Synthesis of β,β-Disubstituted γ-Butyrolactones by Chemoselective Oxidation of 1,4-Diols and γ-Hydroxy Olefins with RuCl₃/NaIO₄

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Supplementary data

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General Methods

Unless otherwise specified, all starting materials, reagents and solvents are commercially available and were used without further purification. The flash chromatography was run on silica gel with particle size of 40-63 µm. NMR spectra were recorded with a Bruker 400 NMR spectrometer for \textsuperscript{1}H-NMR, 100 MHz for \textsuperscript{13}C-NMR. High resolution mass spectra were taken with a quadrupole mass spectrometer.

Compounds 2a–2d\textsuperscript{1}, 4a, 4b\textsuperscript{2}, 3d-3f\textsuperscript{3} are prepared based on reported procedures with minimum modification.

General procedures for 3a – 3c

This reaction was performed in oven-dried glassware under a nitrogen atmosphere. To a well-stirred solution in THF the starting allylic acid/ester (2a, 2c or 2d, 9.73 mmol) and LiAlH\textsubscript{4} (3.5 M suspension, 8.3 mL) were added drop wise over 0.5 hours at 0 °C. The reaction mixture was stirred at room temperature for 4 h, quenched with water and 10% HCl (while cooling in ice bath) until acidic. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic phases were combined and washed with saturated sodium bicarbonate solution and brine. The solution was then dried over MgSO\textsubscript{4} and concentrated in vacuo to afford a crude oil which was then purified with flash chromatography (silica gel, ethyl acetate/hexanes, 10% ~ 40%).

2,2-diphenylpent-4-en-1-ol (3a)

Colorless oil; yield: 86%; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ} 7.32-7.03 (m, 10H), 5.36 (m, 1H), 5.10-4.85 (m, 2H), 4.07 (d, J = 6.9 Hz, 2H), 2.89 (d, J = 7.1 Hz, 2H), 1.11 (t, J = 6.9 Hz, 1H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \textit{δ} 145.4, 134.7, 128.4, 128.3, 126.5, 118.3, 68.0, 51.7, 41.1.

(1-allylcyclopentyl)methanol (3b)

Colorless oil; yield: 90%; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{δ} 5.86 (m, 1H), 5.17-4.98 (m, 2H), 3.40 (d, J = 6.0 Hz, 2H), 2.16 (dt, J = 7.4, 1.1 Hz, 2H), 1.68 - 1.52 (m, 4H), 1.52-1.34 (m, 5H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \textit{δ} 136.4, 117.1, 69.2, 47.3, 42.1, 34.3, 25.3.


(1-allylcyclohexyl)methanol (3c)

Colorless oil; yield: 86%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.86 (dd, $J = 17.0, 10.1$ Hz, 1H), 5.06 (dddd, $J = 10.2, 6.6, 2.3, 1.2$ Hz, 2H), 3.41 (s, 2H), 2.18-2.03 (m, 2H), 1.55-1.21 (m, 11H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 135.5, 117.2, 68.9, 40.1, 37.9, 32.4, 26.5, 21.6.

**General procedures for 5a ~ 5c**

Lactone 4a (1 g, 4.22 mmol) was dissolved under a nitrogen atmosphere in anhydrous CH$_2$Cl$_2$ (20 mL) and cooled to -76 °C. A solution of DIBAL (5.04 mL, 1.0 M in hexanes) was added drop wise within 5 min. The mixture was stirred at -76 °C for 1 h, MeOH (1 mL) was then added and the mixture was warmed to 0 °C in an ice bath. H$_2$O was added and the slurry was vigorously stirred. After 15 min, the mixture was filtered through a pad of Celite and the mother liquors was evaporated to dryness to give the crude lactol as a yellowish solid (0.91 g) which was used for the next step without further purification.

