# The Total Regioselective Control of Tartaric Acid

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## I: GENERAL REMARKS

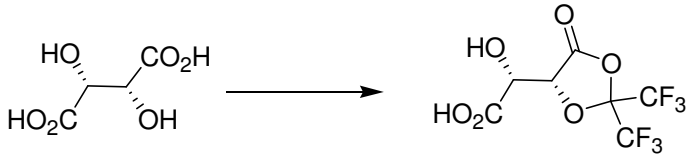
Abbreviations: AcCl, acetyl chloride; ACN, acetonitrile; AcOEt, ethyl acetate; AcOH, acetic acid; DCM, dichloromethane; DMA, *N,N*-dimethylacetamide; DMF, *N,N*-dimethylformamide; HOAc, acetic acid; TEBAC, triethylbenzylammonium chloride; TLC, thin layer chromatography.

All commercial reagents and solvents were used as received unless otherwise indicated. TLC was performed with TLC aluminium sheets coated with silica gel 60 $F_{254}$. Spots were observed with UV or after staining as indicated and heating [$KMnO_4$ staining solution: 6 g $KMnO_4$, 40 g $K_2CO_3$ and 5 mL NaOH in 600 mL water]. For column chromatography, Silice 35-70 μm was used.

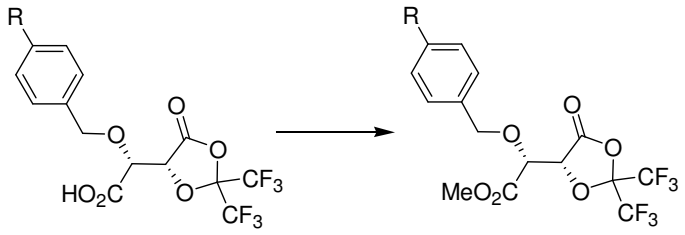
$^{1}$H-NMR spectra were acquired at 400.125 MHz, $^{13}$C at 100.625 MHz with TMS as internal reference, and $^{19}$F at 376.494 MHz. The following abbreviations are used to indicate multiplicity: s, singlet; d, doublet, dd, double doublet; t, triplet; dt, double triplet; m, multiplet, br s, broad signal. Chemical shifts (δ) are expressed in parts per million downfield from tetramethylsilyl chloride. Concentrations for optical rotation values are given in g*100mL$^{-1}$. Melting points are uncorrected. High resolution mass spectroscopy (HRMS) was performed with the electrospray (ion spray) (ESI-MS) method in positive or negative mode (as indicated).

## II. GENERAL PROCEDURES

The **general procedure A** (Reaction of tartaric acid and derivatives with hexafluoroacetone) and all products are described in the experimental section of the article.



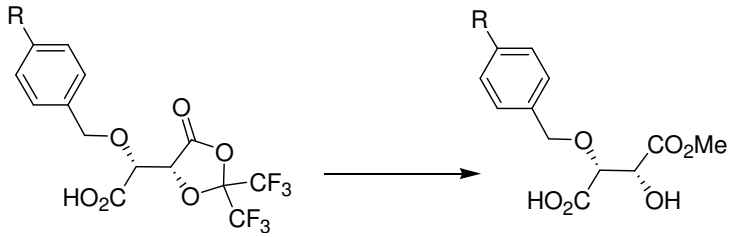
**General procedure B:** Esterification of (5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl)-acetic acids with diazomethane




**CAUTION: Diazomethane is a toxic and explosive gas. All operations must be performed in a well-ventilated fume hood with properly protection of skin and eyes in the absence of open fire or sparks.**

To a solution of **1** or **9** (2 mmol) in diethyl oxide (20 mL) was added a solution of excess of diazomethane (approx. 5 equiv.) in diethyl ether (50 mL). After 15 min the solution was dried ($MgSO_4$). The diethyl ether was removed in vacuo to give the methyl esters **5** and **11**, respectively.

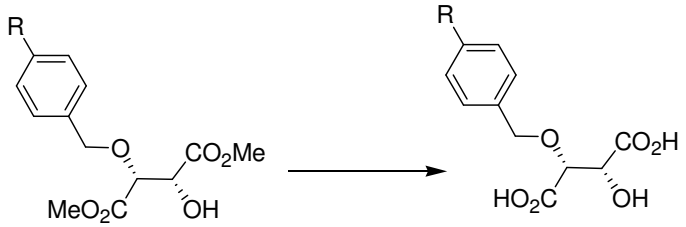
**General procedure C:** Nucleophilic ring opening of the dioxolanones




The dioxolane (1.5 mmol) was stirred in DCM/MeOH 1:1 (20 mL) for the preparation of methyl esters or, for the preparation of the carboxylic acid in 2-PrOH/$H_2O$ 2:1 (20 mL), until complete conversion of starting material (approx. 15 h, TLC control). Then, the solvents were removed in vacuo and the residue was purified by flash chromatography with DCM/MeOH/AcOH 10:1:0.5. The fractions with product were pooled and the solvents were removed in vacuo. Then, the remaining acetic acid was removed by co-evaporation with toluene. For the preparation of the sodium salt, the oily residue was stirred with a

solution of $NaHCO_3$ (1.0 molar equiv. corresponding to the amount of oily product obtained) in acetone/water 1:1 (20 mL) for 30 min. After solvent removal at 50°C the white residue was suspended in 2-PrOH and dried on a filter plate.

**General procedure D:** Saponification of the dimethyltartrates




To a solution of the dimethyltartrate **7a-c**, 18 (approx. 5 mmol) in dioxane (15 mL) was added an aqueous solution of 2.1 equiv. LiOH (10 mL). After complete conversion of starting material (1-2 h with stirring, TLC), the solvents were evaporated and the residue was dissolved in water (15 mL). The solution was extracted with DCM (2 x 5 mL). Then, conc. aqueous HCl (5 mL) was added (check for acidic pH) and it was extracted with AcOEt (3 x 25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo to give **8a-c** or **19**, respectively.

III: COMPOUND SYNTHESIS AND CHARACTERIZATION

**(*2R*)-Acetoxy-{(4*R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetic acid** (**3**): 3.15 g (10.55 mmol) of **1** was stirred in AcCl (25 mL) under exclusion of moisture for 15 h. Then, the volatiles were evaporated (CAUTION). The residue was dissolved in DCM (100 mL), washed with cold water (3 x 20 mL), and dried over $MgSO_4$. Removal of the solvent gave 3.0 g (84 %) of **3** as crystalline product. Mp.: 151-152 °C (recryst. from $CHCl_3$); $^1$H NMR (acetone-$d_6$): δ = 2.14 (s, 3H), 5.70 (d, *J* = 1.9 Hz, 1H), 5.91 (d, *J* = 1.8 Hz, 1H) ppm; $^{13}$C NMR (acetone-$d_6$): δ = 20.9, 70.6, 77.3, 98.7 (m), 120.8 (q, *J* = 286 Hz), 121.6 (q, *J* = 288 Hz), 166.2, 167.0, 170.6 ppm; $^{19}$F NMR (acetone-$d_6$): δ = -82.23 (m, 3F), -

80.96 (m, 3F) ppm; IR (KBr): ν = 1851, 1778, 1741, 1708 $cm^{-1}$; $\alpha_D^{20}$ +37.6 (*c* 2.0, acetone); HRMS ($ES^-$): calc. for $[C_9H_6F_6O_7 - H]^-$ 338.9939, found 338.9944.

**(*2R,3R*)-3-*O*-Acetyl-1-methyl tartrate** (**4**): Following the general procedure C, 0.94 g (2.76 mmol) of **3** gave **4** (510 mg, 90 %) as oil [$R_f$ = 0.1 ($KMnO_4$: yellow)]. A small portion was converted into the sodium salt (quantitative yield). Mp. (sodium salt): 181 °C (decomposition); $^1H$ NMR ($CDCl_3$): δ = 2.15 (s, 3H), 3.83 (s, 3H), 4.81 (d, *J* = 2.1 Hz, 1H), 5.49 (d, *J* = 2.2 Hz, 1H) ppm; $^{13}C$ NMR (sodium salt in $D_2O$): δ = 19.9, 53.3, 70.3, 73.8, 170.6, 172.3, 172.8 ppm; IR (sodium salt, KBr): ν = 1730, 1626, 1394 $cm^{-1}$; $\alpha_D^{20}$ (sodium salt) -5.1 (*c* 2.0, $H_2O$); HRMS ($ES^-$): calc. for $[C_7H_{10}O_7 - H]^-$ 205.0348, found 205.0347.

**(*2R*)-(Acetyoxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-methylacetate** (**5**): Following the general procedure B with 1.09 g (3.2 mmol) **3** gave 5 (0.99 g, 88 %) as slowly crystallizing oil. Mp. (recryst. from toluene): 82-84 °C; $^1H$ NMR ($CDCl_3$): δ = 2.15 (s, 3H), 3.86 (s, 3H), 5.25 (d, *J* = 1.8 Hz, 1H), 5.56 (d, *J* = 2.0 Hz, 1H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 19.8, 53.5, 68.9, 74.9, 97.9 (m), 118.5 (q, *J* = 187 Hz), 119.5 (q, *J* = 189 Hz), 164.1, 164.9, 168.8 ppm; $^{19}F$ NMR ($CDCl_3$): δ = -81.34 (q, *J* = 8.0 Hz, 3F), -80.07 (q, *J* = 8.0 Hz, 3F) ppm; IR (KBr): ν = 1855, 1760, 1441, 981 $cm^{-1}$; $\alpha_D^{20}$ +42.2 (*c* 2.5, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{10}H_8F_6O_7 + Na]^+$ 377.0072, found 377.0073.

