# Functionalised tetrahydrofuran fragments from carbohydrate or sugar beet pulp biomass

Laure Benhamou, Robert W. Foster, David P. Ward, Katherine Wheelhouse, Lisa Sloan, Christopher J. Tame, Dejan-Krešimir Bučar, Gary J. Lye, Helen C. Hailes,* and Tom D. Sheppard*

Department of Chemistry, University College London, Christopher Ingold Laboratories, 20 Gordon St, London, WC1H 0AJ, UK; Email: h.c.hailes@ucl.ac.uk; tom.sheppard@ucl.ac.uk

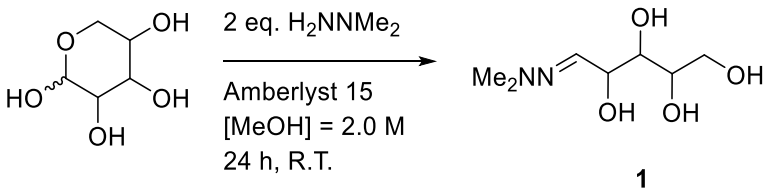
## I. General

Column chromatography was carried out using a Biotage® automated purification system using SNAP or GraceResolv flash cartridges. When stated, neutral Alumina (Brockmann I, from Sigma) was used for purification. Thin layer chromatography was carried out using Merck TLC Silica gel 60 F254 plates and products were visualised using combinations of UV light (254 nm) and potassium permanganate staining solutions.

$^{1}$H NMR spectra were recorded at 400, 500, 600 or 700 MHz, on Bruker Avance 400, 500, 600 or 700 spectrometers using the residual protic solvent stated as the internal standard. Chemical shifts are quoted in ppm to the nearest 0.01 ppm using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), m (multiplet) defined as all multi-peak signals where overlap or complex coupling of signals make definitive descriptions of peaks difficult. $^{13}$C{$^{1}$H} NMR spectra were recorded at 125, 150 or 175 MHz on Bruker Avance 500, 600 or 700 MHz spectrometers at 25 °C using the stated solvent as standard. Chemical shifts are reported to the nearest 0.1 ppm. The coupling constants are defined as *J* and quoted in Hz. Mass spectra were performed in the Department of Chemistry (University College London) and by the EPSRC UK National Mass Spectrometry Facility at Swansea University. Infrared spectra were obtained as thin film on a Perkin Elmer Spectrum 100 FT-IR Spectrometer operating in ATR mode. Melting points were measured with a Gallenkamp apparatus and were uncorrected. All optical rotations were measured on a Perkin-Elmer 343 polarimeter with a path length of 1 dm.

## II. Synthesis of chiral THFs from pentose sugars

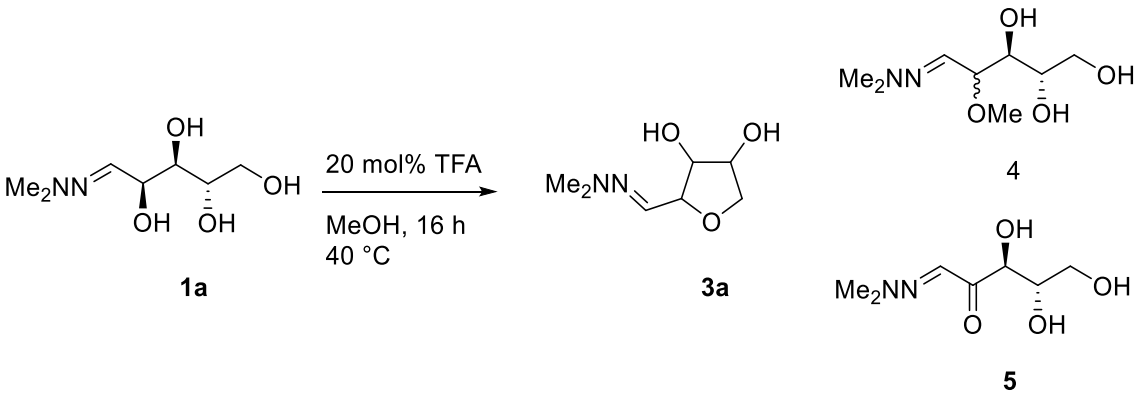
### 1. Synthesis of sugar-hydrazones




Sugar hydrazones **1** were prepared by following the procedure reported previously.[1] *N,N*-dimethylhydrazine (2 eq.) and Amberlyst 15 (1.00 g/100 mmol sugar) were added to a mixture of the pentose sugar in methanol (2.0 mol/L). The resulting mixture was stirred at room temperature for 24 hours before filtration. The clear solution was then evaporated to dryness and washed with $Et_2O$ to afford the sugar hydrazone **1**.

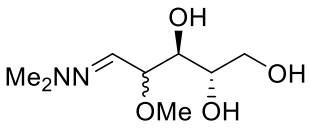
### 2. Synthesis of chiral THFs under acidic conditions

a) Procedure previously developed[1]



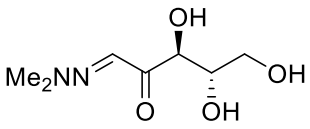

Sugar hydrazone **1a** (4.00 g, 20.8 mmol, 1 eq.) was treated with TFA (320 µL, 4.20 mmol, 0.2 eq.) in **methanol** (42 mL) and the reaction was stirred at 40 °C for 16 hours. The reaction was then quenched with solid $NaHCO_3$ and concentrated *in vacuo* to give the crude hydrazone. The residue was purified by column chromatography on silica using a gradient of petrol:acetone (50:50 to 0:100) and afforded **3a** (2.46 g, 68%) as a first fraction, **4** (0.95 g, 22 %) as second fraction and **5** (0.20 g, 5%) as a third fraction.

**(*2S,3S*)-5-(2,2-Dimethylhydrazineylidene)-4-methoxypentane-1,2,3-triol (4)**



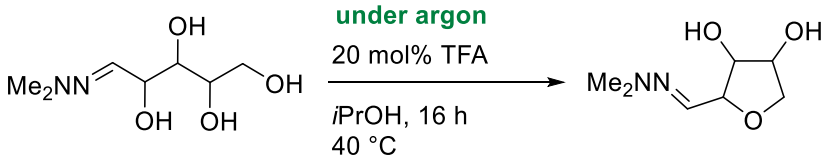
Yellow oil (*dr* = 57:43); $^{1}$H NMR (600 MHz, MeOH-$d_4$) δ = 6.67 (d, *J* = 7.2, 1H, NC*H*$_{Maj}$), 6.61 (d, *J* = 7.2, 1H, NC*H*$_{min}$), 3.96 (dd, *J* = 7.2, 3.0, 1H, MeOC*H*$_{Maj}$), 3.92 (dd, *J* = 7.2, 4.2, 1H, MeOC*H*$_{min}$), 3.79 – 3.73 (m, 3H, OC*H*H'$_{Maj}$, OC*H*H'$_{min}$, C*H*$_{min}$), 3.71 (ddd, *J* = 8.2, 6.1, 3.2, 1H, OCH$_2$C*H*$_{Maj}$), 3.63 – 3.55 (m, 3H; OCH*H*'$_{Maj}$, OCH*H*'$_{min}$, C*H*$_{min}$), 3.51 (dd, *J* = 8.1, 3.0, 1H, OCH$_2$CHC*H*$_{Maj}$), 3.32 (s, 3H, OC*H*$_3$), 3.31 (s, 3H, overlap MeOH, OC*H*$_3$) 2.81 (s, 6H, N(C*H*$_3$)$_{2\text{-}min}$), 2.80 (s, 6H, N(C*H*$_3$)$_{2\text{-}Maj}$) ; $^{13}$C{$^{1}$H} NMR (151 MHz, MeOH-$d_4$) δ = 136.9 (N*C*H$_{Maj}$), 136.0 (N*C*H$_{min}$), 83.4 (MeO*C*H$_{min}$), 81.7 (MeO*C*H$_{Maj}$), 75.3 (OCH$_2$CH*C*H$_{Maj}$), 74.6 (OCH$_2$CH*C*H$_{min}$), 73.2 (OCH$_2$*C*H$_{min}$), 72.5 (OCH$_2$*C*H$_{Maj}$), 64.8 (O*C*H$_{2\text{-}Maj}$), 64.7 (O*C*H$_{2\text{-}min}$), 56.9 (O*C*H$_3$), 56.6 (O*C*H$_3$), 43.0 (2 x N(*C*H$_3$)$_2$) ppm; FT-IR (ATR) v = 3380, 2934, 2827, 2788, 1706, 1467 cm$^{-1}$; HRMS (ESI) *m/z* found [M+Na]$^+$ 229.1159, $C_8H_{18}N_2O_4Na$ requires 229.1159.

**(*3S,4S*)-1-(2,2-Dimethylhydrazineylidene)-3,4,5-trihydroxypentan-2-one (5)**



Yellow oil; $^{1}$H NMR (600 MHz, DMSO-$d_6$) δ = 6.63 (s, 1H, NC*H*), 4.73 (d, *J* = 7.3, 1H, O*H*), 4.67 (dd, *J* = 7.3, 6.2, 1H, OCH$_2$CHC*H*), 4.51 (d, *J* = 6.0, 1H, O*H*), 4.32 (t, *J* = 5.7, 1H, CH$_2$O*H*), 3.71 (m, 1H, OCH$_2$C*H*), 3.49 – 3.41 (m, 1H, OC*H*H'), 3.37 – 3.30 (m, 1H, overlaps with water peak, OCH*H*'), 3.12 (s, 6H, N(C*H*$_3$)$_2$) ppm; $^{13}$C{$^{1}$H} NMR (151 MHz, DMSO-$d_6$) δ = 196.6 (*C*=O), 126.0 (N*C*H), 73.4 (OCH$_2$*C*H), 71.7 (OCH$_2$CH*C*H), 62.6 (O*C*H$_2$), 40.1 (N(*C*H$_3$)$_2$ below DMSO peak) ppm.

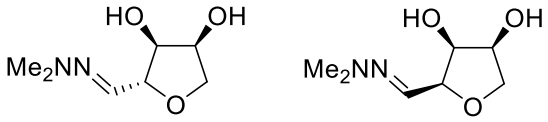
b) Optimised procedure – Large scale




**1** **3**

**General procedure 1:** Sugar-hydrazone **1** was treated with TFA (20 mol%) at room temperature in isopropanol (0.5 mol/L) and the reaction was stirred at 40 °C for 16 hours. The reaction was then quenched with solid $NaHCO_3$ and concentrated *in vacuo* to give the crude hydrazone. The product was purified by column chromatography on silica using a gradient of petrol/acetone (50:50 to 0:100) as eluent. Evaporation to dryness afforded the desired THFs **3** as a mixture of two diastereomers in agreement with the data previously reported.[1]

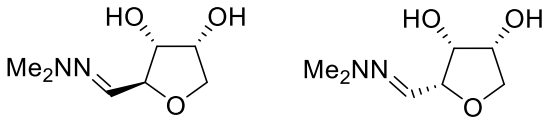
**(*2R,3S,4S*)-2-((*E*)-(2,2-Dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*anti*-3a) and (*2S,3S,4S*)-2-((*E*)-(2,2-dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*syn*-3a)**




*dr* 78 22

A mixture of ***anti*-3a** and ***syn*-3a** was obtained following the **General procedure 1** using (*2S,3R,4S*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetraol **1a** (23.8 g, 124 mmol, 1 eq.), TFA (1.90 mL, 25.0 mmol, 0.2 eq.) in *i*PrOH (250 mL). After purification by column chromatography, the mixture of ***anti*-3a** and ***syn*-3a** was isolated as a yellow thick oil (17.4 g, 81%, *dr* = 78:22); $^1$H NMR (600 MHz, MeOH-d$_4$) δ = 6.71 (d, *J* = 7.1, 1H, NC*H*$_{syn}$), 6.51 (d, *J* = 6.6, 1H, NC*H*$_{anti}$), 4.37 – 4.30 (m, 2H, NCHC*H*$_{syn}$, OCH$_2$C*H*$_{syn}$), 4.23 – 4.18 (m, 2H, NCHC*H*$_{anti}$, OCH$_2$C*H*$_{anti}$), 4.16 (app t, *J* = 4.8, 1H, OCH$_2$CHC*H*$_{syn}$), 4.08 (dd, *J* = 9.6, 4.7, 1H, OCH*H*'$_{anti}$), 4.02 (dd, *J* = 7.2, 4.8, 1H, OCH$_2$CHC*H*$_{anti}$), 3.90 (dd, *J* = 8.8, 6.2, 1H, OCH*H*'$_{syn}$), 3.75 (dd, *J* = 8.8, 5.7, 1H, OC*H*H'$_{syn}$), 3.74 (dd, *J* = 9.6, 2.9, 1H, OC*H*H'$_{anti}$), 2.79 (s, 12H, N(C*H*$_3$)$_2$). $^1$H NMR data are consistent with the data previously reported.[1] Pure ***anti*-3a** could be obtained by recrystallisation of the material from THF/Petrol.

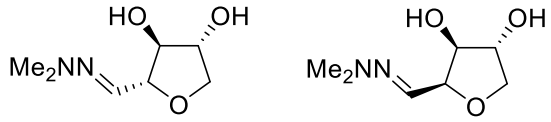
**(*2S,3R,4R*)-2-((*E*)-(2,2-Dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*anti*-3b) and (*2R,3R,4R*)-2-((*E*)-(2,2-dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*syn*-3b)**




*dr* 77 23

A mixture of ***anti*-3b** and ***syn*-3b** was obtained following the **General procedure 1** using (*2R,3S,4S*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetraol **1b** (24.7 g, 128 mmol, 1 eq.), TFA (2.00 mL, 26.0 mmol, 0.2 eq.) in *i*PrOH (250 mL). After purification by column chromatography, the mixture of ***anti*-3b** and ***syn*-3b** was isolated as a yellow thick oil (15.2 g, 68%, *dr* = 77:23); $^1$H NMR data are consistent with compound **3a** and with the data previously reported by our group.[1] Pure ***anti*-3b** could be obtained by recrystallisation of the material from THF/Petrol.

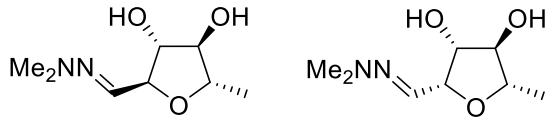
**(*2R,3S,4R*)-2-((*E*)-(2,2-dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*anti*-3c) and (*2S,3S,4R*)-2-((*E*)-(2,2-dimethylhydrazineylidene)methyl)tetrahydrofuran-3,4-diol (*syn*-3c)**




*dr* 55 45

A mixture of ***anti*-3c** and ***syn*-3c** was obtained following the **General procedure 1** using (*2R,3R,4S*)-5-(2,2-dimethylhydrazineylidene)pentane-1,2,3,4-tetraol **1c** (15.5 g, 81.0 mmol, 1 eq.), TFA (1.20 mL, 16.0 mmol, 0.2 eq.) in *i*PrOH (115 mL). After purification by column chromatography, the mixture of ***anti*-3c** and ***syn*-3c** was isolated as a yellow thick oil (9.30 g, 66%, *dr* = 55:45). $^1$H NMR (600 MHz, $D_2O$) δ = 6.92 (d, *J* = 6.6, 1H, NC*H*$_{Major}$), 6.88 (d, *J* = 6.4, 1H, NC*H*$_{minor}$), 4.60 (dd, *J* = 6.4, 3.6, 1H, NCHC*H*$_{minor}$), 4.40 – 4.38 (m, 1H, $OCH_2$C*H*$_{minor}$), 4.35 – 4.33 (m, 2H, $OCH_2$C*H*$_{Major}$, NCHC*H*$_{Major}$), 4.26 – 4.23 (m, 2H, $OCH_2$CHC*H*$_{minor}$, OC*H*H'$_{minor}$), 4.20 – 4.19 (m, 1H, $OCH_2$CHC*H*$_{Major}$), 4.10 (dd, *J* = 10.0, 4.1, 1H, OC*H*H'$_{Major}$), 3.98 (dd, *J* = 10.0, 2.0, 1H, OCH*H*'$_{Major}$), 3.83 (dd, *J* = 10.0, 1.1, 1H, OCH*H*'$_{minor}$), 2.80 (s, 6H, N(C*H*$_3$)$_{2\text{-minor}}$), 2.78 (s, 6H, N(C*H*$_3$)$_{2\text{-Major}}$). $^1$H NMR data are consistent with the data previously reported by our group.[1]

**(*2S,3R,4R,5S*)-2-((*E*)-(2,2-Dimethylhydrazineylidene)methyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-3d) and (*2R,3R,4R,5S*)-2-((*E*)-(2,2-dimethylhydrazineylidene)methyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-3d)**




*dr* 60 40

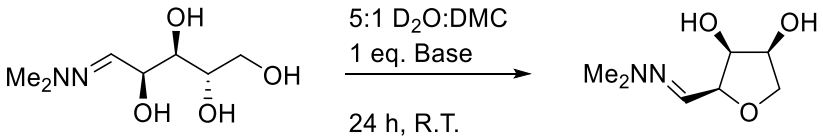
A mixture of ***anti*-3d** and ***syn*-3d** was obtained following the **General procedure 1** using (*2S,3S,4S,5S*)-1-(2,2-dimethylhydrazineylidene)hexane-2,3,4,5-tetraol **1d** (10.8 g, 52.0 mmol, 1 eq.), TFA (0.80 mL, 10.0 mmol, 0.2 eq.) in *i*PrOH (105 mL). After purification by column chromatography, the mixture of ***anti*-3d** and ***syn*-3d** was isolated as a yellow thick oil (7.30 g, 75%, *dr* = 60:40). $^1$H NMR (600 MHz, MeOH-$d_4$) δ = 6.64 (d, *J* = 6.9, 1H, NC*H*$_{minor}$), 6.61 (d, *J* = 6.5, 1H, NC*H*$_{Major}$), 4.41 (dd, *J* = 6.9, 4.3, 1H, NCHC*H*$_{minor}$), 4.25 (app t, *J* = 6.5, 1H, NCHC*H*$_{Major}$), 4.03 (app t, *J* = 5.8, 1H, NCHCHC*H*$_{Major}$), 4.00 (dd, *J* = 4.3, 2.1, 1H, NCHCHC*H*$_{minor}$), 3.88 (q, *J* = 6.3, 1H, $CH_3$C*H*$_{Major}$), 3.79 – 3.73 (m, 1H, $CH_3$CHC*H*$_{minor}$), 3.69 (dd, *J* = 6.3, 5.7, 1H, $CH_3$CHC*H*$_{Major}$), 2.81 (s, 6H, N(C*H*$_3$)$_{2\text{-minor}}$), 2.79 (s, 6H, N(C*H*$_3$)$_{2\text{-Major}}$), 1.33

(d, *J* = 6.3, 3H, C*H*$_{3\text{-minor}}$), 1.28 (d, *J* = 6.3, 3H, C*H*$_{3\text{-Major}}$). $^1$H NMR data are consistent the data previously reported.[1]

## 3. Synthesis of chiral THFs under basic conditions

a) Optimisation

**Base Screen**




**10** **3a**

A screen of bases in $D_2O$ revealed that three inorganic bases ($K_2CO_3$, KOH and $Na_3PO_4$) gave broadly consistent conversion. Of the organic bases screened only DBU and $NEt_3$ resulted in 50% conversion after 24 h in both cases.

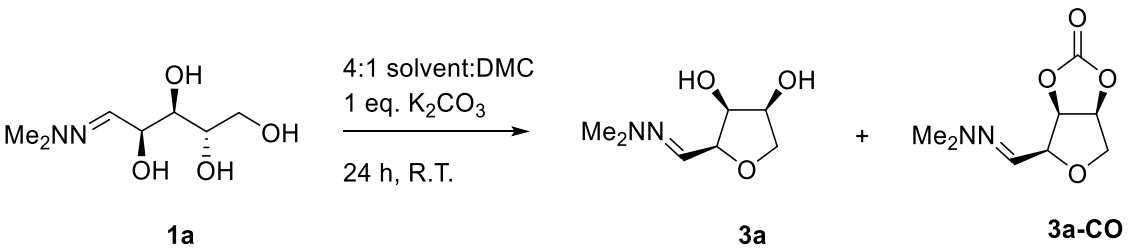
**Table 1:** Solvent screen for the cyclisation under basic condition

| Entry | Base | Conversion (%) | *Syn:anti* |
|---|---|---|---|
| **1** | $K_2CO_3$ | 35 | 75:25 |
| **2** | KPH | 35 | 70:30 |
| **3** | $Na_3PO_4$ | 40 | 75:25 |
| **4** | DBU | 50 | 70:30 |
| **5** | $HNC(N(CH_3)_2)_2$ | 0 | - |
| **6** | DABCO | 0 | - |
| **7** | $NEt_3$ | 50 | 75:25 |
| **8** | Pyridine | 0 | - |
| **9** | DMAP | 0 | - |
| **10** | NaI | 0 | - |

**Solvent Screen**

A series of solvents were screened for the DMC-mediated cyclization. Low conversion was observed using neat DMC. CPME and 1,4-dioxane similarly resulted in low conversion. However, in acetone, methanol, water and *i*PrOH a reaction was observed. MeOH gave the

greatest conversion, however cyclic carbonate **3a-CO** was formed as a significant side product.



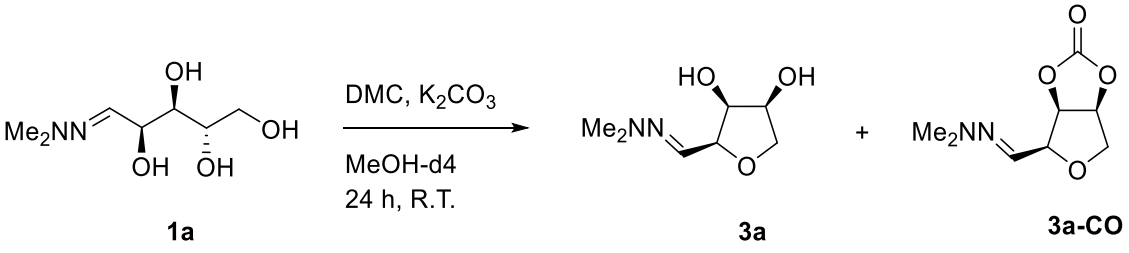

**1a** **3a** **3a-CO**

**Table 2:** Solvent screen for the cyclisation under basic condition

| Entry | Solvent | Conversion (%) | 3a:3a-CO |
|---|---|---|---|
| **1** | DMC | 0 | - |
| **2** | CPME | 0 | - |
| **3** | Acetone | 75 | 60:40 |
| **4** | 1,4-dioxane | 0 | - |
| **5** | *i*PrOH | 45 | 70:30 |
| **6** | MeOH | 90 | 70:30 |
| **7** | $H_2O$ | 25 | 75:25 |

**Stoichiometry of DMC and $K_2CO_3$**

The reaction was then screened using methanol as a solvent, varying the amount of base and DMC added. The loading of base was very important, with 20 mol% $K_2CO_3$ giving significantly reduced conversion. In contrast the loading of DMC was less important. With lower DMC loading the formation of carbonate **3a-CO** was reduced to 10%.

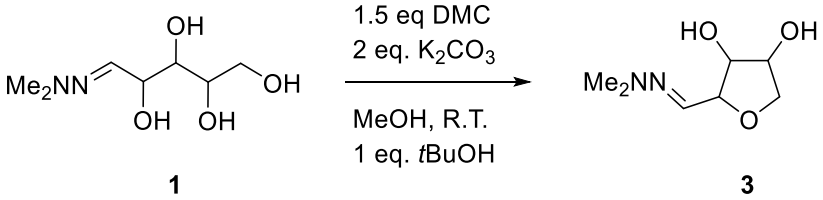



**1a** **3a** **3a-CO**

**Table 3:** Stoichiometry of DMC and $K_2CO_3$

| Entry | DMC (mol%) | $K_2CO_3$ (mol%) | Conversion (%) | *3a:3a-CO* | *syn:anti* |
|---|---|---|---|---|---|
| **1** | 0 | 200 | - | - | - |
| **2** | 50 | 200 | 43 | - | 75:25 |
| **3** | 100 | 200 | 78 | - | 75:25 |
| **4** | 120 | 20 | 20 | > 20:1 | 75:25 |
| **5** | 150 | 0 | 0 | - | - |
| **6** | 150 | 20 | 20 | > 20:1 | 75:25 |
| **7** | 150 | 100 | 85 | > 10:1 | 70:30 |
| **8** | 150 | 200 | 87 | - | 80:20 |
| **9** | 300 | 20 | 20 | > 20:1 | 75:25 |

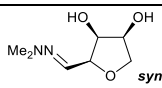
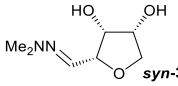
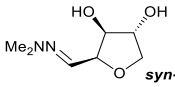
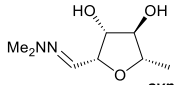
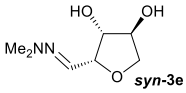
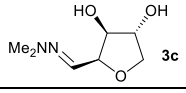
b) Optimised procedure for the basic cyclisation - Quantification




**1** **3**

Dimethylcarbonate (20 µL, 0.23 mmol, 1.5 eq.), $K_2CO_3$ (43 mg, 0.31 mmol, 2 eq.) and a solution of internal standard *tert*-butanol (160 µL, 1M in MeOH-$d_4$, 1 eq.) were added to a solution of sugar hydrazone **1** (30 mg, 0.16 mmol, 1 eq.) in MeOH-$d_4$ (0.75 mL). The solution was stirred overnight at room temperature, filtered through a pad of Celite and analysed by NMR spectroscopy. The results are reported in the **Table 4**.

**Table 4:** Cyclisation of sugar-hydrazones **1** under basic conditions

| Pentose | Product | Yield (%) | *dr (syn:anti)* |
|---|---|---|---|
| **L-arabinose** |  *syn*-3a | > 95 | 69:31 |
| **D-ribose** |  *syn*-3b | 87 | 79:21 |
| **D-xylose** |  *syn*-3c | > 95 | 75:25 |
| **L-rhamnose** |  *syn*-3d | 92 | 74:26 |
| **L-xylose** |  *syn*-3e | 84 | 83:17 |
| **D-lyxose** |  3c | > 95 | 78:22 |

## Basic cyclisation – Selectivity

## From L-arabinose-hydrazone 1a

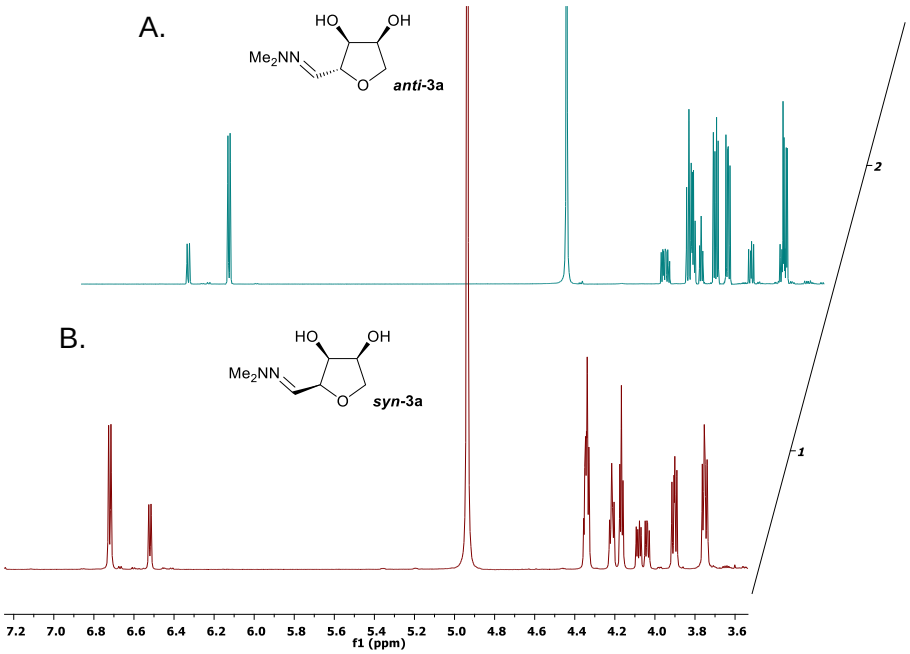



**Figure 1:** $^{1}$H NMR (600 MHz, MeOH-$d_4$). A. Cyclisation of hydrazone **1a** under acidic conditions; B. Cyclisation of hydrazone **1a** under basic conditions

## From D-ribose-hydrazone 1b

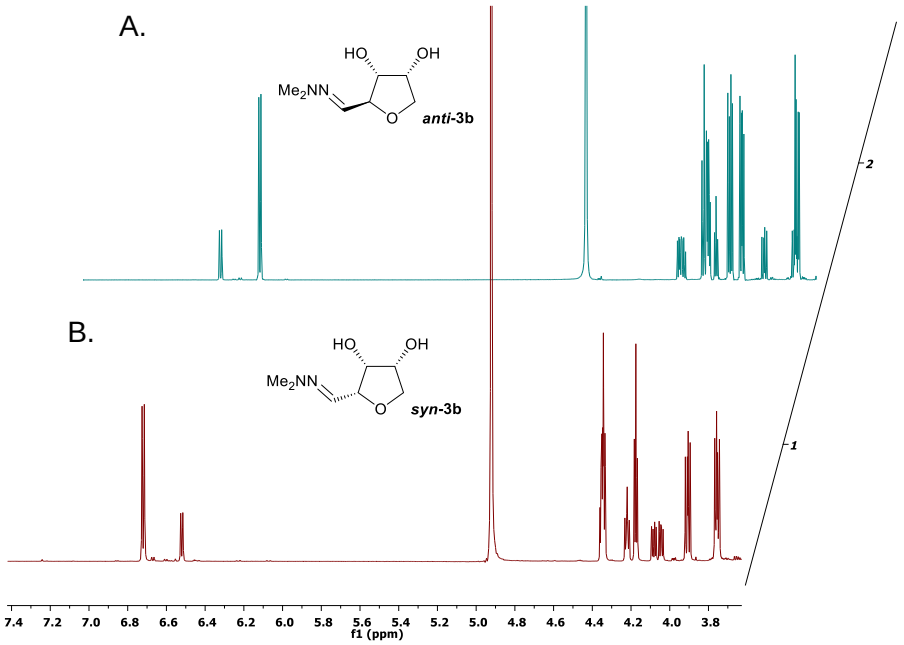



**Figure 2:** $^{1}$H NMR (600 MHz, MeOH-$d_4$). A. Cyclisation of hydrazone **1b** under acidic conditions; B. Cyclisation of hydrazone **1b** under basic conditions

