Syntheses of α-Amino Squaric Acids Using an Aminomalonate Equivalent Bearing a Squaryl Group

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Abstract: The synthesis of an amino acid analogue bearing a squaryl group as a carboxylic acid surrogate (sq-AA; 2) has been developed. Aminomalonate equivalent 6 was used as a nucleophilic synthon whose alkylation or conjugate addition reaction followed by deprotection and decarboxylation reaction gave sq-AAs.

Key words: amino acids, squaric acid, malonate, alkylations, addition reactions

α-Amino acid analogues bearing other acidic functional groups, e.g., sulfonic acid,1 phosphonic acid,2 boronic acid,3 and tetrazole,4 as a carboxylic acid surrogate are an important probe in the area of biological and medicinal chemistries. We have recently developed a novel analogue 2 (sq-AA) of α-amino acids where the carboxylic acid moiety of α-amino acids 1 is replaced by a 4-hydroxy-2,3-dioxocyclobut-1-enyl (sq) group (Figure 1).5,6

Squaric acid is a kind of oxocarbon.7 In view of its unique physicochemical properties, e.g., strong acidity, aromaticity, ring strain, electron deficiency, and metal chelating ability, many applications have been initiated in the fields of medicinal chemistry,5,6 bioconjugate chemistry,8 materials science,9 organic chemistry,10 and inorganic chemistry11 since the first synthesis by Cohen.12

In the course of our studies regarding a carbon–carbon bond forming reaction of a sq group, we have established a facile synthetic method to access 2 via an addition of a di-anion enolate 3 derived from easily available N-Boc amino acid esters to disopropyl squarate 4 followed by concomitant deprotection and decarboxylation reactions (method A).5 Although various amino acids are commercially available, the number of sq-AAs provided by method A is dependent upon the number of available α-amino acids. Moreover, the synthesis of sq-Asp and sq-Glu would suffer problems since addition to 4 with a dianion enolate from Asp or Glu occurs non-selectively at the α-position and the β- or γ-position.13

To compliment method A, we planned a new method using an aminomalonate equivalent 613 (method B) (Scheme 1) that resembles the classical acetamidomalonate method for the synthesis of α-amino acids.14 The methine proton in 6 would be acidic enough to generate a carbonion in the presence of a mild base owing to the dual electron-withdrawing effects of the carboxylate and sq groups. In this regard, this carbonion can be viewed as a versatile nucleophilic synthon for an alkylation or a conjugate addition reaction to give various sq-AAs.

Scheme 1

Since carbon–carbon bond forming reaction using 6 was unprecedented, we attempted a model study using a benzylation reaction of 6 (Table 1). Treatment of 6 with BnBr (1.5 equiv) in the presence of an amine base (Et₃N, 1.2 equiv or EtNi-Pr₂, 1.5 equiv) at room temperature afforded the desired adduct 5a in moderate yield (entries 1, 2). Analysis of 1H and 13C NMR data of 5a and the corresponding sq-AA confirmed that the alkylation occurred chemoselectively to form a quaternary amino carbon center. Undesired N-alkylation reaction was not observed at all, due probably to the steric bulkiness of the Boc group. The yield was raised to 50% by using K₂CO₃ as a base in MeCN (entry 3). However, further improvement in yields was not obtained in spite of a systematic survey of the bases and solvents. Monitoring of this benzylolation reaction indicated that the alkylation reaction was found to be slow. Moreover, 6 was completely decomposed by treatment with K₂CO₃ in the absence of benzyl bromide for 12...
h. These results suggested that the benzylation reaction competed with decomposition of 6 under the reaction conditions. To accelerate the desired alkylation, tetrabutylammonium iodide (TBAI), known as a phase-transfer reagent as well as a reagent for halogen exchange reaction from bromide to more reactive iodide in situ, was tested as an additive. As expected, the benzylation reaction using 1 equiv of TBAI proceeded smoothly (1 h) to afford 5a in 70% yield (entry 4). The best result was obtained when 6 was treated with K₂CO₃ (1.5 equiv), BnBr (3 equiv), and TBAI (3 equiv) in MeCN to give 5a in 90% yield in 0.5 h (entry 5).

Having the optimal conditions in hand, the addition reactions with various electrophiles were examined (Table 2). Alkylation reactions using allylic bromides, an ammonium salt derived from gramine, methyl iodide, and bromoacetate smoothly provided the corresponding adducts in good to moderate yields, except in the case of i-PrI (entries 1–7). Michael addition reactions of 6 with unsaturated ketone, ester, and nitrile gave the corresponding adducts in good to moderate yields (entries 8–11). It is noteworthy that the sterically congested methine carbon was alkylated with different kinds of electrophiles.

