

## PAPER

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# Development of a synthetic equivalent of $\alpha,\alpha$ -dicationic acetic acid leading to unnatural amino acid derivatives *via* tetrafunctionalized methanes†

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Diethyl mesoxalate (**DEMO**) exhibits high electrophilicity and accepts the nucleophilic addition of a less nucleophilic acid amide to afford *N,O*-hemiacetal. However, our research showed that elimination of the amide moiety proceeded more easily than dehydration upon treatment with a base. This problem was overcome by reacting **DEMO** with an acid amide in the presence of acetic anhydride to efficiently obtain *N,O*-acetal. Acetic acid was eliminated leading to the formation of *N*-acylimine *in situ* upon treatment with the base. *N*-Acylimine is also electrophilic, accepting the second nucleophilic addition by pyrrole or indole to form  $\alpha,\alpha$ -disubstituted malonates. Subsequent hydrolysis followed by decarboxylation resulted in ( $\alpha$ -indolyl- $\alpha$ -acylamino)acetic acid formation; homologs of tryptophan. Through this process, **DEMO** serves as a synthetic equivalent of  $\alpha,\alpha$ -dicationic acetic acid to facilitate nucleophilic introduction of the two substituents.

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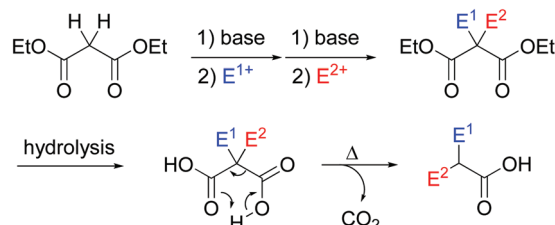
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## Introduction

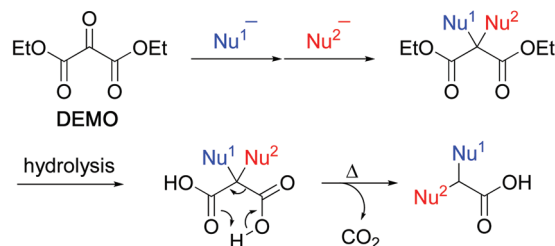
Malonic ester synthesis is an important tool for elaborate organic synthesis. The acidic methylene group readily generates enolate, which reacts with up to two electrophiles, and subsequent hydrolysis and decarboxylation lead to the formation of  $\alpha,\alpha$ -disubstituted acetic acids (Scheme 1, upper).<sup>1,2</sup> Through this process, diethyl malonate serves as a synthetic equivalent of  $\alpha,\alpha$ -dianionic acetic acid (Fig. 1, upper). In contrast, the central carbonyl carbon of **DEMO** (diethyl mesoxalate, diethyl oxomalonate, diethyl ketomalonate), one of the vicinal tricarbonyl compounds, is highly electrophilic and reacts with versatile nucleophiles to afford hemiacetals (Fig. 2,

path a).<sup>3,4</sup> High electrophilicity facilitates the nucleophilic addition of acid amide, which is considered a masked amino group but is not generally applied as a nucleophile.<sup>4</sup> If

### Malonic ester synthesis



### Present work



**Scheme 1** Synthetic schemes of  $\alpha,\alpha$ -disubstituted acetic acids using diethyl malonate (upper) and using **DEMO** (lower).

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†Electronic supplementary information (ESI) available: Spectral data and copies of NMR spectra of compounds 5–12 and 16, crystallographic data of 11j and 16h, and computational study for 5. CCDC 2130060 and 2130061. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ob02482e



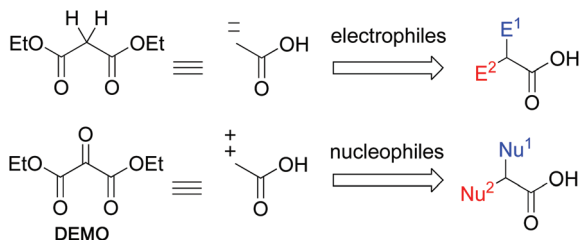


Fig. 1 Synthetic equivalents of  $\alpha,\alpha$ -dianionic and  $\alpha,\alpha$ -dicationic acetic acids.

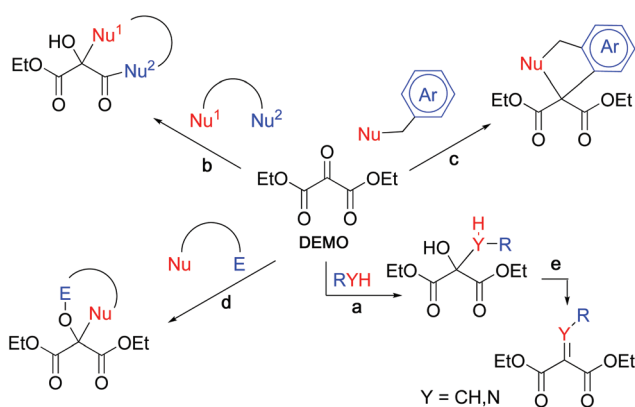


Fig. 2 Synthetic equivalents of  $\alpha,\alpha$ -dianionic and  $\alpha,\alpha$ -dicationic acetic acids.

$\alpha,\alpha$ -disubstituted malonates can be prepared from **DEMO** by successive nucleophilic reactions,  $\alpha,\alpha$ -disubstituted acetic acid can be obtained upon hydrolysis followed by decarboxylation (Scheme 1, lower). In this process, two types of substituents are introduced nucleophilically, indicating that **DEMO** acts as a synthetic equivalent of  $\alpha,\alpha$ -dicationic acetic acid (Fig. 1, lower).

Numerous organic reactions using **DEMO** have been reported in the literature, and can be categorized into several types (Fig. 2). In the reaction of **DEMO** with a dinucleophile, a new ring is formed between the central carbon and the adjacent ester functionality in almost all cases (path **b**).<sup>5</sup> Double addition to the central carbonyl group of **DEMO**, it is limited to intramolecular ring closure (path **c**);<sup>6</sup> however, to the best of our knowledge, the introduction of two substituents *via* successive double nucleophilic addition to the central carbon has not been performed. The chemical conversion of hemiacetals has been extensively studied. When reagents possess nucleophilic and electrophilic sites, the formed hemiacetal attacks the electrophilic site of the nucleophile *via* dipolar cycloaddition (path **d**).<sup>7</sup> Conversely, dehydration of the hemiacetal forms an electron-deficient double bond (path **e**),<sup>8–10</sup> which subsequently accepts the addition of less nucleophilic reagents, such as pyrrole.<sup>10</sup>

We focused on *N*-acylimines ( $Y = N$ ,  $R = \text{acyl}$ ), which can accept nucleophilic addition to form  $\alpha,\alpha$ -disubstituted malonates. However, the synthesis of *N*-acylimines involves multi-step reactions: nitrosoation at the  $\alpha$ -position of malonate,<sup>11</sup>

reduction to an amino group,<sup>11</sup> *N*-acylation,  $\alpha$ -bromination<sup>12</sup> and dehydrobromination.<sup>12</sup> Although *N*-acetylamine is directly prepared from **DEMO** *via* the aza-Wittig reaction, the *N*-substituent is limited to an acetyl group.<sup>9</sup> In our previous work, we demonstrated that **DEMO** efficiently reacted with versatile acid amides to afford the corresponding hemiacetals,<sup>4</sup> which serves as precursors of *N*-acylimines modifiable by the acyl group upon dehydration.

Considering the above-mentioned background and our previous work,<sup>4,10</sup> we planned a new synthetic strategy for unnatural amino acid derivatives using double nucleophilic addition to **DEMO**. The high electrophilicity of **DEMO** allows the attack of less nucleophilic acid amides, which facilitates the introduction of protected amino groups in a single step.<sup>4</sup> Dehydration of the obtained hemiacetals facilitates the formation of *N*-acylimines possessing versatile acyl groups, which are subjected to reactions with second nucleophiles such as pyrroles and indoles.<sup>10</sup> Subsequent hydrolysis, followed by decarboxylation, leads to the formation of *N*-protected unnatural amino acids.

Oligopeptides are widely used in medicinal chemistry; however, the diversity of the resulting framework is limited when natural amino acids are used as building blocks. Hence, the development of facile methods for the synthesis of unnatural amino acids has gained attention recently. Amino acids are generally synthesized by connecting small molecules *via* new bond formation (Fig. 3, methods **a–c**). Method **a** involves the substitution of  $\alpha$ -substituted  $\alpha$ -bromoacetic acid with ammonia or ammonium salt.<sup>13</sup> Method **b**, the Strecker reaction,<sup>14</sup> provides amino acids by the addition of cyanide to the  $\alpha$ -substituted imine, followed by hydrolysis of the cyano group. In these cases, precursors possessing a substituent at the  $\alpha$ -position should be prepared beforehand, which is a significant disadvantage when constructing a compound library. Reactions of masked amino acids (hydantoin) with aldehydes or ketones (method **c**) facilitate the modification of the  $\alpha$ -substituents; however, it is necessary to use a strong base and the subsequent hydrogenation limits usable substrates possessing a functional group.<sup>15</sup> A combination of methods **b** and **c**, referred as the Bucherer–Berger reaction, also furnishes

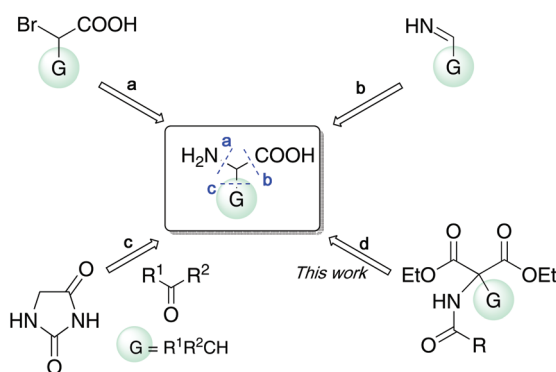


Fig. 3 Commonly used synthetic methods for  $\alpha$ -substituted amino acids.

