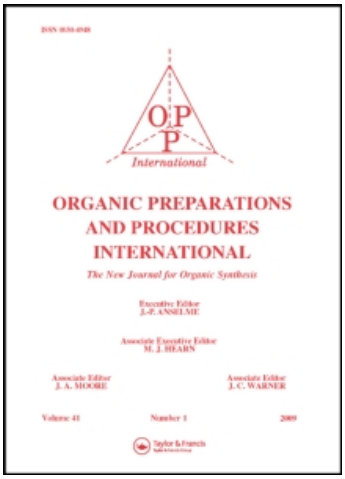

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SYNTHESIS OF THE FOUR STEREOISOMERS OF 1,1,1-TRIFLUOROBUTANE-2,3-DIOL

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SYNTHESIS OF THE FOUR STEREOISOMERS OF 1,1,1-TRIFLUOROBUTANE-2,3-DIOL

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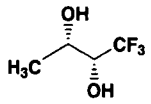
In connection with our studies on the mechanism of adenosylcobalamin-dependent diol dehydratases,[1] we needed the four stereoisomers of 1,1,1-trifluorobutane-2,3-diol (**1-4**) as potential substrates or inhibitors of *meso*-2,3-butanediol-dehydratase.[2] To our knowledge no preparation of these compounds in pure form has been described in literature; only an unresolved mixture of them has been reported as a by-product of 1,1,1-trifluoro-2,3-epoxybutane ethanolysis.[3] We report here a facile synthesis of compounds **1-4** in high optical purity through the addition of a formal trifluoromethyl anion[4] to hydroxy-protected lactaldehyde.



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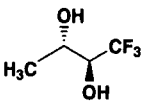

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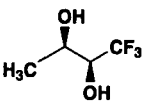

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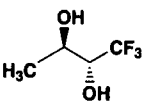
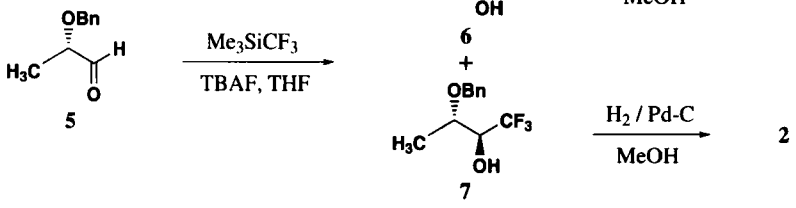


4

Enantiomerically pure (*S*)-2-(benzyloxy)propanal (**5**), prepared from commercially available ethyl (*S*)-lactate,[5] was treated with (trifluoromethyl)trimethylsilane in the presence of a catalytic amount of tetra-(*n*-butyl)ammonium fluoride to give a 1:1 mixture of 3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (**6** and **7**). These diastereomeric compounds were separated by silica gel chromatography to give **6** and **7** as optically pure enantiomers (*Scheme 1*).



Scheme 1

Hydrogenolysis of each of them with palladium on charcoal gave the desired 1,1,1-trifluorobutane-2,3-diols, designated **1** and **2** on the basis of their GC retention times. They showed similar ^{1}H NMR spectra, which appeared consistent with the diastereomeric relationship between them, but

were useless in determining their relative configuration. This was assigned through conversion of each diol into a five-membered cyclic derivative.

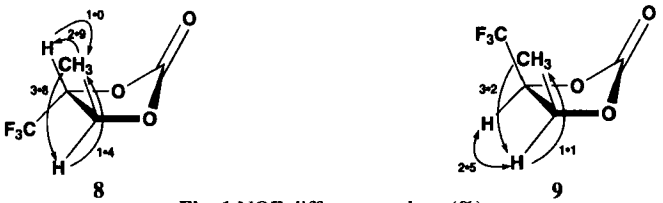


Fig. 1 NOE difference values (%)