These adducts were converted to sq-AAs 7–14 (Table 3). Adducts 5a–c,g,l were treated with concd HCl which allowed concomitant removal of all protecting groups and decarboxylation to give sq-Phe 7, sq-Asp 8, sq-Allylgly 9, sq-Ala 13, and sq-Glu 14, respectively (entries 1–3, 7, and 8). Thus, sq-AAs 8 and 14, which could not be synthesized by method A, were obtained. Sq-Norvaline 10, sq-Leu 11, and sq-Phenylethylgly 12 were provided by an initial reduction of the carbon–carbon double bond of 5c–e using H₂/Pd-C and subsequent decarboxylation reaction (entries 4–6).

In summary, we have developed a new approach to access sq-AAs by an operationally simple alkylation or conjugate addition reaction of the aminomalonic equivalent 6. Complementary use of methods A and B would extend the scope for the synthesis of a variety of sq-AAs. Biological activities of sq-Glu and sq-Asp as a novel ligand to glutamate receptors as well as its incorporation into biologically active peptides are being further studied.

Reagents, solvents, and anhydrous solvents were purchased from either Aldrich Chemical Company, Inc., Merck & Co., Inc., Nacalai Tesque Company, Ltd., Peptide Institute, Tokyo Kasei Kogyo Co., Ltd., or Wako Pure Chemical Industries, Ltd., and used without purification.

### Table 1  Benzylation of Compound 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>BnBr (equiv)</th>
<th>Additive (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr₂NEt (1.5)</td>
<td>1.5</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N (1.2)</td>
<td>1.5</td>
<td>-</td>
<td>CH₂Cl₂</td>
<td>9</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>K₂CO₃ (1.5)</td>
<td>1</td>
<td>-</td>
<td>MeCN</td>
<td>12</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃ (1.5)</td>
<td>1</td>
<td>TBAI (1)</td>
<td>MeCN</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>K₂CO₃ (1.5)</td>
<td>3</td>
<td>TBAI (3)</td>
<td>MeCN</td>
<td>0.5</td>
<td>90</td>
</tr>
</tbody>
</table>

### Table 2  Alkylation and Conjugate Addition Reaction of 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Equiv</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br→CO₂t-Bu</td>
<td>3</td>
<td>0.5</td>
<td>5b</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>3</td>
<td>0.5</td>
<td>5c</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>3</td>
<td>0.5</td>
<td>5d</td>
<td>82</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>3</td>
<td>0.5</td>
<td>5e</td>
<td>quant</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>5</td>
<td>2.5</td>
<td>5f</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>MeI</td>
<td>30</td>
<td>12</td>
<td>5g</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>i-PrI</td>
<td>30</td>
<td>12</td>
<td>5h</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>CO₂Me</td>
<td>5</td>
<td>5</td>
<td>5i</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>CN</td>
<td>30</td>
<td>12</td>
<td>5j</td>
<td>33</td>
</tr>
<tr>
<td>10</td>
<td>CO₂Me</td>
<td>30</td>
<td>12</td>
<td>5k</td>
<td>35</td>
</tr>
<tr>
<td>11</td>
<td>CO₂t-Bu</td>
<td>30</td>
<td>12</td>
<td>5l</td>
<td>12</td>
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</table>

* TBAI (3 equiv) was added.
Table 3 Conversion of 5a–e, g, l to sq-AAs 7–14

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>R</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>5a</td>
<td>7</td>
<td>Bu</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>5b</td>
<td>8</td>
<td>CH₃CO₂H</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>5c</td>
<td>9</td>
<td>allyl</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>5e</td>
<td>10</td>
<td>n-Pr</td>
<td>40⁺</td>
</tr>
<tr>
<td>5</td>
<td>5d</td>
<td>11</td>
<td>2-methylpropyl</td>
<td>20⁺</td>
</tr>
<tr>
<td>6</td>
<td>5e</td>
<td>12</td>
<td>(CH₂)₃Ph</td>
<td>42⁺</td>
</tr>
<tr>
<td>7</td>
<td>5g</td>
<td>13</td>
<td>Me</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>5l</td>
<td>14</td>
<td>(CH₂)₃CO₂H</td>
<td>67</td>
</tr>
</tbody>
</table>

* Two steps.