## From D-xylose-hydrazone 1c

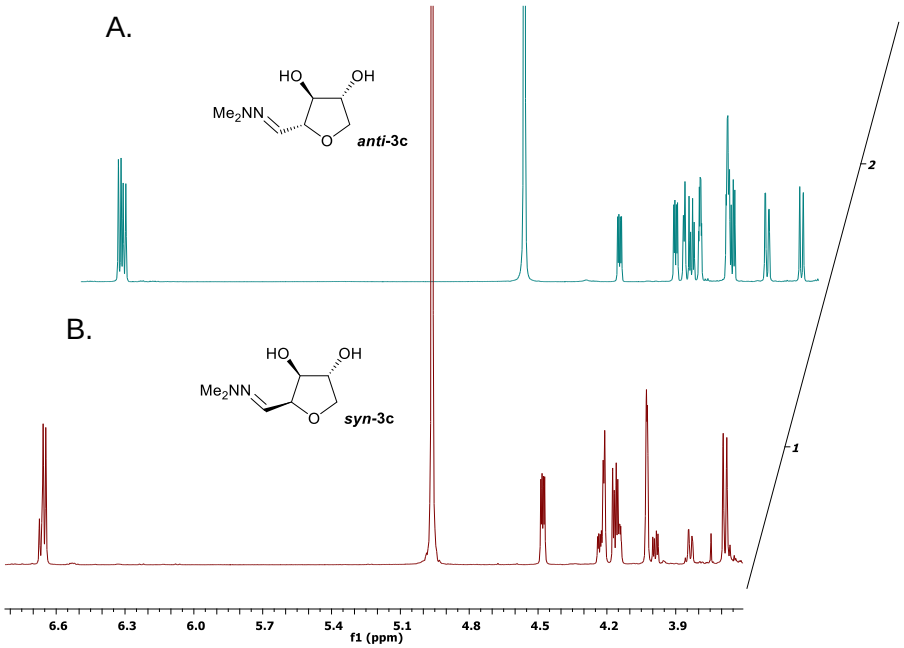



**Figure 3:** $^{1}$H NMR (600 MHz, MeOH- $d_4$). A. Cyclisation of hydrazone **1c** under acidic conditions; B. Cyclisation of hydrazone **1c** under basic conditions

**From L-Rhamnose-hydrazone 1d**

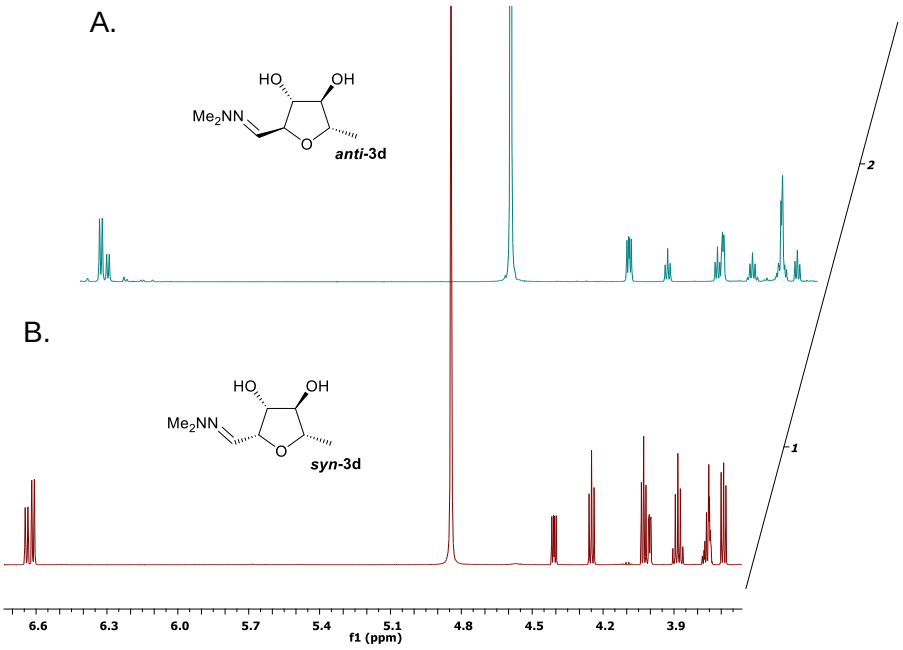



**Figure 4:** $^{1}$H NMR (600 MHz, MeOH-$d_4$). A. Cyclisation of hydrazone **1d** under acidic conditions; B. Cyclisation of hydrazone **1d** under basic conditions

**From L-xylose-hydrazone 1e**

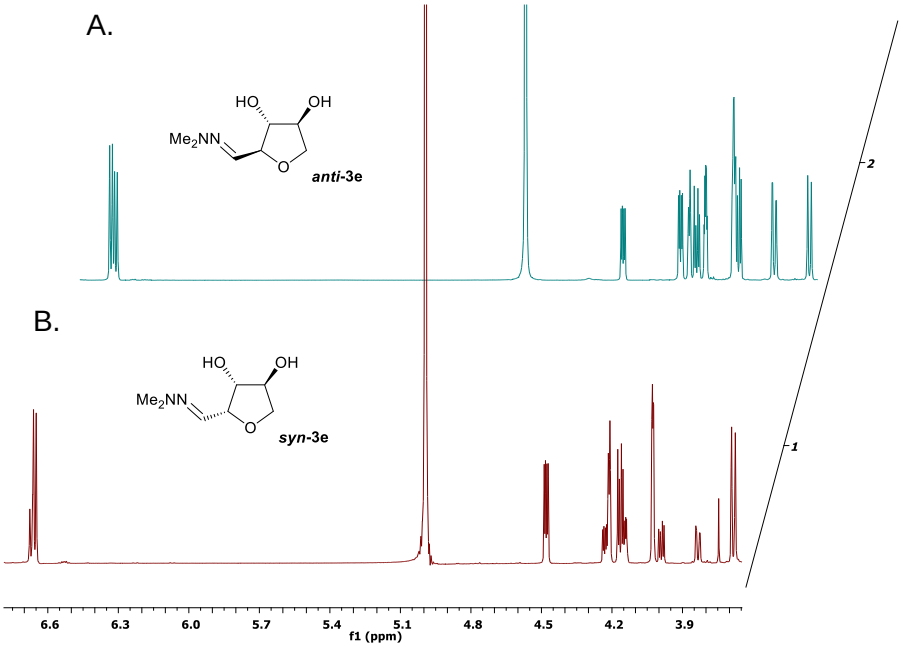



**Figure 5:** $^{1}$H NMR (600 MHz, MeOH- $d_4$). A. Cyclisation of hydrazone **1e** under acidic conditions; B. Cyclisation of hydrazone **1e** under basic conditions

**From D-lyxose-hydrazone 1f**

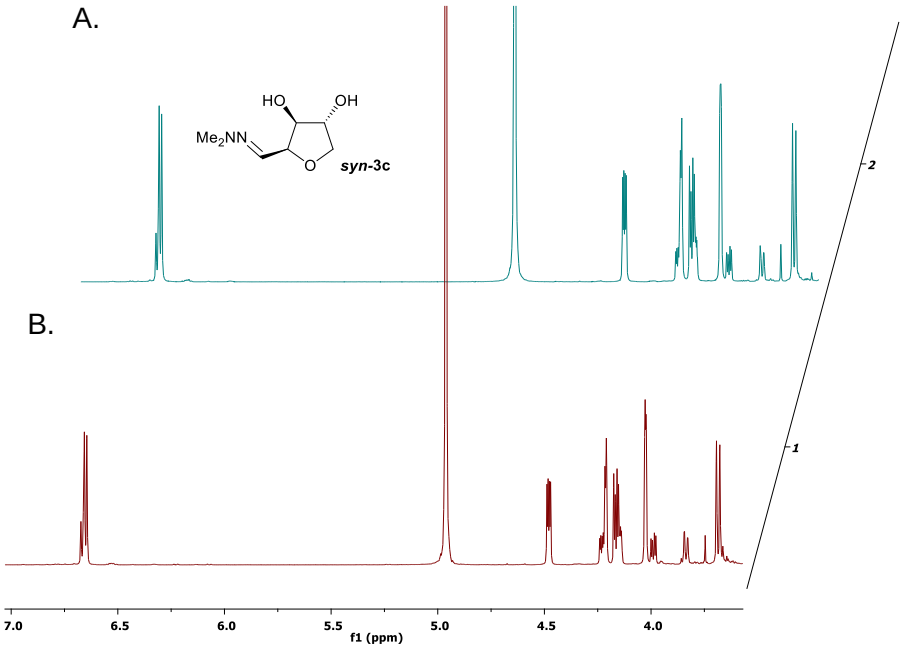
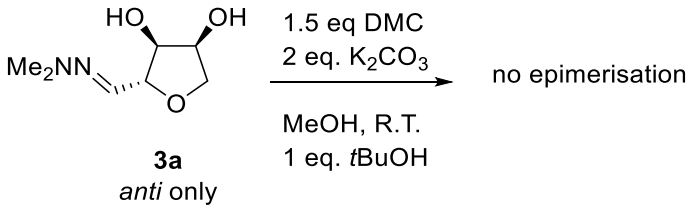


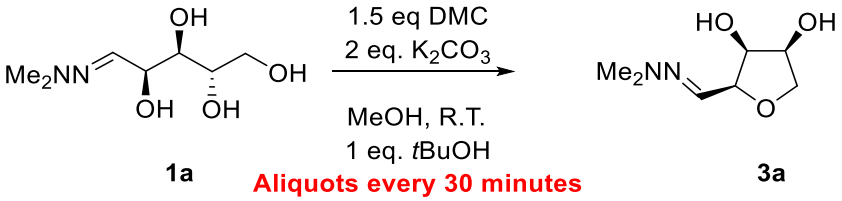

**Figure 6:** $^{1}$H NMR (600 MHz, MeOH-d$_4$). A. Compound ***syn*-3c**; B. Cyclisation of hydrazone **1f** under basic conditions

c) Mechanistic investigations




Dimethylcarbonate (22 µL, 0.26 mmol, 1.5 eq.), $K_2CO_3$ (47 mg, 0.34 mmol, 2 eq.) and a solution of internal standard *tert*-butanol (172 µL, 1M in MeOH-d4, 0.17 mmol, 1 eq.) were added to a solution of chiral THF *anti*-**3a** (30 mg, 0.17 mmol, 1 eq.) in MeOH-d$_4$ (0.75 mL). The resulting mixture was stirred overnight at room temperature before filtration through a small pad of celite. The clear solution obtained was analysed by NMR. No epimerisation was observed after 24 hours.

d) Kinetics




The reaction was followed by NMR by taking aliquots every 30 minutes.

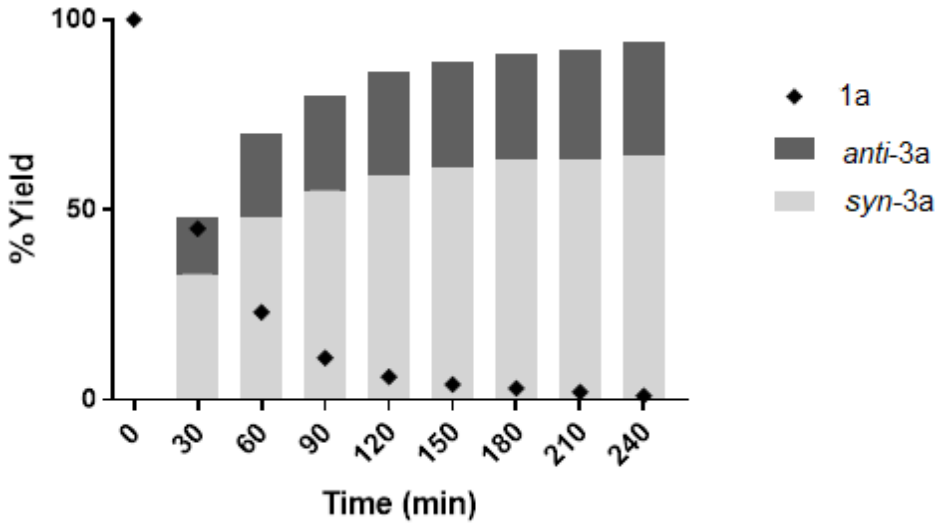
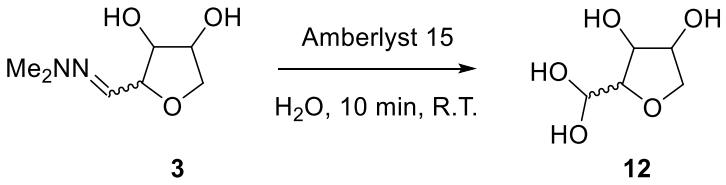



**Figure 7:** Timecourse experiment for the cyclisation of sugar-hydrazone **1a** under basic conditions. No change in the diastereomeric ratio was noted during the cyclisation reaction.

After 30 minutes, ≈ 50% of the arabinose hydrazone **1a** was consumed and after 3 hours the conversion was complete.

## III. Chiral functionalised THFs - Fragments for medicinal chemistry

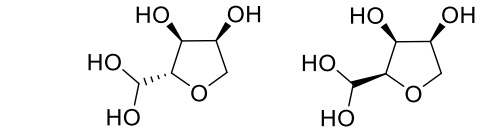
### 1. Synthesis of THF-hydrates




**3** **12**

**General procedure 2:** Amberlyst 15 (0.5 g/mmol) was added to a solution of THF **3** in water (0.2 mol/L). The resulting mixture was stirred at room temperature. After 10 minutes the reaction was filtered and concentrated *in vacuo.* The resulting thick oil was lyophilised to give the hydrate **12** as a white foam.

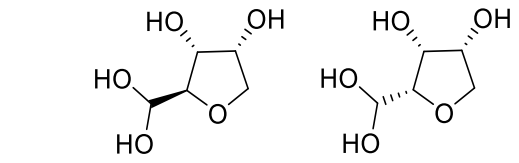
**(*2S,3S,4S*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-12a) and (*2R,3S,4S*)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-12a)**




*dr* 80 20

The THF-hydrate **12a** was obtained following the **General procedure 2** using Amberlyst 15 (7 g) and THF-hydrazone **3a** (2.41 g, 13.8 mmol, *dr* = 50:50 (*anti:syn*)). After lyophilisation, the hydrate was isolated as an hygroscopic white foam (1.59 g, 77%, *dr* = 80:20 (*anti:syn*)); $^{1}$H NMR (600 MHz, $D_2O$) δ = 5.16 (app. d, *J* = 7.2, 1H, C*H*$(OD)_{2\text{-}syn}$), 5.04 (app. d, *J* = 4.6, 1H, C*H*$(OD)_{2\text{-}anti}$), 4.47 (td, *J* = 7.4, 4.6, 1H, $CH_2CH_{syn}$), 4.31 – 4.26 (m, 2H, $CH_2CH_{anti}$, $OCH_2CHCH_{syn}$), 4.22 (dd, *J* = 6.1, 5.0, 1H, $OCH_2CHCH_{anti}$), 4.05 – 4.02 (m, 2H, OC*H*H'$_{anti}$, OC*H*H'$_{syn}$), 3.81 (dd, *J* = 10.0, 3.2, 1H, OCH*H*'$_{anti}$), 3.78 (dd, *J* = 7.2, 3.7, 1H, $CH(OD)_2CH_{syn}$), 3.74 (dd, *J* = 6.1, 4.6, 1H, $CH(OD)_2CH_{anti}$), 3.71 (dd, *J* = 8.6, 7.7, 1H, OCH*H*'$_{syn}$); $^{13}$C{$^{1}$H} NMR (150 MHz, $D_2O$ with MeOH standard) δ = 89.9 (*C*H$(OD)_{2\text{-}anti}$), 88.7 (*C*H$(OD)_{2\text{-}syn}$), 83.7 ($CH(OD)_2CH_{anti}$), 82.7 ($CH(OD)_2CH_{syn}$), 72.4 ($OCH_2CH_{anti}$), 72.2 (O*C*H$_{2\text{-}anti}$), 71.3 ($OCH_2CHCH_{anti}$), 71.3 ($OCH_2CHCH_{syn}$), 71.0 ($OCH_2CH_{syn}$), 70.3 (O*C*H$_{2\text{-}syn}$). NMR Data were consistent with the data previously reported.[1,2]

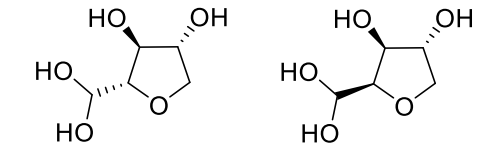
**(*2R,3R,4R*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-12b) and (*2S,3R,4R*)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-12b)**




*dr* 90 10

The THF-hydrate was obtained following the **General procedure 2** using Amberlyst 15 (7 g) and THF-hydrazone **3b** (2.22 g, 12.7 mmol, *dr* = 80:20 (*anti:syn*)). After lyophilisation, the hydrate was isolated as an hygroscopic white foam (1.54 g, 79%, *dr* = 90:10 (*anti:syn*)); $^{1}$H NMR (600 MHz, $D_2O$) δ = 5.09 (app. d, *J* = 7.2, 1H, C*H*$(OD)_{2\text{-}syn}$), 4.97 (d, *J* = 4.7, 1H, C*H*$(OD)_{2\text{-}anti}$), 4.42 (td, *J* = 7.4, 4.6, 1H, $OCH_2CH_{syn}$), 4.24 – 4.20 (m, 2H, $OCH_2CH_{anti}$, $CH_2CHCH_{syn}$), 4.19 - 4.15 (m, 1H, $CH_2CHCH_{anti}$), 4.00 - 3.94 (m, 2H, OC*H*H'$_{anti}$, OC*H*H'$_{syn,}$), 3.75 (dd, *J* = 10.0, 3.2, 1H, OCH*H*'$_{anti}$), 3.72 (dd, *J* = 7.2, 3.7, 1H, $CH(OD)_2CH_{syn}$), 3.68 (dd, *J* = 6.1, 4.7, 1H, $CH(OD)_2CH_{anti}$), 3.66 - 3.61 (m, 1H, OCH*H*'$_{syn}$); $^{13}$C{$^{1}$H} NMR δ = (150 MHz, $D_2O$) 90.4 ($CH(OD)_{2\text{-}anti}$), 89.2 ($CH(OD)_{2\text{-}syn}$), 84.1 ($CH(OD)_2CH_{anti}$), 83.3 ($CH(OD)_2CH_{syn}$), 73.0 ($OCH_2CH_{anti}$), 72.7 ($OCH_{2\text{-}anti}$), 71.9 ($CH_2CHCH_{anti}$), 71.8 ($CH_2CHCH_{syn}$), 71.5 ($OCH_2CH_{syn}$), 70.7 ($OCH_{2\text{-}syn}$). NMR Data were consistent with the data previously reported.[2]

**(*2S,3S,4R*)-2-(Dihydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-12c) and (*2R,3S,4R*)-2-(dihydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-12c)**

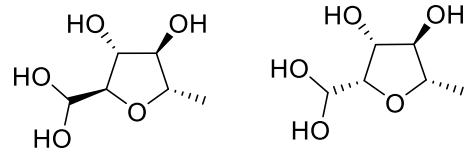



*dr* 60 40

The THF-hydrate was obtained following the **General procedure 2** using Amberlyst 15 (7 g) and THF-hydrazone **3c** (2.12 g, 12.1 mmol, *dr* = 55:45 (*anti:syn*)). After lyophilisation, the hydrate was isolated as an hygroscopic white foam (1.66 g, 91%, *dr* = 60:40 (*anti:syn*)). $^{1}$H NMR (600 MHz, $D_2O$) δ = 5.07 (app. d, *J* = 7.5, 1H, C*H*$(OD)_{2\text{-}syn}$), 5.00 (d, *J* = 6.5, 1H, C*H*$(OD)_{2\text{-}anti}$), 4.26 (app. d, *J* = 3.4, 1H, $OCH_2CH_{syn}$), 4.19 – 4.17 (m, 1H, $OCH_2CH_{anti}$), 4.16 ( app. d, *J* = 3.4, 1H, $CH_2CHCH_{syn}$), 4.15 - 4.11 (m, 2H, $CH_2CHCH_{anti}$, OC*H*H'$_{syn}$), 3.97 (dd, *J* = 10.2, 4.0, 1H, OC*H*H'$_{anti}$), 3.86 - 3.81 (m, 2H, OCH*H'*$_{anti}$, $CH(OD)_2CH_{syn}$), 3.73 (d, *J* = 10.2, 1H, OC*H*H'$_{syn}$), 3.62 (dd, *J* = 6.5, 3.0, 1H, $CH(OD)_2CH_{anti}$); $^{13}$C{$^{1}$H} NMR (150 MHz, $D_2O$ with MeOH standard) δ = 89.6 ($CH(OD)_{2\text{-}anti}$), 88.6 ($CH(OD)_{2\text{-}syn}$), 87.7 ($CH(OD)_2CH_{anti}$), 82.1 ($CH(OD)_2CH_{syn}$), 78.1

($OCH_2CHCH_{anti}$), 76.9 ($CH_2CH_{anti}$), 76.6 ($CH_2CH_{syn}$), 75.9 ($OCH_2CHCH_{syn}$), 73.4 ($OCH_{2\text{-}syn}$), 73.2 ($OCH_{2\text{-}anti}$). NMR Data were consistent with the data previously reported.[2]

**(*2R,3R,4R,5S*)-2-(Dihydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-12d) and (*2S,3R,4R,5S*)-2-(dihydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-12d)**

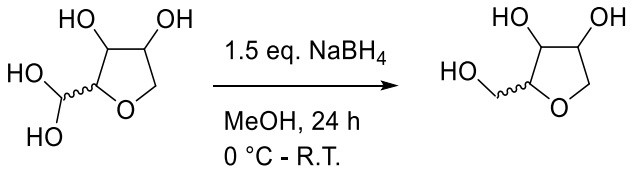


*dr* 70 30

The THF-hydrate was obtained following the **General procedure 2** using Amberlyst 15 (13 g) and the THF-hydrate **3d** (5.00 g, 26.6 mmol, *dr* = 60:40 (*anti:syn*)). After lyophilisation, the THF-hydrate was isolated as an hygroscopic white foam (3.23 g, 81%, *dr* = 70:30 (*anti:syn*)). $^1$H NMR (600 MHz, $D_2O$) δ = 5.10 (app. d, *J* = 7.2, 1H, C*H*$(OD)_{2\text{-}syn}$), 5.02 (d, *J* = 5.6, 1H, C*H*$(OD)_{2\text{-}anti}$), 4.12 - 4.09 (m, 2H, $CH_3CHCH_{syn}$, $CH(OD)_2CH_{anti}$), 3.89 (dq, *J* = 12.7, 6.3, 1H, $CH_3CH_{anti}$), 3.84 - 3.78 (m, 2H, $CH_3CH_{syn}$**,** $CH(OD)_2CHCH_{syn}$), 3.78 - 3.72 (m, 2H, $CH_3CHCH_{anti}$, $CH(OD)_2CH_{syn}$), 3.67 (m, 2H, $CH(OD)_2CHCH_{anti}$), 1.31 (d, *J* = 6.3, 3H, $CH_{3\text{-}syn}$), 1.24 (d, *J* = 6.3, 3H, $CH_{3\text{-}anti}$) ; $^{13}$C{$^1$H} NMR (150 MHz, $D_2O$ with MeOH standard) δ = 89.9 ($CH(OD)_{2\text{-}anti}$), 88.6 ($CH(OD)_{2\text{-}syn}$), 84.0 ($CH(OD)_2CH_{anti}$), 82.9 ($CH(OD)_2CH_{syn}$), 81.9 ($CH_3CHCH_{anti}$), 81.7 ($OCH_{3\text{-}syn}$), 78.8 ($CH_3CH_{anti}$), 77.7 ($CH(OD)_2CHCH_{anti}$), 77.5 ($CH_3CHCH_{syn}$), 18.5 ($CH_{3\text{-}syn}$), 17.7 ($CH_{3\text{-}anti}$). NMR Data were consistent with the data previously reported.[2]

## 2. Synthesis of triol derivatives

a) Triols derived from L-arabinose (**9b**) and D-ribose (**9b**)

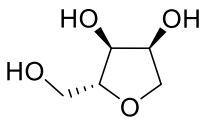



**12** **9**

**General procedure 3:** Sodium borohydride (1.5 eq.) was added portionwise to a solution of hydrate **12** (1 eq.) in MeOH (0.5 M) at 0 °C. After addition, the mixture was warmed up at room temperature and stirred overnight. The reaction was then quenched with $H_2O$ (10 eq) and evaporated to dryness. The oil obtained was dissolved in a mixture of $CH_3CN$:$H_2O$ (2:1) and filtered through neutral alumina (brockmann 1) before evaporation of the solvents under

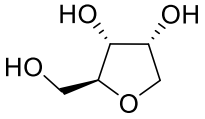
reduced pressure. The residue was heated in hot acetone and filtered through cotton. The filtrate was evaporated under reduced pressure to afford the alcohol.

**(*2R,3S,4S*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (9a)**



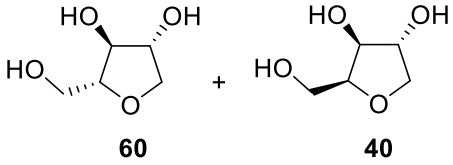
Triol **9a** was obtained following the **General procedure 3** using sodium borohydride (0.52 g, 13.6 mmol, 1.5 eq.), THF-hydrate **12a** (1.36 g, 9.00 mmol, 1 eq.) in MeOH (40 mL, 0.5 M) at 0 °C. After evaporation of the volatiles under reduced pressure, the alcohol was obtained as a white solid. $^{1}$H NMR indicated a mixture *anti* and *syn*-**9a** (1.15 g, 95%, *dr* = 95:5). Recrystallization from acetone afforded *anti*-**9a** as white crystals; mp = 103-104 °C (acetone), lit mp = 102–103 °C;[3] $[\alpha]_D^{20}$ + 61 (c 0.5, MeOH); lit $[\alpha]_D^{20}$ + 66 (c 0.1, $H_2O$);[4] $^{1}$H NMR (600 MHz, MeOH- $d_4$) δ = 4.13 (td, *J* = 4.9, 3.5, 1H, $OCH_2CH$), 4.01 (dd, *J* = 9.5, 4.9, 1H, OC*H*H'), 3.96 (dd, *J* = 6.7, 5.0, 1H, $OCH_2CHCH$), 3.79 – 3.74 (m, 1H, $HOCH_2CH$), 3.72 (m, 2H, OCH*H*', HOC*H*H'), 3.56 (dd, *J* = 11.9, 4.7, 1H, HOCH*H*'); $^{13}$C{$^{1}$H} NMR (151 MHz, MeOH-$d_4$) δ = 84.1 ($HOCH_2CH$), 73.8 ($OCH_2$), 73.2 ($OCH_2CHCH$), 72.5 ($OCH_2CH$), 63.2 ($HOCH_2$); FT-IR (ATR) v = 3462, 3293, 3224, 2924 cm$^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 152.0918, $C_5H_{14}NO_4$ requires 152.0917.

**(*2S,3R,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (9b)**



Triol **9b** was obtained following the **General procedure 3** using sodium borohydride (0.38 g, 10.0 mmol, 1.5 eq.), THF-hydrate **12b** (1.00 g, 6.70 mmol, 1 eq.) in MeOH (40 mL, 0.5 M) at 0 °C. After evaporation of the volatiles under reduced pressure, the alcohol was obtained as a white solid. $^{1}$H NMR spectroscopic analysis indicated a mixture *anti* and *syn*-**9b** (0.67 g, 74%, *dr* = 90:10). Recrystallization from acetone afforded *anti*-**9b** (*dr* = 95:5) as colourless crystals; mp = 102-103 °C (acetone); lit mp = 99 °C;[3] $[\alpha]_D^{20}$ − 62 (c 0.5, MeOH); lit $[\alpha]_D^{20}$ - 66 (c 0.7, $H_2O$);[4] $^{1}$H NMR (600 MHz, $D_2O$, *anti*-**9b**) δ = 4.23 (dd, *J* = 7.3, 4.4, 1H, $OCH_2CH$), 4.06 (dd, *J* = 7.3, 4.9, 1H, OC*H*H'), 4.01 (dd, *J* = 10.2, 4.4, 1H, $OCH_2CHCH$), 3.84 – 3.79 (m, 1H, $HOCH_2CH$), 3.79 – 3.73 (m, 2H, OCH*H'*, HOC*H*H'), 3.60 (dd, *J* = 12.4, 5.1, 1H, HOCH*H'*); $^{13}$C{$^{1}$H} NMR (151 MHz, $D_2O$ + drop of MeOH, *anti*-**9b**) δ = 82.1 ($HOCH_2CH$), 72.8 ($OCH_2$), 72.2 ($OCH_2CHCH$), 71.7 ($OCH_2CH$), 61.9 ($HOCH_2$) ppm; FT-IR (ATR) v = 3463, 3228, 2924 cm$^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 152.0918, $C_5H_{14}NO_4$ requires 152.0917.

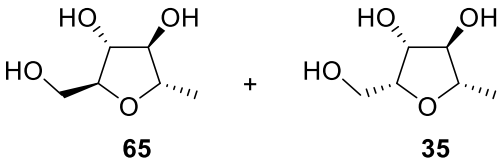
**(*2R,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-9c) and (*2S,3S,4R*)-2-(hydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-9c)**




**60** **40**

Triol **9c** was obtained following the **General procedure 3** using sodium borohydride (0.80 g, 21.0 mmol, 1.5 eq.), THF-hydrate **12c** (2.03 g, 14.0 mmol, 1 eq., *dr* = 60:40 (*anti:syn*)) in MeOH (56 mL) at 0 °C. After evaporation of the volatiles under reduced pressure, the alcohol was obtained as a colourless oil (1.72 g, 95 %, *dr* = 60:40). *Anti*-**9c** and *syn*-**9c** were separated following the procedure described in the following section (**III.2.b)**.

**(*2S,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-9d) and (*2R,3R,4R,5S*)-2-(hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-9d)**

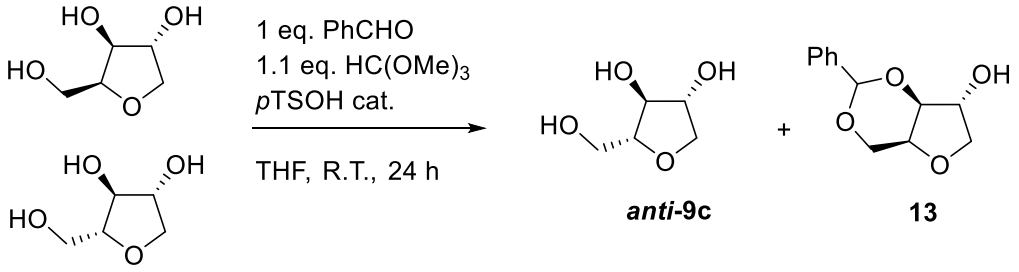



**65** **35**

Triol **9d** was obtained following the **General procedure 3** using sodium borohydride (0.76 g, 20.0 mmol, 1.5 eq.), THF-hydrate **12d** (2.00 g, 13.3 mmol, 1 eq., *dr* = 70:30 (*anti:syn*)) in MeOH (56 mL). After evaporation of the volatiles under reduced pressure, the alcohol was obtained as a colourless oil (2.00 g, Quant., *dr* = 65:35). *Anti*-**9d** and *syn*-**9d** were separated following the procedure described in the following section (**III.2.b)**.

b) Separation of the *anti* and *syn*-triols of D-Xylose (**9c**) and L-rhamnose (**9d**)

*Step 1: Acetal formation*




*anti*-**9c** + *syn*-**9c** ***anti*-9c** **13**

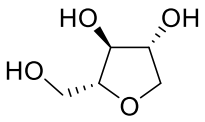
**General procedure 4:** The mixture of *anti* and *syn*-isomers was dissolved in THF (0.5 mol/L) and benzaldehyde (1 eq.), triethylorthoformate (1.1 eq.) and *p*-toluenesulfonic acid (20 mol%) were added. The resulting mixture was stirred at room temperature overnight. The progress of the reaction was followed by NMR. After completion, the reaction was quenched with solid $NaHCO_3$ and filtered through cotton. After evaporation, the crude residue was purified by column chromatography on silica using a gradient of petrol:acetone as eluent (100:0 to 0:100).