The crude lactol (1 g, 4.16 mmol) was dissolved in anhydrous THF (20 mL) and cooled to 0 °C. A solution of Grignard reagent (methylmagnesium bromide, ethylmagnesium bromide or propylmagnesium bromide, 12.48mmol) was added drop wise within 5 min. After stirring overnight at room temperature, the mixture was quenched with water and 10% HCl (while cooling in ice bath) until acidic. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The organic phases were combined and washed with saturated sodium bicarbonate solution and brine. The solution was then dried over MgSO$_4$ and concentrated in vacuo to afford a crude oil which was purified with flash chromatography (silica gel, ethyl acetate/hexanes, 10% ~ 50%).

3,3-diphenylpentane-1,4-diol (5a)

Yellowish semisolid, yield: 75%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.05 (m, 10H), 4.63 (d, $J = 6.1$ Hz, 1H), 3.48-3.29 (m, 2H), 2.58 (dt, $J = 13.5, 6.7$ Hz, 1H), 2.45-2.21 (m, 2H), 1.71 (broad, 1H), 0.95 (d, $J = 6.3$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.2, 144.2, 129.5, 129.1, 128.1, 126.5, 126.4, 70.6, 59.7, 55.3, 39.8, 19.4.

3,3-diphenylhexane-1,4-diol (5b)

Yellowish semisolid, yield: 72%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.08 (m, 10H), 4.25 (d, $J = 9.3$ Hz, 1H), 3.49-3.30 (m, 2H), 2.71-2.55 (m, 1H), 2.29 (m, 1H), 1.75 (broad, 1H), 1.48 (m, 7.4, 1.5 Hz, 1H), 0.91 (t, $J = 7.2$ Hz, 3H), 0.85- 0.70 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 145.1, 144.6, 129.3, 129.1, 128.1, 128.0, 126.4, 76.6, 59.7, 55.3, 40.0, 26.1, 11.6.
3,3-diphenylheptane-1,4-diol (5e)

Yellowish semisolid, yield: 73%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.41-7.17 (m, 10H), 4.45 (d, J = 9.8 Hz, 1H), 3.57-3.41 (m, 2H), 2.71 (m, 1H), 2.46-2.27 (m, 2H), 1.85 (broad, 1H), 1.69-1.54 (m, 1H), 1.53-1.43 (m, 1H), 1.42-1.30 (m, 1H), 0.94-0.82 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 145.0, 144.5, 129.3, 129.1, 128.1, 128.0, 126.3, 74.7, 59.7, 55.2, 40.1, 35.26, 20.2, 14.2.

General procedures for 5d and 5e

Under a nitrogen atmosphere lactone 4b (1 g, 8.76 mmol) was dissolved in anhydrous THF (100 mL) and cooled to –76 °C. A solution of DIBAL (10.51 mL, 1.0 M in hexanes) was added within 5 min. After stirring for 30 min more at –76 °C, a solution of the Grignard reagent (phenylmagnesium bromide or (4-fluorobenzyl)magnesium bromide, 26.28 mmol) as added. After complete addition the mixture was allowed to warm to ambient temperature. The mixture was cooled again to 0 °C, diluted with ether (50 mL) and hydrolyzed by the drop wise addition of 10% HCl. Phases were separated and the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with saturated sodium bicarbonate solution and brine. The solution was dried over MgSO$_4$ and concentrated in vacuo to afford a crude oil which was purified with flash chromatography (silica gel, ethyl acetate/hexanes, 10% ~ 50%).

2,2-dimethyl-1-phenylbutane-1,4-diol (5d)

Yellowish oil, yield: 68%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.29-7.10 (m, 5H), 4.40 (broad, 1H), 4.28 (s, 1H), 4.11 (broad, 1H), 3.57 (d, J = 4.7 Hz, 2H), 1.70-1.57 (m, 1H), 1.34 (m, 1H), 0.75 (d, J = 13.2 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.8, 128.1, 127.6, 127.3, 81.0, 58.9, 42.3, 38.0, 26.0, 23.1.

