Synthesis and crystallographic analysis of meso-2,3-difluoro-1,4-butanediol and meso-1,4-dibenzyloxy-2,3-difluorobutane

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Abstract

A large-scale synthesis of meso-2,3-difluoro-1,4-butanediol in 5 steps from (Z)-but-2-enediol is described. Crystallographic analysis of the diol and the corresponding benzyl ether reveals an anti conformation of the vicinal difluoride moiety. Monosilylation of the diol is high-yielding but all attempts to achieve chain extension through addition of alkyl Grignard and acetylide nucleophiles failed.

Introduction

Selective fluorination of bioactive compounds is a widely employed strategy for the modification of their properties [1]. Fluorine atoms can be introduced to modulate the pKₐ of adjacent acidic and basic functional groups as well as the lipophilicity, chemical and metabolic stability of the compound. Recent exciting reports describe weak but stabilising interactions between a C–F moiety and protein residues, which is certain to have implications in drug design [2,3]. Further important applications include molecular imaging using ¹⁸F [4], and modification of high-performance materials [5].

In recent years, the vicinal difluoride motif has received increasing attention due to the conformational properties instilled by the 'gauche effect' [6], which results in the vicinal difluoro gauche conformation being more stable than the corresponding anti conformation [7-9]. O’Hagan has demonstrated that vicinal difluoride substitution along a hydrocarbon chain of a fatty acid leads to conformational rigidity or disorder depending on the relative stereochemistry of the fluorine atoms, which originates from the enforcing or opposing fluorine gauche and hydrocarbon anti low-energy conformations [10]. As an extension, multi-vicinal tri- to hexafluorinated chains have been synthesised [11-16], which revealed yet another effect on the conformational behaviour, i.e. that conformations containing parallel 1,3-C–F bonds are destabilised. As an application, liquid crystals have been prepared containing a vicinal difluoride motif [14,17,18].

Efficient stereodefined synthesis of vicinal difluoride moieties is not straightforward. Direct methods include fluorination of...
alkenes with F₂ [19], XeF₂ [20], or hypervalent iodine species [21]. Such approaches often display poor stereoselectivity or result in rearrangement products. Treatment of 1,2-diols with SF₄ [22,23], DAST [24], or deoxofluor [25] also leads to vicinal difluorides. Reaction with vicinal triflates has also been successful in some cases [7,26]. A common two-step method involves opening of an epoxide to give the corresponding fluorohydrin [27], followed by the conversion of the alcohol moiety to the fluoride [28]. Another two-step method is halofluorination of alkenes and subsequent halide substitution with silver fluoride [9,29,30].

The introduction of multiple fluorine atoms is often a cumbersome process, and in many cases a fluorinated building block approach [31,32] is more efficient. Known vicinal difluoride containing building blocks include (racemic) C₂-symmetric and meso-2,3-difluorosuccinic acids (or esters) 1,2 (Figure 1) [9,22,23,33,34].

![Figure 1: Vicinal difluoride containing building blocks.](image)

Herein we describe the first synthesis of meso-2,3-difluoro-1,4-butanediol 3 as a further simple vicinal difluoride building block as well as its successful monosilylation, and our attempts to employ 3 for the synthesis of fluorinated hydrocarbons.

### Results and Discussion

#### Synthesis

The synthesis of 3 was achieved from meso-epoxide 4, which was obtained from (Z)-2-butene-1,4-diol in excellent yield according to the published two-step sequence [35]. The optimisation of the reaction of 4 with fluoride sources is shown in Table 1.

Reaction with Olah’s reagent [29] proceeded in excellent yield (Table 1, entry 1), however, the product was isolated as a mixture of isomers, which were not further characterised. Reaction with potassium hydrogen difluoride in ethylene glycol [36,37] gave the fluorohydrin in only modest yield (entry 2). Interestingly, the product arising from epoxide ring opening by ethylene glycol, 6, was isolated in 50% yield. The addition of molecular sieves (entry 3) led to complete conversion to 6 (TLC analysis). No reaction took place when DMSO (entry 4) or DMF/18-crown-6 were used as solvents [38,39] (entry 5). With Bu₄NH₂F₃ as the fluoride source [40,41], 11% of the desired product (together with some elimination byproducts) was obtained when xylene was used as solvent (entry 6). However, reaction with a mixture of Bu₄NH₂F₃ and KHF₂ in the absence of solvent [42-44] led to an excellent 91% yield of the desired product 5 albeit after a relatively long reaction time (entry 8).

