

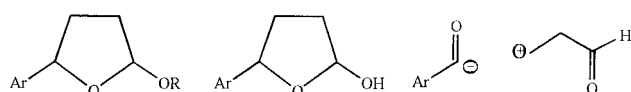
# A novel and convenient approach to 5-aryltetrahydro-2-furanols<sup>†</sup>

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Various aryl and heteroaryl tetrahydrofuranols (**2a–h**) have been conveniently prepared in good yields by reaction of synthetic equivalents of an acyl anion and a  $\beta$ -electrophilic propionaldehyde.

Due to the involvement of platelet activating factor (PAF) in many inflammatory disorders,<sup>1–3</sup> there has been considerable interest in the search for and design of a lead structure for PAF receptor antagonist as they may be of clinical benefit. On this front, the cyclic ether acetals **1** have shown the most promising activity as PAF receptor antagonists. Both the diastereoisomers of **1** have been evaluated for the activity.<sup>4</sup> Recently,<sup>5</sup> Whittaker elegantly obtained this interesting class of compound in good yields as 1:1 mixture of stereoisomers by the reaction of corresponding 5-aryltetrahydro-2-furanols **2** with variety of alcohols in presence of trifluoroacetic anhydride. The attractive feature of the method was the use of lactols **2** as mixture of *cis* and *trans* isomers, thereby removing the need for separation at the starting substrate stage. Hence the ready accessibility to stereoisomeric mixtures of lactols **2** becomes highly desirable.



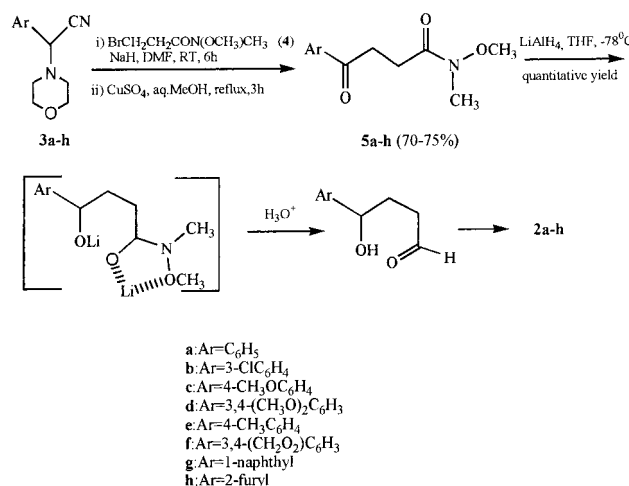
Scheme 1

Traditionally these lactols have been obtained by reduction of the corresponding aryl substituted  $\gamma$ -butyrolactone or acidic hydrolysis of suitably substituted  $\gamma$ -hydroxy acetals. In the former case,<sup>6a</sup> to avoid any over reduction, the use of the pyrophoric and expensive diisobutylaluminium hydride, coupled with careful control of the reaction conditions, becomes imperative. In the latter case,<sup>6b</sup> stringent reaction conditions are required, both for the formation and reaction of the Grignard reagent derived from the acid-sensitive acetal of  $\beta$ -bromopropionaldehyde.

The strategy adopted by us envisages a reaction between acyl anion **A** and a three-carbon synthon **B** (Scheme 1). Bearing in mind that there appears to be no dearth of synthetic equivalents for synthon **A** in the literature,<sup>7</sup> it became clear that for the success of the proposed strategy the synthetic equivalent of synthon **B** must satisfy two requirements. It should contain a masked aldehyde stable to acidic hydrolysis conditions, and it should be generated quantitatively under reductive conditions without any fear of over reduction. Based on our own interest and experience in the chemistry of *N*-methoxy-*N*-methyl amides,<sup>8</sup> popularly known as Weinreb amides, the corresponding amide of 3-bromopropanoic acid fulfils both requirements. Furthermore, its use to this end appears to be unexplored in the literature. Herein we report the success met therewith, which paved the way for a simple and novel route to the synthesis of important 5-aryltetrahydro-2-furanols **2** in high yields.