5-(4-fluorophenyl)-3,3-dimethylpentane-1,4-diol (5e)

Yellowish oil, yield: 66%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.22-7.13 (m, 2H), 7.06-6.92 (m, 2H), 3.80-3.64 (m, 2H), 3.47 (dd, J = 10.8, 2.0 Hz, 1H), 2.97 (broad, 2H), 2.85 (dd, J = 13.8, 1.2 Hz, 1H), 2.57 (dd, J = 13.8, 10.8 Hz, 1H), 1.84 (ddd, J = 14.6, 8.6, 4.7 Hz, 1H), 1.45 (ddd, J = 14.8, 5.8, 4.0 Hz, 1H), 1.01 (d, J = 10.7 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 162.9, 160.5, 135.6, 135.6, 130.9, 130.8, 115.5, 115.3, 79.6, 59.2, 42.1, 37.5, 37.3, 25.1, 24.7.

2-oxaspiro[4.5]decane-3-one (6b)

Colorless oil, yield: 73%; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.03 (s, 2H), 2.36 (s, 2H), 1.50 (m, 10H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.2, 78.3, 40.8, 40.4, 35.3, 25.6, 23.0.

4,4-diphenyldihydrofuran-2(3H)-one (6c)
Yellowish semisolid, yield: 83%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 °C 7.22 (m, 4H), 7.22-7.16 (m, 2H), 7.09 (m, 4H), 4.76 (s, 2H), 3.12 (s, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.6, 144.0, 129.1, 127.5, 126.6, 77.2, 52.6, 42.1.

5-phenyldihydrofuran-2(3H)-one (6d)

Colorless oil, yield: 52%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.46 °C 7.29 (m, 5H), 5.51 (dd, J = 7.8, 6.4 Hz, 1H), 2.73-2.56 (m, 3H), 2.31-2.08 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.0, 139.6, 128.9, 128.6, 125.4, 81.3, 31.1, 29.1.

5-(4-(trifluoromethyl)phenyl)dihydrofuran-2(3H)-one (6f)

Yellowish oil, yield: 47%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.66 (d, J = 8.2 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 5.62-5.50 (m, 1H), 2.82-2.63 (m, 3H), 2.25-2.10 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.5, 126.0, 126.0, 125.6, 80.3, 31.1, 28.9.

5-ethyl-4,4-diphenyldihydrofuran-2(3H)-one (7b)

Colorless semisolid, yield: 72%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.46-7.23 (m, 6H), 7.23-7.13 (m, 2H), 7.12-6.97 (m, 2H), 5.15 (dd, J = 9.8, 1.8 Hz, 1H), 3.49 (d, J = 16.9 Hz, 1H), 2.98 (d, J = 16.9 Hz, 1H), 1.52 (m, 1H), 1.18-0.99 (m, 4H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.5, 145.2, 142.3, 128.9, 128.5, 128.1, 127.3, 127.3, 127.1, 88.0, 55.2, 43.5, 25.8, 11.2; HRMS (Cl): [M+H], calcd for C$_{18}$H$_{18}$O$_2$, 267.1385, found 267.1391.

4,4-diphenyl-5-propyldihydrofuran-2(3H)-one (7c)

Colorless semisolid, yield: 73%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.34-7.13 (m, 6H), 7.12-7.04 (m, 2H), 6.92 (m, 2H), 5.14 (dd, J = 11.0, 1.8 Hz, 1H), 3.38 (d, J = 16.9 Hz, 1H), 2.90 (d, J = 17.0 Hz, 1H), 1.52 (m, 1H), 1.47-1.25 (m, 2H), 0.98 (m, 1H), 0.83 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.6, 145.2, 142.4, 129.0, 128.5, 128.2, 127.4, 127.3, 127.2, 86.3, 55.2, 43.7, 34.5, 20.0, 13.9; HRMS (Cl): [M+H], calcd for C$_{19}$H$_{20}$O$_2$, 281.1542, found 281.1542.

4,4-dimethyl-5-phenyldihydrofuran-2(3H)-one (7d)

Yellowish semisolid, yield: 62%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (m, 3H), 7.21 (m, 2H), 5.11 (s, 1H), 2.46 (dd, J = 42.4, 16.8 Hz, 2H), 1.22 (s, 3H), 0.65 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 176.2, 135.3, 128.5, 128.4, 125.9, 89.6, 44.6, 41.3, 25.6, 22.6.

