Supporting Information

One-Pot Sequential 1,4- and 1,2-Reducions of α,β-Unsaturated δ-Lactones to the Corresponding δ-Lactols with CuCl and NaBH₄ in Methanol

Yasunobu Matsumoto,* Masahiro Yonaga
Graduate School of Pharmaceutical Sciences, University of Tokyo 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Discovery Research Laboratories, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan
Fax: +81(0)298472037, E-mail: y7-matsumoto@hhc.eisai.co.jp

Table of Contents

<table>
<thead>
<tr>
<th></th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Information</td>
<td>S1</td>
</tr>
<tr>
<td>Experimental Data</td>
<td></td>
</tr>
<tr>
<td>· General Procedure</td>
<td>S2 – S5</td>
</tr>
<tr>
<td>· Preparation of</td>
<td>S6 – S20</td>
</tr>
<tr>
<td>· Preparation of</td>
<td>S21 – S22</td>
</tr>
<tr>
<td>· Computational Study</td>
<td>S23 – S24</td>
</tr>
<tr>
<td>¹H and ¹³C Spectra</td>
<td>S25 – S59</td>
</tr>
<tr>
<td>Reference</td>
<td>S60 – S61</td>
</tr>
</tbody>
</table>

General Information

¹H, ¹³C NMR spectra were recorded on a JEOL ECA-400, ECX-400 or Bruker Avance 600 MHz spectrometer. Chemical shifts for ¹H-NMR were reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in Hertz (Hz). The following abbreviations are used for spin multiplicity: s= singlet, d= doublet, t= quartet, m= multiplet and br= broad. Chemical shifts for ¹³C-NMR were reported in parts per million (ppm), relative to the central line of the triplet for CDCl₃ at 77.0 ppm or the central line of the triplet for (CD₃)₂CO at 205.87 ppm. High-resolution mass spectral analyses (HRMS) were carried out using LTQ Orbitrap XL (Thermo Fisher Scientific) and GCT premier (Waters). FT-IR spectra were recorded on a FT/IR-620 (JASCO) with attenuated total reflection (ATR) method.
Experimental data

General Procedure for Reduction of α,β-Unsaturated δ-Lactones into δ-Lactols:
NaBH₄ (10 mmol, 10 equiv) was added in three roughly equal portions to a stirred solution of an α,β-unsaturated δ-lactone (1.0 mmol) in MeOH (10 mL; lactone concentration, 0.1 M) at −50 °C in a reaction flask connected to a drying tube containing calcium carbonate. After the solution was stirred for 15 min at −50 °C, the drying tube was removed, and CuCl (0.5 mmol, 0.5 equiv) was added to the reaction mixture, which immediately turned into a black suspension and evolved H₂ gas (the flask was kept open to let out the gas). The reaction temperature was warmed to −20 °C over the course of 1 h, and the reaction was quenched at that temperature with saturated aqueous NH₄Cl. Then EtOAc and water were added to the mixture, which was vigorously stirred for 30 min at room temperature. The resulting clear solution was extracted with EtOAc, and the combined organic layers were washed with brine, dried over MgSO₄, and concentrated \textit{in vacuo}. The crude mixture of products was purified by silica gel flash column chromatography with gradient of EtOAc and n-heptane as eluents to afford the desired δ-lactol.

6-benzyltetrahydro-2H-pyran-2-ol (5b)
White solid (90%, cis:trans= 1.4:1); ¹H-NMR (600 MHz, CDCl₃) δ 7.30-7.27 (m, 4H, cis trans), 7.22-7.20 (m, 6H, cis trans), 5.28 (brs, 1H, trans), 4.66 (m, 1H, cis), 4.19 (m, 1H, trans), 3.64 (m, 1H, cis), 3.06 (d, J = 4.0 Hz, 1H, cis-OH), 2.95 (dd, J = 14.0, 7.0 Hz, 1H, cis), 2.81 (dd, J = 14.0, 7.0 Hz, 1H, trans), 2.73 (dd, J = 14.0, 7.0 Hz, 1H, cis), 2.67 (dd, J = 14.0, 7.0 Hz, 1H, trans), 2.55 (brs, 1H, trans-OH), 1.87-1.80 (m, 3H, cis trans), 1.71-1.42 (m, 6H, cis trans), 1.35-1.28 (m, 2H, cis trans), 1.25-1.18 (m, 1H, cis); ¹³C-NMR (150 MHz, CDCl₃) δ 138.7 (trans), 138.5 (cis), 129.4 (cis), 129.4 (trans), 128.2 (cis), 128.2 (trans), 126.2 (cis), 126.1 (trans), 96.5 (cis), 92.0 (trans), 77.3 (cis), 69.7 (trans), 42.8 (trans), 42.6 (cis), 32.5 (cis), 30.9 (trans), 30.0 (cis), 29.6 (trans), 21.9 (cis), 17.3 (trans); IR (ATR) ν 3318, 2942, 2861, 1353, 1142, 1047, 1010, 903, 746, 700 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₂₀NO₂ ([M+NH₄]⁺): 210.1489, found: 210.1489.

3-benzyltetrahydro-2H-pyran-2-ol (7a)
Colorless oil (92%, cis:trans= 1:1); ¹H-NMR (500 MHz, CDCl₃) δ 7.30-7.17 (m, 10H), 4.97 (t, J = 3.5 Hz, 1H), 4.52 (dd, J = 7.0, 6.0 Hz, 1H), 4.01-3.95 (m, 2H), 3.58-3.55 (m, 1H), 3.50 (ddd, J = 13.5, 10.5, 3.5 Hz, 1H), 3.07 (dd, J = 13.5, 4.5 Hz, 1H), 3.03 (d, J = 6.0 Hz, 1H), 2.71 (dd, J = 14.0, 7.5 Hz, 1H), 2.60 (dd, J = 3.5, 1.5 Hz, 1H), 2.51 (dd, J = 13.5, 1.5 Hz, 1H), 2.40 (dd, J = 13.5, 8.0 Hz, 1H), 1.98-1.92 (m, 1H), 1.77-1.44 (m, 8H), 1.23-1.16 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 140.1, 139.7, 129.3, 129.1, 128.2, 125.9, 125.9, 98.9, 93.4, 65.3, 59.8, 43.3, 41.7, 38.0, 37.3, 26.5, 25.3, 24.6, 23.3; IR (ATR) ν 3376, 3026, 2939, 2854, 1496, 1454, 1069, 983, 747, 699 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₁₆NaO₂ ([M+Na]⁺): 215.1043, found: 215.1044.

4-benzyltetrahydro-2H-pyran-2-ol (7b)
Colorless oil (83%, cis:trans= 1:1); ¹H-NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 4H), 7.22-7.17 (m, 2H), 7.16-7.13 (m, 4H), 5.30 (brs, 1H), 4.63 (ddd, J = 9.0, 6.0, 2.0 Hz, 1H), 4.00 (m, 1H), 3.95 (m,
1H), 3.62 (dd, J = 11.5, 5.0, 2.0 Hz, 1H), 3.44 (dt, J = 12.0, 2.0 Hz, 1H), 2.98 (d, J = 6.0 Hz, 1H), 2.59-2.54 (m, 3H), 2.48-2.44 (m, 2H), 2.24-2.16 (m, 1H), 1.92-1.88 (m, 1H), 1.87-1.80 (m, 1H), 1.80-1.77 (m, 1H), 1.57-1.48 (m, 2H), 1.41-1.22 (m, 3H), 1.09 (ddd, J = 12.0, 12.0, 9.0 Hz, 1H); \[^{13}C\text{-NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 139.7, 139.6, 129.1, 128.3, 128.2, 125.9, 96.1, 91.6, 65.4, 59.6, 43.3, 43.0, 39.4, 36.7, 36.5, 31.8, 31.4, 30.5; \[^{1}\text{H}\text{-NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.26 (m, 4H), 7.21-7.18 (m, 2H), 7.16-7.13 (m, 4H), 5.16 (q, J = 3.0 Hz, 1H), 4.74 (ddd, J = 8.5, 5.5, 2.0 Hz, 1H), 3.97-3.93 (m, 1H), 3.71 (t, J = 11.0 Hz, 1H), 3.52 (dd, J = 11.5, 4.0 Hz, 1H), 3.24 (dd, J = 12.0, 10.0 Hz, 1H), 2.81 (d, J = 5.5 Hz, 1H), 2.58-2.41 (m, 5H), 1.92-1.83 (m, 4H), 1.77-1.56 (m, 4H), 1.42-1.35 (m, 1H), 1.27-1.23 (m, 1H); \[^{13}C\text{-NMR}\] (125 MHz, CDCl\(_3\)) \(\delta\) 139.8, 139.7, 129.0, 128.9, 128.4, 128.3, 126.1, 126.0, 96.1, 91.9, 70.1, 65.0, 38.8, 38.2, 37.0, 36.6, 32.0, 29.7, 27.9, 24.0; \[^{1}\text{H}\text{-NMR}\] (500 MHz, CDCl\(_3\)) \(\delta\) 8.01-7.98 (m, 4H), 7.40 (dd, J = 16.5, 9.0 Hz, 4H), 5.45 (brs, 1H), 5.06 (dd, J = 12.0, 2.5 Hz, 1H), 4.86 (ddd, J = 9.5, 6.0, 2.0 Hz, 1H), 4.51 (dd, J = 11.5, 2.0 Hz, 1H), 3.90 (s, 6H), 3.73 (brd, J = 4.5 Hz, 1H), 3.25 (brs, 1H), 2.10-2.02 (m, 1H), 1.96-1.63 (m, 7H), 1.54 (dq, J = 14.0, 4.0 Hz, 1H),
1.47-1.39 (m, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 167.0, 167.0, 148.2, 147.1, 129.6, 129.1, 129.0, 125.8, 125.7, 96.9, 92.2, 77.9, 70.5, 52.0, 33.7, 32.7, 32.2, 29.4, 22.4, 17.7; IR (ATR) ν 3354, 2948, 1721, 1612, 1435, 1275, 1109, 990, 762, 705 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{13}$H$_{20}$NO$_4$ ([M+NH$_4$]$^+$): 254.1387, found: 254.1385.

