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Synthesis of Unnatural Amino Acids from Serine Derivatives by β-Fragmentation of Primary Alkoxyl Radicals

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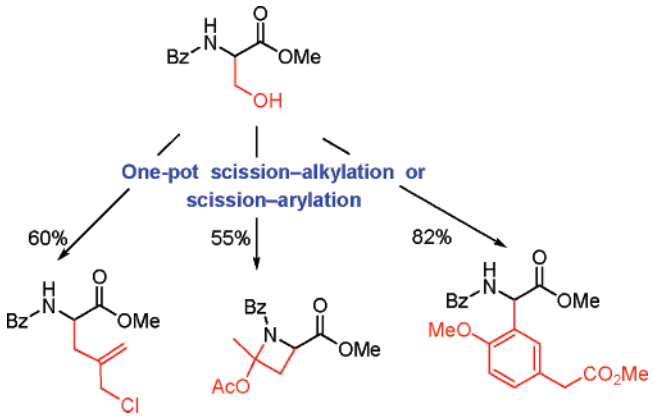

The fragmentation of primary alkoxyl radicals has been scarcely used in synthesis since other competing processes (such as oxidation or hydrogen abstraction) usually predominate. However, when serine derivatives were used as substrates, the scission took place in excellent yields. Tandem scission−allylation, −alkylation, or −arylation reactions were subsequently developed. This one-pot methodology was applied to the synthesis of unnatural amino acids, which are useful synthetic blocks or amino acid surrogates in peptidomimetics.

Introduction

Nonproteinogenic amino acids are important building blocks in the synthesis of alkaloids, peptides, and other biologically active products.[1] Thus, they have been used to prepare alkaloids such as the antiviral castanospermine[2] and the cytotoxic dragmacidins.[3] They are also components of glycopeptide[4] and β-lactam antibiotics,[5] glutamate antagonists,[6] and other drugs.[7] Besides, these amino acids have been incorporated into peptides[8] to modulate their activity and to improve their hydrolytic stability or bioavailability. Moreover, recent advances have allowed incorporation of unnatural amino acids into proteins, using cellular machinery, providing new tools to study protein function and to create peptides and proteins with enhanced properties.[9]

As a result, the methods to prepare these amino acids have deserved much interest.[10] The best known among them is the Strecker reaction,[11] because of its simplicity and the availability of the starting aldehydes and amines. However, it requires toxic cyanide reagents, so safer alternatives have been explored.

A competitive route should use readily available substrates and proceed in few (ideally one) steps. We reasoned that the fragmentation of O-radicals derived from serine derivatives

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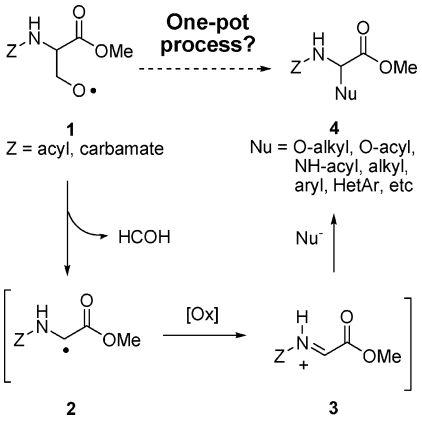
SCHEME 1. Synthetic Strategy toward Nonproteinogenic Amino Acids, Based on the Fragmentation of Primary Alkoxyl Radicals Derived from Serine Derivatives

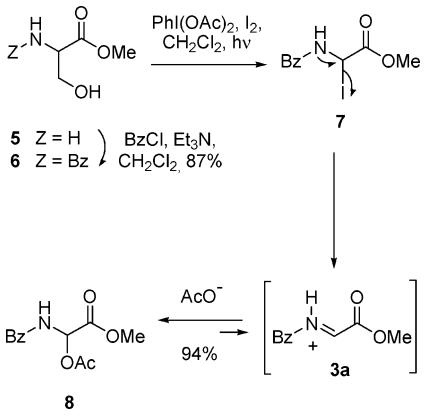


could match these requirements (Scheme 1). Although primary alkoxyl radicals **1** undergo oxidation or hydrogen abstraction[12] rather than scission, in the case of serine derivatives the fragmentation would be favored, since the resulting C-radical **2** would be stabilized by the adjacent nitrogen function.[13] Under appropriate conditions, these radicals would undergo oxidation to acyliminium ions **3**,[14] which could be trapped by nucleophiles,[15] affording a variety of nonproteinogenic amino acids **4**. The feasibility of this approach is discussed herein.

Results and Discussion

Fragmentation of Serine Derivatives. To explore the β-fragmentation of primary O-radicals derived from serine, the commercial methyl ester **5** (Scheme 2) was transformed into the scission substrate **6**.[16] The latter was treated with (diacetoxyiodo)benzene (DIB) and iodine, at 26 °C and under visible light irradiation (sunlight or 80-W tungsten-filament lamp), to generate an alkoxyl radical, which underwent β-fragmentation. Plausibly, the resulting C-radical reacted with iodine, to give the unstable α-iodoglycine **7**.[17] Extrusion of iodide formed the glycine cationic intermediate **3a**, which was trapped by acetate ions from the reagent (DIB), to give the α-acetoxy glycine **8** in excellent yield (94%).

SCHEME 2. Fragmentation of Primary Alkoxyl Radicals in Serine Derivatives



When dry methanol was added after the fragmentation step, the α-methoxy glycine **9**[18] (Table 1, entry 1) was formed in 93% yield. No side reactions (such as oxidation of the alkoxyl radical to a carbonyl group or hydrogen abstraction) were observed.

A similar strategy was used to introduce other heteroatom functions: the scission of substrate **6** was followed by addition of sulfur or nitrogen nucleophiles. Dissapointingly, when thiophenol was added (entry 2), only acetate **8** was isolated. The same result was obtained when pure acetate **8** was treated with thiophenol in dichloromethane. Finally, the desired α-phenylthioglycine **10**[19] was formed by addition of $BF_3{\cdot}OEt_2$ to the reaction mixture (entry 3; 81% global yield for the two-step procedure and 37% yield for the one-step method). The α-phenylthioglycines are phenylglycine bioisosteres and have been incorporated to peptides with anti-HIV[20] or antibiotic activity.[21]

When thiophenol was replaced by nitrogen nucleophiles such as 2-oxazolidinone or 4-phenylurazole (entries 4−7), similar results were obtained. In the absence of a Lewis acid (entries 4 and 6), the acetate **8** was the only product isolated. However, the addition of $BF_3{\cdot}OEt_2$ to the reaction mixture afforded the oxazolidinone **11** (entry 5) and the urazole **12** (entry 7). The

