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Expeditious Access to Unprotected Racemic Pyroglutamic Acids

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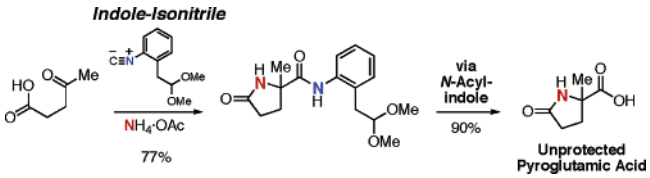

A series of biologically intriguing pyroglutamic acids were synthesized in racemic form by employing indole−isonitrile and ammonium acetate in the Ugi 4-center-3-component reaction of γ-ketoacids.

The pyroglutamic acid moiety is found in such natural products as lactacystin,[1] salinosporamide A,[2] dysibetaine,[3] and oxazolomycin[4] and is a common building block in asymmetric synthesis.[5] Despite their abundance in nature, there is no straightforward general synthesis available for this simple framework. The Ugi 4-center-3-component reaction (U4C-3CR)[6] of γ-ketoacids, [RCO(CH$_2$)$_2$CO$_2$H], provides ready access to the carbon framework of many pyroglutamic acid analogues.[7] However, until recently it has not been possible to hydrolyze the hindered *C*-terminal amides of pyroglutamic acid amides that result from the Ugi reaction of γ-ketoacids to the corresponding carboxylic acids, severely limiting the usefulness of this method. We reported the development of a convertible isonitrile, 1-isocyano-2-(2,2-dimethoxyethyl)benzene, also known as indole−isonitrile **(1)**, for use in the Ugi reaction and demonstrated the ready selective cleavage of the resulting *C*-terminal amide bond with the total synthesis of omuralide.[8] The synthetic utility of the pyroglutamic acid moiety would be increased further if ammonia or equivalents could be used as the amine component in the Ugi 4C-3CR. We now report an expansion of the scope of this discovery by demonstrating the expeditious synthesis of a series of unprotected pyroglutamic acids.

Levulinic acid (**2**) is known to participate in the U4C-3CR to give an anilide of type **3**, so this γ-ketoacid was used in our initial screen of amines (Table 1). Although *p*-methoxybenzylamine gives the Ugi product in good yield,[8] we preferred to find an alternative nitrogen source because the use of this amine generally requires subsequent deprotection, using harsh conditions such as ceric ammonium nitrate.[9] Ammonia in MeOH and ammonium carboxylate salts[6,10] (trifluoroacetate, formate, and acetate) were initially screened with 1.1 equiv of isonitrile **1**, and only ammonium acetate (1.1 equiv) was found to participate in the U4C-3CR with reasonable yield (entry 1). Ammonium halide salts did not afford the Ugi product. It was necessary to use 2 equiv of ammonium acetate to achieve a good conversion (entry 2), but further excess (>3 equiv) did not increase the yield (not shown). Pleasantly, the acetate counterion was not incorporated into the condensation products, presumably due to the intramolecular relationship between the imine and carboxylic acid. This also explains the suppression of six-component couplings and other byproducts sometimes observed when using ammonia equivalents in the Ugi reaction.[11] Using 2 equiv of isonitrile **1** afforded only a moderate increase in yield (entry 3). Consequently, we chose the condition listed in entry 2 as the standard procedure. Recent results have shown that the addition of 4 Å molecular sieves (20 mg/mmol) effects a significant increase in yield, and we recommend their use (entry 4). A commercially available, cheap, and stable solid, ammonium acetate is a user-friendly source of ammonia. We found that hexamethyldisilazane (2 equiv), a known ammonia equivalent, also participates in the Ugi reaction in acceptable yield (72%, entry 5).