4-(6-hydroxytetrahydro-2H-pyran-2-yl)benzonitrile (7g)

White solid (80%, cis:trans= 1:1); $^1$H-NMR (500 MHz, CDCl$_3$) δ 7.64-7.61 (m, 4H), 7.47 (dd, $J = 17.0, 9.0$ Hz, 4H), 5.47 (bs, 1H), 5.07 (dd, $J = 11.5, 2.5$ Hz, 1H), 4.90 (ddd, $J = 9.5, 6.0, 2.0$ Hz, 1H), 2.13-2.03 (m, 1H), 2.02-1.95 (m, 2H), 1.88-1.67 (m, 6H), 1.56-1.34 (m, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 148.4, 147.2, 132.1, 126.5, 118.9, 110.9, 96.8, 92.2, 77.4, 70.2, 33.7, 32.7, 32.1, 29.3, 22.3, 17.6; IR (ATR) ν 3336, 2947, 2228, 1733, 1278, 1192, 1028, 980, 888, 829 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{12}$H$_{13}$NNaO$_2$ ([M+Na]$^+$): 226.0838, found: 226.0837.

Ethyl 3-(6-hydroxytetrahydro-2H-pyran-2-yl)propanoate (7h)

Colorless oil (88%, cis:trans= 1.5:1); $^1$H-NMR (600 MHz, CDCl$_3$) δ 5.28 (brs, 1H, trans), 4.69 (m, 1H, cis), 4.13 (q, $J = 7.0$ Hz, 4H, cis trans), 3.94 (m, 1H, trans), 3.42 (m, 1H, cis), 3.20 (d, $J = 3.5$ Hz, 1H, cis-OH), 2.70 (brs, 1H, trans-OH), 2.03 (s, 6H, cis trans), 1.36-1.13 (m, 9H, cis trans); $^{13}$C-NMR (150 MHz, CDCl$_3$) δ 173.8 (cis), 173.7 (trans), 96.4 (cis), 91.8 (trans), 75.2 (cis), 67.7 (trans), 60.3 (cis trans), 32.7 (cis), 31.1 (trans), 31.0 (trans), 30.9 (cis), 30.5 (trans), 29.7 (cis), 22.0 (cis), 17.4 (trans), 14.2 (cis trans); IR (ATR) ν 3422, 2939, 2869, 1732, 1443, 1372, 1269, 1181, 1030, 971 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{10}$H$_{19}$O$_4$ ([M+H]$^+$): 203.1278, found: 203.1278.

3-(6-hydroxytetrahydro-2H-pyran-2-yl)propyl acetate (7i)

Colorless oil (83%, cis:trans= 1.5:1); $^1$H-NMR (600 MHz, CDCl$_3$) δ 5.28 (bs, 1H, trans), 4.69 (m, 1H, cis), 4.07 (m, 4H, cis trans), 3.94 (m, 1H, trans), 3.42 (m, 1H, cis), 3.20 (d, $J = 3.5$ Hz, 1H, cis-OH), 2.70 (brs, 1H, trans-OH), 2.03 (s, 6H, cis trans), 1.32-1.14 (m, 3H, cis trans); $^{13}$C-NMR (150 MHz, CDCl$_3$) δ 171.2 (cis trans), 96.4 (cis), 91.8 (trans), 75.8 (cis), 68.1 (trans), 64.5 (trans), 64.4 (cis), 32.7 (cis), 32.4 (trans), 32.2 (cis), 31.2 (trans), 30.4 (cis), 29.7 (trans), 24.8 (cis), 24.7 (trans), 22.0 (cis), 21.0 (cis trans), 17.4 (trans); IR (ATR) ν 3417, 2939, 2866, 1736, 1441, 1366, 1236, 1032, 973, 903 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{10}$H$_{22}$NO$_4$ ([M+NH$_4$]$^+$): 220.1543, found: 220.1546.

6-allyltetrahydro-2H-pyran-2-ol (7j)

Colorless oil (70%, cis:trans= 1.4:1); $^1$H-NMR (600 MHz, CDCl$_3$) δ 5.87-5.77 (m, 2H, cis trans), 5.31 (brs, 1H, trans), 5.10-5.04 (m, 4H, cis trans), 4.71 (m, 1H, cis), 4.01 (m, 1H, trans), 3.48 (m, 1H, cis), 3.13 (d, $J = 6.0$ Hz, 1H, cis-OH), 2.61 (brs, 1H, trans-OH), 2.38-2.34 (m, 1H, cis), 2.26-2.22 (m, 2H, cis trans), 2.19-2.15 (m, 1H, trans), 1.91-1.84 (m, 3H, cis trans), 1.72-1.47 (m, 6H, cis trans).
1.33-1.15 (m, 3H, cis trans); $^{13}$C-NMR (150 MHz, CDCl$_3$) δ 134.9 (trans), 134.7 (cis), 116.9 (cis), 116.7 (trans), 96.5 (cis), 92.0 (trans), 75.9 (cis), 68.3 (trans), 40.6 (trans), 40.5 (cis), 32.7 (cis), 30.7 (trans), 29.9 (cis), 29.7 (trans), 21.9 (cis), 17.3 (trans); IR (ATR) v 3392, 2939, 2863, 1642, 1440, 1195, 1027, 978, 912, 733 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_8$H$_{14}$NaO$_2$ ([M+Na]$^+$): 165.0886, found: 165.0887.

(5S,6S)-5-methyl-6-((triisopropylsilyl)ethynyl)tetrahydro-2H-pyran-2-ol (7k)

Colorless oil (91%, cis:trans= 1.8:1); $^1$H-NMR (600 MHz, CDCl$_3$) δ 5.35 (brs, 1H, trans), 4.72 (m, 1H, cis), 4.41 (d, J = 10.0 Hz, 1H, trans), 3.88 (d, J = 10.5 Hz, 1H, cis), 3.06 (d, J = 6.0 Hz, 1H, cis-OH), 3.05 (d, J = 6.0 Hz, 1H, trans-OH), 2.58 (brs, 1H, trans-OH), 1.88-1.44 (m, 10H, cis trans), 1.07 (brs, 1H, cis trans), 1.05 (d, J = 6.5 Hz, 3H, cis), 1.01 (d, J = 6.5 Hz, 3H, trans); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ, 106.3 (trans), 105.0 (cis), 96.5 (cis), 91.7 (trans), 86.2 (cis), 85.7 (trans), 73.1 (cis), 66.7 (trans), 36.2 (trans), 35.9 (cis), 32.5 (cis), 30.6 (cis), 29.4 (trans), 25.5 (trans), 18.6 (cis trans), 18.1 (trans), 17.3 (cis), 11.2 (cis trans); IR (ATR) v 3412, 2942, 2865, 1461, 1148, 1063, 994, 882, 735, 668 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{19}$H$_{40}$NO$_2$Si ([M+C$_2$H$_5$NH$_3$]$^+$): 342.2823, found: 342.2820.

6-(prop-2-yn-1-yl)tetrahydro-2H-pyran-2-ol (7l)

Colorless oil (78%, cis:trans= 1:1); $^1$H-NMR (500 MHz, CDCl$_3$) δ 5.34 (brs, 1H), 4.75 (ddd, J = 9.5, 6.5, 2.0 Hz, 1H), 4.11 (dddd, J = 12.0, 6.5, 6.5, 2.5 Hz, 1H), 3.64-3.59 (m, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.54-2.52 (m, 1H), 2.50 (dd, J = 6.5, 2.0 Hz, 1H), 2.41 (dd, J = 7.0, 2.0 Hz, 1H), 2.37 (dd, J = 6.5, 3.0 Hz, 1H), 2.34 (dd, J = 6.5, 3.0 Hz, 1H), 2.03-2.01 (m, 2H), 1.93-1.86 (m, 3H), 1.80-1.70 (m, 3H), 1.66-1.50 (m, 3H), 1.41-1.21 (m, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 96.5, 92.1, 81.0, 80.7, 74.4, 70.1, 69.9, 67.2, 32.4, 30.3, 29.5, 29.4, 25.8, 25.7, 21.6, 17.1; IR (ATR) v 3395, 3295, 2944, 2864, 1440, 1194, 1035, 981, 916, 732 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_8$H$_{12}$NaO$_2$ ([M+Na]$^+$): 163.0730, found: 163.0727.
Preparation of \(\alpha,\beta\)- Unsaturated lactones

6-benzyl-5,6-dihydro-2H-pyran-2-one (4)

![Chemical Structure]

1-phenylpent-4-en-2-ol (S1)

To a stirred solution of allylmagnesium bromide (100 mL, 70 mmol, 0.7 M in Et₂O solution) in Et₂O (100 mL) at 0 °C was added phenylacetaldehyde (4.67 g, 35 mmol, 90% purity). After stirred overnight at room temperature, the reaction mixture was quenched with sat. NH₄Cl aqueous solution and 1N-HCl aqueous solution at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% EtOAc/n-hexane) to afford S1 (4.27 g, 69%) as a colorless oil. The spectral data was in agreement with the data previously reported.³

1-phenylpent-4-en-2-yl acrylate (S2)

To a stirred solution of S1 (4.27 g, 24.2 mmol) and in CH₂Cl₂ (50 mL) at 0 °C was added iPr₂EtN (9.7 mL, 60.5 mmol), N,N-dimethyl-4-aminopyridine (148 mg, 1.21 mmol) and acryloyl chloride (3.95 mL, 48.4 mmol). After stirred overnight at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (5% EtOAc/n-hexane) to afford S2 (4.13 g, 74%) as a colorless oil. The spectral data is in agreement with the data previously reported.³

6-benzyl-5,6-dihydro-2H-pyran-2-one (4)

To a stirred solution of S2 (4.13 g, 17.9 mmol) in CH₂Cl₂ (400 mL) at room temperature was added Grubbs 1st catalyst (295 mg, 0.36 mmol). After refluxing stirred for 3 h, Grubbs 1st catalyst (295 mg, 0.36 mmol) was additionally added to the reaction mixture. Moreover refluxing stirred for 3 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (50% EtOAc/n-hexane) to afford impure 4, and then repurified by NH-silica gel column chromatography (50% EtOAc/n-hexane) to afford 4 (2.32 g, 69%) as a white solid. The spectral data is in agreement with the data previously reported.³

3-benzyl-5,6-dihydro-2H-pyran-2-one (6a)

![Chemical Structure]

3-benzyltetrahydro-2H-pyran-2-one (S3)

To a stirred solution of tetrahydropyran-2-one (2.0 g, 20 mmol) in THF (40 mL) at -78 °C was slowly added LDA (20 mL, 22 mmol, 1.09 M THF solution). After stirred at that temperature for 30 min, benzyl bromide (2.85 mL, 24
mmol) was added to the reaction mixture. The resultant mixture was warmed to -30 °C over 3 h, quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (40% EtOAc/n-heptane) to afford S3 (2.58 g, 68%) as a colorless oil. The spectral data is in agreement with the data previously reported.⁴

3-benzyl-5,6-dihydro-2H-pyran-2-one (6a)⁵

To a stirred solution of S3 (1.8 g, 9.46 mmol) in THF (38 mL) at -78 °C was slowly added LHMDS (10 mL, 10.9 mmol, 1.09 M THF solution). After stirred at that temperature for 30 min, N-tert-butyl phenylsulfinimidoyl chloride (2.55 g, 11.8 mmol, as a solution in THF (10 mL)), was added to the reaction mixture. The resultant mixture was stirred for 1 h, quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (35% EtOAc/n-heptane) to afford 6a (1.17 g, 66%) as a pale yellow oil.