From the plethora of reagents available<sup>7</sup> for acyl anion, we were attracted to the less frequently used  $\alpha$ -amino nitriles<sup>9</sup> by the simplicity and convenience involved in their preparation on multigram scale. Various aromatic and heterocyclic  $\alpha$ -amino nitriles **3a–h**, prepared according to the procedure of Dyke,<sup>10</sup> underwent clean alkylation with *N*-methoxy-*N*-methyl-3-bromopropionamide,<sup>11</sup> **4**, using NaH in dry DMF (Scheme 2).

The alkylated products, without purification, on hydrolysis using CuSO<sub>4</sub> in aqueous methanol under reflux conditions,<sup>12</sup> afforded the corresponding  $\gamma$ -keto Weinreb amides **5a–h** in good overall yields (70–75%). It is during this unmasking of the keto-functionality under acidic conditions that the stability of the Weinreb amide as a latent aldehyde offered its advantage. Subsequent reduction of these bifunctional amides with 1.5 equivalent of LiAlH<sub>4</sub> at –78°C in THF followed by mild acidic work up furnished the lactols **2a–h** as diastereoisomeric mixtures in quantitative yields. The inherent ability of Weinreb amides to deter over-reduction is now seen to be operative, as evidenced by the quantitative yields of the lactols obtained.



Scheme 2

In conclusion, this paper presents a simple, highly convenient three-step method for an efficient synthesis of 5-aryltetrahydro-2-furanols. The added advantage being that, the immediate precursor, namely  $\gamma$ -keto Weinreb amides are very stable, can be made on multigram scale and stored.

## Experimental

All the solvents and reagents were distilled before use. Dry solvents were prepared as per standard procedures. Melting points were determined in capillary with a Toshniwal melting point apparatus and are uncorrected. NMR spectra were recorded on Bruker (300 MHz <sup>1</sup>H, 75 MHz <sup>13</sup>C) or Jeol (400 MHz <sup>1</sup>H, 100 MHz <sup>13</sup>C) NMR spectrometers

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using TMS as a reference compound. Electron impact mass spectra were obtained at 70 eV using a Finnigan MAT 8230 spectrometer. IR spectra were recorded on Shimadzu IR 470. Microanalyses were performed on a Heraeus CHN analyser. The TLC for monitoring the completion of the reaction was carried out on silica gel coated glass plates (7cm × 2.5 cm) followed by staining in iodine vapour.

**General procedure for the alkylation of an aminonitrile (3a-h) with 4:** Sodium hydride (0.36 g, 15 mmol, 60% suspension in paraffin oil) was washed with dry hexane and suspended in dry DMF (10 ml) under nitrogen. An aminonitrile (10 mmol) in dry DMF (10 ml) was added at room temperature (0°C in the case of 3h). The resulting orange or red suspension was stirred for 0.5h and *N*-methoxy-*N*-methyl-3-bromopropionamide (4)<sup>11</sup> (2 g, 10 mmol) in dry DMF (10 ml) was added. After stirring for 6h, the excess of NaH was destroyed with saturated aqueous NH<sub>4</sub>Cl. The organic portion was extracted with EtOAc (3 × 50ml). The combined organic extracts were washed with H<sub>2</sub>O and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent afforded the crude product, which was directly hydrolysed without further purification following a literature procedure.<sup>12</sup>

**General procedure for the hydrolysis of an alkylated aminonitrile:** To the crude product obtained from the above reaction the solution of CuSO<sub>4</sub>·5H<sub>2</sub>O (2.5 g, 10 mmol) in 3:1 aqueous CH<sub>3</sub>OH (15 ml) was added and heated at reflux. After stirring 3 h, the reaction mixture was cooled to room temperature and organic portion was extracted with EtOAc (3 × 30ml). The combined organic extracts were dried over Na<sub>2</sub>SO<sub>4</sub> and evaporated to give the crude product which on purification by column chromatography (10% EtOAc in hexane) afforded the pure alkylated product 5a-h in good yields (70–75%).