Scheme 1 shows the conversion of levulinic acid (**2**) into 2-methylpyroglutamic acid.[12] Ammonium acetate (2 equiv) and **2** (1 equiv) were premixed in trifluoroethanol with gentle heating (60 °C) to promote imine formation. After addition of the isonitrile (1.1 equiv) to the mixture the U4C-3CR was complete within 2 h. A small amount (<5%) of Passerini product (**3a**)[13] is formed in the reaction, indicating incomplete imine formation, and is easily removed by chromatography. No acetal exchange was observed between trifluoroethanol and the dimethoxy acetal. All Ugi and Passerini products described (**3**, **3a** in Scheme 1

(1) (a) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiot.* **1991**, *44*, 113−116. (b) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A. *J. Antibiot.* **1991**, *44*, 117−118.

(2) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355−357.

(3) Sakai, R.; Oiwa, C.; Takaishi, K.; Kamiya, H.; Tagawa, M. *Tetrahedron Lett.* **1999**, *40*, 6941−6944.

(4) Mori, T.; Takahashi, K.; Kashiwabara, M.; Uemura, D.; Katayama, C.; Iwadare, S.; Shizuri, Y.; Mitomo, R.; Nakano, F.; Matsuzaki, A. *Tetrahedron Lett.* **1985**, *26*, 1073−1076.

(5) Nájera, C.; Yus, M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 2245−2303.

(6) For a comprehensive review of the Ugi reaction: Ugi, I.; Dömling, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.

(7) (a) Short, K. M.; Mjalli, A. M. M. *Tetrahedron Lett.* **1997**, *38*, 359−362. (b) Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591−5594. (c) Hanusch-Kompa, C.; Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725−2728. (d) Tye, H.; Whittaker, M. *Org. Biomol. Chem.* **2004**, *2*, 813−815.

(8) Indole−isonitrile (**1**) was named after the facilitation of hydrolysis of the resulting 2-(2,2-dimethoxyethyl)anilide **3** by Ugi/(Passerini) multicomponent condensation reaction, via *N*-acylindole **4**. The first demonstration of the utility as a convertible isonitrile in the Ugi reaction and its application to natural product synthesis were reported from our laboratory: Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Angew. Chem., Int. Ed.* Submitted for publication.

(9) Corey, E. J.; Li, W.; Nagamitsu, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 1676−1679.

(10) Polyakov, A. J.; Aseeva, V. G.; Bezrukova, V. G. *Izv. Akad. Nauk SSSR Ser. Khim.* **1974**, *7*, 1597.

(11) (a) Kazmaier, U.; Hebach, C. *Synlett* **2003**, *11*, 1591−1594. (b) Pick, R.; Bauer, M.; Kazmaier, U.; Hebach, C. *Synlett* **2005**, *5*, 757−760.

(12) (a) Takenishi, T.; Simamura, O. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 207−209. (b) Pfister, K., III; Leanza, W. J.; Conbere, J. P.; Becker, H. J.; Matzuk, A. R.; Rogers, E. F. *J. Am. Chem. Soc.* **1955**, *77*, 697−700.

(13) Application of indole−isonitrile (**1**) to Passerini reaction, see: Vamos, M.; Ozboya, K.; Kobayashi, Y. *Synlett.* Submitted for publication.

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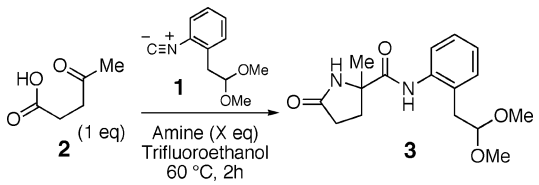
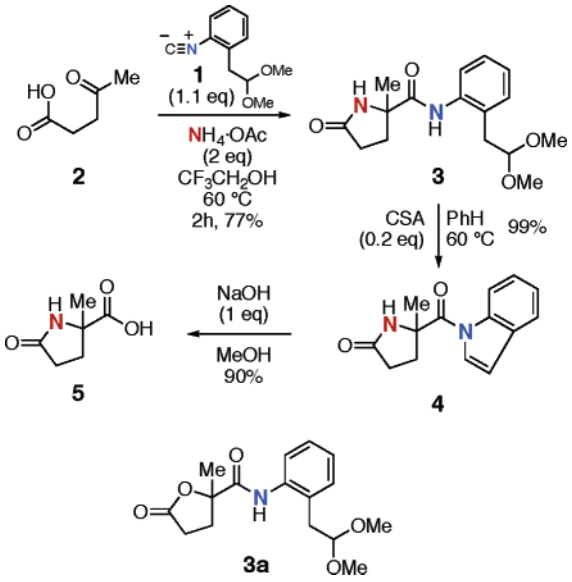
TABLE 1. Screening of Amine and the Reaction Condition of the Ugi Reaction



