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# Cobalt-Catalyzed One-Pot Three-Component Coupling Route to β-Acetamido Carbonyl Compounds: A General Synthetic Protocol for γ-Lactams

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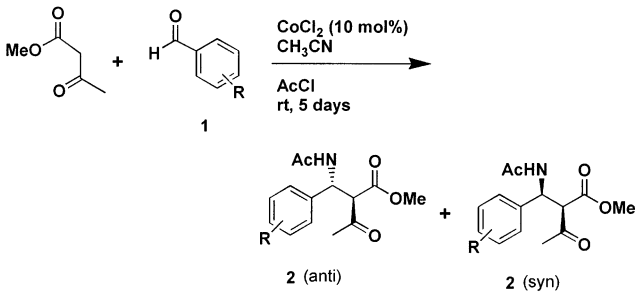
**Abstract:** An efficient improved procedure for the synthesis of β-acetamido carbonyl compounds is developed by a cobalt(II) chloride-catalyzed three-component coupling protocol. The procedure is also amenable to the synthesis of γ-lactams by a three-component coupling reaction with use of 2-carbomethoxybenzaldehyde. The β-acetamido carbonyl compounds derived from 2-carbomethoxybenzaldehyde are useful intermediates as they can be transformed to the corresponding γ-lactams on treatment with base.

The multicomponent coupling reactions[1] are emerging as a useful source for accessing small drug-like molecules with several levels of structural diversity. Pioneering work by several research groups in this area has already established the versatility of one-pot multicomponent coupling protocols as a powerful methodology for the synthesis of diverse structural scaffolds required in search of novel therapeutic molecules. In an earlier study[2] we have shown that cobalt(II) chloride catalyzes the coupling between a ketone or ketoester, an aldehyde, and acetonitrile in the presence of acetyl chloride to provide a general route to β-acetamido carbonyl compounds. This transformation, however, is influenced by the presence of molecular oxygen, which induces the formation of α,β-unsaturated compounds (Knoevenagel product) along with the expected β-acetamido ketones. On the other hand, the moderate to good yield of β-acetamido ketones was obtained under a nitrogen atmosphere, which suppresses the formation of α,β-unsaturated carbonyl compounds to a larger extent as only traces of the latter were observed in the crude reaction mixture. To broaden the synthetic scope, we have explored the possibility of improving the reaction condition and elaborating the intermediate β-acetamido ketones to the corresponding γ-lactams. We now describe a detailed account of our findings on cobalt-catalyzed three-component coupling reactions (Scheme 1).

**SCHEME 1**




In our earlier investigations[2] we demonstrated that a mixture of enolizable ketone, aldehyde, and acetyl chloride when heated (70−80 °C) in acetonitrile in the presence of a catalytic amount (10 mol %) of cobalt(II) chloride for 12−14 h affords β-acetamido ketones in moderate yields. To optimize the reaction conditions, we explored an alternative procedure, which resulted in a more operationally efficient process. Thus, instead of heating the reaction in acetonitrile, we stirred the reaction at room temperature for 5 days. Interestingly, this change in procedure afforded the corresponding β-acetamido ketones as crystalline solids, which can be obtained after aqueous workup thus circumventing the process of purification with column chromatography. This clearly is an advantage over the previously described procedure. According to this procedure, the reaction of methyl acetoacetate with benzaldehyde and substituted benzaldehydes proceeded smoothly in the presence of cobalt(II) chloride and acetyl chloride to afford the corresponding β-acetamido esters in good yields (Table 1).