**(*2R,3R*)-2-*O*-Acetyl-1-methyl tartrate** (**6**): Following the general procedure C, 0.61 g (1.72 mmol) of **5** gave **6** (280 mg, 79 %) as oil [$R_f$ = 0.1 ($KMnO_4$: yellow)]. $^1H$ NMR ($CDCl_3$): δ = 2.16 (s, 3H), 3.83 (s, 3H), 4.82 (m, 1H), 5.51 (m, 1H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 20.2, 53.1, 70.2, 72.9, 167.6, 170.3, 173.2 ppm, IR (film): ν = 1750, 1221, 1074 $cm^{-1}$; $\alpha_D^{20}$ -34.5 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_7H_{10}O_7 - H]^-$ 205.0348, found 205.0341.

***L*-*O*-Mono-benzylated-dimethyltartrates** (**7a-c**): The compounds **7a-c** were obtained from dimethyl *L*-tartrate (typically in 10 g - scale) in 96 (**7a**), 82 (**7b**) and 80 % (**7c**) yield according to published procedure [S. Nakamura, Y. Hirata, T. Kurosaki, M. Anada, O. Kataoka, S. Kitagaki, S. Hashimoto,

*Angew. Chem. Int. Ed.* **2003**, *42*, 5351-5355]. The $^1$H NMR data are identical with those reported [N. Nagashima, M. Ohno, *Chem. Pharm. Bull.* **1991**, *39*, 1972-1982.].

***L-O*-Monobenzyl tartaric acid** (**8a**): Following the general procedure D, 1.48 g (5.52 mmol) **7a** gave 1.30 g **8a** as white crystalline solid (89 %). Mp.: 128-129 °C; $^1$H NMR (acetone-$d_6$): δ = 4.51 (m, 2H), 4.66 (d, *J* = 2.5 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 7.31 (m, 5H) ppm; $^{13}$C NMR (acetone-$d_6$): δ = 73.9, 74.6, 81.1, 129.4, 129.6, 139.8, 172.0, 173.9 ppm; IR (KBr): ν = 1741, 1707, 1379 cm$^{-1}$; $\alpha_D^{20}$ +54.1 (*c* 2.0, acetone); HRMS (ES$^-$): calc. for [$C_{11}H_{12}O_6$ – H]$^-$ 239.0556, found 239.0557.

***L-O*-Mono-(4-nitrobenzyl) tartaric acid** (**8b**): Following the general procedure D, 5.73 g (18.29 mmol) **7b** gave 4.31 g **8b** as yellow crystalline solid (82 %). Mp.: 197-198 °C; $^1$H NMR (acetone-$d_6$): δ = 4.57 (m, 1H), 4.68 (m, 2H), 5.03 (d, *J* = 13.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H) ppm; $^{13}$C NMR (acetone-$d_6$): δ = 73.3, 73.9, 81.6, 125.0, 129.9, 147.8, 149.2, 171.8, 173.9 ppm; IR (KBr): ν = 1724, 1674, 1518, 1343 cm$^{-1}$; $\alpha_D^{20}$ +52.7 (*c* 2.0, acetone); HRMS (ES$^-$): calc. for [$C_{11}H_{11}NO_8$ – H]$^-$ 284.0406, found 284.0415.

***L-O*-Mono-(4-methoxybenzyl) tartaric acid** (**8c**): Following the general procedure D, 6.54 g (21.92 mmol) **7c** gave 4.57 g **8c** as white crystalline solid (77 %). Mp.: 174-176 ºC; $^1$H NMR (DMSO-$d_6$): δ = 3.32 (br s, 1H), 3.74 (s, 3H), 4.27 (d, *J* = 11.2 Hz, 1H), 4.31 (d, *J* = 2.8 Hz, 1H), 4.38 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 11.2 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H), 12.78 (br s, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$): δ = 55.0, 71.6, 71.8, 79.2, 113.4, 129.3, 129.8, 158.69, 170.9, 172.7 ppm; IR (KBr): ν = 3302, 1744, 1710, 1612, 1511, 1382, 1255, 1241, 1134, 1078 cm$^{-1}$; $\alpha_D^{20}$ +48.0 (*c* 2.0, acetone); HRMS (ES$^-$): calc. for [$C_{12}H_{14}O_7$ – H]$^-$ 269.0661, found 269.0669.

**Sodium (*2R,3R*)-3-*O*-benzyl-1-methyl tartrate** (**10a**): Following the general procedure C with **9a** (585 mg, 1.51 mmol), the free acid was obtained after flash chromatography ($R_f$ = 0.3, $KMnO_4$: yellow), which was transformed into the sodium salt to give **10a** (340 mg, 81 %) as white powder. Mp.: 186 °C (decomposition); $^1$H NMR ($D_2O$): δ = 3.60 (s, 3H), 4.13 (d, *J* = 2.8 Hz, 1H), 4.36 (d, *J* = 12.1 Hz, 1H),

4.61 (d, *J* = 2.8 Hz, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 7.41 (m, 5H) ppm; $^{13}$C NMR ($D_2O$): δ = 52.9, 72.3, 72.7, 79.9, 128.5, 128.8, 129.0, 137.2, 174.1, 176.3 ppm; IR (KBr): ν = 1746, 1596, 1399, 1128, 702 $cm^{-1}$; $\alpha_D^{20}$ +69.3 (*c* 2.0, $H_2O$); HRMS ($ES^-$): calc. for $[C_{12}H_{14}O_6 - H]^-$ 253.0712, found 253.0717.

**Sodium (*2R,3R*)-3-*O*-(4-nitrobenzyl)-1-methyl tartrate** (**10b**): Following the general procedure C with **9b** (1.0 g, 2.31 mmol), the free acid was obtained after flash chromatography ($R_f$ = 0.2, UV), which was transformed into the sodium salt to give **10b** (700 mg, 98 %) as white scales. Mp.: 216 °C (decomposition); $^1$H NMR ($D_2O$): δ = 3.50 (s, 3H), 4.04 (d, *J* = 2.8 Hz, 1H), 4.37 (d, *J* = 13.1 Hz, 1H), 4.52 (d, *J* = 2.8 Hz, 1H), 4.76 (d, *J* = 13.1 Hz, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 8.13 (d, *J* = 8.7 Hz, 2H) ppm; $^{13}$C NMR ($D_2O$): δ = 52.8, 71.3, 72.7, 81.0, 123.8, 129.0, 145.4, 147.3, 174.1, 176.0 ppm; IR (KBr): ν = 1738, 1603, 1515, 1352, 1090 $cm^{-1}$; $\alpha_D^{20}$ +66.3 (*c* 2.0, $H_2O$); HRMS ($ES^-$): calc. for $[C_{12}H_{13}NO_8 - H]^-$ 298.0563, found 298.0570.

**(*2R,3R*)-3-*O*-(4-methoxybenzyl)-1-methyl tartrate** (**10c**): Following the general procedure C with **9c** (0.38 g, 0.92 mmol), the free acid **10c** (0.24 g, 92%) was obtained as a yellowish oil after purification by flash chromatography (DCM/MeOH/AcOH 20:1:1, $R_f$ = 0.25, UV). $^1$H NMR ($CDCl_3$): δ = 3.66 (s, 3H), 3.80 (s, 3H), 4.35 (d, *J* = 2.0 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.63 (d, *J* = 1.8 Hz, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 6.32 (br s, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}$C NMR (DMSO-$d_6$): δ = 52.7, 55.2, 72.1, 72.6, 77.3, 113.8, 128.4, 130.1, 159.6, 171.4, 173.5 ppm; IR (film): ν = 3180, 2955, 1748, 1612, 1515, 1251, 1135, 1090, 1031 $cm^{-1}$; $\alpha_D^{20}$ +20.0 (*c* 1.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{13}H_{16}O_7 - H]^-$ 283.0818, found 283.0823.

**Methyl-(*2R*)-(benzyloxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetate** (**11a**): Following the general procedure B, **9a** (0.88 g, 2.21 mmol) gave **11a** (0.84 g, 95 %) as dense yellowish oil. $^1$H NMR ($CDCl_3$): δ = 3.86 (s, 3H), 4.38 (d, *J* = 2.4 Hz, 1H), 4.56 (d, *J* = 11.3 Hz, 1H), 4.88 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 2.3 Hz, 1H), 7.32 (m, 5H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 53.0, 74.0, 74.9, 76.5, 98.2 (m), 118.4 (q, *J* = 287 Hz), 119.7 (q, *J* = 289 Hz), 128.2, 128.3, 128.4, 135.7, 165.0, 167.7 ppm; $^{19}$F NMR ($CDCl_3$): δ = -81.4 (q, *J* = 7.9 Hz), -79.8 (q, *J* = 8.1 Hz) ppm; IR (film): ν = 1854, 1766, 1320,

1132 $cm^{-1}$; $\alpha_D^{20}$ +81.4 (*c* 2.5, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{15}H_{12}F_6O_6 + NH_4^+]^+$ 420.0882, found 420.0882.

