Redox-Annulation of Cyclic Amines and β-Ketoaldehydes

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Supporting Information

General Information: Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. 1,2,3,4-Tetrahydroisoquinoline (THIQ), acetic acid and 2-ethylhexanoic acid (2-EHA) were distilled prior to use. Benzoic acid was recrystallized from toluene/ethanol. Purification of reaction products was carried out by flash column chromatography using Sorbent Technologies Standard Grade silica gel (60 Å, 230–400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60 F$_{254}$ plates. Visualization was accomplished with UV light, potassium permanganate or Dragendorff-Munier stains, followed by heating. Melting points were recorded on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis Series FT-Infrared spectrophotometer. Proton nuclear magnetic resonance spectra ($^1$H-NMR) were recorded on a Varian VNMRS-500 MHz, Varian VNMRS-400 MHz or Varian VNMRS-300 MHz and chemical shifts are reported in ppm using the solvent as an internal standard (CDCl$_3$ at 7.26 ppm). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad; coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra ($^{13}$C-NMR) spectra were recorded on a Varian VNMRS-500 MHz, Varian VNMRS-400 MHz or Varian VNMRS-300 MHz and chemical shifts are reported in ppm using the solvent as an internal standard (CDCl$_3$ at 77.0 ppm). Mass spectra were recorded on a Finnigan LCQ-DUO mass spectrometer. Ratios of diastereomeric products were determined by $^1$H-NMR analysis of the crude reaction mixture. 6,7-Methylenedioxy-1,2,3,4-tetrahydroisoquinoline,$^1$ 9-methyltryptoline,$^2$ 2,2-dimethyl-3-oxobutyraldehyde,$^3$ 1-acetylcyclohexanecarbaldehyde,$^4$ 2,2-dimethyl-3-oxo-4-phenylbutyraldehyde,$^5$ 4-benzyloxy-1-bromobutane,$^6$ and 3-ethylpentane-2,4-dione$^7$ were prepared according to literature procedures. Compounds 1n,$^8$ 4a-4d,$^9$ 6a,$^{10}$ and 6d$^{11}$ were previously reported and their published characterization data matched our own in all respects.
Scheme S1: Synthesis of 2-alkyl-3-oxobutyraldehydes.\textsuperscript{12,13}

\textbf{methyl 2-acetyl-6-(benzyloxy)hexanoate (4e):} To a suspension of NaH (60\% in mineral oil, 0.96 g, 24 mmol, 1.2 equiv) in a mixture of dry toluene (12 mL) and DMF (10 mL) was slowly added methyl acetoacetate (2.16 mL, 20 mmol, 1 equiv) over 20 minutes at room temperature. The mixture was then allowed to stir for 15 minutes at room temperature before benzyloxy-1-bromobutane (5.83 g, 24 mmol, 1.2 equiv) was added in one portion. The reaction mixture was allowed to stir at 100 \(^\circ\)C for 8 hours. After cooling to room temperature, the reaction was quenched by the addition of saturated aqueous NH\(_4\)Cl. 6 M HCl (5 mL) was then added to the reaction mixture. The reaction mixture was washed with water (2 x 75 mL), and the combined aqueous layers were extracted with ethyl ether (3 x 50 mL). The combined organic layers were then washed with brine (150 mL) and dried over anhydrous Na\(_2\)SO\(_4\). Solvent was then removed under reduced pressure. The residue was purified by silica gel chromatography and compound 4e was obtained as a yellow oil in 77\% yield (4.29 g), (R\(_f\) = 0.22 in hexanes/EtOAc 90:10 v/v); IR (KBr) 2951, 2861, 1742, 1716, 1643, 1496, 1455, 1433, 1360, 1245, 1208, 1151, 1095, 737, 699 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37–7.29 (comp, 4H), 7.29–7.24 (m, 1H), 4.51–4.45 (comp, 2H), 3.72 (s, 3H), 3.48–3.40 (comp, 3H), 2.21 (s, 3H), 1.92–1.79 (comp, 2H), 1.67–1.57 (comp, 2H), 1.42–1.31 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 203.0, 170.2, 138.5, 128.3, 127.6, 127.5, 72.9, 69.8, 59.6, 52.3, 29.4, 28.8, 28.0, 24.1; \(m/z\) (ESI–MS) 301.2 [M + Na]\(^+\).

\textbf{General Procedure A for converting 4 to 5:}

A mixture of 2-alkyl methyl acetoacetate (20 mmol, 1 equiv), ethylene glycol (1.34 mL, 24 mmol, 1.2 equiv) and \(p\)-TSA monohydrate (76 mg, 0.4 mmol, 0.02 equiv) in toluene (30 mL) was heated under reflux with a Dean-Stark apparatus for 18 hours. The reaction mixture was allowed to cool to room temperature and then diluted with ethyl ether (30 mL). The mixture was washed with saturated aqueous NaHCO\(_3\) (3 x 30 mL), and the combined
aqueous layers were washed with ethyl ether (3 x 30 mL). The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was further dried under high vacuum. The crude product was directly used in the next step without further purification.

**General Procedure B for converting 5 to 6:**

To an ice-cooled suspension of LiAlH₄ (1.43 g, 37.5 mmol, 2.5 equiv) in dry THF (60 mL) was slowly added a solution of compound 5 (15 mmol, 1 equiv) in dry THF (15 mL). The mixture was allowed to stir at room temperature for 2 hours, followed by quenching with 30% aqueous ammonia cooled in an ice bath. The lithium and aluminum hydroxide salts were then filtered through a short pad of celite and washed with EtOAc (6 x 50 mL). The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography.