entry	amine	X (equiv)	isonitrile **1** (equiv)	yield (%)[a]
1	NH_4·OAc	1.1	1.1	61
2	NH_4·OAc	2	1.1	77
3	NH_4·OAc	2	1.1	82
4[b]	NH_4·OAc	2	1.1	84
5	HMDS[c]	2	1.1	72

[a] Isolated yield (1 mmol scale). [b] MS4Å was added (20 mg/mmol). [c] HMDS = hexamethyldisilazane.

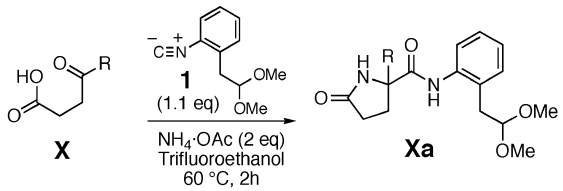
SCHEME 1. Synthesis of 2-Methylpyroglutamic Acid (5) by Ugi Reaction with Indole−Isonitrile (1)

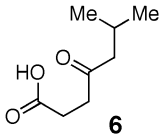
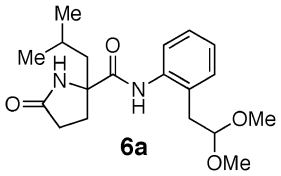
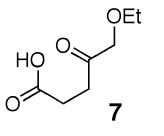
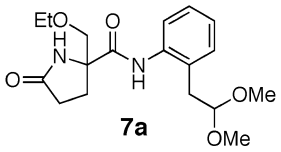
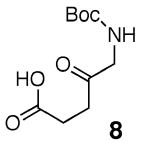
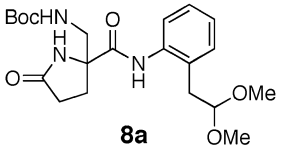
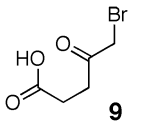
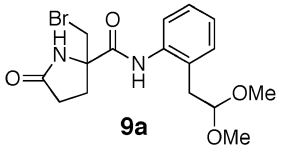
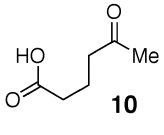
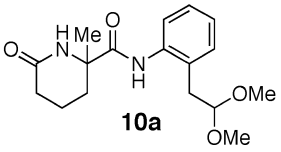


and **6a**−**10a** in Table 2) were obtained as racemic mixtures. The Ugi product **3** was successfully converted to the *N*-acylindole **4** upon treatment with a catalytic amount of camphorsulfonic acid (0.2 equiv) in benzene and gentle heating for 1 h.

Despite the steric congestion at the neighboring fully substituted carbon, the *N*-acylindole **4** is readily cleaved to the free pyroglutamic acid **5**[14] by treatment with sodium hydroxide (1 equiv) via the intermediate methyl ester. The methyl ester **5a**[15] (not shown) can be isolated in high yield (90%) by stirring for 1 h in methanol, using only a catalytic amount (0.03 equiv) of the base. Isolation of the final products was initially difficult due to their strong hydrophilicity. However, the free acid is readily obtained by recrystallization of the resulting sodium salt from methanol/diethyl ether, removing the indole byproduct, followed by treatment with acid resin. The methyl ester, on the other hand, is readily separated from the less polar indole by column chromatography.