The reactions with benzaldehyde and 4-substituted benzaldehydes (4-chloro, 4-nitro, 4-bromo, 4-methyl) were diastereoselective leading to the formation of one diastereomer as the major product (Table 1). It is interesting to note that the opposite diastereoselectivity[3] was observed between 4-bromobenzaldehyde and 2-bromobenzaldehyde. For example, the reaction with 4-bromobenzaldehyde gives the anti diastereomer ($J = 7-9$ Hz) as the major product whereas in the case of 2-bromobenzaldehyde the corresponding syn diastereomer ($J = 3-5$ Hz) predominates (Table 1; entries 4 and 5). It is also noteworthy that there was no diastereoselectivity in the case of 4-methoxybenzaldehyde (Table 1; entries 3 and 6). During the course of these reactions, we have observed that the diastereoselectivity of β-acetamido-ketone or ketoester formation is influenced by the temperature of the reaction. For example, the reaction of benzaldehyde and 4-chlorobenzaldehyde with methylacetoacetate afforded an equal mixture (Table 2) of diastereomers **2a** and **2b** respectively upon heating, whereas the *anti*-**2a** and *anti*-**2b** were found to be the major

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(1) (a) For a review see: Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Terret, N. K.; Gardner, M.; Gordon, D. W.; Kobylecki, R. J.; Steele, J. *Tetrahedron* **1995**, *51*, 8135. (c) Thomson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (d) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132.

(2) (a) Bhatia, B.; Reddy, M. M.; Iqbal, J. *J. Chem. Soc., Chem. Commun.* **1994**, 713. (b) Reddy, M. M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1995**, *36*, 4877. (c) Mukhopadhyay, M.; Bhatia, B.; Iqbal, J. *Tetrahedron Lett.* **1997**, *38*, 1083. (d) Prbhakaran, E. N.; Iqbal, J. *J. Org. Chem.* **1999**, *64*, 3339. (e) For related three-component coupling, see: Armstrong, R. W.; Combs, A. W.; Templest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123 and ref 2b.

(3) The ratio of anti/syn diastereomer was determined by $^1$H NMR based on the coupling constants between the methine protons in **2**.

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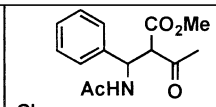
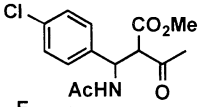
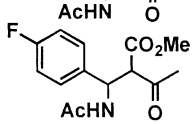
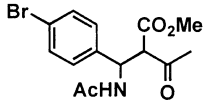
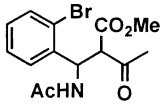
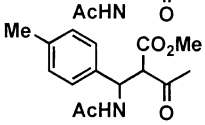
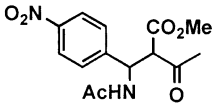
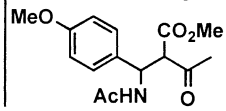
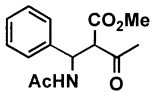
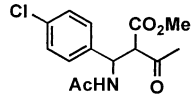
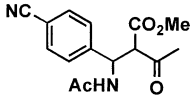
**TABLE 1. Cobalt(II) Chloride-Catalyzed Synthesis of *β*-Acetamido Ketoesters at 25 °C**

| Entry | β-Acetamido Ketoester | | % Yield[a,b] | m.p. (°C)[c] | Syn/Anti[d] |
|---|---|---|---|---|---|
| 1 |  | **2a** | 63 | 129-31 | 25 / 75 |
| 2 |  | **2b** | 65 | 130-32 | 25 / 75 |
| 3 |  | **2c** | 76 | 120-22 | 50 / 50 |
| 4 |  | **2d** | 70 | 160-61 | 25 / 75 |
| 5 |  | **2e** | 69 | gum | 70 / 30 |
| 6 |  | **2f** | 57 | 138-40 | 10 / 90 |
| 7 |  | **2g** | 30 | 149-51 | 25 / 75 |
| 8 |  | **2h** | 23 | 142-44 | 50 / 50 |

[a] Yield of the product obtained by aqueous workup and crystallization. [b] The product was obtained as a mixture of diastereomers. [c] Melting point of the major diastereomer. [d] Ratio obtained from $^1$H NMR of the crude reaction mixture.