The column chromatography allowed separation of the acetal-protected *syn*-triol and the unprotected *anti*-triol.

**(*2R,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-9c) and (*4aS,7R,7aS*)-2-phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (13)**

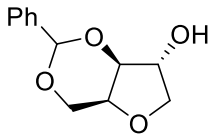
The acetal formation was performed using **General procedure 4** on the mixture of triols **9c** (1.32 g, 9.84 mmol, 1 eq.), benzaldehyde (1.00 mL, 9.84 mmol, 1 eq.), triethylorthoformate (1.20 mL, 10.8 mmol, 1.1 eq.), *p*-toluenesulfonic acid (0.37 g, 1.97 mmol, 0.2 eq.) in THF (20 mL). After purification by column chromatography, *anti*-**9c** was obtained as a colourless oil (0.63 g, 47%) and the acetal **13** as a white solid (0.72 g, 32%).

**(*2R,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-9c)**



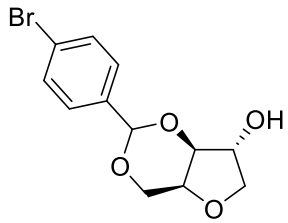

Colourless oil; $[\alpha]_D^{20}$ +23 (c 0.5, MeOH), lit $[\alpha]_D^{20}$ +25 (MeOH);[5] $^1$H NMR (600 MHz, $D_2O$) δ = 4.34 (dt, *J* = 4.6, 2.4, 1H, $OCH_2CH$), 4.14 – 4.10 (m, 2H, $OCHH'$, $OCH_2CHCH$), 3.95 (m, 2H, $OCHH'$, $HOCH_2CH$), 3.86 (dd, *J* = 12.0, 4.0, 1H, $HOCHH'$), 3.80 (dd, *J* = 12.0, 6.5, 1H, $HOCHH'$); $^{13}C\{^1H\}$ NMR (151 MHz, $D_2O$ + drop of MeOH) δ = 86.2 ($HOCH_2CH$), 78.6 ($OCH_2CHCH$), 77.6 ($OCH_2CH$), 73.5 ($OCH_2$), 62.3 ($HOCH_2$) ppm; FT-IR (ATR) ν =3319, 2926, 2876 $cm^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 152.0918, $C_5H_{14}NO_4$ requires 152.0917.

**(*4aS,7R,7aS*)-2-Phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (13)**




White solid; mp = 144-145 °C; $[\alpha]_D^{20}$ +10 (c 0.8, MeOH); lit $[\alpha]_D^{20}$ +3 (c 0.06, MeOH);[6] $^1$H NMR (600 MHz, $CDCl_3$) δ = 7.48 (dd, *J* = 7.6, 1.6, 2H, 2 x $CH_{Ph}$), 7.40 – 7.33 (m, 3H, 3 x $CH_{Ph}$), 5.48 (s, 1H, $(O_2)CH$), 4.48 – 4.41 (m, 3H, $OCHH'$, $HOCH$, $HOCHCHH'$), 4.37 (d, *J* = 1.9, 1H, $HOCHCH$), 4.16 (dd, *J* = 13.2, 1.8, 1H, $HOCHCHH'$), 4.03 (br s, 1H, $OCH_2CH$), 3.86 (d, *J* = 9.4, 1H, $OCHH'$), 1.76 (d, *J* = 3.5, 1H, $OH$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ = 137.8 ($C_{Ph}$), 129.3 ($CH_{Ph}$), 128.4 ($CH_{Ph}$), 126.3 ($CH_{Ph}$), 99.4 ($(O_2)CH$), 81.3 ($OCH_2CHCH$), 76.5 ($OCH_2CH$), 75.5 ($OCH_2$), 72.4 ($OCH_2CH$), 67.8 ($HOCH_2$) ppm; FT-IR (ATR) ν =3389, 2985 $cm^{-1}$; HRMS (CI) *m/z* found $[M+H]^+$ 223.0966, $C_{12}H_{15}O_4$ requires 223.0965.

**(*4aS,7R,7aS*)-2-(4-bromophenyl)tetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (13-Br)**

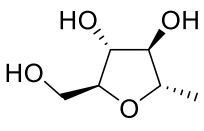


Compund **13-Br** was obtained by using **General procedure 4** on the mixture of triols **9c** (0.42 g, 3.10 mmol, 1eq.), **4-bromo-benzaldehyde** (0.69 g, 3.70 mmol, 1 eq.), *p*-toluenesulfonic acid (0.12 g, 0.62 mmol, 0.2 eq.) in THF (5 mL). After purification by column chromatography, *anti*-**9c** was obtained as a colourless oil (0.20 g, 48%) and the acetal **13-Br** as a white solid (0.34 g, 36%); mp = 148-149 °C; $[\alpha]_D^{20}$ +6 (c 0.9, MeOH); $^1$H NMR (600 MHz, MeOH-$d_4$) δ = 7.50 (d, *J* = 8.5, 2H, 2 x C$H_{Ph}$), 7.37 – 7.34 (d, *J* = 8.5, 2H, 2 x C$H_{Ph}$), 5.51 (s, 1H, ($O_2$)C*H*), 4.33 (d, *J* = 2.3, 1H, C*H*), 4.31 – 4.25 (m, 3H, OC*H*H', HOCHC*H*H', C*H*), 4.19 (dd, *J* = 13.1, 1.9, 1H, OCH*H*'), 3.96 (dd, *J* = 3.3, 2.0, 1H, C*H*), 3.79 – 3.75 (m, 1H, OCH*H*'); $^{13}$C{$^1$H} NMR (151 MHz, MeOH-$d_4$) δ = 139.0 ($C_q$), 132.3 (*C*H), 129.3 (*C*H), 123.7 ($C_q$), 99.4 (Ph*C*H), 82.5(*C*H), 76.8 (*C*H), 76.1 ($CH_2$), 73.9 (*C*H), 68.4 ($CH_2$) ppm; FT-IR (ATR) v =3367, 2945, 2885, 1483 cm$^{-1}$; HRMS (CI) *m/z* found $[M+H]^+$ 301.0069, $C_{12}H_{14}BrO_4$ requires 301.0070.

**(*2S,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-9d) and (*4aR,6S,7S,7aR*)-6-Methyl-2-phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (15)**

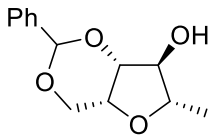
The acetal formation was performed using **General procedure 4** on the mixture of triols **9d** (2.00 g, 13.4 mmol, 1eq.), benzaldehyde (1.37 mL, 13.4 mmol, 1 eq.), triethylorthoformate (1.60 mL, 14.8 mmol, 1.1 eq.), *p*-toluenesulfonic acid (0.51 g, 2.70 mmol, 0.2 eq.) in THF (25 mL). After purification by column chromatography, the *anti*-**9d** was obtained as a colourless oil (1.12 g, 56%) and the acetal **15** as a white solid (0.94 g, 30%).

**(*2S,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-9d)**



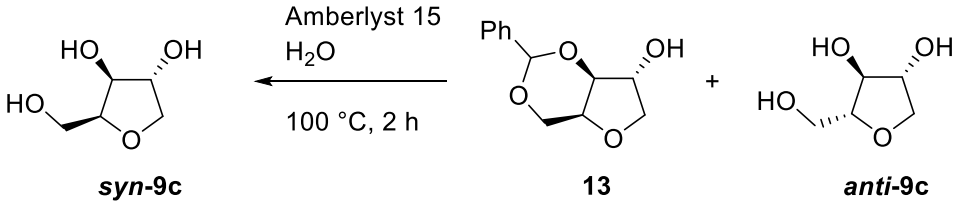
Colourless oil; $[\alpha]_D^{20}$ −42 (c 0. 4, MeOH) ; $^1$H NMR (700 MHz, $D_2O$) δ = 3.97 (app. t, *J* = 6.4, 1H, $OCH_2CHCH$), 3.87 (m, 2H, $CH_3CH$, $OCH_2CH$), 3.75 (dd, *J* = 7.2, 6.4, 1H, $CH_3CHCH$), 3.70 (dd, *J* = 12.4, 3.3, 1H, OC*H*H'), 3.64 (dd, *J* = 12.4, 5.9, 1H, OCH*H*'), 1.26 (d, *J* = 6.3, 3H, $CH_3$) ; $^{13}$C{$^1$H} NMR (176 MHz, $D_2O$ + drop of MeOH ) δ = 82.5, 82.2, 78.6, 77.2, 61.8 ($CH_2$), 18.2 ($CH_3$) ppm, NMR data are consistent with the data previously reported by our group.[1] FT-IR (ATR) v = 3403, 2916, 1458 cm$^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 166.1075, $C_6H_{16}NO_4$ requires 166.1074.

**(*4aR,6S,7S,7aR*)-6-Methyl-2-phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (15)**



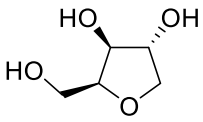
White solid; mp = 134-135 °C ; $[\alpha]_D^{20}$ −38 (c 1.4, MeOH); $^1$H NMR (700 MHz, $CDCl_3$) δ = 7.48 (dt, *J* = 8.4, 2.2, 2H, C*H*$_{o\text{-}Ph}$), 7.40 – 7.32 (m, 3H, (C*H*$_{m,p\text{-}Ph}$), 5.45 (s, 1H, $(O)_2$C*H*), 4.42 (app. d, *J* = 13.1, 1H, OC*H*H'), 4.28 (app. d, *J* = 2.4, 1H, $OCH_2CHCH$), 4.15 (dd, *J* = 13.1, 2.1, 1H, OCH*H*'), 4.06 (br s, 1H, $CH_3CHCH$), 4.02 (qd, *J* = 6.6, 2.2, 1H, $CH_3CH$), 3.98 – 3.95 (m, 1H, $OCH_2CH$), 1.90 (s, 1H, O*H*), 1.46 (d, *J* = 6.6, 3H, C*H*$_3$) ; $^{13}$C{$^1$H} NMR (176 MHz, $CDCl_3$) δ = 138.1 (*C*$_{Ph}$), 129.3 (*C*H$_{Ph}$), 128.5 (*C*H$_{Ph}$), 126.4 (*C*H$_{Ar}$), 99.9 ($O_2CH$), 83.8 ($CH_3CH$), 83.1 ($OCH_2CHCH$), 82.2 ($CH_3CHCH$), 73.1 ($OCH_2CH$), 67.4 ($OCH_2$), 19.9 (*C*H$_3$) ppm; FT-IR (ATR) v = 2980, 2914, 2850, 1763, 1450 cm$^{-1}$; HRMS (CI) *m/z* found $[M+H]^+$ 237.1122, $C_{13}H_{17}O_4$ requires 237.1121.

*Step 2: Acetal deprotection*



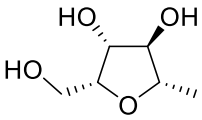

**General procedure 5:** The acetal-protected triol was then heated in water with a catalytic amount of Amberlyst 15 for 2 hours. After filtration and evaporation, the resulting product was washed with $Et_2O$ to give the pure *syn*-triol.

**(*2S,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-9c)**



*Syn*-**9c** was prepared following **General procedure 5** by deprotection of the acetal **13** (340 mg, 1.52 mmol, 1 eq.) with Amberlyst 15 (100 mg) in water (10 mL) and was obtained as a colourless oil (183 mg, 90%); Colourless oil; $[\alpha]_D^{20}$ +20 (c 0. 4, MeOH) ; $^1$H NMR (600 MHz, $D_2O$) δ = 4.37 (dt, *J* = 4.2, 1.5, 1H, $OCH_2CH$), 4.29 (dd, *J* = 3.6, 1.5, 1H, $OCH_2CHCH$), 4.23 (dd, *J* = 10.2, 4.2, 1H, OC*H*H'), 4.20 (ddd, *J* = 7.4, 4.6, 3.6, 1H, $HOCH_2CH$), 3.92 (dd, *J* = 11.8, 4.6, 1H, HOC*H*H'), 3.85 - 3.77 (m, 2H, OCH*H*', HOCH*H*') ; $^{13}$C{$^1$H} NMR (151 MHz, $D_2O$ + drop of MeOH) δ = 81.5 (HO*C*H), 77.3 ($OCH_2CH$), 76.8 ($OCH_2CHCH$), 73.3 ($OCH_2$), 60.5 ($HOCH_2$) ppm ; FT-IR (ATR) v =3313, 2934, 2883 cm$^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 152.0918, $C_5H_{14}NO_4$ requires 152.0917.

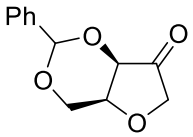
**(*2R,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-9d)**



S*yn*-**9d** was prepared following **General procedure 5** by deprotection of the acetal **15** (0.83 g, 3.60 mmol, 1 eq.) with Amberlyst 15 (100 mg) in water (15 mL). *Syn*-**9d** was obtained as a colourless oil (0.54 g, Quant.); Colourless oil; $[\alpha]_D^{20}$ −13 (c 0. 7, MeOH) ; $^1$H NMR (700 MHz, $D_2O$) δ = 4.14 (dd, *J* = 4.6, 1.5, 1H, $OCH_2CHCH$), 4.01 (dt, *J* = 6.9, 4.6, 1H, $OCH_2CH$), 3.78 (dd, *J* = 6.9, 4.6, 1H, OCHH'), 3.77 - 3.73 (m, 2H, $CH_3CH$, $CH_3CHCH$), 3.69 (dd, *J* = 11.9, 6.9, 1H, OCHH'), 1.29 (d, *J* = 5.7, 3H, $CH_3$) ; $^{13}$C{$^1$H} NMR (176 MHz, $D_2O$ + drop of MeOH) δ = 83.3 ($CH_3CH$ or $CH_3CHCH$), 81.2 ($OCH_2CH$), 80.7 ($CH_3CH$ or $CH_3CHCH$), 78.1 ($OCH_2CHCH$), 60.6 ($OCH_2$), 18.6 ($CH_3$) ppm, NMR data are consistent with the data previously reported by our group.[1] FT-IR (ATR) v = 3342, 2972, 2930, 1448 cm$^{-1}$; HRMS (CI) *m/z* found $[M+NH_4]^+$ 166.10744, $C_6H_{16}NO_4$ requires 166.1074.

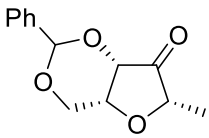
c) Oxidation of alcohols **13** and **15**

**(*4aS,7aR*)-2-Phenyldihydro-4H-furo[3,2-d][1,3]dioxin-7(6H)-one (14)**



TEMPO (42 mg, 0.3 mmol, 0.2 eq.) and (diacetoxy)iodobenzene (543 mg, 1.69 mmol, 1.25 eq.) were added at 0 °C to a solution of alcohol **13** (300 mg, 1.40 mmol, 1 eq.) dissolved in $CH_3CN$:$H_2O$ (1:1, 3 mL, 0.50 mol/L). The solution was warmed up at room temperature and stirred for 6 hours at room temperature before addition of ethanol. After 15 minutes, the solution was evaporated to dryness and the yellow residue was purified by column chromatography on silica using a gradient of petrol:acetone (100:0 to 40:60). After evaporation, the ketone was obtained as a white solid (270 mg, 90%) ; mp = 145–148 °C ; $[\alpha]_D^{20}$ −21 (c 0.7, MeOH), lit $[\alpha]_D^{22}$ −32.4 (c 0.07, MeOH);[6] $^1$H NMR (600 MHz, $CDCl_3$) δ = 7.52 – 7.48 (m, 2H, $CH_{o\text{-}Ph}$), 7.40 – 7.34 (m, 3H, $CH_{m,p\text{-}Ph}$), 5.57 (s, 1H, $(O)_2CH$), 4.51 (d, *J* = 6.0, 1H, OCHH'), 4.48 (d, *J* = 10.6, 1H, COCHH'), 4.33 – 4.29 (m, 2H, OCHH', COCH), 4.05 – 4.00 (m, 2H, COCHH', OCH2CH); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) δ = 208.3 (C=O), 137.1 ($C_q$), 129.4 ($CH_{p\text{-}Ph}$), 128.4 ($CH_{m\text{-}Ph}$), 126.3 ($CH_{o\text{-}Ph}$), 99.6 ($O_2CH$), 73.9 (COCH), 72.8 (OCH2CH), 71.1 ($COCH_2$), 67.1 ($OCH_2$) ppm ; FT-IR (ATR) v = 2982, 2907, 2867, 1760, 1452 cm$^{-1}$; HRMS (ESI) *m/z* found $[M+H]^+$ 221.0810, $C_{12}H_{13}O_4$ requires 221.0808.

**(*4aR,6S,7aS*)-6-Methyl-2-phenyldihydro-4H-furo[3,2-d][1,3]dioxin-7(6H)-one (16)**

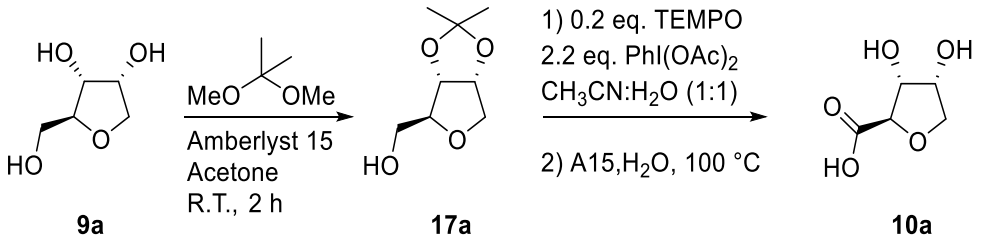


TEMPO (30 mg, 0.18 mmol, 0.2 eq.) and (diacetoxy)iodobenzene (366 mg, 1.14 mmol, 1.25 eq.) were added at 0 °C to a solution of alcohol **15** (215 mg, 0.91 mmol, 1 eq.) dissolved in a mixture $CH_3CN$:$H_2O$ (1:1, 3 mL, 0.5 mol/L).

The solution warmed up at room temperature and stirred for 6 hours at room temperature before addition of ethanol. After 15 minutes, the solution was evaporated to dryness and the yellow residue was purified by column chromatography on silica using a gradient of petrol:acetone (100:0 to 40:60). After evaporation, the ketone was obtained as a white solid (164 mg, 74%) ; mp = 100–101 °C ; $[\alpha]_D^{20}$ −3 (c 0.7, MeOH) ; $^1$H NMR (600 MHz, $CDC_{l3}$) δ = 7.52 – 7.45 (m, 2H, C*H*$_{o\text{-Ph}}$), 7.41 – 7.33 (m, 3H, CH$_{m,p\text{-Ph}}$), 5.54 (s, 1H, $(O)_2$C*H*), 4.49 (d, *J* = 13.3, 1H, OC*H*H'), 4.35 – 4.26 (m, 2H, OCH*H*', COC*H*), 4.05 (q, *J* = 6.8, 1H, $CH_3$C*H*), 3.95 (s, 1H, $OCH_2$C*H*), 1.51 (d, *J* = 6.8, 3H, $CH_3$); $^{13}$C{$^1$H} NMR (151 MHz, $CDCl_3$) δ = 210.1 (*C*=O), 137.3 (*C*$_q$), 129.5 (*C*$_{p\text{-Ph}}$), 128.4 (*C*$_{m\text{-Ph}}$), 126.4 (*C*$_{p\text{-Ph}}$), 99.8 ($O_2$*C*H), 77.8 ($CH_3$*C*H), 74.1 (CO*C*H), 70.9 ($OCH_2$*C*H), 67.0 (O*C*$H_2$), 17.1(*C*$H_3$) ppm; FT-IR (ATR) v = 2980, 2914, 2850, 1736, 1450 cm$^{-1}$; HRMS (ESI) *m/z* found $[M+H]^+$ 235.0968, $C_{13}H_{15}O_4$ requires 235.0965.

### 3. Synthesis of carboxylic acid

a) From alcohol **9a**



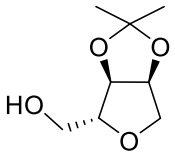

**9a** **17a** **10a**

A solution of triol **9a** (430 mg, 3.20 mmol, 1 eq.) in acetone (10 mL, 0.5 mol/L) was treated with 2,2-dimethoxypropane (2.00 mL, 16.2 mmol, 5 eq.) in presence of Amberlyst 15 (1 spatula). After addition, the mixture was stirred overnight at room temperature. The mixture was filtered through celite and concentrated under vacuum to afford the protected alcohol **17a**.

TEMPO (47 mg, 0.3 mmol, 0.2 eq), and (diacetoxy)iodobenzene (1.10 g, 3.30 mmol, 2.2 eq) were added to a solution of alcohol **17a** (260 mg, 1.20 mmol, 1 eq) dissolved in $CH_3CN$:$H_2O$ (1:1, 3 mL, 0.5 mol/L). The resulting solution was stirred at room temperature for 6 hours before quenching with ethanol. After 15 minutes, the solution was evaporated to dryness and the residue was purified by column chromatography on silica using a gradient of petrol:acetone (100:0 to 0:100) to give the protected-carboxylic acid as a colourless oil (147 mg, 65%).

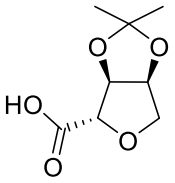
Deprotection of the diol was performed by heating at 100 °C a solution of the acetal-protected carboxylic acid (123 mg, 0.65 mmol, 1 eq.) in water (5 mL, 0.15 M) in presence of Amberlyst 15 for 1h30. The mixture was then allowed to cool down at room temperature before filtration through cotton. The sample was freeze-dried overnight to afford the carboxylic acid **10a** as a colourless oil (101 mg, Quant.).

**((*3aR,4R,6aS*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (17a)**



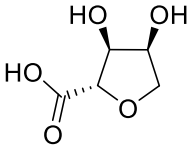
Colourless oil (537 mg, 96%) ; $[\alpha]_D^{20}$ +37 (c 0.7, MeOH), lit $[\alpha]_D^{20}$ +37 (c 0.5, $CHCl_3$);[7] $^1$H NMR (600 MHz, $CDCl_3$) δ = 4.82 (ddd, *J* = 6.3, 4.2, 2.1, 1H, $OCH_2CH$), 4.61 (dd, *J* = 6.3, 2.0, 1H, $OCH_2CHCH$), 4.20 – 4.08 (m, 1H, $HOCH_2CH$), 3.99 (dd, *J* = 10.5, 2.1, 1H, $OCH$H'), 3.96 (dd, *J* = 10.5, 4.2, 1H, OCH*H*'), 3.70 – 3.64 (m, 1H, HOC*H*H'), 3.63 – 3.57 (m, 1H, HOCH*H*'), 1.82 (br s, 1H, O*H*), 1.53 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ = 113.2 ($C_q$), 85.0 ($HOCH_2CH$), 82.0 ($OCH_2CHCH$), 81.2 ($OCH_2CH$), 73.0 ($OCH_2$), 61.9 ($HOCH_2$), 26.8 ($CH_3$), 25.1 ($CH_3$); FT-IR (ATR) v = 3420, 2983, 2937, 2875, 1459 cm$^{-1}$; HRMS (ESI) *mi/z* found $[M+H]^+$ 175.0963, $C_8H_{15}O_4$ requires 175.0965.

**(*3aS,4S,6aS*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid (18a)**



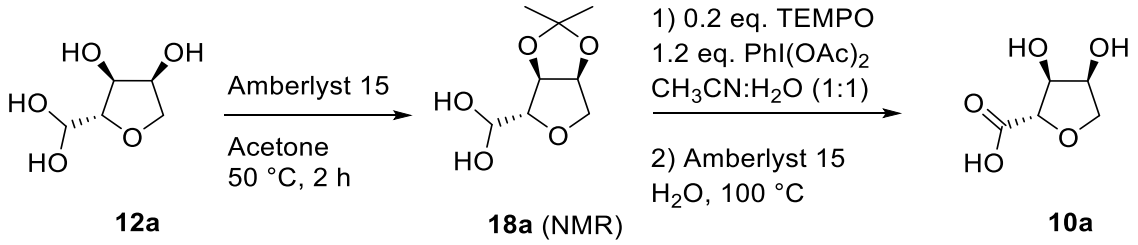
Colourless oil (147 mg, 65%); $[\alpha]_D^{20}$ +64 (c 0.8, MeOH) ; $^1$H NMR (600 MHz, $CDCl_3$) δ = 5.01 (d, *J* = 6.0, 1H, $OCH_2CHCH$), 4.84 (app. dd, *J* = 6.0, 3.9, 1H, $OCH_2CH$), 4.63 (br s, 1H, $COCH$), 4.17 (d, *J* = 10.8, 1H, $OCH$H'), 3.97 (dd, *J* = 10.8, 3.9, 1H, OCH*H*'), 1.53 (s, 3H, $CH_3$), 1.35 (s, 3H, $CH_3$); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ = 174.7 (*C*=O), 113.4 ($C_q$), 84.0 ($OCH_2CHCH$), 83.1 ($COCH$), 80.7 ($OCH_2CH$), 74.2 ($OCH_2$), 26.5 ($CH_3$), 25.0 ($CH_3$) ppm ; FT-IR (ATR) v = 2985, 2940, 1734, 1459 cm$^{-1}$; HRMS (ESI) *m/z* found $[M+H]^+$ 189.0768, $C_8H_{13}O_5$ requires 189.0763.

**(*2S,3S,4S*)-3,4-Dihydroxytetrahydrofuran-2-carboxylic acid (10a)**



Colourless oil (101 mg, Quant.) ; $[\alpha]_D^{20}$ +55 (c 0.6, MeOH) ; $^1$H NMR (600 MHz, $D_2O$) δ = 4.42 (dd, *J* = 6.8, 4.7, 1H, $CH$), 4.36 – 4.32 (m, 2H, 2 x $CH$), 4.15 (dd, *J* = 10.1, 4.0, 1H, $OCH$H'), 3.93 (dd, *J* = 10.1, 2.5, 1H, OCH*H*') ; $^{13}C\{^1H\}$ NMR (151 MHz, $D_2O$) δ = 176.3 (*C*=O), 79.9 (*C*H), 75.7 (*C*H), 73.6 ($CH_2$), 71.6 (*C*H) ppm ; FT-IR (ATR) v = 3369, 2941, 1720 cm$^{-1}$ HRMS (ESI) *m/z* found $[M+NH_4]^+$ 166.0710, $C_5H_{12}NO_5$ requires 166.0709.

b) From hydrate **12a**

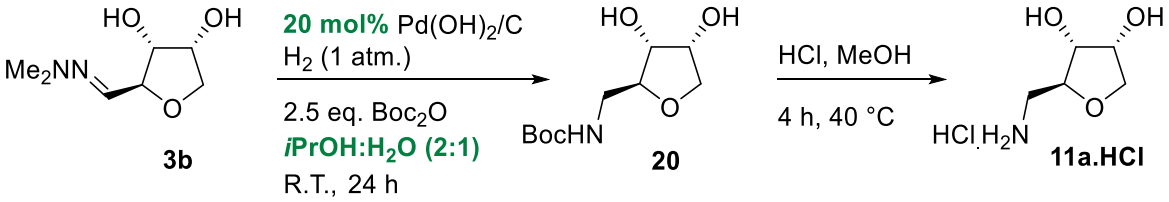



**12a** **18a** (NMR) **10a**

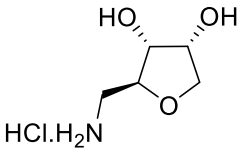
The aldehyde (1 eq.) was stirred in acetone (0.25 mol/L) at 40 °C for 4 hours in presence of Amberlyst 15 (1 spatula). The mixture was filtered through a small pad of celite and rinse with acetone. After evaporation to dryness, the acetal was obtained as a foam used without further purification. TEMPO (0.2 eq) and diacetoxyiodobenzene (1.5 eq) were added to a mixture of acetal (1 eq.) in a mixture of $CH_3CN$:$H_2O$ (1:1, C = 0.5 mol/L). The resulting mixture was stirred at room temperature for 4 hours before evaporation to dryness. The residue was dry-loaded on celite and purified by column chromatography on silica using a gradient petrol:acetone (100:0 to 0:100) to afford the protected carboxylic acid.

## 4. Synthesis of amine-functionalised chiral THFs

a) Direct hydrogenation of THF hydrazones using palladium catalyst



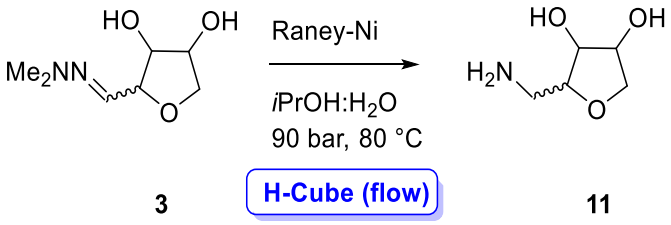

**(*2S,3R,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol hydrochloride (11a.HCl)**




THF *anti*-**3b** (50 mg, 0.29 mmol, 1 eq.) was dissolved in a mixture of isopropanol:water (2 mL, 2:1, 0.05 mol/L). The solution was degassed with 3 vacuum / argon cycles before addition of di-*tert*-butyl dicarbonate (165 µL, 0.72 mmol, 2.5 eq.) and $Pd(OH)_2$ (20% on carbon, 40 mg, 0.06 mmol, 0.2 eq.). The resulting mixture was degassed with 3 vacuum / hydrogen cycles before hydrogen was bubbled for 5 minutes directly into the solution. The reaction was stirred under hydrogen atmosphere (1 atm., 1 balloon) at room temperature for 24 hours before filtration through celite. The filtrate was then concentrated under reduced pressure and the crude residue was purified by column chromatography using a gradient of petrol:acetone (100:0 to 50:50) to give the boc-amine **20** as a colourless oil (41 mg, 61%, *anti* only).

The protected amine **20** (179 mg, 0.77 mmol, 1 eq.) was solubilised in a solution of HCl in MeOH (4.60 mL, 2.30 mmol, 3 eq., 0.5 M in MeOH) and heated at 40 °C for 4 hours. The solution was then evaporated to dryness. The residue was washed with $Et_2O$ and dried under high vacuum to give the ammonium salt **11a.HCl** as a white solid (129 mg, Quant. *anti* only); mp = 175-176 °C (dec.); $[\alpha]_D^{20}$ −49 (c 0.5, MeOH), lit $[\alpha]_D^{20}$ −57 (c 1.56, $H_2O$);[8] $^1$H NMR (600 MHz, $CD_3OD$) δ = 4.18 (td, *J* = 4.6, 2.4, 1H, $OCH_2CH$), 4.10 (dd, *J* = 9.9, 4.6, 1H, $OCH'H$), 3.91 – 3.88 (m, 1H, $NCH_2CH$), 3.85 (dd, *J* = 7.7, 4.6, $NCH_2CHCH$), 3.78 (dd, *J* = 9.9, 2.4, 1H, $OCHH'$) 3.22 (dd, *J* = 13.0, 2.9, 1H, $NCH'H$), 2.97 (dd, *J* = 13.0, 8.7, 1H, $NCHH'$); $^{13}C\{^1H\}$ NMR (151 MHz, $CD_3OD$) δ = 78.7 ($NCH_2CH$), 75.3 ($NCH_2CHCH$), 74.6 ($OCH_2$), 72.3 ($OCH_2CH$), 43.2 ($NCH_2$); FT-IR (ATR) v = 3445, 3234, 3144, 2999, 2940, 2913; 1587, 1515 $cm^{-1}$; HRMS (ESI) *m/z* found $[M+H]^+$ 134.0811, $C_5H_{12}NO_3$ requires 134.0812.