New compounds were characterized as below:

**2-(2-methyl-1,3-dioxolan-2-yl)hexan-1-ol (6b):** Following the general procedures A and B over two steps (1.72 g), (R_f = 0.34 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3385, 2956, 2935, 2866, 2357, 2330, 1701, 1650, 1458, 1369, 1085, 1041, 882 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 3.99–3.94 (comp, 4H), 3.67–3.58 (comp, 2H), 2.96 (br s, 1H), 1.79–1.72 (m, 1H), 1.51–1.21 (comp, 8H), 1.17–1.08 (m, 1H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 113.1, 64.5, 64.2, 62.7, 47.8, 30.2, 26.6, 22.9, 20.5, 13.9; m/z (ESI–MS) 167.0 [M + Na – C₂H₄O]⁺.

**4-methyl-2-(2-methyl-1,3-dioxolan-2-yl)pentan-1-ol (6c):** Following the general procedures A and B over two steps (1.81 g), (R_f = 0.34 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3385, 2957, 2935, 2873, 1701, 1643, 1465, 1418, 1369, 1247, 1208, 1166, 1085, 1041, 882 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 3.92 (comp, 4H), 3.81 (comp, 2H), 3.00 (br s, 1H), 1.81–1.83 (m, 1H), 1.68–1.57 (m, 1H), 1.29 (s, 3H), 1.89 (br d, J = 13.7 Hz, 1H), 1.08 (s, J = 13.7 Hz, 1H), 0.88 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 113.2, 64.5, 64.2, 63.1, 45.4, 36.2, 25.9, 23.8, 21.7, 20.5; m/z (ESI–MS) 167.0 [M + Na – C₂H₄O]⁺.

**6-(benzyloxy)-2-(2-methyl-1,3-dioxolan-2-yl)hexan-1-ol (6e):** Following the general procedures A and B over two steps (3.09 g), (R_f = 0.26 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3422, 2938, 2863, 2360, 2337, 1647, 1453, 1364, 1098, 1040, 946, 860 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.37–7.32 (comp, 4H), 7.30–7.25 (m, 1H), 4.50 (s, 2H), 4.00–3.92 (comp, 4H), 3.69–3.59 (comp, 2H), 3.47 (app t, J = 6.6 Hz, 2H), 3.00 (br s, 1H), 1.81–1.75 (m, 1H), 1.73–1.44 (comp, 4H), 1.43–1.33 (m, 1H), 1.30 (s, 3H), 1.21–1.12 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 170.1, 136.9, 136.5, 131.6, 131.4, 130.0, 126.0, 125.7, 123.6, 123.1, 120.7, 116.7, 105.3, 104.2, 64.4, 64.3, 63.2, 45.3, 36.2, 25.9, 23.8, 21.7, 20.5; m/z (ESI–MS) 303.0 [M + Na – C₂H₄O]⁺.
CDCl$_3$ δ 138.6, 128.3, 127.6, 127.5, 113.0, 72.9, 70.2, 64.5, 64.2, 62.7, 47.9, 30.0, 26.8, 24.7, 20.5; m/z (ESI–MS) 317.2 [M + Na]$^+$.  

**General Procedure C for converting 6 to 7:**

To a stirred solution of oxalychloride (1.71 mL, 20 mmol, 2 equiv) in dry CH$_2$Cl$_2$ (20 mL) was slowly added dry DMSO (2.84 mL, 40 mmol, 4 equiv) at −78 ºC. The mixture was allowed to stir at the same temperature for 15 minutes, then a solution of the alcohol 6 (10 mmol, 1 equiv) in CH$_2$Cl$_2$ (25 mL) was slowly added. After stirring at −78 ºC for 30 minutes, NEt$_3$ (8.36 mL, 60 mmol, 6 equiv) was slowly added and the reaction mixture was allowed to warm to room temperature and stirred for another hour. The reaction mixture was diluted with ethyl ether (50 mL) and washed with water (3 x 50 mL). The combined aqueous layers were extracted with ethyl ether (3 x 50 mL). The combined organic layers were then washed with brine and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the crude product was directly used in the next step without further purification.

**General Procedure D for converting 7 to 8:**

The crude compound 7 (10 mmol) was dissolved in a mixture of THF (15 mL) and 3 M HCl (10 mL). The mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was then diluted with ethyl ether (20 mL) and washed with water (3 x 30 mL). The combined aqueous layers were extracted with ethyl ether (3 x 30 mL). The combined organic layers were then washed with brine and dried over anhydrous Na$_2$SO$_4$. Solvent was then removed under reduced pressure and the residue was purified by Kugelrohr distillation (8a-c), recrystallization from EtOAc/hexanes (8d) or silica gel chromatography (8e).

New compounds were characterized as below:

**2-ethyl-3-oxobutanal (8a):** Following the general procedures C and D compound 8a was obtained from compound 6a as a white solid in 85% yield over two steps (0.97 g), (R$_f$ = 0.39 in hexanes/EtOAc 90:10 v/v); mp: 39–41 ºC; IR (KBr) 2972, 2925, 2871, 1634, 1435, 1366, 1258, 1212, 1117, 1071, 1024, 912 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.86 (br s, 1H), 2.18 (q, $J$ = 7.5 Hz, 2H), 2.14 (s, 3H), 1.05 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 195.7, 175.5, 114.4, 24.0, 21.0, 15.4; m/z (ESI–MS) 169.1 [M + Na + MeOH]$^+$.  

**2-acetylhexanal (8b):** Following the general procedures C and D compound 8b was obtained from compound 6b as a yellow oil in 87% yield over two steps (1.24 g), (R$_f$ = 0.56 in hexanes/EtOAc 80:20 v/v); IR (KBr) 2958, 2930, 2862, 2686, 1718, 1617, 1406, 1354, 1277, 1216, 1126, 1026, 961, 919 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.93 (d, $J$ = 6.8 Hz, 1H), 2.17–2.11 (comp, 5H), 1.42–1.27 (comp, 4H), 0.91 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 194.7, 177.0, 112.9, 33.1, 27.4, 23.7, 22.1, 13.8; m/z (ESI–MS) 142.7 [M + H]$^+$.  