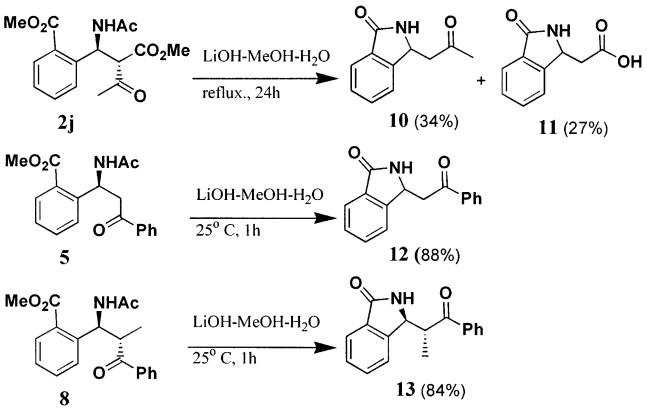
**TABLE 2. Effect of Temperature on Diastereoselectivity**

| Compound | Temperature °C | Diastereomeric Ratio (*Syn* :*Anti*) |
|---|---|---|
|  **2a** | 25 | 25 : 75 |
| | 80 | 50 : 50 |
|  **2b** | 25 | 25 : 75 |
| | 80 | 50 : 50 |
|  **2i** | 25 | 50 : 50 |
| | 80 | 50 : 50 |

products (75/25) when the reaction was carried out at room temperature (25 °C). It is also pertinent to mention that the temperature does not influence the diastereoselectivity in the reaction with 4-cyanobenzaldehyde as under either conditions an equal mixture of the diastereomers **2i** was obtained (Table 2).

The cobalt-catalyzed three-component coupling with 2-carbomethoxybenzaldehyde results in the formation of *γ*-lactam as one of the products. Thus, the reaction of

**SCHEME 2. Synthesis of *γ*-Lactams by Base Hydrolysis of *β*-Acetamido Carbonyl Compounds**




methylacetoacetate and 2-carbomethoxybenzaldehyde under the conditions described earlier affords a mixture of *β*-acetamido esters **2j** and the two *γ*-lactams **3** and **4** in the ratio of 2:1:1 at room temperature; however, the ratio of these products changed to 2:4:1 upon heating (Table 3). Similarly, the reaction with acetophenone and 2-carbomethoxybenzaldehyde leads to a mixture of *β*-acetamidoketone **5** and the corresponding *γ*-lactam **6** in nearly equal ratio. The *γ*-lactone **7** was also obtained in minor amounts and it may arise due to the reaction of 2-carbomethoxybenzaldehyde with acetyl chloride. Once again, the ratio of the products (**5**, **6**, and **7**) changed in this reaction upon heating to 80 °C for 8 h, which resulted in the formation of *γ*-lactam **6** as the major product. The reaction with propiophenone and 2-carbomethoxybenzaldehyde at room temperature afforded the corresponding *β*-acetamido ketone **8** as the only product; however, the *γ*-lactam **9** was also formed when the reaction was subjected to heating at 80 °C for 10 h (Table 3).

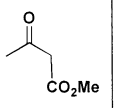
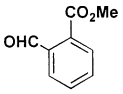
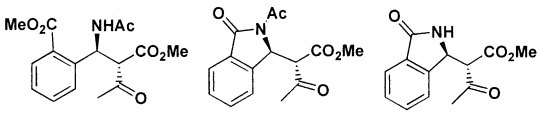
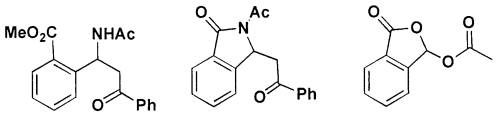
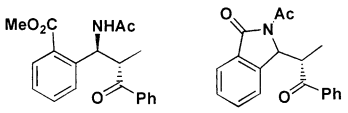
Interestingly, the *β*-acetamido ester **2j** can be hydrolyzed by lithium hydroxide at reflux temperature leading to the formation of a mixture of *γ*-lactams **10** and **11**[4] obtained by retro-aldol and decarboxylation processes, respectively (Scheme 2). These *γ*-lactams are obtained as crystalline solids in good yields. Similarly, the *β*-acetamido ketones **5** and **8** on treatment with lithium hydroxide at room temperature gave the corresponding *γ*-lactams **12** and **13**, respectively. This synthesis of *γ*-lactams is quite useful as it enhances the synthetic utility of our cobalt-catalyzed three-component coupling procedure. The synthesis of lactam **11** has been reported earlier;[4] however, its synthesis with the protocol discussed here is better in terms of yield and efficiency.