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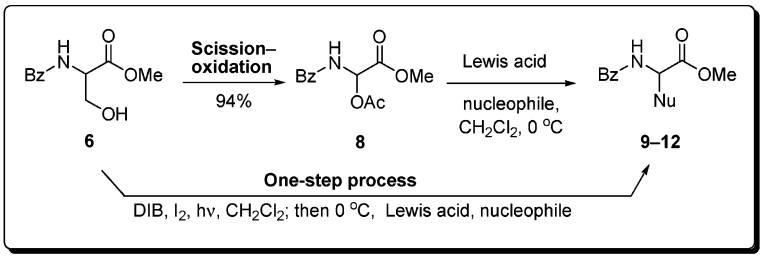
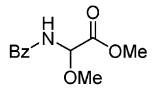
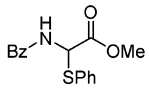
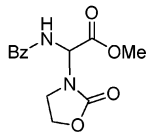
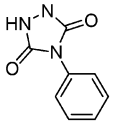
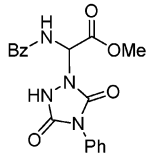
TABLE 1. Scission and Addition of Oxygen, Sulfur, and Nitrogen Nucleophiles



entry	Lewis acid	nucleophile	products	two-step global yield (%)[a]	one-step yield (%)[a]
1	—	MeOH	 **9**	—	**9** (93%)
2	—	PhSH	 **10**	**8** (90%) **10** (0%)	**8** (92%) **10** (0%)
3	$BF_3 \cdot OEt_2$	PhSH		**10** (86%)	**10** (37%)
4	—		 **11**	**8** (90%) **11** (0%)	**8** (92%) **11** (0%)
5	$BF_3 \cdot OEt_2$			**11** (70%)	**11** (43%)
6	—			**8** (90%) **12** (0%)	**8** (92%) **12** (0%)
7	$BF_3 \cdot OEt_2$		**12**	**12** (27%)	**12** (14%)

[a] Yields for products purified by chromatography.

yields for the two-step procedure (70% and 27%, respectively) were superior to those for the one-step method (43% and 14%).

The addition of nonaromatic carbon nucleophiles, such as allylsilanes and enol ethers, was studied as well (Table 2). In all cases, in the absence of the Lewis acid, only acetate **8** was isolated (about 90% yield). When $BF_3 \cdot OEt_2$ was added, products **13**−**19** were formed (entries 1−4). Using allylTMS as the nucleophile (entry 1), the two-step process afforded the allyl glycine **13**[22] in good yield (70%). However, the one-step method initially gave complex product mixtures. The results improved when the conversion of acetate intermediate **8** into the allyl glycine **13** was not forced to completion. Thus, product **13** was obtained (35%) together with acetate **8** (52%), which was later transformed into the allylglycine.

In contrast, when a more substituted allylsilane was used as the nucleophile (entry 2), the two-step and the one-pot procedures gave similar yields. Thus, the tandem fragmentation−allylation method with (chloromethyl)allylTMS gave the desired allyl glycine **14** in 60% yield, while the two-step process afforded compound **14** in 58% global yield. In both cases, trace amounts of the proline derivative **15** were detected. The conversion of compound **14** into product **15** by intramolecular N-alkylation with NaH proceeded in quantitative yield. This transformation exemplifies the utility of allyl glycines as precursors of bioactive products, since racemic 4-methylene proline (first isolated from the seeds of loquat) is a potent enzyme inhibitor.[23]

The fragmentation−nucleophilic addition procedure is also useful to obtain γ-oxo-α-amino acids (entries 3 and 4), which are components of antibiotic, antiinflammatory, or antihypertensive drugs.[24] Thus, the tandem fragmentation−alkylation with phenyl(trimethylsilyloxy)ethylene and $BF_3 \cdot OEt_2$ (entry 3) af-

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forded the γ-oxo-homophenylalanine **16**[25] (30%), together with the α-acetoxyglycine **8** (55%). In this case, the two-step procedure gave better results, affording compound **16** in 67% global yield.

A variation of this reaction gave an unexpected result (entry 4). The scission of substrate **6**, followed by addition of boron trifluoride and isopropenyl acetate, gave the methyl ketone **17** as the minor product, and the azetidines **18** and **19** as the major products. The stereochemistry of β-lactamols **18** and **19** was determined by NOESY experiments[26] and supported by MMFF calculations.[27] The reaction results can be explained as shown in Table 2 (footnote b). The scission of the O−COMe bond (route a) would generate a highly electrophilic $[Me-CO]^+$ intermediate; therefore, the nucleophilic attack by the amide function (route b) is preferred.

The β-lactamols **18** and **19** were hydrolyzed to the ketone **17** in excellent yield. However, azetidine carboxylic acids are important on their own: these cyclic amino acids have been incorporated into peptides to decrease their backbone flexibility and to improve their bioactivity.[28] In spite of their usefulness, very few of these amino acids are commercially available and are quite expensive. This route would provide a direct access to these compounds,[29] incorporating a variety of side-chains. The *N*,*O*-acetal group would also allow to introduce new functionalities. The synthesis of new azetidine carboxylic acids is in progress and will be reported in due course.

Other nonproteinogenic amino acids with biological significance are the aryl glycines, which are constituents of antibiotics such as vancomycin[4] and the nocardicins,[5] antineurodegenerative agents,[6] and alkaloids.[30] Therefore, the synthesis of new aryl glycines has elicited much interest.[31]

The fragmentation of the serine derivative **6**, followed by treatment with boron trifluoride and different aromatic nucleophiles, is shown in Table 3. All the nucleophiles were commercial products or were obtained therefrom. Most of the unreacted reagent was recovered, being easily separated from the desired products.

To our satisfaction, although aromatic rings are poorer nucleophiles than allylsilanes or enol silyl ethers, the scission−arylation reaction provided different aryl glycines in moderate to excellent yields. The arylation was favored by electron-donating groups (EDG) on the aromatic ring. Thus, the reaction yields increased from naphthyl glycine **20**[13,32] (63%, entry 1) to the 2-methoxynaphthyl analogue **21** (95%, entry 2). Another example is shown in entries 3 and 4. When phenyl acetate was used as the nucleophile (entry 3), the desired phenyl glycine was not isolated. However, when methoxy and (to a lesser extent) alkyl groups were activating the ring (entry 4), the arylation took place, affording products **22** and **23** in good global yield. The *p*-methoxy derivative **22** predominated over the *o*-methoxy product **23**.