The subsequent conversion to 3 is shown in Scheme 1. Treatment of 5 with DAST in DCM at reflux temperature only gave 7 in 29% yield (not shown). A slight improvement (40% yield) was obtained when the reaction was conducted in hexane or toluene, but a procedure in which DAST was added to a solution of 5 in toluene at room temperature, followed by the add-

| Entry | Reaction conditions | 5<sup>a</sup> | 6<sup>a</sup> | 4<sup>a</sup> |
|-------|---------------------|---------------|---------------|---------------|
| 1     | HF•py (70% HF), r.t., 3 h | 80<sup>b</sup> | –             | –             |
| 2     | KHF₂, ethylene glycol, 150 °C, 3 h | 34 | 50           | –             |
| 3     | KHF₂, ethylene glycol, mol. Sieves, 150 °C, 3 h | – | –             | –             |
| 4     | KHF₂, DMSO, 150 °C, 16 h | –           | –             | –             |
| 5     | KHF₂, DMF, 18-crown-6, reflux, 16 h | –           | –             | –             |
| 6     | Bu₄NH₂F₃ (1 equiv), xylene, reflux, 3 d | 11 | 57           | –             |
| 7     | Bu₄NH₂F₃ (1 equiv), KHF₂ (1 equiv), 130 °C, 16 h | 71 | –             | –             |
| 8     | Bu₄NH₂F₃ (1 equiv), KHF₂ (1 equiv), 115 °C, 2.5 d | 91 | –             | –             |

<sup>a</sup> Isolated yield.

<sup>b</sup> Mixture of isomers.

<sup>c</sup> Complete conversion to 6 (TLC analysis).

<sup>d</sup> No reaction observed.
Scheme 1: Synthesis of meso-2,3-difluoro-1,4-butanediol.

Scheme 2: Monoprotection of 3, and activation of the remaining alcohol.

Scheme 3: Reaction of 12 leading to defluorinated products.

Crystallographic analysis

Compounds 7 and 3 yielded colourless crystals suitable for study by single crystal X-ray diffraction [48]. The dibenzyl ether 7 crystallises in the monoclinic $P2_1/c$ space group with half a molecule of 7 in the asymmetric unit. The molecule possesses crystallographic inversion symmetry. Two conformers are present in the crystal (55:45) which differ only in the sign of the torsion angle of the rings (Figure 2). The disparity in the amounts of each conformer present gives rise to the disorder observed in the crystal structure.
The vicinal difluoro group adopts an anti conformation with the F–C–C–F dihedral angle exactly 180°, which manifests itself in the crystallographic inversion centre. Nevertheless, each benzyloxy group does adopt a gauche conformation with its adjacent fluoro substituent where the F–C–C–O dihedral angle is 71.5°. Although strong H-bonding interactions are absent within the crystal, each molecule displays eight short contacts less than the sum of the van der Waals radii to its four nearest neighbours; three C–F···H–C contacts (2.554 Å, 2.581 Å and 2.637 Å) for each fluorine, and a pair of C–H···π contacts (2.662 Å to centroid of ring). The hydrogen atoms involved in the C–F contacts are an aromatic proton, the CHF and a CHHOBn proton (Figure 3).

The diol 3 crystallises in the tetragonal space group I41/a with half a molecule of 3 in the asymmetric unit. This molecule also displays crystallographic inversion symmetry. In common with 7, the vicinal difluoro group of 3 adopts an anti conformation with a symmetry-constrained dihedral angle of 180°, and the hydroxyl groups adopt gauche conformations with the adjacent fluoro atoms with F–C–C–O dihedral angles of 66.8° (Figure 4).