The *γ*-lactam **11** is a useful starting material for the synthesis of peptidomimetic[5,1c] as it was converted to the corresponding dipeptide **14** by a mixed anhydride coupling with the methyl ester of leucine (Scheme 3). The

(4) For a synthesis of a similar *γ*-lactam see: Gellert, A.; Wong, C. *Aust. J. Chem.* **1984**, *37*, 1931.

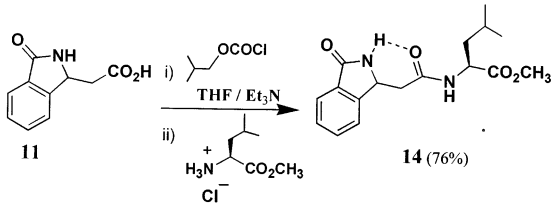
(5) (a) Goodman, M.; Ro, S. *Berger's Medicinal Chemistry and Drug Discovery*, 5th ed.; Vol. 1, Principles and Practice; Wolff, M. E., Ed.; 1995. (b) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039. (c) Frchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (d) Aube, J. *In Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A.; JAI Press: Greenwich, CT, 1997; Vol. 1, pp 193−232.

**TABLE 3. One-Pot Synthesis of $\gamma$-Lactams**

| Carbonyl Compound | Aldehyde | Products (Yield %) [a] |
|---|---|---|
|  |  |  **2j** (41%) (20%)[b] **3** (23%) (42%)[b] **4** (20%) (10%)[b] |
|  | |  **5** (30%) (20%)[b] **6** (25%) (40%)[b] **7** (20%) (nil)[b] |
|  | |  **8** (73%) (51%)[b] **9** (nil) (30%)[b] |

[a] Reaction conditions: carbonyl compound (1 mmol), 2-carbomethoxybenzaldehyde (1 mmol), and acetyl chloride (3 mmol) were stirred in acetonitrile (dry, 10 mL) in the presence of $CoCl_2$ (5 mol %) for 5 days at room temperature. [b] These yields are obtained by heating the reaction mixture to 80 °C for 5−10 h.

**SCHEME 3. Synthesis of Dipeptide from $\gamma$-Lactam**




dipeptide mimetic **14** is a very useful small molecule and has the potential of being developed into a therapeutic agent. A careful analysis of $^1$H NMR of the dipeptide **14** revealed that it possesses an intramolecular hydrogen bond that may be formed between the NH hydrogen of $\gamma$-lactam and the carbonyl of $\beta$-amino acid.

In conclusion, this note describes an efficient procedure for the synthesis of $\beta$-acetamido carbonyl compounds with use of the cobalt-catalyzed three-component coupling reaction involving aldehyde, ketone, or ketoester in acetonitrile medium. The methodology described here is a distinct improvement over our previous protocol in terms of enhanced yield and easy workup procedure. We have also demonstrated that the $\gamma$-lactams can be obtained in a one-pot three-component coupling procedure using 2-carbomethoxybenzaldehyde and ketoester/ketones. Also, the $\beta$-acetamido keto esters **2**, derived from 2-carbomethoxybenzaldehyde, are useful intermediates as they can be transformed to the corresponding $\gamma$-lactams on treatment with base. Further studies are in progress in our laboratory to transform $\beta$-amino acids and $\gamma$-lactams to the corresponding peptidomimetics and cyclic peptides as potential protease inhibitors.