In most cases, the one-step process was similar to the two-step procedure. An exception is biphenylglycine **24** (entry 5), which was formed in low yield using the one-pot method, while the two-step process gave moderate yields.

To study the directing effect of EDG, several aromatic nucleophiles with ether, carbamate, and alkyl groups were prepared (entries 6−11). The one-pot process afforded products **25**−**32** in good to excellent yields. When 2,3-dihydrobenzo-[*b*][1,4]dioxine was used as the nucleophile (entry 6), benzodioxolane **25** predominated over the more hindered analogue **26**. In the case of the benzoxazolidinone nucleophile (entry 7), the directing effect of the nitrogen function was superior to the effect of the oxygen function, and only isomer **27** was formed.

In a similar way, product **28** (entry 8) was formed exclusively, since the directing effect of the methoxy group predominated over that of the alkyl group. It should be noted that amino acid **28** can be linked to other amino acids in modified peptides through its side chain carboxylate group,[33] inducing turns in the peptidic chain.

If a bulky substituent is introduced ortho to the directing group, the regioselectivity is improved (entries 9 and 10, the H substituent is replaced by Br). Thus, when methyl 2-phenoxyacetate was used as the nucleophile (entry 9), a mixture of *p*- and *o*-alkoxyphenylglycines **29** and **30** was formed. Using methyl 3-bromo-2-phenoxyacetate (entry 10), the *p*-alkoxy isomer **31** was formed exclusively; no ortho products were detected. Similarly, when the nucleophile was 1-(allyloxy)-2-iodobenzene (entry 11), only the *p*-allyloxyglycine **32** was isolated (89%).

The preparation of halogenated aryl glycines such as compounds **31** and **32** is quite interesting, since the halo substituent can be replaced by aryl, vinyl, alkynyl, or alkyl groups using sp^2-sp^2 coupling reactions.[34] For instance, compound **32** (entry 11) underwent a Heck reaction affording the benzofuran glycine **33** in 71% yield. To our knowledge, it is the first time that a 5-methylene benzofuran glycine has been obtained. A variety of alkyl chains could be introduced from differently substituted allyl groups. These chains may belong to amino acid sequences in peptidomimetics.

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(26) In the NOESY experiment of compound **19**, spatial correlations were observed between δ_H 4.45 (1H, dd, 4-H) and δ_H 1.92 (3H, s, 2-Me). In the NOESY experiment of compound **18**, no correlations between δ_H 4.41 (1H, dd, 4-H) and δ_H 1.96 (3H, s, 2-Me) were detected.

(27) (a) Theoretical coupling constants were calculated over the minimized structures for both diastereomers, by using the Karplus−Altona equation implemented in the Macromodel 7.0 program. The calculations were performed with an MMFF force field, using high-quality parameters, and repeated with an AMBER force field. Similar results were obtained in both cases. (b) Theoretical *J* for the minimized structure corresponding to diastereomer **18**: $J_{2,3} = 5.2$, 9.8 Hz (experimental: $J_{2,3} = 5.0$, 12.6 Hz). The minimized structure for diastereomer **19** showed $J_{2,3} = 3.9$, 9.3 Hz (experimental: $J_{2,3} = 3.7$, 7.3 Hz). (c) For information on the Karplus−Altona equation, see: Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792. (d) For more information on this software, see: Mohamadi, F.; Richard, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrikson, T.; Stille, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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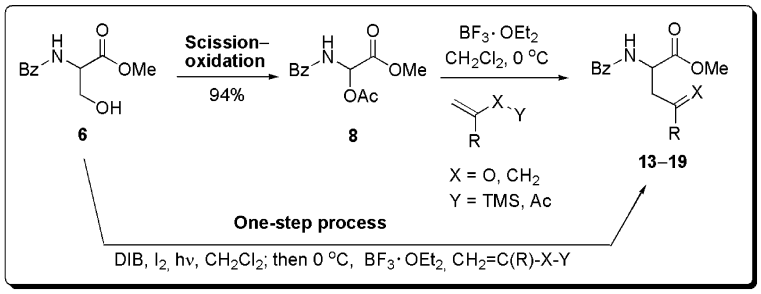
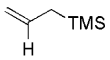
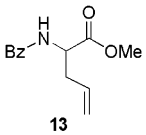
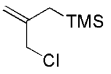
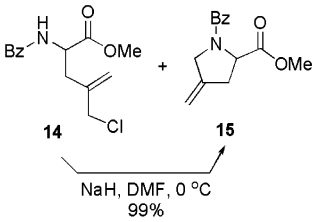
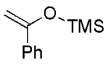
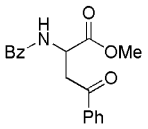
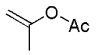
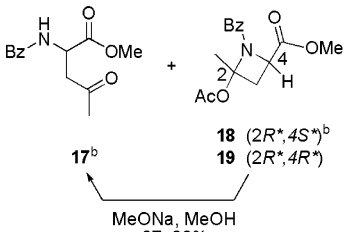
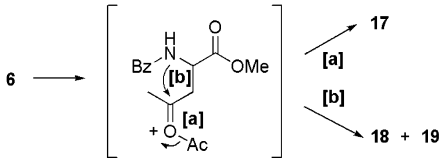
(34) (a) Wang, W.; Zhang, J.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 2137−2140. (b) Lutz, C.; Bleicher, K. H. *Tetrahedron Lett.* **2002**, *43*, 2211−2214. (c) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

TABLE 2. Addition of Nonaromatic Carbon Nucleophiles



entry	nucleophile	products	two-step global yield (%)[a]	one-step yield (%)[a]
1		 **13**	**13** (70%)	**13** (35%) **8** (52%)
2		 **14** **15** NaH, DMF, 0 °C 99%	**14** (58%) **15** (traces)	**14** (60%) **15** (traces)
3		 **16**	**16** (67%)	**8** (55%) **16** (30%)
4		 **17**[b] **18** (2*R*,4S**)[b] **19** (2*R*,4R**) MeONa, MeOH 97–99%	**17** (15%) **18** (17%) **19** (52%)	**17** (9%) **18** (11%) **19** (44%)

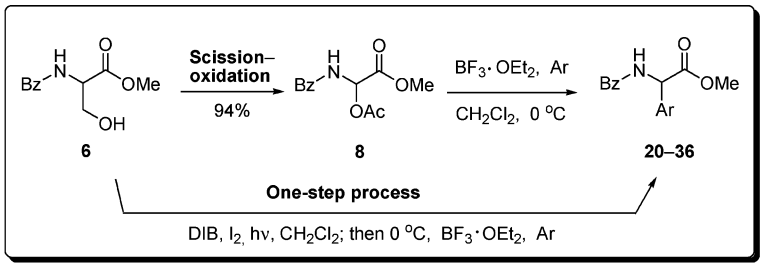
[a]Yields for products purified by chromatography. [b]The formation of products **17**–**19** can be explained via the intermediate below.



