Supporting Information

A hypervalent iodine-mediated spirocyclization of 2-(4-hydroxybenzamido)acrylates – Unexpected formation of δ-spirolactones

Christian Hempel, Nicole M. Weckenmann, C. Maichle-Moessmer and Boris J. Nachtsheim

Institut für Organische Chemie, Eberhard Karls Universität Tübingen,

Auf der Morgenstelle 18, 72076 Tübingen, Germany
General Methods

$^1$H NMR spectra were recorded on an Avance 400 MHz instrument in deuterated chloroform (CDCl$_3$), water (D$_2$O) or methanol (CD$_3$OD). Chemical shifts (δ) are given in parts per million (ppm). $^1$H NMR spectra were referenced to the residual hydrogen signal in CDCl$_3$ at δ = 7.26 ppm, to the residual hydrogen signal in D$_2$O at δ = 4.79 ppm or to residual hydrogen singlet signal at δ = 4.84 ppm when measured in methanol-d$_4$. $^{13}$C NMR spectra were recorded on 100 MHz and were fully decoupled by broad band decoupling. $^{13}$C spectra were referenced to the CDCl$_3$ triplet signal at δ = 77.0 ppm or to septet signal at δ = 49.05 ppm in methanol-d$_4$. The following abbreviations were used to describe splitting patterns: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet. Coupling constants $J$ are given in Hz. Mass spectra were recorded on a Finnigan MAT95 by using EI or FAB method. Thin layer chromatography was performed on fluorescence indicator marked precoated silica gel 60 plates (Macherey-Nagel, ALUGRAM Xtra SIL G/UV$_{254}$) and visualization was achieved by UV light (254 nm). Flash chromatography was performed on silica gel (0.040 – 0.063 mm). Unless otherwise stated all reactions were carried out under air. For air or moisture sensitive reactions standard Schlenk-techniques were applied under an argon atmosphere. Schlenk-glassware was heated in vacuo and flushed with argon several times before they were used. Reagents and solvents were added by syringe/septum techniques. IR spectra were recorded on JASCO FT/IR-4100. A selection of signals is given in reciprocal centimeters (cm$^{-1}$).

Solvents and reagents

Solvents for flash chromatography (hexane, ethyl acetate, dichloromethane) were distilled before use. Acetonitrile was dried over Al$_2$O$_3$ and stored over molecular sieve. Triethylamine was dried over calciumhydride and distilled before use. Unless stated, all other commercially available substances and reagents were used as received from their suppliers (Acros, Alfa Aesar, Sigma Aldrich) without further purification. 2-(4-Hydroxybenzamido)acrylates 3 were synthesized and purified as described. O-TMS protected 4-Hydroxybenzoyl chloride 1 and N-benzyl serine alkyl ester 2 were prepared from described procedures.$^{[1],[2]}$ The serine alkyl esters were also synthesized based on literature procedures.$^{[3],[4],[5]}$
Synthesis of N-Benzyl serine alkyl ester 2a-2e

General preparation procedure according to literature:\textsuperscript{[2]} To a solution of the corresponding serine alkyl ester (30 mmol, 1.00 equiv.), benzaldehyde (1.20 equiv.) and MgSO\textsubscript{4} (3.00 g) in dry DCM (50 mL) was added NEt\textsubscript{3} (1.20 equiv.) dropwise. The reaction mixture was stirred at room temperature for 24 hours, filtered and concentrated under reduced pressure. The residue was dissolved in MeOH (80 mL) and cooled to 0 °C before NaBH\textsubscript{4} (1.20 equiv.) was added portionwise. The resulting mixture was further stirred for 4 hours at room temperature and then quenched with water (35 mL) and EtOAc (35 mL). The aqueous layer was extracted with EtOAc (5 x 30 mL), and the combined organic layers were washed with brine (10 mL), dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated under reduced pressure. The residue was again dissolved in CHCl\textsubscript{3}, filtered and concentrated under reduced pressure.

