Supporting Information
for DOI: 10.1055/s-0028-1088130
© Georg Thieme Verlag KG Stuttgart · New York 2009
Supporting information

A mild and efficient bisaldolization of ketones and its application towards spirocyclic 1,3–dioxanes and novel 1,3,5–trioxocanes

Nagarapu Srinivas, Vijay K. Marrapu and Kalpana Bhandari*

Division of Medicinal and Process Chemistry, Central Drug Research Institute, Lucknow 226001 India.

General Information:

All reagents were commercial and were used without further purification. Chromatography was carried on silica gel (60–120 mesh) and florisil (60–100). All reactions were monitored by TLC; silica gel plates with fluorescence F254 were used. Melting points were uncorrected. The 1H NMR, 2D-NMR (COSY, HMBC, HSQC, NOESY and NOE DIFF) and 13C NMR spectra were determined on a 200, 300 MHz and 50, 75 MHz, respectively, and TMS as internal standard. All shifts are given in ppm. IR spectra were recorded on in the range of 400~4000 cm⁻¹. And multiplicity (s = singlet, bs = broad singlet, bm = broad multiplet, d = dublet, dd = duble-dublets, t = triplet, m = multiple
Compounds 1a-8a was prepared according to the general procedure as described in the manuscript.

**2,2-Bis-hydroxymethyl-indan-1-one (1a).** Mp 83–84 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.11 (s, 2H, H-3), 3.47 (bs, 2H, 2 x OH), 3.71 (s, 4H, 2 x CH\(_2\)OH), 7.27 (m, 1H, ArH), 7.44 (d, \(J = 8.5\) Hz, 1H, H-4), 7.54 (t, \(J = 6.7\) Hz, 1H, ArH), 7.64 (d, \(J = 6.7\) Hz, 1H, H-7); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 33.4, 57.2, 64.2 (2C), 123.7, 126.6, 127.3, 135.3, 136.3, 154.3, 209.7; MS (ESI): m/z (%): 193 (33) [M+1]\(^+\), 232 (100) [M+39]\(^+\).

**2,2-Bis-hydroxymethyl-6-methoxy-3,4-dihydro-2H-naphthalen-1-one (3a).** Mp 105–106 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.03 (t, \(J = 6.5\) Hz, 2H, H-3), 3.05 (t, \(J = 6.6\) Hz, 2H, H-4), 3.67 (bs, 2H, 2 x OH), 3.86 (s, 3H, OCH\(_3\)), 3.73–3.95 (dd, \(J = 11.8\) Hz, 4H, 2 x CH\(_2\)OH), 7.30 (m, 1H, H-5), 7.49 (t, \(J = 7.8\) Hz, 1H, ArH), 7.99 (d, \(J = 8.7\) Hz, 1H, H-8); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 25.7, 26.8, 51.1, 55.9, 64.6 (2C), 112.8, 114.1, 125.6, 130.5, 146.9, 164.6, 202.3; MS (ESI): m/z (%): 237 (100) [M+1]\(^+\).

**3,3-Bis-hydroxymethyl-chroman-4-one (4a).** Mp 77–78 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.25 (bs, 2H, 2 x OH), 3.88–3.92 (m, 4H, 2 x CH\(_2\)OH), 4.43 (s, 2H, H-2), 7.03 (m, 2H, ArH), 7.51 (t, \(J = 7.1\) Hz, 1H, ArH), 7.84–7.87 (d, \(J = 7.8\) Hz, 1H, H-5); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 51.7, 61.6 (2C), 69.2, 117.9, 120, 121.7, 127.3, 136.6, 161.5, 196.2; MS (ESI): m/z (%): 209 (100) [M+1]\(^+\), 210 (21) [M+2]\(^+\).