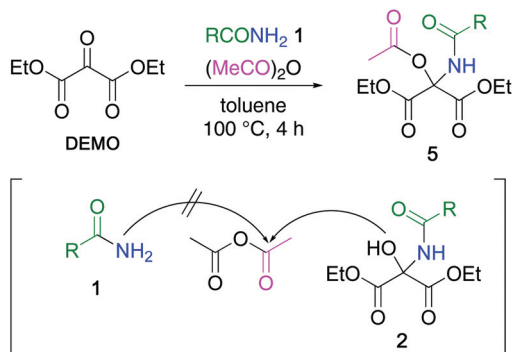


5,5-disubstituted hydantoin.<sup>16</sup> In contrast, our synthetic method (method **d**) achieved the synthesis of amino acid derivatives by decarboxylation<sup>17</sup> of  $\alpha,\alpha$ -disubstituted malonate, in which the  $\alpha$ -substituent is easily modified by altering the nucleophile. Because  $\alpha,\alpha$ -disubstituted malonate has multiple coordination sites, control of stereochemistry is expected to be easier than methods **a**–**c**.

## Results and discussion

4-Methylbenzamide **1a** (Scheme 1, R = 4-MeC<sub>6</sub>H<sub>4</sub>) was selected as a model substrate for the first nucleophile. Upon heating at 60 °C for 18 h in acetonitrile, **DEMO** reacted with **1a** to afford *N,O*-hemiacetal **2a** with 92% yield. When **2a** was subjected to the reaction with the second nucleophile, pyrrole **3**, under the same conditions, no reaction proceeded, presumably due to the congested structure and low electrophilicity of **2a**. Thus, the dehydration of **2a** leading to *N*-acylimine **4a** was studied. Although microwave heating (at 140 °C) and treatment with acids (BF<sub>3</sub>·OEt<sub>2</sub>, H<sub>2</sub>SO<sub>4</sub>), bases (NEt<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, *tert*-BuOK), or molecular sieves 3 Å were attempted, the recovery of **2a** or elimination of amide **1a** yielding **DEMO** was observed without any detectable **4a**. The low reactivity of **2a** was due to the reduced elimination ability and high acidity of the hydroxy group. This disadvantage was addressed by using the reaction between **DEMO** and **1a** in the presence of acetic anhydride. Although the less nucleophilic **1a** cannot attack acetic anhydride, the formed *N,O*-hemiacetal **2a** can attack it by mooring the amide functionality to afford *N,O*-acetal **5a** (Scheme 2). However, only trace amounts of **5a** were detected, which was due to the competitive hydration of **DEMO** leading to the formation of *gem*-diol (Table 1, entry 1). The addition of molecular sieves 3 Å considerably increased the yield, and **5a** was quantitatively obtained when two equivalents of acetic anhydride were utilized (entries 2 and 3).

The preparative method was applied to other acid amides **1b–j** (R = Ph **1b**, C<sub>6</sub>F<sub>5</sub> **1c**, Me **1d**, Et **1e**, Pr **1f**, Me(CH<sub>2</sub>)<sub>10</sub> **1g**, *tert*-Bu **1h**, CF<sub>3</sub> **1i**, *tert*-BuO **1j**) to quantitatively afford the corresponding *N,O*-acetals **5b–j**, except for **5i** (94% yield). It is



**Scheme 2** Synthesis of *N,O*-acetal **5** by nucleophilic addition of amide **1** to **DEMO** in the presence of acetic anhydride.

**Table 1** Optimization of reaction conditions for forming **5a**

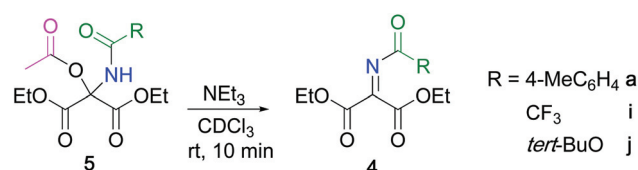
|   | Ac <sub>2</sub> O/equiv. | Additive             | Yield of <b>5a</b> /% |
|---|--------------------------|----------------------|-----------------------|
| 1 | 1                        | —                    | 4                     |
| 2 | 1                        | Molecular sieves 3 Å | 72                    |
| 3 | 2                        | Molecular sieves 3 Å | Quant.                |

noteworthy that the reaction proceeded efficiently even in the case of highly electron-deficient amides such as pentafluorobenzamide **1c** and trifluoroacetamide **1i**, and bulky pivalamide **1h**. In addition, this protocol enabled the direct introduction of Boc-protected amino group by using urethane **1j**.

Next, the formation of *N*-acylimine **4** was investigated (Scheme 3). When *N,O*-acetal **5a** was treated with triethylamine at room temperature in chloroform-*d*, acetic acid was easily eliminated, leading to *N*-acylimine **4a** *in situ*, which was confirmed by the <sup>1</sup>H and <sup>13</sup>C NMR spectra. Other *N*-acylimines, **4i** and **4j**, were similarly obtained from **5i** and **5j**, respectively.

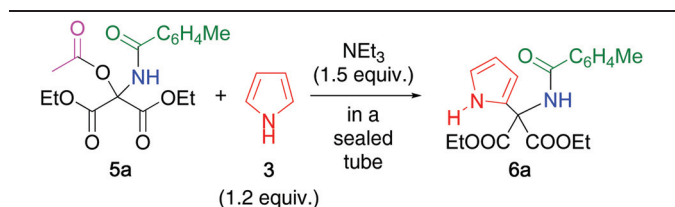
The generated *N*-acylimines **4** were subjected to a second nucleophilic addition in one-pot without the isolation of **4** because they gradually hydrolyze leading to **DEMO** and amide **1**. To a solution of *N,O*-acetal **5a** in toluene, were added triethylamine and pyrrole **3**, and the resulting mixture was heated at 50 °C for 1 d in a sealed tube to produce the double adduct **6a** with 26% yield (Table 2, entry 1). Elevating the temperature and using 1.2 equiv. of **3** increased reaction efficiency (entries 2–5). Among the solvents tested, toluene was the most suitable (entries 6–8). Consequently, the reaction conditions in entry 4 were determined to be optimal.

In the series of reactions listed in Table 2, the reaction mixture was washed with hydrochloric acid to remove the base, during which adduct **6a** was obtained without decomposition. Approximately half of the **6a** decomposed to **DEMO** and amide **1a** upon treatment with column chromatography on silica gel. This was presumably because of the difference in time under acidic conditions. A plausible mechanism for this phenomenon is shown in Scheme 3. After prototropy from 1-position to 2-position of the pyrrole ring, pyrrole **3** was eliminated to afford **DEMO** and benzamide **1a** *via* the hydrolysis of the intermediately formed *N*-acylimine **4a** (Scheme 4).



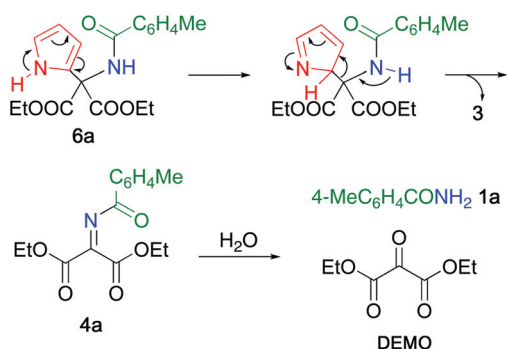
**Scheme 3** Conversion of *N,O*-acetal **5** to *N*-acylimine **4**.