\textbf{N-Benzyl serine methyl ester 2a:} Yield: 82\%, brown oil.\textsuperscript{[2]} \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.28-7.25 (m, 5H), 3.81 (d, 1H, \(^2\)J\textsubscript{HH} = 12.8 Hz), 3.70-3.60 (m, 1H), 3.67 (s, 3H), 3.64 (d, 1H, \(^2\)J\textsubscript{HH} = 12.8 Hz), 3.56-3.36 (m, 1H), 3.35-3.34 (m, 1H), 2.48 (bs, 2H). \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 173.4, 139.2, 128.5, 128.2, 127.3, 62.4, 61.8, 52.2, 52.0. MS (FAB) m/z = 210.3 [M+H]\textsuperscript{+}. IR \(\nu\)\textsubscript{max}/cm\textsuperscript{-1} 1741, 1462, 1430, 1207, 1167, 1135, 1055, 1015, 744, 695. Compound is known to literature.\textsuperscript{[2]}

\textbf{N-Benzyl serine ethyl ester 2b:} Yield: 67\%, brown oil.\textsuperscript{[2]} \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.27-7.16 (m, 5H), 4.12 (q, 2H, \(^3\)J\textsubscript{HH} = 7.1 Hz), 3.81 (d, 1H, \(^2\)J\textsubscript{HH} = 12.9 Hz), 3.71-3.67 (m, 1H), 3.68 (d, 1H, \(^2\)J\textsubscript{HH} = 12.9 Hz), 3.55-3.50 (m, 1H), 3.34-3.31 (m, 1H), 2.63 (bs, 2H), 1.21 (t, 3H, \(^3\)J\textsubscript{HH} = 7.1 Hz). \textsuperscript{13}C\textsuperscript{1}H\textsuperscript{1}NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 172.8, 139.1, 128.5, 128.3, 127.3, 62.3, 61.8, 61.3, 52.0, 14.2. MS (FAB) m/z = 224.2 [M+H]\textsuperscript{+}. IR \(\nu\)\textsubscript{max}/cm\textsuperscript{-1} 1709, 1230, 1207, 1127, 1055, 1023, 855, 752, 695, 600. Compound is known to literature.\textsuperscript{[6]}

\textbf{N-Benzyl serine isopropyl ester 2c:} Yield: 77\%, yellow oil.\textsuperscript{[2]} \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.34-7.27 (m, 5H), 5.07 (sep, 1H, \(^3\)J\textsubscript{HH} = 6.3 Hz), 3.89 (d, 1H, \(^2\)J\textsubscript{HH} = 12.9 Hz), 3.79-3.73 (m, 1H), 3.74 (d, 1H, \(^2\)J\textsubscript{HH} = 12.9 Hz), 3.61-3.56 (m, 1H), 3.40-3.38 (m, 1H), 2.50 (bs, 2H), 1.27 (d, 3H, \(^3\)J\textsubscript{HH} = 6.1 Hz), 1.25 (d, 3H,
$^{3}J_{HH} = 6.2$ Hz). $^{13}$C{$^{1}$H}_2-NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 139.2, 128.5, 128.3, 127.4, 68.9, 62.4, 61.9, 52.1, 21.9, 21.8. MS (FAB) m/z = 238.3 [M+H]$^+$. IR $\nu_{max}$/cm$^{-1}$ 1709, 1454, 1374, 1254, 1207, 1151, 1143, 1047, 735, 680. HRMS (ESI) m/z calculated to C$_{13}$H$_{19}$NO$_3$ [M+H]$^+$: 238.143770, found: 238.143697.

**N-Benzyl serine benzyl ester 2d:** Yield: 90%, brown oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.18 (m, 10H), 5.14 (s, 2H), 3.80 (d, 1H, $^2J_{HH} = 12.9$ Hz), 3.75-3.71 (m, 1H), 3.66 (d, 1H, $^2J_{HH} = 12.9$ Hz), 3.60-3.56 (m, 1H), 3.42-3.39 (m, 1H), 2.63 (bs, 2H). $^{13}$C{$^{1}$H}_2-NMR (100 MHz, CDCl$_3$) $\delta$ 172.7, 139.0, 135.4, 128.6, 128.5, 128.4, 128.2, 127.4, 67.0, 62.4, 61.8, 52.0. MS (FAB) m/z = 286.3 [M+H]$^+$. IR $\nu_{max}$/cm$^{-1}$ 3026, 1717, 1510, 1454, 1167, 1127, 1023, 727, 695, 568. HRMS (ESI) m/z calculated to C$_{17}$H$_{19}$NO$_3$ [M+H]$^+$: 286.143770, found: 286.143771. Compound is known to literature.[7]