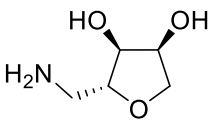
b) Direct hydrogenation under flow conditions




**General procedure 6:** Raney®-Nickel 2800 (W.R. Grace and Co. Raney®, obtained from Sigma-Aldrich, product 221678) was packed in a long catalyst cartridge (70 mm). The cartridge was placed in the H-cube and washed with *i*PrOH:water (2:1) until stable at 90 bar, 80 °C, 0.5 mL/min.

THF **3** was dissolved in *i*PrOH:water (2:1, 0.05 mol/L, unless otherwise stated). The solution was flushed through the H-cube (90 bar, 80 °C, 0.5 mL/min, 100% $H_2$) for the time necessary for the starting material solution to circulate in the system. After that time the lines were switched to the solvent system (*i*PrOH:water 2:1) and the remaining reactants were flushed through the catalyst cartridge using the solvent for additional 15 minutes. All processed solution was collected in the collection pot. Upon completion of the reaction run the sample was concentrated under vacuum to afford the desired amine **11**. $^1$H NMR in MeOH-$d_4$ showed clean conversion to the amine with no sign of epimerisation.

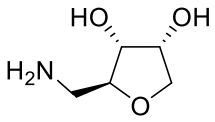
**(*2R,3S,4S*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (11a)**




The amine was obtained by following the **General procedure 6** using the THF **3a** (450 mg, 2.50 mmol, 1 eq., *anti* only*)* and Raney-Nickel (1.60 g, 18.7 mmol) in *i*PrOH:water (2:1). The solution collected was evaporated

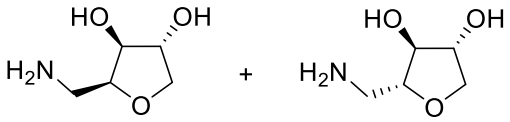
under vacuum to afford the amine **11a** as a faintly yellow oil (301 mg, 89%, *anti* only) ; $[\alpha]_D^{20}$ +47 (c 0.9, MeOH); $^1$H NMR (600 MHz, MeOH-d4) δ = 4.13 (td, *J* = 4.9, 3.1, 1H, OCH$_2$C*H*), 4.03 (dd, *J* = 9.7, 4.9, 1H, OC*H*H'), 3.80 (dd, *J* = 7.2, 4.9, 1H, OCH$_2$CHC*H*), 3.75 – 3.67 (m, 2H, OCH*H*', NCH$_2$C*H*), 2.88 (dd, *J* = 13.3, 3.6, 1H, NC*H*H'), 2.70 (dd, *J* = 13.3, 7.0, 1H, NCH*H*'); $^{13}$C{$^1$H} NMR (151 MHz, MeOH-d4) δ = 83.3 (NCH$_2$*C*H), 74.7 (OCH$_2$CH*C*H), 73.9 (O*C*H$_2$), 72.5 (OCH$_2$*C*H), 44.6 (N*C*H$_2$) ; FT-IR (ATR) v = 3353, 3297, 2921, 2872, 1590, 1466 cm$^{-1}$; HRMS (ESI) *m/z* found [M+Na]$^+$ 156.0628, $C_5H_{11}NO_3Na$ requires 156.0631.

**(*2S,3R,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (11b)**



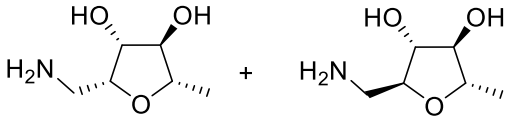
The amine **11b** was obtained by following the **General procedure 6** using the THF **3b** (302 mg, 1.70 mmol, 1 eq., *anti* only*)* and Raney-Nickel (1.58 g, 15.6 mmol). The solution collected was evaporated under vacuum to afford the amine **11b** as a faintly yellow oil (216 mg, 94 %, *anti* only) ; $[\alpha]_D^{20}$ −59 (c 0.7, MeOH);$^1$H NMR (600 MHz, MeOH-d4) δ = 4.13 (td, *J* = 4.9, 3.2, 1H, OCH$_2$C*H*), 4.02 (dd, *J* = 9.7, 4.9, 1H, OC*H*H'), 3.80 (dd, *J* = 7.2, 4.9, 1H, OCH$_2$CHC*H*), 3.74 – 3.67 (m, 2H, OCH*H*', NCH$_2$C*H*), 2.86 (dd, *J* = 13.3, 3.7, 1H, NC*H*H'), 2.69 (dd, *J* = 13.3, 6.9, 1H, NCH*H*') ; $^{13}$C{$^1$H} NMR (151 MHz, MeOH-d4) δ = 83.6 (NCH$_2$*C*H), 74.7 (OCH$_2$CH*C*H), 73.9 (O*C*H$_2$), 72.5 (OCH$_2$*C*H), 44.7 (N*C*H$_2$) ppm ; FT-IR (ATR) v = 3353, 3297, 2919, 2869, 1595, 1465cm$^{-1}$; HRMS (ESI) *m/z* found [M+Na]$^+$ 156.0627, $C_5H_{11}NO_3Na$ requires 156.0631.

**(*2S,3S,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (*anti*-11c) & (*2R,3S,4R*)-2-(aminomethyl)tetrahydrofuran-3,4-diol (*syn*-11c)**



The mixture of amines *anti* and *syn*-**11c** was obtained by following the **General procedure 6** using the THF **3c** (160 mg, 0.92 mmol) and Raney-Nickel (1.60 g, 18.6 mmol). The solution collected was evaporated under vacuum to afford the amine **11c** as a faintly yellow oil (83 mg, 68 %, *dr* = 55:45) ; $^1$H NMR (600 MHz, MeOH-d4) δ = 4.14 – 4.08 (m, 2H, OC*H*H'$_{min}$, OCH$_2$C*H*$_{min}$), 4.06 – 4.02 (m, 2H, OCH$_2$CHC*H*$_{min}$, OCH$_2$C*H*$_{Maj}$), 4.01 – 3.98 (td, *J* = 5.6, 3.6, 1H, NCH$_2$C*H*$_{min}$), 3.95 (dd, *J* = 9.6, 4.0, 1H, OC*H*H'$_{Maj}$), 3.86 – 3.83 (m, 1H, OCH$_2$CHC*H*$_{Maj}$), 3.79 (d, *J* = 9.6, 1H, OCH*H*'$_{Maj}$), 3.72 (m, 1H, NCH$_2$C*H*$_{Maj}$), 3.64 (dd, *J* = 9.2, 0.8, 1H, OCH*H*'$_{min}$), 2.93 (m, 1H, NC*H*H'$_{min}$), 2.91 (dd, *J* = 12.5, 5.6, 1H, NCH*H*'$_{min}$), 2.86 (dd, *J* = 13.3, 4.1, 1H, NC*H*H'$_{Maj}$), 2.82 (dd, *J* = 13.3, 6.4, 1H, NCH*H*'$_{Maj}$); $^{13}$C{$^1$H} NMR (151 MHz, MeOH-d4) δ = 87.8 (NCH$_2$*C*H$_{Maj}$), 81.6 (NCH$_2$*C*H$_{min}$), 81.0 (NCH$_2$CH*C*H$_{Maj}$), 78.8 (NCH$_2$CH*C*H$_{min}$), 78.7 (OCH$_2$*C*H$_{Maj}$), 78.6 (OCH$_2$*C*H$_{min}$), 74.8 (O*C*H$_{2\text{-}Maj}$), 74.3 (O*C*H$_{2\text{-}min}$), 44.2 (N*C*H$_{2\text{-}Maj}$), 41.5 (N*C*H$_{2\text{-}min}$) ppm ; FT-IR (ATR) v = 3343, 3295, 2923, 2871, 1572, 1462 cm$^{-1}$; HRMS (ESI) *m/z* found [M+H]$^+$ 134.0810, $C_5H_{12}NO_3$ requires 134.0812.

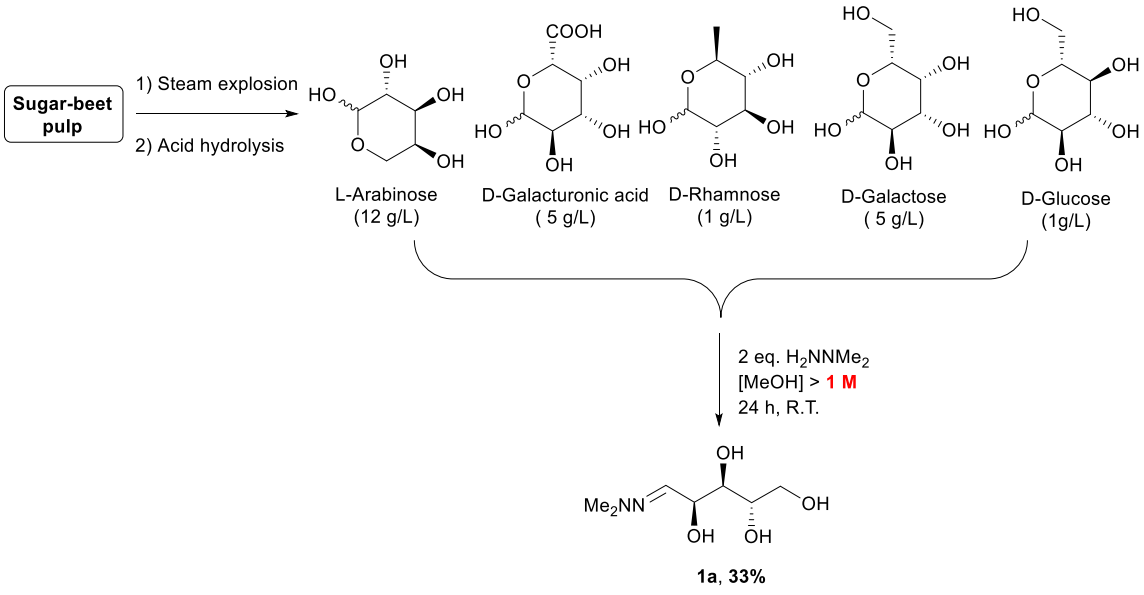
**(*2R,3R,4R,5S*)-2-(Aminomethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-11d) & (2S,3R,4R,5S)-2-(aminomethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-11d)**



The mixture of amines *anti* and *syn*-**11d** was obtained by following the **General procedure 6** using a solution of THF **3d** (175 mg, 0.94 mmol, 0.055 mol/L) and Raney-Nickel (1.63 g, 19.0 mmol). The solution collected was evaporated under vacuum to afford the amine **11d** as a faintly yellow oil (107 mg, 78 %, *dr* = 66:34) ; $^{1}$H NMR (600 MHz, MeOH-d4) δ = 4.02 (dd, *J* = 4.8, 2.7, 1H, $NCH_2CHCH_{min}$), 3.90 (dd, *J* = 10.7, 5.4, 1H, $NCH_2CH_{min}$), 3.82 (m, 1H, $CH_3CH_{Maj}$), 3.80 – 3.74 (m, 2H, $CH_3CHCH_{Maj}$, $NCH_2CH_{Maj}$), 3.70 (m, 1H, $CH_3CH_{min}$), 3.67 – 3.62 (m, 2H, $NCH_2CHCH_{Maj}$, $CH_3CHCH_{min}$), 2.89 (m, 1H, $NCHH'_{min}$), 2.86 (dd, *J* = 13.3, 6.2, 1H, $NCHH'_{min}$), 2.80 (dd, *J* = 13.3, 3.8, 1H, $NCHH'_{Maj}$), 2.75 (dd, *J* = 13.3, 6.9, 1H, $NCHH'_{Maj}$), 1.31 (d, *J* = 6.3, 3H, $CH_{3\text{-}min}$), 1.27 (d, *J* = 6.3, 3H, $CH_{3\text{-}Maj}$) ppm ; $^{13}C\{^{1}H\}$ NMR (151 MHz, MeOH-d4) δ = 85.2 ($CH_3CHCH_{min}$), 84.7 ($CH_3CHCH_{Maj}$ or $NCH_2CH_{Maj}$), 84.0 ($NCH_2CHCH_{Maj}$), 82.1 ($NCH_2CH_{min}$), 81.6 ($CH_3CH_{min}$), 80.7 ($CH_3CHCH_{Maj}$ or $NCH_2CH_{Maj}$), 80.1 ($NCH_2CHCH_{min}$), 80.0 ($CH_3CH_{Maj}$), 44.7 ($NCH_{2\text{-}Maj}$), 42.1 ($NCH_{2\text{-}min}$), 19.3 ($CH_{3\text{-}min}$), 19.2 ($CH_{3\text{-}Maj}$) ppm ; FT-IR (ATR) v = 3347, 3291, 2968, 2874, 1595, 1449 $cm^{-1}$; HRMS (ESI) *m/z* found $[M+H]^+$ 148.0964, $C_6H_{14}NO_3$ requires 148.0968.

## IV. Synthesis of sugar hydrazones from a hydrolysed sample of raw sugar beet pulp

### Synthesis of 1a from a sample of sugar beet pulp



A sample of sugar beet pulp treated by steam explosion followed by acidic hydrolysis and neutralization was prepared as described previously by D. P. Ward.[9,10] This crude material (200 mL, ≈ 2.40 g of L-arabinose, 16.0 mmol, 1 eq.) containing around 12 g/L of L-arabinose, 5 g/L of D-galacturonic acid and D-galactose, 1 g/ of D-Rhamnose and D-glucose and unknown coloured impurities giving the material a black colour) was evaporated to dryness before addition of methanol (10 mL) and *N,N*-dimethylhydrazine (2.40 mL, 32.0 mmol, 2 eq.). The resulting mixture was stirred at room temperature overnight. Activated charcoal was then added and the solution was stirred for 30 minutes before filtration through a pad of celite. The orange solution was evaporated to dryness. $^{1}$H NMR of the crude residue showed the L-arabinose sugar hydrazone **1a** as the major product with only traces of other hydrazones. Purification by column chromatography on silica using petrol:acetone as eluent (20:80 to 0:100) gave the arabinose sugar hydrazone **1a** as a white solid (910 mg, 30%). NMR data of **1a** obtained are consistent with the data previously reported by our group.[1]

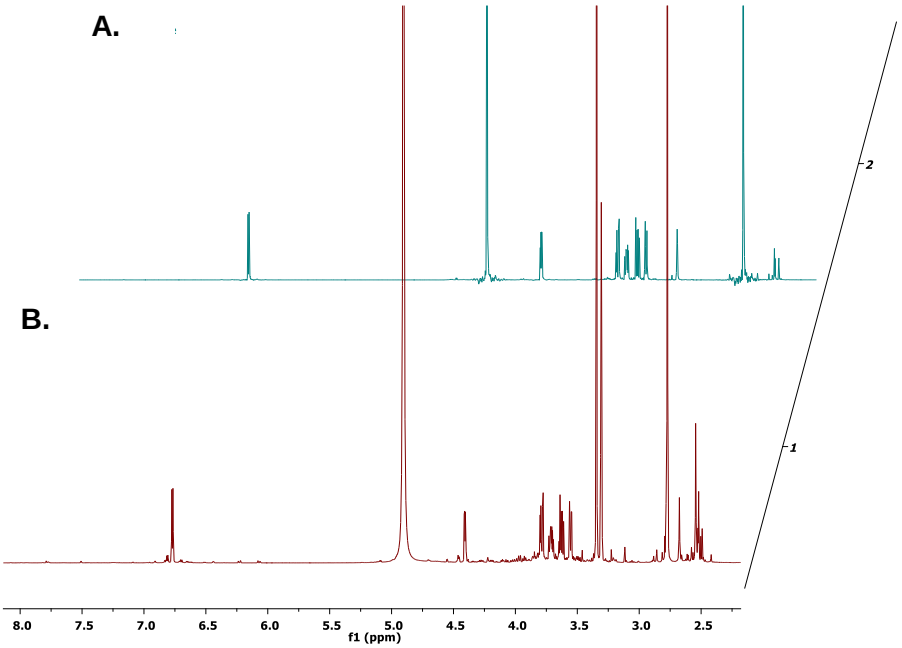



**Figure 8:** $^{1}$H NMR (600 MHz, MeOH-$d_4$). **A**. Reference L-arabinose-hydrazone **1a**, **B.** Crude residue after treatment by activated charcoal and filtration through celite.

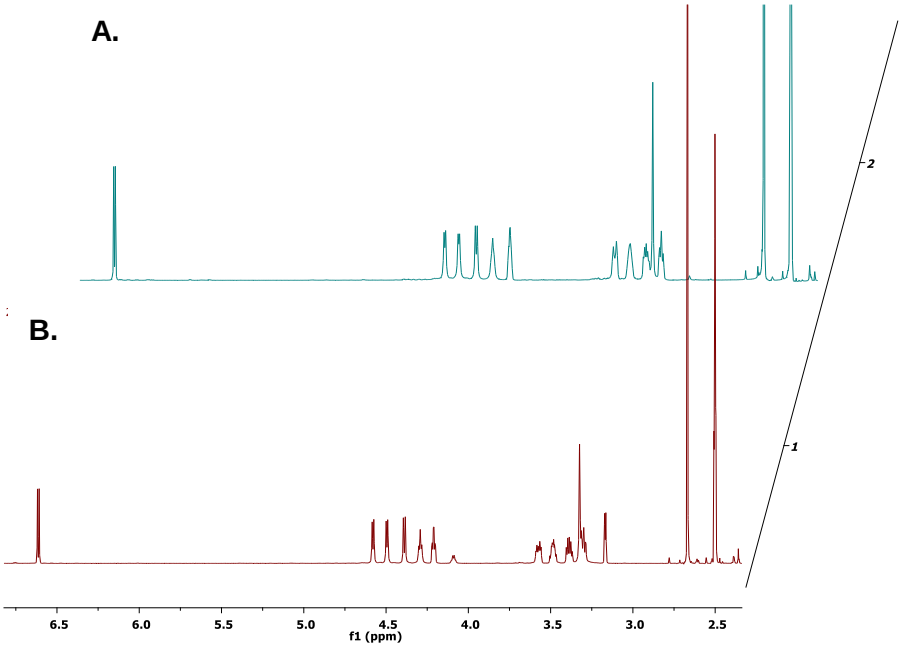



**Figure 9:** $^{1}$H NMR (600 MHz, DMSO-$d_6$) **A.** Arabinose hydrazone **1a** obtained from the sample of pre-treated sugar beet pulp after purification by column chromatography; **B.** Arabinose hydrazone **1a** obtained from pure L-arabinose.

**Synthesis of 1a from a synthetic mixture of sugars and sodium sulfate analogous to the sugar beet pulp mixture.**

A synthetic mixture of sugars and sodium sulfate was prepared using L-arabinose (1.24 g, 8.00 mmol, 1 eq.), D-galactose (0.50 g, 2.30 mmol), D-galacturonic acid (0.52 g, 2.8 mmol), L-rhamnose (0.20 g, 1.10 mmol), D-glucose (0.20 g, 1.1 mmol), $Na_2SO_4$ (8.00 g, 56 mmol) in methanol (5 mL). *N,N*-dimethylhydrazine (1.20 mL, 16.0 mmol, 2 eq.) was added and the resulting mixture was stirred at room temperature overnight before filtration through a pad of celite. The white residue was evaporated to dryness. $^{1}$H NMR of the crude residue showed the L-arabinose sugar hydrazone **1a** as the major product with only trace of another hydrazone. Purification by column chromatography on silica using petrol:acetone as eluent (20:80 to 0:100) gave the arabinose sugar hydrazone **1a** as a white solid (1.60 g, Quant.). The NMR spectra of **1a** obtained were consistent with the data previously reported by our group.

## V. Single crystal X-ray diffraction studies of compounds 9b and 13-Br

All diffraction data were collected by using a four-circle Agilent SuperNova (Dual Source) single crystal X-ray diffractometer with a micro-focus CuKα X-ray beam (λ = 1.54184 Å) and an Atlas CCD detector. The crystal temperature was controlled by using an Oxford Instruments cryojet. Unit cell determination, data reduction and analytical numeric absorption correction using a multifaceted crystal were carried out using the CrysAlisPro programme.* The crystal structures were solved with the ShelXT programme and refined by least squares on the basis of F2 with the ShelXL programme.[11,12] All non-hydrogen atoms were refined anisotropically by the full-matrix least-squares method. Hydrogen atoms affiliated with oxygen atoms were refined isotropically [Uiso(H) = 1.5Ueq(O)] in positions identified by the difference Fourier map, or in geometrically constrained positions. Hydrogen atoms associated with carbon atoms were refined isotropically [Uiso(H) = 1.2Ueq(C)] in geometrically constrained positions. The absolute configurations of compounds **9b** and **13-Br** were assigned by reference to an unchanging chiral centre in the synthetic procedure and was then determined by anomalous-dispersion effects in the diffraction measurements on the respective single crystal. The crystallographic and refinement parameters for compounds **9b** and **13-Br** are shown in Table 5.

**Compounds 9b and 13-Br**

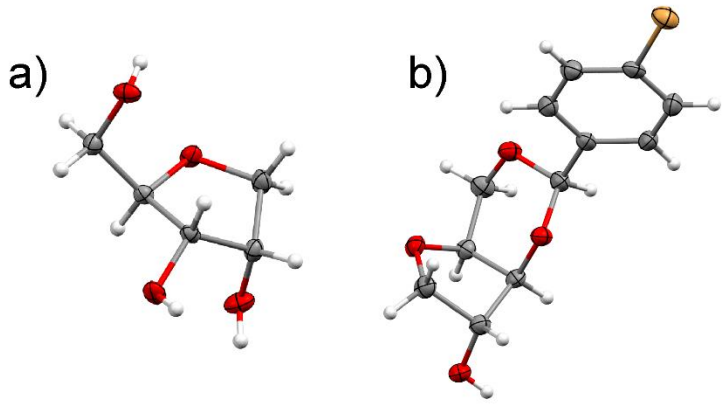



**Figure 10.** X-ray crystal structure of compounds: a) **9b** and b) **13-Br**. The thermal ellipsoids are shown at the 50% probability level, while hydrogen atoms are drawn as fixed spheres with a radius of 0.15 Å.

* *CrysAllisPro*. *Agilent Technologies*, Inc. (2014).

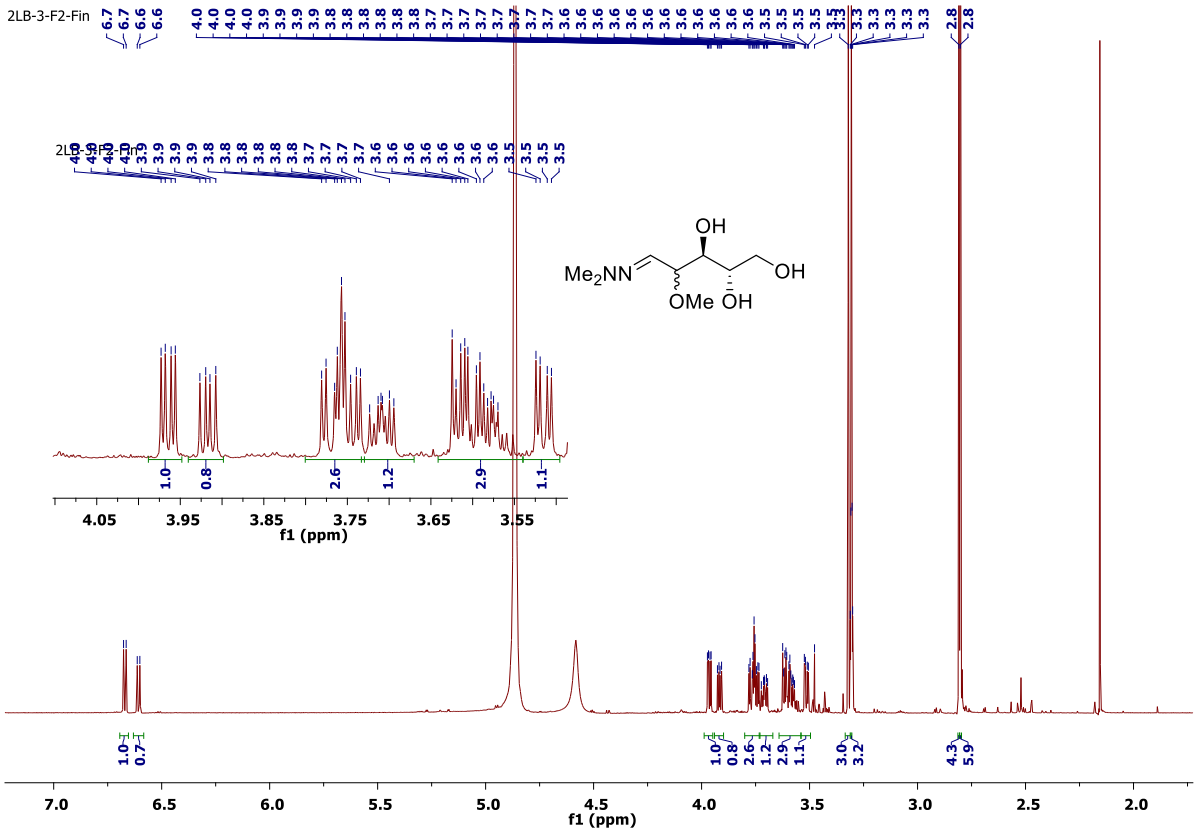
**Crystallographic and refinement parameters**

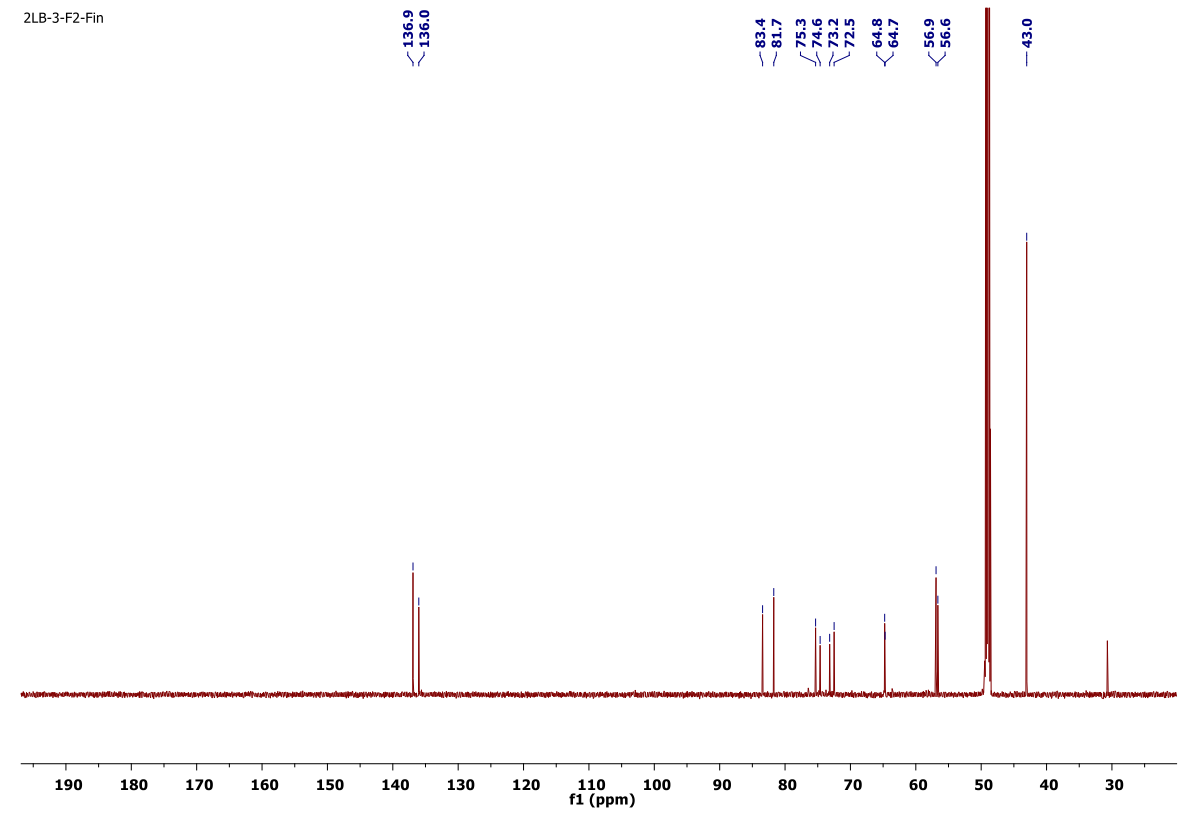
**Table 5.** Crystallographic and refinement parameters for **9b and 13-Br**.

| *C**ompound*** | ***9b*** | ***13-Br*** |
|---|---|---|
| chemical formula | $C_5H_{10}O_4$ | $C_{12}H_{13}BrO_4$ |
| $M_r$ / g mol$^{-1}$ | 134.13 | 301.13 |
| crystal system | orthorhombic | monoclinic |
| space group | $P2_12_12_1$ | $C2$ |
| $a$ / Å | 5.01554(7) | 22.3597(5) |
| $b$ /Å | 7.52021(7) | 5.5295(2) |
| $c$ / Å | 15.90107(16) | 9.5976(2) |
| $\alpha$ / ° | 90 | 90 |
| $\beta$ / ° | 90 | 90.661(2) |
| $\gamma$ / ° | 90 | 90 |
| $V$ / Å$^3$ | 599.755(12) | 1186.55(6) |
| $Z$ | 4 | 4 |
| $D_c$ / gcm$^{-3}$ | 1.485 | 1.686 |
| $F$(000) | 288 | 608 |
| $\mu$(Cu$K_\alpha$) / mm$^{-1}$ | 1.115 | 4.754 |
| $T$ / K | 150(1) | 150.0(1) |
| crystal size / mm | 0.38 × 0.09 × 0.05 | 0.44 × 0.08 × 0.04 |
| index range | −6 → 6<br>−9 → 9<br>−19 → 19 | −27 → 27<br>−6 → 6<br>−11 → 11 |
| collected reflections | 20216 | 8533 |
| unique reflections | 1192 | 2218 |
| $R_{int}$ | 0.0440 | 0.0288 |
| reflections with $I > 2\sigma(I)$ | 1167 | 2195 |
| no. parameters | 88 | 156 |
| $R(F)$, $F > 2\sigma$(F) | 0.0267 | 0.0224 |
| $wR(F^2)$, $F > 2\sigma$(F) | 0.0658 | 0.0599 |
| $R(F)$, all data | 0.0271 | 0.0227 |
| $wR(F^2)$, all data | 0.0662 | 0.0604 |
| $\Delta_r$ (min., max.) e Å$^{-3}$ | −0.179, 0.201 | −0.344, 0.385 |
| CCDC deposition number | 1877937 | 1877938 |