Table 2 Optimization of reaction conditions for the synthesis of **6a**

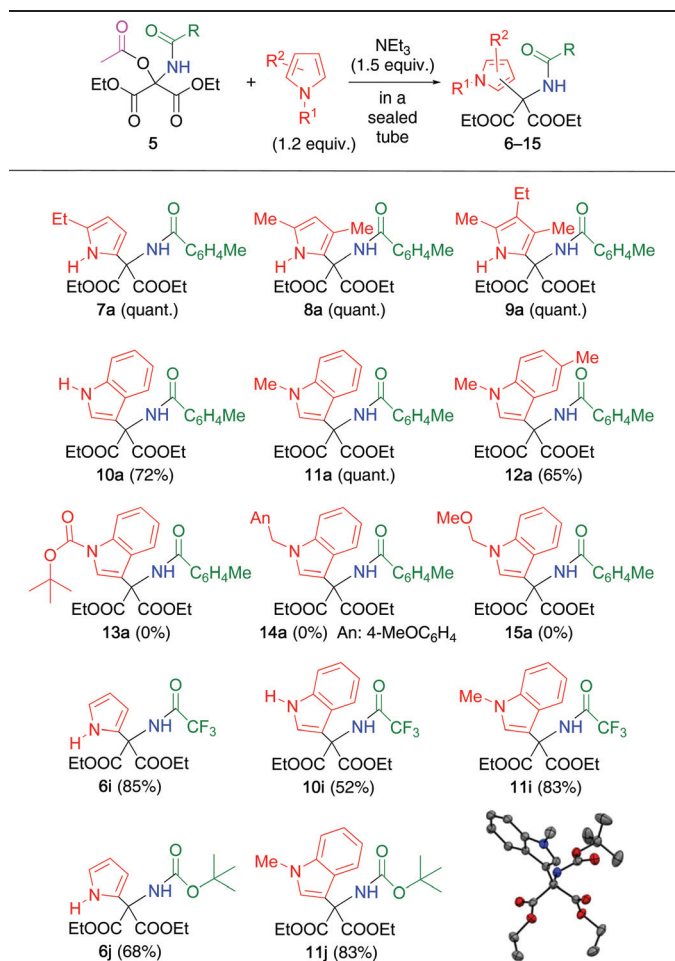
| Entry          | Solv.           | Temp./°C | Time/h | Yield <sup>a</sup> /% |
|----------------|-----------------|----------|--------|-----------------------|
| 1              | Toluene         | 50       | 24     | 26                    |
| 2              | Toluene         | 80       | 24     | 82                    |
| 3              | Toluene         | 80       | 3      | 75                    |
| 4              | Toluene         | 120      | 3      | 88                    |
| 5 <sup>b</sup> | Toluene         | 120      | 3      | 67                    |
| 6              | $\text{CHCl}_3$ | 120      | 3      | 64                    |
| 7              | THF             | 120      | 3      | 42                    |
| 8              | Acetonitrile    | 120      | 3      | 37                    |

<sup>a</sup> Determined by  $^1\text{H}$  NMR. <sup>b</sup> 1.0 equiv. of **3** was used.

Scheme 4 A plausible mechanism for the decomposition of double adduct **6a**.

The optimized conditions were applied to other *N,O*-acetals **5** and pyrroles/indoles (Table 3). Although double adducts **6–11** were purified by extraction or recrystallization, it was sometimes difficult, depending on the structure of the substrates **1** and pyrroles/indoles. Alkyl-substituted pyrroles efficiently underwent nucleophilic addition to **5a**, leading to adducts **7a–9a** because of the high electron density on the pyrrole ring. Indole (benzo[*b*]pyrrole) reacted with **5a** to produce adduct **10a**, which was also unstable under acidic conditions. In this case, prototropy from the 1-position to the 3-position of the indole ring was a key step. Adducts **11a** and **12a** obtained from the corresponding *N*-methylindoles, respectively, were stable for purification by using column chromatography on silica gel. Hence, other *N*-protected indoles were employed; however, adducts **13a–15a** were not detected because of the electron-withdrawing properties and steric hindrance of the *N*-substituent. *N*-Trifluoroacetyl and *N*-Boc *N,O*-acetals **5i** and **5j**, respectively, exhibited similar reactivities to furnish the corresponding double adducts **6** and **11**.

Surprisingly, the reaction of *N*-acetyl-*N,O*-acetal **5d** with *N*-methylindole resulted in only trace amounts of adduct **11d**,

Table 3 Synthesis of other double adducts **6–15**<sup>a</sup>

<sup>a</sup> A toluene solution of *N,O*-acetal **5** and pyrrole/indole (1.2 equiv.), and triethylamine (1.5 equiv.) was heated at 120 °C for 3 h in a sealed tube. The yields were determined by  $^1\text{H}$  NMR.

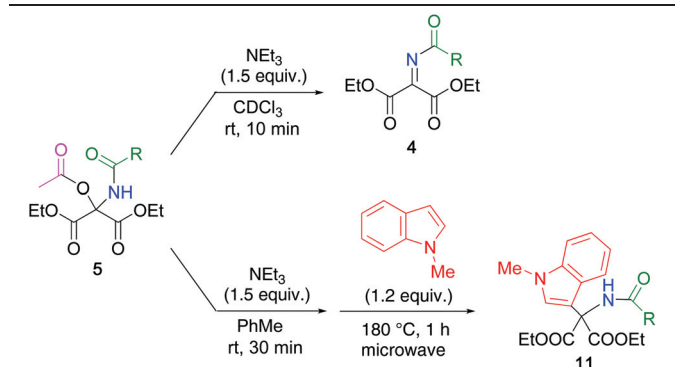
even though severe reaction conditions were utilized (Table 4, entry 1). When the reaction was monitored by  $^1\text{H}$  NMR, only a small amount of *N*-acylimine **4d** was detected, which indicates that the yield of **11d** has a parallel relationship with the efficiency generation of **4d**. Interestingly, the longer the alkyl group, the higher the yield of **11** (entries 1–4), and the bulkiness of the alkyl group was found to increase the reactivity of *N,O*-acetal **5**. *N,O*-Acetal **5h** derived from pivalamide **1h** exhibited considerably higher reactivity to afford **11h** with 57% yield (entry 5).

To gain insight into this steric effect, DFT calculations were conducted for **5d** (*R* = Me), **5h** (*R* = *tert*-Bu), and **5k** (*R* = Bu); however, notable differences in bond lengths and bond angles between them were not confirmed. Although no clear evidence was obtained, one possible reason is as follows: when the bulky *N*-acyl group repels with ethoxycarbonyl groups, the *N*-H and acetyl groups are closed together, which accelerates the elimination of acetic acid (Fig. 4).

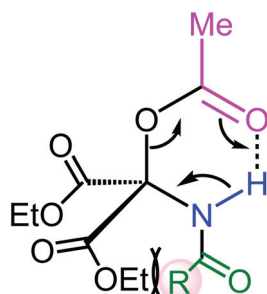
The synthesized  $\alpha,\alpha$ -disubstituted malonates **11** were subjected to hydrolysis under various conditions. In the cases of





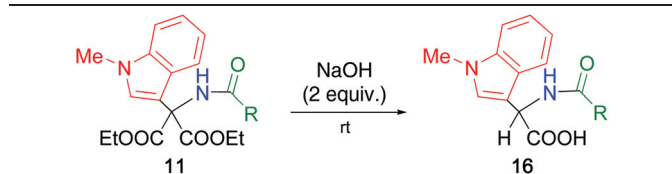
**Table 4** Effect of the alkyl group of *N,O*-acetal **5** for the formation of **4** and for the second addition of *N*-methylindole leading to **11**

| Entry | R                  |          | Yield of <b>4</b> <sup>a</sup> /% | Yield of <b>11</b> <sup>a</sup> /% |
|-------|--------------------|----------|-----------------------------------|------------------------------------|
| 1     | Me                 | <b>d</b> | 0                                 | 2                                  |
| 2     | Et                 | <b>e</b> | 5                                 | 11                                 |
| 3     | Pr                 | <b>f</b> | 12                                | 23                                 |
| 4     | Undec <sup>b</sup> | <b>g</b> | 8                                 | 21                                 |
| 5     | <i>tert</i> -Bu    | <b>h</b> | 42                                | 57                                 |

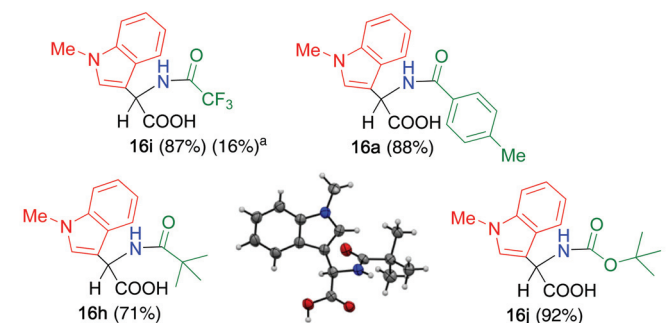
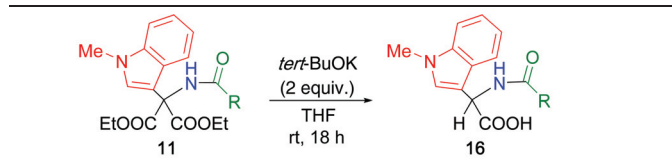
<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Undec: -(CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>.**Fig. 4** Elimination of acetic acid leading to *N*-acylimine **4**.

**6a** and **10a**, all attempts failed because the presence of the N-H group caused prototropy followed by elimination of the heteroaromatic moiety, as shown in Scheme 3. However, such decomposition was not observed for **11a** derived from *N*-methylindole. Hence, the reaction conditions were investigated using **11** (Table 5). When the double adduct **11a** was treated with sodium hydroxide in ethanol, hydrolysis and subsequent decarboxylation proceeded quantitatively to afford α,α-disubstituted acetic acid **16a** (entry 1). Boc-substituted adduct **11j** also supplied only decarboxylated product **16j** without any detectable malonic acid (entry 2). In the case of trifluoroacetyl adduct **11i**, only a complex mixture was obtained under both the reaction conditions (entries 3 and 4).