5-(4-fluorobenzyl)-4,4-dimethylidihydrofuran-2(3H)-one (7e)

Yellowish semisolid, yield: 67%; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.33-7.18 (m, 2H), 7.01 (m, 2H), 4.26 (dd, J = 9.4, 3.6 Hz, 1H), 2.84 (m, 2H), 2.40 (q, J = 16.9 Hz, 2H), 1.17 (d, J = 12.5 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.9, 163.1, 160.7, 133.4, 133.4, 130.7, 130.6,
115.6, 115.4, 89.4, 44.9, 39.7, 34.8, 25.1, 21.6; HRMS (CI): [M+H], calec for C$_{13}$H$_{15}$FO$_2$, 223.11343, found 233.11248.

5-(4-chlorophenyl)dihydrofuran-2(3H)-one (7f)

Yellowish oil, yield: 48%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.19 (m, 4H), 5.45 (dd, J = 8.3, 6.2 Hz, 1H), 2.73-2.56 (m, 3H), 2.12 (ddd, J = 11.0, 9.0, 5.6 Hz, 1H).

methyl-3,3-diphenyldihydrofuran-2(3H)-one (7g)

Colorless semisolid, yield: 74%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.09 (m, 10H), 4.49-4.34 (m, 1H), 2.99 (dd, J = 12.9, 4.7 Hz, 1H), 2.52 (dd, J = 12.9, 10.4 Hz, 1H), 1.40 (d, J = 6.1 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.3, 142.2, 140.1, 129.0, 128.5, 127.9, 127.8, 127.5, 127.3, 73.7, 58.8, 45.5, 20.5.

3-methyl-2-oxaspiro[4.4]nonan-1-one (7h)

Colorless oil, yield: 70%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.51 (dp, J = 9.5, 6.1 Hz, 1H), 2.28-2.10 (m, 2H), 1.95-1.78 (m, 3H), 1.69 (m, 5H), 1.40 (d, J = 6.2 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 182.7, 74.2, 50.8, 45.0, 37.5, 37.0, 25.6, 25.5, 21.1; HRMS (CI): [M+H], calec for C$_9$H$_{14}$O$_2$, 155.1072, found 155.1076.

3-methyl-2-oxaspiro[4.5]decan-1-one (7i)

Colorless oil, yield: 74%; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.53 (dp, J = 9.6, 6.2 Hz, 1H), 2.39 (dd, J = 12.9, 6.2 Hz, 1H), 1.91-1.67 (m, 3H), 1.59 (m, 4H), 1.49 (m, 1H), 1.44-1.17 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.8, 73.8, 45.5, 41.4, 34.5, 31.7, 25.5, 22.3, 22.3, 21.6.

General procedure for 5g–5i

![Reaction Scheme](attachment:image)

Starting allylic acid (11.67 mmol) is stirred with THF (34 mL), ether (12 mL) and saturated NaHCO$_3$ solution (57 mL). The mixture is protected from light. I$_2$ was dissolved in 12mL of THF and added to the mixture in one portion at 0 degree. The mixture was allowed to stir overnight at room temperature. Saturated sodium thiosulfate is added to the mixture to
quench the reaction. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was dried over MgSO₄ and concentrated in vacuo to give a crude oil which was used for the next step without further purification.

The crude iodo lactone (11 mmol) was then refluxed with LAH (1M, 5 equiv) in THF for 1 h. The reaction was quenched with water and acidified with 10% HCl. The mixture was then washed with Ethyl acetate (3 x 50 mL). Combined organic phase was washed with NaHCO₃, dried over MgSO₄ and concentrated in vacuo to give a crude oil which was purified with flash chromatography (silica gel; Ethyl acetate/Hexanes, 0% – 50%).

2,2-diphenylpentane-1,4-diol (5g)

¹H NMR (400 MHz, CDCl₃) δ 7.45-7.09 (m, 10H), 4.23 (dd, J = 81.5, 11.4 Hz, 2H), 3.96 (broad, 1H), 3.82 (dt, J = 7.9, 3.0 Hz, 1H), 3.14 (broad, 1H), 2.45 (m, 2H), 1.22 (d, J = 6.3 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 147.7, 144.8, 128.5, 128.5, 128.3, 127.7, 126.4, 69.2, 65.1, 51.8, 47.0, 25.3.