There is strong hydrogen bonding between the hydroxyl groups of the molecule with each hydroxyl group acting both as donor and acceptor (O–H···O: 2.685 Å, 170.1°). The hydrogen bonded molecules are arranged helically about the crystallographic 41 screw axes. Thus the crystal structure comprises of alternating left and right handed hydrogen bonded helical constructs with each molecule part of two adjacent helices (Figure 5).

Conclusion
The synthesis of meso-2,3-difluoro-1,4-butandiol 3 was achieved in 5 steps from (Z)-1,4-butenedio1 in 40% overall yield on a multigram scale. A high-yielding (94%) monosilylation
was also achieved, but all attempts for chain extension met with failure. Crystallographic analysis revealed that the vicinal fluorine atoms in 3 and its dibenzyl ether 7 are in the anti conformation.

**Experimental**

$^1$H and $^{13}$C NMR spectra were recorded at room temperature on a Bruker DPX400 or AV300 spectrometer as indicated. Low resolution ES mass and EIMS were recorded on a Waters ZMD and Thermoset TraceMS quadrupole spectrometers, respectively. Infrared spectra were recorded as neat films on a Nicolet Impact 380 ATR spectrometer. Melting points were recorded on a Gallenkamp Melting Point Apparatus and are uncorrected.

Column chromatography was performed on 230–400 mesh Matrex silica gel. Preparative HPLC was carried out using a Biorad Biosil D 90-10, 250 × 22 mm column eluting at 20 mL min$^{-1}$, connected to a Kontron 475 refractive index detector. Reaction solvents were dried before use as follows: THF and Et$_2$O were distilled from sodium/benzophenone; CH$_2$Cl$_2$ and Et$_2$N were distilled from CaH$_2$; toluene was distilled from Et$_3$N, connected to a Kontron 475 refractive index detector. The structures were determined in SHELXS-97 and refined using SHELXL-97 [53]. All non-hydrogen atoms were refined anisotropically with hydrogen atoms inserted in SHELXS-97 and refined using SHELXL-97 [53]. All absorption by using SADABS [52]. The structures were determined in SHELXS-97 and refined using SHELXL-97 [53]. All non-hydrogen atoms were refined anisotropically with hydrogen atoms included in idealised positions with thermal parameters riding on those of the parent atom.

**syn-1,4-Bis(benzyloxy)-3-fluorobutan-2-ol (5)**

KHF$_2$ (9.57g, 123 mmol) was added to a mixture of epoxide 4 (17.4 g, 61.3 mmol) and Bu$_4$NH$_2$F$_3$ (10.6 g, 35.2 mmol) and the mixture stirred at 115 °C for 2.5 days. Et$_2$O (300 mL) was added and the solution poured into sat. NaHCO$_3$ (200 mL). The organic layer was washed successively with sat. NaHCO$_3$ (100 mL) and brine (200 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether 10% to 20%) to afford fluorohydrin 5 as a colourless oil (17.0 g, 91%). IR $\nu_{max}$ (cm$^{-1}$) 3062 w, 3030 w, 2993 w, 2858 w, 1496 w, 1453 m, 1369 w, 1088 s; $^1$H NMR (400 MHz, CDCl$_3$) 7.42–7.20 (10H, m, ArH), 4.74 (1H, ddt, $J = 47.5, 5.5, 3.5$ Hz, CHF), 4.60 (1H, d, $J = 12.0$ Hz, CH$_2$H$_3$Ph), 4.58 (1H, d, $J = 12.0$ Hz, CH$_2$H$_3$Ph), 5.45 (1H, d, $J = 12.0$ Hz, CH$_2$H$_3$Ph), 4.54 (1H, d, $J = 12.0$ Hz, CH$_2$H$_3$Ph), 4.04 (1H, dm, $J = 22.0$ Hz, CH$_2$OH), 3.80 (1H, ddd, $J = 23.0, 11.0, 4.0$ Hz, CH$_2$H$_3$OBn), 3.76 (1H, ddd, $J = 24.0, 11.0, 5.0$ Hz, CH$_2$H$_2$OBn), 3.63 (1H, ddd, $J = 10.0, 5.0, 1.0$ Hz, CH$_2$H$_2$OBn), 2.61 (1H, bd, $J = 4.0$ Hz, OH) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 137.9 (CH$_2$Ar), 137.7 (CH$_2$Ar), 128.6 (CH$_2$Ar), 128.0 (CH$_2$Ar), 127.9 (CH$_2$Ar), 91.8 (d, $J = 175.0$ Hz, CHF), 73.9 (CH$_2$Ph), 73.7 (CH$_2$Ph), 70.37 (d, $J = 5.5$ Hz, CH$_2$OBn), 73.34 (d, $J = 20.0$ Hz, COH), 69.8 (d, $J = 23.0$ Hz, CH$_2$OBn) ppm; $^{19}$F NMR (282 MHz, CDCl$_3$) −204.3 (1F, dq, $J = 46.7, 23.4$) ppm; ES$^+$ m/z (%) 715 ((2M+Na)$^+$ 261) for C$_{18}$H$_{20}$F$_5$O$_2$Na$^+=(M+Na)$^+$; Caled 715.1367; Measured 715.1364.