The reaction conditions were tested again using **11i**, which is more reactive than **11a** and **11j**. Several bases and solvents were evaluated, among which a combination of potassium *tert*-butoxide and THF was effective for hydrolysis, followed by decarboxylation, leading to **16i** with 87% yield (Table 6). In this reaction, the water contained in THF acted as a source of hydroxide. The yield considerably decreased when the same

**Table 5** Hydrolysis of adduct **11** leading to α,α-disubstituted acetic acid **16**

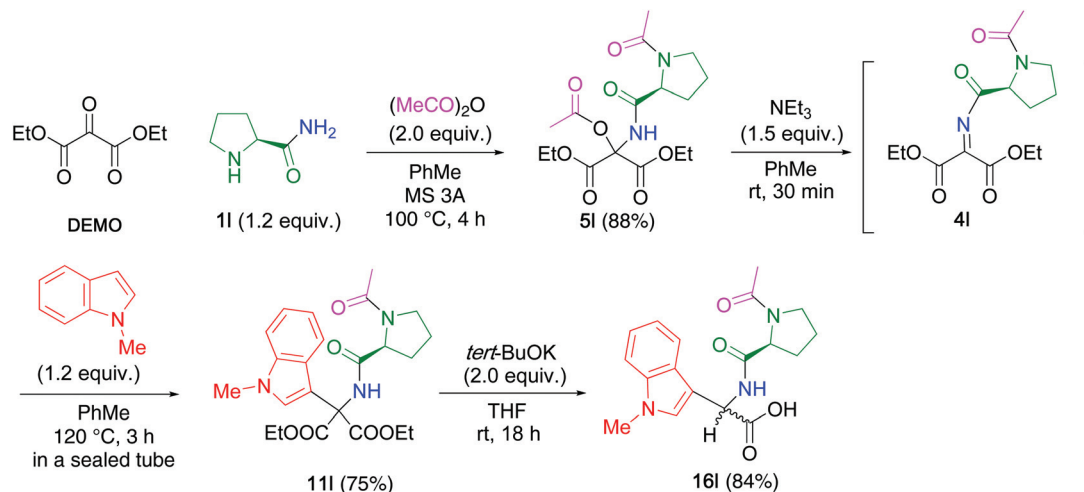
| Entry | R                | Substrate  | Solv. | Time/h | Yield <sup>a</sup> /% |
|-------|------------------|------------|-------|--------|-----------------------|
| 1     | Tol              | <b>11a</b> | EtOH  | 3      | Quant.                |
| 2     | <i>tert</i> -BuO | <b>11j</b> | EtOH  | 3      | 80                    |
| 3     | CF <sub>3</sub>  | <b>11i</b> | EtOH  | 3      | — <sup>b</sup>        |
| 4     | CF <sub>3</sub>  | <b>11i</b> | MeCN  | 18     | — <sup>b</sup>        |

<sup>a</sup> Determined by <sup>1</sup>H NMR. <sup>b</sup> Complex mixture.**Table 6** Hydrolysis and decarboxylation of double adducts **11**<sup>a</sup> Dry THF was used in an argon atmosphere.

reaction was conducted under the same conditions in an argon atmosphere using dry THF as the solvent. Optimized conditions were applied to the other adducts **11**. Toluoyl-substituted adduct **11a** was efficiently converted to **16a**. Adducts possessing a bulky acyl group, such as pivaloyl and *tert*-butoxycarbonyl (Boc) groups, underwent hydrolysis and decarboxylation to produce the corresponding α,α-disubstituted acetic acids **16h** and **16j**, respectively. The α-amino acid derivatives **16** are homologs of tryptophan, which is expected to be useful for identifying new biologically active compounds.

This protocol facilitates modification of the acyl group by altering amide **1**. Synthesis of dipeptide was attempted using this feature (Scheme 5). When **DEMO** was reacted with *L*-prolineamide **11** in the presence of acetic anhydride, protection of not only the hydroxy group but also the ring nitrogen of the pyrrolidine was achieved. This is because amine can attack anhydride while amide cannot, by which doubly acetyl-





**Scheme 5** Synthesis of amino acid derivative **7Lf** using prolineamide **1L**.

ated *N,O*-acetal **5I** was obtained with 88% yield. After the generation of *N*-acylimine **4I** by triethylamine *in situ*, a second nucleophilic addition by *N*-methylindole formed **11I** with 75% yield. Subsequent treatment with potassium *tert*-butoxide in THF resulted in the hydrolysis of ester functions, followed by decarboxylation, and resulted in the dipeptide **16I** with 84% yield. In the  $^1\text{H}$  NMR of **16I**, signals of four kinds of isomers were observed. When this compound was subjected to the measurement of temperature-variable NMR spectra, each type of signals coalesced (see ESI†). Hence, these isomers are not diastereomers caused by two chiral centers but rotamers caused by two amide functions.

## Conclusions

A new approach for unnatural amino acid derivatives was demonstrated using **DEMO**. The high electrophilicity of **DEMO** facilitates the acceptance of the double nucleophilic addition *via* *N*-acylimine **4**. In this protocol, an even less nucleophilic acid amide can be used as the first nucleophile, and pyrroles and indoles **3** are used as the second nucleophile, which produced  $\alpha,\alpha$ -disubstituted malonates **6–12**. Subsequent hydrolysis followed by decarboxylation furnished ( $\alpha$ -indolyl- $\alpha$ -acylamino)acetic acids **11**, which are homologs of tryptophan. Through this process, **DEMO** served as a synthetic equivalent of  $\alpha,\alpha$ -dicationic acetic acid to nucleophilically introduce two substituents. The application of this method by using other nucleophiles is currently being studied, and the results will be shown in subsequent papers.

## Experimental section

### General

All reagents were purchased from commercial sources and used without further purification. Dry acetonitrile was also

purchased from commercial source and used as received.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on Bruker DPX-400 and JEOL JMN-ECZ400S spectrometers (400 MHz and 100 MHz, respectively) using TMS as an internal standard. The assignments of the  $^{13}\text{C}$  NMR were performed by DEPT experiments. IR spectra were recorded on a JASCO FT/IR-4200 spectrometer equipped with an ATM detector. High-resolution mass spectra were obtained on an AB SCEIX Triplet TOF 4600 mass spectrometer. Melting points were recorded on an SRS-Optimelt automated melting point system and were uncorrected. HPLC analysis was directly performed with chiral stationary phase column, DAICEL CHIRALPAK or CHIRALCEL. Diffraction data were collected at 93 K under a cold  $\text{N}_2$ -gas stream on a Rigaku XtaLAB Synergy-S/Mo system ( $\lambda = 0.71073 \text{ \AA}$  (Mo-K $\alpha$ )). The integrated data were analyzed by using an Olex2 crystallographic software package.<sup>18</sup> The structures were solved with the ShelXT structure solution program<sup>19</sup> using Intrinsic Phasing and refined with the ShelXL refinement package<sup>20</sup> using the least-squares minimization. Anisotropic refinement was performed for all non-hydrogen atoms, and all the hydrogen atoms were put at calculated positions.<sup>18–20</sup> The geometrical optimization was carried out for at the B3LYP/6-31 g(d,p) level of theory implemented on Gaussian 09 package.<sup>21</sup>

### General procedure for synthesis of *N,O*-acetal **5**

To a solution of **DEMO** (0.87 g, 5.0 mmol) in toluene (20 mL), 4-methylbenzamide **1a** (0.81 g, 6.0 mmol), molecular sieves 3A (1.7 g) and acetic anhydride (1.1 g, 10 mmol) were added, and the resultant mixture was heated at 100 °C for 4 h. After filtration of molecular sieves, the filtrate was washed with water (30 mL  $\times$  2), dried over magnesium sulfate, and concentrated *in vacuo* to afford *N,O*-acetal **5a** (1.36 g, 4.94 mmol, yield 99%) as a white solid.

For the synthesis of other *N,O*-acetals **5b–j**, the same experiments were conducted.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -[(4-methylbenzoyl)amino]malonate (**5a**).** Yield 99%. White solid, mp 121–122 °C.  $^1\text{H}$  NMR (400 MHz,



$\text{CDCl}_3$ )  $\delta$  8.07 (1H, br s), 7.74 (2H, d,  $J$  = 8.0 Hz), 7.26 (2H, d,  $J$  = 8.0 Hz), 4.33 (4H, q,  $J$  = 7.2 Hz), 2.41 (3H, s), 2.19 (3H, s), 1.28 (6H, t,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 21.6 ( $\text{CH}_3$ ), 63.6 ( $\text{CH}_2$ ), 82.1 (C), 127.5 (CH), 129.4 (CH), 143.3 (C), 163.7 (C), 165.9 (C), 170.2 (C), one signal for quaternary carbon was not observed presumably due to overlapping; IR (ATR, KBr)  $\nu$  = 1679, 1758, 3427  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{21}\text{O}_7\text{N}$   $[\text{M} + \text{H}]^+$  352.1391; found 352.1393.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(benzoylamino)malonate (5b).**<sup>4</sup> Yield quant. White solid, mp 50.5–51.2 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.11 (1H, s), 7.84 (2H, d,  $J$  = 7.2 Hz), 7.56 (1H, t,  $J$  = 7.2 Hz), 7.47 (2H, dd,  $J$  = 7.2, 7.2 Hz), 4.34 (4H, q,  $J$  = 7.2 Hz), 2.20 (3H, s), 1.29 (6H, t,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.9 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 63.7 ( $\text{CH}_2$ ), 82.1 (C), 127.5 (CH), 128.8 (CH), 132.3 (C), 132.6 (CH), 163.6 (C), 165.9 (C), 170.2 (C); IR (ATR)  $\nu$  = 1672, 1744, 3318  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{19}\text{NNaO}_7$   $[\text{M} + \text{Na}]^+$ : 360.1054; found 360.1059.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(pentafluorobenzoylamino)malonate (5c).** Yield 99%. White solid, mp 131–132 °C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.01 (1H, br s), 4.40–4.25 (4H, m), 2.23 (3H, s), 1.29 (3H, dd,  $J$  = 7.2, 7.2 Hz), 1.27 (3H, dd,  $J$  = 7.2, 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 20.6 ( $\text{CH}_3$ ), 64.0 ( $\text{CH}_2$ ), 81.5 (C), 128.8 (C), 130.9 (C), 156.6 (C), 162.7 (C), 169.8 (C); IR (ATR, KBr)  $\nu$  = 1690, 1761, 3299  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{15}\text{O}_7\text{NF}_5$   $[\text{M} + \text{H}]^+$  428.0763; found 428.0782.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(acetylamino)malonate (5d).**<sup>4</sup> Yield 99%. White solid, mp 96.4–96.7 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (1H, br s), 4.30 (4H, q,  $J$  = 7.2 Hz), 2.19 (3H, s), 2.07 (3H, s), 1.28 (6H, t,  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 22.8 ( $\text{CH}_3$ ), 63.6 ( $\text{CH}_2$ ), 81.8 (C), 163.5 (C), 169.3 (C), 170.1 (C); IR (ATR, KBr)  $\nu$  = 1694, 1765, 3359  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_{18}\text{O}_7\text{N}$   $[\text{M} + \text{H}]^+$  276.1078; found 276.1078.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(propanoylamino)malonate (5e).** Yield quant. White solid, mp 67.1–67.7 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.41 (1H, br s), 4.30 (4H, q,  $J$  = 7.2 Hz), 2.30 (2H, q,  $J$  = 7.6 Hz), 2.27 (3H, s), 1.27 (6H, t,  $J$  = 7.2 Hz), 1.15 (3H, t,  $J$  = 7.6 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  9.1 ( $\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 29.0 ( $\text{CH}_2$ ), 63.6 ( $\text{CH}_2$ ), 81.8 (C), 163.6 (C), 170.2 (C), 172.8 (C); IR (ATR, KBr)  $\nu$  = 1698, 1765, 3284  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{12}\text{H}_{21}\text{O}_7\text{N}$   $[\text{M} + \text{H}]^+$  290.1234; found 290.1234.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(butanoylamino)malonate (5f).** Yield quant. White solid, mp 65.9–66.1 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.42 (1H, br s), 4.30 (4H, q,  $J$  = 7.2 Hz), 2.24 (2H, t,  $J$  = 7.6 Hz), 2.18 (3H, s), 1.66 (2H, tq,  $J$  = 7.6, 7.6 Hz), 1.27 (6H, t,  $J$  = 7.2 Hz), 0.95 (3H, t,  $J$  = 7.6 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.5 ( $\text{CH}_3$ ), 13.9 ( $\text{CH}_3$ ), 18.7 ( $\text{CH}_2$ ), 20.9 ( $\text{CH}_3$ ), 37.7 ( $\text{CH}_2$ ), 63.6 ( $\text{CH}_2$ ), 81.7 (C), 163.5 (C), 170.1 (C), 172.1 (C); IR (ATR, KBr)  $\nu$  = 1694, 1758, 3363  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{13}\text{H}_{23}\text{O}_7\text{N}$   $[\text{M} + \text{H}]^+$  304.1399; found 304.1391.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(dodecanoylamino)malonate (5g).** Yield quant. Brown solid, mp 58–59 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.39 (1H, br s), 4.30 (4H, q,  $J$  = 7.2 Hz), 2.25 (2H, t,  $J$  = 7.6 Hz), 2.17 (3H, s), 1.62 (2H, tt,  $J$  = 7.2, 7.2 Hz), 1.25–1.29 (22H, m),

0.88 (3H, t,  $J$  = 6.8 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 14.1 ( $\text{CH}_3$ ), 20.8 ( $\text{CH}_3$ ), 22.7 ( $\text{CH}_3$ ), 25.1 ( $\text{CH}_2$ ), 29.0 ( $\text{CH}_2$ ), 29.2 ( $\text{CH}_2$ ), 29.3 ( $\text{CH}_2$ ), 29.4 ( $\text{CH}_2$ ), 29.6 ( $\text{CH}_2$ ), 31.9 ( $\text{CH}_2$ ), 35.9 ( $\text{CH}_2$ ), 63.5 ( $\text{CH}_2$ ), 81.7 (C), 163.5 (C), 170.1 (C), 172.1 (C); IR (ATR, KBr)  $\nu$  = 1756, 3363  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{37}\text{O}_7\text{NNa}$   $[\text{M} + \text{Na}]^+$  438.2462; found 438.2442.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -(pivaloylamino)malonate (5h).** Yield quant. White solid, mp 67.6–68.3 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.62 (1H, br s), 4.31 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.27 (2H, dq,  $J$  = 7.2, 10.8 Hz), 2.18 (3H, s), 1.27 (6H, dd,  $J$  = 7.2, 7.2 Hz), 1.22 (9H, s);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 20.9 ( $\text{CH}_3$ ), 27.0 ( $\text{CH}_3$ ), 38.7 (C), 63.4 ( $\text{CH}_2$ ), 81.9 (C), 163.6 (C), 170.1 (C), 177.4 (C); IR (ATR, KBr)  $\nu$  = 1694, 1762, 3438  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_7\text{N}$   $[\text{M} + \text{H}]^+$  318.1547; found 318.1555.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -[(trifluoroacetyl)amino]malonate (5i).** Yield 97%. White solid, mp 39.8–40.3 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (1H, br s), 4.36 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.31 (2H, dq,  $J$  = 7.2, 10.8 Hz), 2.21 (3H, s), 1.28 (6H, dd,  $J$  = 7.2, 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.7 ( $\text{CH}_3$ ), 20.5 ( $\text{CH}_3$ ), 64.3 ( $\text{CH}_2$ ), 80.9 (C), 115.0 (q,  $J_{\text{C-F}}$  = 286 Hz), 156.0 (q,  $J_{\text{C-F}}$  = 39 Hz), 162.2 (C), 169.6 (C); IR (ATR, KBr)  $\nu$  = 1753 (br), 3327  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{11}\text{H}_{14}\text{O}_7\text{N}_2\text{F}_3\text{Na}$   $[\text{M} + \text{Na}]^+$  352.0615; found 352.0624.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -[(*tert*-butoxycarbonyl)amino]malonate (5j).** Yield 93%. Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.63 (1H, br s), 4.36–4.23 (4H, m), 2.19 (3H, s), 1.272 (3H, dd,  $J$  = 7.2, 7.2 Hz), 1.268 (3H, dd,  $J$  = 7.2, 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), 28.1 ( $\text{CH}_3$ ), 30.9 (C), 63.4 ( $\text{CH}_2$ ), 83.0 (C), 153.0 (C), 163.5 (C), 170.0 (C); IR (ATR, KBr)  $\nu$  = 1762 (br), 3426  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_8\text{N}$   $[\text{M} + \text{H}]^+$  334.1496; found 334.1491.

**Diethyl  $\alpha$ -acetoxy- $\alpha$ -[1-acetyl-L-prolylamino]malonate (5l).** Yield 88%. Colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.71 (br s, 1H), 4.57 (dd,  $J$  = 8.2, 2.5 Hz, 1H), 4.45–4.06 (m, 4H) (ddd,  $J$  = 7.2, 2.5 Hz, 2H), 3.56 (ddd,  $J$  = 9.3, 7.9, 3.4 Hz, 1H), 3.44 (ddd,  $J$  = 9.3, 9.3, 7.1 Hz, 1H), 2.30 (ddd,  $J$  = 9.3, 6.3, 3.4 Hz, 1H), 2.16 (s, 3H), 2.11 (s, 3H), 2.09–1.83 (m, 3H), 1.26 (td,  $J$  = 7.2, 2.5 Hz, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.0 (C), 170.9 (C), 169.8 (C), 163.6 (C), 82.2 (C), 63.50 ( $\text{CH}_2$ ), 63.47 ( $\text{CH}_2$ ), 59.5 ( $\text{CH}_3$ ), 48.2 ( $\text{CH}_2$ ), 27.6 ( $\text{CH}_2$ ), 25.1 ( $\text{CH}_2$ ), 22.4 ( $\text{CH}_3$ ), 21.0 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ); IR (ATR, KBr)  $\nu$  = 1762 (br), 3426  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{14}\text{H}_{24}\text{O}_8\text{N}$   $[\text{M} + \text{H}]^+$  334.1496; found 334.1491.