## Experimental Section

**General Methods.** THF and acetonitrile were distilled from sodium and phosphorus pentoxide respectively and acetonitrile was preserved over 4 Å molecular sieves. Laboratory grade methanol was used. Triethylamine was preserved over anhydrous potassium hydroxide. Isobutyl chloroformate was used immediately after distillation. The catalyst $CoCl_2$ was procured from LOBA (India) and dried before use by heating at 150 °C for 1.5 h. Column chromatographic separations were carried out with ACME silica gel (100−200 mesh). NMR spectra were recorded by JEOL 400 and JEOL 200 spectrometers where chemical shifts are reported in parts per million referred to TMS (0.00 ppm) and chloroform (7.26 ppm).

**General Procedure for the Synthesis of $\beta$-Acetamido Keto Ester.** A freshly dried cobalt(II) chloride (10 mol %) solution was added to a solution of methylacetoacetate/ketone (10 mmol) and acetyl chloride (30 mmol) in acetonitrile (30 mL). The reaction mixture was stirred at ambient temperature for 5 days. After the completion of the reaction the solvent was removed under reduced pressure to afford a residue that was taken into ethyl acetate (100 mL), washed with water (225 mL), saturated sodium bicarbonate (225 mL), and brine (25 mL), dried ($Na_2SO_4$), and filtered. The filtrate was evaporated under reduced pressure. The crude product was crystallized from ethyl acetate−hexane to afford the $\beta$-ketoamides **2** as pale yellow solids in good yields and in high purity. The spectral data of the compounds **2a**, **2b,** and **2g** have been reported previously (ref 2d).

**Methyl 2-Acetyl-3-acetamido-3-(*p*-fluorophenyl)propionate (2c).** Yield (major diastereomer): 37%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.29−7.27 (m, 2H), 7.06−6.96 (m, 2H), 5.86 (dd, $J$ = 4.0 and 9.4 Hz, 1H), 4.10−4.02 (m, 1H), 3.71 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3284, 1746, 1720, 1657, 1512 cm$^{-1}$. CI-MS $m/z$ (rel intensity): 282 ($M^+ + 1$, 5%), 166 (100%).

**Methyl 2-Acetyl-3-acetamido-3-(*p*-bromophenyl)propionate (2d).** Yield (major diastereomer): 39%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.43 (d, $J$ = 8.3 Hz, 2H), 7.17 (d, $J$ = 8.3 Hz, 2H), 6.97 (d, $J$ = 9.3 Hz, $D_2O$ exchangeable, 1H), 5.69 (dd, $J$ = 5.3 and 9.3 Hz, 1H), 4.06 (d, $J$ = 5.4 Hz, 1H), 3.72 (s, 3H), 2.16 (s, 3H), 2.01 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3327, 1745, 1715, 1651, 1541 cm$^{-1}$. MS $m/z$ (rel intensity): 344 ($M^+$ with $^{81}$Br, 8%), 342 ($M^+$ with $^{79}$Br, 10%), 226 (100%).

**Methyl 2-Acetyl-3-acetamido-2-(*o*-bromophenyl)propionate (2e).** Yield (major diastereomer): 33%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.63−7.53 (m, 1H), 7.36−7.24 (m, 3H), 7.20−7.01 (m, $D_2O$ exchangeable, 1H), 6.10 (dd, $J$ = 3.0 and 9.2 Hz, 1H), 4.24 (d, $J$ = 3.6 Hz, 1H), 3.66 (s, 3H), 2.45 (s, 3H), 2.05 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3419, 1740, 1678 cm$^{-1}$. MS $m/z$ (rel intensity): 344 ($M^+$ with $^{81}$Br, 8%), 342 ($M^+$ with $^{79}$Br, 10%), 226 (100%).

**Methyl 2-Acetyl-3-acetamido-3-(*p*-methylphenyl)propionate (2f).** Yield (major diastereomer): 32%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.20−7.07 (m, 4H), 6.88 (d, $J$ = 9.3 Hz, $D_2O$ exchangeable, 1H), 5.75−5.68 (m, 1H), 4.06 (d, $J$ = 5.9 Hz, 1H), 3.69 (s, 3H), 2.30 (s, 3H), 2.15 (s, 3H), 1.99 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3336, 1747, 1720, 1649, 1531 cm$^{-1}$. MS $m/z$ (rel intensity): 277 ($M^+$, 5%), 162 (100%).