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2-acetyl-4-methylpentanal (8c): Following the general procedures C and D compound 8c was obtained from compound 6c as a white solid in 86% yield over two steps (1.23 g). (R<sub>t</sub> = 0.56 in hexanes/EtOAc 80:20 v/v); mp: 49–52 °C; IR (KBr) 2958, 2866, 2364, 2340, 1705, 1637, 1408, 1235, 1129, 973 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) 8.00 (d, <i>J</i> = 5.5 Hz, 1H), 2.12 (s, 3H), 2.02 (d, <i>J</i> = 7.2 Hz, 2H), 1.69–1.54 (m, 1H), 0.90 (d, <i>J</i> = 6.8 Hz, 6H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 193.6, 179.3, 111.7, 36.8, 29.3, 23.5, 22.0; <i>m/z</i> (ESI–MS) 142.7 [M + H]<sup>+</sup>.

2-benzyl-3-oxobutanal (8d): Following the general procedures C and D compound 8d was obtained from compound 6d as a white solid in 90% yield over two steps (1.58 g). (R<sub>f</sub> = 0.38 in hexanes/EtOAc 80:20 v/v); mp: 98–101 °C; IR (KBr) 3111, 2672, 1962, 1836, 1652, 1559, 1496, 1390, 1275, 1193, 1076, 1023, 973, 841, 808, 795, 726, 701, 654, 615, 526 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.87 (d, <i>J</i> = 7.4 Hz, 1H), 7.35–7.28 (comp, 2H), 7.23 (app t, <i>J</i> = 7.5 Hz, 1H), 7.20–7.16 (comp, 2H), 3.54 (s, 2H), 2.04 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 197.3, 174.9, 139.3, 128.3, 127.6, 126.1, 111.4, 33.4, 24.7; <i>m/z</i> (ESI–MS) 199.0 [M + Na]<sup>+</sup>, 231.0 [M + Na + MeOH]<sup>+</sup>.

2-acetyl-6-(benzyloxy)hexanal (8e): Following the general procedures C and D compound 8e was obtained from compound 6e as a yellow oil in 93% yield (2.31 g). (R<sub>f</sub> = 0.18 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3064, 3030, 2969, 2955, 1707, 1617, 1496, 1454, 1406, 1362, 1265, 1212, 1103, 1028, 959, 907, 737, 699 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 7.94 (d, <i>J</i> = 6.8 Hz, 1H), 7.38–7.25 (comp, 5H), 4.50 (s, 2H), 3.49 (t, <i>J</i> = 6.1 Hz, 2H), 2.18 (t, <i>J</i> = 7.7 Hz, 2H), 2.13 (s, 3H), 1.68–1.60 (m, 2H), 1.55–1.47 (m, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 194.7, 177.1, 138.4, 128.4, 127.6(1), 127.5(6), 112.6, 73.0, 69.9, 29.2, 27.6, 27.5, 23.8; <i>m/z</i> (ESI–MS) 249.0 [M + H]<sup>+</sup>.

General Procedure for the Redox-Annulation Involving Non-enolizable β-Ketoaldehydes:

To a mixture of the aldehyde (0.5 mmol, 1 equiv) and 4Å MS (150 mg) in toluene (2 mL) were added acetic acid (0.29 mL, 5 mmol, 10 equiv) and the amine (0.75 mmol, 1.5 equiv). The mixture was heated under reflux for 2 hours. The reaction mixture was then allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO<sub>3</sub> (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.
General Procedure for the Redox-Annulation Involving Enolizable β-Ketoaldehydes:

To a suspension of 4Å MS (150 mg) in toluene (2 mL) were added acetic acid (0.29 mL, 5 mmol, 10 equiv) and the amine (0.75 mmol, 1.5 equiv). The mixture was heated under reflux and a solution of the aldehyde (0.5 mmol, 1 equiv) in toluene was delivered through the top of the reflux condenser over 15 hours via syringe pump. The reaction was stopped immediately after the slow addition was completed. The reaction mixture was then allowed to cool to room temperature and filtered through a short pad of celite and washed with EtOAc (6 x 5 mL). The filtrate was then washed with saturated aqueous NaHCO₃ (3 x 10 mL). The combined aqueous layers were extracted with EtOAc (3 x 10 mL), and the combined organic layers were washed with water (40 mL), brine (40 mL), and dried over anhydrous Na₂SO₄. Solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography.

3,3-dimethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (1a):

Following the general procedure compound 1a was obtained from THIQ (95 µL) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow oil in 71% yield (82 mg), (Rₙ = 0.47 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3063, 3022, 2961, 2923, 2805, 2758, 1713, 1633, 1495, 1469, 1453, 1427, 1377, 1355, 1300, 1248, 1188, 1145, 1133, 1112, 1035, 956, 770, 745, 729, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24–7.12 (comp, 3H), 7.12–7.06 (m, 1H), 3.52–3.44 (m, 1H), 3.24 (ddd, J = 15.7, 11.8, 5.7 Hz, 1H), 3.03 (ddd, J = 11.3, 5.8, 1.2 Hz, 1H), 2.88 (dd, J = 14.6, 3.3 Hz, 1H), 2.82 (d, J = 11.5 Hz, 1H), 2.79–2.72 (m, 1H), 2.68 (dd, J = 14.6, 12.1 Hz, 1H), 2.54 (app td, J = 11.8, 3.5 Hz, 1H), 2.45 (d, J = 11.5 Hz, 1H), 1.34 (s, 3H), 1.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 213.2, 136.9, 134.3, 128.9, 126.4, 126.0, 124.6, 67.9, 62.8, 51.3, 46.0, 44.3, 29.7, 25.7, 21.5; m/z (ESI–MS) 230.2 [M + H]⁺, 262.0 [M + H + MeOH]⁺.