1H-NMR (500 MHz, CDCl₃) δ 7.33-7.30 (m, 2H), 7.25-7.20 (m, 3H), 6.43 (t, J= 4.0Hz, 1H), 4.35 (t, J= 6.0 Hz, 2H), 3.63 (d, J= 1.5 Hz, 2H), 2.43-2.39 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 164.8, 140.1, 138.2, 132.9, 129.2, 128.5, 126.5, 66.3, 36.7, 24.4; IR (ATR) ν 3060, 3028, 2902, 1710, 1398, 1274, 1112, 997, 856, 699 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₁₃O₂ ([M+H⁺]: 189.0910, found: 189.0912.

4-benzyltetrahydro-2H-pyran-2-one (S4)

To a stirred solution of CuI (3.9 g, 20.4 mmol) in THF (80 mL) at room temperature was added TMEDA (3.34 mL, 22.4 mmol). After stirred at that temperature for 10 min, the reaction flask was cooled to -78 °C and benzyl magnesium bromide (22.7 mL, 20.4 mmol, 0.9 M THF solution) was added followed by stirring for 15 min at -78 °C. TMSCl (6.47 mL, 51 mmol) and 5,6-dihydro-2H-pyran-2-one (1.0 g, 10.2 mmol), as a mixture in THF (10 mL), was then injected and stirring continued while the temperature was allowed to rise to -10 °C over 6 h. The mixture was quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (30% EtOAc/n-heptane) to afford S4 (1.06 g, 54%) as a colorless oil. The spectral data is in agreement with the data previously reported.⁶

4-benzyltetrahydro-2H-pyran-2-one (6b)

To a stirred solution of S4 (600 mg, 3.15 mmol) in THF (21 mL) at -78 °C was added LDA (4.3 mL, 4.73 mmol, 1.09 M THF solution). After stirred at that temperature for 15 min, TMSCl (2.85 mL, 24 mmol) was added to the
reaction mixture followed by stirring for 15 min at -78 °C. Then, PhSeCl (906 mg, 4.73 mmol), as a solution in THF (5 mL), was injected and stirring continued for 30 min at -78 °C. The resultant mixture was quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in THF (12 mL) and EtOAc (24 mL), added NaHCO₃ (2.6 g, 31.5 mmol). To this stirred mixture at 0 °C was injected H₂O₂ (3.06 mL, 31.5 mmol, 35% aqueous solution). After stirred at that temperature for 4 h, the reaction was quenched with sat. Na₂S₂O₃ aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (30% EtOAc/n-heptane) to afford 6b (440 mg, 74%, 2 steps) as a colorless oil.

1H-NMR (500 MHz, CDCl₃) δ 7.35-7.32 (m, 2H), 7.29-7.27 (m, 1H), 7.17 -7.16 (m, 2H), 5.80 (brs, 1H), 4.33 (t, J = 6.0 Hz, 2H), 3.56 (s, 2H), 2.34 (t, J = 6.0 Hz, 2H); 13C-NMR (125 MHz, CDCl₃) δ 164.6, 160.0, 135.8, 129.0, 128.8, 127.2, 117.0, 66.0, 43.0, 27.4; IR (ATR) ν 3061, 3028, 2947, 2899, 1714, 1714, 1278, 1223, 1079, 1045, 701 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₁₃O₂ ([M+H]⁺): 189.0910, found: 189.0911.

5-benzyl-5,6-dihydro-2H-pyran-2-one (6c)

2-benzylpropane-1,3-diol(S5)

Et₂O (70 mL) was slowly added to the flask on ice bath injected LAH (2.23 g, 60 mmol). To this stirred mixture at 0 °C was slowly added 2-benzylmalonic acid diethyl ester as a solution of Et₂O (20 mL). After stirred overnight at room temperature, the reaction mixture was cooled to 0 °C and quenched with H₂O (2 mL), 2N-NaOH aqueous solution (2 mL) and then H₂O (6 mL). The residue was filtered on celite pad and washed with EtOAc. The filtrate was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was through a short pad of silica gel (EtOAc as a eluent) to afford S5 (2.55 g, 77%) as a white solid. The spectral data is in agreement with the data previously reported.⁷

2-benzyl-3-((tert-butyldimethylsilyl)oxy)propan-1-ol (S6)

To a stirred solution of S5 (5.91 g, 35.5 mmol) in THF (60 mL) at -78 °C was added n-BuLi (25 mL, 40.8 mmol, 1.64 M in hexane). After stirred for 1 h at room temperature, the reaction temperature was cool to -78 °C. To this stirred mixture was added TBSCI (5.9 g, 39.1 mmol), as a solution in THF (20 mL), and stirred overnight at room temperature. The reaction was quenched with H₂O and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H₂O, brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (5-10% EtOAc/n-heptane) to afford S6 (8.51 g, 85%) as a colorless oil. The spectral data is in agreement with the data previously reported.⁸
(Z)-ethyl 4-benzyl-5-((tert-butyldimethylsilyl)oxy)pent-2-enoate (S7)

To a stirred solution of S6 (1.5 g, 5.35 mmol) in CH$_2$Cl$_2$ (20 mL), DMSO (10 mL) and Et$_3$N (3.7 mL, 26.8 mmol) at 0 °C was added pyridine sulfur trioxide complex (SO$_3$ x Py, 2.55 g, 16 mmol). After stirred for 5 h at room temperature, the reaction mixture was quenched with H$_2$O. The aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layer was washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was through a short pad of silica gel (EtOAc as a eluent) to afford crude aldehyde which was used in the next step further purification. In the separated flask, to a stirred solution of (diphenoxyphosphoryl)acetic acid ethyl ester (1.88 g, 5.9 mmol) in THF (30 mL) at 0 °C was added NaH (236 mg, 5.9 mmol, 60% dispersion in mineral oil). After stirred for 10 min, the reaction mixture was cooled to -78 °C and that crude aldehyde as a solution in THF (5 mL) was injected. The reaction mixture was warmed to -20 °C over 1 h and quenched with sat. NH$_4$Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (5-10% EtOAc/ n-heptane) to afford S7 (1.35 g, 73%, 2 steps) as a colorless oil.

$^1$H-NMR (500 MHz, CDCl$_3$) δ 7.27-7.14 (m, 5H), 6.19 (dd, $J = 11.0$, 9.5 Hz, 1H), 5.76 (d, $J = 13.0$ Hz, 1H), 4.11 (q, $J = 7.5$ Hz, 2H), 3.88-3.81 (m, 1H), 3.51 (d, $J = 4.5$ Hz, 2H), 2.84 (dd, $J = 13.5$, 7.5 Hz, 1H), 2.65 (dd, $J = 13.5$, 7.0 Hz, 1H), 1.24 (t, $J = 7.5$ Hz, 3H), 0.88 (s, 9H), -0.01 (s, 6H);

$^{13}$C-NMR (125 MHz, CDCl$_3$) δ 166.1, 151.1, 139.7, 129.3, 128.1, 125.9, 120.3, 64.1, 59.8, 42.0, 37.0, 25.9, 18.2, 14.2, -5.4; IR (ATR) ν 2954, 2929, 2857, 1717, 1254, 1182, 1099, 832, 775, 699 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{20}$H$_{33}$O$_3$Si ([M+H]$^+$): 349.2193, found: 349.2192.

5-benzyl-5,6-dihydro-2H-pyran-2-one (6c)

To a stirred solution of S7 (2.0 g, 5.74 mmol) in CH$_2$Cl$_2$ (30 mL) at room temperature was added TFA (0.64 mL, 8.61 mmol). After refluxing stirred for 6 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (45% EtOAc/ n-heptane) to afford 6c (932 mg, 86%) as a colorless oil.

$^1$H-NMR (500 MHz, CDCl$_3$) δ 7.36-7.32 (m, 2H), 7.29-7.25 (m, 1H), 7.20-7.19 (m, 2H), 6.86-6.84 (m, 1H), 6.02 (dd, $J = 10.5$, 1.0 Hz, 1H), 4.38-4.35 (m, 1H), 4.20-4.17 (m, 1H), 2.82-2.74 (m, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$) δ 163.8, 149.5, 137.5, 128.9, 128.8, 126.9, 120.8, 70.0, 36.6, 35.7; IR (ATR) ν 3061, 3028, 2923, 1720, 1225, 1085, 1017, 822, 737, 700 cm$^{-1}$; HRMS (ESI$^+$) calcd. for: C$_{12}$H$_{13}$O$_2$ ([M+H]$^+$): 189.0910, found: 189.0911.

6-phenyl-5,6-dihydro-2H-pyran-2-one (6d)

6-(4-methoxyphenyl)-5,6-dihydro-2H-pyran-2-one (6e)
1-phenylbut-3-en-1-ol (S8)
This experimental procedure was used preparation of S1 as a reference. Benzaldehyde (2.5 g, 23.6 mmol) was employed as a starting material and desired S8 was given with 95% as a colorless oil. The spectral data is in agreement with the data previously reported.10

1-(4-methoxyphenyl)but-3-en-1-ol (S9)
This experimental procedure was used preparation of S1 as a reference. 4-methoxy-benzaldehyde (1.0 g, 7.3 mmol) was employed as a starting material and desired S9 was given with 77% as a colorless oil. The spectral data is in agreement with the data previously reported.11

1-phenylbut-3-en-1-yl acrylate (S10)
This experimental procedure was used preparation of S2 as a reference. S8 (2.0 g, 13.5 mmol) was employed as a starting material and desired S10 was given with 95% as a colorless oil. The spectral data is in agreement with the data previously reported.12

1-(4-methoxyphenyl)but-3-en-1-yl acrylate (S11)
This experimental procedure was used preparation of S2 as a reference. S9 (1.23 g, 6.9 mmol) was employed as a starting material and desired S11 was given with 69% as a colorless oil.