TABLE 2. Ugi 4-Center-3-Component Condensation Reaction of γ-Ketoacids with Indole−Isonitrile (1)



Entry	Substrate	Product	Yield (%)[a]
1			63%
2			76%
3			67%
4			49%
5[b]			59%

[a] Isolated yield (1 mmol scale). [b] Homopyroglutamic acid.

We explored the utility of this methodology for the synthesis of a series of pyroglutamic acids. The mild conditions of the U4C-3CR should make it amenable to a wide variety of functional groups (Table 2). To test the hypothesis we conducted the reaction with levulinic acid derivatives (**6**−**9**) containing nitrogen, oxygen, and bromine and all successfully gave the corresponding anilide (**6a**−**9a**). The decreased yield for the reaction of **9** may be due to nucleophilic displacement of bromine; however, we did not detect any significant side product (entry 4). Commercially available 4-acetylbutyric acid (**10**, entry 5) successfully participates in the U4C-3CR to afford the expected homopyroglutamic acid anilide (**10a**) in surprisingly high yield considering the intermediacy of a seven-membered cyclic acylimidate.[7a]

Compounds **6**,[16] **8**,[17] and **9**[18] were prepared according to literature precedents. Compound **7** was synthesized in four steps from the commercially available benzyl succinate (Scheme 2). Benzyl succinate was converted into the corresponding acid

(14) For previous preparations of **5**, see ref 12.
(15) For previous preparations of **5a**: (a) Gillan, T.; Mor, G.; Pepper, F. W.; Cohen, S. G. *Bioorg. Chem.* **1977**, *6*, 329−342. (b) Mkhairi, A.; Hamelin, J. *Tetrahedron Lett.* **1986**, *27*, 4435−4436.
(16) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773−2784.
(17) Battah, S. H.; Chee, C-E.; Nakanishi, H.; Gerscher, S.; MacRobert, A. J.; Edwards, C. *Bioconj. Chem.* **2001**, *12*, 980−988.
(18) MacDonald, S. F. *Can. J. Chem.* **1974**, *52*, 3257−3258.

SCHEME 2. Preparation of Compound 7

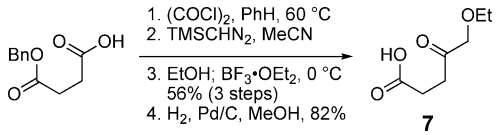
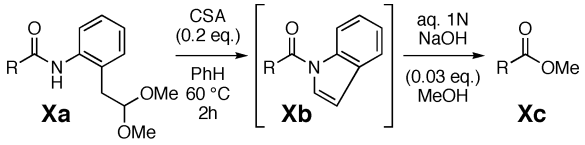


TABLE 3. Facile Conversion of Anilide to Ester via *N*-Acylindole



Entry	Substrate	Yield (%)[b]	Product
1	**6a**	86	**6c**
2	**7a**	94	**7c**
3	**8a**	98	**8c**
4	**9a**	96	**9c**
5[b]	**10a**	83	**10c**

[a] Isolated yield of **Xc** (2 steps from **Xa**, 0.2−0.5 mmol scale). [b] Homopyroglutamic acid.

chloride by using oxalyl chloride in benzene. The crude acid chloride was dissolved in acetonitrile and was treated with 2 equiv of (trimethylsilyl)diazomethane to create the unstable diazoketone intermediate that was captured in situ by ethanol after the addition of boron trifluoride etherate to give benzyl 5-ethoxy-4-oxopentanoate in 56% yield over 3 steps.[19] Finally the benzyl ester was removed by hydrogenolysis to give the desired ketoacid **7**.