$N$-Benzyl serine tert-butyl ester 2e: Yield: 66%, yellow oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.20 (m, 5H), 3.80 (d, 1H, $^2J_{HH} = 12.8$ Hz), 3.70-3.66 (m, 1H), 3.65 (d, 1H, $^2J_{HH} = 12.8$ Hz), 3.51-3.47 (m, 1H), 3.26-3.24 (m, 1H), 2.52 (bs, 2H), 1.41 (s, 9H). $^{13}$C{$^{1}$H}_2-NMR (100 MHz, CDCl$_3$) $\delta$ 172.1, 128.5, 128.4, 128.2, 126.9, 81.9, 65.2, 62.5, 52.1, 28.1. IR $\nu_{max}$/cm$^{-1}$ 1725, 1663, 1503, 1452, 1359, 1230, 1147, 1018, 740, 689. HRMS (ESI) m/z calculated to C$_{14}$H$_{21}$NO$_3$ [M+H]$^+$: 252.159420, found: 252.159292. Compound is known to literature.[8]
Synthesis of 2-(4-hydroxybenzamido)acrylates 3a-3e

General preparation procedure:[9] In a vial, the N-Benzyl serine alkyl ester 2 (1.40 mmol, 1.0 equiv.) was dissolved in dry toluene (9 mL), followed by simultaneous addition of NEt₃ (440 µL, 3.10 mmol, 2.2 equiv.) and p-OTMS-benzoylchloride 1 (981 mg, 4.25 mmol 3.0 equiv.) at 0 °C. The resulting homogenous mixture was stirred at room temperature for 17 hours and extracted with 1M KHSO₄ solution (2 × 4 mL). The aqueous layer was extracted with EtOAc (3 × 4 mL), and combined organic layers were washed with brine (4 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in dry DCM (9 mL) and cooled to 0 °C before DBU (470 µL, 3.10 mmol, 2.2 equiv.) was added dropwise. The mixture was stirred at 0 °C for 5 hours, and washed with 1M KHSO₄ solution (2 × 4 mL). The aqueous layer was extracted with DCM (4 × 4 mL), and the combined organic layers were washed with brine (4 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The products were obtained after flash chromatography using DCM and MeOH.

*N-Benzyl-2-(4-hydroxybenzamido)methylacrylate 3a*: Yield: 55%, white solid. ¹H-NMR (400 MHz, CDCl₃) δ 7.28-7.17 (m, 7H), 6.59-6.57 (m, 2H), 5.88 (s, 1H), 5.22 (s, 1H), 4.85 (s, 2H), 3.50 (s, 3H). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ 172.0, 164.5, 158.9, 140.4, 136.7, 130.1, 128.5, 128.3, 128.1, 127.5, 126.3, 115.2, 52.7, 52.5. MS (FAB) m/z = 312.3 [M+H]⁺. IR ν max/cm⁻¹ 1735, 1601, 1580, 1266, 1194, 1152, 848, 761, 725, 648. HRMS (ESI) m/z calculated to C₁₈H₁₇NO₄ [M+Na]⁺: 334.104979, found: 334.104783.