1H-NMR (500 MHz, CDCl3) δ 7.29 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 6.42-6.38 (m, 1H), 6.16-6.10 (m, 1H), 5.85-5.80 (m, 2H), 5.70 (ddt, J = 18.0, 10.5, 7.5 Hz, 1H), 5.10-5.03 (m, 2H), 3.80 (s, 3H), 2.73-2.67 (m, 1H), 2.61-2.56 (m, 1H); 13C-NMR (125 MHz, CDCl3) δ 165.4, 159.3, 133.3, 132.0, 130.7, 128.6, 128.0, 118.0, 113.8, 75.1, 55.2, 40.5; IR (ATR) v 2937, 2837, 1720, 1612, 1515, 1248, 1173, 1035, 982, 829 cm⁻¹; HRMS (EI⁺) calcd. for: C14H16O3 [M⁺]: 232.1099, found: 232.1101.

6-phenyl-5,6-dihydro-2H-pyran-2-one (6d)
To a stirred solution of S10 (1.5 g, 7.4 mmol) in toluene (300 mL) at room temperature was added Grubbs 2nd catalyst (128 mg, 0.15 mmol). After stirred at 60 °C for 6 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (40% EtOAc/n-heptane) to afford 6d (400 mg, 35%) as a white solid. The spectral data is in agreement with the data previously reported.12

6-(4-methoxyphenyl)-5,6-dihydro-2H-pyran-2-one (6e)
To a stirred solution of S11 (1.1 g, 4.7 mmol) in CH₂Cl₂ (200 mL) at room temperature was added Grubbs 1ˢᵗ catalyst (580 mg, 0.71 mmol). After refluxing stirred for 6 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (50% EtOAc/n-heptane) to afford impure 6e, and then repurified by NH-silica gel column chromatography (50% EtOAc/n-heptane) to afford 6e (450 mg, 47%) as a white solid. The spectral data is in agreement with the data previously reported.¹³

**Methyl 4-(6-oxo-3,6-dihydro-2H-pyran-2-yl)benzoate (6f)**

4-(6-oxo-3,6-dihydro-2H-pyran-2-yl)benzonitrile (6g)

**Methyl 4-(1-(acryloyloxy)but-3-en-1-yl)benzoate (S12)**¹⁴

To a stirred solution of 4-formylbenzoic acid methyl ester (2.0 g, 12.2 mmol) and tetrabutylammonium iodide (0.45 g, 1.22 mmol) in CH₂Cl₂ (40 mL) and H₂O (40 mL) at room temperature was added potassium allyltrifluoroborate (1.98 g, 13.4 mmol). After vigorously stirred for 15 min at that temperature, organic layer was separated, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in CH₂Cl₂ (20 mL) at 0 °C, added iPr₂EtN (5.34 mL, 30.5 mmol), N,N-dimethyl-4-aminopyridine (75 mg, 0.61 mmol) and acryloyl chloride (2.0 mL, 24.4 mmol). After stirred overnight at room temperature, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc/n-heptane) to afford S12 (2.62 g, 82%, 2 steps) as a colorless oil.

**1H-NMR** (500 MHz, CDCl₃) δ 8.02 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 6.46-6.43 (m, 1H), 6.17 (dd, J = 17.0, 10.0 Hz, 1H), 5.92-5.86 (m, 2H), 5.70 (ddt, J = 17.0, 10.5, 7.0 Hz, 1H), 5.09-5.05 (m, 2H), 3.91 (s, 3H), 2.72-2.66 (m, 1H), 2.63-2.58 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 166.7, 165.2, 145.0, 132.6, 131.3, 129.8, 129.7, 128.3, 126.3, 118.6, 74.8, 52.1, 40.6; IR (ATR) ν 2952, 1719, 1614, 1405, 1275, 1180, 1111, 983, 919, 706 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₅H₁₇O₄ [M+H]+: 261.1121, found: 261.1122.

**1-(4-cyanophenyl)but-3-en-1-yl acrylate (S13)**

This experimental procedure was used preparation of S12 as a reference. 4-cyanobenzaldehyde (2.0 g, 15.2 mmol) was employed as a starting material and desired S13 was given with 87% (2 steps) as a colorless oil.

**1H-NMR** (500 MHz, CDCl₃) δ 7.65 (d, J = 8.5 Hz, 2H), 7.45 (d, J = 8.5 Hz, 2H), 6.45 (dd, J = 17.5, 1.5 Hz, 1H), 6.17 (dd, J = 17.5, 10.5 Hz, 1H), 5.90-5.86 (m, 2H), 5.68 (ddt, J = 18.0, 11.0, 7.0 Hz, 1H), 5.09-5.05 (m, 2H), 2.71-2.65 (m, 1H), 2.62-2.56 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 165.1, 145.2, 132.3, 132.1, 131.7, 128.0, 127.1, 119.0, 118.6, 111.8, 74.5, 40.5; IR (ATR) ν 3079, 2982, 2229, 1723, 1611, 1404, 1266, 1183, 983, 808 cm⁻¹; HRMS (EI⁺) calcd. for: C₁₄H₁₁NO₂ [M⁺]: 227.0946, found: 227.0945.
Methyl 4-(6-oxo-3,6-dihydro-2H-pyran-2-yl)benzoate (6f)
To a stirred solution of S12 (1.5 g, 5.76 mmol) in CH₂Cl₂ (300 mL) at room temperature was added Grubbs 2nd
catalyst (244 mg, 0.29 mmol). After refluxing stirred for 6 h, the reaction mixture was concentrated in vacuo. The
residue was purified by silica gel column chromatography (50% EtOAc/n-heptane) to afford impure 6f, and then
repurified by NH-silica gel column chromatography (50% EtOAc/n-heptane) to afford 6f (550 mg, 41%) as a white
solid.
¹H-NMR (500 MHz, CDCl₃) δ 8.08 (d, J = 8.5 Hz, 2H), 7.50 (d, J = 8.5 Hz, 2H), 7.00-6.97 (m, 1H), 6.18-6.16 (m,
1H), 5.53 (dd, J = 10.0, 6.0 Hz, 1H), 3.93 (s, 3H), 2.66-2.63 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 166.6, 163.6,
144.6, 143.3, 130.3, 130.0, 125.8, 121.8, 78.5, 52.2, 31.6; IR (ATR) ν 2962, 1712, 1427, 1277, 1245, 1109,
916, 814, 768 cm⁻¹; RSM (ESI⁺) calcd. for: C₁₃H₁₃O₄ ([M+H⁺]: 233.0808, found: 233.0808.

4-(6-oxo-3,6-dihydro-2H-pyran-2-yl)benzonitrile (6g)
This experimental procedure was used preparation of 6f as a reference. S12 (1.2 g, 5.3 mmol) was employed as a
starting material and desired 6g was given with 43% as a white solid.
¹H-NMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.0 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 6.99 (ddd, J = 9.0, 6.5, 3.0 Hz,
1H), 6.17 (dt, J = 10.5, 1.0 Hz, 1H), 5.53 (dd, J = 12.0, 4.5 Hz, 1H), 2.69-2.53 (m, 2H); ¹³C-NMR (125 MHz,
CDCl₃) δ 163.2, 144.5, 143.5, 132.5, 126.5, 121.7, 118.3, 112.4, 78.0, 31.4; IR (ATR) ν 2230, 1714, 1385,
1249, 1151, 1062, 1031, 907, 813 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₁₀NO₂ ([M+H⁺]: 200.0706, found: 200.0706.

3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propyl acetate (6i)
4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (S14)
To a stirred solution of 1,4-butanediol (82.0 g, 0.91 mol) and imidazole (7.4 g, 109 mmol) in DMF (300 mL) at
0 °C was slowly added TBDPSCI (25.0 g, 91 mmol) over 1 h. After stirred at room temperature for 2 days, the
reaction mixture was quenched with H₂O and extracted with 1/1 mixture of EtOAc and n-heptane. The combined
organic layer was washed with H₂O, brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified
by silica gel column chromatography (25% EtOAc/n-heptane) to afford S14 (25.0 g, 84%) as a colorless oil. The
spectral data is in agreement with the data previously reported.15
7-((tert-butyldiphenylsilyl)oxy)hept-1-en-4-ol (S15)

To a stirred solution of S14 (25.0 g, 76.1 mmol) in CH₂Cl₂ (150 mL), DMSO (150 mL) and Et₃N (53 mL, 381 mmol) at 0 °C was added pyridine sulfur trioxide complex (SO₃·Py, 36 g, 228 mmol). After stirred for 1 h at that temperature, the reaction mixture was concentrated in vacuo to remove almost CH₂Cl₂. The resultant mixture was diluted with EtOAc, washed with H₂O, brine, dried over MgSO₄ and concentrated in vacuo. The residue was through a short pad of silica gel (1/2: EtOAc/n-heptane as a eluent) to afford crude aldehyde which was used in the next step further purification. This crude aldehyde was dissolved in Et₂O (250 mL) and allylmagnesium bromide (163 mL, 114 mmol, 0.7 M Et₂O solution) at 0 °C was slowly added. After stirred overnight at room temperature, the reaction mixture was quenched with sat. NH₄Cl aqueous solution and 1N-HCl aqueous solution at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (20% EtOAc/n-heptane) to afford S15 (20.9 g, 75%, 2 steps) as a colorless oil. The spectral data is in agreement with the data previously reported.¹⁵

7-((tert-butyldiphenylsilyl)oxy)hept-1-en-4-yl acrylate (S16)

This experimental procedure was used preparation of S2 as a reference. S15 (7.51 g, 20.4 mmol) was employed as a starting material and desired S16 was given with 93% as a colorless oil.¹⁴

1H-NMR (500 MHz, CDCl₃) δ 7.66-7.64 (m, 4H), 7.44-7.36 (m, 6H), 6.37 (dd, J = 17.0, 2.0 Hz, 1H), 6.09 (dd, J = 17.5, 10.5 Hz, 1H), 5.80 (dd, J = 10.5, 1.5 Hz, 1H), 5.75 (ddt, J = 17.0, 10.5, 7.0 Hz, 1H), 5.10-5.05 (m, 2H), 5.03-4.98 (m, 1H), 3.69-3.62 (m, 2H), 2.36-2.33 (m, 2H), 1.77-1.70 (m, 3H), 1.68-1.52 (m, 3H), 1.04 (s, 9H); 13C-NMR (125 MHz, CDCl₃) δ 165.9, 135.5, 133.9, 133.5, 130.4, 129.5, 128.8, 127.6, 117.8, 73.3, 63.5, 38.6, 29.9, 28.3, 26.8, 19.2; IR (ATR) v 3072, 2931, 2858, 1720, 1427, 1253, 1106, 818, 740, 701 cm⁻¹; HRMS (ESI⁺) calcd. for: C₂₆H₃₅O₃Si ([M+H]+): 423.2350, found: 423.2350.