The Ugi products (**6a**−**10a**) were successfully converted to the *N*-acylindoles (**Xb**), which were all easily cleaved to their corresponding methyl esters (**Xc**) in excellent yields (Table 3). The methyl esters were prepared due to the ease of isolation, and the corresponding acids could be made by employing additional base, as above. Compound **6c**[20] contains the full carbon backbone of the biologically interesting lactacystin.[1] The bromine in compound **9c** is a particularly useful synthetic handle because of the potential for further elaboration of the backbone by radical reaction or nucleophilic substitution. Homopyroglutamic acid analogue **10a** was also readily cleaved to the corresponding methyl ester (**10c**),[15b,21] suggesting the potential of this method for the preparation of various homopyroglutamic acids.

The synthesis of this series of pyroglutamic acid derivatives shows the utility of the indole−isonitrile **(1)** for cleaving the *C*-terminal amides products of the U4C-3CR to the more useful carboxylic acids. Furthermore, we demonstrated the mild and high yielding cleavage of such amides adjacent to a highly hindered carbon center. The use of an ammonia equivalent as the amine component in these reactions allows for the quick construction of complex heterocycles with no protecting groups. By varying the substitution pattern of the γ-ketoacid starting material more substituted pyroglutamic acids and homopyroglutamic acids can be accessed. Current studies are underway in our laboratory toward the application of this methodology to the synthesis of the pyroglutamic acid natural product dysibetaine.

Experimental Section

General Procedure for the Ugi Reaction: **Preparation of 3.** Ammonium acetate (2.0 mmol) was added to levulinic acid (**2**) (1.0 mmol) in 2,2,2-trifluoroethanol (2 mL) and the reaction was heated to 60 °C. After 30 min, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**1**) (1.1 mmol) was added and the reaction continued to stir at 60 °C until the isonitrile was consumed according to TLC (about 2 h). The reaction was removed from heat and the 2,2,2-trifluoroethanol was evaporated. The residue was diluted with water (10 mL) then extracted with ethyl acetate (2 × 15 mL). The combined organic portions were washed with brine (10 mL), dried over Na_2SO_4, then concentrated. Ugi product **3** (0.236 g, 77%) as colorless solid and Passerini product **3a** (<5%) as a colorless oil were recovered after purification by silica gel column chromatography (100% EtOAc).

3: Mp 142−143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 6.87 (s, 1H), 4.45 (t, J = 5.3 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.88 (dd, J = 3.8, 5.3 Hz, 2H), 2.58−2.44 (m, 3H), 2.19−2.14 (m, 1H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 172.8, 136.3, 131.3, 128.5, 127.8, 125.5, 124.3, 106.8, 63.8, 54.8, 54.6, 37.3, 34.4, 30.5, 26.0. HR-EI-MS $C_{16}H_{22}N_2O_4$ calcd 306.1574, obsd 306.1579.

3a (oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (br s, 1H), 7.81 (dd, J = 8.2, 0.8 Hz, 1H), 7.28 (td, J = 7.7, 1.4 Hz, 1H), 7.91 (dd, J = 7.7, 1.4 Hz, 1H), 7.12 (td, J = 7.7, 1.4 Hz, 1H), 4.52 (t, J = 4.8 Hz, 1H), 3.45 (s, 3H), 3.42 (s, 3H), 2.95−2.84 (m, 2H), 2.81−2.75 (m, 1H), 2.67−2.61 (m, 2H), 2.26−2.18 (m, 1H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 171.0, 136.1, 131.7, 128.9, 127.8, 125.7, 124.2, 105.8, 86.1, 54.1, 37.1, 32.6, 28.7, 25.3. HR-EI-MS $C_{16}H_{21}NO_5$ calcd 307.1414, obsd 307.1410.