**Methyl 2-Acetyl-3-acetamido-3-(*p*-methoxyphenyl)propionate (2h).** Yield (major diastereomer): 45%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.32−7.24 (m, 2H), 6.93−6.88 (m, 2H), 5.90 (dd, $J$ = 3.8 and 9.2 Hz, 1H), 4.12−4.10 (m, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 2.22 (s, 3H), 2.05 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3338, 1742, 1716, 1650, 1517 cm$^{-1}$. CI-MS $m/z$ (rel intensity): 294 ($M^+$ + 1, 5%), 178 (100%).

**Methyl 2-Acetyl-3-acetamido-3-(*p*-cyanophenyl)propionate (2i).** Yield (major diastereomer): 32%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.66−7.61 (m, 2H), 7.44−7.30 (m, 2H), 7.08 (d, $J$ = 8.4 Hz, $D_2O$ exchangeable, 1H), 5.90 (dd, $J$ = 3.4 and 9.2 Hz, 1H), 4.08 (dd, $J$ = 3.9 and 9.8 Hz, 1H), 3.74 (s, 3H), 2.36 (s, 3H), 2.03 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3283, 2230, 1745, 1720, 1659 cm$^{-1}$. MS $m/z$ (rel intensity): 289 ($M^+$ + 1, 100%), 173 (80%).

**Methyl 2-Acetyl-3-acetamido-3-(2-carbomethoxyphenyl)propionate (2j).** Yield (major diastereomer): 35%. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.03 (d, $J$ = 7.9 Hz, 1H), 6.69 (d, $J$ = 9.3 Hz, $D_2O$ exchangeable, 1H), 7.52−7.48 (m, 2H), 7.38−7.30 (m, 1H), 6.59 (dd, $J$ = 3.2 and 8.8 Hz, 1H), 4.39 (d, $J$ = 3.4 Hz, 1H), 3.95 (s, 3H), 3.59 (s, 3H), 2.48 (s, 3H), 2.03 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3399, 1742, 1709, 1682, 1504 cm$^{-1}$. MS $m/z$ (rel intensity): 278 ($M^+$ − 43, 60%), 172 (100%), 132 (95%).

In this reaction along with the desired product *N*-acetyl $\gamma$-lactam **3** and $\gamma$-lactam **4** were isolated in 50 mg (3%), mp 96−98 °C, and 240 mg (14%), mp 118−120 °C, respectively.

***N*-Acetyl $\gamma$-Lactam 3.** $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.86 (d, $J$ = 8.0 Hz, 1H), 7.59−7.50 (m, 3H), 5.82 (d, $J$ = 2.0 Hz, 1H), 4.67 (d, $J$ = 2.0 Hz, 1H), 3.27 (s, 3H), 2.68 (s, 3H), 2.34 (s, 3H). FT-IR (KBr): $\nu_{max}$ 1745, 1694 cm$^{-1}$. MS $m/z$ (rel intensity): 289 ($M^+$, 22%), 204 (45%), 172 (50%), 132 (100%).

**$\gamma$-Lactam 4**.$^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.92 (d, $J$ = 8.0 Hz, 1H), 7.72−7.67 (m, 3H), 6.12 (d, $J$ = 8.4 Hz, 1H), 3.90 (d, $J$ = 8.4 Hz, 1H), 3.75 (s, 3H), 2.40 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3419, 1748, 1709 cm$^{-1}$. MS $m/z$ (rel intensity): 247 ($M^+$, 6%), 205 (70%), 173 (100%), 133 (80%).