The synthesis of heteroaryl glycines was studied as well. Two representative examples are shown in entries 12 and 13. The fragmentation of substrate **6**, followed by arylation with furan, gave the furyl glycine[35] **34** in good yield. The one-pot and the two-step procedure gave similar results (80% versus 79%). The scission−heteroarylation reaction was then tried with methyl 1-indolecarboxylate, affording the indole glycines **35** and **36**, which are tryptophan surrogates.[36] In this case the two-step procedure gave better results than the one-pot procedure, since the indolic rings can be oxidized by the system DIB-iodine.

In summary, primary alkoxyl radicals derived from serine (by treatment with (diacetoxyiodo)benzene and iodine) undergo β-fragmentation in excellent yield. When no external nucleophiles are added, an α-acetoxy glycine is formed. However, the fragmentation can be coupled with the addition of heteroatom or carbon nucleophiles, providing uncommon amino acids such

TABLE 3. Synthesis of Aryl Glycines



entry	nucleophile	products two-step yield / one-step yield[a]
1	X = H	**20** X = H (65% / 63%)
2	X= OMe	**21** X = OMe (90% / 95%)
3	Ph-OAc	—
4		**22** (53% / 45%) **23** (27% / 22%)
5	Biphenyl	**24** (40% / 8%)
6		**25** (67% / 60%) **26** (21% / 19%)
7		**27** (90% / 59%)
8		**28** (76% / 82%)
9	X = H	X = H **29** (57% / 61%) **30** (29% / 31%)
10	X = Br	X = Br **31** (59% / 63%)
11		**32** (82% / 86%) **33** (–/–) $Pd(PPh_3)_4$, Ag_2CO_3, DMF, 80 °C, 71%
12	furan	**34** (80% / 79%)
13	Methyl Indole-1-carboxylate	**35** (61% / 43%) **36** (27% / 20%)

[a] Yields for purified products.

as α-alkoxy, α-thiophenyl, α-amino, α-allyl, α-alkyl, and α-aryl glycines. These amino acids can be used as synthetic intermediates for different bioactive compounds or as peptidomimetic constituents.

Experimental Section

Methyl (Acetyloxy)(benzoylamino)acetate (8). The serine derivative **6**[16] (223 mg, 1 mmol) in dry dichloromethane (14 mL) was treated with DIB (805 mg, 2.5 mmol) and iodine (254 mg, 1

mmol). The mixture was stirred at room temperature (26 °C) under visible light irradiation (sunlight or 80-W tungsten-filament lamp). After 3 h, the solution was poured into aqueous 10% $Na_2S_2O_3$ and extracted with CH_2Cl_2. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 95:5), giving the acetate **8** (94%): Crystalline solid; mp 87−88.5 °C (from EtOAc/*n*-hexane); IR 3441, 1754, 1682, 1513 cm^{-1}; ^1H NMR (500 MHz) δ_H 2.09 (3H, s), 3.79 (3H, s), 6.59 (1H, d, J = 8.8 Hz), 7.42 (2H, dd, J = 7.6, 7.9 Hz), 7.52 (1H, dd, J = 7.4, 7.5 Hz), 7.75 (1H, d, J = 8.8 Hz), 7.82 (2H, d, J = 7.3 Hz); ^{13}C NMR (100.6 MHz) δ_C 20.4 (CH_3), 53.1 (CH_3), 72.5 (CH), 127.3 (2 × CH), 128.5 (2 × CH), 132.3 (CH + C), 166.8 (C), 167.2 (C), 170.2 (C); MS (EI) *m*/*z* (rel intensity) 251 (M^+, <1), 192 (M^+ − COOMe, 11), 105 (COPh, 100); HRMS calcd for $C_{12}H_{13}NO_5$, 251.0794; found, 251.0825; calcd for C_7H_5O, 105.0340; found, 105.0342. Anal. Calcd for $C_{12}H_{13}NO_5$: C, 57.37; H, 5.22; N, 5.58. Found: C, 57.14; H, 5.31; N, 5.53.

Methyl 2-Benzamido-2-methoxyacetate (9). The serine derivative **6**[16] (223 mg, 1 mmol) in dry dichloromethane (14 mL) was treated with DIB (805 mg, 2.5 mmol) and iodine (254 mg, 1 mmol). The mixture was stirred at room temperature (26 °C) under visible light irradiation. After 3 h, dry methanol (1 mL) was injected and the solution was stirred for 1 h. Workup and purification as previously described afforded compound **9** (207 mg, 93%).[18]

Standard Procedure for the Two-Step Decarboxylation−Addition of Nucleophiles. The serine derivative **6** (223 mg, 1 mmol) underwent fragmentation to afford acetate **8** as previously commented. Then compound **8** was dissolved in dry dichloromethane and cooled to 0 °C, and $BF_3{\cdot}OEt_2$ (2 equiv) and an excess of the nucleophile (5 equiv for compounds **10**−**19**, **22**−**31**, and **35**−**36**; 10 equiv. for compounds **20**, **21**, **32**, and **34**) were added. The reaction was allowed to reach rt and stirred for 4 h. Afterward, it was poured into aq $NaHCO_3$ and extracted with CH_2Cl_2. The yields are given for products purified by chromatography on silica gel.

Standard Procedure for the One-Pot Decarboxylation−Addition of Nucleophiles Reaction. To a solution of methyl *N*-benzoylserine **6** (223 mg, 1 mmol) in dry dichloromethane (14 mL) was added (diacetoxyiodo)benzene (805 mg, 2.5 mmol) and iodine (254 mg, 1 mmol). The reaction was stirred at room temperature (26 °C) and under visible light irradiation (sunlight or 80-W tungsten-filament lamp) for 2−3 h, till complete disappearance of the starting material. Then the reaction mixture was cooled to 0 °C with an ice bath and $BF_3{\cdot}OEt_2$ was added dropwise (2 mmol), followed by addition of an excess of the nucleophile (5 or 10 mmol). The reaction mixture was allowed to reach room temperature and then was stirred for 4 h. Finally, it was poured into 10% aqueous sodium thiosulfate containing sodium bicarbonate and extracted with dichloromethane. The organic layers were dried with sodium sulfate and filtered, and the solvent was removed under vacuum. Then the residue was purified by column chromatography on silica gel. The column was eluted with hexanes/ethyl acetate mixtures to give the desired products in good to excellent yields (see below).

Methyl 2-Benzamido-2-(phenylthio)acetate (10). The two-step fragmentation−nucleophilic addition procedure, using thiophenol as the nucleophile, afforded compound **10** (81%). The one-step procedure also gave compound **10** (37%).[19]

Methyl 2-Benzamido-2-(2-oxooxazolidin-3-yl)acetate (11). The two-step fragmentation−nucleophilic addition procedure, using oxazolidin-2-one as the nucleophile, afforded compound **10** (70%). The one-step procedure also gave compound **11** (43%). Colorless oil; IR 3434, 3024, 1762, 1669 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.83 (1H, ddd, J = 7.1, 8.3, 8.8 Hz), 3.85 (3H, s), 4.01 (1H, ddd, J = 6.9, 8.5, 8.5 Hz), 4.36−4.43 (2H, m), 5.88 (1H, d, J = 7.4 Hz), 7.45 (2H, dd, J = 7.4, 7.9 Hz), 7.54 (1H, dd, J = 7.4, 7.4 Hz), 7.77 (1H, br d, J = 7.2 Hz), 7.85 (2H, d, J = 8.0 Hz); ^{13}C NMR (125.7 MHz) δ_C 44.7 (CH_2), 53.5 (CH_3), 60.4 (CH), 63.1 (CH_2), 127.3 (2 × CH), 128.7 (2 × CH), 132.4 (CH), 132.6 (C), 157.9 (C), 167.5 (2 × C); MS (FAB) *m*/*z* (rel intensity) 301 (M^+ + Na, 12), 279 (M^+ + H, 94), 192 (M^+ + H − oxazolidin-2-one, 37), 158 (M^+ − NHCOPh, 52), 105 (COPh, 100); HRMS *m*/*z* calcd for $C_{13}H_{14}N_2O_5Na$, 301.0800; found, 301.0793; calcd for C_7H_5O, 105.0340; found, 105.0338. Anal. Calcd for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.22; H, 5.34; N, 9.68.

Methyl 2-Benzamido-2-(3,5-dioxo-4-phenyl-1,2,4-triazolidin-1-yl)acetate (12). The two-step fragmentation−nucleophilic addition procedure, using 4-phenylurazole as the nucleophile, afforded the urazole glycine **12** (27%). The one-step procedure also gave compound **12** (14%). White solid; mp 180−181 °C (from EtOAc/*n*-hexane); IR 3433, 3306, 1749, 1720, 1656, 1601 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.88 (3H, s), 6.31 (1H, d, J = 7.1 Hz), 7.37−7.50 (8H, m), 7.57 (1H, dd, J = 7.4, 7.5 Hz), 7.70 (1H, br d, J = 7.0 Hz), 7.84 (2H, d, J = 7.2 Hz); ^{13}C NMR (125.7 MHz) δ_C 54.0 (CH_3), 63.0 (CH), 125.5 (2 × CH), 127.5 (2 × CH), 128.5 (CH), 128.8 (2 × CH), 129.2 (2 × CH), 130.8 (C), 132.0 (C), 132.8 (CH), 152.9 (C), 153.2 (C), 166.2 (C), 167.9 (C); MS *m*/*z* (rel intensity) 368 (M^+, <1), 309 (M^+ − $COOCH_3$, <1), 249 (M^+ + H − NHCOPh, 5), 105 (COPh, 100), 77 (Ph, 49); HRMS *m*/*z* calcd for $C_{18}H_{16}N_4O_5$, 368.1121; found, 368.1138; calcd for C_7H_5O, 105.0340; found, 105.0339.

Methyl 2-Benzoylamino-4-pentenoate (13).[22] The two-step fragmentation−allylation procedure, using allyltrimethylsilane as the nucleophile, afforded compound **13** (66%). The one-step procedure gave compounds **13** (35%) and **8** (52%).

Methyl 2-Benzoylamino-4-(chloromethyl)-4-pentenoate (14). The tandem scission−allylation procedure, using 2-(chloromethyl)-allyltrimethylsilane as the nucleophile, afforded compound **14** (60%) and trace amounts of the cyclic product **15** (0.6%). Compound **14**: crystalline solid; mp 64−66 °C (from EtOAc/*n*-hexane); IR ($CHCl_3$) 3432, 1740, 1664, 1486, 1206 cm^{-1}; ^1H NMR (500 MHz) δ_H 2.65 (1H, dd, J = 8.5, 14.6 Hz), 2.92 (1H, dd, J = 5.1, 14.6 Hz), 3.78 (3H, s), 4.06 (1H, d, J = 11.9 Hz), 4.16 (1H, d, J = 11.9 Hz), 4.97 (1H, ddd, J = 5.2, 8.1, 8.3 Hz), 5.08 (1H, s), 5.25 (1H, s), 6.71 (1H, br d, J = 6.8 Hz), 7.42 (2H, dd, J = 7.3, 7.9 Hz), 7.50 (1H, dd, J = 7.4, 7.4 Hz), 7.76 (2H, d, J = 7.1 Hz); ^{13}C NMR (125.7 MHz) δ_C 36.0 (CH_2), 47.5 (CH_2), 50.9 (CH), 52.6 (CH_3), 118.6 (CH_2), 127.0 (2 × CH), 128.6 (2 × CH), 131.8 (CH), 133.7 (C), 140.4 (C), 167.1 (C), 172.4 (C); MS *m*/*z* (rel intensity) 283/281 (M^+, 3/1), 246 (M^+ − Cl, 19), 105 (PhCO, 100), 77 (Ph, 24); HRMS calcd for $C_{14}H_{16}{}^{37}ClNO_3/C_{14}H_{16}{}^{35}ClNO_3$, 283.0839/281.0819; found, 283.0891/281.0815; calcd for $C_{14}H_{16}NO_3$, 246.1130; found, 246.1126; calcd for C_7H_5O, 105.0340; found, 105.0347. Anal. Calcd for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.41; H, 5.97, N, 4.95.