**Representative data for  $\gamma$ -keto Weinreb amides (5d and 5h):** 5d: Yield 73% (Solid, m.pt. 45–48°C); R<sub>f</sub> 0.55 (hexane/EtOAc, 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  2.80 (t, 3H, *J* = 6.8 Hz), 3.30 (t, 3H, *J* = 6.8Hz), 3.20 (s, 3H), 3.70 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 6.90 (d, 1H, *J* = 8.4Hz), 7.53 (d, 1H, *J* = 1.9 Hz), 7.67 (dd, 1H, *J* = 8.4, 1.9 Hz); <sup>13</sup>CNMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  26.2, 32.5, 32.8, 55.9, 56.0, 61.2, 110.0, 110.1, 122.7, 130.0, 148.9, 153.2, 176.0, 197.5 IR (CHCl<sub>3</sub>):  $\nu$  = 2912, 1680, 1648, 1593, 1452, 1260 cm<sup>-1</sup>; MS (EI) *m/z* (%): 281 (M<sup>+</sup>, 4), 221 (100), 193 (10), 165 (59), 79 (18), 55 (20); Anal. Calcd. for C<sub>11</sub>H<sub>13</sub>NO<sub>5</sub>: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.65; H, 7.01; N, 4.88

5h: Yield 75% (Colourless syrup); R<sub>f</sub> 0.45 (hexane/EtOAc, 8:2); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  2.85 (t, 3H, *J* = 6.8 Hz), 3.18 (t, 3H, *J* = 6.8Hz), 3.20 (s, 3H), 3.75 (s, 3H), 6.54 (dd, 1H, *J* = 3.1, 1.4Hz), 7.22 (d, 1H, *J* = 3.0), 7.62 (d, 1H, *J* = 1.1 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  25.6, 32.6, 32.0, 61.1, 66.8, 111.1, 116.8, 146.7, 152.4, 174.2, 187.9; IR (CHCl<sub>3</sub>)  $\nu$  = 2944, 1690, 1657, 1563, 1446, 1257, 1161 cm<sup>-1</sup> MS (EI) *m/z* (%): 211 (M<sup>+</sup>, <1), 151 (12), 123 (66), 109 (16), 95 (100), 79 (12), 67 (56) Anal. Calcd. for C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.95; H, 6.05; N, 6.58

**General procedure for the LiAlH<sub>4</sub> reduction of  $\gamma$ -keto Weinreb amides (4a-h):** To a suspension of LiAlH<sub>4</sub> (0.150 mg, 3 mmol) in ether (10 ml), the appropriate  $\gamma$ -keto Weinreb amide (2mmol) dissolved in ether (5 ml) was added under nitrogen atmosphere at -78 °C and the reaction mixture was stirred for 0.5 h at 0 °C. After quenching the excess of LiAlH<sub>4</sub> by usual procedure the reaction mixture was filtered through celite. The filtrate was evaporated and the resulting crude product was purified by column chromatography (15% EtOAc in hexane) to give pure 5-aryltetrahydro-2-furanols (2a-h) in quantitative yield. 5-aryltetrahydro-2-furanols (2a-h) were obtained as a mixture of *cis* and *trans* isomers (overall yield 65–72%) and NMR spectrum showed a 1:1 mixture of isomers. These compounds are sensitive to air and oxidizing to 5-aryl- $\gamma$ -butyrolactone.<sup>13</sup> Overall yields, physical, and spectroscopic data as well as literature references for known compounds, follow.