9,10-dimethoxy-3,3-dimethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (1b):

Following the general procedure compound 1b was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2,2-dimethyl-3-oxobutyraldehyde (57 mg) as a yellow solid in 86% yield (124 mg), (Rₙ = 0.56 in hexanes/EtOAc 60:40 v/v); mp: 127–128 ºC; IR (KBr) 3383, 2957, 2928, 2863, 2836, 2816, 2777, 2762, 2246, 1702, 1611, 1522, 1454, 1379, 1361, 1261, 1227, 1150, 1106, 1021, 919, 867, 88, 741, 711, 575 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.59 (s, 1H), 6.53 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.41–3.29 (m, 1H), 3.20–3.04 (m, 1H), 2.97 (ddd, J = 11.2, 5.7, 1.1 Hz, 1H), 2.85–2.72 (comp, 2H), 2.70–2.55 (comp, 2H), 2.53–2.35 (comp, 2H), 1.29 (s, 3H), 1.03 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 213.2, 147.5, 147.3, 128.6, 126.3, 111.3, 107.6, 67.7, 62.4, 55.8, 55.7, 51.4, 45.9, 44.5, 29.2, 25.6, 21.4; m/z (ESI–MS) 290.2 [M + H]⁺, 322.0 [M + H + MeOH]⁺.
3,3-dimethyl-3,4,6,7-tetrahydro-1H-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinolinin-2(12H)-one (1e): Following the general procedure compound 1e was obtained from 6,7-methyleneoxy-1,2,3,4-tetrahydroisoquinoline (133 mg) and 2,2-dimethyl-3-oxobuturaldehyde (57 mg) as a yellow solid in 69% yield (94 mg), (Rf = 0.46 in hexanes/EtOAc 80:20 v/v); mp: 121–123 °C; IR (KBr) 3382, 2947, 2879, 2808, 1860, 1705, 1483, 1380, 1355, 1327, 1292, 1233, 1139, 1039, 934, 867, 820, 773, 743, 546 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.56 (s, 1H), 6.53 (s, 1H), 5.91–5.86 (comp, 2H), 3.41–3.28 (m, 1H), 3.19–3.04 (m, 1H), 3.02–2.92 (m, 1H), 2.84–2.68 (comp, 2H), 2.67–2.54 (comp, 2H), 2.53–2.33 (comp, 2H), 1.30 (s, 3H), 1.04 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 213.0, 146.0(8), 146.0(7), 129.7, 127.6, 108.4, 104.7, 100.7, 67.7, 62.7, 51.4, 45.9, 44.5, 29.7, 25.6, 21.5; m/z (ESI–MS) 274.2 [M + H]⁺, 306.0 [M + H + MeOH]⁺.

3,3-dimethyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolinin-2(12H)-one (1d): Following the general procedure compound 1d was obtained from tryptoline (129 mg) and 2,2-dimethyl-3-oxobutraldehyde (57 mg) as a yellow solid in 67% yield (90 mg), (Rf = 0.37 in hexanes/EtOAc 80:20 v/v); mp: 193–194 °C; IR (KBr) 3059, 2965, 2921, 2846, 1705, 1623, 1467, 1455, 1383, 1370, 1352, 1324, 1283, 12231, 1173, 1162, 1121, 1005, 961, 798, 739, 709, 667, 625 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.61 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 213.3, 136.2, 133.3, 126.9, 121.6, 119.5, 118.1, 111.1, 108.4, 67.2, 59.5, 52.1, 46.5, 42.7, 25.8, 21.7(3), 21.6(9); m/z (ESI–MS) 269.2 [M + H]⁺, 301.1 [M + H + MeOH]⁺.

3,3-dimethyl-11b-phenyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolinin-2(11bH)-one (1e): Following the general procedure compound 1e was obtained from 1-phenyl-THIQ (157 mg) and 2,2-dimethyl-3-oxobuturaldehyde (57 mg) as a yellow solid in 51% yield (78 mg), (Rf = 0.64 in hexanes/EtOAc 80:20 v/v); mp: 101–104 °C; IR (KBr) 3061, 3022, 2960, 2908, 2846, 1969, 1954, 1929, 1895, 1813, 1698, 1596, 1443, 1393, 1372, 1347, 1300, 1167, 1128, 958, 765, 745, 707 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78–7.22 (comp, 2H), 7.22–7.07 (comp, 6H), 7.01 (d, J = 7.7 Hz, 1H), 3.27–3.21 (m, 1H), 3.21–3.06 (m, 3H), 3.00–2.93 (m, 1H), 2.82–2.75 (m, 1H), 2.68–2.60 (comp, 2H), 1.25–1.17 (comp, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 214.4, 144.6, 140.0, 134.0, 129.0, 128.1, 127.9, 127.7, 126.8, 126.5, 126.1, 66.3, 61.0, 49.1, 46.2, 46.0, 27.7, 25.3, 23.1; m/z (ESI–MS) 306.2 [M + H]⁺.