6-(3-((tert-butyldiphenylsilyl)oxy)propyl)-5,6-dihydro-2H-pyran-2-one (S17)

This experimental procedure was used preparation of 6e as a reference. S16 (5.7 g, 13.5 mmol) was employed as a starting material and desired S17 was given with 46% as a colorless oil.

1H-NMR (500 MHz, CDCl₃) δ 7.66-7.65 (m, 4H), 7.45-7.37 (m, 6H), 6.88-6.84 (m, 1H), 6.01 (dt, J = 9.5, 1.5 Hz, 1H), 4.44-4.39 (m, 1H), 3.71 (t, J = 6.0 Hz, 2H), 2.32-2.29 (m, 2H), 1.91-1.83 (m, 1H), 1.83-1.73 (m, 2H), 1.70-1.61 (m, 1H), 1.05(s, 9H); 13C-NMR (125 MHz, CDCl₃) δ 164.5, 145.0, 135.5, 133.7, 129.6, 127.7, 121.4, 77.7, 63.2, 31.4, 29.4, 27.7, 26.8, 19.2; IR (ATR) v 3070, 2931, 2857, 1721, 1405, 1270, 1191, 1108, 984, 700 cm⁻¹; HRMS (ESI⁺) calcd. for: C₂₄H₃₄NO₃Si ([M+H⁺]): 423.2350, found: 423.2350.

6-(3-hydroxypropyl)-5,6-dihydro-2H-pyran-2-one (S18)

To a stirred solution of S17 (1.45 g, 3.67 mol) and AcOH (0.31 mL, 5.5 mmol) in THF (20 mL) at 0 °C was added tetra-n-butylammonium fluoride (4.0 mL, 4.0 mmol, 1.0 M THF solution ). After stirred at room temperature for 2 h, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography
(10% MeOH/EtOAc) to afford S18 (572 mg, quant.) as a colorless oil. The spectral data is in agreement with the data previously reported.\textsuperscript{16}

3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propyl acetate (6i)
To a stirred solution of S18 (300 mg, 1.92 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) at 0 °C was added Et\textsubscript{3}N (0.8 mL, 5.76 mmol), N,N-dimethyl-4-aminopyridine (11.7 mg, 0.01 mmol) and acetyl chloride (0.27 mL, 3.84 mmol). After stirred at that temperature for 30 min, the reaction mixture was quenched with sat. NaHCO\textsubscript{3} aqueous solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by silica gel column chromatography (30% EtOAc/n-heptane) to afford 6i (309 mg, 81%) as a colorless oil.

\begin{align*}
\text{S18} & \xrightarrow{\text{Et3N, N,N-dimethyl-4-aminopyridine, acetyl chloride}} \\
& \text{6i} (309 \text{ mg, 81%})
\end{align*}

\begin{align*}
1H-NMR & (500 MHz, CDCl\textsubscript{3}) \delta 6.90 (ddd, J = 10.5, 6.0, 4.0 Hz, 1H), 6.03 (dt, J = 10.0, 2.5 Hz, 1H), 4.49-4.43 (m, 1H), 4.16-4.07 (m, 2H), 2.38-2.34 (m, 2H), 2.06 (s, 3H), 1.96-1.72 (m, 4H); \\
13C-NMR & (125 MHz, CDCl\textsubscript{3}) \delta 171.0, 164.2, 144.9, 121.4, 77.3, 63.7, 31.3, 29.3, 24.1, 20.9; \\
IR & (ATR) \nu 2957, 1715, 1386, 1366, 1233, 1154, 1097, 1036, 959, 814 \text{ cm}^{-1}; \\
HRMS & (ESI+) calcd. for: C\textsubscript{10}H\textsubscript{15}O\textsubscript{4} ([M+H]+): 199.0965, found: 199.0968.
\end{align*}

Ethyl 3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propanoate (6h)

3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propanal (S19)
To a stirred solution of S18 (1.0 g, 6.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (200 mL) at 0 °C was added Dess-Martin periodinane (4.07 g, 9.6 mmol). After stirred at room temperature for 3 h, the reaction mixture was quenched with sat. NaHCO\textsubscript{3} aqueous solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by silica gel column chromatography (100% EtOAc) to afford S19 (592 mg, 60%) as a colorless oil.

\begin{align*}
\text{S18} & \xrightarrow{\text{Dess-Martin periodinane}} \\
& \text{S19} (592 \text{ mg, 60%})
\end{align*}

\begin{align*}
1H-NMR & (500 MHz, CDCl\textsubscript{3}) \delta 9.84 (s, 1H), 6.90 (ddd, J = 9.5, 5.5, 3.0 Hz, 1H), 6.04-6.02 (m, 1H), 4.51-4.45 (m, 1H), 2.78-2.75 (m, 2H), 2.44-2.32 (m, 2H), 2.11-1.97 (m, 2H); \\
13C-NMR & (125 MHz, CDCl\textsubscript{3}) \delta 201.0, 164.0, 144.9, 121.3, 76.6, 39.1, 29.5, 26.9; \\
IR & (ATR) \nu 2934, 2734, 1707, 1389, 1249, 1152, 1086, 1038, 959, 814 \text{ cm}^{-1}; \\
HRMS & (ESI+) calcd. for: C\textsubscript{8}H\textsubscript{11}O\textsubscript{3} ([M+H]+): 155.0703, found: 155.0705.
\end{align*}

Ethyl 3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propanoate (6h)

3-(6-oxo-3,6-dihydro-2H-pyran-2-yl)propanal (S19)
To a stirred solution of S18 (1.0 g, 6.4 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (200 mL) at 0 °C was added Dess-Martin periodinane (4.07 g, 9.6 mmol). After stirred at room temperature for 3 h, the reaction mixture was quenched with sat. NaHCO\textsubscript{3} aqueous solution and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated \textit{in vacuo}. The residue was purified by silica gel column chromatography (100% EtOAc) to afford S19 (592 mg, 60%) as a colorless oil.

\begin{align*}
\text{S18} & \xrightarrow{\text{Dess-Martin periodinane}} \\
& \text{S19} (592 \text{ mg, 60%})
\end{align*}

\begin{align*}
1H-NMR & (500 MHz, CDCl\textsubscript{3}) \delta 9.84 (s, 1H), 6.90 (ddd, J = 9.5, 5.5, 3.0 Hz, 1H), 6.04-6.02 (m, 1H), 4.51-4.45 (m, 1H), 2.78-2.75 (m, 2H), 2.44-2.32 (m, 2H), 2.11-1.97 (m, 2H); \\
13C-NMR & (125 MHz, CDCl\textsubscript{3}) \delta 201.0, 164.0, 144.9, 121.3, 76.6, 39.1, 29.5, 26.9; \\
IR & (ATR) \nu 2934, 2734, 1707, 1389, 1249, 1152, 1086, 1038, 959, 814 \text{ cm}^{-1}; \\
HRMS & (ESI+) calcd. for: C\textsubscript{8}H\textsubscript{11}O\textsubscript{3} ([M+H]+): 155.0703, found: 155.0705.
\end{align*}
overnight at that temperature, the reaction mixture was quenched with H₂O extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (50% EtOAc/n-heptane) to afford 6h (236 mg, 53%, 2 steps) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 6.89 (ddd, J = 9.5, 5.5, 3.0 Hz, 1H), 6.04-6.01 (m, 1H), 4.50 (dddd, J = 12.5, 7.5, 7.5, 5.5 Hz, 1H), 4.14 (q, J = 7.5 Hz, 2H), 2.59-2.52 (m, 2H), 2.40-2.31 (m, 2H), 2.07-2.02 (m, 2H), 1.26 (dd, J = 7.5, 6.0 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃) δ 172.8, 164.1, 144.9, 121.4, 76.7, 60.6, 29.8, 29.4, 29.3, 14.2; IR (ATR) ν 2981, 2936, 1714, 1380, 1247, 1185, 1077, 1036, 957, 815 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₀H₁₅O₄ ([M+H]+): 199.0965, found: 199.0968.