**2-Hydroxy-5-phenyltetrahydrofuran (2a):**<sup>6a, 13</sup> yield: 70% (colourless syrup); R<sub>f</sub> 0.5 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  1.78–2.46 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 4.96–4.99 (m, 0.5 H, -OCHAr), 5.22 (t, 0.5H, -OCHAr *J* = 7.2Hz), 5.58 (d, 0.5H, -CHOO *J* = 3.5Hz), 5.69–5.71 (m, 0.5H, -CHOO), 7.24–7.53 (m, 5H); <sup>13</sup>CNMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  32.6, 32.6, 32.9, 34.2, 79.4, 82.6, 98.3, 98.7, 125.1, 125.2, 126.1, 127.1, 127.4, 128.4, 142.2, 142.6; IR (CHCl<sub>3</sub>):  $\nu$  = 3408, 2928, 1603, 1491, 1324, 1030 cm<sup>-1</sup>.

**2-Hydroxy-5-(3-chlorophenyl)tetrahydrofuran (2b):** yield: 67% (colourless syrup); R<sub>f</sub> 0.55 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  1.65–2.55 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 4.97–5.06 (m, 0.5H, -OCHAr), 5.08–5.19 (m, 0.5H, -OCHAr), 5.65 (dd, 0.5H, -CHOO *J* = 3.9, 1.1Hz), 5.76 (dd, 0.5H, -CHOO *J* = 5.2, 2.3Hz), 7.12–7.50 (m, 4H); <sup>13</sup>CNMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  31.9, 32.7, 33.6, 79.3, 81.1, 99.9, 123.8, 124.3, 125.6, 127.3, 129.8, 134.5, 141.3, 144.5 IR (CHCl<sub>3</sub>):  $\nu$

= 3518, 3008, 1613, 1471, 1424, 1043 cm<sup>-1</sup>; MS (EI) *m/z* (%): 198 (M<sup>+</sup>, 20), 181 (19), 141 (100), 124 (32) 113 (42), 88, (15), 58 (5).

**2-Hydroxy-5-(4-methoxyphenyl)tetrahydrofuran (2c):**<sup>4, 6b</sup> yield: 72% (colourless syrup); R<sub>f</sub> 0.45 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  1.65–2.40 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 3.73 (s, 3H) 4.87–4.91 (m, 0.5H, -OCHAr), 5.13 (t, 0.5H, -OCHAr *J* = 7.3Hz), 5.50 (d, 0.5H, -CHOO *J* = 3.9Hz), 5.62 (dd, 0.5H, -CHOO *J* = 5.1, 2.3Hz), 7.24–7.53 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  32.4, 32.8, 33.9, 54.6, 78.7, 82.0, 97.7, 98.1, 113.2, 113.2, 126.6, 127.4, 134.0, 134.4, 158.4, 158.5; IR (CHCl<sub>3</sub>):  $\nu$  = 3452, 2912, 1596, 1456, 1392, 1056 cm<sup>-1</sup>.

**2-Hydroxy-5-(3,4-dimethoxyphenyl)tetrahydrofuran (2d):**<sup>4, 6b</sup> yield: 65% (colourless syrup); R<sub>f</sub> 0.35 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  1.72–2.10 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 3.85 (s, 3H), 3.87 (s, 3H), 4.96–5.10 (m, 0.5H, -OCHAr), 5.21 (t, 0.5 H, -OCHAr *J* = 7.3Hz), 5.58–5.60 (m, 0.5H, -CHOO), 5.69–5.71 (m, 0.5 H, -CHOO), 6.79–7.24 (m, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  29.6, 32.4, 33.2, 34.5, 55.8, 55.9, 79.5, 82.9, 98.5, 108.9, 109.6, 110.9, 118.0, 135.6, 158.4, 158.4; IR (CHCl<sub>3</sub>):  $\nu$  = 3401, 3008, 1601, 1466, 1382, 1050 cm<sup>-1</sup>.