1',6',7',11b'-tetrahydrospiro[cyclohexane-1,3'-pyrido[2,1-a]isoquinolinin]-2'(4'H)-one (1f): Following the general procedure compound 1f was obtained from THIQ (95 µL) and 1-acetylcyclohexanecarbaldehyde (77 mg) as a yellow oil in 71% yield (96 µL), (Rf = 0.53 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3063, 3022, 2922, 2854, 2801, 2754, 1708, 1632, 1494, 1452, 1426, 1364, 1300, 1275, 1241, 1223, 1153, 1112, 1031, 879, 747, 769, 730 cm⁻¹; ¹H NMR (500 MHz,
CDCl$_3$) 7.21–7.11 (comp, 3H), 7.11–7.04 (m, 1H), 3.50–3.41 (m, 1H), 3.23 (ddd, $J = 15.8$, 11.6, 5.8 Hz, 1H), 3.14 (d, $J = 11.7$ Hz, 1H), 3.08–2.99 (m, 1H), 2.84 (dd, $J = 14.0$, 3.2 Hz, 1H), 2.79–2.65 (comp, 2H), 2.54 (app td, $J = 11.6$, 3.0 Hz, 1H), 2.28 (d, $J = 11.7$ Hz, 1H), 2.02–1.87 (comp, 2H), 1.85–1.71 (comp, 2H), 1.62–1.52 (m, 1H), 1.52–1.29 (comp, 4H), 1.23–1.11 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.4, 136.9, 134.2, 128.8, 126.3, 126.0, 124.5, 64.8, 62.9, 51.5, 49.5, 44.4, 33.5, 30.4, 29.7, 26.1, 21.7, 21.6; $\text{m/z} (\text{ESI–MS})$ 270.3 [M + H]$^+$, 302.1 [M + H + MeOH]$^+$.

**11-cis-3,3-dimethyl-1-phenyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (cis-1g):** Following the general procedure compound cis-1g was obtained from THIQ (95 µL) and 2,2-dimethyl-3-oxo-4-phenylbutyraldehyde (95 mg) as a yellow solid in 35% yield (53 mg), ($R_f$ = 0.64 in hexanes/EtOAc 80:20 v/v); mp: 114–117 °C; IR (KBr) 3061, 2950, 2755, 1698, 1597, 1494, 1466, 1401, 1379, 1353, 1291, 1247, 1113, 1047, 1031, 921, 897, 741, 719, 693, 628 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.60–7.52 (comp, 2H), 7.12 (d, $J = 7.6$ Hz, 1H), 7.09–6.98 (comp, 4H), 6.98–6.90 (comp, 2H), 4.34 (d, $J = 4.4$ Hz, 1H), 3.99 (d, $J = 4.4$ Hz, 1H), 3.49–3.38 (m, 1H), 3.26–3.17 (m, 1H), 2.93 (d, $J = 11.4$ Hz, 1H), 2.90–2.83 (m, 1H), 2.63–2.55 (m, 1H), 2.51 (d, $J = 11.4$ Hz, 1H), 1.10 (s, 3H), 1.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.1, 136.0, 135.3, 134.7, 129.8, 128.6, 127.6, 126.1(9), 126.1(6), 125.9, 124.6, 68.9, 65.2, 57.8, 52.4, 46.5, 29.7, 27.5, 23.4; $\text{m/z} (\text{ESI–MS})$ 306.2 [M + H]$^+$.

**11-trans-3,3-dimethyl-1-phenyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (trans-1g):** Following the general procedure compound trans-1g was obtained from THIQ (95 µL) and 2,2-dimethyl-3-oxo-4-phenylbutyraldehyde (95 mg) as a yellow solid in 18% yield (27 mg), ($R_f$ = 0.54 in hexanes/EtOAc 80:20 v/v); mp: 98–100 °C; IR (KBr) 3059, 3026, 2829, 1697, 1601, 1490, 1452, 1374, 1352, 1144, 1063, 946, 761, 726, 701 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.43–7.35 (comp, 2H), 7.35–7.29 (m, 1H), 7.25–7.20 (comp, 2H), 7.14–7.04 (comp, 2H), 6.84–6.77 (m, 1H), 6.39 (d, $J = 8.1$ Hz, 1H), 4.33 (d, $J = 8.7$ Hz, 1H), 3.86 (d, $J = 8.7$ Hz, 1H), 3.28–3.13 (comp, 2H), 3.01 (d, $J = 12.2$ Hz, 1H), 2.97–2.86 (comp, 2H), 2.79–2.68 (m, 1H), 1.33 (s, 3H), 1.14 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 213.0, 138.8, 135.0, 130.3, 128.8, 128.6, 127.1, 127.0, 126.3, 125.3, 66.4, 65.4, 60.5, 51.6, 46.0, 29.4, 26.3, 23.5; $\text{m/z} (\text{ESI–MS})$ 306.2 [M + H]$^+$.

**11-trans-3-ethyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (1h):** Following the general procedure compound 1h was obtained from THIQ (95 µL) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 40% yield (46 mg, 6:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid ($R_f$ = 0.32 in hexanes/EtOAc 80:20 v/v); mp: 96–98 °C; IR (KBr) 3026, 2956, 2873, 2792, 1697, 1493, 1452, 1431, 1406, 1366, 1288, 1231, 1147, 1109, 1031, 889, 752, 735, 722 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) 7.20–7.11 (comp, 3H), 7.10–7.05 (m, 1H), 3.63–3.56 (m, 1H), 3.33 (dd, $J = 11.6$, 6.2 Hz, 1H), 3.25–3.12 (comp, 2H), 2.94 (dd, $J = 13.7$, 3.1 Hz, 1H), 2.86–2.79 (m, 1H), 2.68–2.50 (comp, 3H), 2.39 (app t, $J = 11.6$ Hz, 1H), 1.95–1.83 (m, 1H), 1.32–1.21 (m, 1H), 0.96 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR
(125 MHz, CDCl₃) δ 209.5, 136.5, 133.8, 128.9, 126.6, 126.1, 124.8, 62.6, 60.6, 50.9, 50.4, 47.1, 29.6, 19.2, 11.6; m/z (ESI–MS) 262.0 [M + H + MeOH]⁺.