6-allyl-5,6-dihydro-2H-pyran-2-one (6j)

2-allylcyclopentanone (S20)

To a stirred solution of methyl 2-oxo-cyclopentane-1-carboxylate (2.0 g, 14.1 mmol) in acetone (30 mL) at room temperature was added allyl bromide (4.76 mL, 56.3 mmol) and potassium carbonate (7.8 g, 56.3 mmol). After refluxing stirred for 4 h, the reaction mixture was filtered through a pad of celite and filtrate was concentrated in vacuo. The residue was dissolved in MeOH (40 mL) and 5N-HCl aqueous solution (40 mL) and stirred refluxing for 1 day. The reaction mixture was diluted with H₂O at room temperature and extracted Et₂O. The combined organic layer was washed with sat. NaHCO₃ aqueous solution and brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (25% EtOAc/n-heptane) to afford S20 (1.0 g, 57%, 2 steps) as a colorless oil. The spectral data is in agreement with the data previously reported.¹⁷

6-allyltetrahydro-2H-pyran-2-one (S21)

To a stirred solution of S20 (1.9 g, 15.3 mmol) in CH₂Cl₂ (30 mL) at 0 °C was added mCPBA (4.6 g, 18.4 mmol, contains 30% H₂O reagent) and NaHCO₃ (2.57 g, 30.6 mmol). After stirred overnight at room temperature, the reaction mixture was quenched with sat. Na₂S₂O₃ aqueous solution. The aqueous layer was extracted with CH₂Cl₂. The combined organic layer was washed with sat. NaHCO₃ aqueous solution and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (35% EtOAc/n-heptane) to afford S21 (998 mg, 48%) as a colorless oil. The spectral data is in agreement with the data previously reported.¹⁸

6-allyl-5,6-dihydro-2H-pyran-2-one (6j)

This experimental procedure was used preparation of 6a as a reference. S21 (382 mg, 2.73 mmol) was employed as a starting material and desired 6j was given with 34% as a colorless oil. The spectral data is in agreement with the data previously reported.¹⁹
(5S,6S)-5-methyl-6-((triisopropylsilyl)ethynyl)-5,6-dihydro-2H-pyran-2-one (6k)

To a stirred solution of X (2.15 g, 6.35 mmol) in toluene (32 mL) at room temperature under N₂ atmosphere was added p-toluenesulfonic acid monohydrate (121 mg, 0.64 mmol). After stirring at 60 °C for 30 min, the reaction mixture was quenched with sat. NH₄Cl aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc/n-heptane) to afford 6k (2.22 g, 6.56 mmol, 63%) as a colorless oil.

[α]₁₀⁰ +46.2 (c 0.61, CHCl₃); [¹H-NMR (500 MHz, CDCl₃) δ 6.11 (dd, J = 11.5, 9.5 Hz, 1H), 5.88 (d, J = 11.5 Hz, 1H), 4.25 (t, J = 7.5 Hz, 1H), 4.18 (q, J = 7.5 Hz, 2H), 3.75-3.68 (m, 1H), 2.40 (d, J = 6.5 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.07 (s, 21H); [¹³C-NMR (125 MHz, CDCl₃) δ 166.6, 150.4, 121.1, 106.9, 86.7, 66.5, 60.2, 39.8, 18.6, 15.9, 14.2, 11.1; [IR (ATR) ν 3459, 2943, 2866, 1720, 1463, 1183, 1031, 882, 675 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₉H₃₅O₃Si ([M+H⁺]): 339.2350, found: 339.2340.

(4S,5S,Z)-ethyl 5-hydroxy-4-methyl-7-(triisopropylsilyl)hept-2-en-6-ynoate (S22)²⁰

Flask A: To a stirred solution of 3-isopropylsilylpropynal (2.18 g, 10.4 mmol) in 1,4-dioxane (10.4 mL) and H₂O (0.56 mL) at room temperature under N₂ atmosphere was added propanal (1.12 mL, 15.5 mmol) and ((R)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol (1.09 g, 2.07 mmol). The resulting mixture was stirred at that temperature for 4 h. Meanwhile, in the separated flask B, to a stirred solution of (diphenoxypophosphoryl)acetic acid ethyl ester (4.98 g, 15.5 mmol) in THF (70 mL) at 0 °C under N₂ atmosphere was added NaH (622 mg, 15.5 mmol, 60% dispersion in mineral oil). The resulting mixture was stirred at that temperature for 15 min, then cooled to -78 °C. The reaction mixture of flask A was diluted with THF (10 mL) and transferred by cannula to the flask B at -78 °C over 5 min. After stirring at that temperature for 1.5 h, the reaction mixture was quenched with sat. NH₄Cl aqueous solution and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by silica gel column chromatography (10% EtOAc/n-heptane) to afford X (2.22 g, 6.56 mmol, 63%) as a colorless oil.

[α]₀ +46.2 (c 0.61, CHCl₃); [¹H-NMR (500 MHz, CDCl₃) δ 6.11 (dd, J = 11.5, 9.5 Hz, 1H), 5.88 (d, J = 11.5 Hz, 1H), 4.25 (t, J = 7.5 Hz, 1H), 4.18 (q, J = 7.5 Hz, 2H), 3.75-3.68 (m, 1H), 2.40 (d, J = 6.5 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H), 1.18 (d, J = 6.5 Hz, 3H), 1.07 (s, 21H); [¹³C-NMR (125 MHz, CDCl₃) δ 166.6, 150.4, 121.1, 106.9, 86.7, 66.5, 60.2, 39.8, 18.6, 15.9, 14.2, 11.1; [IR (ATR) ν 3459, 2943, 2866, 1720, 1463, 1183, 1031, 882, 675 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₉H₃₅O₃Si ([M+H⁺]): 339.2350, found: 339.2340.

(5S,6S)-5-methyl-6-((triisopropylsilyl)ethynyl)-5,6-dihydro-2H-pyran-2-one (6k)

To a stirred solution of X (2.15 g, 6.35 mmol) in toluene (32 mL) at room temperature under N₂ atmosphere was added p-toluenesulfonic acid monohydrate (121 mg, 0.64 mmol). After stirring at 60 °C for 30 min, the reaction
mixture was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (15% EtOAc/n-heptane) to afford X (1.59 g, 5.44 mmol, 85%, 98% ee) as a colorless oil.

\[ \alpha \]D\textsuperscript{19} +1.8 (c 0.56, CHCl\textsubscript{3}); \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 6.73 (dd, \( J = 10.0, 3.5 \) Hz, 1 H), 6.00 (dd, \( J = 10.0, 2.0 \) Hz, 1 H), 4.81 (d, \( J = 8.5 \) Hz, 1H), 2.81-2.74 (m, 1H), 1.27 (d, \( J = 7.5 \) Hz, 3H), 1.07 (s, 21H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 162.7, 150.2, 120.3, 102.1, 89.2, 73.4, 35.3, 18.5, 16.3, 11.0; IR (ATR) v 2943, 2866, 1731, 1462, 1228, 1084, 1020, 882, 811, 665 cm\textsuperscript{-1}; HRMS (ESI\textsuperscript{+}) calcd. for: \( \text{C}_{17}\text{H}_{29}\text{O}_{2}\text{Si} ([M+H]\textsuperscript{+}): 293.1931, \) found: 293.1924.

Enantiomeric excess was determined by HPLC (Waters HPLC system; Alliance 2695 Separations Module, 2998 Photodiode Array (PDA Detector) using a Chiralpak AS-3 (DAICEL corporation; 0.46 cm x 25 cm) column (200/1= n-hexane/i-PrOH; flow rate 1.0 mL/min, 220 nm, major enantiomer; \( t_R = 17.9 \) min, minor enantiomer; \( t_R = 21.3 \) min)

**6-(prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (6l)**

![Image of the chemical structure of 6-(prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (6l)](image)

2-(3-(trimethylsilyl)prop-2-yn-1-yl)cyclopentanone (S23)

To a stirred solution of cyclopentanone (0.88 mL, 10 mmol) at room temperature was added \( N,N \)-dimethylhydrazine (2.28 mL, 30mmol). After stirred 6 h at room temperature, the reaction mixture was quenched with sat. NH\textsubscript{4}Cl aqueous solution. The aqueous layer was extracted with Et\textsubscript{2}O. The combined organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated *in vacuo* to afford crude hydrazone (980 mg, 5.15 mmol) which was dissolved in THF (20 mL). To this stirred solution at -40 °C was added LDA (5.2 mL, 5.67 mmol, 1.09 M THF solution) and stirred for 1 h as that temperature. To this stirred solution at -40 °C was added 3-bromo-1-(trimethylsilyl)-1-propyne (1.18 g, 6.18 mmol) and warmed to room temperature over 3 h. After stirred overnight at room temperature, the reaction mixture was quenched with sat. NH\textsubscript{4}Cl aqueous solution. The aqueous layer was extracted with Et\textsubscript{2}O. The combined organic layer was washed with brine, dried over MgSO\textsubscript{4} and concentrated *in vacuo*. The residue was dissolved in THF (20 mL) and added oxalic acid (1.4 g, 15.5 mmol) dissolved in H\textsubscript{2}O (20 mL). After stirred at 60 °C for 3 h, the reaction mixture was cooled to room temperature and extracted with Et\textsubscript{2}O. The combined organic layer was washed with sat. NaHCO\textsubscript{3} aqueous solution and brine, dried over MgSO\textsubscript{4}, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20% EtOAc/n-heptane) to afford S23 (480 g, 25%, 3 steps) as a colorless oil. The spectral data is in agreement with the data previously reported.\textsuperscript{22}
6-(3-(trimethylsilyl)prop-2-yn-1-yl)tetrahydro-2H-pyran-2-one (S24)
This experimental procedure was used preparation of S21 as a reference. S23 (777 mg, 4.0 mmol) was employed as a starting material and desired S24 was given with 63% as a colorless oil.

\[^1\text{H-NMR}\ (500\ MHz, CDCl_3)\ \delta\ 4.45-4.39\ (m, 1H),\ 2.72\ (dd, J = 17.0, 4.5 Hz, 1H),\ 2.64-2.59\ (m, 1H),\ 2.56\ (dd, J = 17.0, 8.5 Hz, 1H),\ 2.50-2.43\ (m, 1H),\ 2.17-2.11\ (m, 1H),\ 2.02-1.94\ (m, 1H),\ 1.91-1.82\ (m, 1H),\ 1.66\ (dd, J = 14.0, 10.0, 5.0 Hz, 1H),\ 0.15\ (s, 9H);\ ^{13}\text{C-NMR}\ (125\ MHz, CDCl_3)\ \delta\ 171.0,\ 100.8,\ 88.0,\ 78.1,\ 29.5,\ 27.1,\ 26.8,\ 18.3,\ -0.1;\ IR\ (ATR)\ \nu\ 2954,\ 2180,\ 1741,\ 1445,\ 1247,\ 1186,\ 1054,\ 1029,\ 835,\ 757\ cm^{-1};\ HRMS\ (ESI^+)\ \text{calcd. for:}\ C_{11}H_{19}O_2Si\ ([M+H]^+):\ 211.1149,\ \text{found:}\ 211.1149.\]

6-(3-(trimethylsilyl)prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (S25)
This experimental procedure was used preparation of 6a as a reference. S24 (415 mg, 1.97 mmol) was employed as a starting material and desired S25 was given with 57% as a colorless oil.

