Supporting Information
for
The Grob/Eschenmoser Fragmentation of Cycloalkanones Bearing
β-Electron Withdrawing Groups: A General Strategy to Acyclic
Synthetic Intermediates

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I. General Procedures

For general experimental information as well as the synthesis and characterization of all new compounds see full paper.

II. Preparation of fragmentation precursors 1

a. Alkylation following the procedure of Beckwith (1a, 1b, 1d, 1g-1l, 1o, 1p)

NaH (48 mg of a 60% dispersion in mineral oil, 1.2 mmol) was washed twice with hexane, residual hexane removed under reduced pressure, and then suspended in dry DMSO (5 mL). A solution of β-ketoester (1.0 mmol) in dry DMSO (2.5 mL) was added dropwise and the resulting mixture stirred for 15 min or until gas development ceased. Then a solution of dihalomethane (2 mmol) in dry DMSO (2.5 mL) was added dropwise and the reaction mixture stirred at room temperature for 14 h. H2O (10 mL) was added and the product extracted with EtOAc (3 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried (MgSO4) and concentrated under reduced pressure. The resultant oil was purified via flash column chromatography.

Ethyl 1-(iodomethyl)-2-oxocyclohexanecarboxylate (1a). Rf 0.5 (1:3, v/v EtOAc:hexane); IR νmax 2943, 2867, 1713, 1646, 1490, 1228, 1249, 1213, 1158, 1019; 1H-NMR (400 MHz, CDCl3) δ 1.24 (t, J = 7.0 Hz, 3H), 1.48-1.56 (m, 1H), 1.59-1.69 (m, 1H), 1.72-1.80 (m, 2H), 1.94-2.01 (m, 1H), 2.41 (dd, J = 9.0 Hz, 5.5 Hz, 2H), 2.57-2.63 (m, 1H), 3.29 (d, J = 10.5 Hz, 1H), 3.56 (d, J = 10.5 Hz, 1H), 4.14-4.25 (m, 2H); 13C-NMR (100 MHz, CDCl3) δ 8.60, 14.18, 22.32, 27.43, 37.24, 40.85, 60.72, 62.03, 168.95, 205.32.

Ethyl 1-(bromomethyl)-2-oxocyclohexanecarboxylate (1b). Rf 0.6 (3:7, v/v EtOAc:hexane); IR νmax 2952, 2868, 1714, 1438, 1286, 1267, 1240, 1197, 1175; 1H-

NMR (400 MHz, CDCl₃) δ 1.26 (t, J = 7.0 Hz, 3H), 1.53-1.61 (m, 1H), 1.62-1.80 (m, 1H), 1.87-1.98 (m, 2H), 2.01-2.07 (m, 1H), 2.41-2.45 (m, 2H), 2.67 (dq, J = 14.0 Hz, 3.5 Hz, 1H), 3.50 (d, J = 11.0 Hz, 1H), 3.82 (d, J = 11.0 Hz, 1H), 4.15-4.28 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 14.81, 22.22, 27.42, 35.41, 35.60, 41.02, 61.54, 62.08, 168.99, 205.64.

**Ethyl 1-(iodomethyl)-2-oxocyclopentanecarboxylate** (1g). Rₐ 0.5 (1:3, v/v EtOAc:hexane); IR νₘₐₓ 2979, 2904, 1754, 1725, 1446, 1277, 1233, 1206, 1183, 1122, 1026; ¹H-NMR (400 MHz, CDCl₃) δ 1.24 (t, J = 7.0 Hz, 3H), 1.93-2.02 (m, 1H), 2.03-2.12 (m, 2H), 2.29-2.38 (m, 1H), 2.42-2.49 (m, 1H), 2.55-2.62 (m, 1H), 3.33 (d, J = 10.0 Hz, 1H), 3.57 (d, J = 10.0 Hz, 1H), 4.11-4.23 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ 7.21, 14.13, 19.18, 34.78, 38.13, 60.95, 62.19, 168.37, 211.00.