Thus, the cyclic carbonates **8** and **9** were prepared by reaction of the two diols with trichloromethyl chloroformate in the presence of pyridine. Carbonate **8**, derived from diol **1**, showed signals at δ 4.47 and 4.83, assignable to the hydrogen atoms in position 2 and 3 (diol numbering), both appearing as a quintet (a quartet of doublets with J = 6.0 Hz). The carbonate **9**, derived from diol **2**, showed the corresponding resonances at δ 4.85 and 5.03 both as quintets with the same J = 6.0 Hz. A double resonance experiment carried out by irradiating the doublet due to the methyl group (at 1.59 δ in the spectrum of the carbonate from diol **1** and at 1.61 δ for the carbonate from diol **2**), allowed us to assign the resonance at lower field (4.83 for **8** and 5.03 for **9**) to the proton coupled to the methyl group. Due to the conformational flexibility of the five-membered ring and the same value of the coupling constants for H-H and H-F, the ^{1}H NMR spectra did not allow the unequivocal determination of the relative position of the adjacent hydrogen atoms. However, from NOE-difference experiments, the relative orientation of the two hydrogen atoms was established in both the carbonates (see *Figure 1*). By inference, taking into account that no reaction involved the stereocentre of the starting material ethyl (*S*)-lactate, we were able to assign the absolute stereochemistry (2*R*,3*S*)-1,1,1-trifluorobutane-2,3-diol to compound **1** and (2*S*, 3*S*)-1,1,1-trifluoro-butane-2,3-diol to compound **2**.

1,1,1-Trifluorobutane-2,3-diols **3** and **4** were obtained from ethyl (*R*)-lactate using the same reaction sequence. The e.e.'s of **1-4** were determined by ^{1}H NMR analysis of the corresponding 3-benzyloxy derivatives in the presence of Eu(hfc)$_3$ as chiral shift reagent. In repeated preparations, the optical purity of each enantiomer (**1-4**) was found to be in the range 93-97%, depending on the e.e. of the starting aldehyde.[5]

EXPERIMENTAL SECTION

Melting points were measured with a Büchi apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC 300 spectrometer in $CDCl_3$; chemical shifts are given in ppm (δ) with respect to the solvent signal as internal standard (δ_H 7.26, δ_C 77.00); for enantiomeric purity measurements the molar ratio of Eu(hfc)$_3$ to the substrate was *ca.* 0.1; ^{19}F NMR were recorded with 1% sample concentration using trifluoroacetic acid as external standard and $CFCl_3$ as reference. EIMS spectra were run on a VG 7070 EQ spectrometer operating at 70 eV. Optical rotations were measured on a Perkin Elmer 241 polarimeter. GC analyses were carried out on a Dani 3865 gas chromatograph using a home made glass column (2m x 2mm i.d.) packed with 20% Carbowax 20 M on Chromosorb

W (60-80 mesh); operating conditions : detector, FID, 220°; injector, 210°; oven, *conditions A*, isothermal analysis at 200°; *conditions B*, 4 min at 60°, then to 200° at 10°/min. Analytical TLC was performed on Merck Si gel 60 F_{254} aluminum sheet; Merck silica gel (40-63 μm) was used for flash chromatography. Ethyl (*R*)- and (*S*)-lactate and (trifluoromethyl)trimethylsilane were from Fluka.

(2*R*,3*S*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (6) and **(2*S*,3*S*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (7)**.- To a stirred solution of (*S*)-2-(benzyloxy)propanal (**5**)[5] (0.88 g, 5.36 mmol) and (trifluoromethyl)trimethylsilane (0.99 mL, 7.00 mmol) in dry THF (6 mL) cooled at 0° was added a catalytic amount of tetra-(*n*-butyl)ammonium fluoride (TBAF). After stirring at 0° for 15 min and at room temperature for 45 min, the reaction mixture was diluted with 1M HCl (7 mL) and stirred at r.t. overnight. Diethyl ether (10 mL) was then added, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 x 10 mL); the combined organic layers were washed with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave a 1:1 mixture of compounds **6** and **7**, which were separated by flash column chromatography (silica gel, diethyl ether/light petroleum 1:4): (2*R*,3*S*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (**6**), pale yellow oil (370 mg, 29% yield); (2*S*,3*S*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (**7**), pale yellow oil (410 mg, 33% yield); unseparated fraction (210 mg, 21% yield).

Compound 6: GC (*conditions A*): R_t 7.1 min; $[\alpha]_D$: +22.9° (*c* 5.4, $CHCl_3$); ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.32 (d, 3H, J = 6.4 Hz, C*H*$_3$), 3.07 (d, 1H, J = 8.7 Hz, O*H*), 3.73 (qdd, 1H, $J_a = J_b$ = 8.7 Hz, J_c = 2.8 Hz, C*H*CF_3), 3.88 (qd, 1H, J_a = 6.4 Hz, J_b = 2.8 Hz, C*H*CH_3), 4.52 (d, 1H, J = 11.4 Hz, C*H*$_2$Ph), 4.65 (d, 1H, J = 11.4 Hz, C*H*$_2$Ph), 7.37 (m, 5H, aromatic); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 16.89 (*C*H$_3$), 71.37 (*C*HCH_3), 71.51 (*C*H$_2$O), 73.27 (q, $^2J_{CF}$ = 30.0 Hz, *C*HCF_3), 124.52 (q, $^1J_{CF}$ = 281.6 Hz, *C*F$_3$), 128.26, 128.39, 128.82 and 137.93 (aromatic); ^{19}F NMR (188.14 MHz, $CDCl_3$): δ - 79.66 (d, $^3J_{FH}$ = 7.3 Hz, CF_3); EIMS *m/z* (%) 234 (M^+, 5), 135 (74), 107 (18), 91 (100).

Anal. Calcd for $C_{11}H_{13}F_3O_2$: C, 56.41; H, 5.59. Found : C, 56.23; H, 5.65

Compound 7: GC (*conditions A*): R_t 12.6 min; $[\alpha]_D$: +19.5° (*c* 5.3, $CHCl_3$); ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.33 (d, 3H, J = 6.4 Hz, C*H*$_3$), 2.55 (d, 1H, J = 4.9 Hz, O*H*), 3.82 (m, 1H, C*H*CF_3), 4.12 (m, 1H, C*H*CH_3), 4.52 (d, 1H, J = 11.6 Hz, C*H*$_2$Ph), 4.67 (d, 1H, J = 11.6 Hz, C*H*$_2$Ph), 7.38 (m, 5H, aromatic); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 14.57 (*C*H$_3$), 71.59 (*C*H$_2$O), 72.33 (q, $^2J_{CF}$ = 29.3 Hz, *C*HCF_3), 73.58 (*C*HCH_3), 124.73 (q, $^1J_{CF}$ = 281.6 Hz, CF_3), 127.95, 128.07, 128.52 and 137.31 (aromatic); ^{19}F NMR (188.14 MHz, $CDCl_3$): δ - 79.91 (d, $^3J_{FH}$ = 7.3 Hz, CF_3).

Anal. Calcd for $C_{11}H_{13}F_3O_2$: C, 56.41; H, 5.59. Found : C, 56.54; H, 5.71

By the same procedure, starting from (*R*)-2-(benzyloxy)propanal, (2*S*,3*R*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol and (2*R*,3*R*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol were obtained in 29% and 43% yield, respectively, together with a 15% yield of an unseparated fraction.

(2*R*,3*S*)-1,1,1-trifluorobutane-2,3-diol (1). - To a suspension of 10% Pd/C (430 mg) in 30 mL of methanol, a solution of (2*R*,3*S*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol (**6**) (540 mg, 2.30 mmol) in 10 mL of methanol was added. The suspension was stirred at r.t. under hydrogen atmosphere until disappearance of the starting material (GC detection). The catalyst was filtered off and washed with

methanol. Cautious evaporation of the solvent under reduced pressure and at r.t. gave a white solid (267 mg, 80% yield): mp 97-99°; GC (*conditions B*): R_t 16.5 min; $[a]_D$: +6.3° (*c* 1.4, CH_3OH); ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.32 (d, 3H, *J* = 6.3 Hz, CH_3), 2.15 (br s, 1H, O*H*), 3.11 (br s, 1H, O*H*), 3.72 (m, 1H, C*H*), 4.18 (m, 1H, C*H*); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 19.68 (CH_3), 64.85 ($CHCH_3$), 73.20 (q, $^2J_{CF}$ = 30.1 Hz, $CHCF_3$), 124.50 (q, $^1J_{CF}$ = 281.0 Hz, CF_3); ^{19}F NMR (188.14, $CDCl_3$): δ - 79.83 (d, $^3J_{FH}$ = 7.3 Hz, CF_3);); EIMS *m/z* (%) 143 (M - H^+, 7), 129 (62), 124 (33), 99 (8), 81 (100), 80 (90).

