Supporting Information

Effective Synthesis of 2,5-Disubstituted Tetrahydrofurans from Glycerol by Catalytic Alkylation of Ketones

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1. General Remarks

Unless otherwise noted, all chemicals were purchased from commercial sources and were used without further purification. Solvents for chromatography were technical grade and distilled prior to use. Preparative column or thin layer chromatography were carried out using silica gel 60 (0.063-0.200 mm).

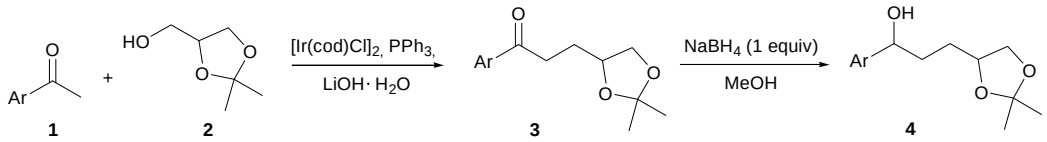
^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AM 300 or Bruker AM 400 spectrometer in $CDCl_3$. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated br s (broadened singlet), s (singlet), q (quartet), m (multiplet); coupling constants (*J*) are in Hertz (Hz).

IR spectra were recorded on a Perkin Elmer Spectrum 100 spectrometer and are reported in terms of frequency of absorption (cm^{-1}).

Mass spectra (MS-EI, 70 eV) were conducted on a Finnigan SSQ 7000 mass spectrometer.

2. General procedures

2.1

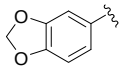
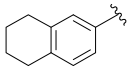


1 2 3 4

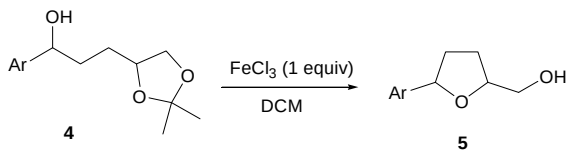
A typical experimental procedure for the reaction of acetophenone (**1a**) with solketal (**2**) catalyzed by $[IrCl(cod)]_2$ and subsequent reduction.

$LiOH{\cdot}H_2O$ (56% LiOH) (17 mg, 0.4 mmol), $[IrCl(cod)]_2$ (13.5 mg, 0.02 mmol), and PPh_3 (15.7 mg, 0.06 mmol) were place in a 10-mL Schlenk tube under N_2. Ketone **1a** (120.1 mg, 1.0 mmol), solketal (237.8 mg, 1.8 mmol) and toluene (0.2 ml) were added successively. The resulting reaction mixture was stirred at 110 °C for 17 h. Toluene was removed under reduced pressure and the residue was taken in methanol (3 ml) and cooled to 10 °C. $NaBH_4$ (1 equiv) was added slowly and the reaction mixture was allowed to warm to room temperature and stirred for 2 h. Solvent was removed, the crude was quenched with saturated NH_4Cl and diluted with EtOAc (10 ml), phases were separated and extracted again with EtOAc (10 ml). The combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (Silica gel, EtOAc/n-hexane, 1/3) to yield 203 mg (80%) of 3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1-phenylpropan-1-ol (**4a**, Ar = Ph) as a pale yellow oil.

Supplementary Table. Reaction time for alkylation for the individual substrates.

Entry	**1**, Ar	**3**, reaction time (h)	Entry	**1**, Ar	**3**, reaction time (h)
1	Ph	17	8		30
2	4-F-C_6H_4	26			
3	3-CF_3-C_6H_4	22	9		28
4	4-C_6H_5-C_6H_4	30			
5	4-*t*-Bu-C_6H_4	32	10		34
6	3,4-CH_3-C_6H_3	25			
7	4-$MeOC_6H_4$	28	11		20

2.2



4 5

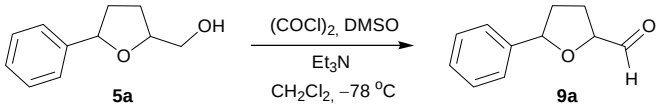
Deprotection and cyclization of intermediate **4a**: To a solution of alcohol (**4a**, Ar = Ph) (59 mg, 0.25 mmol) in CH_2Cl_2 (4 mL), anhydrous $FeCl_3$ (41 mg, 0.25 mmol) was added and the

mixture was stirred at room temperature for 45 min. After completion of the reaction (TLC analysis), it was diluted with CH_2Cl_2 (5 mL) and washed with saturated aq. $NaHCO_3$ solution (10 mL), water (10 mL), brine (10 mL) and dried (Na_2SO_4). Evaporation of solvent and purification by column chromatography (silica gel, EtOAc/n-hexane, 1/3) gave **5a** (Ar = Ph) in 86% yield.