**Data for syn-3-(2-hydroxyethyl)-1,4-bis(benzyloxy)butan-2-ol (6)**

![Image of compound 6](image)

Colourless oil. IR $\nu_{max}$ (cm$^{-1}$) 3399 br, 3062 w, 3030 w, 2863 w, 1496 w, 1483 m, 1377 m, 1285 m, 1254 m, 1091 s; $^1$H NMR (400 MHz, CDCl$_3$) 7.40–7.27 (10H, m), 7.36–7.30 (7H, m), 3.78–3.60 (7H, m), 3.58 (1H, ddd, $J = 10.0, 5.0, 3.5$ Hz, CHF), 3.51 (1H, ddd, $J = 9.5, 6.0$ Hz), 3.25–2.30 (2H, br, OH) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 137.9 (CH$_2$Ar), 137.7 (CH$_2$Ar), 128.6 (CH$_2$Ar), 128.0 (CH$_2$Ar), 127.9 (CH$_2$Ar), 91.8 (d, $J = 175.0$ Hz, CHF), 73.9 (CH$_2$Ph), 73.7 (CH$_2$Ph), 70.37 (d, $J = 5.5$ Hz, CH$_2$OBn), 73.34 (d, $J = 20.0$ Hz, COH), 69.8 (d, $J = 23.0$ Hz, CH$_2$OBn) ppm; $^{19}$F NMR (282 MHz, CDCl$_3$) −204.3 (1F, dq, $J = 46.7, 23.4$) ppm; ES$^+$ m/z (%) 327 ((M+Na)$^+$, 100); HRMS (ES$^+$) for C$_{19}$H$_{22}$O$_3$Na$^+$ (M+Na)$^+$: Caled 327.1367; Measured 327.1364.