*N-Benzyl-2-(4-hydroxybenzamido)ethylacrylate 3b*: Yield: 54%, white solid. ¹H-NMR (400 MHz, CDCl₃) δ 7.44-7.42 (m, 2H), 7.34-7.28 (m, 5H), 6.70-6.68 (m, 2H), 5.96 (s, 1H), 5.30 (s, 1H), 4.94 (s, 2H), 4.00 (q, 2H, 3 JHH = 7.0 Hz), 1.13 (t, 3H, 3 JHH = 7.1 Hz). ¹³C{¹H}-NMR (100 MHz, CDCl₃) δ 171.6, 164.0, 158.6, 140.9, 136.9, 130.3, 128.5, 128.4, 128.3, 127.5, 126.9, 115.1, 61.8, 52.8, 13.9. MS (FAB) m/z = 326.4 [M+H]⁺. IR ν max/cm⁻¹ 1717, 1589, 1446, 1366, 1342, 1254, 1158, 839, 744, 704. HRMS (ESI) m/z calculated to C₁₉H₁₉NO₄ [M+Na]⁺: 348.120629, found: 348.120610.
N-Benzyl-2-(4-hydroxybenzamido)isopropylacrylate 3c: Yield: 63%, white solid. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44-7.42 (m, 2H), 7.34-7.28 (m, 5H), 6.72-6.70 (m, 2H), 5.96 (s, 1H), 5.31 (s, 1H), 4.94 (s, 2H), 4.84 (sep, 1H, \(J_{HH} = 6.2\) Hz), 1.09 (d, 6H, \(J_{HH} = 6.2\) Hz). \(^{13}\)C\{\(^1\)H\}\(-\)NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.3, 163.1, 158.6, 140.8, 136.5, 130.1, 128.2, 128.0, 127.1, 126.2, 115.2, 114.8, 69.4, 52.7, 21.1. MS (FAB) m/z = 340.2 [M+H]\(^+\). IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 1606, 1382, 1350, 1289, 1207, 1167, 799, 735, 695, 608. HRMS (ESI) m/z calculated to C\(_{20}\)H\(_{21}\)NO\(_4\) [M+Na]\(^+\): 362.136279, found: 362.136299.

N-Benzyl-2-(4-hydroxybenzamido)benzylacrylate 3d: Yield: 31%, white solid. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.19 (m, 12H), 6.66-6.64 (m, 2H), 6.00 (s, 1H), 5.32 (s, 1H), 5.00 (s, 2H), 4.94 (s, 2H). \(^{13}\)C\{\(^1\)H\}\(-\)NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.2, 163.2, 161.2, 152.4, 136.0, 134.5, 132.2, 129.1, 128.3, 128.2, 128.0, 127.9, 127.4, 121.4, 120.3, 115.3, 67.6, 67.3. MS (FAB) m/z = 388.4 [M+H]\(^+\). IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 1725, 1606, 1574, 1374, 1262, 1190, 848, 759, 695, 600. HRMS (ESI) m/z calculated to C\(_{24}\)H\(_{21}\)NO\(_4\) [M+Na]\(^+\): 410.136279, found: 410.136040.

N-Benzyl-2-(4-hydroxybenzamido)tert-butylacrylate 3e: Yield: 20%, white solid. \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42-7.40 (m, 2H), 7.34-7.23 (m, 5H), 6.68-6.65 (m, 2H), 5.96 (s, 1H), 5.35 (s, 1H), 4.92 (s, 2H), 1.19 (s, 9H). \(^{13}\)C\{\(^1\)H\}\(-\)NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.8, 158.7, 142.1, 136.9, 132.3, 130.5, 128.4, 128.3, 127.4, 120.9, 115.3, 115.0, 82.4, 53.3, 27.4. IR \(\nu_{\text{max}}/\text{cm}^{-1}\) 2364, 2338, 1745, 1606, 1565, 1282, 1235, 1142, 843, 719. HRMS (ESI) m/z calculated to C\(_{21}\)H\(_{23}\)NO\(_4\) [M+Na]\(^+\): 376.151929, found: 376.151978.