11-trans-3-ethyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (1i): Following the general procedure compound 1i was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 51% yield (74 mg, 6:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rᵣ = 0.25 in hexanes/EtOAc 60:40 v/v); mp: 104–106 °C; IR (KBr) 2937, 2835, 2795, 1705, 1609, 1519, 1467, 1410, 1370, 1331, 1289, 1262, 1232, 1158, 1146, 1105, 1007, 861, 771 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.60 (s, 1H), 6.53 (s, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.53 (app d, J = 11.8 Hz, 1H), 3.32 (dd, J = 11.6, 6.2 Hz, 1H), 3.19–3.05 (comp, 2H), 2.87 (dd, J = 13.6, 2.8 Hz, 1H), 2.77–2.68 (m, 1H), 2.67–2.49 (comp, 3H), 2.38 (app t, J = 11.6 Hz, 1H), 1.93–1.81 (m, 1H), 1.29–1.17 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.5, 147.8, 147.4, 128.2, 125.9, 111.4, 107.7, 62.3, 60.5, 55.9, 55.8, 50.8, 50.4, 47.3, 29.1, 19.2, 11.6; m/z (ESI–MS) 322.1 [M + H + MeOH]⁺.

12-trans-3-ethyl-3,4,6,7-tetrahydro-1H-[1,3]dioxolo[4,5-g]pyrido[2,1-a]isoquinolin-2(12bH)-one (1j): Following the general procedure compound 1j was obtained from 6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (133 mg) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 44% yield (60 mg, 7:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rᵣ = 0.51 in hexanes/EtOAc 60:40 v/v); mp: 143–145 °C; IR (KBr) 3046, 2965, 2926, 2836, 2755, 1709, 1489, 1382, 1347, 1285, 1235, 1142, 1030, 921, 899, 869, 795, 753 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 6.57 (s, 1H), 6.52 (s, 1H), 5.89 (s, 2H), 3.52–3.45 (m, 1H), 3.30 (dd, J = 11.5, 6.2 Hz, 1H), 3.16–3.03 (comp, 2H), 2.81 (dd, J = 13.7, 3.0 Hz, 1H), 2.74–2.66 (m, 1H), 2.65–2.53 (comp, 2H), 2.49 (app t, J = 13.0 Hz, 1H), 2.36 (app t, J = 11.5 Hz, 1H), 1.93–1.82 (m, 1H), 1.30–1.18 (m, 1H), 0.94 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.3, 146.3, 146.2, 129.5, 127.1, 108.5, 104.9, 100.8, 62.6, 60.5, 50.8, 50.4, 47.4, 29.7, 19.2, 11.6; m/z (ESI–MS) 306.1 [M + H + MeOH]⁺.

12-trans-3-ethyl-12-methyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolinizin-2(12H)-one (1k): Following the general procedure compound 1k was obtained from 9-methyltryptoline (140 mg) and 2-ethyl-3-oxobutyaldehyde (57 mg) in 45% yield (64 mg, 8:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rᵣ = 0.51 in hexanes/EtOAc 60:40 v/v); mp: 177–178 °C; IR (KBr) 3046, 2958, 2923, 2876, 2835, 2803, 1701, 1471, 1425, 1380, 1363, 1316, 1299, 1283, 1184, 1150, 1087, 1000, 736, 696 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.53 (d, J = 7.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.15–7.10 (m, 1H), 4.10 (dd, J = 11.4, 2.8 Hz, 1H), 3.64 (s, 3H), 3.48 (dd, J = 12.9, 6.1 Hz, 1H), 3.38–3.30 (m, 1H), 3.07–2.90 (comp, 3H), 2.85 (app t, J = 12.9 Hz, 1H), 2.77 (dd, J = 13.6, 3.2 Hz, 1H), 2.73–2.58 (comp, 2H), 1.97–1.86 (m, 1H), 1.34–1.21 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.0, 137.6, 135.0, 126.3,
11-trans-3-butyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11b H)-one (II): Following the general procedure compound II was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-n-butyl-3-oxobutyaldehyde (71 mg) in 56% yield (89 mg, 13:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.4 in hexanes/EtOAc 60:40 v/v); mp: 110–111 °C; IR (KBr) 2960, 2854, 2760, 1701, 1610, 1514, 1466, 1408, 1363, 1297, 1248, 1220, 1144, 1109, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.59 (s, 1H), 6.52 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.48 (dd, J = 12.0, 2.2 Hz, 1H), 3.29 (dd, J = 12.0, 6.3 Hz, 1H), 3.17–3.03 (comp, 2H), 2.86 (dd, J = 13.6, 3.0 Hz, 1H), 2.76–2.45 (comp, 4H), 2.35 (app t, J = 11.7 Hz, 1H), 1.91–1.80 (m, 1H), 1.43–1.24 (comp, 4H), 1.21–1.11 (m, 1H), 0.95–0.86 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 209.8, 147.7, 147.3, 128.4, 126.0, 111.3, 107.7, 62.3, 61.0, 55.8, 55.7, 50.4, 49.4, 47.4, 29.3, 29.2, 25.7, 22.7, 13.9; m/z (ESI–MS) 318.3 [M + H⁺].