2.3

The synthesis of **5a** in a one-pot three-step procedure has been performed according to the above described procedures with the remark that in this case, no chromatographic purification of the intermediates has been performed.

2.4

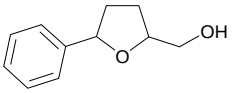


5a trans:cis = 1.8:1 → **9a** 74%, trans:cis = 2.2:1

Oxidation of (5-phenyltetrahydrofuran-2-yl)methanol: At −78 °C, a solution of DMSO (71 µl, 1.66 equiv.) in CH_2Cl_2 (2.5 ml) was added dropwise to a 2 M solution of oxalyl chloride (51.8 µl, 1.2 equiv) in CH_2Cl_2 (1 ml). The mixture was stirred for 20 min and then a solution of **5a** (89.1 mg) in CH_2Cl_2 (1 ml) was added dropwise. The mixture was stirred for 10 min and then Et_3N (698 µl) was slowly added. The reaction mixture was warmed up to room temperature, stirred for 30 min and H_2O was added. When the mixture turned clear, it was extracted with CH_2Cl_2. The solvent was evaporated and the product was purified by flash chromatography (silica gel, EtOAc/n-hexane, 1/1) to give **9a** in 74% yield.

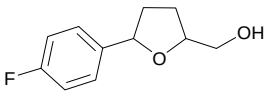
3. Spectral data:

(5-phenyltetrahydrofuran-2-yl)methanol 5a.



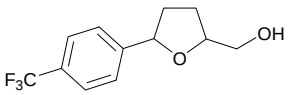
^{1}H NMR (300 MHz, CDCl3): δ 7.48-7.21 (m, 5H), 4.99-4.86 (m, 1H), 4.40-4.10 (m, 1H), 3.82-3.50 (m, 2H), 2.44-2.22 (m, 1H), 2.18-1.99 (m, 1H), 1.96-1.65 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.0, 142.3, 128.5, 128.4, 127.5, 127.4, 126.8, 126.0, 81.7, 81.2, 80.4, 80.2, 65.8, 65.5, 35.7, 34.4, 28.3, 27.8; GC-MS: ($C_{11}H_{14}O_2$) 178.10. **IR** (KBr) ν = 3437, 2927, 1715, 1451, 1276, 1111, 1028, 756 cm^{-1}. **EI-MS**: m/z (%) 178.2 (12). 160.2 (20), 147.2 (79).

(5-(4-fluorophenyl)tetrahydrofuran-2-yl)methanol 5b.



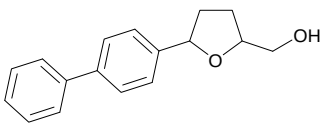
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.18 (m, 2H), 7.01-6.85 (m, 2H), 4.92-4.75 (m, 1H), 4.35-4.05 (m, 1H), 3.78-3.41 (m, 2H), 2.35-1.61 (m, 5H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.8, 163.7, 160.5, 160.5, 138.6, 138.0, 127.5, 127.3, 115.3, 115.0, 80.9, 80.3, 80.1, 79.9, 65.3, 65.1, 35.5, 34.3, 27.8, 27.5. **IR** (KBr) ν = 3404, 2932, 1716, 1684, 1601, 1509, 1275, 1229, 1066, 838 cm^{-1}. **EI-MS**: m/z (%) 196.2 (3), 195.2 (18), 123.2 (100).

(5-(3-(trifluoromethyl)phenyl)tetrahydrofuran-2-yl)methanol 5c.



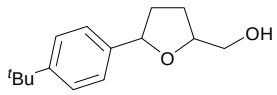
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.30 (m, 4H), 5.00-4.84 (m, 1H), 4.35-4.10 (m, 1H), 3.78-3.48 (m, 2H), 2.38-2.22 (m, 1H), 2.10-1.91 (m, 2H), 1.86-1.70 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.1, 143.5, 129.1, 128.9, 128.8, 128.8, 125.5 (q, $J_{C\text{-}F}$ = 272.2 Hz), 124.2 (q, $J_{C\text{-}F}$ = 3.8 Hz), 122.4 (q, $J_{C\text{-}F}$ = 32.5 Hz), 80.7, 80.3, 80.2, 80.2, 65.3, 65.0, 35.5, 34.3, 27.8, 27.4. **IR** (KBr) ν = 3431, 2924, 1722, 1446, 1335, 1255, 1127, 903 cm^{-1}. **EI-MS**: m/z (%) 246.2 (14), 245.2 (100).