**4,4-Bis-hydroxymethyl-7-methyl-3,4-dihydro-2H-benzo[b]oxepine-5-one (5a).** Mp 83–84 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.89 (t, \(J = 6.5\) Hz, 2H, H-3), 2.29 (s, 3H, ArCH\(_3\)), 3.22 (bs, 2H, 2 x OH), 3.74–3.96 (dd, \(J = 12.1\) Hz, 4H, 2 x CH\(_2\)OH), 4.21 (t, \(J = 6.6\) Hz, 2H, H-2), 6.86–6.89 (d, \(J = 8.8\) Hz, 1H,), 7.19–7.23 (dd, \(J = 2.2, 8.3\) Hz, 1H, ArH), 7.46 (s, 1H, H-6); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 20.4, 32.4, 58.2, 67.2 (2C), 71.6, 119.3, 126, 130.6, 131.7, 134.7, 158, 205.5; MS (ESI): m/z (%): 237.1 (100) [M+1]\(^+\), 238 (13) [M+2]\(^+\).

**3-Hydroxy-2-hydroxymethyl-2-methyl-1-phenyl-propan-1-one (6a).** Oil; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 1.15 (s, 3H, CH\(_3\)), 3.2 (bs, 2H, 2 x OH), 3.83–4.25 (dd, \(J = 4.7, 11.7\) Hz, 4H, 2 x CH\(_2\)OH ), 7.50 (m, 3H, ArH), 7.81–7.84 (d, \(J = 7.6\) Hz, 2H, ArH); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 17.7, 54.3, 70 (2C), 127.6 (2C), 128.4 (2C), 131.9, 138.1, 209.1; MS (ESI): m/z (%): 195 (100) [M+1]\(^+\).

**1-(3-Chloro-phenyl)-3-hydroxy-2-hydroxymethyl-2-methyl-propan-1-one (7a).** Mp 89-90 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.69 (s, 3H, CH\(_3\)), 3.44–3.72 (m, 6H, 2 x CH\(_2\)OH), 7.20 (m, 3H, ArH), 7.33 (s, 1H, ArH); \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 15.6, 43.7, 66.6, 67.6, 126.3, 127.9, 128, 129.5, 134.2, 143.8, 212.2; IR (KBr, cm\(^{-1}\)): 3391, 2360, 1647, 1572, 1470, 1427, 1216, 1036, 762; MS (ESI): m/z (%): 229 (100) [M+1]\(^+\).
5-Chloro-2,2-bis-hydroxymethyl-3,4-dihydro-2H-naphthalen-1-one (8a). Mp 92-93 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 2.05 (t, \textit{J} = 6.4 Hz, 2H, H-3), 3.07 (t, \textit{J} = 6.6 Hz, 2H, H-4), 3.46 (bs, 2H, 2 x OH), 3.74–3.96 (dd, \textit{J} = 12.3 Hz, 4H, 2 x CH\textsubscript{2}OH), 7.28 (t, \textit{J} = 6.5 Hz, 1H, ArH), 7.57 (d, \textit{J} = 8.9 Hz, 1H, H-6), 7.93 (d, \textit{J} = 7.8 Hz, 1H, H-8); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 22.8, 25.4, 50.6, 64.3 (2C), 126.2, 127.5, 133.4, 134.2, 134.5, 141, 202.1; MS (ESI): m/z (%): 241 (88) [M+1]+, 243 (70) [M+3]+.

General procedure for the synthesis of spiro 1,3–dioxane and spiro 1,3,5–trioxocane derivatives

A mixture of Bis-adol derivative (1.0 equiv), paraformaldehyde (4.0 equiv) and catalytic amount (0.05 equiv) of paratoluene sulfonic acid in Dichloromethane (2mL/100mg scale) was stirred at room temperature for 8-12 h. after completion of the reaction (monitored by TLC) the reaction mixture was filtered through sintered funnel and the filtrate was washed with 1 % aq. NaHCO\textsubscript{3} (2 x 1 mL) solution followed by distilled water (3 x 1 mL). Dried over Na\textsubscript{2}SO\textsubscript{4} and removal of the solvent under \textit{vacuo} gives the crude product is latter separated in hexane/ethylacetate (99:1) by using florisil chromatography (60-100 mesh) to afford the desired products.