\[^1\text{H-NMR}\ (500\ MHz, CDCl_3)\ \delta\ 6.93\ (ddd, J = 10.0, 6.0, 2.5 Hz, 1H),\ 6.06-6.03\ (m, 1H),\ 4.55\ (ddt, J = 11.5, 9.5, 4.5 Hz, 1H),\ 2.78\ (dd, J = 17.0, 5.0 Hz, 1H),\ 2.66\ (dd, J = 17.0, 8.5 Hz, 1H),\ 2.62-2.57\ (m, 1H),\ 2.51-2.44\ (m, 1H),\ 0.16\ (s, 9H);\ ^{13}\text{C-NMR}\ (125\ MHz, CDCl_3)\ \delta\ 163.6,\ 144.8,\ 121.2,\ 100.3,\ 88.6,\ 75.4,\ 28.2,\ 26.1,\ -0.1;\ IR\ (ATR)\ \nu\ 2959,\ 2179,\ 1719,\ 1386,\ 1248,\ 1060,\ 1036,\ 838,\ 813,\ 759\ cm^{-1};\ HRMS\ (ESI^+)\ \text{calcd. for:}\ C_{11}H_{17}O_2Si\ ([M+H]^+):\ 209.0992,\ \text{found:}\ 209.0993.\]

6-(prop-2-yn-1-yl)-5,6-dihydro-2H-pyran-2-one (6l)
To a stirred solution of S25 (233 mg, 1.12 mmol) in THF (5 mL) at room temperature was added tetra-n-butylammonium fluoride (1.68 mL, 1.68 mmol, 1.0 M THF solution) which was mixed THF (1.5 mL) and AcOH (0.11 mL, 1.9 mmol). After stirred at that temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (50% EtOAc/n-heptane) to afford 6l (139 mg, 91%) as a pale yellow oil.

\[^1\text{H-NMR}\ (500\ MHz, CDCl_3)\ \delta\ 6.93\ (ddd, J = 10.5, 6.5, 3.0 Hz, 1H),\ 6.06-6.04\ (m, 1H),\ 4.58\ (ddt, J = 12.5, 8.0, 4.5 Hz, 1H),\ 2.75-2.62\ (m, 2H),\ 2.62-2.51\ (m, 2H),\ 2.11\ (t, J = 2.5 Hz, 1H);\ ^{13}\text{C-NMR}\ (125\ MHz, CDCl_3)\ \delta\ 163.5,\ 144.8,\ 121.2,\ 78.2,\ 75.2,\ 71.9,\ 28.1,\ 24.7;\ IR\ (ATR)\ \nu\ 3284,\ 2919,\ 1715,\ 1387,\ 1256,\ 1228,\ 1148,\ 1053,\ 1037,\ 812\ cm^{-1};\ HRMS\ (ESI^+)\ \text{calcd. for:}\ C_8H_9O_2\ ([M+H]^+):\ 137.0597,\ \text{found:}\ 137.0599.\]

5-benzylfuran-2(5H)-one (6m)

1-phenylbut-3-en-2-ol (S26)
To a stirred solution of phenylacetaldehyde (3.0 g, 25 mmol, 90% purity) in Et₂O (50 mL) at 0 °C was added vinyllmagnesium bromide (37.5 mL, 37.6 mmol, 1.0 M THF solution). After stirred overnight at room temperature,
the reaction mixture was quenched with sat. NH₄Cl aqueous solution and 1N-HCl aqueous solution at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (5-10% EtOAc/n-heptane) to afford S26 (1.87 g, 46%) as a colorless oil. The spectral data is in agreement with the data previously reported.²³

1-phenylbut-3-en-2-yl acrylate (S27)
This experimental procedure was used preparation of S2 as a reference. S26 (1.87 g, 11.5 mmol) was employed as a starting material and desired S27 was given with 80% as a colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 7.23-7.20 (m, 3H), 6.38 (dd, J₁ = 17.5, 1.0 Hz, 1H), 6.11 (dd, J₂ = 17.0, 10.0 Hz, 1H), 5.87-5.80 (m, 2H), 5.56-5.52 (m, 1H), 5.24-5.16 (m, 2H), 3.02 (dd, J₁ = 13.5, 6.5 Hz, 1H), 2.93 (dd, J₂ = 13.5, 6.5 Hz, 1H); ¹³C-NMR (125 MHz, CDCl₃) δ 165.3, 136.8, 135.6, 130.8, 129.6, 128.6, 128.3, 126.6, 117.1, 75.2, 40.8; IR (ATR) ν 3031, 2925, 1721, 1635, 1404, 1265, 1184, 984, 808, 699 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₃H₁₄NaO₂ ([M+Na⁺]: 225.0886, found: 225.0885.

5-benzylfuran-2(5H)-one (6m)
To a stirred solution of S27 (1.7 g, 7.86 mmol) in toluene (400 mL) at room temperature was added Grubbs 2nd catalyst (200 mg, 0.24 mmol). After stirred overnight at 70 °C, the reaction mixture was concentrated in vacuo. The residue was purified by silica gel column chromatography (55% EtOAc/n-heptane) to afford 6m (1.05 g, 77%) as a colorless oil. The spectral data is in agreement with the data previously reported.²⁴

7-benzyl-6,7-dihydrooxepin-2(5H)-one (6n)
2-benzylcyclohexanone (S28)
To a stirred mixture of cyclohexanone (6.4 g, 65.2 mmol) in H₂O (150 mL) at room temperature was added NaOH (1.3 g, 32.6 mmol). After stirred at that temperature for 5 min, benaldehyde (2.38 g, 22.4 mmol) was added to a mixture and continued stirring at room temperature for 3 days. The reaction mixture was neutralized with glacial acetic acid. The mixture was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was dissolved in EtOAc (100 mL), added Pd/C (240 mg) and stirred under H₂ atmosphere at room temperature for 1 day. The residue was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (1-5% EtOAc/n-heptane) to afford S28 (2.07 g, 49%, 2 steps) as a colorless oil. The spectral data is in agreement with the data previously reported.²⁵

7-benzyloxepan-2-one (S29)
To a stirred solution of S28 (1.0 g, 5.3 mmol) in CHCl₃ (13 mL) at 0 °C was added mCPBA (931 mg, 5.31 mmol, contains 30% H₂O reagent). After stirred at room temperature for 2 days, the reaction mixture was quenched with sat. Na₂S₂O₃ aqueous solution. The aqueous layer was extracted with CHCl₃. The combined organic layer was washed with sat. NaHCO₃ aqueous solution and brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by through a pad of silica gel (EtOAc as eluent) to afford S29 (950 mg, 88%) as a colorless oil. The spectral data is in agreement with the data previously reported.²⁶

7-benzyl-6,7-dihydrooxepin-2(5H)-one (6n)
To a stirred solution of S29 (354 mg, 1.73 mmol) in THF (12 mL) at -78 °C was slowly added LDA (2.4 mL, 2.6 mmol, 1.09 M THF solution). After stirred at that temperature for 30 min, N-tert-butyl phenylsulfinimidoyl chloride (560 mg, 2.60 mmol, as a solution in THF (3 ml)) was added to the reaction mixture. The resultant mixture was stirred for 1 h, quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (30% EtOAc/n-heptane) to afford 6n (220 mg, 63%) as a colorless oil. The spectral data is in agreement with the data previously reported.²⁷
Preparation of authentic compounds in Table 1

**methyl 5-hydroxy-6-phenylhexanoate (5c)**

![Chemical Structure](image)

To a stirred solution of 4 (374 mg, 1.99 mmol) in EtOAc (10 ml) at room temperature was added Pd/C (37 mg). After stirred at that temperature under H₂ atmosphere for 2 h, the reaction mixture was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to afford 5a (380 mg, quant.) as a semisolid. The spectral data is in agreement with the data previously reported.²⁸

**6-benzyltetrahydro-2H-pyran-2-one (5a)**

To a stirred solution of 4 (374 mg, 1.99 mmol) in EtOAc (10 ml) at room temperature was added Pd/C (37 mg). After stirred at that temperature under H₂ atmosphere for 2 h, the reaction mixture was filtered through a pad of celite and washed with EtOAc. The filtrate was concentrated *in vacuo* to afford 5a (380 mg, quant.) as a semisolid. The spectral data is in agreement with the data previously reported.²⁸

**methyl 5-hydroxy-6-phenylhexanoate (5c)**

To a stirred solution of 5a (47 mg, 0.25 mmol) in MeOH (2.5 mL) at 0 °C was added sodium meth oxide (40 mg, 0.74 mmol). After stirred at room temperature for , the reaction mixture was quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (45% EtOAc/n-heptane) to afford 5c (42.5 mg, 76%) as a colorless oil.

**1H-NMR** (500 MHz, CDCl₃) δ 7.33-7.30 (m, 2H), 7.26-7.20 (m, 3H), 3.83 (octet, J = 4.0 Hz, 1H), 3.67 (s, 3H), 2.83 (dd, J = 13.5, 4.5 Hz, 1H), 2.66 (dd, J = 13.5, 8.5 Hz, 1H), 2.36 (t, J = 7.5 Hz, 2H), 1.89-1.80 (m, 1H), 1.79-1.70 (m, 1H), 1.62-1.48 (m, 3H); **¹³C-NMR** (125 MHz, CDCl₃) δ 174.1, 138.3, 129.4, 128.6, 126.5, 72.2, 51.5, 44.0, 36.1, 33.8, 21.1; IR (ATR) ν 3448, 2949, 1734, 1437, 1198, 1173, 1084, 1011, 743, 700 cm⁻¹; **HRMS** (ESI⁺) calcd. for: C₁₃H₁₉O₃ ([M+H⁺]): 223.1329, found: 223.1331.

**(Z)-6-phenylhex-2-ene-1,5-diol (5d)**

![Chemical Structure](image)
To a stirred solution of 4 (94.1 mg, 0.5 mmol) in MeOH (5 mL) at 0 °C was added CeCl₃·7H₂O (372 mg, 1 mmol).

After stirred at that temperature for 5 min, NaBH₄ (37.8 mg, 1 mmol) was added and the mixture was continued stirring at 0 °C for 30 min. The reaction mixture was quenched with sat. NH₄Cl aqueous solution, and extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (90% EtOAc/n-heptane) to afford 5d (80 mg, 83%) as a colorless oil.