11-trans-3-isobutyl-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11bH)-one (1m): Following the general procedure compound 1m was obtained from THIQ (95 µL) and 2-i-butyl-3-oxobutyaldehyde (71 mg) as a yellow oil in 34% yield (44 mg, 3:1 mixture of two diastereomers) (Rf = 0.41 in hexanes/EtOAc 90:10 v/v); IR (KBr) 3061, 3019, 2954, 2920, 2866, 2806, 2757, 1712, 1630, 1585, 1550, 1490, 1466, 1367, 1297, 1247, 1220, 1144, 1109, 742 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (Note: due to overlapping peaks, integration values of the diastereomers are reported together) 7.21–7.11 (comp, 3.14H), 7.11–7.05 (comp, 1.14H), 3.64–3.50 (comp, 1.21H), 3.30 (dd, J = 11.5, 6.3 Hz, 1H00H), 3.26–3.11 (comp, 2.09H), 3.07–2.70 (comp, 4.18H), 2.69–2.50 (comp, 2.63H), 2.36 (app t, J = 11.7 Hz, 1.04H), 1.86–1.74 (comp, 1.29H), 1.73–1.60 (comp, 1.11H), 1.59–1.48 (m, 0.59H), 1.09–0.99 (m, 1.08H), 0.99–0.82 (comp, 6.83H); ¹³C NMR of the diastereomers (125 MHz, CDCl₃) δ 209.7, 136.5, 133.8, 128.9(5), 128.8(9), 126.6, 126.5, 126.1, 124.8, 124.7, 62.6, 61.4, 50.4, 47.4, 47.2, 35.0, 29.6, 25.7, 25.3, 23.2, 22.6, 22.3, 22.0; m/z (ESI–MS) 290.1 [M + H + MeOH⁺].

11-trans-3-benzyl-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrido[2,1-a]isoquinolin-2(11b H)-one (1o): Following the general procedure compound 1o was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-benzyl-3-oxobutyraldehyde (88 mg) in 60% yield (105 mg, 6.5:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (Rf = 0.39 in hexanes/EtOAc 60:40 v/v); mp: 114–117 °C; IR (KBr) 3009, 2930, 2834, 2809, 2761, 1701, 1611, 1514, 1465, 1453, 1366, 1328, 1256, 1228, 1151, 1112, 1098, 1028, 1010, 911, 857, 766, 735, 704 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.31–7.25 (comp, 2H), 7.23–7.15 (comp, 3H), 6.59 (s, 1H), 6.54 (s, 1H), 3.82(5) (s, 3H), 3.81(6) (s, 3H), 3.56–3.49 (m, 1H), 3.33 (dd, J = 14.2, 4.4 Hz, 1H), 3.13
(dd, J = 11.6, 6.2 Hz, 1H), 3.08–2.91 (comp, 4H), 2.73–2.61 (m, 1H), 2.61–2.48 (comp, 2H), 2.47–2.34 (comp, 2H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 208.8, 147.6, 147.3, 139.3, 128.8, 128.3, 128.2, 126.0, 125.9, 111.3, 107.7, 62.2, 60.3, 55.8, 55.7, 50.9, 50.2, 47.3, 32.4, 29.1; m/z (ESI–MS) 384.0 [M + H + MeOH]\\(^+\).

12-trans-3-benzyl-12-methyl-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizin-2(12H)-one (1p): Following the general procedure compound 1p was obtained from 9-methyltryptoline (140 mg) and 2-benzyl-3-oxobutyraldehyde (88 mg) in 53% yield (91 mg, 8:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow oil (R\(_f\) = 0.47 in hexanes/EtOAc 70:30 v/v); IR (KBr) 3057, 3027, 2950, 2918, 2843, 1701, 1496, 1470, 1454, 1421, 1385, 1338, 1309, 1273, 1216, 1188, 1142, 1077, 1031, 1013, 910, 737, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.54–7.50 (m, 1H), 7.37–7.31 (comp, 2H), 7.31–7.21 (comp, 5H), 7.16–7.11 (m, 1H), 4.12 (dd, J = 11.6, 2.6 Hz, 1H), 3.65 (s, 3H), 3.41–3.33 (comp, 2H), 3.24 (dd, J = 11.0, 6.2 Hz, 1H), 3.06–2.98 (m, 1H), 2.96–2.79 (comp, 5H), 2.74 (app t, J = 12.1 Hz, 1H), 2.46 (dd, J = 14.3, 8.8 Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 208.2, 139.4, 137.6, 134.8, 128.9, 128.5, 126.3, 126.2, 118.2, 108.9, 107.8, 60.1, 57.8, 49.4, 47.3, 45.2, 32.4, 30.4, 22.2; m/z (ESI–MS) 377.1 [M + H + MeOH]\\(^+\).

11-trans-(4-(benzoxyl)butyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-1H-pyrdo[2,1-a]isoxquinolin-2(11bH)-one (1q): Following the general procedure compound 1q was obtained from 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (145 mg) and 2-(4-benzoxyl)butyl-3-oxobutyraldehyde (124 mg) in 57% yield (121 mg, 5:1 mixture of two diastereomers). The major diastereomer was isolated as a yellow solid (R\(_f\) = 0.23 in hexanes/EtOAc 60:40 v/v); mp: 101–103 °C; IR (KBr) 2992, 2940, 2849, 1702, 1609, 1517, 1463, 1367, 1328, 1291, 1262, 1210, 1156, 1141, 1100, 1011, 867, 734 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) 7.37–7.30 (comp, 4H), 7.30–7.24 (m, 1H), 6.61 (s, 1H), 6.54 (s, 1H), 4.50 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.51–3.46 (comp, 3H), 3.31 (dd, J = 11.4, 6.2 Hz, 1H), 3.17–3.05 (comp, 2H), 2.88 (dd, J = 13.6, 2.4 Hz, 1H), 2.77–2.63 (comp, 2H), 2.63–2.47 (comp, 2H), 2.38 (app t, J = 11.8 Hz, 1H), 1.95–1.83 (m, 1H), 1.72–1.56 (comp, 2H), 1.50–1.36 (comp, 2H), 1.28–1.14 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 209.7, 147.8, 147.4, 138.6, 128.4, 128.3, 127.6, 127.5, 126.0, 111.4, 107.8, 72.9, 70.1, 62.3, 61.0, 55.9, 55.8, 50.4, 49.4, 47.5, 29.9, 29.3, 25.9, 23.8; m/z (ESI–MS) 456.0 (\(^{35}\)Cl/\(^{37}\)Cl) [M + H + MeOH]\\(^+\).
2D-NMR Analysis for Compound cis-1g, Selected Interactions:

| Proton | Chemical Shift (ppm) |
|--------|----------------------|
| H1, H2 | 7.60–7.52            |
| H3     | 4.34                 |
| H4     | 3.99                 |
| H5     | 2.93                 |
| H6     | 2.51                 |
| Me1    | 1.10                 |
| Me2    | 1.01                 |