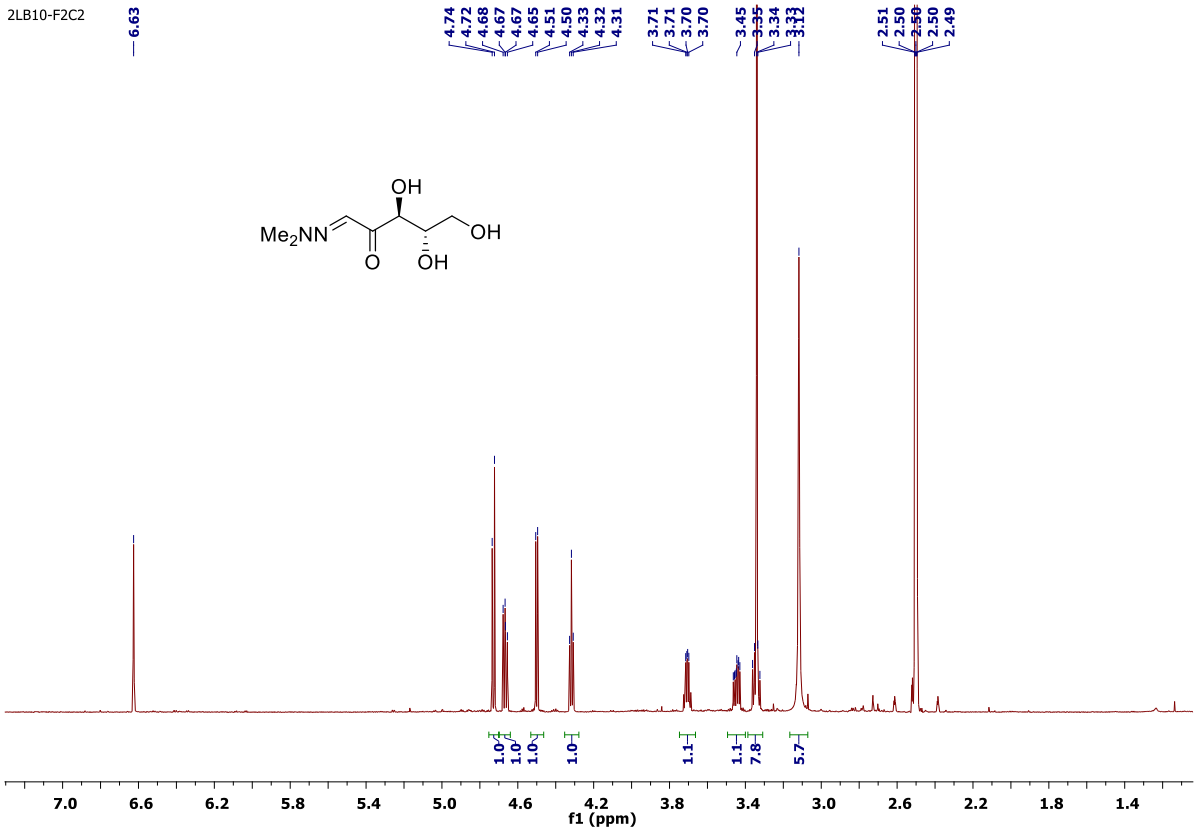
## VI. Spectra

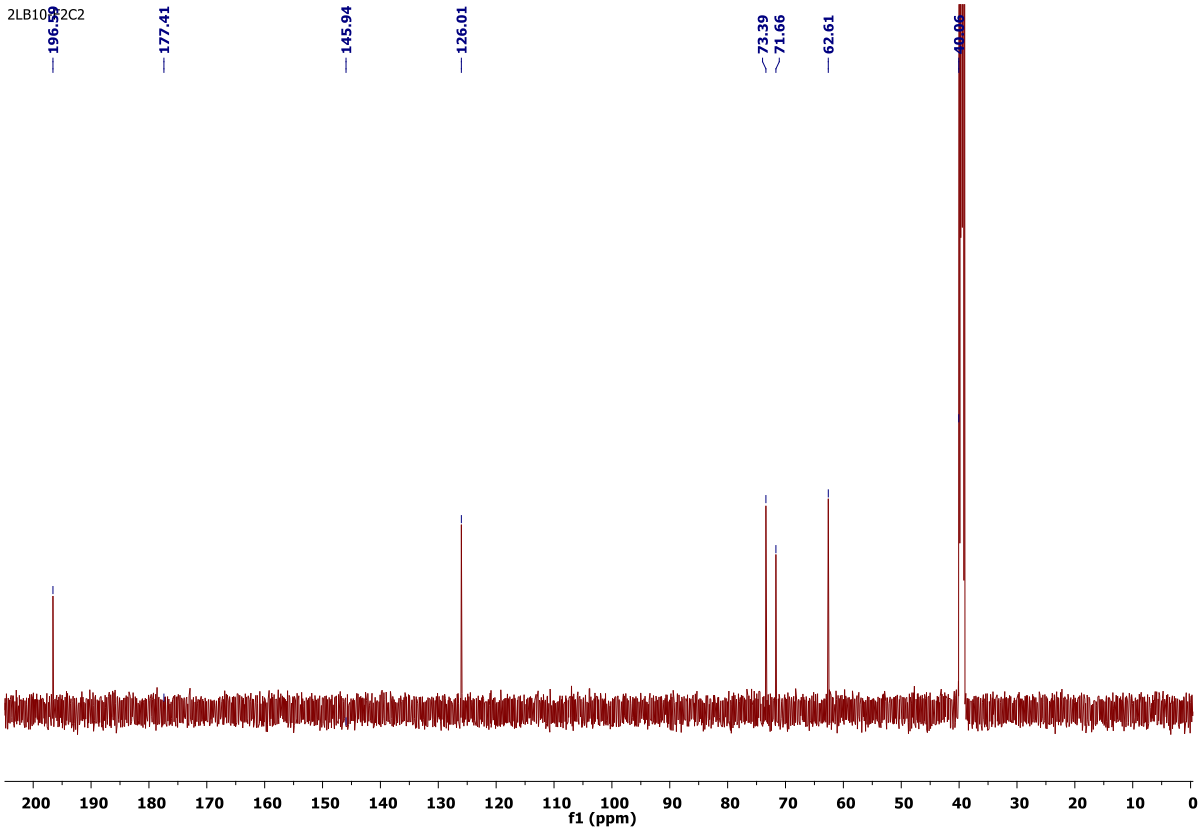
### (*2S,3S*)-5-(2,2-Dimethylhydrazineylidene)-4-methoxypentane-1,2,3-triol (4)



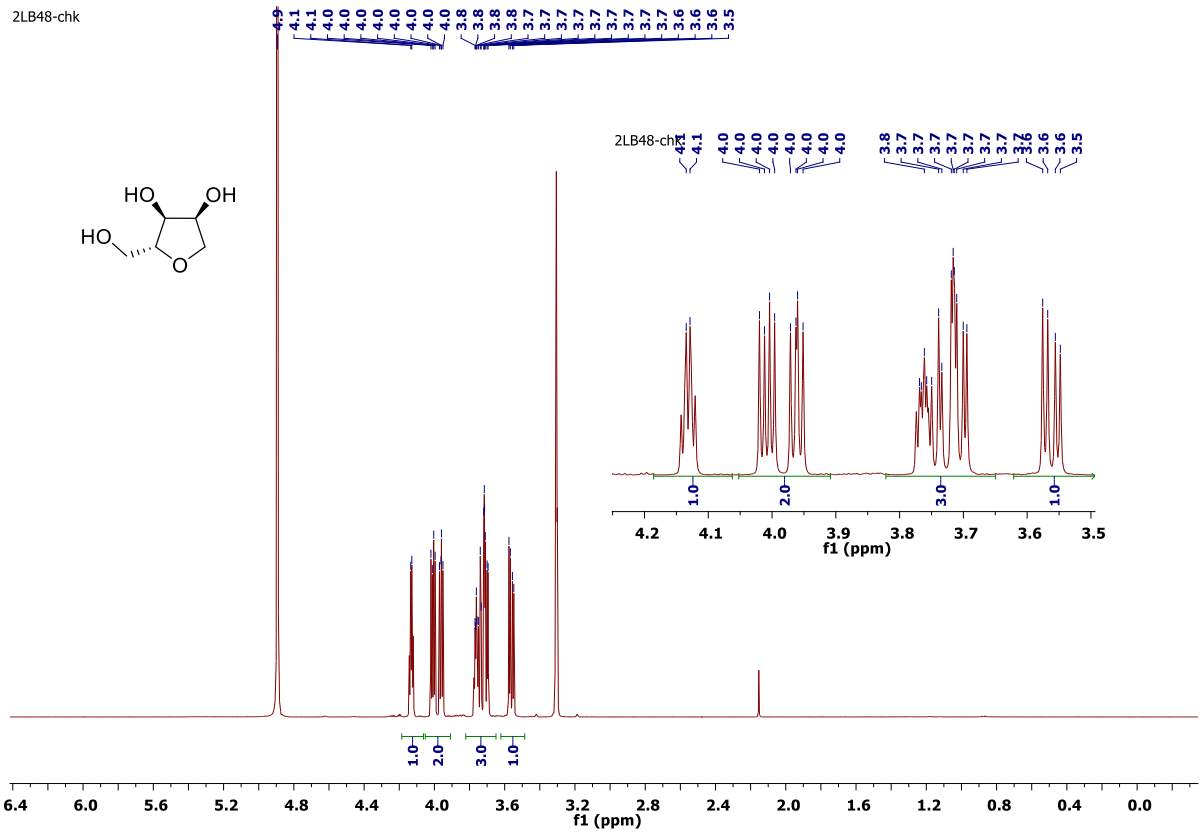



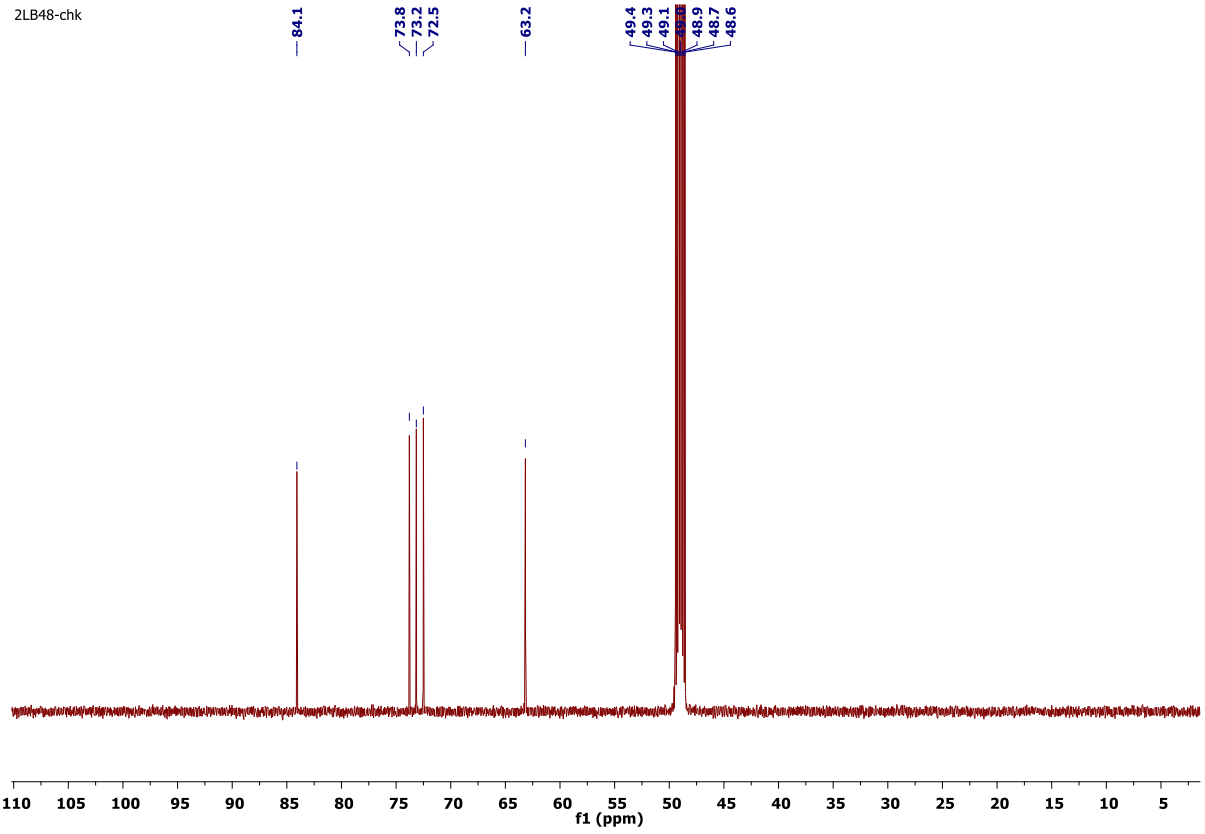
**(*3S,4S*)-1-(2,2-Dimethylhydrazineylidene)-3,4,5-trihydroxypentan-2-one (5)**



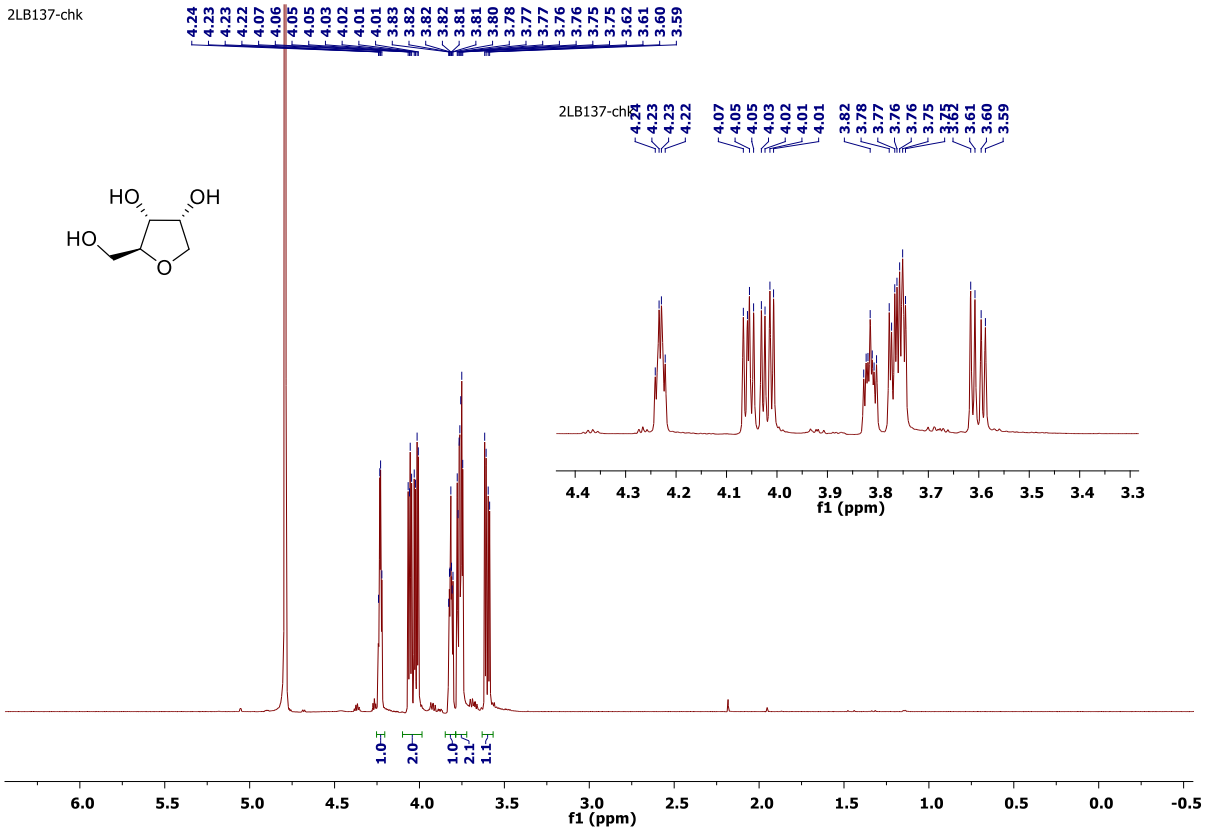



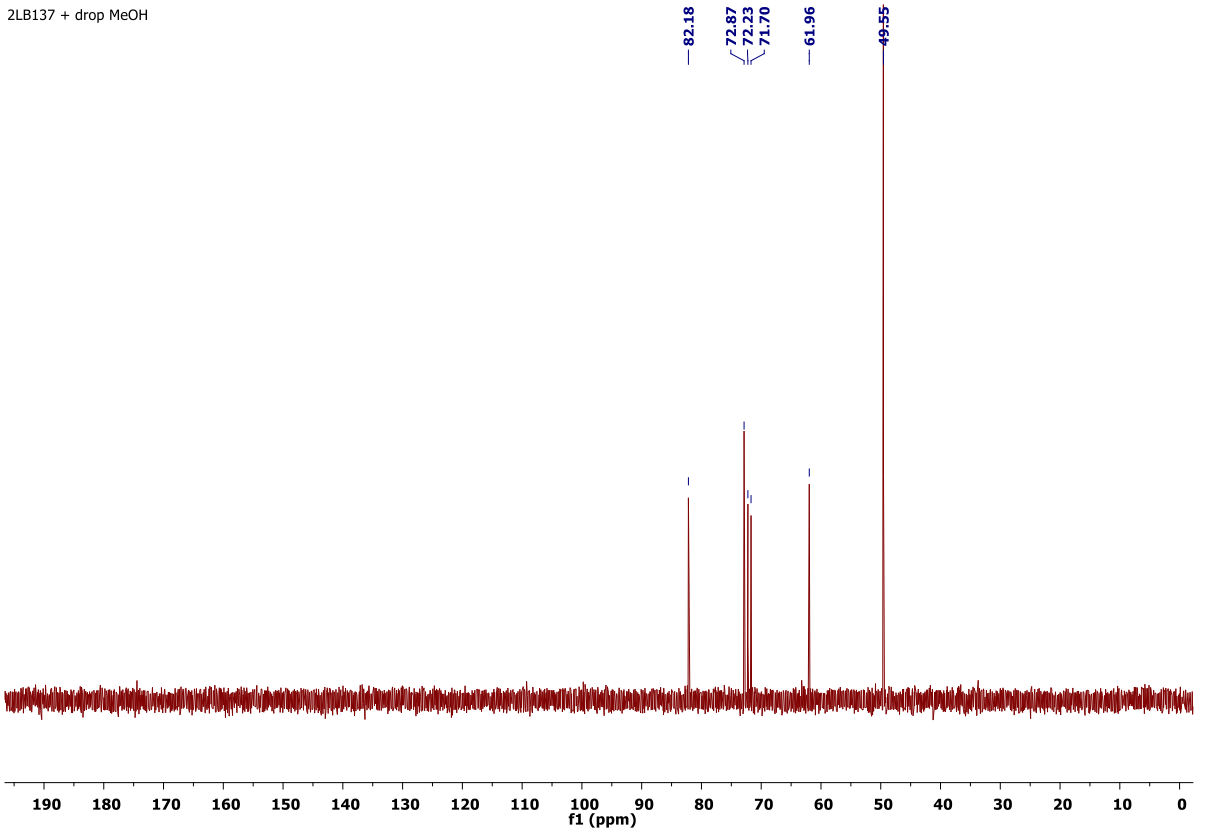
## (*2R,3S,4S*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (9a)



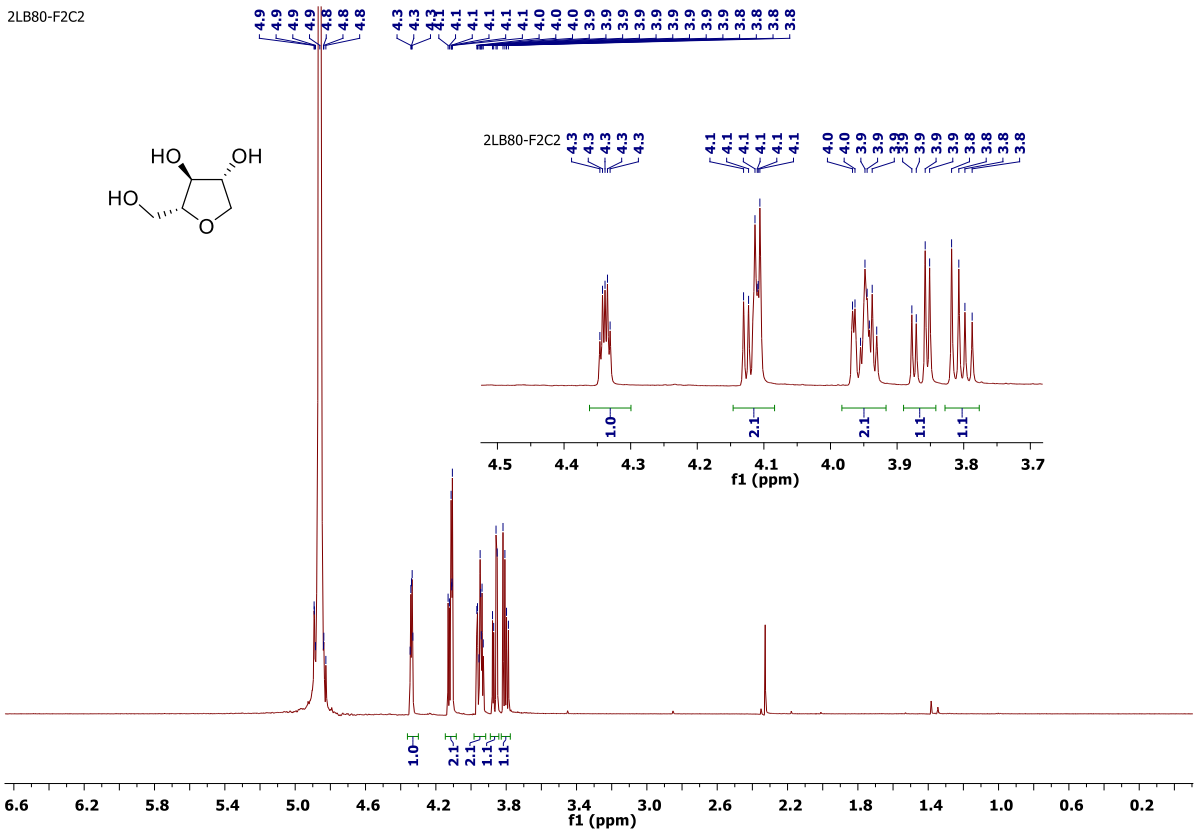



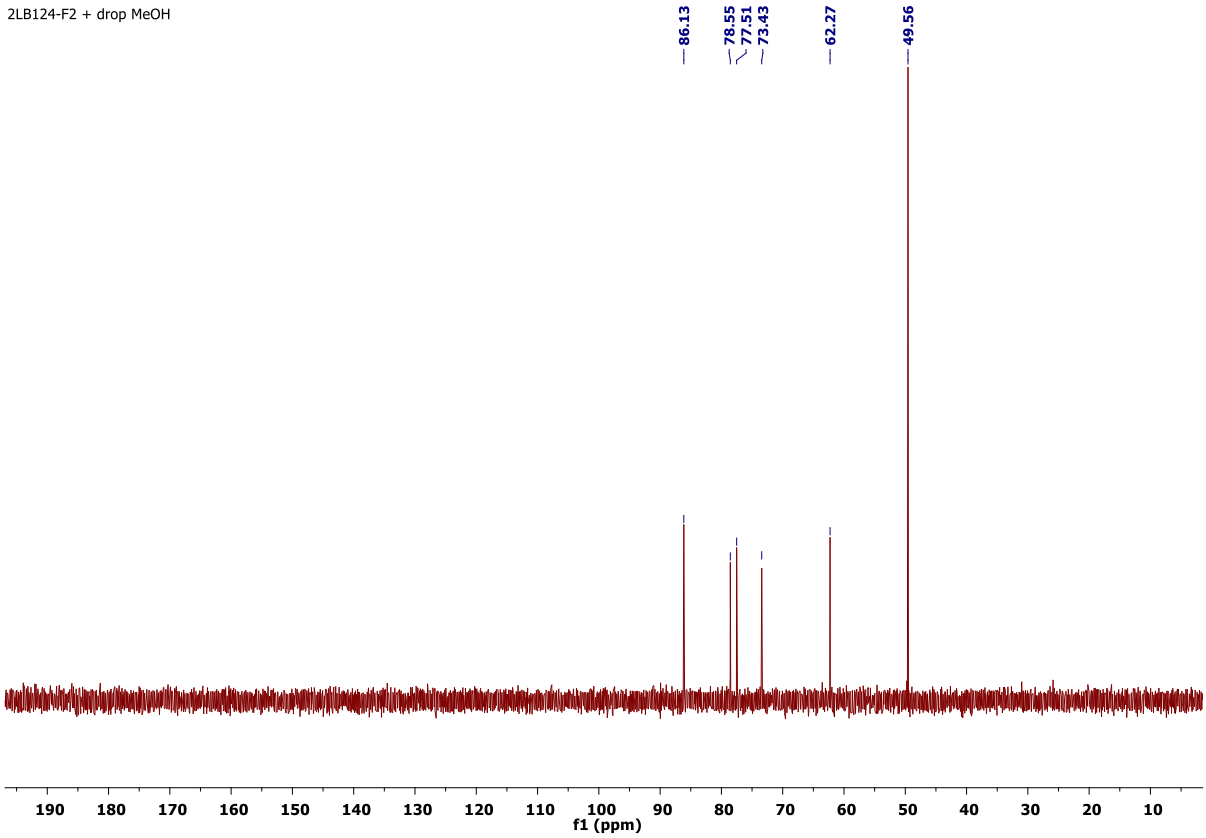
## (*2S,3R,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (9b)



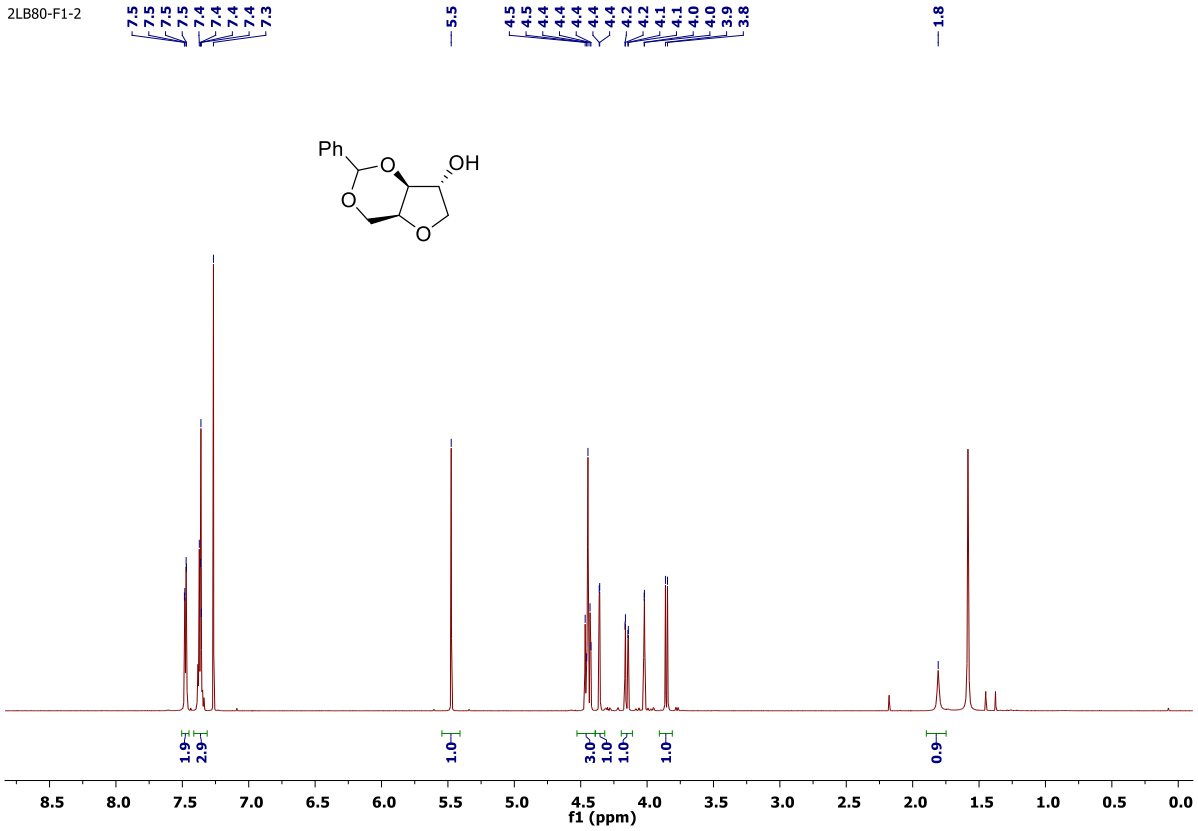



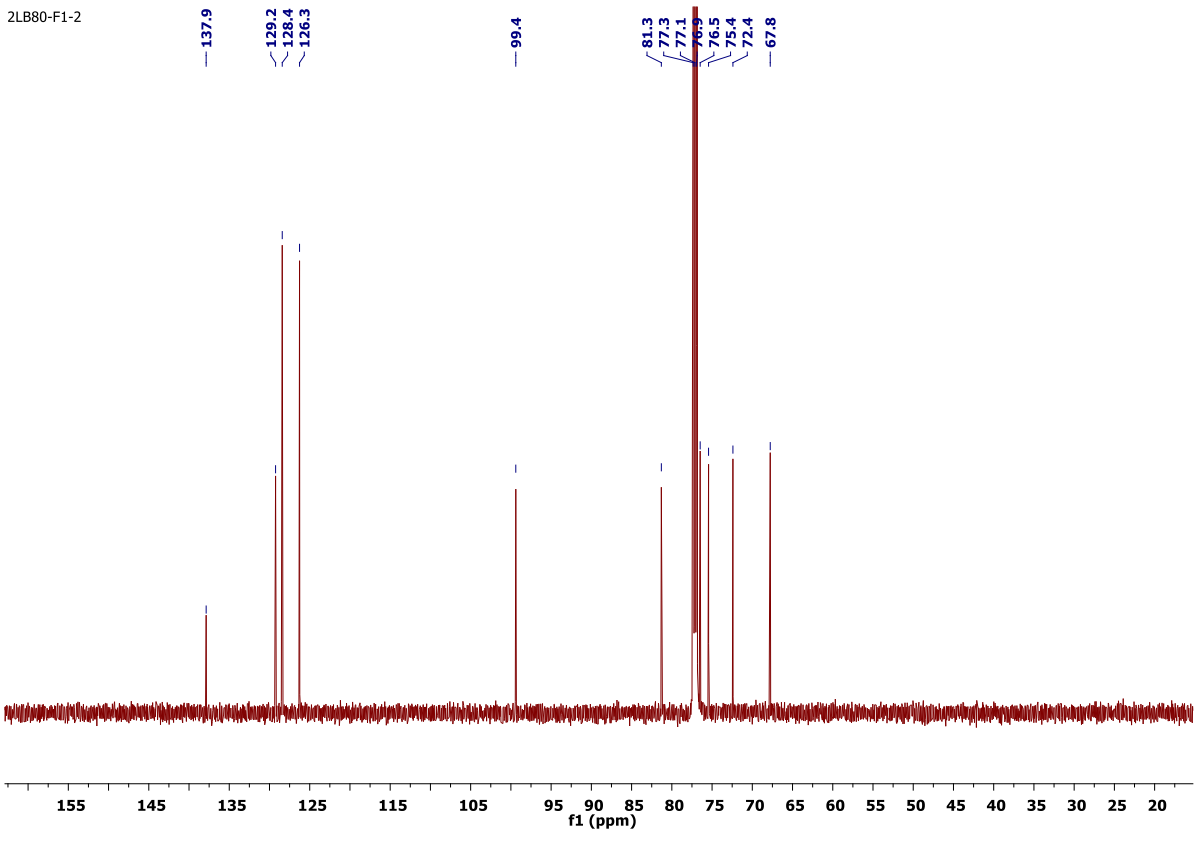
## (*2R,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*anti*-9c)