¹H-NMR (500 MHz, CDCl₃) δ 7.34-7.31 (m, 2H), 7.26-7.21 (m, 3H), 5.93-5.87 (m, 1H), 5.71-5.66 (m, 1H), 4.20 (dd, J = 12.5, 7.5 Hz, 1H), 4.10 (dd, J = 12.5, 7.5 Hz, 1H), 3.90-3.85 (m, 1H), 2.84 (dd, J = 14.0, 4.5 Hz, 1H), 2.74 (dd, J = 14.0, 8.0 Hz, 1H), 2.41-2.30 (m, 2H), 2.05 (brs, 2H); ¹³C-NMR (125 MHz, CDCl₃) δ 138.3, 131.4, 129.3, 129.1, 128.5, 126.5, 71.5, 57.5, 43.6, 34.3; IR (ATR) ν 3326, 3025, 2919, 1454, 1351, 1078, 1018, 849, 742, 698 cm⁻¹; HRMS (ESI⁺) calcd. for: C₁₂H₁₇O₂ ([M+H]⁺): 193.1223, found: 193.1225.

6-phenylhexane-1,5-diol (5e)

To a stirred solution of 4 (94.1 mg, 0.5 mmol) in MeOH (5 mL) at 0 °C was added NaBH₄ (56.7 mg, 1.5 mmol).

After stirred at room temperature for 3 h, the reaction mixture was quenched with sat. NH₄Cl aqueous solution. The aqueous layer was extracted with EtOAc and the combined organic layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography (90% EtOAc/n-heptane) to afford 5e (68.9 mg, 71%) as a colorless oil. The spectral data is in agreement with the data previously reported.
Computational studies
To evaluate the differences in reactivity between five-, six-, and seven-membered-ring lactones, we used density functional theory to calculate the energies of model compounds \(\gamma\)-butyrolactone, \(\delta\)-valerolactone, and \(\varepsilon\)-caprolactone and their coordination complexes with CuH. Table S1 shows the calculated differences in energy (\(\Delta E\)) between the anti and syn forms of the CuH-coordinated lactones and the corresponding free lactones. Table S2 shows the energy differences (\(\Delta H\)) between pairs of CuH-coordinated lactones. The calculations indicated that the \(\delta\)-valerolactone/CuH complexes were more stable than the \(\gamma\)-butyrolactone/CuH complexes, but the \(\Delta H\) values were only 1–2 kcal/mol. This computational model did not show a clear difference in reactivity between \(\gamma\)-butyrolactone and \(\delta\)-valerolactone. Moreover, there was almost no difference in energy between \(\delta\)-valerolactone and \(\varepsilon\)-caprolactone.

Computational Methods
All calculations were performed in Jaguar\(^{31}\) with the B3LYP hybrid functional\(^{32}\) and the LACVP** basis set.\(^{33}\) The complexes were modeled with the Maestro graphic user interface and were optimized in the gas phase. To validate the nature of all stationary points, we calculated the number of negative eigenvalues from the vibrational analysis (0 or 1 for minima and transition states, respectively).

**Table S1** Energies of CuH-Coordinated Lactones and Free Lactones.

<table>
<thead>
<tr>
<th>Compound</th>
<th>(E) (Hartree)</th>
<th>(\Delta E) (Hartree)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\gamma)-butyrolactone-CuH (anti)</td>
<td>-503.253347</td>
<td>-196.757893</td>
</tr>
<tr>
<td>(\gamma)-butyrolactone-CuH (syn)</td>
<td>-503.253087</td>
<td>-196.757633</td>
</tr>
<tr>
<td>(\gamma)-butyrolactone</td>
<td>-306.495454</td>
<td></td>
</tr>
<tr>
<td>(\delta)-valerolactone-CuH (anti)</td>
<td>-542.568307</td>
<td>-196.759953</td>
</tr>
<tr>
<td></td>
<td>$\Delta E$ (Hartree)</td>
<td>$\Delta E$ (kcal/mol)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>$\delta$-valerolactone-CuH ($\text{syn}$)</td>
<td>-542.568761</td>
<td>-196.760407</td>
</tr>
<tr>
<td>$\delta$-valerolactone</td>
<td>-345.808354</td>
<td></td>
</tr>
<tr>
<td>$\epsilon$-caprolactone-CuH ($\text{anti}$)</td>
<td>-581.882443</td>
<td>-196.759622</td>
</tr>
<tr>
<td>$\epsilon$-caprolactone-CuH ($\text{syn}$)</td>
<td>-581.88337</td>
<td>-196.760549</td>
</tr>
<tr>
<td>$\epsilon$-caprolactone</td>
<td>-385.122821</td>
<td></td>
</tr>
</tbody>
</table>

**Table S2** Energy Differences between Pairs of CuH-Coordinated Lactones.
$^{1}H$ and $^{13}C$ spectra
single_pulse

DFILE: YM13701 3-196 1H.als
COMNT: single_pulse
DATIM: 2013-07-01 11:12:45
OBNUC: 1H
EXMOD: single_pulse.ex2
OBFRQ: 495.13 MHz
OBSET: 4.38 KHz
OBFIN: 9.64 Hz
POINT: 13107
FREQU: 7429.31 Hz
SCANS: 16
ACQTM: 1.7642 sec
PD: 1.5000 sec
PW1: 6.00 usec
IRNUC: 1H
CTEMP: 21.3 c
SLVNT: CDCl3
EXREF: 0.00 ppm
BF: 0.12 Hz
RGAIN: 48

single_pulse decoupled gated NOE

DFILE: YM13701 3-196 13C.als
COMNT: single_pulse decoupled ga
OBNUC: 13C
EXMOD: single_pulse_dec
OBFRQ: 124.51 MHz
OBSET: 3.45 KHz
OBFIN: 6.00 Hz
POINT: 26214
FREQU: 31152.17 Hz
SCANS: 151
ACQTM: 0.8415 sec
PD: 1.5000 sec
PW1: 3.70 usec
IRNUC: 1H
CTEMP: 21.3 c
SLVNT: CDCl3
EXREF: 77.00 ppm
BF: 0.12 Hz
RGAIN: 50
single_pulse

DFILE YM13620 3-182 pure.als
COMNT single_pulse
DATIM 2013-06-20 11:22:20
OBNUC 1H
EXMOD single_pulse
OBFRQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 9.64 Hz
POINT 13107
FREQU 7429.31 Hz
SCANS 16
ACQTM 1.7642 sec
PD 1.5000 sec
PW1 6.00 usec
HBNUC 1H
CTEMP 21.3 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 42

single pulse decoupled gated NOE

DFILE YM13620 3-182 13C-2.als
COMNT single pulse decoupled gate
DATIM 2013-06-20 11:43:05
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 124.51 MHz
OBSET 3.45 KHz
OBFIN 6.00 Hz
POINT 26214
FREQU 31152.17 Hz
SCANS 101
ACQTM 0.8415 sec
PD 1.5000 sec
PW1 3.70 usec
HBNUC 1H
CTEMP 21.3 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50
single_pulse

single pulse decoupled gated NOE

S39
single pulse

O

MeO

S11

DFILE YM13612 3-166 1H.als
COMNT single_pulse
DATIM 2013-06-12 14:25:01
OBNUC 1H
EXMOD single_pulse
OBFRQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 9.64 Hz
POINT 13107
FREQU 7429.31 Hz
SCANS 16
ACQTM 1.7642 sec
PD 1.50 sec
PW1 6.00 usec
BINUC 1H
CTEMP 21.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 48

single pulse decoupled gated NOE

O

MeO

S11

DFILE YM13612 3-166 13C.als
COMNT single pulse decoupled ga
DATIM 2013-06-12 14:21:18
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 124.51 MHz
OBSET 3.45 KHz
OBFIN 6.00 Hz
POINT 26214
FREQU 31152.17 Hz
SCANS 85
ACQTM 0.8415 sec
PD 1.5000 sec
PW1 3.70 usec
BINUC 1H
CTEMP 21.4 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50

S42
single pulse

DFILE YM13618 3-176 pure.als
COMNT single pulse
DATIM 2013-06-18 14:20:30
OBNUC 1H
EXMOD single_pulse.ex2
OBFRQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 6.64 Hz
POINT 13107
FREQU 7429.31 Hz
SCANS 16
ACQTM 1.7642 sec
PD 1.5000 sec
PW1 6.00 usec
HNUC 1H
CTEMP 21.2 c
SLVNT CDCL3
EXREF 0.00 ppm
RGAIN 42

single pulse decoupled gated NOE

DFILE YM13618 3-176 13C.als
COMNT single pulse decoupled gated NOE
DATIM 2013-06-18 14:24:16
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 124.51 MHz
OBSET 3.45 KHz
OBFIN 3.00 Hz
POINT 26214
FREQU 31152.17 Hz
SCANS 78
ACQTM 0.8415 sec
PD 1.5000 sec
PW1 3.70 usec
HNUC 1H
CTEMP 21.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 0.12 Hz
RGAIN 50
**single_pulse**

DFILE YM13907 4-75-2.als
COMNT single_pulse
DATIM 2013-09-07 15:40:11
OBNUC 1H
EXMOD single_pulse_ex2
OBFRQ 495.13 MHz
OBSET 4.38 KHz
OBFIN 9.64 Hz
POINT 13107
FREQU 7429.31 Hz
SCANS 32
ACQTM 1.7642 sec
PD 1.5000 sec
PW1 6.00 usec
BHNUC 1H
CTEMP 25.2 c
SLVNT CDCL3
EXREF 0.00 ppm
BF 0.12 Hz
RGAIN 58

**single pulse decoupled gated NOE**

DFILE YM13X29 4-126_13C.als
COMNT single pulse decoupled ga
DATIM 2013-10-26 00:00:07
OBNUC 13C
EXMOD single_pulse_dec
OBFRQ 123.26 MHz
OBSET 2.31 KHz
OBFIN 6.71 Hz
POINT 26214
FREQU 30863.73 Hz
SCANS 231
ACQTM 0.8493 sec
PD 1.5000 sec
PW1 3.40 usec
BHNUC 1H
CTEMP 27.6 c
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.20 Hz
RGAIN 60
References


(31) Jaguar, version 8.0; Schrodinger, LLC, New York, 2005. For current versions, see:
