, was added to the reaction mixture dropwise, with the temperature kept at or below –50 °C. The reaction mixture was maintained at this low temperature until all excess Vitride was decomposed, then allowed to warm to room temperature. Diethyl ether (100 ml) was added with stirring to the reaction mixture, forming a two-phase system. The layers were separated and the aqueous layer was extracted with 2–3 aliquots of ether (15–20 ml each). The combined ether extracts were washed to neutrality with brine and dried over sodium sulfate overnight. Solvents were evaporated on a rotary evaporator and the residue was further dried using a vacuum pump. The product was a pale yellow oil consisting of *cis*- and *trans*-2*H*,7*H*-perfluorooxepane-2,7-diol **3** (11.67 g, theor. 9.17 g; tenaciously bound THF was present). The yield was essentially quantitative, as revealed by conversion of the mixture to diol **6** in 95% yield based on starting diester (see below). ^{19}F NMR (CD_3CN): *cis* isomer, –116.5 (d, $^2J_{FF}$ = 265, 2 F), –127.6 (s, 4 F), –135.1 (d, $^2J_{FF}$ = 265, 2 F); *trans* isomer, –119.6 (d, $^2J_{FF}$ = 277, 2 F), –124.3, –129.7 (ABq, $^2J_{FF}$ = 289, 4 F), –132.9 (d, $^2J_{FF}$ = 277, 2 F). ^{1}H NMR (CD_3CN): *cis* isomer, 5.32 (dd, $^3J_{HF}$ = 12.6, 3.4, 2 H); *trans* isomer, 5.51 (dd, $^3J_{HF}$ = 12.0, 4.3, 2 H); both isomers, 5.9 (very broad, OH).

In another run with 30 g (94 mmol) of the diester, the product was 1*H*,6*H*-perfluorohexane-1,1,6,6,-tetrol (**2**), obtained as a very viscous oil. Crystallization from hexane and ether gave a white solid (20 g, 72%), m.p. 91–92 °C. ^{19}F NMR (CD_3CN): –122.2 (s, 4 F), –127.8 (s, 4 F). ^{1}H NMR (CD_3CN): 4.9 (d, $^3J_{HH}$ = 7.5, 4 H), 5.24 (m, 2 H).

Tetrol **2** (5 g) was dissolved in dry benzene (50 ml), and the solvent was removed by rotary evaporator. This was repeated until ^{19}F NMR revealed that the dehydration was complete, and remaining benzene was removed under reduced pressure. The ^{19}F NMR spectrum of the residual oil was identical with that of the *cis*- and *trans*-2*H*,7*H*-perfluorooxepane-2,7-diol **3** obtained above directly by ester reduction.

cis-2,7-Bis(*tert*-butyldiphenylsiloxy)-2*H*,7*H*-perfluorooxepane (**4**)[7]

To a stirred solution of diol **3** (1.2 g, 4.3 mmol) in acetonitrile (15 ml) DBU (2.17 g, 14.3 mmol) was added dropwise at 0 °C under N_2. *tert*-Butyldiphenylsilyl chloride (3.9 g, 14 mmol) was added slowly to this mixture, and the color became dark green. The mixture was stirred at this temperature for another 4 h. Solvent was removed under reduced pressure to give a viscous oil. Purification by column chromatography yielded a white solid (1.0 g,

31%), m.p. 133–134 °C. ^{1}H NMR ($CDCl_3$): 0.97 (s, 18 H), 4.60 (m, 2 H), 7.18–7.52 (m, 20 H). ^{19}F NMR ($CDCl_3$): –117.45, –130.10 (ABq, $^2J_{FF}$ = 285, 4 F), –128.15, –130.29 (ABq, $^2J_{FF}$ = 308, 4 F). For $C_{38}H_{40}F_8O_3Si_2$ (752.9) calculated: 60.62% C, 5.36% H, 20.19% F; found: 60.60% C, 5.31% H, 19.93% F.

trans-2,7-Bis(*tert*-butyldiphenylsiloxy)-2*H*,7*H*-perfluorooxepane (**5**)[7]

To a stirred solution of diol **3** (4.8 g, 17 mmol) in acetonitrile (60 ml) was added *tert*-butyldiphenylsilyl chloride (14.4 g, 52.4 mmol) at 0 °C under N_2. DBU (8.14 g, 53.6 mmol) was added to the mixture slowly, and the reaction mixture was stirred at this temperature for another 3 h. The crude product obtained upon evaporation of the solvent under reduced pressure was purified by column chromatography, giving a mixture of *trans* and *cis* isomers (5.2 g, 41%). HPLC revealed that the dominant product (87.5%) was the *trans* isomer. ^{1}H NMR ($CDCl_3$): 0.93 (s, 18 H), 5.50 (m, 2 H), 7.31–7.66 (m, 20 H). ^{19}F NMR ($CDCl_3$): –123.46, –138.95 (ABq, $^2J_{FF}$ = 298, 4 F), –130.15, –133.44 (ABq, $^2J_{FF}$ = 314, 4 F).