**tert-Butyl (tert-Butoxycarbonyl)-1-(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)-2-phenylethylcarbamate (5a)**

To a solution of 6 (0.109 g, 0.29 mmol) in MeCN (2.8 mL) was added K₂CO₃ (0.061 g, 0.44 mmol) at r.t. The mixture was stirred at r.t. for 5 min. The mixture was added BuBr (0.099 mL, 0.84 mmol) and TBAI (0.31 g, 0.84 mmol) at r.t. The mixture was stirred for 30 min at r.t., filtered through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel; n-hexane–EtOAc; 9:1–1:1) to give 5a.

Yield: 0.114 g (90%); pale yellow oil.

**tert-Butyl 1-(tert-Butoxycarbonyl)-1-(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)-2-phenylethylcarbamate (5b)**

To a solution of 6 (0.102 g, 0.28 mmol) in MeCN (2.8 mL) was added K₂CO₃ (0.06 g, 0.42 mmol) at r.t. The mixture was stirred at r.t. for 5 min. To the mixture was added BrCH₂CO₂H (0.13 mL, 0.88 mmol) and TBAI (0.31 g, 0.84 mmol) at r.t. The mixture was stirred for 30 min at r.t., filtered through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel; n-hexane–EtOAc; 9:1–1:1) to give 5b.

Yield: 0.12 g (86%); pale yellow oil.

**tert-Butyl 1,2-Di-(tert-butoxycarbonyl)-1-(2-isopropoxy-3,4-dioxo-cyclobut-1-enyl)-2-phenylethylcarbamate (5a)**

According to the procedure for the synthesis of 5a, 6 (0.109 g, 0.29 mmol) was treated with K₂CO₃ (0.061 g, 0.44 mmol), BrCH₂CO₂t-Bu (0.13 mL, 0.88 mmol), and TBAI (0.33 g, 0.88 mmol). The crude product was purified by flash column chromatography (silica gel; n-hexane–EtOAc; 9:1–1:1) to give 5b.

Yield: 0.12 g, 86%; pale yellow oil.
\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 195.3, 193.6, 191.0, 178.3, 168.7, 165.9, 153.9, 84.3, 80.3, 81.7, 80.1, 62.3, 38.6, 28.2, 27.9, 27.6, 22.8, 22.7.

HRMS (FAB): \(m/z\) calcd for C\(_{23}\)H\(_{32}\)NO\(_7\) ([M + H]\(^+\)): 484.2547; found: 484.2554.

tert-Butyl 1-(tert-Butyloxy carbonyl)-1-(2-isoproxy-3,4-dioxocyclobut-1-enyl)but-3-enylcarbamate (5c)

According to the procedure for the synthesis of 5a, 6 (0.096 g, 0.28 mmol) was treated with K\(_2\)CO\(_3\) (0.058 g, 0.42 mmol), methallyl bromide (0.13 mL, 0.88 mmol), and TBAI (0.33 g, 0.88 mmol). The crude product was purified by flash column chromatography (silica gel; n-hexane–EtOAc, 9:1–1:1) to give 5c.

Yield: 0.097 g (82%); pale yellow oil.

\([\text{IR (neat): } 3427, 2981, 2935, 1795, 1758, 1738, 1719, 1596, 1485, 1391, 1370, 1157, 1097, 1074 \text{ cm}^{-1}]

\[\text{calcd for C}_{22}\text{H}_{34}\text{NO}_{7} ([\text{M} + \text{H}]^+) : 424.2335 ; \text{found: 424.2335.} \]

HRMS (FAB): \(m/z\) calcd for C\(_{22}\)H\(_{34}\)NO\(_7\) ([M + H]\(^+\)): 424.2335; found: 424.2360.

tert-Butyl 1-(tert-Butyloxy carbonyl)-1-(2-isoproxy-3,4-dioxocyclobut-1-enyl)-4-phenylbut-3-enylcarbamate (5d)

According to the procedure for the synthesis of 5a, 6 (0.108 g, 0.29 mmol) was treated with K\(_2\)CO\(_3\) (0.064 g, 0.46 mmol), cinnamyl bromide (0.13 mL, 0.88 mmol), and TBAI (0.33 g, 0.88 mmol). The crude product was purified by flash column chromatography (silica gel; n-hexane–EtOAc, 9:1–1:1) to give 5d.

Yield: 0.12 g (quantitative); pale yellow oil.

\([\text{IR (neat): } 3429, 2980, 2935, 1795, 1758, 1736, 1716, 1645, 1595, 1390, 1370, 1154, 1098, 1049 \text{ cm}^{-1}]\]

\[\text{calcd for C}_{27}\text{H}_{35}\text{N}_{2}\text{O}_{7} ([\text{M} + \text{H}]^+) : 499.2444 ; \text{found: 499.2444.}\]

HRMS (FAB): \(m/z\) calcd for C\(_{27}\)H\(_{35}\)N\(_2\)O\(_7\) ([M + H]\(^+\)): 499.2444; found: 498.2423.
HRMS (FAB): \textit{m/z} calcd for C\textsubscript{2}H\textsubscript{5}NO\textsubscript{3} ([M + H\textsuperscript{+}]): 440.2284; found: 440.2260.

tert-Butyl 1-(tert-Butoxycarbonyl)-3-cyano-1-(2-isoproxy-3,4-dioxocyclobut-1-enyl)propylcarbamate (5j)

According to the procedure for the synthesis of 5f, 6 (0.53 g, 1.44 mmol) was treated with K\textsubscript{2}CO\textsubscript{3} (0.4 g, 2.88 mmol) and acrylonitrile (2.84 mL, 43.2 mmol). The crude product was purified by flash column chromatography (silica gel; n-hexane–EtOAc, 9:1–1:1) to give 5j.

Yield: 0.198 g (33%); pale yellow oil.

IR (neat): 3429, 2980, 2935, 1796, 1758, 1735, 1720, 1596, 1483, 1391, 1369, 1252, 1154 cm\textsuperscript{-1}.

Yield: 0.083 g (12%); pale yellow oil.

IR (neat): 3429, 2980, 2935, 1796, 1758, 1735, 1720, 1596, 1483, 1391, 1369, 1252, 1154 cm\textsuperscript{-1}.

HRMS (FAB): \textit{m/z} calcd for C\textsubscript{2}H\textsubscript{6}NO\textsubscript{3} ([M + H\textsuperscript{+}]): 498.2703; found: 498.2715.

3-(1-Amino-2-phenylethyl)-4-hydroxycyclobut-3-ene-1,2-dione (7)

To a solution of 5a (0.147 g, 0.32 mmol) in acetonitrile (0.6 mL) was added aq HCl (12 N; 0.5 mL). The mixture was stirred for 2 h at r.t. and concentrated in vacuo. The residue was purified by flash column chromatography on Cosmosil\textsuperscript{\textregistered} (H\textsubscript{2}O–MeOH, 9:1–1:1) to give 7.

Yield: 0.051 g (72%); as a white solid; mp 220–221 °C (decomp.).

IR (neat): 3338–2346 (br), 1769, 1712, 1600, 1571, 1566, 1459, 1377, 1176 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, DMSO-d\textsubscript{6}): \textit{\delta} = 8.39 (br s, 3 H), 7.27 (m, 5 H), 4.25 (br s 1 H), 3.26 (dd, J = 13.0, 9.3 Hz, 1 H), 3.13 (dd, J = 13.0, 4.8 Hz, 1 H).

13\textsuperscript{C} NMR (75 MHz, DMSO-d\textsubscript{6}): \textit{\delta} = 217.5, 197.6, 176.0, 136.4, 129.1, 128.5, 126.9, 47.3, 36.1.

HRMS (FAB): \textit{m/z} calcd for C\textsubscript{2}H\textsubscript{6}NO\textsubscript{3} ([M – H\textsuperscript{-}]): 216.0661; found: 216.0636.

3-Amino-3-(2-hydroxy-3,4-dioxocyclobut-1-yl)propionic Acid (8)

According to the procedure for the synthesis of 7, to a solution of 5b (0.188 g, 0.39 mmol) in acetonitrile (0.6 mL) was added aq HCl (12 N; 0.6 mL). The crude product was purified by flash column chromatography on Cosmosil\textsuperscript{\textregistered} (H\textsubscript{2}O) to give 8.

Yield: 0.058 g (81%); white solid; mp 186–187 °C (decomp.).

IR (neat): 3691–2500 (br), 1783, 1723, 1574, 1403, 1221 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, DMSO-d\textsubscript{6}); \textit{\delta} = 8.25 (br s, 3 H), 4.39 (br s 1 H), 3.0 (dd, J = 17.04, 6.4 Hz, 1 H), 2.78 (dd, J = 17.04, 6.4 Hz, 1 H).