**Spirocyclization of 2-(4-hydroxybenzamido)acrylates 3 to spirolactam 4**

General preparation procedure: To a stirred solution of 2-(4-hydroxybenzamido)acrylate 3 (0.10 mmol, 1.0 equiv.) in 2 mL EtCN containing MS 3 Å at 90 °C was added PIFA (0.12 mmol, 1.2 equiv.) portionwise. After stirring at 90 °C for 10 minutes, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography using DCM and MeOH.
N-Benzyl-3-(methoxycarbonyl)-2-azaspiro[4.5]dec-3,6,9-trien-1,8-dione 4a: Yield: 52%, brown solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.31-7.25 (m, 5H), 6.56-6.47 (m, 4H), 5.97 (s, 1H), 5.10 (s, 2H), 3.81 (s, 3H). $^{13}$C$\{^1$H$\}$-NMR (100 MHz, CDCl$_3$) $\delta$ 184.7, 172.8, 159.5, 140.9, 137.5, 137.0, 132.5, 128.7, 127.8, 127.7, 117.3, 56.7, 52.6, 45.5. MS (FAB) m/z = 310.2 [M+H]$^+$. IR $\nu_{\text{max}}$/cm$^{-1}$ 1720, 1647, 1436, 1328, 1266, 1194, 1147, 1049, 859, 704. HRMS (ESI) m/z calculated to C$_{18}$H$_{15}$NO$_4$ [M+Na]$^+$: 332.089329, found: 332.089236.

N-Benzyl-3-(hydroxy)-3-(methoxycarbonyl)-2-azaspiro[4.5]dec-6,9-dien-1,8-dione 5: pale yellow solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.24 (m, 5H), 7.00-6.88 (m, 2H), 6.50-6.43 (m, 2H), 4.83 (d, 1H, $^{2}$J$_{HH}$ = 15.1 Hz), 4.13 (d, 1H, $^{2}$J$_{HH}$ = 15.1 Hz), 3.29 (s, 3H), 2.81 (d, 1H, $^{2}$J$_{HH}$ = 14.2 Hz), 2.41 (d, 1H, $^{2}$J$_{HH}$ = 14.2 Hz). $^{13}$C$\{^1$H$\}$-NMR (100 MHz, CDCl$_3$) $\delta$ 184.6, 171.3, 170.1, 146.7, 146.4, 134.0, 131.2, 130.3, 128.6, 128.2, 127.7, 86.0, 53.5, 50.3, 43.7, 41.8. MS (FAB) m/z = 328.2 [M+H]$^+$. HRMS (ESI) m/z calculated to C$_{18}$H$_{17}$NO$_5$ [M+Na]$^+$: 350.099894, found: 350.099844.

Optimization studies towards the formation of 5

<table>
<thead>
<tr>
<th>entry</th>
<th>iodine(III)</th>
<th>equiv.</th>
<th>solvent</th>
<th>Additive (equiv.)</th>
<th>T [°C]</th>
<th>T [min]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>-</td>
<td>0</td>
<td>90</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>TFA (1.2)</td>
<td>0</td>
<td>120</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>TFA (1.2) H$_2$O (1.1)</td>
<td>0</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>4</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>-</td>
<td>RT</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>H$_2$O (1.1)</td>
<td>RT</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>H$_2$O (2.1)</td>
<td>RT</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>PIFA</td>
<td>2</td>
<td>MeCN</td>
<td>H$_2$O (1.1)</td>
<td>RT</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>PIFA</td>
<td>2</td>
<td>MeCN</td>
<td>H$_2$O (2.1)</td>
<td>RT</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>TFA (1.2) H$_2$O (1.1)</td>
<td>RT</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>-</td>
<td>60</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>PIFA</td>
<td>1.2</td>
<td>MeCN</td>
<td>TFA (1.2)</td>
<td>60</td>
<td>10</td>
<td>15</td>
</tr>
</tbody>
</table>
**N-Benzyl-3-(ethoxycarbonyl)-2-azaspiro[4.5]dec-3,6,9-trien-1,8-dione 4b:** Yield: 35%, brown solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.30-7.24 (m, 5H), 6.55-6.47 (m, 4H), 5.96 (s, 1H), 5.10 (s, 2H), 4.26 (q, 2H, $^3$J$_{HH}$ = 7.1 Hz), 1.28 (t, 3H, $^3$J$_{HH}$ = 7.1 Hz). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 184.6, 172.8, 159.1, 140.9, 137.9, 137.0, 132.5, 128.7, 127.7, 127.6, 116.9, 62.0, 56.6, 45.5, 13.9. MS (FAB) m/z = 324.2 [M+H]$^+$; IR $\nu_{\text{max}}$/cm$^{-1}$ 1720, 1653, 1328, 1261, 1189, 1137, 1054, 853, 740, 694. HRMS (ESI) m/z calculated to C$_{19}$H$_{17}$NO$_4$ [M+Na]$^+$: 346.104979, found: 346.105199.