## General procedure for synthesis of double adduct 6

In a screw capped test-tube, a toluene solution (3 mL) of *N,O*-acetal **5a** (140 mg, 0.4 mmol), triethylamine (84  $\mu\text{L}$ , 0.6 mmol), and 1-methylindole (63 mg, 0.48 mmol) was heated at 120 °C for 3 h. The resultant solution was poured into chloroform (50 mL), and 12 M hydrochloric acid (1 mL, 12 mmol) was added, then, washed with water (50 mL  $\times$  2). The organic layer was dried over magnesium sulfate and concentrated. The residue was washed with hexane (100 mL) to afford double adduct **11a** (169 mg, 0.4 mmol, yield quant.) as a white solid.



Further purification was performed by recrystallization from mixed solvent (Et<sub>2</sub>O–hexane).

The experimental procedure were conducted in the same way for the synthesis of other double adducts 6–12.

**Diethyl  $\alpha$ -[(4-methylbenzoyl)amino]- $\alpha$ -(1-methylindol-3-yl) malonate (11a).** Yield 97%. Colorless plates (from Et<sub>2</sub>O–hexane), mp 124.2–124.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.01 (1H, br s), 7.76 (1H, s), 7.73 (2H, d,  $J$  = 8.0 Hz), 7.66 (1H, d,  $J$  = 8.0 Hz), 7.27 (1H, d,  $J$  = 8.0 Hz), 7.23 (2H, d,  $J$  = 8.0 Hz), 7.18 (1H, ddd,  $J$  = 8.0, 6.8, 1.2 Hz), 7.07 (1H, ddd,  $J$  = 8.0, 6.8, 1.2 Hz), 4.34 (2H, dq,  $J$  = 6.8, 10.8 Hz), 4.24 (2H, dq,  $J$  = 6.8, 10.8 Hz), 3.76 (3H, s), 2.39 (3H, s), 1.24 (6H, dd,  $J$  = 6.8, 6.8 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  14.0 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 33.0 (CH<sub>3</sub>), 62.8 (CH<sub>2</sub>), 65.1 (C), 108.2 (C), 109.5 (CH), 119.5 (CH), 120.0 (CH), 121.4 (CH), 125.8 (C), 127.2 (CH), 129.2 (CH), 130.5 (CH), 130.8 (C), 137.0 (C), 142.3 (C), 165.6 (C), 167.9 (C); IR (ATR, KBr)  $\nu$  = 1670, 1738, 3418 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>24</sub>H<sub>26</sub>O<sub>5</sub>N<sub>2</sub>Na [M + Na]<sup>+</sup> 446.1812; found 446.1802.

**Diethyl  $\alpha$ -[(4-methylbenzoyl)amino]- $\alpha$ -(1H-pyrrol-2-yl) malonate (6a).** Yield 88%. Yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.8–9.7 (1H, br), 7.92 (1H, br s), 7.72 (2H, d,  $J$  = 8.0 Hz), 7.25 (2H, d,  $J$  = 8.0 Hz), 6.79 (1H, ddd,  $J$  = 0.8, 2.8, 2.8 Hz), 6.10 (1H, ddd,  $J$  = 2.8, 2.8, 3.2 Hz), 6.02 (1H, ddd,  $J$  = 1.6, 2.8, 2.8 Hz), 4.37 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.32 (2H, dq,  $J$  = 7.2, 10.8 Hz), 2.40 (s, 3H), 1.29 (6H, dd,  $J$  = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  14.0 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 63.2 (CH<sub>2</sub>), 65.3 (C), 107.2 (CH), 107.3 (CH), 118.9 (CH), 126.9 (C), 127.3 (CH), 129.3 (CH), 130.1 (C), 142.8 (C), 166.9 (C), 167.0 (C); IR (ATR, KBr)  $\nu$  = 1658, 1741, 3414 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>19</sub>H<sub>23</sub>O<sub>5</sub>N<sub>2</sub> [M + H]<sup>+</sup> 359.1602; found 359.1608.

**Diethyl  $\alpha$ -(5-ethyl-1H-pyrrol-2-yl)- $\alpha$ -[(4-methylbenzoyl)amino]malonate (7a).** Yield quant. Yellow solid, mp 125.8–126.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.5–9.3 (1H, br), 7.89 (1H, br s), 7.71 (2H, d,  $J$  = 8.0 Hz), 7.25 (2H, d,  $J$  = 8.0 Hz), 5.89 (1H, dd,  $J$  = 2.8, 3.2 Hz), 5.79 (1H, ddd,  $J$  = 0.8, 2.8, 3.2 Hz), 4.35 (4H, q,  $J$  = 7.2 Hz), 2.62 (2H, q,  $J$  = 7.6 Hz), 2.40 (3H, s), 1.29 (6H, t,  $J$  = 7.2 Hz), 1.22 (3H, t,  $J$  = 7.6 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  13.3 (CH<sub>3</sub>), 14.0 (CH<sub>3</sub>), 20.9 (CH<sub>2</sub>), 21.5 (CH<sub>3</sub>), 63.1 (CH<sub>2</sub>), 65.1 (C), 103.4 (CH), 107.3 (CH), 125.1 (C), 127.3 (CH), 129.3 (CH), 130.3 (C), 135.5 (C), 142.7 (C), 166.8 (C), 167.1 (C); IR (ATR, KBr)  $\nu$  = 1662, 1742, 3406 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>21</sub>H<sub>27</sub>O<sub>5</sub>N<sub>2</sub> [M + H]<sup>+</sup> 387.1915; found 387.1911.

**Diethyl  $\alpha$ -[(4-methylbenzoyl)amino]- $\alpha$ -(3,5-dimethyl-1H-pyrrol-2-yl)malonate (8a).** Yield quant. Yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.7–9.6 (1H, br), 7.95 (1H, br s), 7.71 (2H, d,  $J$  = 8.0 Hz), 7.23 (2H, d,  $J$  = 8.0 Hz), 5.58 (1H, d,  $J$  = 2.8 Hz), 4.35 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.24 (2H, dq,  $J$  = 7.2, 10.8 Hz), 2.39 (3H, s), 2.21 (3H, s), 1.93 (3H, s), 1.24 (6H, dd,  $J$  = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  11.8 (CH<sub>3</sub>), 13.0 (CH<sub>3</sub>), 13.9 (CH<sub>3</sub>), 21.5 (CH<sub>3</sub>), 63.0 (CH<sub>2</sub>), 63.7 (C), 108.9 (CH), 116.8 (C), 118.9 (C), 126.6 (C), 127.2 (CH), 129.3 (CH), 130.3 (C), 142.5 (C), 165.8 (C), 167.3 (C); IR (ATR, KBr)  $\nu$  = 1662, 1733, 3423 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>21</sub>H<sub>22</sub>O<sub>5</sub>N<sub>2</sub>H [M + H]<sup>+</sup> 387.1915; found 387.1924.

**Diethyl  $\alpha$ -(4-ethyl-3,5-dimethyl-1H-pyrrol-2-yl)- $\alpha$ -[(4-methylbenzoyl)amino]malonate (9a).** Yield quant. Yellow oil. <sup>1</sup>H NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$  9.4–9.3 (1H, br), 7.93 (1H, br s), 7.62 (2H, d,  $J$  = 8.0 Hz), 7.18 (2H, d,  $J$  = 8.0 Hz), 4.17 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.11 (2H, dq,  $J$  = 7.2, 10.8 Hz), 2.27 (3H, s), 2.20 (2H, q,  $J$  = 7.2 Hz), 2.04 (3H, s), 1.78 (3H, s), 1.09 (6H, dd,  $J$  = 7.2, 7.2 Hz), 0.87 (3H, t,  $J$  = 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  9.93 (CH<sub>3</sub>), 11.2 (CH<sub>3</sub>), 14.3 (CH<sub>3</sub>), 16.1 (CH<sub>3</sub>), 17.9 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 63.9 (CH<sub>2</sub>), 65.2 (C), 116.3 (C), 119.0 (C), 121.8 (C), 123.5 (C), 128.2 (CH), 130.3 (CH), 131.3 (C), 143.8 (C), 166.5 (C), 168.2 (C); IR (ATR, KBr)  $\nu$  = 1666, 1733, 3423 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>23</sub>H<sub>31</sub>O<sub>5</sub>N<sub>2</sub> [M + H]<sup>+</sup> 415.2228; found 415.2237.