**Methyl-(*2R*)-(4-nitrobenzyloxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetate** (**11b**): Following the general procedure B, **9b** (0.82 g, 1.89 mmol) gave **11b** (0.75 g, 83 %) as dense yellowish oil. $^1H$ NMR ($CDCl_3$): δ = 3.90 (s, 3H), 4.45 (d, *J* = 2.3 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 5.17 (d, *J* = 2.1 Hz, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 53.2, 72.9, 75.8, 76.4, 98.1 (m), 116.2 (m), 121.9 (m), 123.6, 128.1, 143.3, 147.7, 165.0, 167.1 ppm; $^{19}F$ NMR ($CDCl_3$): δ = -81.3 (q, *J* = 7.8 Hz), -79.8 (q, *J* = 8.0 Hz) ppm; IR (film): ν = 2961, 1855, 1766, 1608, 1525 $cm^{-1}$; $\alpha_D^{20}$ +64.3 (*c* 2.5, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{15}H_{11}F_6NO_8 + Na^+]^+$ 470.0287, found 470.0285.

**Methyl-(*2R*)-(4-methoxybenzyloxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetate** (**11c**): Following the general procedure B, **9c** (0.72 g, 1.58 mmol) gave **11c** (0.55 g, 81 %) as dense yellowish oil. $^1H$ NMR ($CDCl_3$): δ = 3.81 (s, 3H), 3.85 (s, 3H), 4.35 (d, *J* = 2.4 Hz, 1H), 4.50 (d, *J* = 11.1 Hz, 1H), 4.80 (d, *J* = 11.1 Hz, 1H), 5.08 (d, *J* = 2.3 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 52.8, 55.1, 73.6, 74.4, 76.5, 98.1 (m), 113.7, 118.4 (q, *J* = 287.0 Hz), 119.7 (q, *J* = 289.1 Hz), 127.7, 129.9, 159.7, 165.0, 167.7 ppm; $^{19}F$ NMR ($CDCl_3$): δ = -81.4 (q, *J* = 8.1 Hz, 3F), -79.8 (q, *J* = 7.9 Hz, 3F) ppm; IR (film): ν = 1853, 1765, 1516, 1320, 1244, 1193, 1132, 983, 722 $cm^{-1}$; $\alpha_D^{20}$ +30.3 (*c* 1.0, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{16}H_{14}F_6O_7 + NH_4^+]^+$ 450.0987, found 450.0966.

**(*2R,3R*)-2-*O*-Benzyl-1-methyl tartrate** (**12a**): Following the general procedure C, **11a** (0.73 g, 1.81 mmol) gave **12a** (460 mg, 100 %) as crystalline solid. $R_f$ = 0.2 (UV); Mp.: 96-97 °C; $^1H$ NMR ($CDCl_3$): δ = 3.83 (s, 3H), 4.43 (d, *J* = 2.3 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 2.3 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 7.29 (m, 5H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 52.6, 72.0, 73.3, 77.9, 128.2, 128.3, 128.4, 136.1, 169.9, 174.8 ppm; IR (KBr): ν = 1756, 1454, 1104 $cm^{-1}$; $\alpha_D^{20}$ +82.7 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{12}H_{14}O_6 - H]^-$ 253.0712, found 253.0710.

**(*2R,3R*)-2-*O*-(4-Nitrobenzyl)-1-methyl tartrate** (**12b**): Following the general procedure D, **11b** (0.52 g, 1.16 mmol) gave **12b** (290 mg, 83 %) as crystalline solid, $R_f$ = 0.3 (UV). Mp.: 118-119 °C; $^1$H NMR (acetone-$d_6$): δ = 3.77 (s, 3H), 4.60 (d, *J* = 2.6 Hz, 1H), 4.64 (d, *J* = 2.6 Hz, 1H), 4.68 (d, *J* = 13.1 Hz, 1H), 5.00 (d, *J* = 13.1 Hz, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 8.20 (d, *J* = 8.8 Hz, 2H) ppm; $^{13}$C NMR (acetone-$d_6$): δ = 53.3, 73.3, 73.8, 81.9, 125.0, 129.9, 147.8, 149.2, 171.4, 173.7 ppm; IR (KBr): ν = 1751, 1719, 1545, 1531 cm$^{-1}$; $\alpha_D^{20}$ +50.1 (*c* 2.0, acetone); HRMS (ES$^-$): calc. for $[C_{12}H_{13}NO_8 - H]^-$ 298.0563, found 298.0564.

**(*2R,3R*)-2-*O*-(4-Methoxybenzyl)-1-methyl tartrate** (**12c**): Following the general procedure D, **11c** (0.30 g, 0.69 mmol) gave **12c** (173 mg, 88 %) as yellowish solid after purification by flash chromatography with DCM/MeOH/AcOH 10:0.5:0.5 ($R_f$ = 0.23, UV). Mp: 116-118 ºC; $^1$H NMR ($CDCl_3$): δ = 3.78 (s, 3H), 3.83 (s, 3H), 4.40 (d, *J* = 2.4 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.62 (d, *J* = 2.4 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 6.83 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 52.6, 55.2, 72.0, 73.0, 77.5, 113.9, 128.2, 130.1, 159.6, 170.1, 174.5 ppm; IR (film): ν = 3150, 2922, 1724, 1610, 1512, 1249, 1137, 1089, 1029 cm$^{-1}$; $\alpha_D^{20}$ +8.1 (*c* 2.0, MeOH); HRMS (ES$^-$): calc. for $[C_{13}H_{16}O_7 - H]^-$ 283.0818, found 283.0824.

**(*2R,3R*)-3-*O*-(4-Methoxybenzyl)-1-allyl tartrate** (**13**): The dioxolane **9c** (0.199 g, 0.48 mmol) was dissolved in DCM/allyl alcohol 1:1 (10 mL). After stirring the reaction mixture for 15 h at room temperature, it was heated under reflux until complete conversion of starting material (2 h, TLC control). Then, the solvents were removed in vacuo, and the residue was purified by flash chromatography with Hx/AcOEt 1:1 ($R_f$ = 0.15, UV) to give **13** (0.100 g, 93%) as a colourless oil. $^1$H NMR ($CDCl_3$): δ = 3.80 (s, 3H), 4.38 (d, *J* = 2.1 Hz, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 4.50 (m, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.67 (m, 1H), 5.29 (m, 1H), 5.30 (m, 1H), 5.81 (m, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 55.2, 66.6, 72.1, 72.8, 77.5, 113.9, 119.4, 128.3, 130.1, 131.1, 159.7, 170.6, 172.8 ppm; IR (film): ν = 1032, 1092, 1136, 1250, 1514, 1612, 1748, 2929,

3450 $cm^{-1}$; $\alpha_D^{20}$ +14.9 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{15}H_{18}O_7 - H]^-$ 309.0974, found 309.0980.

**Allyl-(*2R*)-(4-methoxybenzyloxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetate** (**14**): The dioxolane **9c** (0.710 g, 1.70 mmol) was dissolved in oxalyl chloride (2.5 mL) under $N_2$ atmosphere. A drop of DMF was added and the reaction mixture was stirred for 15 min. Then, the solvents were removed in vacuo to give the corresponding acid chloride (0.742 g) as a yellowish oil. This intermediate was dissolved in dry diethyl ether (5 mL) and the allyl alcohol (0.115 mL, 1.70 mmol) was added dropwise at room temperature. The reaction mixture was stirred until complete conversion of starting material (4 h, TLC control). Then, the solvents were removed in vacuo and the residue was purified by flash cromatography with Hx/AcOEt 9:1 ($R_f$ = 0.2, UV) to give the ester **14** (0.600 g, 95 %) as a colourless oil. $^1$H NMR ($CDCl_3$): δ = 3.81 (s, 3H), 4.36 (d, *J* = 2.4 Hz, 1H), 4.52 (d, *J* = 11.1 Hz, 1H), 4.75 (dt, *J* = 5.7 Hz, 1.3 Hz, 2H), 4.80 (d, *J* = 11.1 Hz, 1H), 5.09 (d, *J* = 2.3 Hz, 1H), 5.31 (ddt, *J* = 10.5 Hz, 2.3 Hz, 1.1 Hz, 1H), 5.36 (ddt, *J* = 17.2 Hz, 2.8 Hz, 1.4 Hz, 1H), 5.93 (ddt, *J* = 17.0 Hz, 10.5 Hz, 5.7 Hz, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}$C NMR (DMSO-*d*$_6$): δ = 55.2, 66.5, 73.6, 74.4, 76.6, 97.8 (m), 113.8, 118.5 (q, *J* = 287.0 Hz), 119.2, 119.7 (q, *J* = 289.0 Hz), 127.7, 130.0, 130.9, 159.7, 165.0, 167.0 ppm; $^{19}$F NMR ($CDCl_3$): δ = -81.4 (q, *J* = 8.0 Hz, 3F), -79.8 (q, *J* = 8.1 Hz, 3F) ppm; IR (film): ν = 1132, 1192, 1245, 1320, 1515, 1613, 1764, 1856, 2957 $cm^{-1}$; $\alpha_D^{20}$ +29.3 (*c* 2.0, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{18}H_{16}F_6O_7 + NH_4^+]^+$ 476.1144, found 476.1128.

**(*2R,3R*)-2-*O*-(4-Methoxybenzyl)-1-allyl tartrate** (**15**): Following the general procedure D, 0.244 g (0.65 mmol) of **13** gave **15** (143 mg, 97 %) as yellowish oil after purification by flash chromatography with Hx/AcOEt 1:1 ($R_f$ = 0.15, UV). $^1$H NMR ($CDCl_3$): δ = 3.77 (s, 3H), 4.42 (d, *J* = 2.1 Hz, 1H), 4.43 (d, *J* = 10.9 Hz, 1H), 4.64 (d, *J* = 2.3 Hz, 1H), 4.72 (dt, *J* = 5.8 Hz, 1.3 Hz, 2H), 4.78 (d, *J* = 11.3 Hz, 1H), 5.29 (m, 1H), 5.37 (m, 1H), 5.94 (m, 1H), 6.83 (d, *J* = 8.6 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 55.2, 66.2, 72.9, 77.5, 113.8, 119.0, 128.3, 130.1, 131.3, 159.5, 169.1, 174.6,

174.7 ppm; IR (film): ν = 1032, 1091, 1131, 1250, 1515, 1612, 1747, 2938, 3450 $cm^{-1}$; $\alpha_D^{20}$ +33.0 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{15}H_{18}O_7 - H]^-$ 309.0974, found 309.0976.

**(*2R,3R*)-2-*O*-Acetyl-3-*O*-benzyl-1-methyl tartrate** (**16**): **10a** (0.424 g, 1.67 mmol) was stirred in AcCl (7 mL) with a catalytic amount of DMAP until complete conversion (2 h, TLC, UV). Then, the solvent was removed in vacuo (CAUTION!) and the residue was purified by flash chromatography with DCM/AcOH 10:0.5. The fractions with product ($R_f$ = 0.55, UV) were pooled and the solvents were removed in vacuo. Then, the remaining acetic acid was removed by co-evaporation with toluene to give **16** (474 mg, 96 %) as yellowish oil. $^1H$ NMR ($CDCl_3$): δ = 2.17 (s, 3H), 3.66 (s, 3H), 4.54 (d, *J* = 11.8 Hz, 1H), 4.70 (d, *J* = 2.8 Hz, 1H), 4.87 (d, *J* = 11.8 Hz, 1H), 5.56 (d, *J* = 2.8 Hz, 1H), 7.34 (m, 5H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 20.4, 52.7, 72.4, 73.7, 75.9, 128.4, 128.5, 135.9, 166.8, 170.1, 172.9 ppm; IR (film): ν = 700, 749, 1013, 1088, 1138, 1219, 1375, 1438, 1455, 1755, 1956, 3214 $cm^{-1}$; $\alpha_D^{20}$ +55.9 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{14}H_{16}O_7 - H]^-$ 295.0818, found 295.0819.

**(*2R,3R*)-3-*O*-Acetyl-2-*O*-benzyl-1-*tert*-butyl-4-methyl tartrate** (**17**): To a solution of **16** (476 mg, 1.60 mmol) and TEBAC (274 mg, 1.60 mmol) in DMA (20 mL) was added dried $K_2CO_3$ (5.75 g, 41.6 mmol) followed by $^t$BuBr (10.52 g, 76.8 mmol). The mixture was stirred at 55 ºC for 24 h and, after cooling, cold $H_2O$ (100 mL) was added. The product was extracted into AcOEt (75 mL). The organic layer was separated, washed with $H_2O$ (2 x 40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with Hx/AcOEt 4:1 ($R_f$ = 0.41, UV), to give **17** (451 mg, 80 %) as yellowish oil after removal of solvents. $^1H$ NMR ($CDCl_3$): δ = 1.47 (s, 9H), 2.16 (s, 3H), 3.64 (s, 3H), 4.41 (d, *J* = 3.1 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 5.57 (d, *J* = 3.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 7.32 (m, 5H) ppm; $^{13}C$ NMR ($CDCl_3$): δ = 20.3, 27.8, 52.3, 72.7, 73.2, 76.3, 82.6, 127.9, 128.21, 128.24, 136.5, 166.9, 167.0, 169.7 ppm; IR (film): ν = 700, 742, 799, 845, 1028, 1088, 1142, 1224, 1372, 1437, 1455, 1754, 2978 $cm^{-1}$; $\alpha_D^{20}$ +67.0 (*c* 2.0, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{18}H_{24}O_7 + NH_4^+]^+$ 370.1866, found 370.1862.

**(*2R,3R*)-2-*O*-Benzyl-1-*tert*-butyl tartrate** (**18**): Following general procedure D, **17** (0.693 g, 1.97 mmol) gave after flash chromatography with Hx/AcOEt/AcOH 75:25:1 ($R_f$ = 0.38, UV) **18** (0.572 g, 98%) as white solid. Mp: 101-102 ºC; $^1$H NMR ($CDCl_3$): δ = 1.52 (s, 9H), 4.31 (br s, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.57 (br s, 1H), 4.82 (d, *J* = 11.4 Hz, 1H), 7.34 (m, 5H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 28.0, 72.2, 73.1, 78.1, 83.0, 128.1, 128.3, 128.3, 136.4, 168.4, 173.3 ppm; IR (film): ν = 698, 740, 844, 1095, 1159, 1256, 1370, 1456, 1748, 2926, 3200 cm$^{-1}$; $\alpha_D^{20}$ +65.8 (*c* 2.0, $CHCl_3$); HRMS (ES$^-$): calc. for $[C_{15}H_{20}O_6 - H]^-$ 295.1182, found 295.1195.

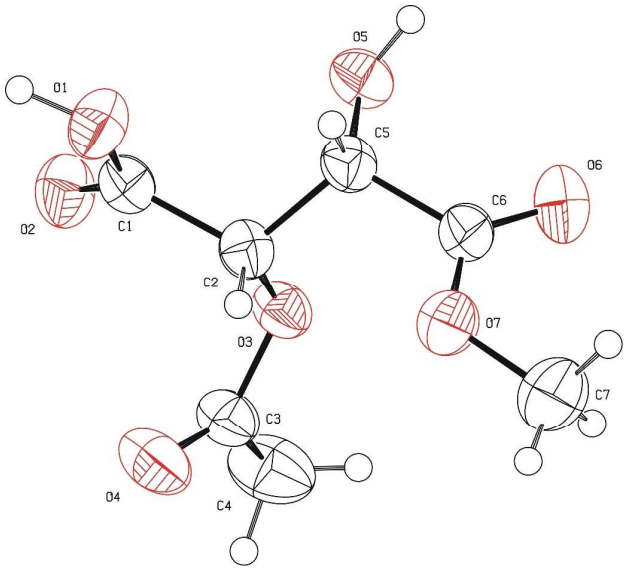
**(*2R,3R*)-3-*O*-Acetyl-2-*O*-benzyl-1-methyl tartrate** (**19**): **12a** (0.724 g, 2.84 mmol) was stirred in AcCl (7 mL) a catalytic amount of DMAP until complete conversion (2 h, TLC, UV). Then, the valatiles were removed in vacuo (CAUTION!) and the residue was purified by flash chromatography with DCM/AcOH 10:0.5. The fractions with product ($R_f$ = 0.55, UV) were pooled and the solvents were removed in vacuo. Then, the remaining acetic acid was removed by co-evaporation with toluene to give **20** (0.793 g, 94 %) as yellowish oil. $^1$H NMR ($CDCl_3$): δ = 2.16 (s, 3H), 3.79 (s, 3H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.55 (d, *J* = 2.9 Hz, 1H), 4.90 (d, *J* = 11.8 Hz, 1H), 5.58 (d, *J* = 2.9 Hz, 1H), 7.31 (m, 5H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 20.4, 52.6, 72.3, 73.6, 75.9, 128.3, 128.4, 136.0, 168.8, 170.0, 171.9 ppm; IR (film): ν = 700, 747, 1026, 1080, 1146, 1226, 1375, 1437, 1455, 1758, 2956, 3214 cm$^{-1}$; $\alpha_D^{20}$ +59.4 (*c* 2.0, $CHCl_3$); HRMS (ES$^-$): calc. for $[C_{14}H_{16}O_7 - H]^-$ 295.0818, found 295.0819.

**(*2R,3R*)-2-*O*-Acetyl-3-*O*-benzyl-1-*tert*-butyl-4-methyl tartrate** (**20**): To a solution of **19** (0.401 g, 1.35 mmol) and TEBAC (251 mg, 1.35 mmol) in DMA (20 mL) was added dried $K_2CO_3$ (4.85 g, 35.1 mmol) followed by $^t$BuBr (8.88 g, 64.8 mmol). The mixture was stirred at 55 ºC for 24 h and, after cooling, cold $H_2O$ (100 mL) was added. The product was extracted into AcOEt (75 mL). The organic layer was separated, washed with $H_2O$ (2 x 40 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (Hx/AcOEt 3:1, $R_f$ = 0.43, UV), to give **20** (0.414 g, 87 %) as yellowish oil. $^1$H NMR ($CDCl_3$): δ = 1.42 (s, 9H), 2.14 (s, 3H), 3.77 (s, 3H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.57 (d, *J* = 3.2 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 5.45 (d, *J* = 3.2 Hz, 1H),

7.31 (m, 5H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 20.4, 27.7, 52.2, 72.8, 73.5, 76.8, 82.9, 128.0, 128.2, 136.3, 165.1, 169.0, 169.8 ppm; IR (film): ν = 700, 746, 800, 845, 1020, 1087, 1160, 1227, 1371, 1437, 1456, 1756, 2978 cm$^{-1}$; $\alpha_D^{20}$ +49.3 (*c* 2.0, $CHCl_3$); HRMS ($ES^+$): calc. for $[C_{18}H_{24}O_7 + NH_4^+]^+$ 370.1866, found 370.1865.

**(*2R,3R*)-3-*O*-Benzyl-1-*tert*-butyl tartrate** (**21**): To a solution of **20** (0.300 g, 0.85 mmol) in THF/$H_2O$ 3:1 (18 mL) was added at 0 ºC with 30% $H_2O_2$ (0.700 mL, 6.80 mmol) followed by LiOH (0.144 g, 3.40 mmol). The resulting mixture was stirred at 0 ºC for 2 h and then at room temperature for 15 h. Then, at 0 ºC an 1.5 M solution of $Na_2SO_3$ (5.0 mL, 7.48 mmol) was added to quench the excess of peroxide. After stirring at 0 ºC for 15 min, the mixture was buffered to pH 9-10 with sat. aqu. $NaHCO_3$ and the THF was evaporated under reduced pressure. The aqueous phase was acidified to pH 1-2 with conc. aqueous HCl and the product was extracted with AcOEt (3 x 20 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography (Hx/AcOEt/AcOH 75:25:1, $R_f$ = 0.31, UV), to give **21** (0.244 g, 97 %) as a colourless oil. $^1$H NMR ($CDCl_3$): δ = 1.44 (s, 9H), 4.40 (d, *J* = 2.1 Hz, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 4.52 (d, *J* = 2.2 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 7.33 (m, 5H) ppm; $^{13}$C NMR ($CDCl_3$): δ = 27.8, 72.2, 73.2, 78.5, 83.4, 128.2, 128.2, 128.4, 136.4, 169.9, 173.9 ppm; IR (film): ν = 698, 747, 844, 1095, 1159, 1258, 1370, 1456, 1738, 2934, 2979 cm$^{-1}$; $\alpha_D^{20}$ +43.8 (*c* 2.0, $CHCl_3$); HRMS ($ES^-$): calc. for $[C_{15}H_{20}O_6 - H]^-$ 295.1182, found 295.1189.

IV. X-RAY STRUCTURE OF COMPOUND 4




Experimental: A prismatic crystal (0.1x0.1x0.2 mm) was selected and mounted on a MAR345 diffractometer with an image plate detector. Unit-cell parameters were determined from 938 reflections ($3 < \theta < 31°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation. 10036 reflections were measured in the range $2.83 \leq \theta \leq 32.42$. 3058 of which were non-equivalent by symmetry (Rint(on I) = 0.056 ). 2194 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. Lorentz-polarization but no absorption corrections were made.

The structure was solved by Direct methods, using SHELXS computer program (Sheldrick, G.M., (1997), A program for automatic solution of crystal structure. Univer Goettingen, Germany) and refined by full-matrix least-squares method with SHELX97 computer program (Sheldrick, G.M., (1997), A program for crystal structure refinement. Univer Goettingen, Germany), using 10036 reflections, (very negative intensities were not assumed). The function minimized was $\Sigma$ w $\left|\ |Fo|^2-|Fc|^2\right|^2$, where w = $[\sigma^2(I)+(0.0662P)^2]$-1, and P = $(|Fo|^2+2|Fc|^2)/3$, f, f' and f'' were taken from International Tables of X-Ray Crystallography (International Tables of X-Ray Crystallography, (1974), Ed. Kynoch press, Vol. IV, pp 99-100 and 149). 4H atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and 6H atoms were located from a difference synthesis and refined, using a riding model, with an isotropic temperature factor equal to 1.2 the equivalent temperature factor of the atom which are linked. The final R(on F) factor was 0.055, wR(on $|F|^2$) = 0.130 and goodness of fit = 1.150 for all observed reflections. Number of refined parameters was 143. Max. shift/esd = 0.00, Mean shift/esd = 0.00. Max. and min. peaks in final difference synthesis was 0.162 and -0.162 $eÅ^{-3}$, respectively.

Crystal data and structure refinement for **4**

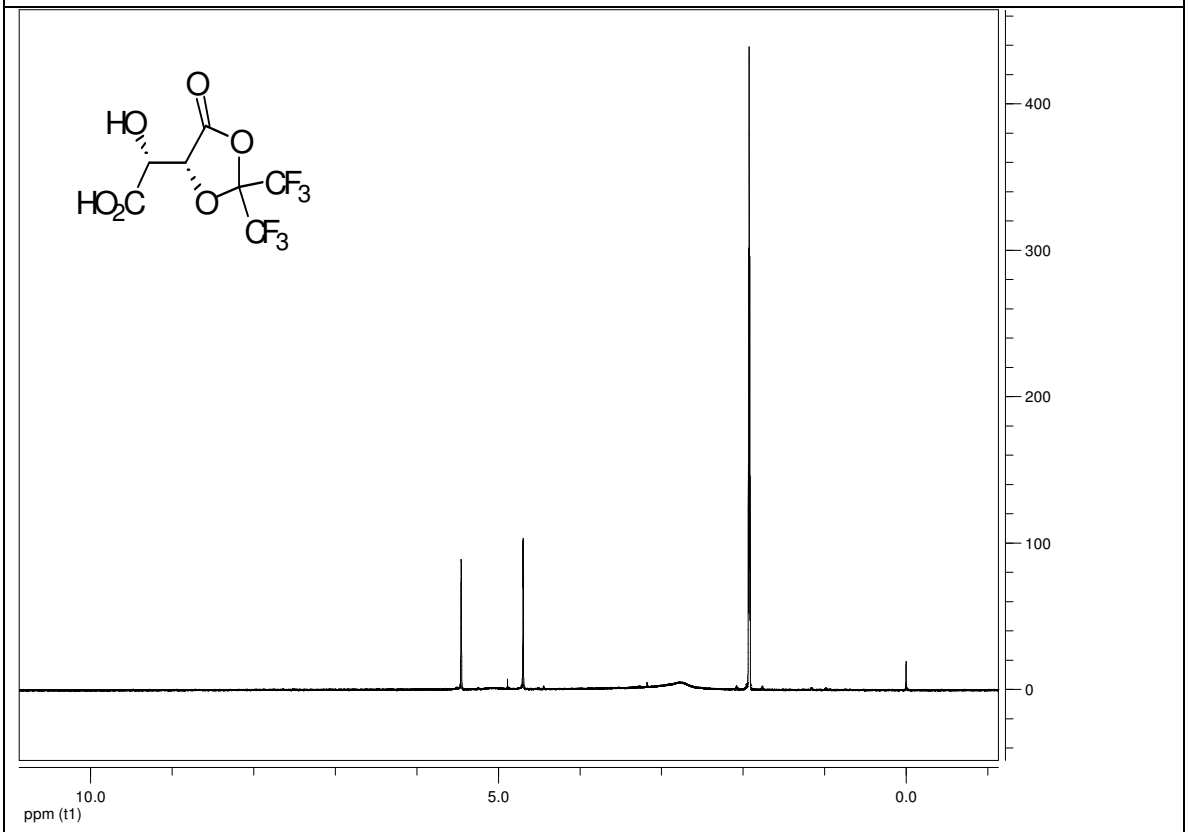
| | |
|---|---|
| Empirical formula | $C_7 H_{10} O_7$ |
| Formula weight | 206.15 |