**N-Benzyl-3-(isopropoxycarbonyl)-2-azaspiro[4.5]dec-3,6,9-trien-1,8-dione 4c:** Yield: 38%, brown solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.32-7.23 (m, 5H), 6.55-6.48 (m, 4H), 5.92 (s, 1H), 5.10 (sep, 1H, $^3$J$_{HH}$ = 6.3 Hz), 5.09 (s, 2H), 1.23 (d, 6H, $^3$J$_{HH}$ = 6.3 Hz). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 184.6, 172.8, 158.7, 141.1, 138.3, 137.0, 132.4, 128.7, 127.7, 127.6, 116.4, 70.1, 56.6, 45.4, 21.5. MS (FAB) m/z = 338.1 [M+H]$^+$; IR $\nu_{\text{max}}$/cm$^{-1}$ 1740, 1720, 1663, 1261, 1179, 1147, 1101, 1049, 859, 694. HRMS (ESI) m/z calculated to C$_{20}$H$_{19}$NO$_4$ [M+Na]$^+$: 360.120629, found: 360.120596.

**N-Benzyl-3-(benzyloxycarbonyl)-2-azaspiro[4.5]dec-3,6,9-trien-1,8-dione 4d:** Yield: 35%, brown solid. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.21 (m, 10H), 6.53-6.47 (m, 4H), 5.99 (s, 1H), 5.22 (s, 2H), 5.10 (s, 2H). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 184.5, 172.7, 158.9, 140.8, 137.6, 136.9, 134.4, 132.4, 128.8, 128.7, 128.5, 127.7, 127.7, 117.4, 67.5, 56.6, 45.4. MS (FAB) m/z = 386.1 [M+H]$^+$; IR $\nu_{\text{max}}$/cm$^{-1}$ 1720, 1653, 1405, 1338, 1266, 1179, 1147, 853, 730, 694. HRMS (ESI) m/z calculated to C$_{24}$H$_{19}$NO$_4$ [M+Na]$^+$: 408.120629, found: 408.120530.

**Spirocyclization of 2-(4-hydroxybenzamido)acrylates 3 to δ-spirolactone 6**

To a stirred solution of 2-(4-hydroxybenzamido)acrylate 3 (0.10 mmol, 1.0 equiv.) in 2 mL TFE containing MS 3 Å at 0 °C was added TFA (0.20 mmol, 2.0 equiv.) and then PIFA (0.20 mmol, 2.0 equiv.). After stirring at 0 °C for 1 hour, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography.
(Hex : EE 5:1 → 3:1) to give the title compound as a pale yellow solid (up to 70%).$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.37-7.15 (m, 5H), 6.89-6.86 (m, 2H), 6.49-6.46 (m, 2H), 6.00 (d, 1H, $^2J_{HH} = 2.1$ Hz), 5.30 (d, 1H, $^2J_{HH} = 2.1$ Hz), 4.99 (s, 2H). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 183.0, 160.7, 157.6, 139.3, 134.0, 132.0, 131.6, 128.9, 127.9, 126.4, 110.3, 76.9, 47.9. MS (FAB) m/z = 296.2 [M+H]$^+$. IR $\nu_{\max}$/cm$^{-1}$ 1741, 1677, 1613, 1342, 1262, 1138, 1055, 911, 839, 688. HRMS (ESI) m/z calculated to C$_{13}$H$_{13}$NO$_4$ [M+Na]$^+$: 318.073679, found: 318.073889.