***N*-Acylindole (4).** Camphorsulfonic acid (0.4 mmol) was added to the Ugi product **3** (2.0 mmol) in benzene (10 mL) and the reaction was heated to 60 °C for 1 h. The reaction was washed with saturated $NaHCO_3$ (aq) and brine, dried over Na_2SO_4, then filtered and concentrated. **4** (0.485 g, 2.0 mmol) was recovered as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 3.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.79 (br s, 1H), 6.70 (d, J = 3.6 Hz, 1H), 2.83−2.77 (m, 1H), 2.66−2.59 (m, 1H), 2.52−2.41 (m, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4, 172.1, 129.7, 128.5, 126.0, 124.6, 124.1, 121.1, 117.4, 110.6, 64.8, 33.3, 30.2, 28.2. HR-EI-MS $C_{14}H_{14}N_2O_2$ calcd 242.1050, obsd 242.1053.

2-Methylpyroglutamic Acid (5). 4 (0.242 g, 1.0 mmol) was dissolved in methanol (3 mL). Solid sodium hydroxide (1.0 mmol)

(19) (a) Newman, M. S.; Beal, P. F., III *J. Am. Chem. Soc.* **1950**, *72*, 5161−5163. (b) Marugán, J.; Anaclerio, B.; Lafrance, L.; Lu, T.; Markotan, T.; Leonard, K. A.; Crysler, C.; Eisennagel, S.; Dasgupta, M.; Tomczuk, B. *J. Med. Chem.* **2005**, *48*, 926−934.

(20) The corresponding ethyl ester of **6c** was prepared previously: Guillena, G.; Mico, I.; Najera, C.; Ezquerra, J.; Pedregal, C. *An. Quim. Int. Ed.* **1996**, *92*, 362−369.

(21) For previous preparations of **10c**: Overberger, C. G.; Shalati, M. D. *Eur. Polym. J.* **1983**, *19*, 1055−1065.

was added and the reaction was stirred until no starting material remained by TLC (about 1 h). The reaction was concentrated and the sodium salt of the product was recrystallized from methanol/diethyl ether to yield 0.162 g (0.98 mmol) of white solid. The sodium salt was treated with Amberlyst 15 in methanol and upon concentration 0.124 g (90% from **3**) of the free carboxylic acid **5** was recovered as a white solid. Mp 144−145 °C (lit.[13] mp 144−145 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (s, 1H), 2.48−2.37 (m, 3H), 2.07−1.99 (m, 1H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.0, 176.4, 62.7, 32.6, 32.5, 24.1. HR-EI-MS $C_6H_9NO_3$ calcd 143.0577, obsd 143.0575.

2-Methylpyroglutamic Acid Methyl Ester (5a). Aqueous sodium hydroxide (1 N, 6 μmol) was added to crude *N*-acylindole **4** (1.0 mmol) dissolved in methanol (3 mL) and the reaction was stirred for 1 h then concentrated and purified by column chromatography (100% CH_2Cl_2 to 9:1 CH_2Cl_2:methanol). The combined fractions were dried over Na_2SO_4 and treated with activated charcoal (if necessary) then filtered and concentrated. White crystalline solid methyl ester **5a** (0.282 g, 90%) was recovered. Mp 87−89 °C (lit.[15a] mp 58−59 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 3.74 (s, 3H), 2.47−2.32 (m, 3H), 2.07−1.99 (m, 1H), 1.49 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.9, 174.9, 62.8, 52.0, 32.5, 29.9, 24.1. HR-EI-MS $C_7H_{11}NO_3$ calcd 157.0733, obsd 157.0736.

6a: Mp 129−131 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.78 (d, J = 7.9 Hz, 1H), 7.28 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 6.33 (s, 1H), 4.48 (t, J = 5.3 Hz, 1H), 3.44 (s, 3H), 3.43 (s, 3H), 2.88 (d, J = 5.3 Hz, 2H), 2.59−2.53 (m, 1H), 2.46−2.39 (m, 2H), 2.22−2.13 (m, 2H), 1.80−1.74 (m, 1H), 1.61 (dd, J = 6.2, 14.1 Hz, 1H), 1.00 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 172.8, 136.5, 131.5, 128.6, 127.9, 125.6, 124.4, 106.6, 66.7, 54.5, 54.4, 47.8, 37.2, 34.9, 29.7, 25.4, 24.4, 23.2. HR-EI-MS $C_{19}H_{28}N_2O_4$ calcd 348.2044, obsd 348.2039.