Methyl *N*-Benzoyl-4-methylenepyrrolidine-2-carboxylate (15). To a solution of the amino acid **14** (60 mg, 0.21 mmol) in dry DMF (5 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 12.6 mg, 0.32 mmol). The mixture was warmed to room temperature (26 °C) and stirred for 14 h; then it was poured into water and extracted with CH_2Cl_2. The organic layer was dried, and the solvent was removed under vacuum. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1), giving pyrrolidine **15** (53 mg, 99%) as a colorless oil; two rotamers at 26 °C (3:1), one rotamer at 70 °C; IR ($CHCl_3$) 3086, 1739, 1636, 1421

(35) (a) Drueckhammer, D. G.; Barbas, C. F., III; Nozaki, K.; Wong, C.-H.; Wood, C. Y.; Ciufolini, M. A. *J. Org. Chem.* **1988**, *53*, 1607−1611. (b) For related furan glycines in anticonvulsivant or sweetening compounds, see: Kohn, H.; Sawhney, K. N.; LeGall, P.; Conley, J. D.; Robertson, D. W.; Leander, J. D. *J. Med. Chem.* **1990**, *33*, 919−926. (c) Janusz, J. M.; Young, P. A.; Blum, R. B.; Riley, C. M. *J. Med. Chem.* **1990**, *33*, 1676−1682.

(36) (a) For the use of indolyl glycines as synthetic intermediates (dragmacidins and dihydrohamacanthin A synthesis), see: Kawasaki, T.; Ohno, K.; Enoki, H.; Umemoto, Y.; Sakamoto, M. *Tetrahedron Lett.* **2002**, *43*, 4245−4248. (b) For other related compounds, see: Zhao, J. L.; Liu, L.; Zhang, H. B.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Synlett* **2006**, 96−100 and references cited therein.

cm^{-1}; ^{1}H NMR (500 MHz, 70 °C) δ_H 2.70 (1H, d, J = 15.9 Hz), 2.97 (1H, dd, J = 11.5, 15.7 Hz), 3.71 (3H, s), 4.15 (1H, br b), 4.23 (1H, d, J = 13.3 Hz), 4.85 (1H, br b), 4.97 (1H, br s), 5.01 (1H, br s), 7.35−7.42 (3H, m), 7.48 (2H, br d, J = 6.2 Hz); ^{13}C (125.7 MHz, 70 °C) δ_C 36.0 (CH_2), 52.1 (CH_3), 52.8 (CH_2), 59.4 (CH), 108.1 (CH_2), 127.0 (2 × CH), 128.4 (2 × CH), 130.1 (CH), 136.6 (C), 142.9 (C), 170.1 (C), 172.0 (C); MS *m*/*z* (rel intensity) 245 (M^+, 3), 186 ($M^+ - CO_2Me$, 28), 140 ($M^+ - PhCO$, 28), 105 (PhCO, 100), 77 (Ph, 42); HRMS calcd for $C_{14}H_{15}NO_3$, 245.1052; found, 245.1042; calcd for C_7H_5O, 105.0340; found, 105.0342. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.54; H, 6.38, N, 5.84.

Methyl 2-Benzoylamino-4-oxo-4-phenylbutanoate (16). The two-step fragmentation−alkylation procedure, using 1-phenyl-1-(trimethylsilyloxy)ethene as the nucleophile, afforded compound **16** (63%). The one-step procedure gave compounds **16** (30%) and **8** (55%). Compound **16**: syrup; IR 3443, 1744, 1661, 1599, 1515, 1486 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 3.72 (1H, dd, J = 4.1, 18.3 Hz), 3.78 (3H, s), 3.86 (1H, dd, J = 4.0, 18.3 Hz), 5.19 (1H, m), 7.35 (1H, d, J = 7.8 Hz), 7.42 (2H, dd, J = 7.3, 7.8 Hz), 7.46 (2H, dd, J = 7.6, 7.8 Hz), 7.49 (1H, dd, J = 7.3, 7.4 Hz), 7.59 (1H, dd, J = 7.4, 7.5 Hz), 7.80 (2H, d, J = 7.3 Hz), 7.95 (2H, d, J = 7.5 Hz); ^{13}C NMR (125.7 MHz) δ_C 40.5 (CH_2), 48.6 (CH), 52.8 (CH_3), 127.2 (2 × CH), 128.2 (2 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 131.8 (CH), 133.6 (C), 133.9 (CH), 135.8 (C), 167.0 (C), 171.7 (C), 198.1 (C); MS (EI) *m*/*z* (rel intensity) 311 (M^+, 1), 279 ($M^+ - MeOH$, 1), 252 ($M^+ - COOMe$, 9), 206 ($M^+ - COPh$, 17), 105 (COPh, 100); HRMS calcd for $C_{18}H_{17}NO_4$, 311.1158; found, 311.1189; calcd for C_7H_5O, 105.0340; found, 105.0339. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.41; H, 5.88; N, 4.53.