**meso-1,4-Bis(benzyloxy)-2,3-difluorobutane (7)**

DAST (9.6 mL, 72.7 mmol) was added to a solution of fluorohydrin 5 (17.0 g, 55.9 mmol) in toluene (75 mL) and the mixture stirred at r.t. for 5 min. Pyridine (11.9 mL, 145 mmol) was then added and the solution stirred at 70 °C for a further 16 h. The reaction mixture was cooled, poured into sat. NaHCO$_3$ (100 mL) and Et$_2$O (100 mL). The organic layer was washed...
successively with sat. NaHCO$_3$ (100 mL) and brine (100 mL), dried over MgSO$_4$, filtered and concentrated in vacuo. The crude product was quickly purified by column chromatography (EtOAc/petroleum ether 0% to 5%) to afford a mixture which was recrystallised from hot petroleum ether. The filtrate was concentrated and recrystallised again from hot petroleum ether. The recrystallisation process was carried out for a third time to afford difluoride 7 as a white crystalline solid (overall yield 10.1 g, 59%). mp 56–57 °C; IR v$_{max}$ (cm$^{-1}$) 3354 br, 2954 m, 2930 m, 2858 m, 1254 s, 1055 s; $^1$H NMR (400 MHz, CDCl$_3$) 4.84–4.58 (2H, m, CHF × 2), 4.03–3.76 (4H, m, CH$_2$O × 2), 2.47 (1H, br, OH), 0.91 (9H, s, Si(CH$_3$)$_3$), 0.09 (6H, s, SiCH$_3$ × 2) ppm; $^1$H$^{19}$F NMR (400 MHz, CDCl$_3$) 4.77 (1H, dd, J = 6.0, 5.0, 3.0 Hz, CHF), 4.69 (1H, dt, J = 6.1, 3.5 Hz, CHF) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 190.8 (dd, J = 170.5, 21.0 Hz, CHF), 90.5 (dd, J = 178.5, 30.5 Hz, CHF), 64.4 (dd, J = 21.5, 5.0 Hz, CH$_2$O), 61.1 (dd, J = 21.5, 5.0 Hz, CH$_2$O), 25.9 (Si(CH$_3$)$_3$), 18.4 (SiC), −5.38 (CH$_3$), −54.3 (CH$_3$) ppm; $^{19}$F NMR (376.5 MHz, CDCl$_3$) −200.16 (d, J = 13.0 Hz), −201.9 (d, J = 13.0 Hz) ppm; ES$^+$ m/z (%) 263 (M+Na)$^+$, 100%; HRMS (ES$^+$) for C$_{10}$H$_{22}$F$_2$O$_2$Na (M+Na)$^+$: Calcd 262.1324; Measured 262.1326.

**anti-4-tert-Butyldimethylsilyloxy-2,3-difluorobutyl methanesulfonate (11)**

MsCl (3.39 mL, 43.8 mmol) was added to a mixture of alcohol 8 (7.0 g, 29.2 mmol) and Et$_3$N (6.6 mL, 46.7 mmol) in DCM (64 mL) and the mixture stirred at r.t. for 2 h. The reaction mixture was cooled to 0 °C, filtered, washed with cold Et$_2$O/petroleum ether 1:1 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford mesylate 11 as a colourless oil (9.29 g, 99%). [TLC monitoring should be performed using DCM/petroleum ether 6:4 until the complete consumption of the starting material, which has the same R$_f$ value as the product when eluted with EtOAc/petroleum ether.] IR v$_{max}$ (cm$^{-1}$) 2955 m, 2931 m, 2858 m, 1473 w, 1360 s, 1256 s, 836 vs; $^1$H NMR (400 MHz, CDCl$_3$) 4.98 (1H, dd, J = 46.9, 10.1, 6.6, 2.0 Hz, CH$_2$OSi), 4.68 (1H, ddd, J = 46.0, 9.6, 6.6, 3.3 Hz, CH$_2$OSi), 4.62 (1H, dt, J = 26.8, 12.1, 2.0 Hz, CH$_2$OSi), 4.49 (1H, ddd, J = 25.3, 12.1, 6.1, 2.0 Hz, CH$_2$OSi), 3.98 (1H, ddd, J = 18.5, 12.5, 3.5, 2.5 Hz, CH$_2$OSi), 3.87 (1H, ddd, J = 30.5, 12.5, 3.5, 2.5 Hz, CH$_2$OSi), 3.06 (3H, s, SCH$_3$), 0.91 (9H, s, Si(CH$_3$)$_3$), 0.09 (6H, s, SiCH$_3$ × 2) ppm; $^{1}$H$^{19}$F NMR (400 MHz, CDCl$_3$) 4.98 (1H, td, J = 6.1, 2.0 Hz, CH$_2$OSi), 4.68 (1H, dt, J = 6.6, 3.0 Hz, CH$_2$OSi) ppm;