**2-Hydroxy-5-(4-methylphenyl)tetrahydrofuran (2e):** yield: 67% (colourless syrup); R<sub>f</sub> 0.6 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  1.67–2.50 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 2.16 (s, 3H), 4.90–5.01 (m, 0.5 H, -OCHAr), 5.22 (t, 0.5H, -OCHAr, *J* = 7.3Hz), 5.59–5.61 (m, 0.5 H, -CHOO), 5.71–5.73 (m, 0.5H, -CHOO), 7.12–7.50 (m, 4H); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta$  21.2, 32.1, 32.7, 79.1, 79.5, 98.6, 98.3, 123.8, 124.3, 125.6, 127.3, 129.8, 134.5, 141.3, 144.5; IR (CHCl<sub>3</sub>):  $\nu$  = 3444, 2980, 1601, 1391, 1324, 1103 cm<sup>-1</sup>; MS (EI) *m/z* (%): 178 (M<sup>+</sup>, 40), 161 (100), 121, (32), 88 (44), 58 (18)

**2-Hydroxy-5-(3,4-methylenedioxyphenyl)tetrahydrofuran (2f):** yield: 68% (colourless syrup); R<sub>f</sub> 0.4 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  1.70–2.60 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 4.85–5.00 (m, 0.5H, -OCHAr), 5.23–5.30 (m, 0.5 H, -OCHAr), 5.58–5.60 (m, 0.5 H, -CHOO), 5.69–5.71 (m, 0.5H, -CHOO), 5.94 (s, 2H), 6.79–7.24 (m, 3H) <sup>13</sup>CNMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  32.3, 32.4, 32.6, 79.3, 82.7, 98.5, 99.5, 100.9, 101.5, 107.6, 107.7, 124.0, 147.8, 151.4; IR (CHCl<sub>3</sub>):  $\nu$  = 3517, 2928, 1603, 1399, 1324, 1030 cm<sup>-1</sup>; MS (EI) *m/z* (%): 208 (M<sup>+</sup>, 15), 191 (80), 151 (100), 88 (21), 72 (12)

**2-Hydroxy-5-(1-naphthyl)tetrahydrofuran (2g):** yield: 69% (colourless syrup); R<sub>f</sub> 0.5 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  1.65–2.68 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 4.90–5.01 (m, 0.5H, -OCHAr), 5.25 (t, 0.5H, -OCHAr *J* = 7.3Hz), 5.60–5.65 (m, 0.5H, -CHOO), 5.70–5.75 (m, 0.5H, -CHOO), 7.45–7.80 (m, 7H); <sup>13</sup>CNMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  34.4, 33.2, 32.6, 33.0, 79.6, 82.8, 98.9, 98.6, 124.9, 125.6, 125.8, 126.2, 127.1, 127.3, 127.8, 128.3, 133.2, 133.28; IR (CHCl<sub>3</sub>):  $\nu$  = 3445, 3007, 1603, 1451, 1336, 1020 cm<sup>-1</sup>; MS (EI) *m/z* (%): 214 (M<sup>+</sup>, 10), 197 (100), 157 (40), 128 (10), 88 (7), 58 (10)

**2-Hydroxy-5-(2-furyl)tetrahydrofuran (2h):** yield: 70% (colourless syrup); R<sub>f</sub> 0.55 (hexane/EtOAc, 7:3); <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz):  $\delta$  1.88–2.42 (m, 4H, -CH<sub>2</sub>CH<sub>2</sub>-), 4.97–5.01 (m, 0.5H, -OCHAr), 5.19 (t, 0.5H, -OCHAr *J* = 7.3Hz), 5.49–5.53 (m, 0.5H, -CHOO), 5.60–5.65 (m, 0.5H, -CHOO), 6.24 (m, 1H), 6.31 (m, 1H), 7.36 (d, 1H, *J* = 1.8Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100MHz):  $\delta$  32.4, 32.8, 34.0, 34.1, 79.7, 81.0, 97.7, 98.1, 106.2, 110.9, 141.2, 152.2. IR (CHCl<sub>3</sub>):  $\nu$  = 3408, 2928, 1603, 1491, 1324, 1030 cm<sup>-1</sup>. MS (EI) *m/z* (%): 154 (M<sup>+</sup>, 40), 137 (100), 97 (62), 81(85), 41 (55)

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