Methyl 2-Benzamido-4-oxo-pentanoate (17), (2*R,4*S**)-*N*-Benzoyl-2-acetoxy-2-methyl-4-(methoxycarbonyl)azetidine (18), and (2*R**,4*R**)-*N*-Benzoyl-2-acetoxy-2-methyl-4-(methoxycarbonyl)azetidine (19).** The one-step scission−alkylation procedure, using isopropenyl acetate as the nucleophile, afforded methyl ketone **17** (9%), and the azetidines **18** and **19** (11% and 44%, respectively). Methyl ketone **17**: colorless oil; IR ($CHCl_3$) 3443, 1744, 1715, 1660 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 2.18 (3H, s), 3.12 (1H, dd, J = 4.2, 18.5 Hz), 3.31 (1H, dd, J = 4.1, 18.5 Hz), 3.76 (3H, s), 4.98 (1H, ddd, J = 4.1, 4.1, 8.1 Hz), 7.20 (1H, br d, J = 7.5 Hz), 7.44 (2H, dd, J = 7.2, 7.6 Hz), 7.51 (1H, dd, J = 7.3, 7.5 Hz), 7.79 (2H, d, J = 7.1 Hz); ^{13}C NMR (125.7 MHz) δ_C 29.9 (CH_3), 44.9 (CH_2), 48.6 (CH), 52.8 (CH_3), 127.2 (2 × CH), 128.6 (2 × CH), 131.9 (CH), 133.7 (C), 166.9 (C), 171.5 (C), 207.0 (C); MS *m*/*z* (rel intensity) 249 (M^+, 3), 206 ($M^+ - COMe$, 14), 190 ($M^+ - CO_2Me$, 42), 105 (PhCO, 100), 77 (Ph, 77); HRMS calcd for $C_{13}H_{15}NO_4$, 249.1001; found, 249.0999; calcd for C_7H_5O, 105.0340; found, 105.0338. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.65; H, 6.15, N, 5.58. Azetidine **18**: Colorless oil; IR ($CHCl_3$) 3090, 1743, 1660, 1437 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 1.93 (1H, dd, J = 12.6, 13.9 Hz), 1.96 (3H, s), 2.03 (3H, s), 2.80 (1H, dd, J = 5.1, 14.0 Hz), 3.83 (3H, s), 4.41 (1H, dd, J = 5.0, 12.6 Hz), 7.38 (2H, dd, J = 7.2, 7.8 Hz), 7.45 (1H, dd, J = 7.3, 7.4 Hz), 8.00 (2H, d, J = 7.2 Hz); ^{13}C NMR (125.7 MHz) δ_C 22.0 (CH_3), 24.7 (CH_3), 32.6 (CH_2), 52.5 (CH_3), 53.1 (CH), 100.7 (C), 127.7 (2 × CH), 128.1 (2 × CH), 131.2 (CH), 132.3 (C), 154.0 (C), 168.6 (C), 172.2 (C); MS *m*/*z* (rel intensity) 291 (M^+, 6), 232 ($M^+ - CO_2Me$, 53), 105 (PhCO, 100), 77 (Ph, 12); HRMS calcd for $C_{15}H_{17}NO_5$, 291.1107; found 291.1110; calcd for C_7H_5O, 105.0340; found, 105.0340. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.77; H, 5.99, N, 4.76. Azetidine **19**: Crystalline solid; mp 104−106 °C (from EtOAc/*n*-hexane); IR ($CHCl_3$) 3092, 1751, 1662, 1437, 1252 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 1.92 (3H, s), 1.93 (3H, s), 2.15 (1H, dd, J = 7.3, 14.1 Hz), 2.88 (1H, dd, J = 3.3, 14.2 Hz), 3.77 (3H, s), 4.45 (1H, dd, J = 3.7, 7.3 Hz), 7.38 (2H, dd, J = 7.2, 7.7 Hz), 7.45 (1H, dd, J = 7.3, 7.4 Hz), 8.00 (2H, d, J = 7.1 Hz); ^{13}C NMR (125.7 MHz) δ_C 21.8 (CH_3), 24.7 (CH_3), 32.7 (CH_2), 52.4 (CH_3), 53.1 (CH), 100.2 (C), 127.8 (2 × CH), 128.1 (2 × CH), 131.2 (CH), 132.6 (C), 154.1 (C), 168.4 (C), 172.0 (C); MS *m*/*z* (rel intensity) 291 (M^+, 4), 232 ($M^+ - CO_2Me$, 45), 105 (PhCO, 100), 77 (Ph, 57); HRMS calcd for $C_{15}H_{17}NO_5$, 291.1107; found, 291.1096; calcd for C_7H_5O, 105.0340; found, 105.0338. Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.95; H, 6.05, N, 4.95.

Hydrolysis of Lactamols 18 and 19. To a solution of azetidine **18** (40 mg, 0.14 mmol) in dry methanol (4 mL) at 0 °C was added MeONa (15 mg, 0.28 mmol), and the mixture was allowed to reach room temperature and stirred for 30 min. Then the acid resin IR-120 was added until pH = 7, and the reaction mixture was filtered and evaporated under vacuum, giving pure ketone **17** (34 mg, 99%). The reaction was repeated with azetidine **19**, affording ketone **17** (97%).

Methyl 2-Benzoylamino-2-(1-naphthyl)acetate (20). The one-step fragmentation−alkylation procedure, using naphthalene as the nucleophile, afforded compound **20** (63%).[13,32]

Methyl 2-Benzoylamino-2-(2-methoxy-1-naphthyl)acetate (21). The one-step fragmentation−arylation procedure, using 2-methoxynaphthalene as the nucleophile, afforded compound **21** (95%): syrup; IR 3450, 1748, 1661, 1599, 1514, 1485, 1271 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 3.70 (3H, s), 3.99 (3H, s), 6.89 (1H, d, J = 8.9 Hz), 7.29 (1H, d, J = 9.0 Hz), 7.39 (1H, dd, J = 6.8, 7.0 Hz), 7.40 (2H, dd, J = 7.0, 7.5 Hz), 7.41 (1H, d, J = 8.8 Hz), 7.47 (1H, ddd, J = 1.2, 7.3, 7.5 Hz), 7.59 (1H, ddd, J = 1.1, 7.0, 8.7 Hz), 7.79 (2H, d, J = 7.0 Hz), 7.82 (1H, d, J = 7.3 Hz), 7.88 (1H, d, J = 9.0 Hz), 8.34 (1H, d, J = 8.7 Hz); ^{13}C NMR (100.6 MHz) δ_C 48.6 (CH), 52.5 (CH_3), 56.5 (CH_3), 113.0 (CH), 118.9 (C), 122.7 (CH), 123.9 (CH), 127.1 (2 × CH), 127.6 (CH), 128.4 (2 × CH), 128.5 (CH), 129.3 (C), 130.6 (CH), 131.5 (CH), 132.3 (C), 134.0 (C), 155.1 (C), 166.8 (C), 172.0 (C); MS *m*/*z* (rel intensity) 349 (M^+, 10), 317 ($M^+ - MeOH$, 8), 290 ($M^+ - COOMe$, 55), 105 (COPh, 100); HRMS calcd for $C_{21}H_{19}NO_4$, 349.1314; found, 349.1299; calcd for C_7H_5O, 105.0340; found, 105.0346. Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.35; H, 5.64; N, 4.07.