**Methyl 1-(iodomethyl)-2-oxocycloheptanecarboxylate** (1j). Rₐ 0.7 (4:1, v/v CH₂Cl₂:hexane); IR νₘₐₓ 2934, 2859, 1740, 1709, 1454, 1267, 1235, 1192, 1163, 1143; ¹H-NMR (400 MHz, CDCl₃) δ 1.29-1.38 (m, 1H), 1.54-1.63 (m, 3H), 1.70-1.78 (m, 2H), 1.98 (ddd, J = 15.0 Hz, 9.5 Hz, 1.5 Hz, 1H), 2.25 (ddt, J = 15.0 Hz, 9.5 Hz, 1.0 Hz, 1H), 2.43-2.49 (m, 1H), 2.65-2.71 (m, 1H), 3.29 (d, J = 10.5 Hz, 1H), 3.72 (s, 3H), 3.75 (dd, J = 10.5 Hz, 1.0 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 9.83, 24.58, 25.78, 29.91, 33.31, 42.04, 52.97, 63.92, 170.08, 206.39.

**Ethyl 2-(iodomethyl)-1-oxo-2,3-dihydro-1H-indene-2-carboxylate** (1l). Rₐ 0.7 (CH₂Cl₂); IR νₘₐₓ 3036, 2980, 2936, 1714, 1607, 1589, 1465, 1417, 1251, 1209; ¹H-NMR (400 MHz, CDCl₃) δ 1.22 (t, J = 7.0 Hz, 3H), 3.25 (t, J = 7.0 Hz, 3H), 3.53 (d, J = 10.0 Hz, 1H), 3.80 (d, J = 17.5 Hz, 1H), 3.82 (d, J = 10.0 Hz, 1H), 4.14-4.22 (m, 2H), 7.40 (td, J = 7.5 Hz, 1.0 Hz, 1H), 7.51 (dt, J = 7.5 Hz, 1.0 Hz, 1H), 7.65 (td, J = 7.5 Hz, 1.0 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H); ¹³C-NMR (100 MHz, CDCl₃) δ 7.70, 14.11, 39.11, 61.34, 62.48, 125.32, 126.53, 128.11, 134.70, 135.96, 152.90, 168.34, 198.94; HRMS Found (M+H)+ 344.9982, C₁₃H₁₃IO₃ requires (M+H)+ 344.9988.

**Ethyl 5-(tert-butyldimethylsilyloxy)-1-(iodomethyl)-2-oxocyclohexanecarboxylate** (1p). Rₐ 0.7 (CH₂Cl₂); IR νₘₐₓ 2954, 2930, 2857, 1737, 1721, 1472, 1464, 1257, 1099; ¹H-NMR (400 MHz, CDCl₃) δ diastereomer 1: 0.11 (s, 3H), 0.13 (s, 3H), 0.91 (s, 9H), 1.29 (t, J = 7.0 Hz, 3H), 1.66-2.72 (m, 7H), 3.40 (d, J = 10.0 Hz, 1H), 3.64 (d, J = 10.0 Hz, 1H), 4.18-4.25 (m, 2H) diastereomer 2: 0.08 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 1.26 (t, J = 7.0 Hz, 3H), 1.66-2.72 (m, 6H), 3.12 (td, J = 14.0 Hz, 6.0 Hz, 1H), 3.29 (d, J = 10.0 Hz, 1H), 3.49 (d, J = 10.0 Hz, 1H), 4.18-4.25 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃) δ diastereomer 1: -4.76, -4.52, 8.93, 14.25, 18.22, 25.97, 35.16, 37.30, 44.02, 59.85, 62.40, 66.69, 168.98, 203.94 diastereomer 2: -4.98, 8.83, 14.09, 18.42, 25.97, 34.46, 35.52, 44.65, 57.34, 62.04, 65.78, 169.73, 205.56; HRMS Found (M+H)+ 441.0950, C₁₆H₂₉JO₃Si requires (M+H)+ 441.0958; found (M+Na)+ 463.0769, requires (M+Na)+ 463.0777.
b. Alkylation following the procedure of Mu$^2$ (1f, 1m)

The 1,3-dicarbonyl (1.0 mmol), anhydrous potassium carbonate (276 mg, 2.0 mmol) and tetrabutylammonium bromide (129 mg, 0.4 mmol) were refluxed in dry toluene (5 mL) for 5 h. The reaction mixture was cooled to 40°C, dihaloalkane (1.1 mmol) was added and the mixture stirred for 2 h at 40°C followed by another 2 h at reflux. After cooling to room temperature the reaction mixture was filtered, the filter cake washed with Et$_2$O (5 mL) and the filtrate concentrated under reduced pressure. The resultant oil was purified via flash column chromatography.