13\textsuperscript{C} NMR (75 MHz, DMSO-d\textsubscript{6}); \textit{\delta} = 217.1, 196.8, 175.5, 171.0, 43.6, 34.6.

HRMS (FAB): \textit{m/z} calcd for C\textsubscript{2}H\textsubscript{6}NO\textsubscript{3} ([M – H\textsuperscript{-}]): 184.0246; found: 184.0234.

3-(1-Aminobut-3-enyl)-4-hydroxycyclobut-3-ene-1,2-dione (9)

According to the procedure for the synthesis of 7, to a solution of 5c (0.153 g, 0.37 mmol) in acetonitrile (0.6 mL) was treated with aq HCl (12 N; 0.6 mL). The crude product was purified by flash column chromatography on Cosmosil\textsuperscript{\textregistered} (H\textsubscript{2}O–MeOH, 9:1–1:1) to give 9.

Yield: 0.0544 g (80%); pale orange solid; mp 198–199 °C (decomp.).

IR (neat): 3545–2935 (br), 1774, 1714, 1566, 1493, 1444 cm\textsuperscript{-1}.

1\textsuperscript{H} NMR (300 MHz, DMSO-d\textsubscript{6}); \textit{\delta} = 8.05 (br s, 3 H), 5.67 (dddd, J = 17.0, 10.1, 6.96, 6.96 Hz, 1 H), 5.06 (d, J = 17.0 Hz, 1 H), 5.00 (d, J = 10.1 Hz, 1 H), 4.07 (br t, J = 6.03 Hz, 1 H), 2.66–2.38 (m, 2 H).

13\textsuperscript{C} NMR (75 MHz, DMSO-d\textsubscript{6}); \textit{\delta} = 217.2, 196.9, 176.2, 132.7, 119.0, 46.6, 35.2.

HRMS (CI): \textit{m/z} calcd for C\textsubscript{2}H\textsubscript{6}NO\textsubscript{3} (M\textsuperscript{+}): 167.0582; found: 167.0571.

3-(1-Aminobutyl)-4-hydroxycyclobut-3-ene-1,2-dione (10)

To a solution of 5e (0.106 g, 0.26 mmol) in MeOH (1.06 mL) was added 10% Pd–C (0.027 g) at r.t. The mixture was stirred under H\textsubscript{2} for 2 h at r.t., filtered through a Celite pad, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel; n-hexane–EtOAc, 9:1–1:1) to give tert-butyl 1-(tert-butoxycarbonyl)-1-(2-isoproxy-3,4-dioxocyclobut-1-yl)propylcarbamate.

Synthesis 2005, No. 16, 2723–2729 © Thieme Stuttgart · New York
Yield: 0.086 g (78%); pale yellow oil.

IR (neat): 3429, 2978, 2936, 2875, 1795, 1759, 1735, 1718, 1594, 1484, 1390, 1369, 1159, 1095, 1073 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 5.79 (br s, 1 H), 5.46 (sept, J = 6.24 Hz, 1 H), 2.43 (ddd, J = 13.9, 13.9, 4.6 Hz, 1 H), 2.23 (ddd, J = 13.9, 11.5, 4.6 Hz, 1 H), 1.46–1.05 (m, 26 H), 0.91 (t, J = 5.5 Hz, 3 H).

13C NMR (75 MHz, CDCl₃): δ = 195.3, 194.2, 191.3, 180.1, 167.6, 153.8, 84.1, 79.9, 79.6, 62.7, 35.1, 28.3, 27.7, 22.8, 16.8, 13.9.

HRMS (FAB): m/z calcd for C₂₅H₃₁NO₄ ([M + H]⁺): 412.2335; found: 412.2335.

According to the procedure for the synthesis of 7, the product (0.101 g, 0.21 mmol) described above in acetone (0.4 mL) was treated with aq HCl (12 N; 0.4 mL). The crude product was purified by flash column chromatography on Cosmosil® (H₂O–MeOH, 9:1–1:1) to give 10.

Yield: 0.021 g (52%); pale yellow solid; mp 186–187 °C (decomp.).

IR (neat): 3417–2956 (br), 1774, 1712, 1574, 1567, 1557 cm⁻¹.

Yield: 0.086 g (78%); pale yellow oil.

IR (neat): 3429, 2980, 2934, 1795, 1758, 1736, 1718, 1593, 1483, 1454, 1390, 1369, 1153, 1097, 1013 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 7.41–7.21 (m, 5 H), 5.95 (br s, 1 H), 5.56 (sept, J = 6.24 Hz, 1 H), 2.85–2.56 (m, 3 H), 2.44 (ddd, J = 16.5, 11.9, 4.4 Hz, 1 H), 1.79 (m, 1 H), 1.6–1.45 (m, 25 H).