**Diethyl  $\alpha$ -(1H-indole-3-yl)- $\alpha$ -[(4-methylbenzoyl)amino]malonate (10a).** Yield 72%. Brown oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 8.63 (br s, 1H), 8.05 (s, 1H), 7.75 (d,  $J$  = 8.2 Hz, 2H), 7.72–7.68 (m, 1H), 7.69–7.62 (m, 1H), 7.24 (d,  $J$  = 8.2 Hz, 2H), 7.21–7.17 (m, 1H), 7.11–6.99 (m, 2H), 4.35 (dq,  $J$  = 10.7, 7.1 Hz, 2H), 4.25 (dq,  $J$  = 10.6, 7.1 Hz, 2H), 2.40 (s, 3H), 1.23 (dd,  $J$  = 7.1, 7.1 Hz, 6H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.9 (C), 166.0 (C), 142.5 (C), 136.4 (C), 130.8 (C), 129.4 (CH), 127.4 (CH), 126.3 (CH), 125.2 (C), 121.8 (CH), 120.0 (CH), 119.8 (CH), 111.7 (CH), 109.5 (C), 65.3 (C), 62.9 (CH<sub>2</sub>), 21.6 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>); HRMS (ESI-TOF) calcd for C<sub>23</sub>H<sub>24</sub>O<sub>5</sub>N<sub>2</sub>Na [M + Na]<sup>+</sup> 431.1577; found 431.1588.

**Diethyl  $\alpha$ -[(4-methylbenzoyl)amino]- $\alpha$ -(1H-5-methylindol-3-yl)malonate (12a).** Yield 65%. White solid, mp 137.1–141.4 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.35 (1H, br), 7.99 (1H, br s), 7.75 (2H, d,  $J$  = 8.0 Hz), 7.73 (1H, d,  $J$  = 2.0 Hz), 7.44 (1H, d,  $J$  = 0.8 Hz), 7.24 (2H, d,  $J$  = 8.0 Hz), 7.16 (1H, d,  $J$  = 8.0 Hz), 6.93 (1H, dd,  $J$  = 8.0, 2.0 Hz), 4.35 (2H, dq,  $J$  = 10.8, 7.2 Hz), 4.26 (2H, dq,  $J$  = 10.8, 7.2 Hz), 2.41 (3H, s), 2.39 (3H, s), 1.34 (6H, dd,  $J$  = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  167.9 (C), 165.9 (C), 142.5 (C), 134.7 (C), 130.9 (C), 129.4 (CH), 129.0 (C), 127.4 (CH), 126.3 (CH), 125.5 (C), 123.5 (CH), 119.7 (CH), 111.2 (CH), 109.3 (C), 65.3 (C), 62.9 (CH<sub>2</sub>), 21.8 (CH<sub>3</sub>), 21.6 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>); HRMS (ESI-TOF) calcd for C<sub>24</sub>H<sub>26</sub>O<sub>5</sub>N<sub>2</sub> [M + H]<sup>+</sup> 423.1915; found 423.1905.

**Diethyl  $\alpha$ -[(trifluoroacetyl)amino]- $\alpha$ -(1H-pyrrol-2-yl)malonate (6i).** Yield 85%. Colorless plates (from Et<sub>2</sub>O–hexane), mp 78.1–78.3 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.6–9.4 (1H, br), 8.10 (1H, br s), 6.82–6.84 (1H, m), 6.13 (1H, ddd,  $J$  = 2.8, 6.0 Hz), 6.02–6.03 (1H, m), 4.37 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.31 (2H, dq,  $J$  = 7.2, 10.8 Hz), 1.28 (6H, dd,  $J$  = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  13.8 (CH<sub>3</sub>), 63.9 (CH<sub>2</sub>), 64.2 (C), 108.0 (CH), 108.0 (CH), 115.4 (q,  $J_{C-F}$  = 285 Hz), 119.7 (CH), 124.0 (C), 156.6 (q,  $J_{C-F}$  = 39 Hz), 165.6 (C); IR (ATR, KBr)  $\nu$  = 1738 (br), 3395 cm<sup>-1</sup>; HRMS (ESI-TOF) calcd for C<sub>13</sub>H<sub>16</sub>O<sub>5</sub>N<sub>2</sub>F<sub>3</sub> [M + H]<sup>+</sup> 337.1006; found 337.1010.

**Diethyl  $\alpha$ -[(trifluoroacetyl)amino]- $\alpha$ -(1H-indole-3-yl)malonate (10i).** Yield 52%. Colorless plates (from Et<sub>2</sub>O–hexane), mp 112.1–112.9 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.5–8.4 (1H, br), 8.22 (1H, br s), 7.73 (1H, d,  $J$  = 2.8 Hz), 7.52 (1H, d,  $J$  = 8.0 Hz), 7.28 (1H, d,  $J$  = 8.0 Hz), 7.16 (1H, dd,  $J$  = 8.0, 8.0 Hz), 7.10 (1H, dd,  $J$  = 8.0, 8.0 Hz), 4.37 (2H, dq,  $J$  = 7.2, 10.8 Hz), 4.31 (2H, dq,  $J$  = 7.2, 10.8 Hz), 1.23 (6H, dd,  $J$  = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  13.8 (CH<sub>3</sub>), 63.9 (CH<sub>2</sub>), 64.7 (C), 108.0 (C), 111.7 (CH), 115.4 (q,  $J_{C-F}$  = 250 Hz), 119.7 (CH), 120.3 (CH), 122.3 (CH), 124.6 (C), 126.3 (CH), 136.1 (C), 156.6 (q,  $J_{C-F}$  = 37





Hz), 165.6 (C); IR (ATR, KBr)  $\nu$  = 1734, 1766, 3390  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{17}\text{H}_{18}\text{O}_5\text{N}_2\text{F}_3$   $[\text{M} + \text{H}]^+$  387.1162; found 387.1154.

**Diethyl  $\alpha$ -[(trifluoroacetyl)amino]- $\alpha$ -(1-methylindol-3-yl)malonate (11i).** Yield 83%. Brown oil. The purity of the product was improved by short column chromatography on silica gel (after elution of 1-methylindole with chloroform-hexane (1/1), eluted with ethyl acetate), but further purification was not possible.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (1H, br s), 7.73 (1H, s), 7.51 (1H, ddd,  $J$  = 0.8, 1.2, 8.0 Hz), 7.30 (1H, ddd,  $J$  = 0.8, 1.2, 8.0 Hz), 7.22 (1H, ddd,  $J$  = 1.2, 8.0, 8.0 Hz), 7.10 (1H, ddd,  $J$  = 1.2, 8.0, 8.0 Hz), 4.39–4.21 (4H, m), 3.76 (3H, s), 1.23 (6H, dd,  $J$  = 7.2, 7.2 Hz);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  13.8 ( $\text{CH}_3$ ), 33.1 ( $\text{CH}_3$ ), 63.5 ( $\text{CH}_2$ ), 65.1 (C), 106.0 (C), 109.8 (CH), 115.4 (q,  $J_{\text{C-F}}$  = 286 Hz), 119.2 (CH), 120.0 (CH), 121.9 (CH), 125.4 (C), 130.7 (CH), 136.8 (C), 156.3 (q,  $J_{\text{C-F}}$  = 38 Hz) 166.3 (C); IR (ATR, KBr)  $\nu$  = 1733 (br), 3386  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{18}\text{H}_{20}\text{O}_5\text{N}_2\text{F}_3$   $[\text{M} + \text{H}]^+$  401.1319; found 401.1316.

**Diethyl  $\alpha$ -(*tert*-butylcarboxyamino)- $\alpha$ -(1-methylindol-3-yl)malonate (11j).** Yield 83%. White solid, 127.9–128.6  $^{\circ}\text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68 (d,  $J$  = 8.2 Hz, 1H), 7.64 (s, 1H), 7.28 (d,  $J$  = 8.2 Hz, 1H), 7.19 (dd,  $J$  = 8.2, 8.2 Hz, 1H), 7.08 (dd,  $J$  = 8.2, 8.2 Hz, 1H), 6.44 (s, 1H), 4.48–4.24 (m, 3H), 4.20 (dq,  $J$  = 10.7, 7.1 Hz, 2H), 3.77 (s, 3H), 1.39 (br s, 9H), 1.24 (dd,  $J$  = 7.1 Hz, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  168.0 (C), 154.0 (C), 137.1 (C), 129.9 (CH), 126.0 (C), 121.6 (CH), 120.6 (CH), 119.5 (CH), 109.4 (CH), 109.0 (C), 80.3 (C), 65.3 (C), 62.7 ( $\text{CH}_2$ ), 33.1 ( $\text{CH}_3$ ), 28.3 ( $\text{CH}_3$ ), 14.1 ( $\text{CH}_3$ ); HRMS (ESI-TOF) calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  427.1840; found 427.1843.

**Diethyl  $\alpha$ -(1-acetyl-L-prolylamino)- $\alpha$ -(1-methylindol-3-yl)malonate (11l).** Yield 75%. Brown oil. The purity of the product was improved by short column chromatography on silica gel (after elution of 1-methylindole with chloroform-hexane (1/1), eluted with ethyl acetate), but further purification was not possible.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.60 (1H, br s), 7.7 (1H, s), 7.68 (1H, d,  $J$  = 8.0 Hz), 7.25 (1H, d,  $J$  = 8.0 Hz), 7.18 (1H, ddd,  $J$  = 8.0, 6.8, 1.2 Hz), 7.07 (1H, ddd,  $J$  = 8.0, 6.8, 1.2 Hz), 4.58 (1H, dd,  $J$  = 7.6, 7.6 Hz), 4.34–4.24 (4H, m), 3.74 (3H, s), 3.59–3.54 (1H, m), 3.48–3.42 (1H, m), 2.33–1.91 (1H, m), 2.14 (3H, s), 2.00–1.91 (3H, m), 1.29–1.21 (6H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  170.8 (C), 169.9 (C), 167.5 (C), 167.4 (C), 137.2 (C), 130.1 (CH), 125.9 (C), 121.3 (CH), 120.9 (CH), 119.1 (CH), 109.3 (CH), 108.3 (C), 65.3 (C), 62.6 ( $\text{CH}_2$ ), 62.5 ( $\text{CH}_2$ ), 59.4 (CH), 48.2 ( $\text{CH}_2$ ), 33.0 ( $\text{CH}_3$ ), 27.5 ( $\text{CH}_2$ ), 24.8 ( $\text{CH}_2$ ), 22.5 ( $\text{CH}_3$ ), 14.0 ( $\text{CH}_3$ ); IR (ATR, KBr)  $\nu$  = 1701, 1757, 3255  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{23}\text{H}_{29}\text{O}_6\text{N}_3$   $[\text{M} + \text{H}]^+$  444.2129; found 444.2121.