Ethyl 2-(iodomethyl)-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (1m).

R$_f$ 0.4 (1:4, v/v EtOAc: hexane); IR $\nu$ max 2980, 2936, 1731, 1682, 1601, 1454, 1293, 1235, 1201, 1016; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.21 (t, $J$ = 7.0 Hz, 3H), 2.39 (ddd, $J$ = 14.0 Hz, 9.0 Hz, 5.0 Hz, 1H), 2.65 (ddd, $J$ = 14.0 Hz, 6.0 Hz, 5.0 Hz, 1H), 2.96 (dt, $J$ = 17.0 Hz, 5.0 Hz, 1H), 3.14 (ddd, $J$ = 17.0 Hz, 9.0 Hz, 5.0 Hz, 1H), 3.66 (d, $J$ = 10.4 Hz, 1H), 3.72 (d, $J$ = 10.4 Hz, 1H), 4.16-4.22 (m, 2H), 7.23 (d, $J$ = 7.6 Hz, 1H), 7.31 (t, $J$ = 7.6 Hz, 1H), 7.49 (dt, 7.6 Hz, 1.2 Hz, 1H) 8.03 (dd, $J$ = 7.6 Hz, 1.2 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) $\delta$ 7.49, 14.14, 25.49, 32.65, 57.65, 62.15, 127.10, 128.34, 128.96, 131.32, 134.09, 143.10, 168.95, 192.37.

c. Synthesis of Mesylates 1e and 1f$^3$

To a solution of Fe(acac)$_3$ (35 mg, 0.1 mmol) and benzaldehyde (20 $\mu$L, 0.2 mmol) in dry MeOH (2.5 mL) was slowly added H$_2$O$_2$ (170 $\mu$L of a 30% solution, 1.5 mmol) at 0°C. The resulting red-brown mixture was stirred for 40 min at room temperature, then the respective ketone (1.0 mmol) was added and the solution stirred for 3-15 h. Hydrolysis with NaHCO$_3$ (10 mL of a saturated aqueous solution) was followed by extraction of the product with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried (MgSO$_4$) and concentrated. The resultant oil was purified immediately via flash column chromatography. To a solution of the thus prepared alcohol (1.0 mmol), NEt$_3$ (167 $\mu$L, 1.2 mmol) and DMAP (12 mg, 0.1 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C was added methanesulfonyl chloride (93 $\mu$L, 1.2 mmol). The mixture was stirred for 30 min at 0°C followed by 2 h at room temperature. Evaporation of the solvent and column chromatography (EtOAc:hexane) yielded pure mesylate.

Ethyl 1-(hydroxymethyl)-2-oxocyclohexancarboxylate. R$_f$ 0.1 (1:4, v/v EtOAc:hexane); IR $\nu$ max 3536, 2941, 2870, 1709, 1451, 1205, 1026; $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.26 (t, $J$ = 7.0 Hz, 3H), 1.55-1.66 (m, 2H), 1.76-1.80 (m, 1H), 1.98-2.05 (m, 1H), 2.31-2.35 (m, 1H), 2.40-2.46 (m, 1H), 2.56-2.65 (m, 1H), 2.81-2.85 (m, 1H), 3.69 (dd, $J$ = 11.0 Hz, 2 X.-J. Mu, J.-P. Zou, Z.-T. Wang and W. Zhang, *Tetrahedron Lett.*, 2005, 46, 4727.

Hz, 9.0 Hz, 1H), 3.80 (dd, J = 11.0 Hz, 4.5 Hz, 1H), 4.23 (qd, J = 7.0 Hz, 1.0 Hz, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 14.22, 22.08, 27.05, 32.91, 41.08, 61.73, 62.71, 66.52, 171.32, 210.76.