13C NMR (75 MHz, CDCl₃): δ = 195.4, 194.1, 191.1, 180.1, 167.3, 153.8, 141.5, 128.4, 128.3, 125.9, 84.2, 80.0, 79.6, 62.6, 35.3, 32.4, 28.3, 27.6, 25.2, 22.8, 22.7.

HRMS (FAB): m/z calcd for C₂₅H₃₁NO₄ ([M + H⁺): 488.2468; found: 488.2625.

According to the procedure for the synthesis of 7, the product (0.101 g, 0.21 mmol) described above in acetone (0.4 mL) was treated with aq HCl (12 N; 0.5 mL). The crude product was purified by flash column chromatography on Cosmosil® (H₂O–MeOH, 9:1–1:1) to give 12.

Yield: 0.032 g (60%); pale orange solid; mp 189–190 °C (decomp.).

IR (neat): 3429, 2925, 2855, 1775, 1710 (br), 1591, 1556, 1463, 1377, 1172 (br) cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 8.1 (br s, 3 H), 7.3–7.1 (m, 5 H), 4.1 (dd, J = 6.5, 5.5 Hz, 1 H), 2.57 (t, J = 7.3 Hz, 2 H), 1.9–1.5 (m, 4 H).

13C NMR (75 MHz, DMSO-d₆): δ = 215.9, 197.1, 177.0, 141.6, 128.3, 128.2, 47.1, 34.7, 31.1, 26.8.

HRMS (FAB): m/z calcd for C₁₄H₇O₅N₂ ([M – H]⁻): 244.0974; found: 244.0975.

3-(1-Aminoethyl)-4-hydroxy-cyclobut-3-ene-1,2-dione (13)

According to the procedure for the synthesis of 7, 5g (0.109 g, 0.28 mmol) was treated with aq HCl (12 N; 0.5 mL). The crude product was purified by flash column chromatography on Cosmosil® (H₂O–MeOH, 9:1–1:1) to give 13.

Yield: 0.025 g (65%); white solid; mp 231–232 °C (decomp.).

IR (neat): 3430–2361 (br), 1770, 1712, 1463, 1377, 1183 cm⁻¹.

1H NMR (400 MHz, DMSO-d₆): δ = 8.21 (br s, 3 H), 7.3–7.1 (m, 5 H), 4.1 (dd, J = 6.5, 5.5 Hz, 1 H), 2.57 (t, J = 7.3 Hz, 2 H), 1.9–1.5 (m, 4 H).

13C NMR (75 MHz, DMSO-d₆): δ = 215.5, 196.8, 177.95, 43.5, 16.8.

HRMS (FAB): m/z calcd for C₁₄H₈NO₄ ([M – H]⁻): 140.0348; found: 140.0352.

4-Amino-4-(2-hydroxy-3,4-dioxocyclobut-1-enyl)butanoic Acid (14)

According to the procedure for the synthesis of 7, 5k (0.079 g, 0.18 mmol) was treated with aq HCl (12 N; 0.3 mL). The crude product was purified by flash column chromatography on Cosmosil® (H₂O–MeOH, 9:1–1:1) to give 14.

Yield: 0.025 g (71%); pale yellow solid; mp 209–210 °C (decomp.).

IR (neat): 3033, 2925, 2855, 1775, 1732, 1712, 1703, 1562, 1498, 1290, 1198, 1165 cm⁻¹.

1H NMR (300 MHz, DMSO-d₆): δ = 8.24 (br s, 3 H), 4.21 (dd, J = 10.8, 5.5 Hz, 1 H), 2.35 (m, 2 H), 2.04 (m, 2 H).

13C NMR (75 MHz, DMSO-d₆): δ = 216.7, 197.0, 176.2, 173.6, 46.5, 29.6, 26.6.

HRMS (FAB): m/z calcd for C₁₄H₈NO₄ ([M – H]⁻): 198.0402; found: 198.0420.

Conversion of tert-Butyl Ester 5l to 14

According to the procedure for the synthesis of 7, the product (0.062 g, 0.12 mmol) derived was purified by flash column chromatography on Cosmosil® (H₂O–MeOH, 9:1–1:1) to give 14.

The physical data was identical with those of 14 derived from 5k.

Yield: 0.016 g (67%); pale yellow solid.

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