Comp.no. (9); Mp 81-82 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 3.44 (s, 2H, H-3), 3.76–4.05 (dd, \textit{J} = 10.9 Hz, 4H, H-10, H-12), 4.82 (d, \textit{J} = 6.1 Hz, 1H, H-11), 5.13 (d, \textit{J} = 6.1 Hz, 1H, H-11), 7.4 (t, \textit{J} = 7.8 Hz, 1H, H-5), 7.56 (d, \textit{J} = 7.7 Hz, 1H, H-5), 7.63 (t, \textit{J} = 7.5 Hz, 1H, H-7), 7.75 (d, \textit{J} = 7.6 Hz, 1H, H-8); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 38, 51.5, 72.6 (2C), 93.9, 124.2, 126.9, 127.8, 135.5, 136, 153.4, 204.5; IR (KBr, cm\textsuperscript{-1}): 3020, 2361, 1703, 1216, 1160, 760, 669; MS (ESI): m/z (%): 205 (100) [M+1]+.

Comp.no. (11a); Mp 101-102 °C; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 2.42 (t, \textit{J} = 6.5 Hz, 2H, H-3), 3.03 (t, \textit{J} = 6.3 Hz, 2H, H-4), 3.87 (s, 3H, OCH\textsubscript{3}), 3.92–4.09 (dd, \textit{J} = 11.5 Hz, 4H, H-11, H-13), 4.75 (d, \textit{J} = 6.0 Hz, 1H, H-12), 5.07 (d, \textit{J} = 6.0 Hz, 1H, H-12), 6.71 (d, \textit{J} = 2.4 Hz, 1H, H-5), 6.84 (dd, \textit{J} = 8.8, 2.5Hz, 1H, H-7), 7.95 (d, \textit{J} = 8.7 Hz, 1H, H-8); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 26.4, 26.9, 45, 54.9, 70.1 (2C), 93.7, 111.8, 113, 124.8, 129.5, 145.2, 163.4, 195.9; IR (KBr, cm\textsuperscript{-1}): 3317, 2358, 1703, 1222, 1201, 769; MS (ESI): m/z (%): 249 (100) [M+1]+.

Comp.no. (11b); Oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 2.24 (t, \textit{J} = 6.5 Hz, 2H, H-3), 3.0 (t, \textit{J} = 6.3 Hz, 2H, H-4), 3.8–4.19 (dd, \textit{J} = 12.0 Hz, 4H, H-11, H-14), 3.87 (s, 3H, OCH\textsubscript{3}), 4.79 (d, \textit{J} = 6.7 Hz, 2H, H-12, H-13), 4.97 (d, \textit{J} = 6.3 Hz, 2H, H-12, H-13), 6.7 (s, 1H, H-5), 6.84 (d, \textit{J} = 8.7 Hz, 1H, H-7), 8.01 (d, \textit{J} = 8.8 Hz, 1H, H-8); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 25.3, 27.6, 29.7, 45.6, 55.4, 70.7 (2C), 94.3, 112.4, 113.6, 125.4, 130.2, 145.8, 164, 196.6; IR (Neat, cm\textsuperscript{-1}): 3027, 2367, 1709, 1217, 1161, 767; MS (ESI): m/z (%): 279(100) [M+1]+, 280 (21) [M+2]+.