6c: Mp 81−84 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.74 (s, 3H), 2.45−2.31 (m, 3H), 2.12−2.05 (m, 1H), 1.85−1.69 (m, 3H), 0.93 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.6, 174.7, 66.1, 52.0, 47.4, 32.0, 29.7, 24.7, 23.7, 22.1. HR-EI-MS $C_{10}H_{17}NO_3$ calcd 199.1203, obsd 199.1199.

5-Ethoxy-4-oxopentanoic Acid (7). Benzyl succinate (6.3 mmol) was treated with oxalyl chloride (8.1 mmol, 1.3 equiv) in benzene (20 mL) and the reaction was heated to 60 °C for 1 h after which time all volatile components were removed by vacuum. The crude acid chloride was dissolved in acetonitrile (15 mL) then (trimethylsilyl)diazomethane (2.0 M solution in Et_2O, 6.3 mL, 2.0 equiv) was slowly added. After 30 min the reaction was cooled to 0 °C then ethanol (5 mL) was added followed by the careful addition of $BF_3{\cdot}OEt_2$ (1.16 mL, 1.5 equiv). After 1 h the reaction was diluted with water (50 mL) then extracted with ethyl acetate (2 × 20 mL). The combined organic portions were washed with brine (20 mL) then dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography, using 4:1 hexanes:ethyl acetate, to yield benzyl 5-ethoxy-4-oxopentanoate (**11**) (3.5 mmol, 56%) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 5.11 (s, 2H), 4.06 (s, 2H), 3.53 (q, J = 7.0 Hz, 2H), 2.79 (t, J = 6.5 Hz, 2H), 2.68 (t, J = 6.5 Hz, 2H), 1.24 (t, J = 7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.8, 172.7, 136.0, 128.8, 128.5, 128.4, 76.0, 67.4, 66.8, 33.7, 27.8, 15.3. HR-EI-MS $C_{14}H_{18}O_4$ calcd 250.1200, obsd 250.1201. **11** (0.46 mmol) was dissolved in methanol (3 mL) and catalytic palladium on carbon (10% w/w, 5 mg) was added. The reaction was stirred under 1 atm of H_2 for 3 h then filtered through Celite and concentrated to yield **7** (0.38 mmol, 82%) as a clear oil. ^{1}H NMR (400 MHz, CD_3OD) δ 4.16 (s, 1H), 3.55 (q, J = 7.0 Hz, 2H), 2.71 (t, J = 6.4 Hz, 2H), 2.57 (t, J = 2.6 Hz, 2H), 1.21 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 208.4, 175.1, 75.2, 66.9, 33.0, 27.1, 14.1. HR-EI-MS $C_7H_{12}O_4$ calcd 160.0730, obsd 160.0728.

7a: Mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.37 (s, 1H), 4.48 (dd, J = 4.4, 6.4 Hz, 1H), 4.02 (d, J = 8.8 Hz, 1H), 3.53−3.47 (m, 2H), 3.42 (s, 6H), 3.39 (d, J = 8.8 Hz, 1H), 2.97 (dd, J = 6.4, 14 Hz, 1H), 2.82 (dd, J = 4.4, 14 Hz, 1H), 2.52−2.36 (m, 3H), 2.11−2.06 (m, 1H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 171.4, 136.1, 131.1, 128.6, 127.5, 125.4, 124.3, 106.1, 75.2, 67.0, 66.6, 54.4, 53.5, 36.8, 29.3, 28.7, 14.9. HR-EI-MS $C_{18}H_{26}N_2O_5$ calcd 350.1836, obsd 350.1843.