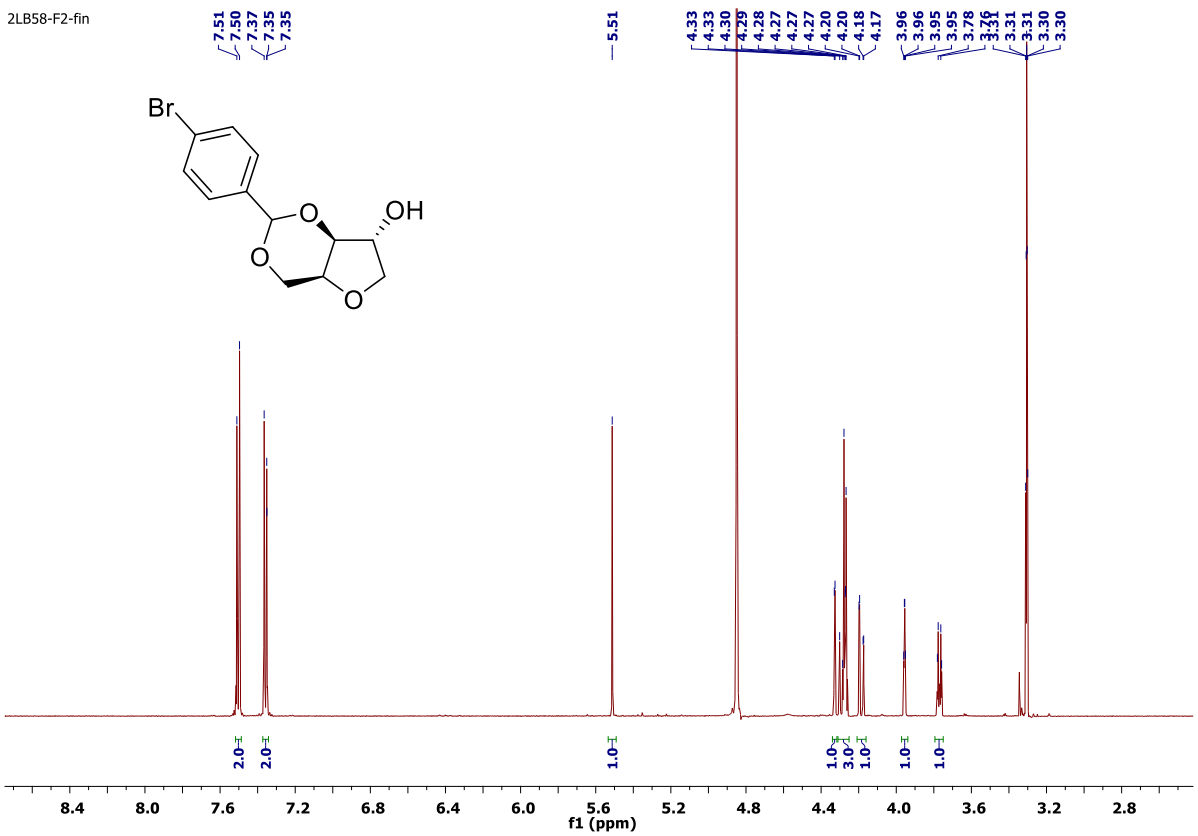



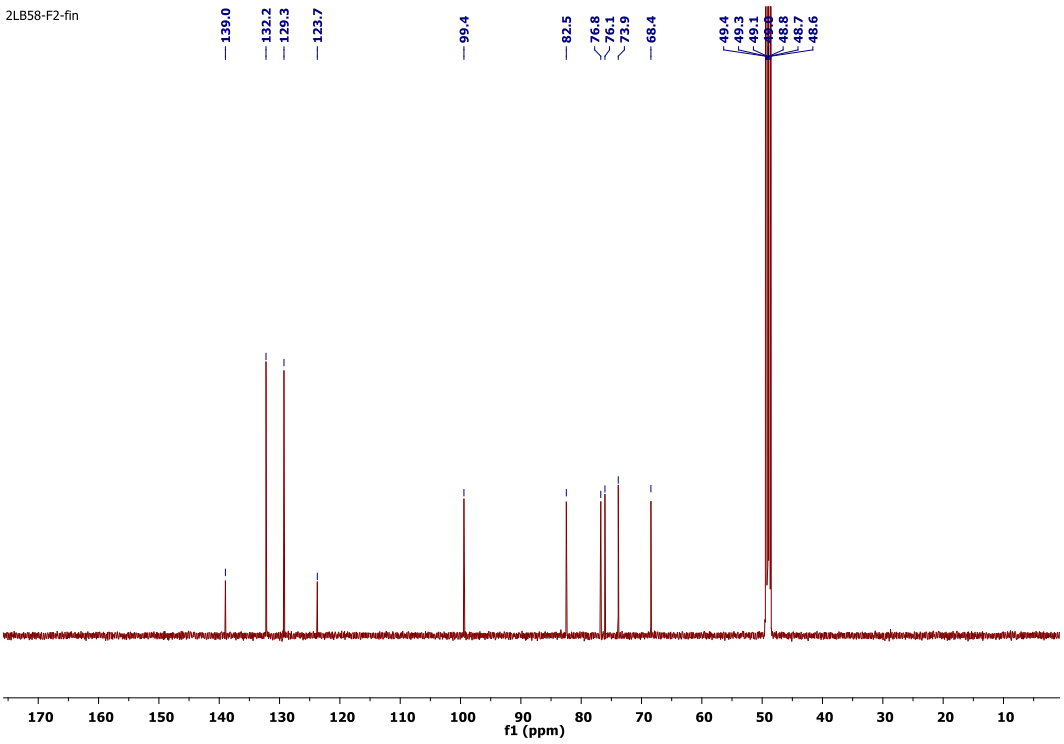
**(*4aS,7R,7aS*)-2-Phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (13)**



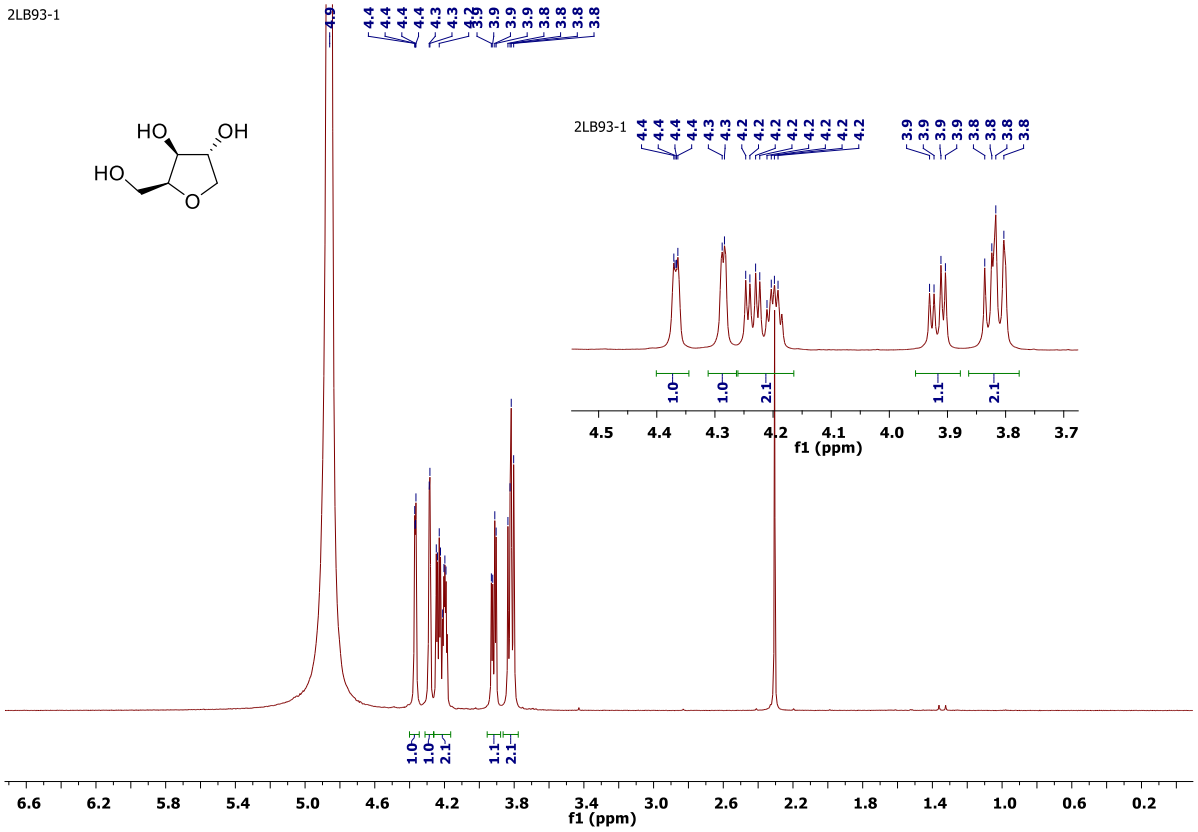



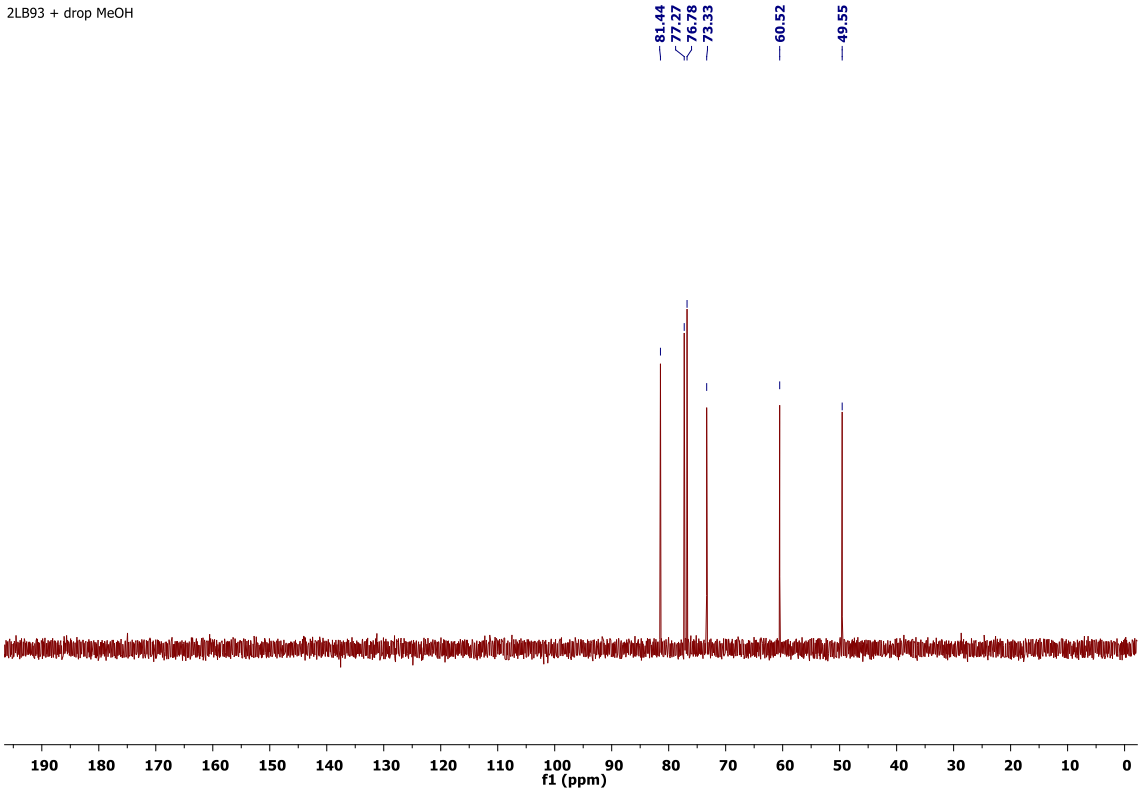
**(*4aS,7R,7aS*)-2-(4-bromophenyl)tetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (13-Br)**



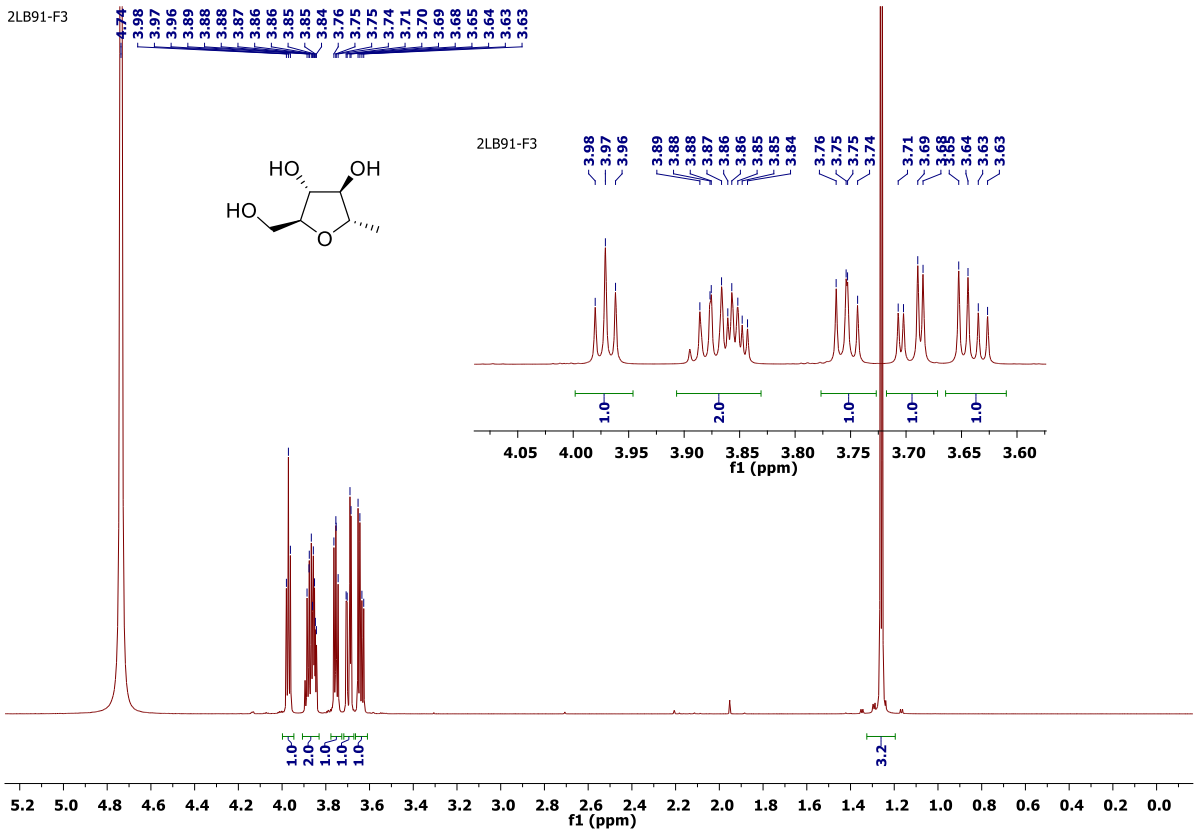



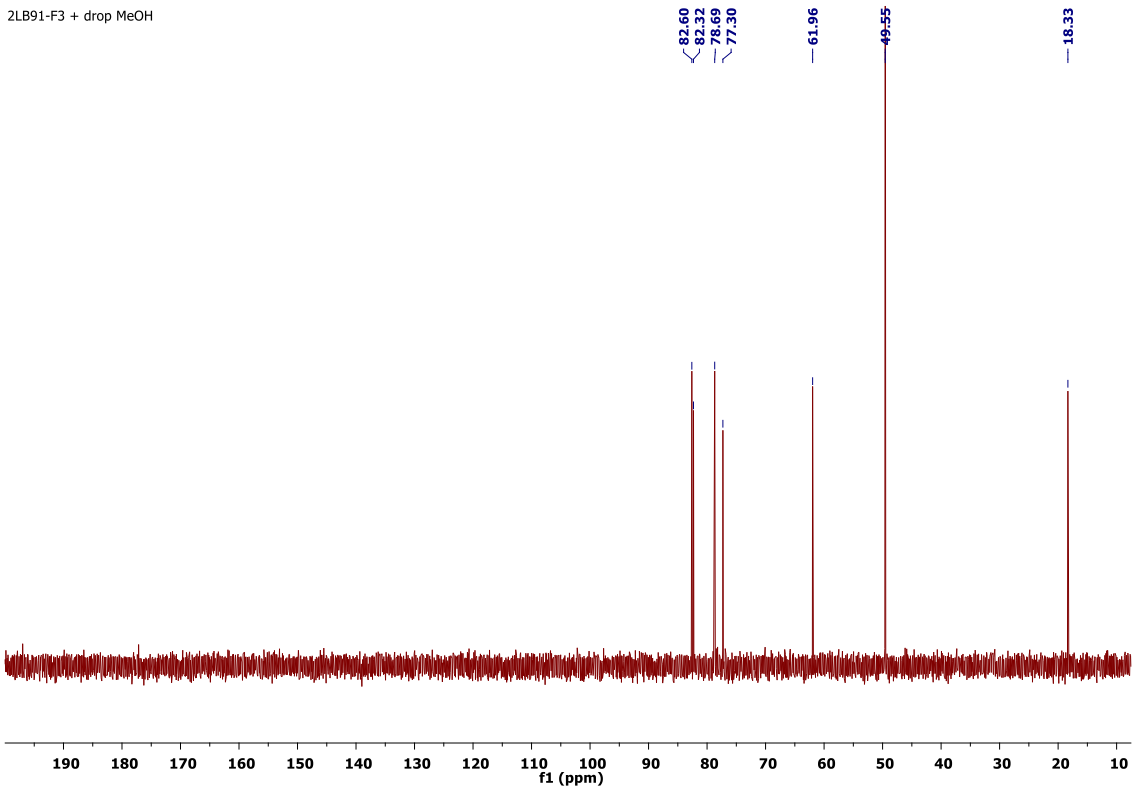
## (*2S,3S,4R*)-2-(Hydroxymethyl)tetrahydrofuran-3,4-diol (*syn*-9c)



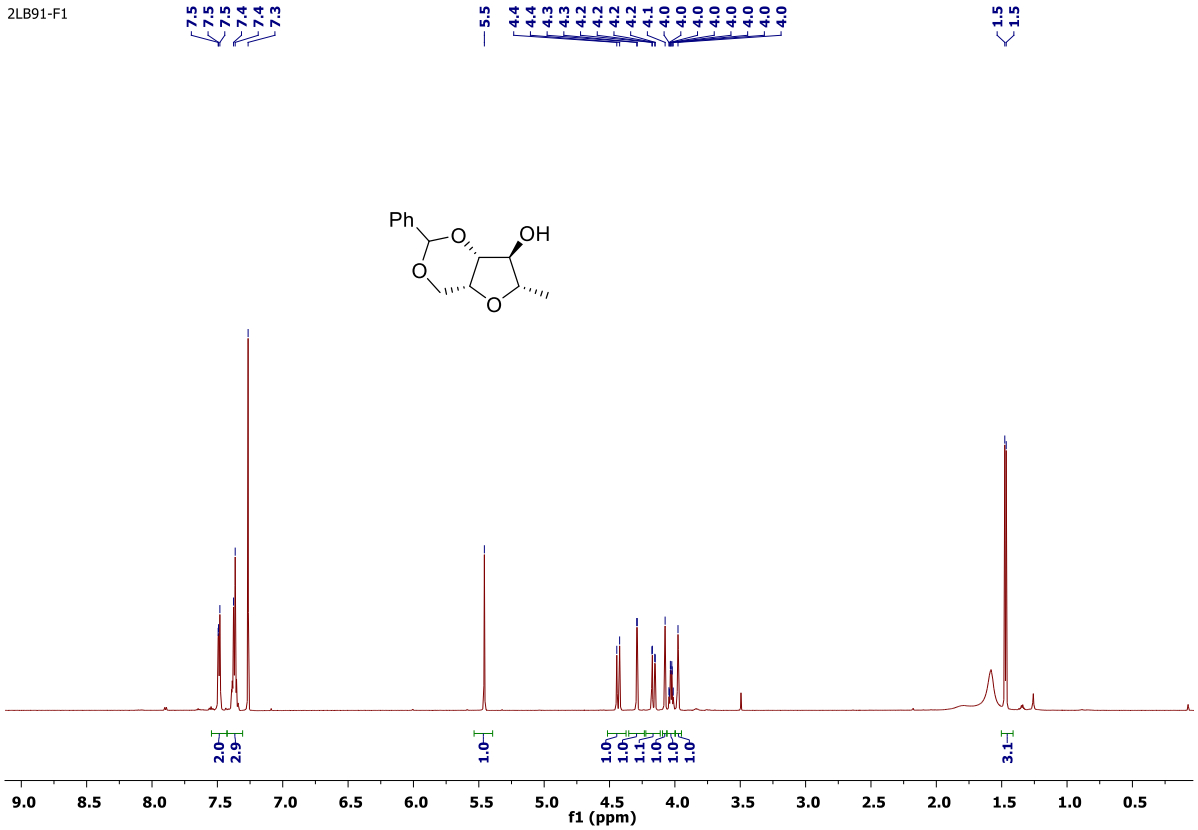



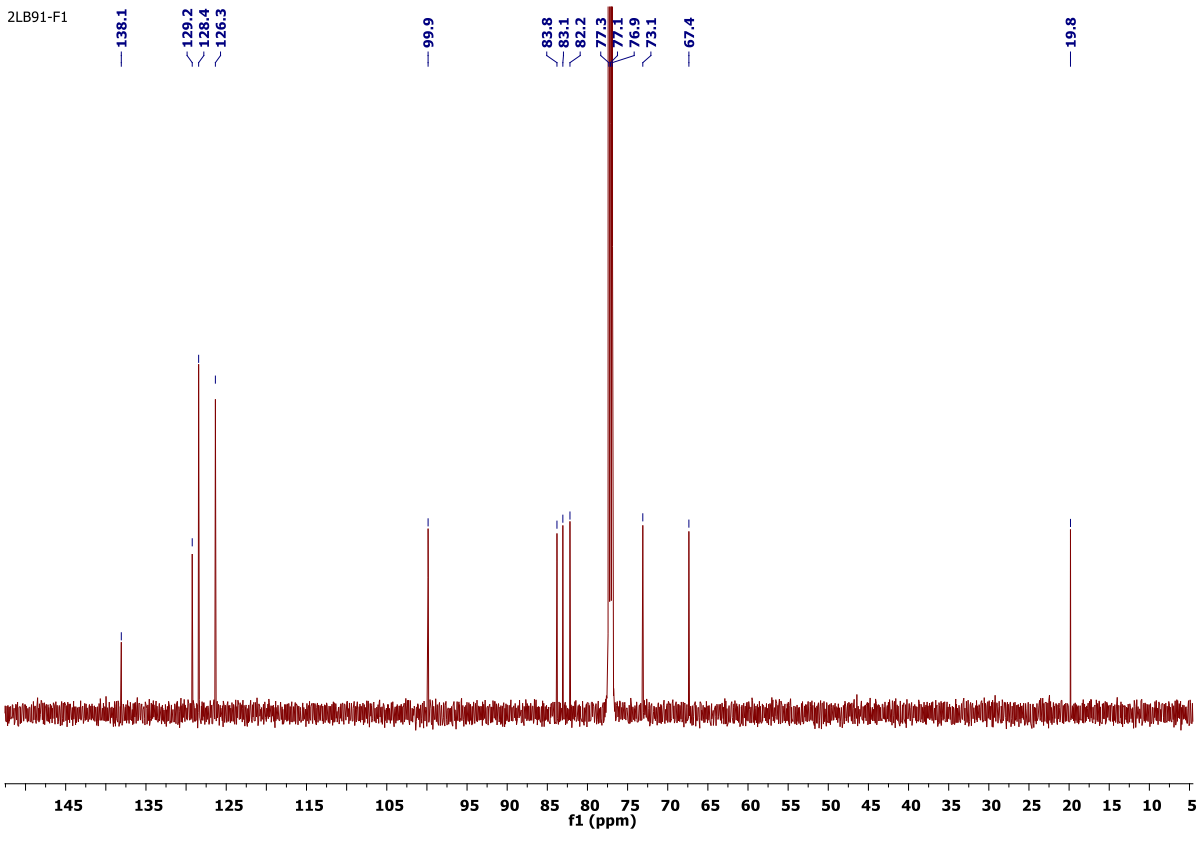
**(*2S,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-9d)**



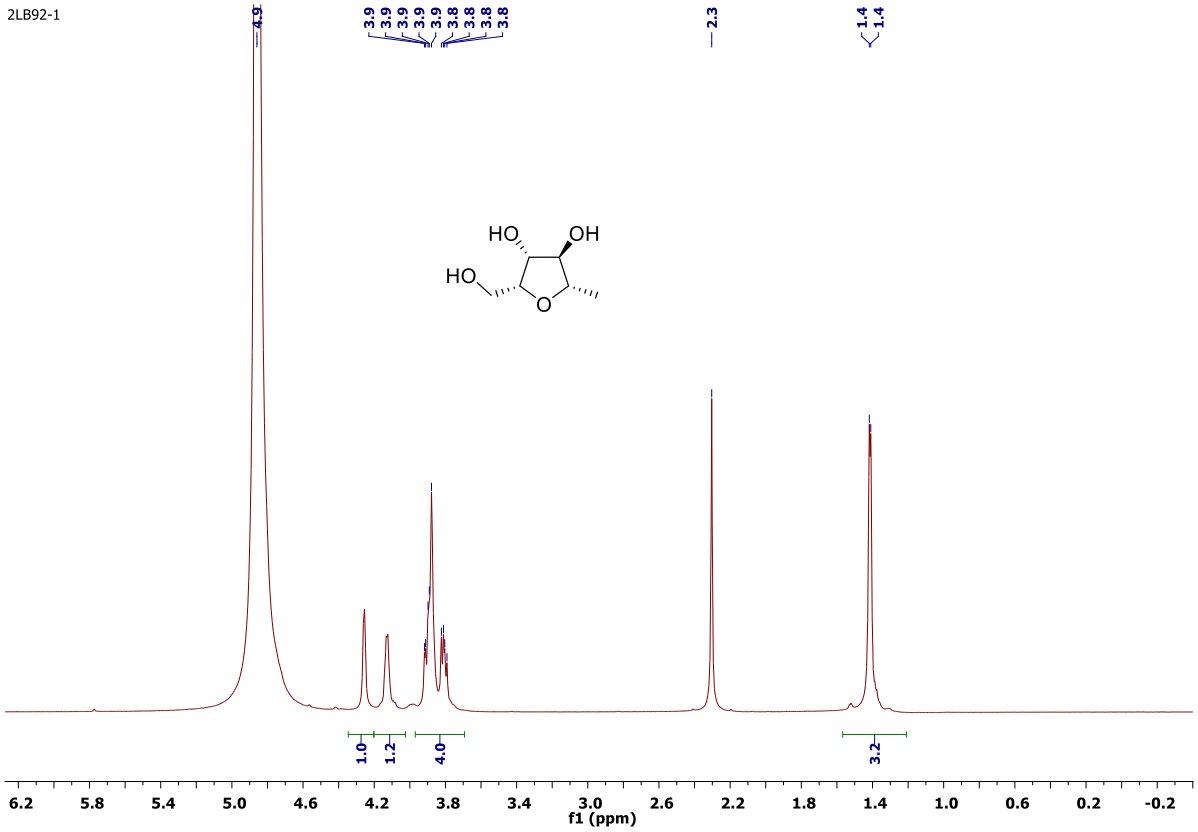



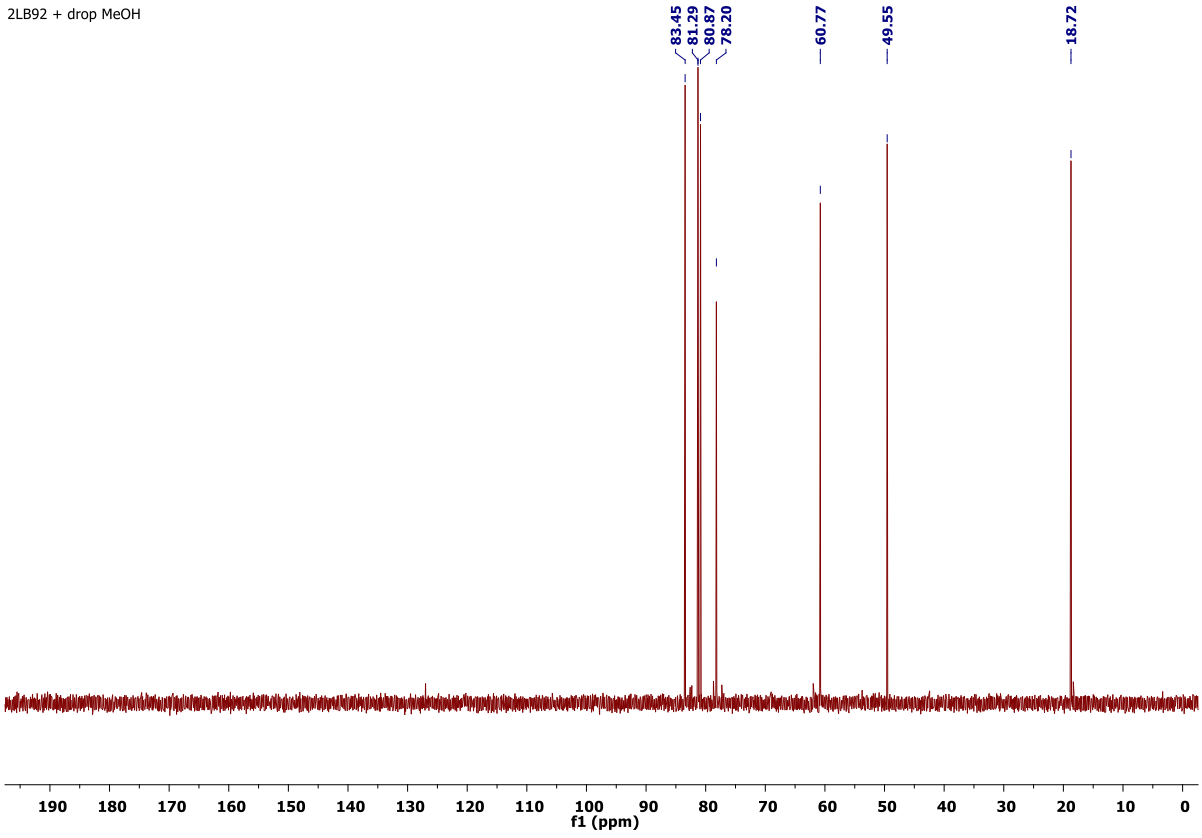
**(*4aR,6S,7S,7aR*)-6-Methyl-2-phenyltetrahydro-4H-furo[3,2-d][1,3]dioxin-7-ol (15)**