Comp.no. (12a); Oil; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) 4.06 (s, 4H, H-11, H-13), 4.71 (s, 2H, H-2), 5.11 (d, \textit{J} = 6.0 Hz, 2H, H-12), 7.03 (m, 2H, ArH), 7.53 (m, 1H, ArH), 7.84 (d, \textit{J} = 7.9 Hz, 1H, H-8); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 45.3, 66.5, 67.7 (2C), 69.7, 116.8, 118.2, 122, 126.7, 130.7, 136.5, 208.9; IR (KBr, cm\textsuperscript{-1}): 3325, 2361, 1698, 1216, 1151, 769, 663; MS (ESI): m/z (%): 221 (100) [M+1]+, 222 (18) [M+2]
Comp no. (12b); Mp 61–62 °C; 1H NMR (300 MHz, CDCl3) δ 3.85–4.23 (dd, J = 12.3 Hz, 4H, H-11, H-14), 4.53 (s, 2H, H-2), 4.83 (d, J = 6.6 Hz, 2H, H-12, H-13), 4.93 (d, J = 6.5 Hz, 2H, H-12, H-13), 7.02 (m, 2H, ArH), 7.51 (m, 1H, ArH), 7.9 (d, J = 8.9 Hz, 1H, H-8); 13C NMR (75 MHz, CDCl3) δ 24.8 (2C), 28.8, 29.7, 49.7, 93.2, 126.8, 127.8, 128.8, 131.5, 133.6, 143.2, 199.5; IR (Neat, cm⁻¹): 3022, 2362, 1704, 1214, 1161, 762, 668; MS (ESI): m/z (%): 251 (100) [M+1]⁺, 252 (11) [M+2]⁺.

Comp no. (13); Mp 88–89 °C; 1H NMR (200 MHz, CDCl3) δ 2.06 (t, J = 6.2 Hz, 2H, H-3), 2.31 (s, 3H, ArCH3), 3.74–4.24 (dd, J = 11.5 Hz, 4H, H-12, H-14), 4.21 (t, J = 6.3 Hz, 2H, H-2), 4.80 (s, 2H, H-13), 6.91 (d, J = 8.3 Hz, 1H, H-9), 7.23 (m, 1H, H-8), 7.44 (d, J = 1.8 Hz, 1H, H-6); 13C NMR (75 MHz, CDCl3) δ 20.4, 33.9, 51, 71.4, 72.8 (2C), 94, 119.4, 126.4, 130.3, 134.2, 132.3, 134.5, 157.6, 202; IR (KBr, cm⁻¹): 3028, 2366, 2339, 1709, 1218, 1161, 760, 679; MS (ESI): m/z (%): 249 (100) [M+1]⁺, 250 (17) [M+2]⁺.

Comp no. (14); Mp 101–102 °C; 1H NMR (300 MHz, CDCl3) δ 1.32 (s, 3H, CH3), 3.7–4.43 (dd, J = 11.5 Hz, 4H, 2x CH2O–), 4.78–4.87 (dd, J = 6Hz, 2H, –OCH2O–), 7.46 (m, 3H, ArH), 7.69 (m, 1H, ArH); 13C NMR (75 MHz, CDCl3) δ 18.8, 47.5, 73.3 (2C), 94.4, 125.5, 127.9, 128.4 (2C), 131.5, 137.8, 203.9; IR (KBr, cm⁻¹): 3020, 2361, 1698, 1215, 1164, 760, 669; MS (ESI): m/z (%): 207 (100) [M+1]⁺.

Comp no. (15); 1H NMR (300 MHz, CDCl3) δ 1.31 (s, 3H, CH3), 3.72–4.41 (dd, J = 11.2 Hz, 4H, 2x CH2O–), 4.75–4.83 (dd, J = 6Hz, 2H, –OCH2O–), 7.19–7.23 (m, 1H, ArH), 7.31 (m, 2H, ArH), 7.42 (d, J = 8.2 Hz, 1H, ArH); 13C NMR (75 MHz, CDCl3) δ 18.6, 46.8, 72.8 (2C), 94.4, 125.5, 127.9, 128.4 (2C), 131.5, 137.8, 203.9; IR (KBr, cm⁻¹): 3028, 2361, 1698, 1215, 1164, 760, 669; MS (ESI): m/z (%): 241 (100) [M+1]⁺.