Anal. Calcd for $C_4H_7F_3O_2$: C, 33.34; H, 4.90. Found : C, 33.11; H, 4.72

Using this general procedure, the following compounds were prepared:

(2*S*,3*S*)-1,1,1-trifluorobutane-2,3-diol (2), obtained from compound **7** in 96% yield: mp 76-77°; GC (*conditions B*): R_t 18.1 min; $[a]_D$: –3.1° (*c* 1.4, CH_3OH); ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.35 (d, 3H, *J* = 6.1 Hz, CH_3), 1.85 (br s, 1H, O*H*), 2.71 (br s, 1H, O*H*), 3.98 (m, 1H, C*H*), 4.10 (m, 1H, C*H*); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 17.51 (CH_3), 66.50 ($CHCH_3$), 73.22 (q, $^2J_{CF}$ = 30.0 Hz, $CHCF_3$), 128.07 (q, $^1J_{CF}$ = 280.6 Hz, CF_3); ^{19}F NMR (188.14, $CDCl_3$): δ - 77.89 (d, $^3J_{FH}$ = 7.1 Hz, CF_3).

Anal. Calcd for $C_4H_7F_3O_2$: C, 33.34; H, 4.90. Found : C, 33.29; H, 4.97

(2*S*,3*R*)-1,1,1-trifluorobutane-2,3-diol (3), obtained from (2*S*,3*R*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol 94% yield : $[\alpha]_D$: –6.2° (*c* 1.4, CH_3OH).

Anal. Calcd for $C_4H_7F_3O_2$: C, 33.34; H, 4.90. Found : C, 33.58; H, 4.65

(2*R*,3*R*)-1,1,1-trifluorobutane-2,3-diol (4) obtained from (2*R*,3*R*)-3-(benzyloxy)-1,1,1-trifluorobutan-2-ol in 97% yield : $[\alpha]_D$: +3.1° (*c* 1.3, CH_3OH).

Anal. Calcd for $C_4H_7F_3O_2$: C, 33.34; H, 4.90. Found : C, 33.30; H, 5.01

(4*S*, 5*R*)-4-methyl-5-trifluoromethyl-1,3-dioxolan-2-one (8).- To a solution of (2*R*,3*S*)-1,1,1-trifluorobutane-2,3-diol (**1**) (144 mg, 1 mmol) in freshly distilled pyridine (1 mL) cooled at 0° trichloromethyl chloroformate (0.13 mL, 1.1 mmol) was added over 15 min with stirring. The reaction mixture was stirred at 0° for 1 h, diluted with ethyl acetate, washed with a small amount of cold water, with saturated NaCl solution and dried (Na_2SO_4). Evaporation of the solvent at reduced pressure, followed by prolonged treatment *in vacuo* at r.t., gave a residue which was purified by flash chromatography (silica gel, ethyl acetate/light petroleum 2 : 8) to afford a yellow oil (104 mg, 61% yield) : GC (*conditions B*): R_t 14.2 min; ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.59 (d, 3H, *J* = 6.0 Hz, CH_3), 4.47 (qd, 1H, $J_a = J_b$ = 6.0 Hz, $CHCF_3$), 4.83 (qd, 1H, $J_a = J_b$ = 6.0 Hz, $CHCH_3$); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 17.55 (CH_3), 70.89 ($CHCH_3$), 75.41 (q, $^2J_{CF}$ = 35.5 Hz, $CHCF_3$), 119.81 (q, $^1J_{CF}$ = 282.6 Hz, CF_3), 149.91 (*C*O).

Anal. Calcd for $C_5H_5F_3O_3$: C, 35.31; H, 2.96. Found : C, 35.51; H, 2.78

The same procedure applied to (2*S*,3*S*)-1,1,1-trifluorobutane-2,3-diol (**2**) gave **(4*S*, 5*S*)-4-methyl-5-trifluoromethyl-1,3-dioxolan-2-one (9)** in 40% yield: GC (*conditions B*): R_t 8.6 min; ^1H NMR (300.13 MHz, $CDCl_3$): δ 1.61 (d, 3H, *J* = 6.8 Hz, CH_3), 4.85 (qd, 1H, $J_a = J_b$ = 6.8 Hz, $CHCF_3$), 5.03 (qd, 1H, $J_a = J_b$ = 6.0 Hz, $CHCH_3$); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 13.98 (CH_3), 70.89 ($CHCH_3$), 74.63 (q, $^2J_{CF}$ = 34.9 Hz, $CHCF_3$), 121.97 (q, $^1J_{CF}$ = 283.0 Hz, CF_3), 142.15 (*C*O).

Anal. Calcd for $C_5H_5F_3O_3$: C, 35.31; H, 2.96. Found : C, 35.59; H, 3.11

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