**Synthesis of 7**

N-Benzyl O-tert-butyl serine tert-butyl ester was prepared according to the procedure described for compounds 2a-2e starting from O-tert-butyl serin tert-butyl-ester.$^4$: Yield: 71%, brown oil. $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 7.28-7.13 (m, 5H), 3.83 (d, 1H, $^2J_{HH} = 12.9$ Hz), 3.63 (d, 1H, $^2J_{HH} = 12.9$ Hz), 3.53-3.41 (m, 2H), 3.23-3.21 (m, 1H), 2.16 (bs, 1H), 1.40 (s, 9H), 1.07 (s, 9H). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 172.6, 139.9, 128.4, 128.3, 126.8, 80.8, 72.8, 63.3, 61.4, 51.84, 28.1, 27.3. MS (FAB) m/z = 308.2 [M+H]$^+$. IR $\nu_{\max}$/cm$^{-1}$ 2977, 1735, 1462, 1359, 1184, 1137, 1085, 1018, 740, 689. HRMS (ESI) m/z calculated to C$_{18}$H$_{29}$NO$_3$ [M+H]$^+$: 308.222020, found: 308.222230.

N-Benzyl O-tert-butyl serine tert-butyl ester (170 mg, 0.60 mmol, 1.0 equiv.) was dissolved in dry toluene (6 mL), followed by simultaneous addition of NEt$_3$ (183 µL, 1.32 mmol, 2.2 equiv.) and p-OTMS-benzoylchloride 1 (412 mg, 1.80 mmol, 3.0 equiv.) at 0 °C. The resulting homogenous mixture was stirred at room temperature for 17 hours and extracted with 1M KHSO$_4$ solution (2 × 4 mL). The aqueous layer was extracted with EtOAc (3 × 4 mL), and combined organic layers were washed with brine (4 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (DCM : MeOH 200:1 → 50:1) to give the title compound 7 as a white solid (164 mg, 0.40 mmol, 66%). $^1$H-NMR (400 MHz, DMSO-d$_6$) $\delta$ 9.84 (s, 1H) 7.33-7.22 (m, 7H), 6.76 (m, 2H), 4.76-3.56 (m, 3H), 3.32 (s, 2H), 1.36 (s, 9H), 0.98 (s, 9H). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) $\delta$ 173.3, 168.1, 158.5, 137.1, 132.4, 128.9, 128.3, 127.3, 126.3, 115.5, 81.8, 73.8, 60.6, 55.2, 51.8, 27.9, 27.3. MS (FAB) m/z = 428.2 [M+H]$^+$. IR $\nu_{\max}$/cm$^{-1}$ 1749, 1613, 1566, 1414, 1279, 1239, 1143, 1111, 848, 727. HRMS (ESI) m/z calculated to C$_{25}$H$_{33}$NO$_5$ [M+Na]$^+$: 450.225094, found: 450.224677.
Spirocyclization of 7 to bis(cyclohexa-2,5-dien-4-one) 9

To a stirred solution of 7 (41 mg, 0.10 mmol, 1.0 equiv.) in 2 mL TFE containing MS 3 Å at 0 °C was added TFA (14.3 µL; 0.20 mmol, 2.0 equiv.) and then PIFA (81.0 mg, 0.20 mmol, 2.0 equiv.). After stirring at 0 °C for 1 hour, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (Hex : EE 3:1 → 1:1) to give the title compound as a pale yellow solid (27.0 mg, 0.06 mmol, 61%).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.21-6.84 (m, 4H), 6.49-6.37 (m, 4H), 4.92-4.90 (m, 1H), 4.02 (d, 1H, $^2$J$_{HH}$ = 10.9 Hz), 3.90-3.86 (m, 1H), 3.81 (d, 1H, $^2$J$_{HH}$ = 10.9 Hz), 3.71-3.68 (m, 1H), 1.49 (s, 9H), 1.20 (s, 9H). $^{13}$C{1H}-NMR (100 MHz, CDCl$_3$) δ 184.2, 184.0, 169.3, 167.3, 146.4, 146.1, 141.9, 141.6, 133.2, 133.2, 131.5, 131.4, 83.1, 73.9, 60.5, 59.2, 55.9, 51.6, 50.7, 28.1, 27.4. MS (FAB) m/z = 442.1 [M+H]$^+$, 464.1 [M+Na]$^+$. IR $\nu_{\text{max}}$/cm$^{-1}$ 1741, 1702, 1663, 1620, 1366, 1230, 1190, 1158, 1087, 871. HRMS (ESI) m/z calculated to C$_{25}$H$_{31}$NO$_6$ [M+Na]$^+$: 464.204359, found: 464.204242.