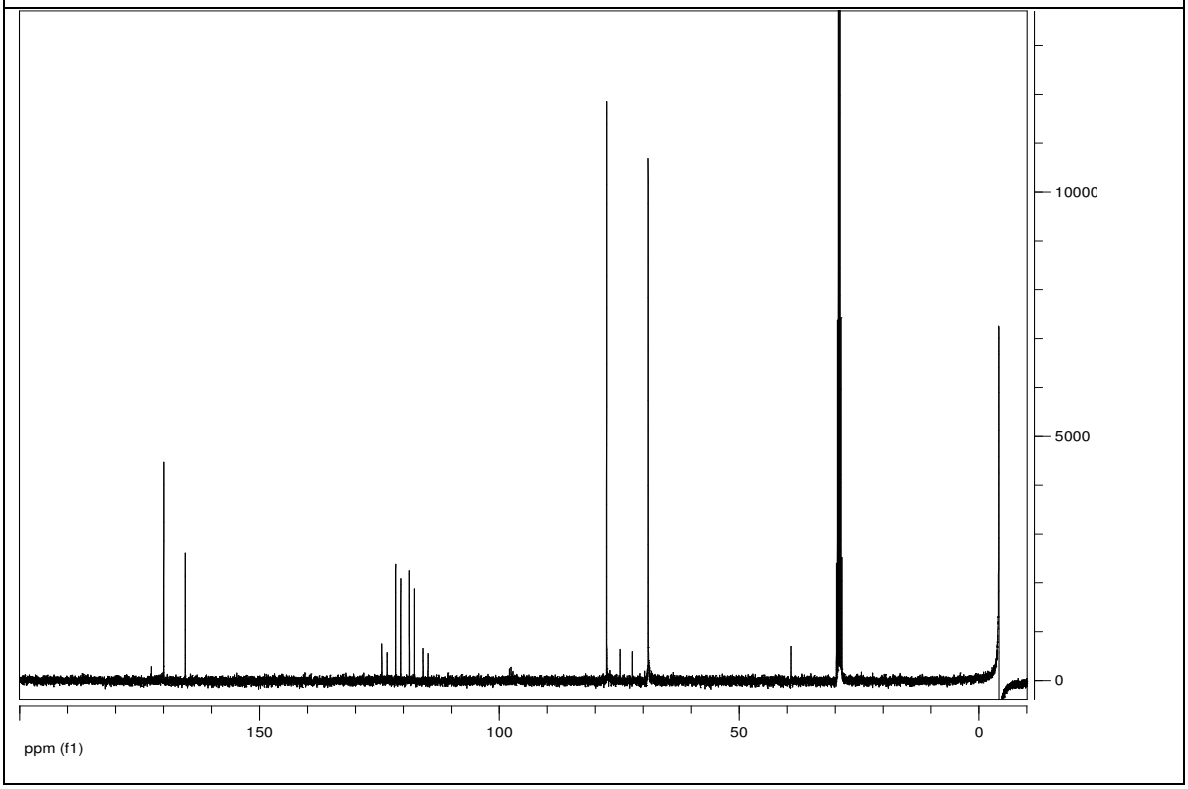
| | |
|---|---|
| Temperature | 293(2) K |
| Wavelength | 0.71073 Å |
| Crystal system, space group | Monoclinic, $P2_1/c$ |
| Unit cell dimensions | a = 9.161(6) Å α = 90 °.<br>b = 9.374(6) Å β = 109.59(3) °.<br>c = 11.956(5) Å γ = 90 °. |
| Volume | 967.3(10) $Å^3$ |
| Z, Calculated density | 4, 1.416 $Mg/m^3$ |
| Absorption coefficient | 0.130 $mm^{-1}$ |
| F(000) | 432 |
| Crystal size | 0.2 x 0.09 x 0.09 mm |
| Theta range for data collection | 2.83 to 32.42 °. |
| Limiting indices | -12<=h<=13, -13<=k<=13, -17<=l<=17 |
| Reflections collected / unique | 10036 / 3058 [R(int) = 0.0564] |
| Completeness to theta = 25.00 | 99.3 % |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 3058 / 0 / 143 |
| Goodness-of-fit on $F^2$ | 1.150 |
| Final R indices [I>2σ(I)] | R1 = 0.0552, wR2 = 0.1302 |
| R indices (all data) | R1 = 0.0876, wR2 = 0.1441 |
| Largest diff. peak and hole | 0.162 and -0.162 $e.Å^{-3}$ |

V. COPIES OF $^{1}H$ AND $^{13}C$ NMR OF COMPOUNDS **1**-**6**

**(*2R*)-(Hydroxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetic acid 1**

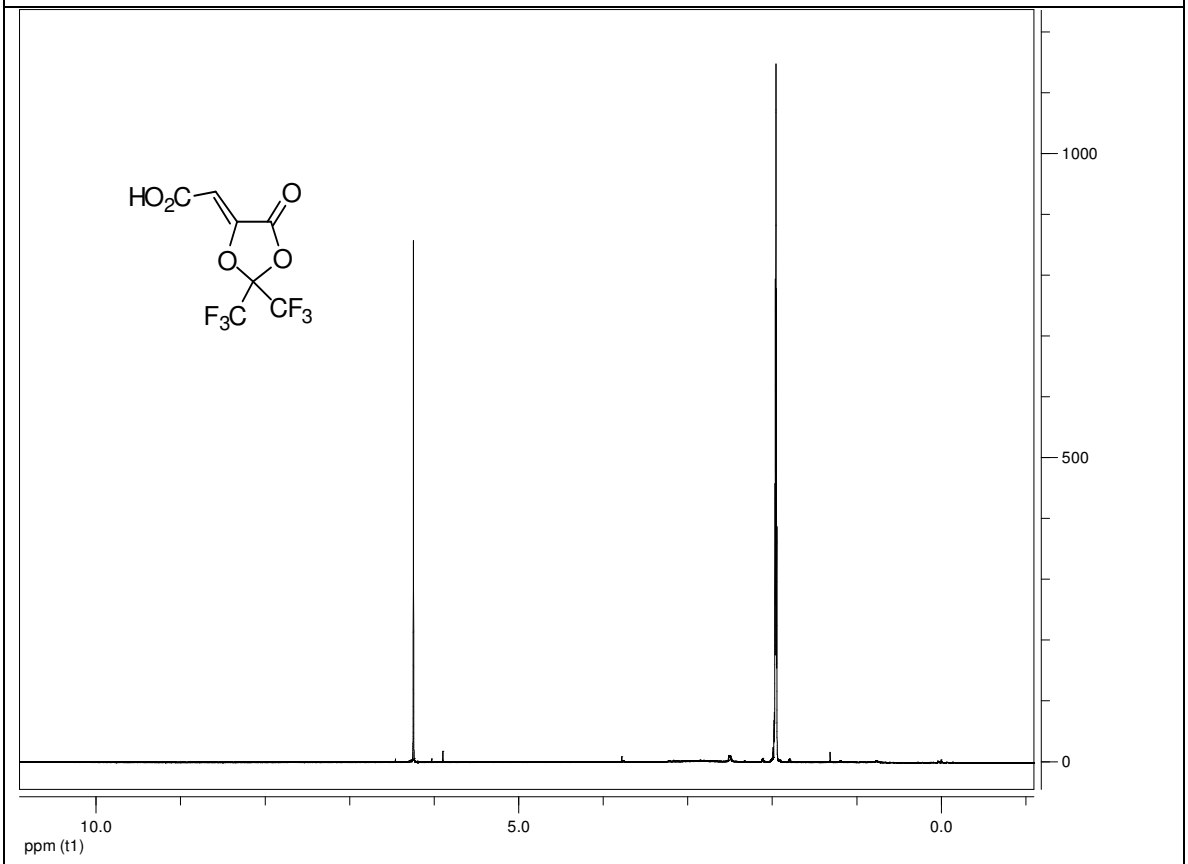
($^{1}H$, $^{13}C$: acetone-$d_6$)