7c (oil): ^{1}H NMR (400 MHz, CD_3OD) δ 3.76 (s, 3H), 3.55−3.49 (m, 4H), 2.38−2.26 (m, 3H), 2.15−2.13 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.9, 173.2, 74.8, 67.1, 66.8, 52.2, 29.6, 27.6, 14.3. HR-EI-MS $C_9H_{15}NO_4$ calcd 201.0996, obsd 201.0995.

8a: Mp 83−86 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.08 (s, 1H), 5.16 (s, 1H), 4.49 (t, J = 5.1 Hz, 1H), 3.58−3.48 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 2.86 (d, J = 5.1 Hz, 2H), 2.50−2.39 (m, 3H), 2.14−2.12 (m, 1H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 172.2, 157.5, 136.1, 131.5, 129.0, 127.7, 125.8, 124.4, 106.1, 80.4, 68.3, 54.3, 54.2, 48.0, 37.0, 30.7, 29.9, 28.5. HR-EI-MS $C_{21}H_{31}N_3O_6$ calcd 421.2207, obsd 421.2213.

8c (oil): ^{1}H NMR (400 MHz, CD_3OD) δ 3.75 (s, 3H), 3.48 (d, J = 14.1 Hz, 1H), 3.38 (d, J = 14.1 Hz, 1H), 2.40−2.14 (m, 4H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, CD_3OD) δ 179.0, 173.2, 157.4, 79.4, 66.9, 52.2, 46.4, 29.5, 27.8, 27.5. HR-EI-MS $C_{12}H_{20}N_2O_5$ calcd 272.1367, obsd 272.1367.

9a: Mp 130 °C dec. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (s, 1H), 7.74 (s, 1H), 7.33−7.15 (m, 3H), 6.23 (s, 1H), 4.51 (t, J = 5.5 Hz, 1H), 4.19 (d, J = 7.5 Hz, 1H), 3.50 (d, J = 7.5 Hz, 1H), 3.45 (s, 3H), 3.44 (s, 3H), 3.01 (dd, J = 5.5, 13.8 Hz, 1H), 2.85 (dd, J = 5.5, 13.8 Hz, 1H), 2.66−2.52 (m, 3H), 2.30−2.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 170.2, 136.1, 131.6, 129.0, 127.9, 126.1, 124.7, 106.5, 66.8, 54.7, 54.1, 39.2, 37.3, 32.0, 30.3. HR-EI-MS $C_{16}H_{21}BrN_2O_4$ calcd 384.0679, obsd 384.0678.

9c: Mp 92−94 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 3.85−3.71 (m, 2H), 3.80 (s, 3H), 2.51−2.21 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.8, 172.0, 66.6, 52.4, 37.4, 29.8, 29.6. HR-EI-MS $C_7H_{10}BrNO_3$ calcd 234.9839, obsd 234.9835.

10a: Mp 157−159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 6.51 (s, 1H), 4.45 (t, J = 5.3 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 2.86 (d, J = 5.3 Hz, 2H), 2.49−2.37 (m, 3H), 1.87−1.80 (m, 2H), 1.65−1.59 (m, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 172.1, 136.4, 131.3, 128.8, 127.7, 125.7, 124.7, 106.6, 61.8, 54.9, 54.3, 37.3, 33.8, 31.3, 27.9, 18.6. HR-EI-MS $C_{17}H_{24}N_2O_4$ calcd 320.1731, obsd 320.1728.

10c: Mp 98−100 °C (lit.[20a] mp 98.5−99.5 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 3.74 (s, 3H), 2.31−2.19 (m, 3H), 1.86−1.82 (m, 1H), 1.74−1.61 (m, 2H), 1.47 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 174.9, 173.6, 59.9, 52.1, 32.4, 30.1, 25.3, 17.8. HR-EI-MS $C_8H_{13}NO_3$ calcd 171.0890, obsd 171.0892.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **3**−**5**, **3a**, **5a**, **7**, **6a**−**10a**, **6c**−**10c**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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