(5-(biphenyl-4-yl)tetrahydrofuran-2-yl)methanol 5d.



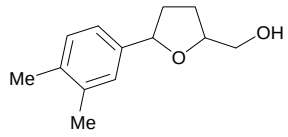
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.20 (m, 9H), 5.04-4.91 (m, 1H), 4.36-4.21 (m, 1H), 3.70-3.48 (m, 2H), 2.36-2.25 (m, 1H), 2.09-1.65 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 141.9, 140.9, 140.3, 128.7, 127.2, 127.2, 127.1, 126.4, 126.1, 80.7, 80.1, 65.2, 35.4, 27.9. **IR** (KBr) ν = 3260, 2870, 1483, 1274, 1036, 759 cm^{-1}. **EI-MS**: m/z (%) 255.1 (41), 254.1 (100), 223.1 (99).

(5-(4-tert-butylphenyl)tetrahydrofuran-2-yl)methanol 5e.



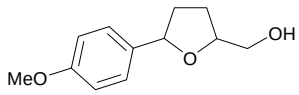
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.15 (m, 4H), 4.94-4.80 (m, 1H), 4.33-4.21 (m, 1H), 3.75-3.43 (m, 2H), 2.76-1.66 (m, 5H), 1.24 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 150.4, 139.6, 125.8, 125.5, 125.3, 125.3, 80.7, 79.9, 65.2, 35.1, 34.5, 34.0, 31.8, 27.9, 27.6. **IR** (KBr) ν = 3402, 2960, 1678, 1605, 1465, 1272, 1062, 833 cm^{-1}. **EI-MS**: m/z (%) 234.2 (13), 232.2 (25), 161.2 (100).

(5-(3,4-dimethylphenyl)tetrahydrofuran-2-yl)methanol 5f.



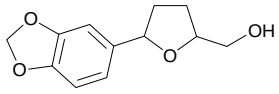
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-6.92 (m, 3H), 4.91-4.80 (m, 1H), 4.32-4.21 (m, 1H), 3.74-3.42 (m, 2H), 2.28-2.20 (m, 1H), 2.19 (s, 3H), 2.17 (s, 3H), 2.14-2.67 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 140.2, 139.6, 136.6, 135.8, 135.7, 129.5, 127.3, 126.9, 123.4, 123.1, 81.5, 80.8, 79.9, 79.7, 65.4, 65.2, 35.3, 34.1, 27.9, 27.6, 19.8, 19.4. **IR** (KBr) ν = 3412, 2925, 1676, 1606, 1452, 1262, 1042, 823 cm^{-1}. **EI-MS**: m/z (%) 205.3 (4), 204.2 (9), 133.2 (100).

(5-(4-methoxyphenyl)tetrahydrofuran-2-yl)methanol 5g.



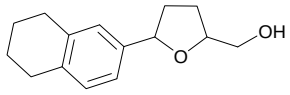
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.14 (m, 2H), 6.83-6.74 (m, 2H), 4.89-4.76 (m, 1H), 4.35-4.02 (m, 1H), 3.58-3.49 (m, 2H), 3.25-3.18 (m, 1H), 2.25-1.42 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.0, 134.7, 134.1, 127.3, 127.2, 127.1, 127.0, 113.8, 113.7, 81.3, 80.6, 79.9, 79.7, 79.0, 73.1, 66.1, 65.4, 64.4, 55.3, 34.1, 33.3, 32.4, 30.3, 27.9, 27.7, 27.6. **IR** (KBr) ν = 3429, 2927, 2851, 1726, 1612, 1514, 1460, 1246, 1037, 827 cm^{-1}. **EI-MS**: m/z (%) 208.2 (57), 207.2 (14), 177.2 (32).

(5-(benzo[d][1,3]dioxol-5-yl)tetrahydrofuran-2-yl)methanol 5h.