Comp no. (16a); Oil; 1H NMR (300 MHz, CDCl3) δ 2.94 (t, J = 7.0 Hz, 2H, H-3), 3.59 (d, J = 6.9 Hz, 2H, H-4), 3.96–4.05 (dd, J = 11.3 Hz, 2H, H-11, H-13), 4.64 (d, J = 5.9 Hz, 2H, H-11, H-13), 5.23 (d, J = 5.9 Hz, 2H, H-12, H-13), 7.17 (d, J = 6.4 Hz, 1H, H-6), 7.31 (m, 1H, H-7), 7.71 (d, J = 8.3 Hz, 1H, H-8); 13C NMR (75 MHz, CDCl3) δ 24.7, 27.5, 45.5, 72.4, 72.9, 94.7, 126.4, 126.8, 128.9, 131.7, 133.4, 147.5, 201.3; IR (KBr, cm⁻¹): 3228, 2404, 1701, 1231, 1125, 772, 679; MS (ESI): m/z (%): 253 (89) [M+1]⁺.

Comp no. (16b); Mp 133–134 °C; 1H NMR (300 MHz, CDCl3) δ 2.24 (t, J = 6.7 Hz, 2H, H-3), 3.02 (t, J = 6.6 Hz, 2H, H-4), 3.79–4.20 (dd, J = 18.0 Hz, 4H, H-11, H-14), 4.75–4.79 (d, J = 10.0 Hz, 2H, H-12, H-13), 4.92–4.95 (d, J = 9.9 Hz, 2H, H-12, H-13), 7.22 (m, 1H, ArH), 7.44 (m, 1H, ArH), 7.98–8.02 (dd, J = 11.6, 2.01 Hz, H-8); 13C NMR (75 MHz, CDCl3) δ 25.2 (2C), 29.2, 30.11, 50.1, 70.4, 96.4, 127.2, 128.3, 129.2, 131.9, 134.1, 143.7, 199.9; IR (KBr, cm⁻¹): 3316, 2362, 1700, 1228, 1200, 766; MS (ESI): m/z (%): 283 (100) [M+1]⁺.
$^1\text{H}$, $^{13}\text{C}$ and 2D-NMR spectra’s of above compounds.

$^1\text{H}$ of Compound 1a
$^{13}$C, DEPT-135, 90 of Compound 1a
$^1$H of Compound 2a

$^{13}$C of Compound 2a
$^1$H of Compound 3a
$^{13}$C of Compound 3a

$^1$H of Compound 4a
$^{13}\text{C}$ of Compound 5a

$^{1}\text{H}$ of Compound 6a
$^{13}$C of Compound 6a

$^1$H of Compound 7a
$^{13}\text{C}$ of Compound 7a

$^{1}\text{H}$ of Compound 8a
$^{13}$C of Compound 8a

$^1$H of compound of 9
$^{13}\text{C}$ of compound of 9

$^1\text{H}$ of compound of 10a
$^{13}$C of compound of \textbf{10a}

$^1$H of compound of \textbf{10b}
$^{13}$C, DEPT-90, 135 of compound of 10b
$^1$H of compound of 11a

$^1$H of compound of 11b
$^{13}$C of compound of 11b

$^1$H of compound of 12a
$^{13}\text{C}$ of compound of $12\text{a}$

$^{1}\text{H}$ of compound of $12\text{b}$
$^{13}$C of compound of 12b

NOESY of compound of 12b
NOESY expansion of compound 12b
NOE DEFF of compd. 12b
$^1$H of compound of 13

$^{13}$C of compound of 13
$^{1}\text{H}^{-1}\text{H}$ Cosy of compound of 13

HMBC of compound of 13
HSQC of compound of 13

^1^H of compound of 14
$^{13}$C of compound of 14

$^{1}$H of compound of 16b
$^{13}\text{C}$ of compound of 16b