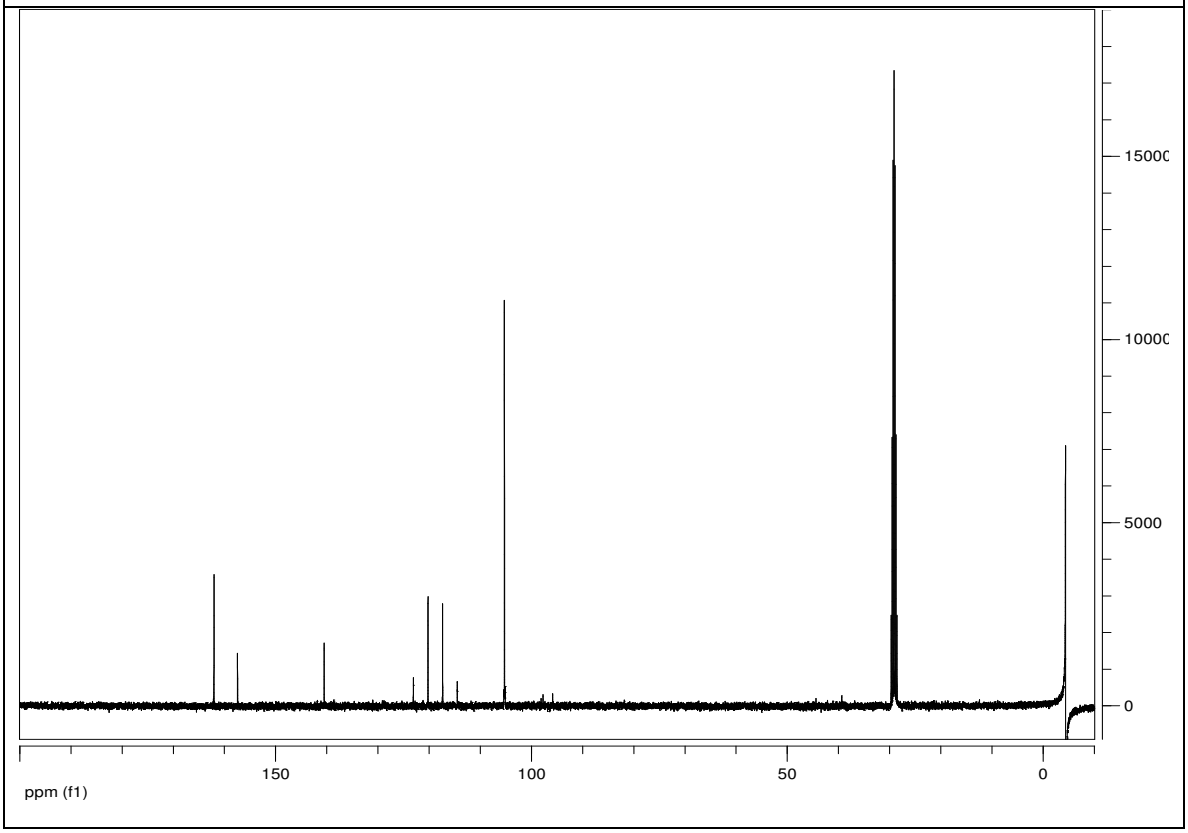


**(5-Oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-ylidene)-acetic acid 2**

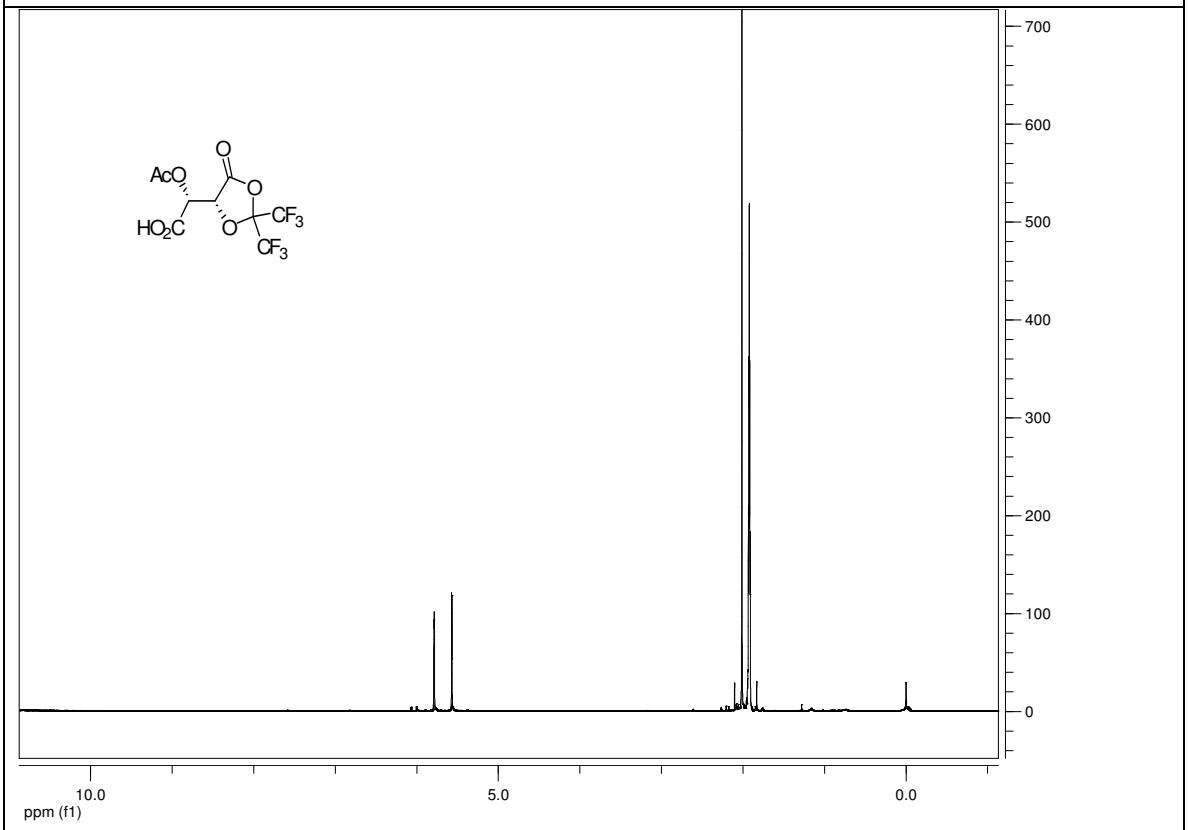
($^{1}$H, $^{13}$C: acetone-$d_6$)

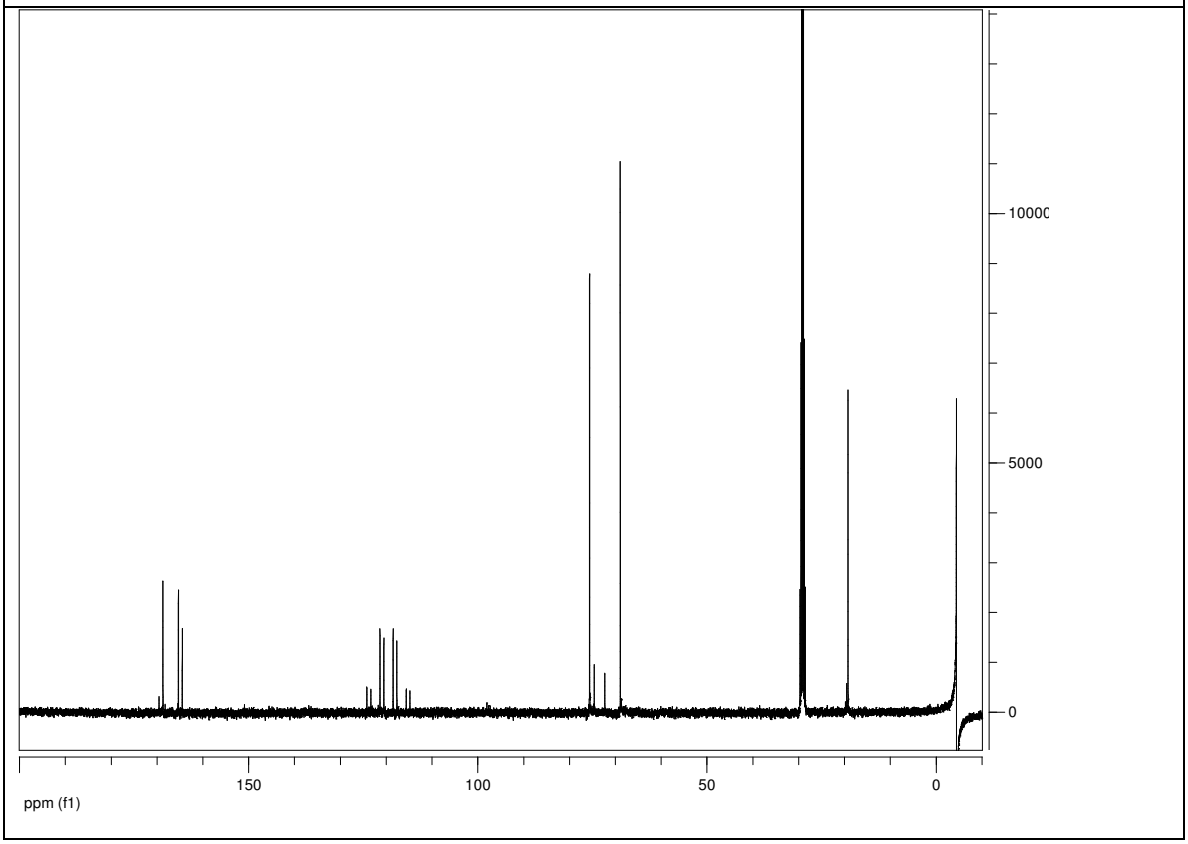


**(*2R*)-Acetoxy-{(4*R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-acetic acid 3**

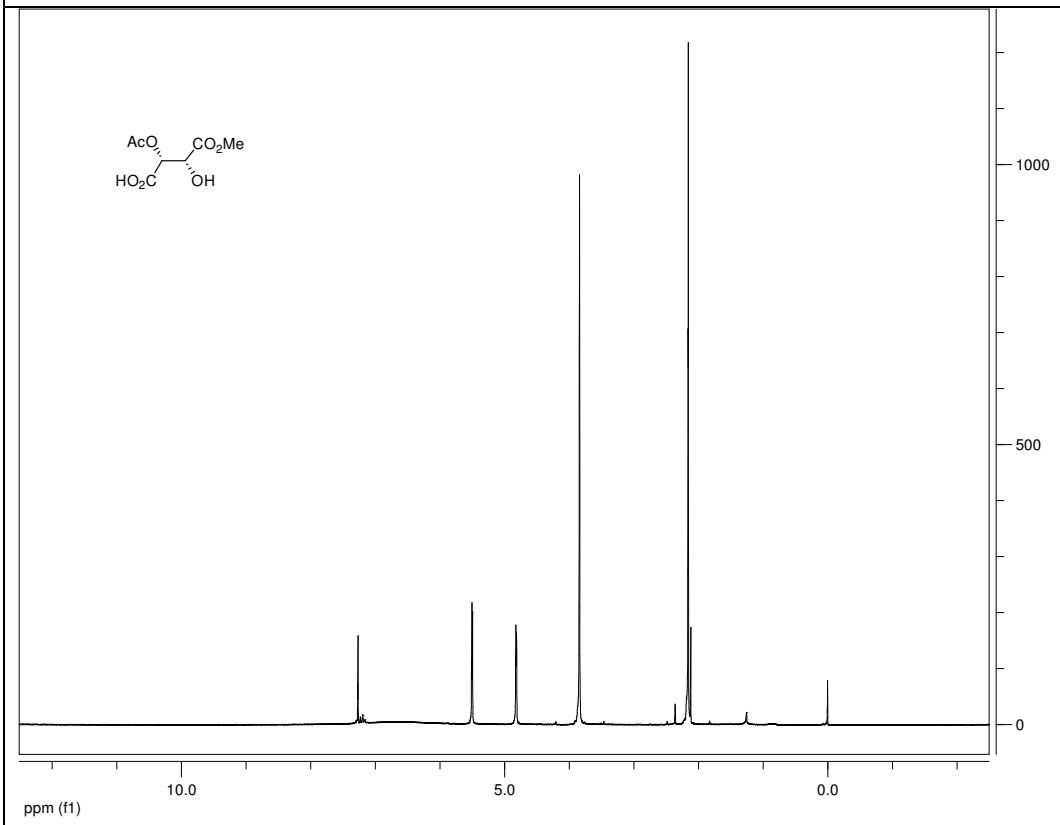
($^{1}$H, $^{13}$C: acetone-$d_6$)