1-(Hydroxymethyl)-2-oxocyclohexanecarbonitrile. R$_f$ 0.2 (3:7, v/v EtOAc: hexane); IR $\nu_{max}$ 3444, 2948, 2871, 2247, 1727, 1715, 1061; $^1$H-NMR (400 MHz, CDCl$_3$) δ 1.66-1.77 (m, 1H), 1.78-1.86 (m, 1H), 1.88-1.93 (m, 1H), 2.02-2.08 (m, 1H), 2.10-2.17 (m, 1H), 2.24-2.30 (m, 1H), 2.44-2.49 (m, 1H), 2.75-2.83 (m, 1H), 2.86 (br t, J = 7.0 Hz 1H), 3.80 (dd, J = 11.5 Hz, 7.0 Hz, 1H), 3.87 (dd, J = 11.5 Hz, 7.0 Hz, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 21.79, 27.61, 34.69, 39.62, 53.00, 64.03, 118.58, 204.42.
III. $^1$H and $^{13}$C NMR of new compounds

Ethyl 1-(((methylsulfonyl)oxy)methyl)-2-oxocyclohexanecarboxylate (1c)
Ethyl 1-(diiodomethyl)-2-oxocyclohexanecarboxylate (1d)
(1-Cyano-2-oxocyclohexyl)methyl methanesulfonate (1e)
2-Benzoyl-2-(iodomethyl)cyclohexanone (1f)
Ethyl 1-(iodomethyl)-2-oxocyclododecanecarboxylate (1k)
Ethyl 1-(iodomethyl)-3-methyl-2-oxocyclohexanecarboxylate (1o)
1-Ethyl 7-isobutyl 2-methyleneheptanedioate (5a, Table 2, entry 1)
1-Benzyl 7-ethyl 2-methyleneheptanedioate (5a, Table 2, entry 2)
7-Butyl 1-ethyl 2-methyleneheptanedioate (5a, Table 2, entry 3)
1-Ethyl 7-isopropyl 2-methyleneheptenedioate (5a, Table 2, entry 5a)
Diisopropyl 2-methyleneheptanedioate (5a, Table 2, entry 5b)
Ethyl 7-(benzylamino)-2-methylene-7-oxoheptanoate (5a, Table 2, entry 7a)
Ethyl 7-(4-methoxybenzylamino)-2-methylene-7-oxoheptanoate (5a, Table 2, entry 7b)
Ethyl 2-methylene-7-oxo-7-(1-phenylethylamino)heptanoate (5a, Table 2, entry 7c)
6-(Ethoxycarbonyl)hept-6-enoic acid (5a, Table 2, entry 8a)
Ethyl 7-hydroxy-2-methyleneheptanoate (5b)
(E)-Diethyl 2-(iodomethylene)heptanedioate (5d)
(Z)-Diethyl 2-(iodomethylene)heptanedioate (5d)
Ethyl 6-cyanohept-6-enoate (5e)
**Ethyl 6-benzoylhept-6-enoate (5f)**
**Ethyl 6-(benzyl(methyl)amino)-2-methylene-6-oxohexanoate (5h)**

![Chemical Structure]

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**Supplementary Material (ESI) for Organic & Biomolecular Chemistry**
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Ethyl 6-(dibenzylamino)-2-methylene-6-oxohexanoate (5i)
Diethyl 2-methylenetridecanedioate (5k)
Ethyl 2-(3-(ethoxycarbonyl)but-3-enyl)benzoate (5m)
Ethyl 4-(2-(4-methoxybenzylcarbamoyl)phenyl)-2-methylenebutanoate (5n)
Diethyl 2-methyl-6-methyleneheptanedioate (5o)
Diethyl 4-((tert-butyldimethylsilyloxy)-2-methyleneheptanedioate (5p)
4-((tert-Butyldimethylsilyl)oxy)-6-(ethoxycarbonyl)hept-6-enoic acid (5r)
Ethyl 2-((5-oxotetrahydrofuran-2-yl)methyl)acrylate (8)
3-(4-Methylene-5-oxotetrahydrofuran-2-yl)propanoic acid (9)