**$\beta$-Acetamido-$\beta$-(2-carbomethoxyphenyl)propiophenone 5 and $\gamma$-lactam 6. 5:** $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.92 (d, $J$ = 7.3 Hz, 2H), 7.60−7.30 (m, 7H), 6.08 (dd, $J$ = 6.3 and 14.7 Hz, 1H), 3.95 (s, 3H), 3.73 (dd, $J$ = 6.4 and 16.1 Hz, 1H), 3.53 (dd, $J$ = 6.4 and 16.6 Hz, 1H), 1.97 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3313, 1713, 1686, 1648, 1549 cm$^{-1}$. MS $m/z$ (rel intensity): 326 ($M^+$ + 1, 100%). **6:** mp 156−158 °C; $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.98−7.90 (m, 3H), 7.62−7.43 (m, 6H), 5.84 (d, $J$ = 9.4 Hz, 1H), 4.11 (dd, $J$ = 2.4 and 17 Hz, 1H), 3.25 (dd, $J$ = 9.4 and 17.6 Hz, 1H), 2.70 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3441, 1733, 1687 cm$^{-1}$. MS $m/z$ (rel intensity): 251 ($M^+$ − 43, 50%), 146 (100%), 132 (65%), 105 (90%).

**α-Methyl-$\beta$-acetamido-$\beta$-(2-carbomethoxyphenyl)propiophenone (8).** $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.91 (d, $J$ = 7.3 Hz, 1H), 7.80 (d, $J$ = 8.0 Hz, $D_2O$ exchangeable, 1H), 7.69 (d, $J$ = 7.8 Hz, 2H), 7.46 (d, $J$ = 7.4 Hz, 1H), 7.37−7.19 (m, 5H), 5.89 (dd, $J$ = 4.3 and 8.3 Hz, 1H), 4.46−4.32 (m, 1H), 3.98 (s, 3H), 2.03 (s, 3H), 1.34 (d, $J$ = 6.8 Hz, 3H). FT-IR (KBr): $\nu_{max}$ 3292, 1723, 1682, 1652, 1547 cm$^{-1}$. CI-MS $m/z$ (rel intensity): 340 ($M^+$ + 1, 100%), 206 (50%).

**Synthesis of $\gamma$-Lactams 10 and 11.** To a solution of **2j** (2.2 g, 6.85 mmol) in MeOH:$H_2O$ (4:1, 50 mL) was added lithium hydroxide (431 mg, 10.28 mmol) and the reaction mixture was refluxed for 24 h. The reaction mixture was cooled to ambient temperature and the solvents were evaporated under vacuum. Water was added to the residue and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under vacuum to yield the desired product **10** as a pink solid (370 mg, 34%): Mp 131−133 °C. $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.86 (d, $J$ = 7.3 Hz, 1H), 7.65−7.36 (m, 3H), 6.77 (br s, $D_2O$ exchangeable, 1H), 4.94 (d, $J$ = 7.8 Hz, 1H), 3.21 (dd, $J$ = 3.2 and 18.4 Hz, 1H), 2.59 (dd, $J$ = 10.2 and 18.5 Hz, 1H), 2.24 (s, 3H). FT-IR (KBr): $\nu_{max}$ 3313, 1717, 1686, 1648 cm$^{-1}$. Anal. Calcd for $C_{11}H_{11}O_2N$: C, 69.84; H, 5.82; N, 7.40. Found: C, 69.79; H, 5.77; N, 7.33. CI-MS $m/z$ (rel intensity): 190 ($M^+$ + 1, 100%).

The aqueous layer obtained in the above experiment was acidified with 1 N hydrochloric acid to pH 2.0 and extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under vacuum to yield the product **11** as a yellow solid (650 mg, 27%): Mp 159−160 °C. $^1$H NMR (DMSO-$d_6$, 200 MHz): $\delta$ 8.59 (br s, $D_2O$ exchangeable, 1H), 7.70−7.40 (m, 4H), 4.86 (t, $J$ = 6.3 Hz, 1H), 2.78 (dd, $J$ = 5.9 and 16.2 Hz, 1H), 2.53−2.48 (m, 1H). FT-IR (KBr): $\nu_{max}$ 3400, 1710, 1651, 1613 cm$^{-1}$. Anal. Calcd for $C_{10}H_9O_3N$: C, 62.82; H, 4.71; N, 7.32. Found: C, 62.73; H, 4.63; N, 7.24. CI-MS $m/z$ (rel intensity): 192 ($M^+$ + 1, 50%), 132 (100%).