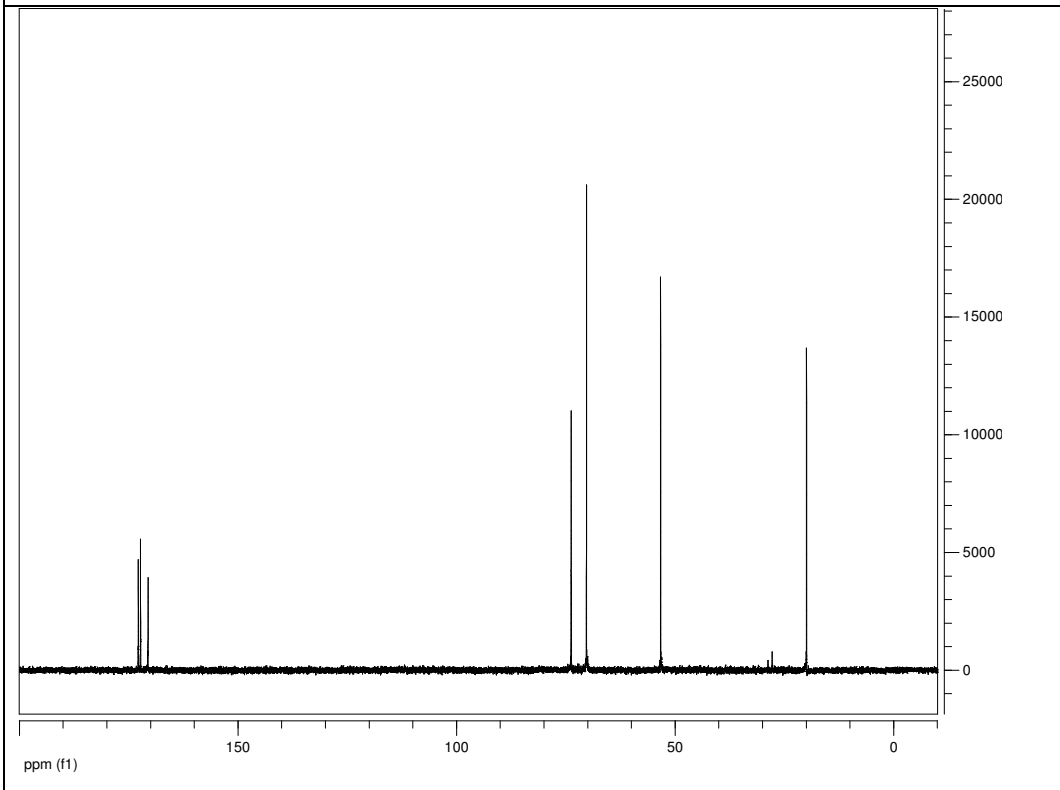


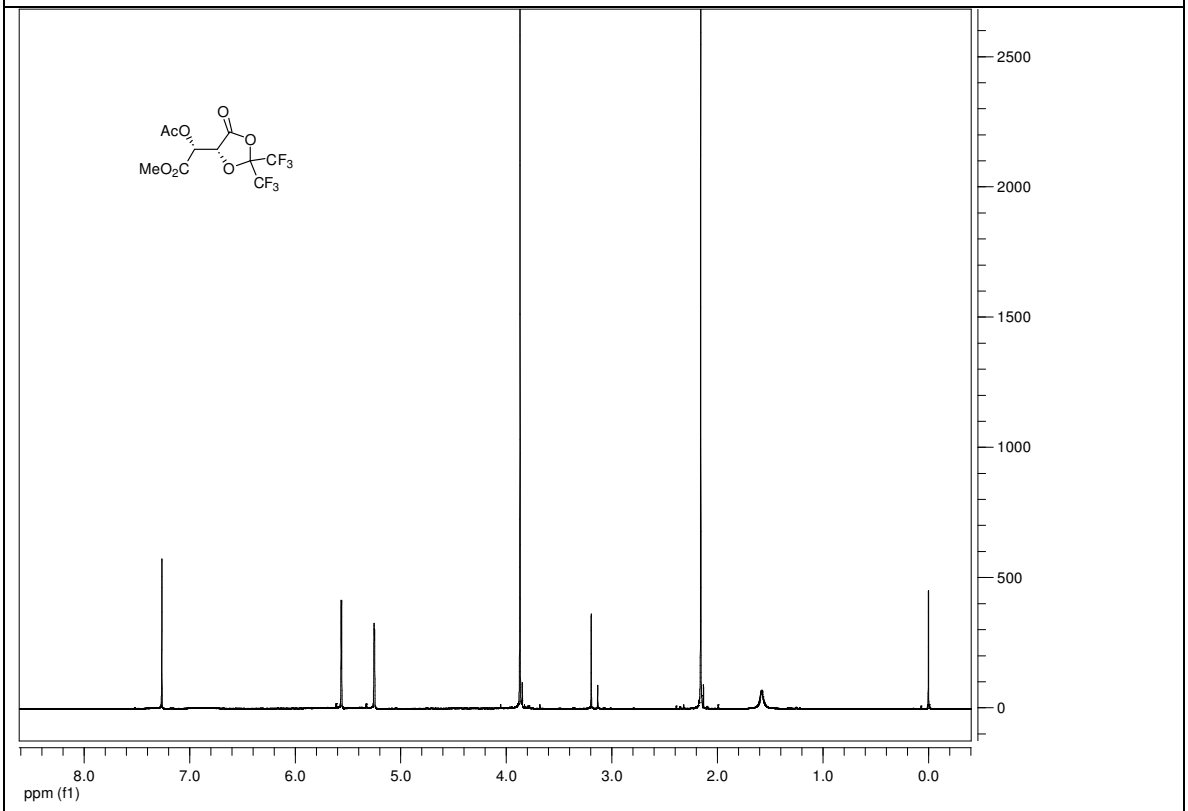
**(*2R,3R*)-3-*O*-Acetyl-1-methyl tartrate 4**

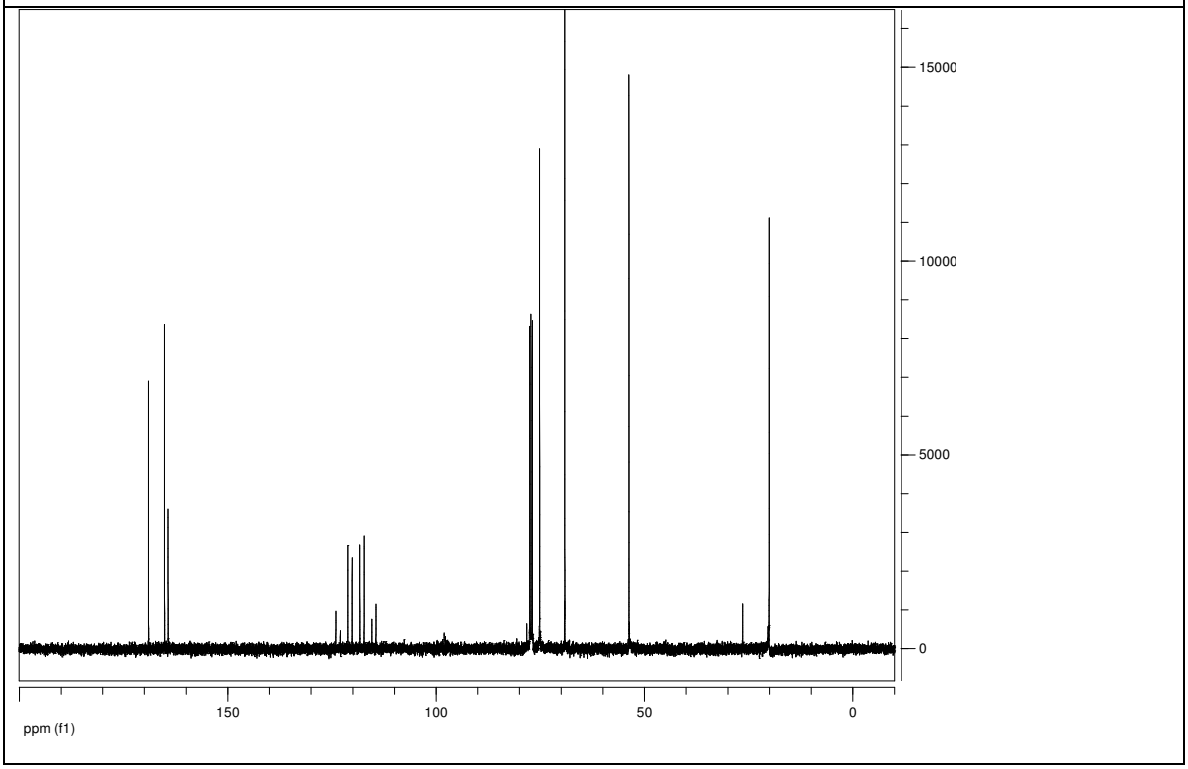
($^{1}$H: $D_2O$, $^{13}$C: acetone-$d_6$)



**(*2R*)-(Acetyoxy)-{(*4R*)-5-oxo-2,2-bis-trifluoromethyl-[1,3]dioxolan-4-yl}-methylacetate 5** ($^{1}H$, $^{13}C$: $CDCl_3$)



**(*2R,3R*)-2-*O*-Acetyl-1-methyl tartrate 6** ($^{1}H$, $^{13}C$: $CDCl_3$)