$^1$H NMR shifts
References:
(1) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573.
(2) Kikuchi, C.; Ando, T.; Watanabe, T.; Nagaso, H.; Okuno, M.; Hiranuma, T.; Koyama, M. *J. Med. Chem.* **2002**, *45*, 2197.
(3) Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1966**, *32*, 404.
(4) Lovechik, M. A.; Goike, A.; Frater, G. *J. Org. Chem.* **2007**, *72*, 2427.
(5) Fujita, T.; Sakoda, K.; Ikeda, M.; Hattori, M.; Ichikawa, J. *Synlett* **2013**, *24*, 57.
(6) Frankowski, K. J.; Golden, J. E.; Zeng, Y.; Lei, Y.; Aubé, J. *J. Am. Soc. Chem.** 2008**, *130*, 6018.
(7) Sun, X.; Zhu, R.; Li, G.; Ma, X.; Gu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 9318.
(8) Yao, Z.; Wei, X.; Wu, X.; Katz, J. L.; Kopajtic, T.; Greig, N. H.; Sun, H. *Eur. J. Med. Chem.* **2011**, *46*, 1841.
(9) a) Nakamura, K.; Miyai, T.; Nagar, A.; Oka, S.; Ohno, A. *Bull. Chem. Soc, Jpn.* **1989**, *62*, 1179; b) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532; c) Biju, A. T.; Padmanaban, M.; Wurz, N. E.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8412; d) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2011**, *133*, 8834.
(10) Bastian, J. A.; Lash, T. D. *Tetrahedron*, **1988**, *54*, 6299.
(11) Martin, V. A.; Murray, D. H.; Pratt, N. E.; Zhao, Y.; Albizati, K. F. *J. Am. Chem. Soc.* **1990**, *112*, 6965.
(12) Riva, R.; Banfi, L.; Basso, A.; Zito, P. *Org. Biomol. Chem.* **2011**, *9*, 2107.
(13) Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 857.
$^{13}$C NMR of 4e in CDCl$_3$
$^1$H NMR of 6b in CDCl$_3$
$^{13}$C NMR of 6b in CDCl$_3$
$^{13}$C NMR of 6c in CDCl$_3$
$^1$H NMR of 6e in CDCl$_3$
$^{13}$C NMR of 6e in CDCl$_3$
$^1\text{H NMR of 8a in CDCl}_3$
$^{13}$C NMR of 8a in CDCl$_3$
$^1$H NMR of 8b in CDCl$_3$
$^{13}$C NMR of 8b in CDCl$_3$
$^1$H NMR of 8c in CDCl$_3$
$^{13}$C NMR of 8c in CDCl$_3$
$^1$H NMR of 8d in CDCl$_3$
$^{13}$C NMR of 8d in CDCl$_3$
$^1$H NMR of 8e in CDCl$_3$
$^1$H NMR of 1a in CDCl$_3$
$^{13}$C NMR of 1a in CDCl$_3$
$^1$H NMR of 1b in CDCl$_3$
$^1$H NMR of 1b in CDCl$_3$,

MeO

MeO

Me

Me

$^1$C NMR of 1b in CDCl$_3$,

147.49
147.25
128.58
126.34
111.28
107.56
77.42
77.00
76.57
67.74
62.44
55.78
55.70
51.37
45.89
44.49
29.21
25.58
21.40
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

S 35
$^1$H NMR of 1c in CDCl$_3$
$^{13}$C NMR of 1c in CDCl$_3$
$^1$H NMR of 1d in CDCl$_3$
$^{13}$C NMR of 1d in CDCl$_3$
$^1$H NMR of 1e in CDCl$_3$
$^{13}$C NMR of 1e in CDCl₃
$^1$H NMR of 1f in CDCl$_3$
$^{13}$C NMR of 1f in CDCl$_3$
$^1$H NMR of cis-1g in CDCl$_3$
$^{13}$C NMR of cis-1g in CDCl$_3$
\(^1\)H NMR of trans-1g in CDCl\(_3\)
$^{13}$C NMR of trans-1g in CDCl$_3$
$^1$H NMR of 1h in CDCl$_3$
$^{13}$C NMR of 1h in CDCl$_3$
$^1$H NMR of 1i in CDCl$_3$
$^{13}$C NMR of 11 in CDCl$_3$
$^1$H NMR of 1j in CDCl$_3$
$^{13}$C NMR of 1j in CDCl$_3$
$^{13}$C NMR of 1k in CDCl$_3$
$^1$H NMR of 11 in CDCl$_3$
$^{13}$C NMR of 1I in CDCl$_3$
$^1$H NMR of 1m in CDCl$_3$
$^{13}$C NMR of 1m in CDCl$_3$
$^1$H NMR of 1o in CDCl$_3$
\(^{13}\text{C NMR of 1o in CDCl}_3\)
$^1$H NMR of 1p in CDCl$_3$
$^{13}$C NMR of 1p in CDCl$_3$
$^1$H NMR of 1q in CDCl$_3$
$^{13}$C NMR of \textit{1q} in CDCl$_3$
GCOSY of cld-1g in CDCl₃