1-(1-(hydroxymethyl)cyclopentyl)propan-2-ol (5h)

¹H NMR (400 MHz, CDCl₃) δ 4.28 (s, 1H), 4.01-3.80 (m, 1H), 3.38 (dd, J = 25.8, 11.0 Hz, 2H), 1.69-1.11 (m, 13H). ¹³C NMR (101 MHz, CDCl₃) 69.2, 65.7, 49.6, 47.3, 38.1, 33.1, 25.4, 24.8, 24.4.

1-(1-(hydroxymethyl)cyclohexyl)propan-2-ol (5i)

¹H NMR (400 MHz, CDCl₃) δ 4.31 (broad, 1H), 4.06 (broad, 1H), 4.01-3.92 (m, 1H), 3.54 (d, J = 11.1 Hz, 1H), 3.35 (d, J = 11.1 Hz, 1H), 1.60-1.08 (m, 15H). ¹³C NMR (101 MHz, CDCl₃) 69.7, 63.7, 47.9, 37.2, 36.0, 31.2, 26.6, 25.6, 21.7, 21.6.

2. Characterization for 8a and 9a

4,4-diphenyltetrahydrofuran-2-ol (8a)

¹H NMR (400 MHz, CDCl₃) δ 7.42-7.16 (m, 10H), 5.65 (dd, J = 9.9, 5.2 Hz, 1H), 4.56-4.45 (m, 2H), 3.45 (m, 1H), 2.96 (dd, J = 13.3, 5.5 Hz, 1H), 2.64 (dd, J = 13.3, 4.4 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 146.3, 145.1, 128.7, 128.5, 127.3, 126.9, 126.8, 126.5, 100.0, 75.9, 55.6, 46.8.
5-methyl-4,4-diphenyltetrahydrofuran-2-ol (9a, mixture of isomers)

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.00 (m, 13H), 6.94-6.77 (m, 2H), 5.74 (dd, J = 6.0, 3.2 Hz, 1H), 5.35 (t, J = 5.9 Hz, 0.4H), 5.01 (q, J = 6.2 Hz, 1H), 4.92 (d, J = 6.5 Hz, 0.4H), 3.20 (dd, J = 14.2, 6.1 Hz, 1.3H), 2.79 (dd, J = 13.0, 6.3 Hz, 1.3H), 2.54 (dd, J = 12.9, 5.6 Hz, 0.5H), 2.38 (dd, J = 14.2, 3.3 Hz, 1H), 1.57 (broad, 0.9H), 0.97 (d, J = 6.5 Hz, 1.2H), 0.91 (d, J = 6.3 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 148.0, 146.6, 144.5, 128.9, 128.6, 128.4, 128.4, 127.9, 127.8, 127.5, 126.6, 126.6, 126.4, 126.3, 98.8, 97.4, 80.5, 78.3, 77.4, 58.7, 58.4, 50.4, 44.7, 20.6, 17.3.
$^1$H NMR (400 MHz, CDCl$_3$)

3,3-diphenylpropene-1,4-diol (5a)
H NMR (400 MHz, CDCl₃) 3,3-Diethylpropane-1,4-diol (6g)
$^{1}H$ NMR (400 MHz, CDCl$_3$) δ 3.3-difluorobenzene-1,4-diol (5b)
$^1$H NMR (400 MHz, CDCl$_3$) δ ppm
H NMR (400 MHz, CDCl3)
6-Chlorophenyl-p-toluenesulfone 2,2-dimethylpropanoate (79)
NMR (1H, NMR, CDC\textsubscript{6})

\begin{align*}
{1} & \text{H} \\
& \text{2.6} \\
& \text{2.4} \\
& \text{2.2} \\
& \text{2.0} \\
& \text{1.8} \\
& \text{1.6} \\
\end{align*}