**Synthesis of $\gamma$-Lactams 12 and 13.** To a solution of **5** and **8** (0.3 mmol) in MeOH:$H_2O$ (4:1, 15 mL) was added lithium hydroxide (0.46 mmol) and the mixture was stirred for 1 h at 25 °C. The reaction mixture was evaporated under vacuum. Water was added to the residue and extracted with ethyl acetate (3 × 10 mL). The organic layer was washed with brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under vacuum to yield the desired products **12** and **13** respectively as a yellow solid (84−88%); the spectral details are given below.

**$\gamma$-Lactam 12.** Mp (124−25 °C). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.00−7.90 (m, 3H), 7.67−7.48 (m, 6H), 6.86 (br s, $D_2O$ exchangeable, 1H), 5.16 (d, $J$ = 8.0 Hz, 1H), 3.77 (dd, $J$ = 2.8 and 18.0 Hz, 1H), 3.12 (dd, $J$ = 10.2 and 18.2 Hz, 1H). FT-IR (KBr): $\nu_{max}$ 3313, 1706, 1678 cm$^{-1}$. CI-MS $m/z$ (rel intensity): 252 ($M^+$ + 1, 100%).

**$\gamma$-Lactam 13.** Mp (91−92 °C). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 8.02 (d, $J$ = 7.3 Hz, 2H), 7.91 (d, $J$ = 7.3 Hz, 1H), 7.68−7.42 (m, 6H), 6.94 (br s, $D_2O$ exchangeable, 1H), 5.04 (br s, 1H), 4.08−3.95 (m, 1H), 0.93 (d, $J$ = 7.3 Hz, 3H). FT-IR (KBr): $\nu_{max}$ 3313, 1709, 1675, 1648, 1549 cm$^{-1}$. MS $m/z$ (rel intensity): 265 ($M^+$, 2%), 160 (15%), 132 (100%).

**Synthesis of Dipeptide 14.** To a solution of **11** (250 mg, 1.30 mmol) and triethylamine (0.20 mL, 1.43 mmol) in THF (5 mL) cooled to −10 °C was added isobutyl chloroformate (0.19 mL, 1.43 mmol) and the reaction mixture was stirred for 1 min. A suspension of methyl L-leucinate hydrochloride (261 mg, 1.43 mmol) in THF (3 mL) was added to the above stirred reaction mixture followed by a solution of triethylamine (0.40 mL, 2.86 mmol) in THF (4 mL). After the addition the reaction was stirred at 25 °C overnight. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with saturated sodium bicarbonate (2 × 10 mL) and brine (10 mL), dried over sodium sulfate, and filtered. The filtrate was evaporated under vacuum and the crude product was column chromatographed with ethyl acetate as eluent to yield the desired product **14** as a hygroscopic foamy solid (210 mg, 50%). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$ 7.84 (d, $J$ = 8.0 Hz, 1H), 7.70−7.61 (m, 1H), 7.52 (dd, $J$ = 12.0 and 8.0 Hz, 1H), 7.43−7.31 (m, 1H), 7.01 (br s, $D_2O$ exchangeable, 1H), 6.12 (d, $J$ = 8.0 Hz, $D_2O$ exchangeable, 1H), 5.04−4.96 (m, 1H), 4.73−4.62 (m, 1H), 3.76 (s, 3H), 2.99−2.87 (m, 1H), 2.45−2.32 (m, 1H), 1.78−1.50 (m, 3H), 0.96 (d, $J$ = 6.0 Hz, 6H). FT-IR (KBr): $\nu_{max}$ 3289, 2957, 1730, 1695, 1670, 1548, 1469 cm$^{-1}$. CI-MS $m/z$ (rel intensity) 319 ($M^+$ + 1, 100%).

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**Supporting Information Available:** Spectral data (NMR, mass, IR) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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