X-Ray Crystal Structure of **4**

A colorless, block crystal (monoclinic, approximate dimensions 0.40 × 0.18 × 0.10 mm) of oxepane **4** ($C_{38}H_{40}F_8O_3Si_2$, M.w. 752.88) was placed onto the tip of a 0.1 mm diameter glass capillary and mounted on a Siemens CCD area detector diffractometer for a data collection at 173(2) K. A preliminary set of cell constants was calculated from reflections harvested from three sets of 20 frames. These initial sets of frames were oriented such that orthogonal wedges of reciprocal space were surveyed. This produced initial orientation matrices determined from 96 reflections. The data collection was carried out using MoKα radiation (graphite monochromator) with a frame time of 30 s and a detector distance of 4.9 cm. A randomly oriented region of reciprocal space was surveyed to the extent of 1.5 hemisphere and to a resolution of 0.77 Å. Three major sections of frames were collected with 0.30° steps in ω at three different ϕ settings and a detector position of –28° in 2θ. The intensity data were corrected for absorption and decay (SADABS)[8]. Final cell constants were calculated from the *xyz* centroids of 3 248 strong reflections from the actual data collection after integration (SAINT 6.01, 1999)[9]. Unit cell dimensions were as follows: a = 12.9701(13) Å, b = 17.800(2) Å, c = 17.570(2) Å; α = 90°, β = 110.443(2)°, γ = 90°, Z = 4.

The structure was solved using SIR92 [10] and refined using SHELXL97 [11]. The space group $P2_1/n$ was determined based on systematic absences and intensity statistics. A direct-methods solution was calculated which provided most non-hydrogen atoms from the E-map. Full-matrix least squares/difference Fourier cycles were performed which located the remaining non-hydrogen atoms. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in ideal positions and refined as riding atoms with relative isotropic displacement parameters. The final full matrix least squares refinement converged to R_1 = 0.0537 and wR_2 = 0.1102 (F^2, all data). The program PLATON [12] was used for checking the structure.

1*H*,6*H*-1,6-Diethoxyperfluorohexane-1,6-diol (**6**)

The mixture of *cis* and *trans* diol (**3**) obtained above (11.6 g) was combined with 15% concentrated HCl/ethanol (50 ml) in a 200 ml round bottomed flask. The flask was fitted with water condenser and the mixture was refluxed for 1 h. After it had cooled, an equal amount

of benzene was added to the solution and the solvents were evaporated. The product, a yellow solid, was washed with benzene on a Büchner funnel until white. M.p. 109 °C (ref.[1] 110–111 °C); yield 95% (based on starting diester). ^{19}F NMR (CD_3CN): –122.0 (s, 4 F), –123.7, –129.2 (ABq, $^2J_{FF}$ = 277, 4 F). ^{1}H NMR (CD_3CN): 1.19 (t, $^3J_{HH}$ = 7.1, 6 H), 3.5–3.8 (m, 4 H), 5.03 (m, 2 H) [ref.[1] in DMSO-d_6: 1.10 (t, 6 H), 3.24–3.90 (m, 4 H), 4.94 (t, 2 H)].

1*H*,6*H*-Perfluorohexane-1,1,6,6-tetrol (**2**) from Dihemiacetal **6**

Dihemiacetal **6** (10.48 g, 0.030 mol) was stirred in water (100 ml) for several hours until all had dissolved. The water was evaporated on a rotary evaporator and the white solid product was further dried on a Büchner funnel. M.p. 91–92 °C, yield 77%. ^{19}F NMR (CD_3CN): –122.2 (s, 4 F), –127.8 (s, 4 F). ^{1}H NMR (CD_3CN): 4.9 (d, $^3J_{HH}$ = 7.5, 4 H), 5.24 (m, 2 H).

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Supporting Information Available: Tables of X-ray crystallographic data for **4**; X-ray crystallographic data (CIF).

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