^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84-6.62 (m, 3H), 5.86 (s, 2H), 4.85-4.71 (m, 1H), 4.32-4.01 (m, 2H), 3.77-3.15 (m, 2H), 2.29-1.44 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.8, 146.8, 136.8, 136.2, 119.4, 119.3, 119.0, 108.1, 106.5, 106.2, 101.0, 81.4, 80.8, 80.0, 79.8, 79.1, 66.1, 65.4, 65.2, 64.4, 35.5, 34.2, 33.3, 32.6, 30.2, 28.0, 27.9, 27.5. **IR** (KBr) ν = 3414, 2882, 2780, 1495, 1443, 1246, 1040, 934 cm^{-1}. **EI-MS**: m/z (%) 223.3 (15), 222.2 (100), 191.2 (92).

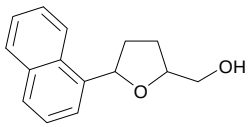
(5-(5,6,7,8-tetrahydronaphthalen-2-yl)tetrahydrofuran-2-yl)methanol 5i.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-6.88 (m, 3H), 4.89-4.80 (m, 1H), 4.31-4.23 (m, 1H), 3.69-3.45 (m, 2H), 2.72-2.59 (m, 4H), 2.29-

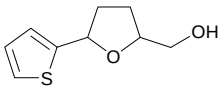
1.95 (m, 2H), 1.91-1.64 (m, 7H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 139.7, 137.1, 136.3, 129.1, 126.3, 122.9, 80.8, 79.9, 65.2, 35.2, 29.5, 29.1, 27.9, 23.2. **IR** (KBr) ν = 3413, 2928, 1679, 1440, 1273, 1059, 827 cm^{-1}. **EI-MS**: m/z (%) 232.2 (37), 201.2 (100).

(5-(naphthalen-1-yl)tetrahydrofuran-2-yl)methanol 5j.



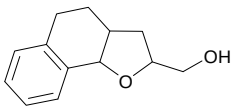
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.32 (m, 7H), 5.74-5.65 (m, 1H), 4.48-4.38 (m, 1H), 3.77-3.55 (m, 2H), 2.61-2.50 (m, 1H), 2.09-1.70 (m, 4H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 138.7, 133.7, 130.2, 128.82, 127.6, 125.8, 125.5, 125.4, 123.2, 121.7, 80.0, 78.4, 65.3, 34.4, 27.7. **IR** (KBr) ν = 3435, 2921, 1613, 1513, 1383, 1246, 1035, 827 cm^{-1}. **EI-MS**: m/z (%) 229.2 (15), 228.2 (87), 197.2 (99).

(5-(thiophen-2-yl)tetrahydrofuran-2-yl)methanol 5k.



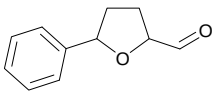
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.16 (m, 1H), 6.95-6.86 (m, 2H), 5.38-5.11 (m, 1H), 4.61-4.44 (m, 1H), 4.13-3.85 (m, 1H), 3.82-3.20 (m, 3H), 2.35-1.46 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 126.5, 124.6, 123.8, 72.9, 65.9, 65.1, 64.9, 64.3, 32.7, 32.1, 29.9, 27.8. **IR** (KBr) ν = 3413, 2928, 1726, 1443, 1244, 1070, 703 cm^{-1}. **EI-MS**: m/z (%) 185.1 (9), 184.1 (83), 166.1 (16).

(2,3,3a,4,5,9b-hexahydronaphtho[1,2-b]furan-2-yl)methanol 5l.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81-7.27 (m, 4H), 4.02-3.83 (m, 1H), 3.71-3.40 (m, 3H), 2.92-2.69 (m, 3H), 2.36-1.88 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 128.3, 127.6, 127.5, 127.2, 126.7, 126.5, 126.2, 125.6, 72.9, 69.8, 66.5, 66.1, 41.5, 39.9, 28.0, 27.3. **IR** (KBr) ν = 3411, 2925, 1720, 1454, 1269, 1074, 752 cm^{-1}. **EI-MS**: m/z (%) 203.3 (5), 202.3 (30), 142.3 (100).

5-phenyltetrahydrofuran-2-carbaldehyde 9a.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (br s, 1H), 7.38-7.15 (m, 5H), 5.08-4.92 (m, 1H), 4.56-4.41 (m, 1H), 2.32-1.78 (m, 4H); **^{13}C NMR** (100 Hz, $CDCl_3$) δ 202.7, 141.6, 128.5, 128.4, 127.7, 127.6, 125.8, 125.5, 83.3, 83.2, 82.6, 82.3, 34.3, 34.0, 28.2, 27.4. **IR** (KBr) ν = 3439, 2942, 1724, 1685, 1451, 1062, 756 cm^{-1}. **EI-MS**: m/z (%) 176.1 (6), 175.1 (8), 147.1 (78).