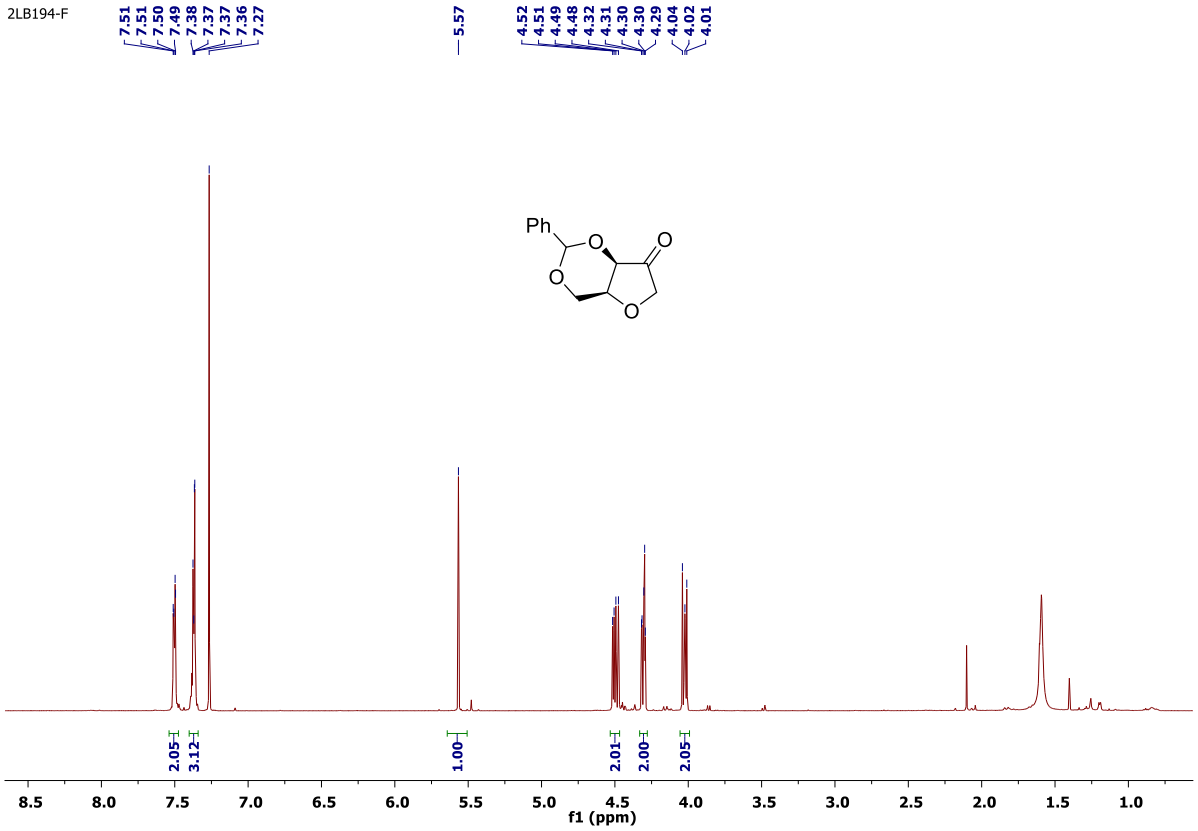



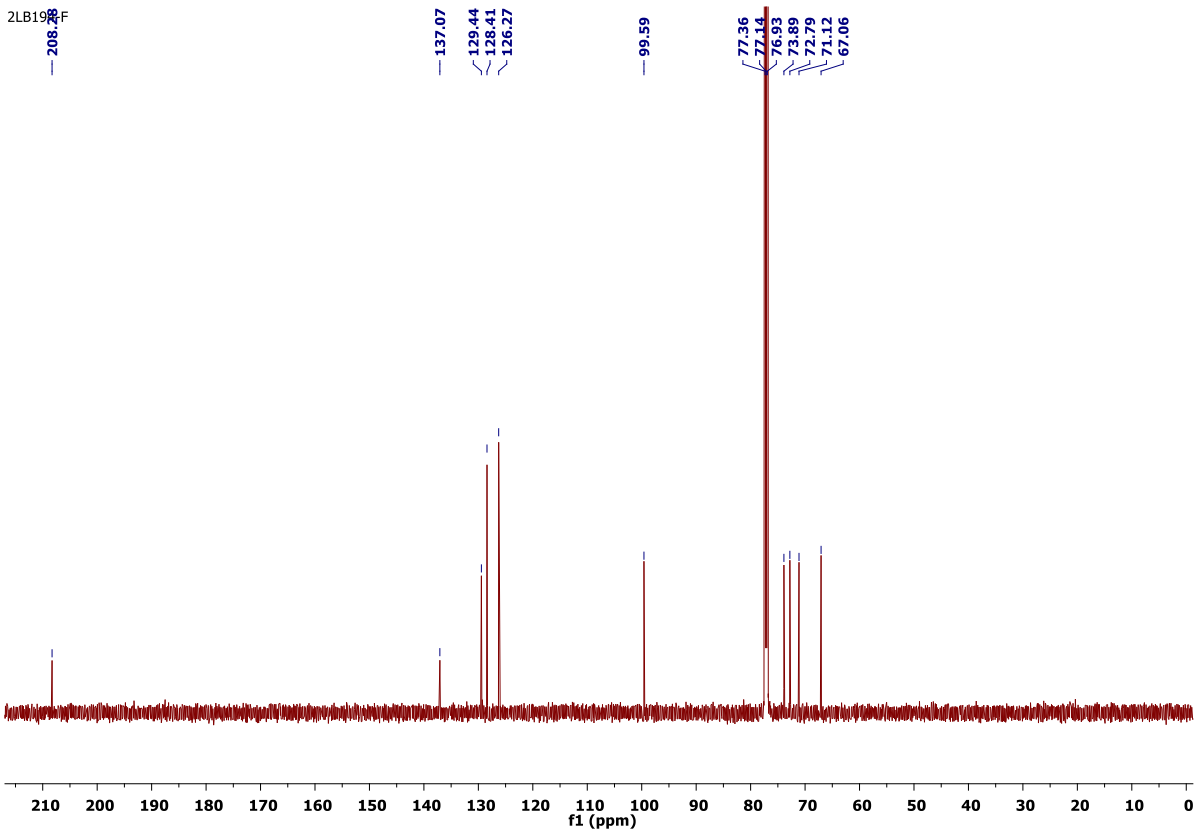
**(*2R,3R,4R,5S*)-2-(Hydroxymethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-9d)**



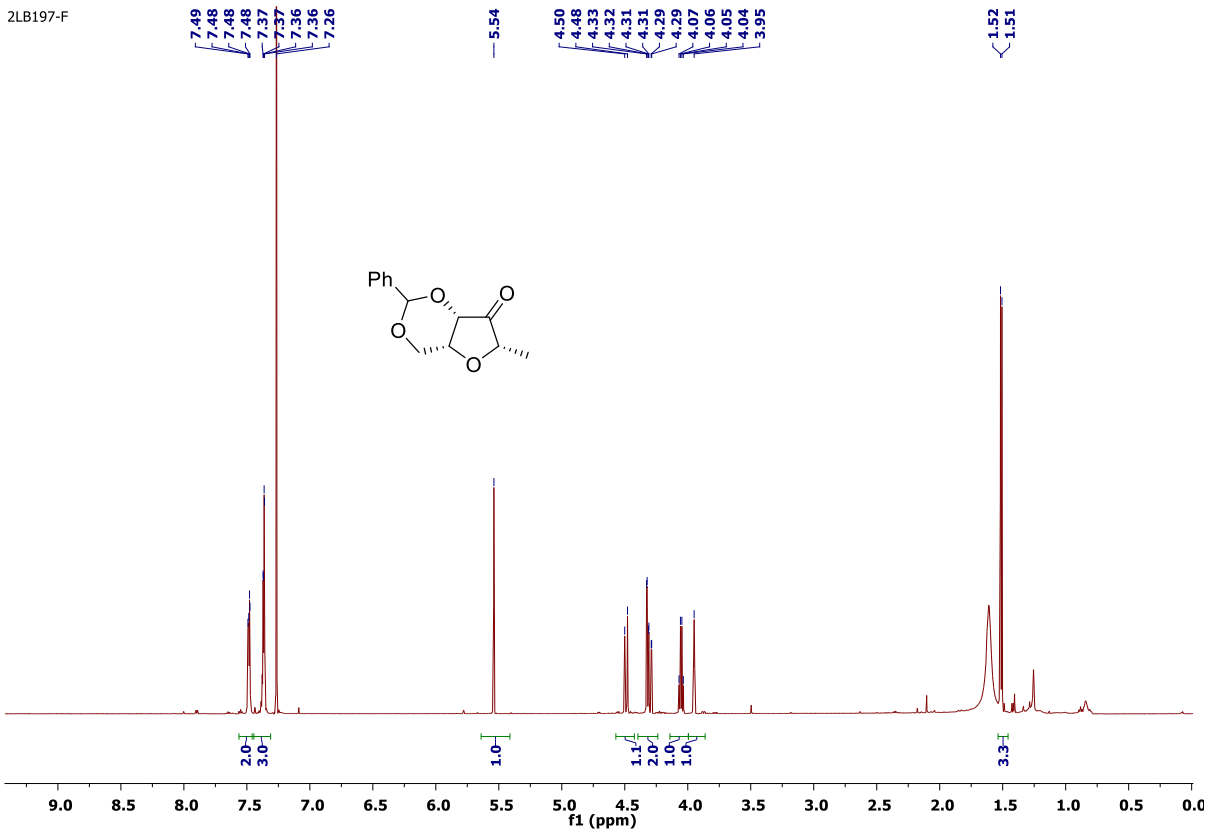



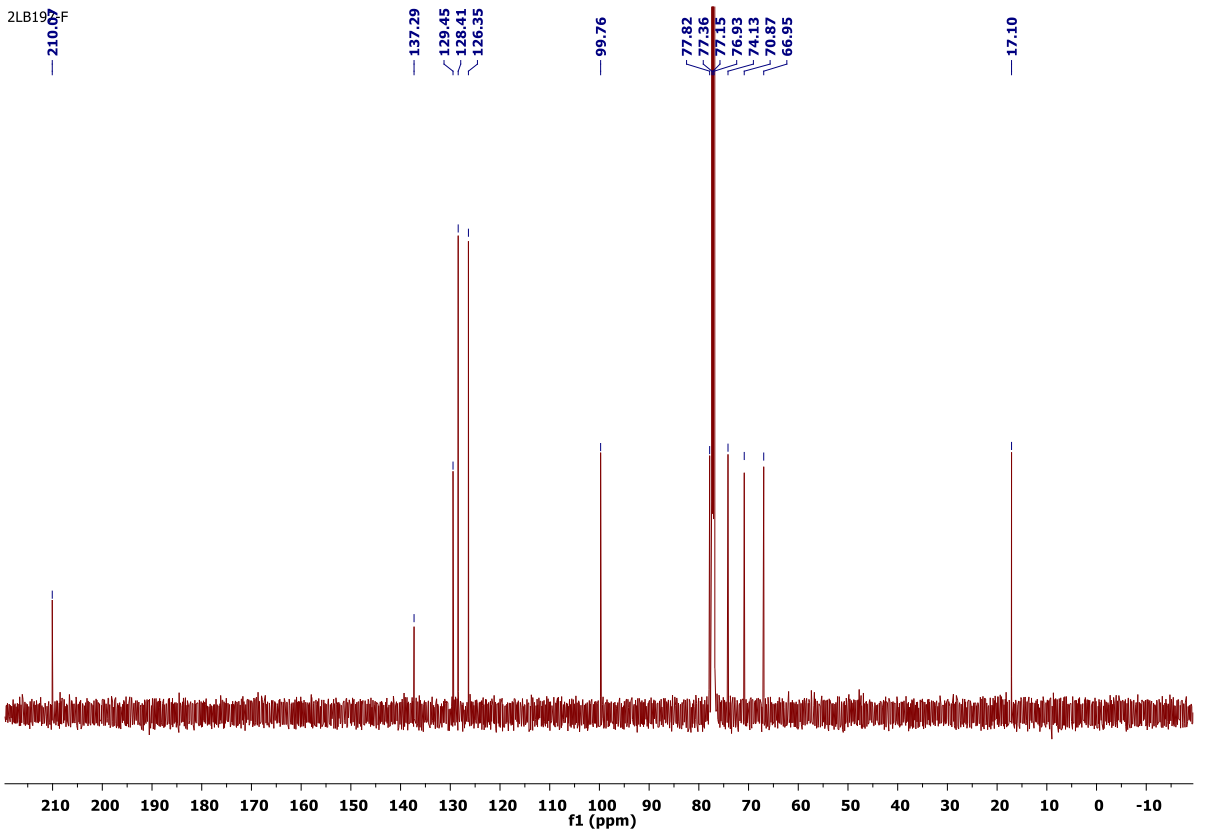
**(*4aS,7aR*)-2-Phenyldihydro-4H-furo[3,2-d][1,3]dioxin-7(6H)-one (14)**



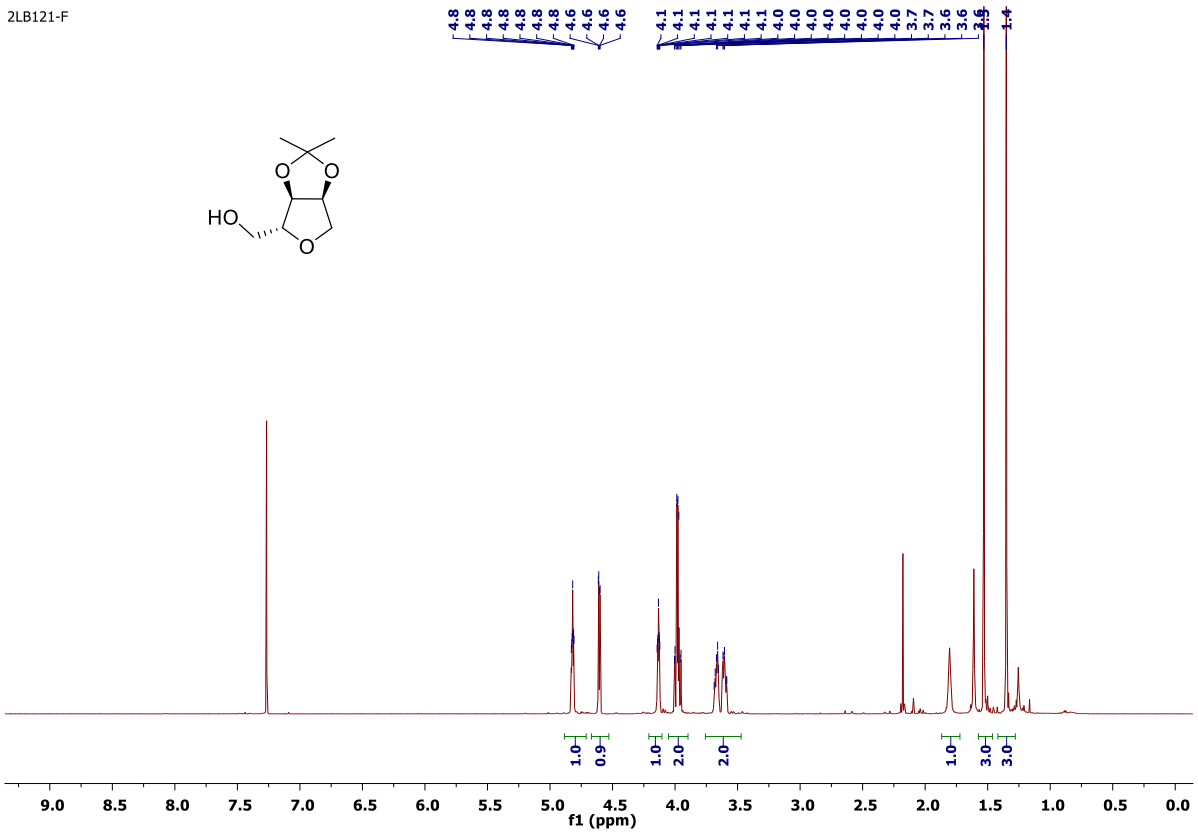



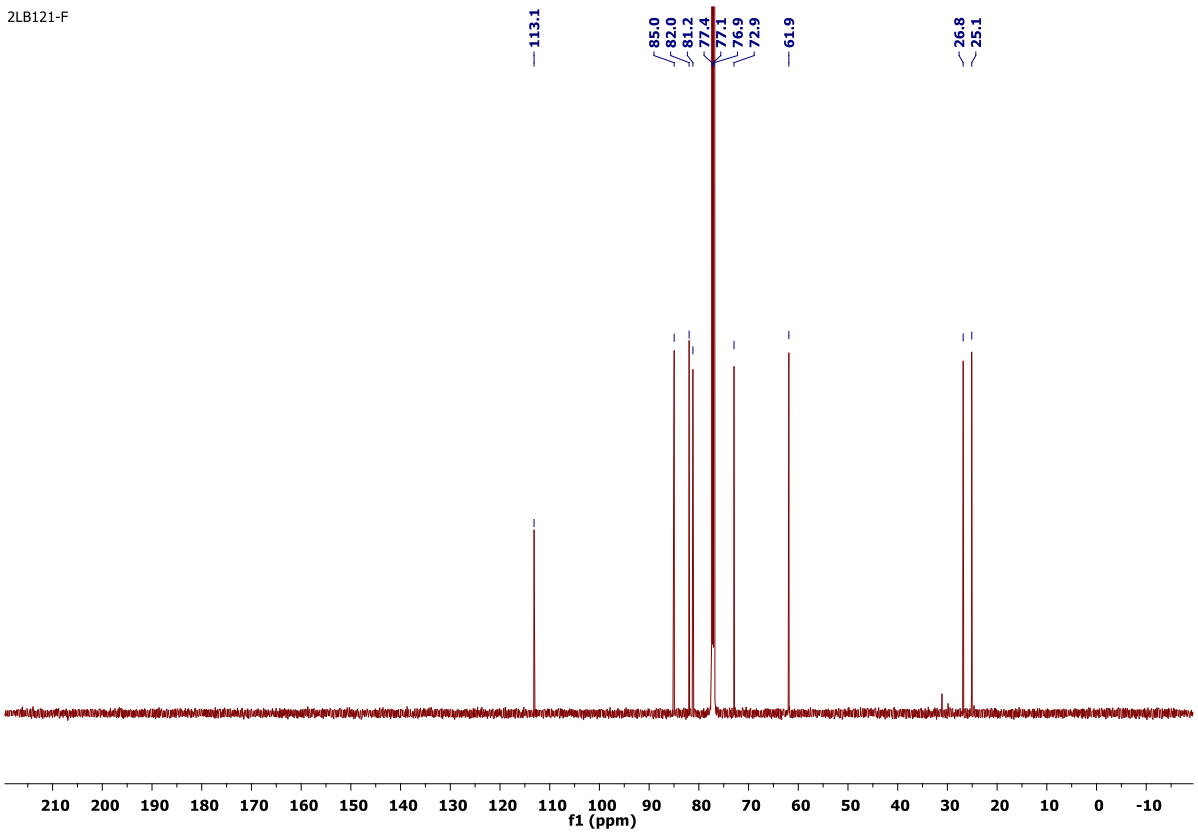
**(*4aR,6S,7aS*)-6-Methyl-2-phenyldihydro-4H-furo[3,2-d][1,3]dioxin-7(6H)-one (16)**



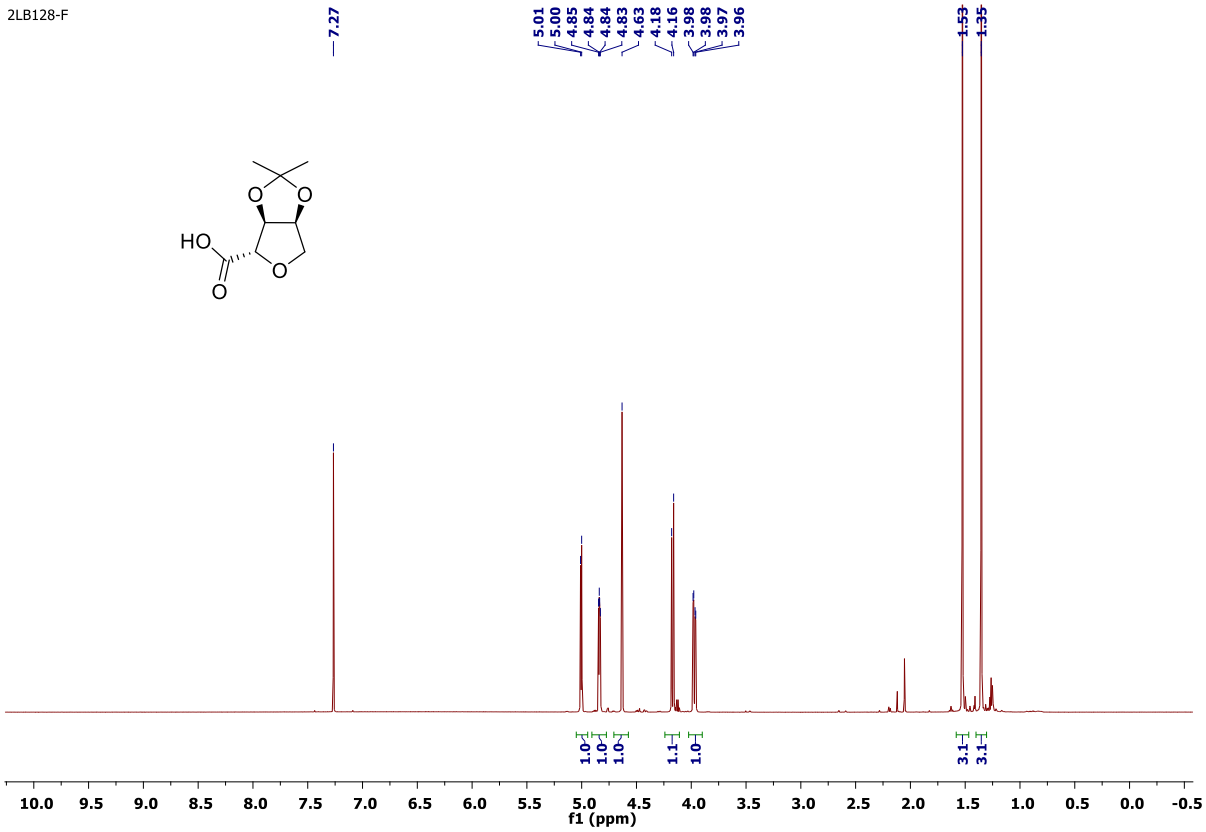



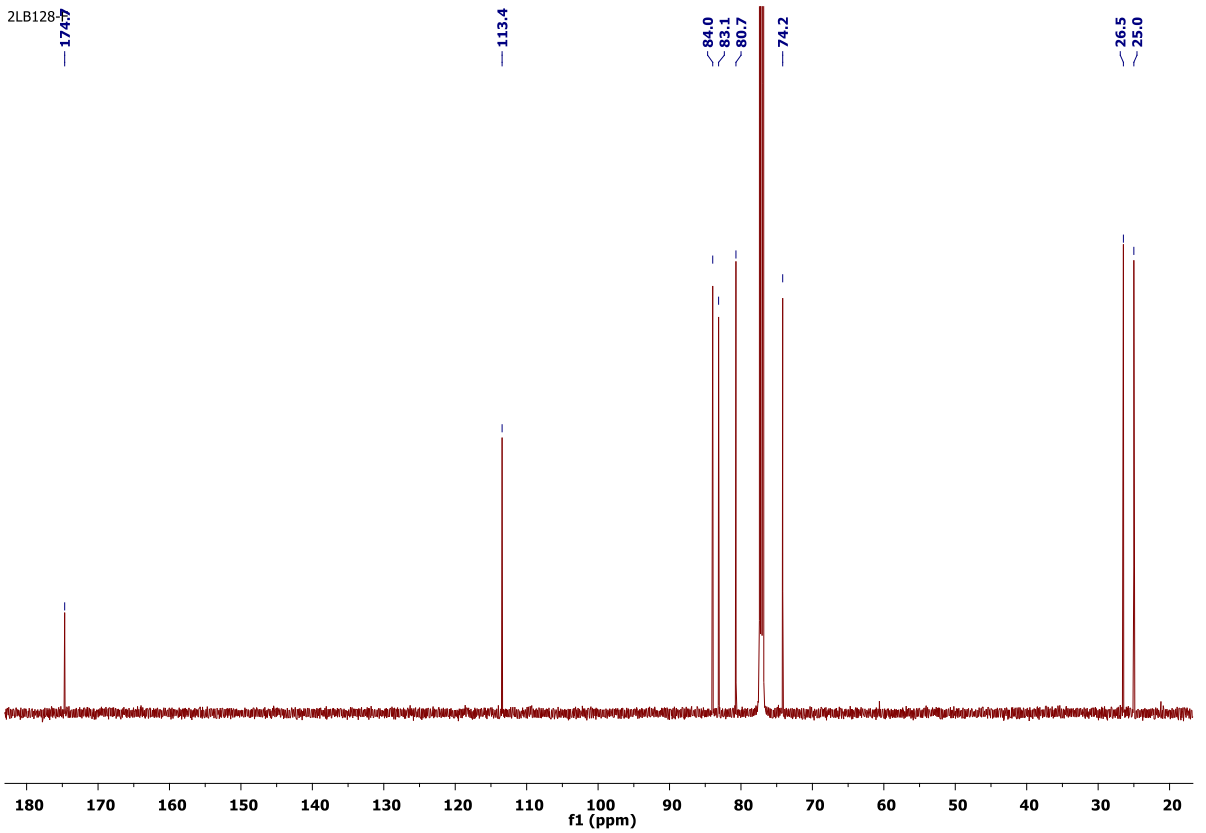
**((*3aR,4R,6aS*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methanol (17a)**



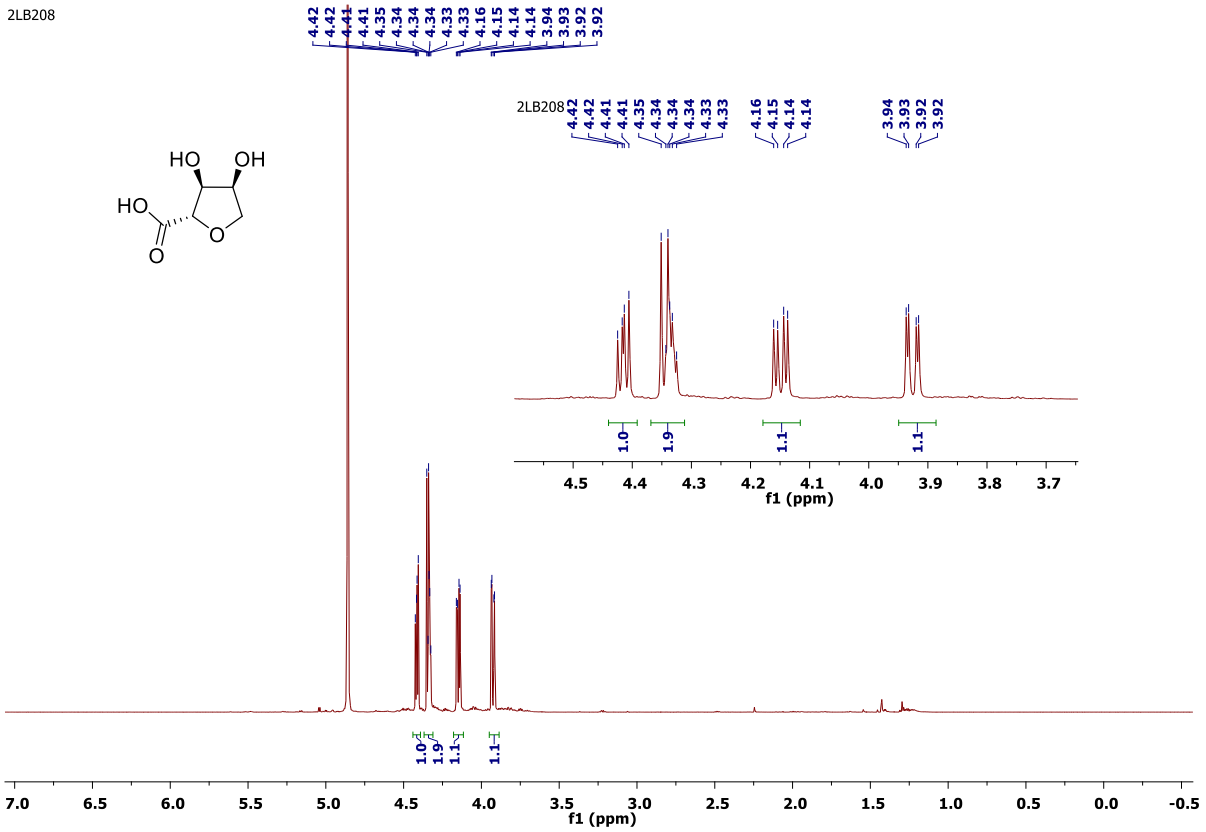



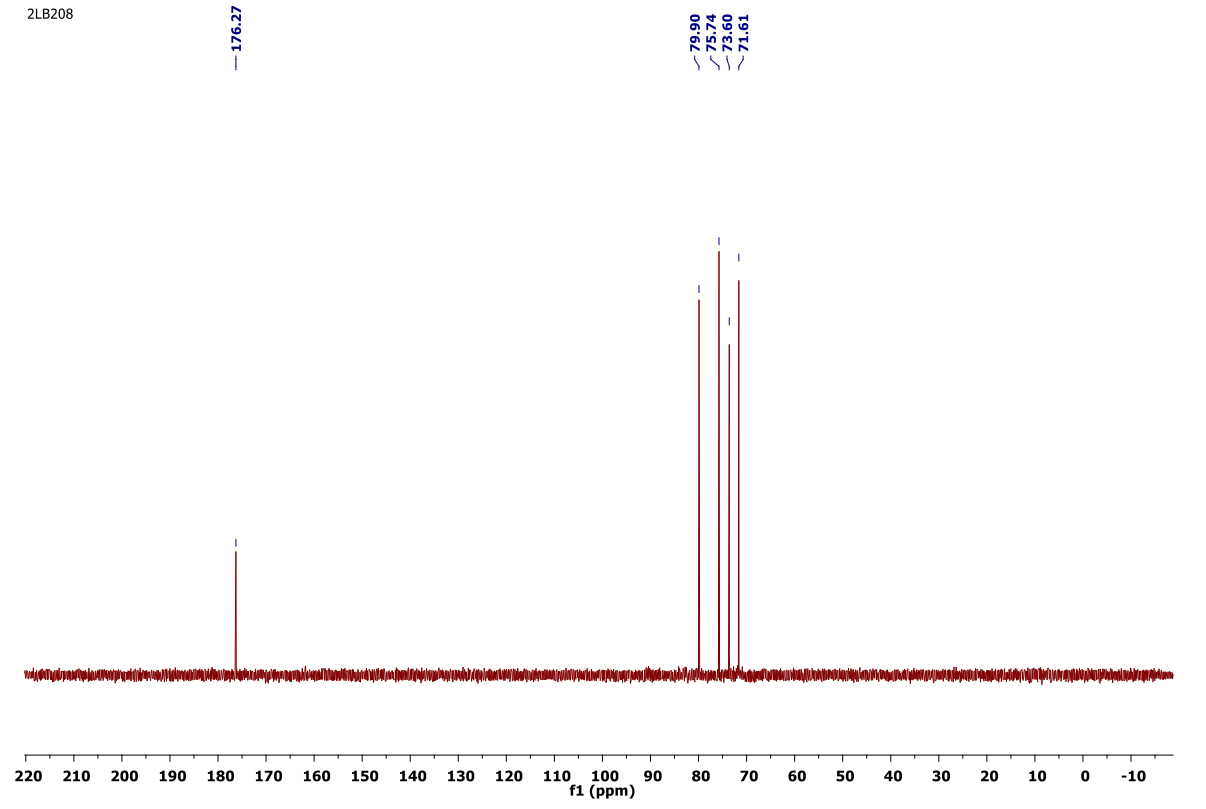
**(*3aS,4S,6aS*)-2,2-Dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carboxylic acid**