### General procedure for hydrolysis and decarboxylation of 11a

To a solution of double adduct **11a** (21 mg, 0.05 mmol) in THF (2 mL), potassium *tert*-butoxide (11 mg, 0.10 mmol) was added, and the resultant mixture was stirred at room temperature overnight. After evaporation, the residue was dissolved in chloroform (20 mL), and 12 M hydrochloric acid (1 mL, 12 mmol) was added, then, washed with water (10 mL). The organic layer was dried over magnesium sulfate and concen-

trated. The residue was washed with hexane (100 mL) to afford amino acid derivative **16a** (14 mg, 0.044 mmol, yield 88%) as a white solid.

The decarboxylation of other double adducts were also performed by the same experimental procedure.

**2-[(4-Methylbenzoyl)amino]-2-(1-methylindol-3-yl)ethanoic acid (16a).** Yield 98%. White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.74 (1H, d,  $J$  = 7.2 Hz), 7.82 (2H, d,  $J$  = 8.0 Hz), 7.63 (1H, d,  $J$  = 7.2 Hz), 7.43 (1H, d,  $J$  = 8.0 Hz), 7.42 (1H, s), 7.23 (2H, d,  $J$  = 8.0 Hz), 7.18 (1H, dd,  $J$  = 7.2, 7.2 Hz), 7.06 (1H, dd,  $J$  = 7.2, 7.2 Hz), 5.80 (1H, d,  $J$  = 7.2 Hz), 3.80 (3H, s), 2.35 (3H, s),  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.9 ( $\text{CH}_3$ ), 32.4 ( $\text{CH}_3$ ), 49.6 (CH), 109.1 (C), 109.8 (CH), 119.0 (CH), 121.4 (CH), 126.5 (C), 127.7 (CH), 127.5 (CH), 128.6 (CH), 128.7 (CH), 131.0 (C), 136.5 (C), 141.2 (C), 166.1 (C), 172.3 (C); HRMS (ESI-TOF) calcd for  $\text{C}_{19}\text{H}_{18}\text{O}_3\text{N}_2$   $[\text{M} + \text{H}]^+$  323.1390; found 323.1396.

**2-(1-Methylindol-3-yl)-2-(pivaloylamino)ethanoic acid (16h).** Yield 71%. Yellow solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (1H, d,  $J$  = 8.0 Hz), 7.25 (1H, d,  $J$  = 8.0 Hz), 7.19 (1H, dd,  $J$  = 7.2, 7.2 Hz), 7.12 (1H, s), 7.06 (1H, dd,  $J$  = 7.2, 7.2 Hz), 6.71 (1H, d,  $J$  = 7.2 Hz), 5.71 (1H, d,  $J$  = 6.4 Hz), 3.66 (3H, s), 1.16 (9H, s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  27.1 ( $\text{CH}_3$ ), 32.7 ( $\text{CH}_3$ ), 38.6 (C), 50.5 (CH), 109.4 (CH), 110.3 (C), 119.4 (CH), 119.5 (CH), 121.8 (CH), 126.3 (C), 128.5 (CH), 137.1 (C), 174.5 (C), 178.2 (C); IR (ATR, KBr)  $\nu$  = 1718  $\text{cm}^{-1}$ ; HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{19}\text{O}_3\text{N}_2$   $[\text{M} + \text{Na}]^+$  311.1366; found 311.1382.

**2-(1-Methylindol-3-yl)-2-(trifluoroacetylaminio)ethanoic acid (16i).** Yield 98%. White solid.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (1H, d,  $J$  = 8.0 Hz), 7.82 (2H, d,  $J$  = 8.0 Hz), 7.33 (1H, dd,  $J$  = 7.2, 7.2 Hz), 7.28 (1H, d,  $J$  = 7.2, 7.2 Hz), 7.18 (1H, dd,  $J$  = 7.2, 7.2 Hz), 7.12 (1H, m), 5.87 (1H, d,  $J$  = 6.8 Hz), 3.79 (3H, s).

**2-(*tert*-Butylcarboxyamino)-2-(1-methylindol-3-yl)ethanoic acid (16j).** Yield quant., yellow oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  7.62 (1H, d,  $J$  = 8.0 Hz), 7.39 (1H, d,  $J$  = 8.0 Hz), 7.23 (1H, dd,  $J$  = 8.0, 8.0 Hz), 7.21 (1H, s), 7.11 (1H, dd,  $J$  = 8.0, 8.0 Hz), 5.92 (1H, br s), 5.42 (1H, d,  $J$  = 3.2 Hz), 3.76 (3H, s), 1.42 (9H, s),  $^{13}\text{C}$  NMR (101 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  173.2 (C), 156.4 (C), 138.0 (C), 129.4 (CH), 127.1 (C), 122.9 (CH), 120.4 (CH), 120.0 (CH), 110.8 (CH), 110.3 (CH), 80.1 (C), 51.5 (CH), 33.2 ( $\text{CH}_3$ ), 28.5 ( $\text{CH}_3$ ); HRMS (ESI-TOF) calcd for  $\text{C}_{16}\text{H}_{19}\text{O}_4\text{N}_2$   $[\text{M} - \text{H}]^-$  303.1350; found 303.1342.

**2-(1-Acetyl-L-prolylamino)-2-(1-methylindol-3-yl)ethanoic acid (16l).** Although a mixture of four isomers was obtained, major isomer could be isolated by reprecipitation from ethyl acetate. White solid, mp 174.8  $^{\circ}\text{C}$  (decomp.).  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ )  $\delta$  8.72 (1H, d,  $J$  = 6.4 Hz), 8.37 (1H, d,  $J$  = 7.6 Hz), 7.58 (2H, d,  $J$  = 7.6 Hz), 7.45 (1H, d,  $J$  = 8.0 Hz), 7.42 (1H, d,  $J$  = 8.0 Hz), 7.36 (1H, s), 7.29 (1H, s), 7.19 (1H, dd, 8.0, 8.0 Hz), 7.17 (1H, dd, 8.0, 8.0 Hz), 7.07 (1H, dd, 8.0, 8.0 Hz), 7.05 (1H, dd, 8.0, 8.0 Hz), 5.56 (1H, d, 7.6 Hz), 5.48 (1H, d, 6.4 Hz), 4.45 (1H, dd, 8.4, 2.1 Hz), 4.41 (1H, dd, 8.0, 2.4 Hz), 3.78 (3H, s), 3.76 (3H, s), 2.19–2.08 (1H, m), 1.98 (3H, s), 1.90 (3H, s), 2.00–1.68 (9H, m),  $^{13}\text{C}$  NMR (100 MHz,  $\text{DMSO}-d_6$ )  $\delta$  22.1 ( $\text{CH}_3$ ), 22.4 ( $\text{CH}_3$ ), 22.7 ( $\text{CH}_2$ ), 24.2 ( $\text{CH}_2$ ), 29.5 ( $\text{CH}_2$ ), 31.9 ( $\text{CH}_2$ ), 32.48 ( $\text{CH}_3$ ), 32.50 ( $\text{CH}_3$ ), 46.4 ( $\text{CH}_2$ ), 47.6 ( $\text{CH}_2$ ), 49.2 ( $\text{CH}_3$ ), 49.6 ( $\text{CH}_3$ ), 58.9 (CH), 59.6 (CH), 108.6 (C), 109.8 (C), 109.9



(CH), 110.0 (CH), 119.1 (CH), 119.1 (CH), 119.15 (CH), 119.24 (CH), 121.6 (CH), 121.7 (CH), 126.1 (C), 126.2 (C), 128.2 (CH), 128.7 (CH), 136.7 (C), 136.7 (C), 168.7 (C), 168.8 (C), 171.4 (C), 172.1 (C), 172.1 (C), 172.2 (C); HRMS (ESI-TOF) calcd for  $C_{18}H_{21}N_3O_4Na [M + Na]^+$  366.1424; found 366.1423.

## Author contributions

Asahara and Nishiwaki came up with the idea for this study and were the main driving force behind it. Bonkohara, Takagi, and Iwai performed experiments. Iwai and Ito conducted X-ray crystallography and DFT calculations. Yoshioka, Tani, and Umezū supplied DEMO and discussed on the Experimental results.

## Conflicts of interest

There are no conflicts to declare.

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