**anti-4-tert-Butyldimethylsilyloxy-2,3-difluorobutyl methanesulfonate (11)**

MsCl (3.39 mL, 43.8 mmol) was added to a mixture of alcohol 8 (7.0 g, 29.2 mmol) and Et$_3$N (6.6 mL, 46.7 mmol) in DCM (64 mL) and the mixture stirred at r.t. for 2 h. The reaction mixture was cooled to 0 °C, filtered, washed with cold Et$_2$O/petroleum ether 1:1 and concentrated in vacuo. The crude product was purified by column chromatography (EtOAc/petroleum ether 15:85) to afford mesylate 11 as a colourless oil (9.29 g, 99%). [TLC monitoring should be performed using DCM/petroleum ether 6:4 until the complete consumption of the starting material, which has the same R$_f$ value as the product when eluted with EtOAc/petroleum ether.] IR v$_{max}$ (cm$^{-1}$) 2955 m, 2931 m, 2858 m, 1473 w, 1360 s, 1256 s, 836 vs; $^1$H NMR (400 MHz, CDCl$_3$) 4.98 (1H, dd, J = 46.9, 10.1, 6.6, 2.0 Hz, CH$_2$OSi), 4.68 (1H, ddd, J = 46.0, 9.6, 6.6, 3.3 Hz, CH$_2$OSi), 4.62 (1H, dt, J = 26.8, 12.1, 2.0 Hz, CH$_2$OSi), 4.49 (1H, ddd, J = 25.3, 12.1, 6.1, 2.0 Hz, CH$_2$OSi), 3.98 (1H, ddd, J = 18.5, 12.5, 3.5, 2.5 Hz, CH$_2$OSi), 3.87 (1H, ddd, J = 30.5, 12.5, 3.5, 2.5 Hz, CH$_2$OSi), 3.06 (3H, s, SCH$_3$), 0.91 (9H, s, Si(CH$_3$)$_3$), 0.09 (6H, s, SiCH$_3$ × 2) ppm; $^{1}$H$^{19}$F NMR (400 MHz, CDCl$_3$) 4.98 (1H, td, J = 6.1, 2.0 Hz, CH$_2$OSi), 4.68 (1H, dt, J = 6.6, 3.0 Hz, CH$_2$OSi) ppm;
was added to a mixture of CuBr (137 mg, 0.955 mmol) in THF (1.2 mL). The mixture was then transferred to a solution of bromide 12 (140 mg, 0.462 mmol) in THF (1.2 mL) at 0 °C, warmed to r.t. and stirred for 3 h. The reaction mixture was quenched with H2O (10 mL) and extracted with Et2O (10 mL × 3). The combined organic layers were dried over MgSO4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (DCM/petroleum ether 0% to 20%) to afford alkene 13 [54] as a mixture of isomers (1:11) as a yellow oil (24.1 mg, ~15%) and alkene 14 as a yellow oil (26.2 mg, ~20%) along with 72.0 mg (51%) of the starting bromide 12.

Alkene 13: IR νmax (cm⁻¹) 2955 w, 2924 s, 2858 w, 1472 m, 1463 w, 1378 w, 1256 m, 836 vs, 1293 w, 1236 m, 8762–8766. doi:10.1021/j100388a004

Alkene 14: Our spectra were in accord with literature copies of the spectra [55]: 1H NMR (400 MHz, CDCl3) 5.99–5.79 (2H, CH–CH), 4.21 (2H, ddd, J = 4.0, 2.5, 1.5 Hz, CH2), 3.98 (2H, ddd, J = 7.5, 2.0, 1.0 Hz, CH2), 0.92 (9H, s, Si(CH3)3), 0.08 (6H, s, Si(CH3)2 × 2) ppm; 13C NMR (100 MHz, CDCl3) 131.8 (CH–CH), 129.3 (CH–CH), 64.3 (CH2O), 32.4 (CH2), 32.0 (CH2), 29.8 (CH2), 29.7 (CH2), 29.5 (CH2), 29.4 (CH2), 26.2 (Si(CH3)2), 22.9 (CH2), 18.6 (SiC), 14.3 (CH3), −4.9 (SiCH3 × 2) ppm; EI m/z (%) 255.3 ((M-Bu)+), 57; HRMS (ES⁺) for C13H13O2SiNa (M+Na)+: Calcd 335.2746; Measured 335.2741.

Acknowledgements

LL and JN thank CRUK for funding.

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