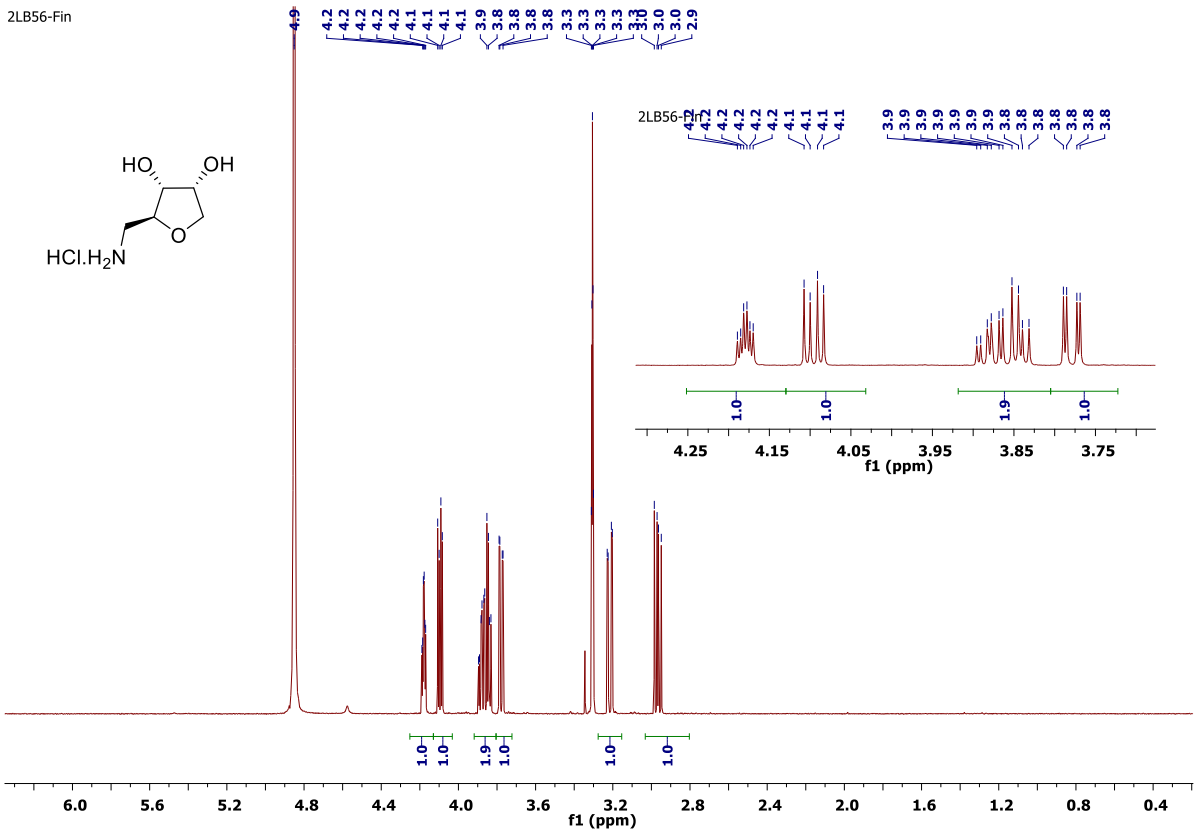



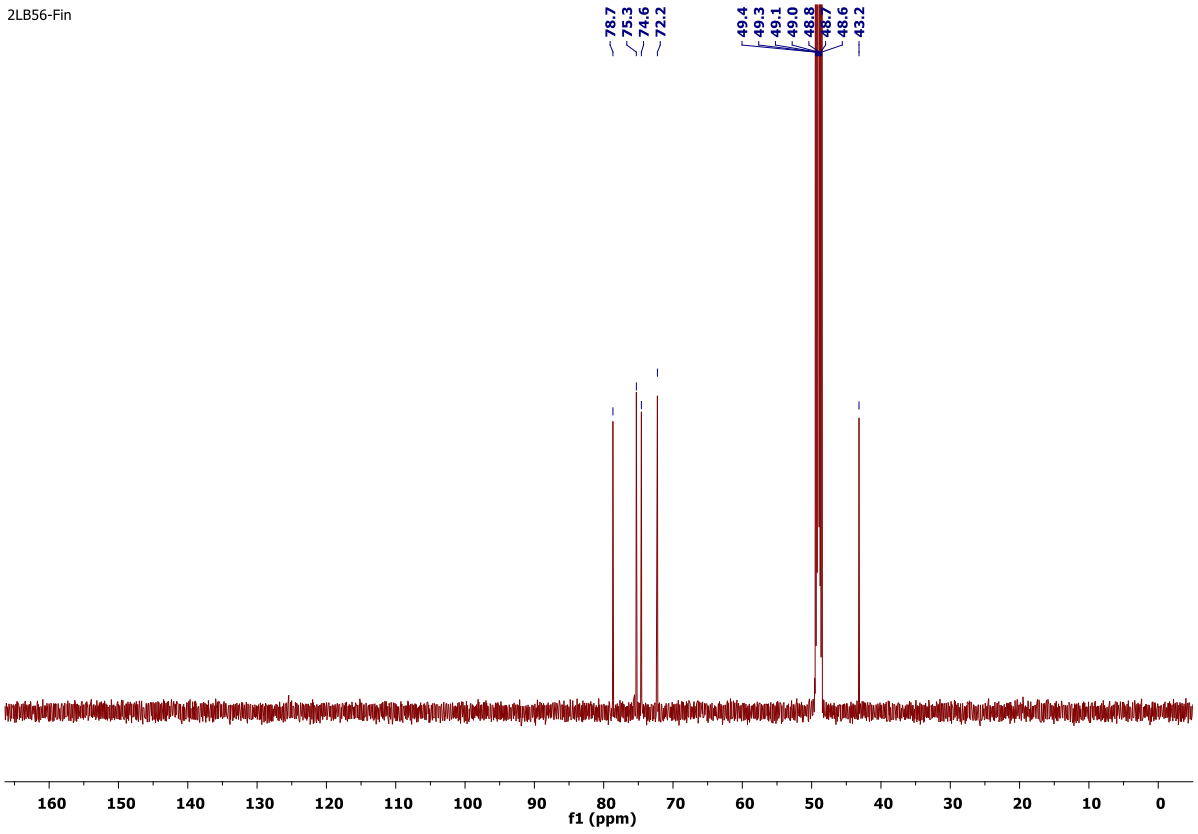
## (*2S,3S,4S*)-3,4-Dihydroxytetrahydrofuran-2-carboxylic acid (10a)



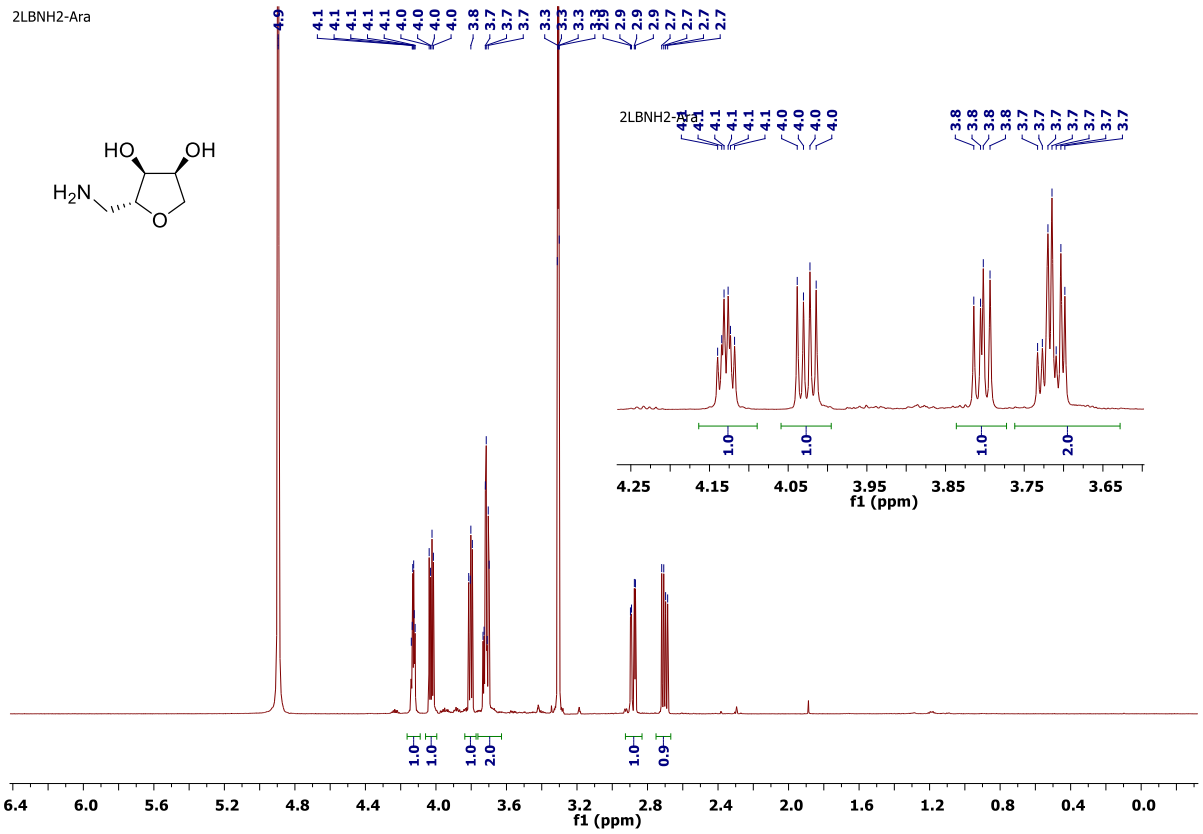



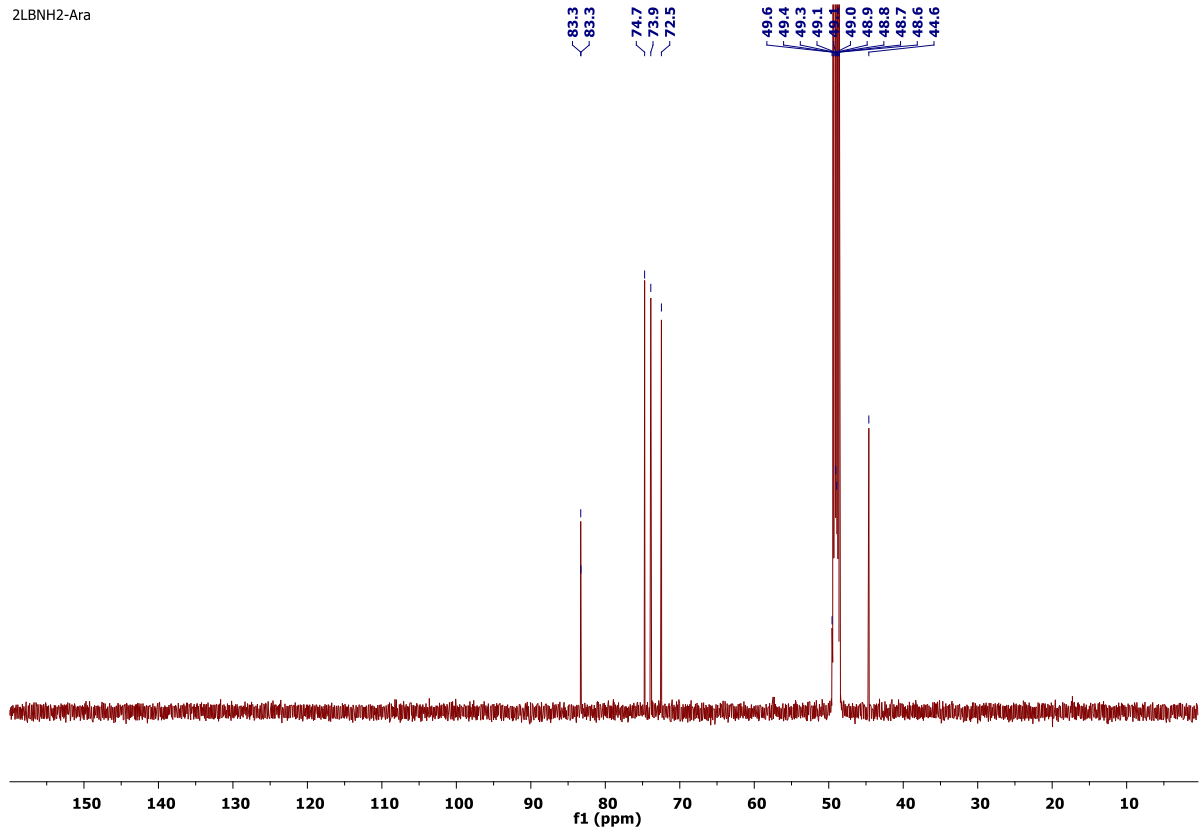
**(*2S,3R,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol hydrochloride (11a.HCl)**



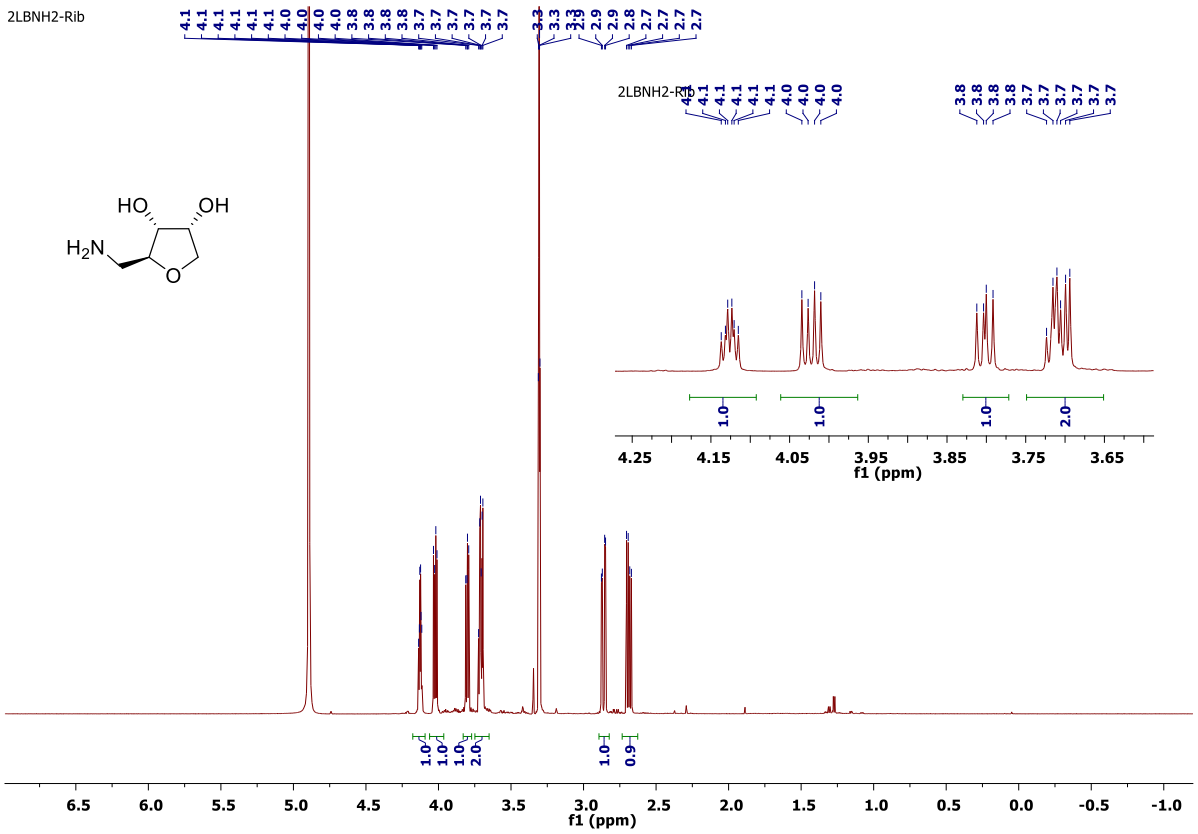



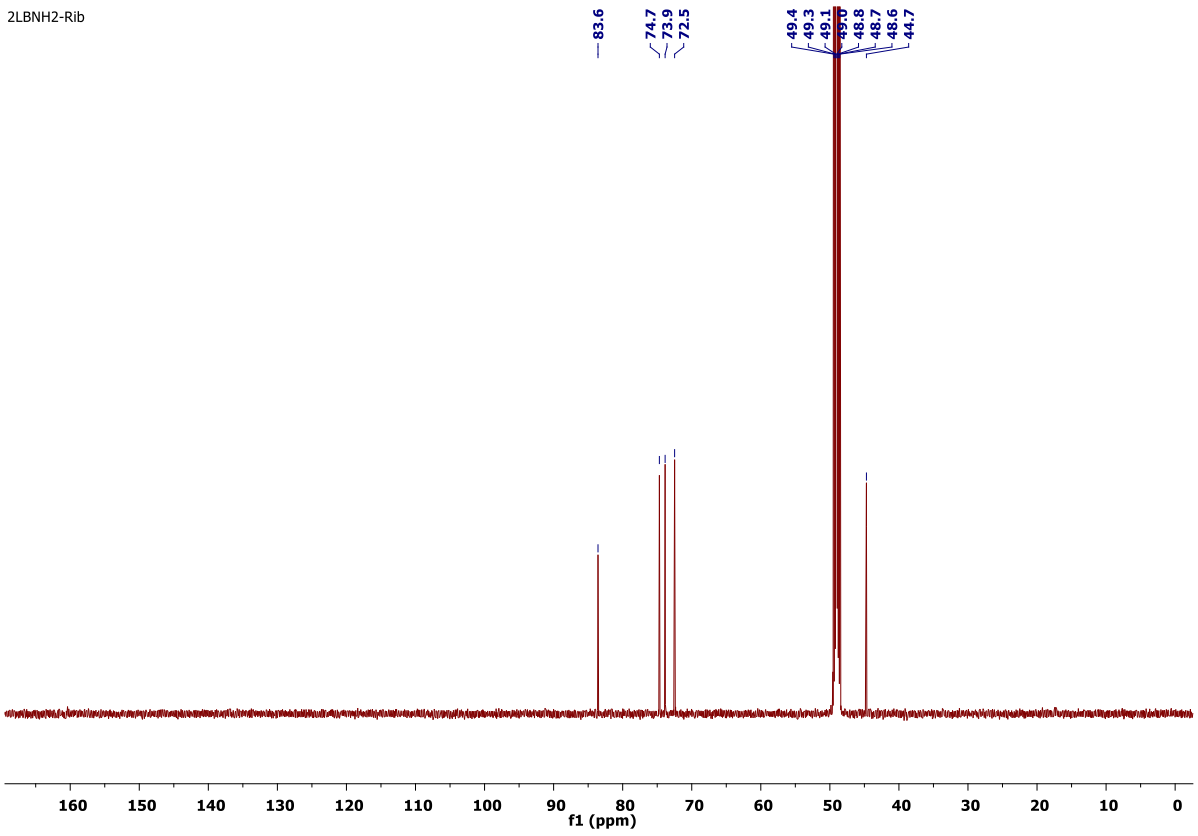
**(*2R,3S,4S*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (11a)**



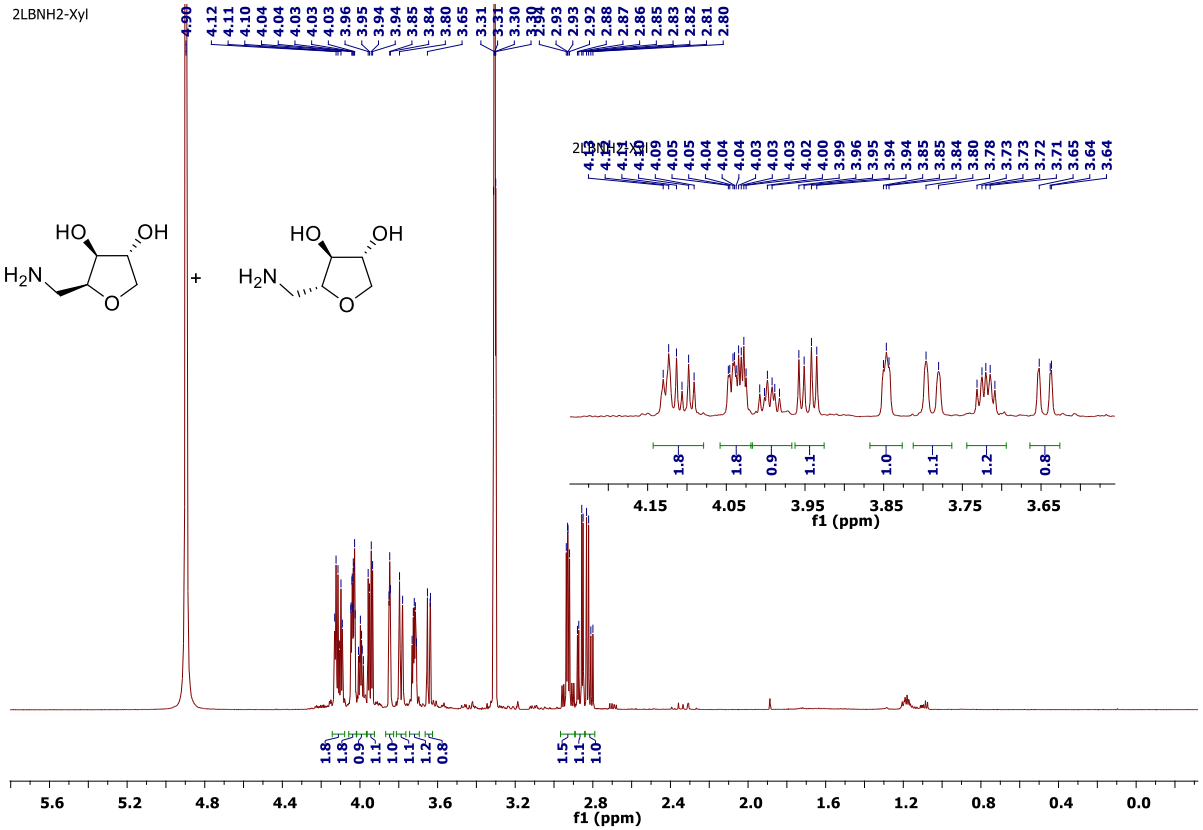



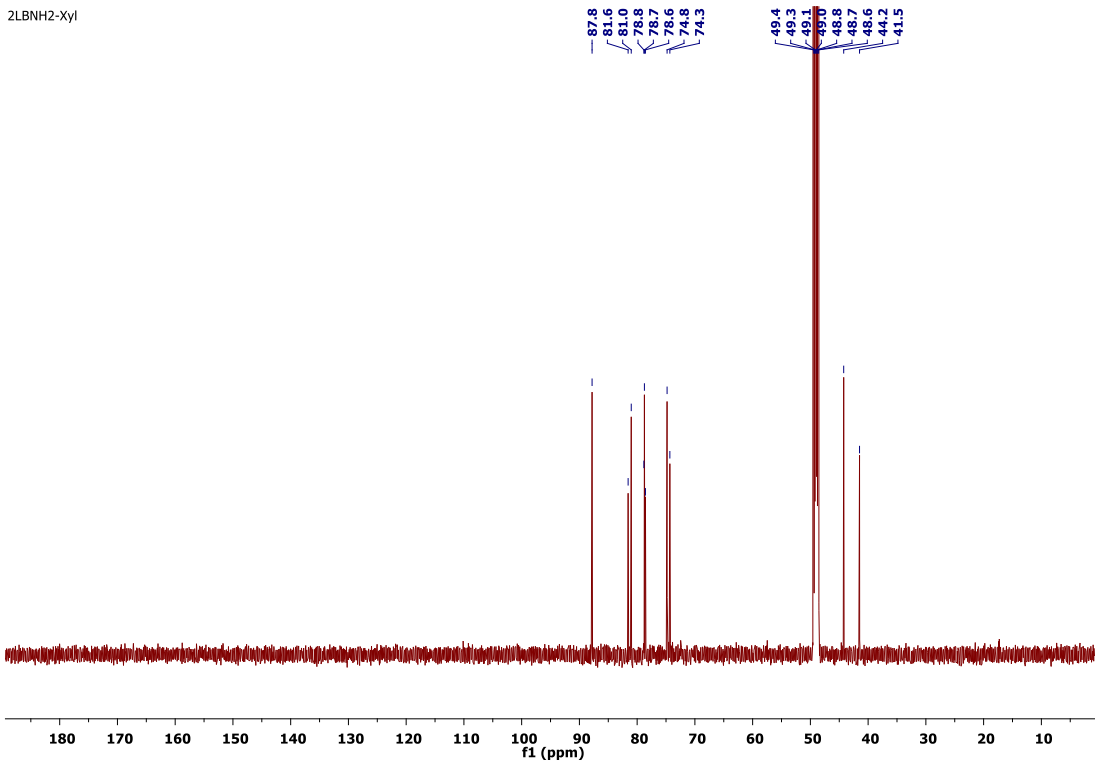
## (*2S,3R,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (11b)



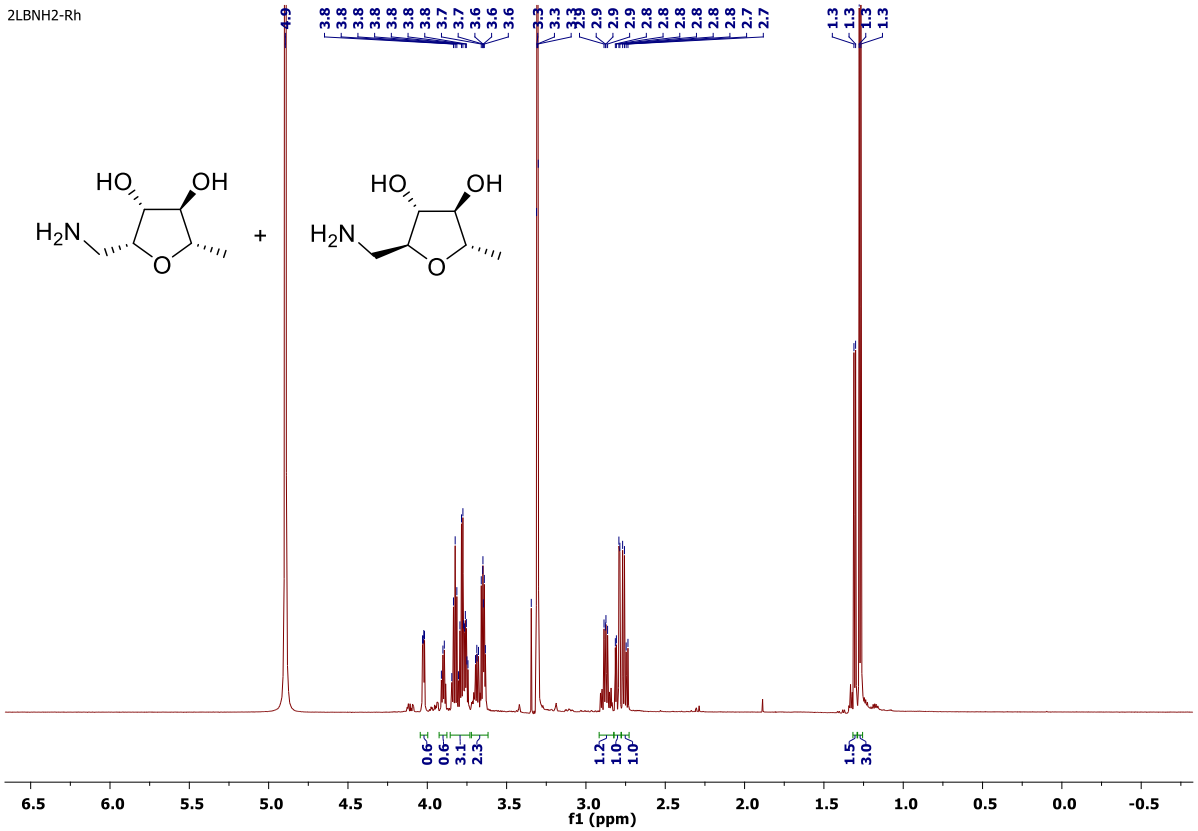



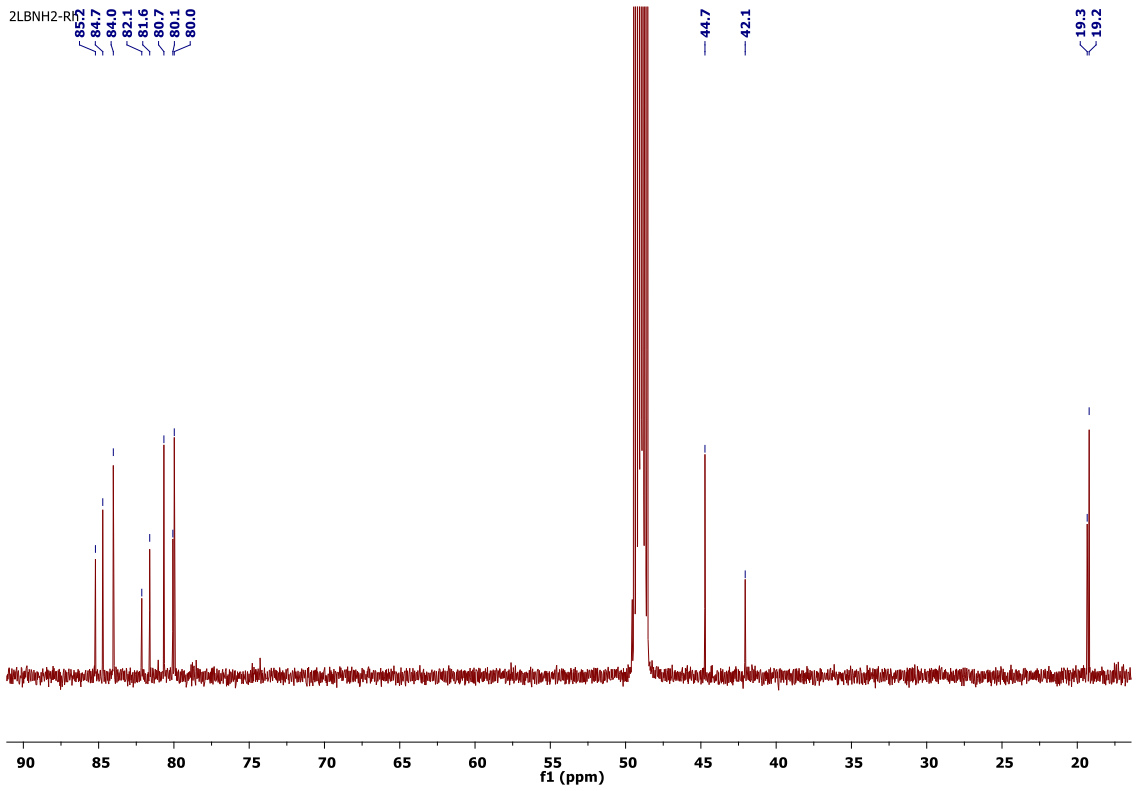
**(*2S,3S,4R*)-2-(Aminomethyl)tetrahydrofuran-3,4-diol (*anti*-11c) and (*2R,3S,4R*)-2-(aminomethyl)tetrahydrofuran-3,4-diol (*syn*-11c)**



**(*2R,3R,4R,5S*)-2-(Aminomethyl)-5-methyltetrahydrofuran-3,4-diol (*anti*-11d) and (2S,3R,4R,5S)-2-(aminomethyl)-5-methyltetrahydrofuran-3,4-diol (*syn*-11d)**



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