***N*-(7-Methoxy-3-oxoisochroman-4-yl)benzamide (22) and Methyl 2-Benzoylamino-2-(4-(hydroxymethyl-2-methoxyphenyl)acetate (23).** The one-step fragmentation−arylation procedure, using 3-methoxybenzyl alcohol as the nucleophile, afforded compounds **22** (45%) and **23** (22%). Compound **22**: white solid; mp 176−177 °C (from EtOAc/*n*-hexane); IR 3433, 3020, 1753, 1669 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 3.82 (3H, s), 5.25 (1H, d, J = 13.7 Hz), 5.48 (1H, d, J = 13.7 Hz), 5.83 (1H, d, J = 5.6 Hz), 6.84 (1H, d, J = 2.4 Hz), 6.90 (1H, dd, J = 2.5, 8.5 Hz), 7.17 (1H, br d, J = 6.8 Hz), 7.19 (1H, dd, J = 1.2, 8.5 Hz), 7.52 (2H, dd, J = 7.2, 7.9 Hz), 7.59 (1H, dd, J = 7.4, 7.4 Hz), 7.97 (2H, d, J = 7.6 Hz); ^{13}C NMR (125.7 MHz) δ_C 51.9 (CH), 55.5 (CH_3), 69.5 (CH_2), 111.0 (CH), 114.3 (CH), 124.1 (C), 125.1 (CH), 127.3 (2 × CH), 128.8 (2 × CH), 132.0 (C), 132.3 (CH), 133.2 (C), 159.6 (C), 167.9 (C), 170.6 (C); MS *m*/*z* (rel intensity) 297 (M^+, 8), 192 ($M^+ - COPh$, 100), 105 (COPh, 79), 77 (Ph, 64); HRMS *m*/*z* calcd for $C_{17}H_{15}NO_4$, 297.1001; found, 297.0996; calcd for $C_{10}H_{10}NO_3$, 192.0661; found, 192.0661. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.43; H, 5.35; N, 4.69. Compound **23**: Colorless oil; IR 3606, 3446, 3013, 1745, 1660 cm^{-1}; ^{1}H NMR (500 MHz) δ_H 3.72 (3H, s), 3.88 (3H, s), 4.68 (2H, s), 5.94 (1H, d, J = 8.1 Hz), 6.95 (1H, d, J = 7.6 Hz), 6.97 (1H, s), 7.31 (1H, br d, J = 8.0 Hz), 7.41 (1H, d, J = 8.1 Hz), 7.42 (2H, dd, J = 7.8, 8.0 Hz), 7.49 (1H, dd, J = 7.2, 7.5 Hz), 7.78 (2H, d, J = 7.2 Hz); ^{13}C NMR (125.7 MHz) δ_C 52.7 (CH_3), 53.5 (CH), 55.7 (CH_3), 65.0 (CH_2), 109.7 (CH), 119.3 (CH), 124.7 (C), 127.1 (2 × CH), 128.5 (2 × CH), 130.8 (CH), 131.6 (CH), 134.0 (C), 143.1 (C), 157.3 (C), 166.6 (C), 171.5 (C); MS *m*/*z* (rel intensity) 329 (M^+, 2), 297 ($M^+ - CH_3OH$, 4), 270 ($M^+ - COOCH_3$, 39), 224 ($M^+ - COPh$, 14), 105 (COPh, 100), 77 (Ph, 42); HRMS *m*/*z* calcd for $C_{18}H_{19}NO_5$, 329.1263; found, 329.1258; calcd for C_7H_5O, 105.0340; found, 105.0345. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.47; H, 5.87; N, 4.35.

Methyl 2-Benzoylamino-2-(biphenyl-4-yl)acetate (24). The one-step fragmentation−arylation procedure, using biphenyl as the nucleophile, afforded compound **24** (8%). The two-step procedure also gave product **24** (40%) as a white solid: mp 127−128 °C (from EtOAc/*n*-hexane); IR 3434, 3013, 1740, 1664 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.80 (3H, s), 5.84 (1H, d, J = 6.9 Hz), 7.21 (1H, br d, J = 6.8 Hz), 7.36 (1H, dd, J = 7.3, 7.4 Hz), 7.44 (2H, dd, J = 7.4, 7.8 Hz), 7.45 (2H, dd, J = 7.2, 7.8 Hz), 7.51 (1H, m), 7.52 (2H, d, J = 8.4 Hz), 7.57 (2H, d, J = 8.1 Hz), 7.60 (2H, d, J = 8.3 Hz), 7.85 (2H, d, J = 7.8 Hz); ^{13}C NMR (125.7 MHz) δ_C 53.0 (CH_3), 56.6 (CH), 127.1 (2 × CH), 127.2 (2 × CH), 127.5 (CH), 127.7 (2 × CH), 127.8 (2 × CH), 128.6 (2 × CH), 128.8 (2 × CH), 131.9 (CH), 133.6 (C), 135.5 (C), 140.4 (C), 141.6 (C), 166.5 (C), 171.5 (C); MS *m*/*z* (rel intensity) 345 (M^+, 4), 313 (M^+ − CH_3OH, 9), 286 (M^+ − $COOCH_3$, 14), 240 (M^+ − COPh, 27), 180 (M^+ − H − $COOCH_3$ − COPh, 26), 105 (COPh, 100), 77 (Ph, 47); HRMS *m*/*z* calcd for $C_{22}H_{19}NO_3$, 345.1365; found, 345.1380; calcd for C_7H_5O, 105.0340; found, 105.0349. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.42; H, 5.60; N, 4.30.

Methyl 2-Benzamido-2-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)-acetate (25) and Methyl 2-Benzamido-2-(2,3-dihydrobenzo-[*b*][1,4]dioxin-5-yl)acetate (26). The one-step fragmentation−arylation procedure, using 2,3-dihydrobenzo[*b*][1,4]dioxine as the nucleophile, afforded compounds **25** (60%) and **26** (19%). Compound **25**: white solid; mp 134−135 °C (from EtOAc/*n*-hexane); IR 3435, 3022, 1739, 1662 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.77 (3H, s), 4.24 (4H, s), 5.66 (1H, d, J = 6.9 Hz), 6.85 (1H, d, J = 8.3 Hz), 6.92 (1H, dd, J = 2.1, 8.3 Hz), 6.95 (1H, d, J = 2.1 Hz), 7.08 (1H, br d, J = 6.7 Hz), 7.43 (2H, dd, J = 7.3, 7.8 Hz), 7.51 (1H, dd, J = 7.3, 7.5 Hz), 7.81 (2H, d, J = 7.8 Hz); ^{13}C NMR (125.7 MHz) δ_C 52.8 (CH_3), 56.2 (CH), 64.3 (2 × CH_2), 116.2 (CH), 117.8 (CH), 120.4 (CH), 127.1 (2 × CH), 128.6 (2 × CH), 129.6 (C), 131.8 (CH), 133.7 (C), 143.8 (C), 143.9 (C), 166.5 (C), 171.5 (C); MS *m*/*z* (rel intensity) 327 (M^+, 10), 295 (M^+ − CH_3OH, 28), 268 (M^+ − $COOCH_3$, 20), 222 (M^+ − COPh, 69), 162 (M^+ − H −CO_2Me − COPh, 36), 105 (COPh, 100); HRMS *m*/*z* calcd for $C_{18}H_{17}NO_5$, 327.1107; found, 327.1100; calcd for C_7H_5O, 105.0340; found, 105.0344. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.02; H, 5.22; N, 4.28. Compound **26**: colorless oil; IR 3446, 3020, 1745, 1662 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.75 (3H, s), 4.27−4.31 (3H, m), 4.35 (1H, m), 5.99 (1H, d, J = 8.0 Hz), 6.83−6.88 (2H, m), 6.98 (1H, dd, J = 2.4, 6.7 Hz), 7.21 (1H, br d, J = 7.7 Hz), 7.43 (2H, dd, J = 7.2, 7.8 Hz), 7.51 (1H, dd, J = 7.3, 7.7 Hz), 7.81 (2H, d, J = 7.8 Hz); ^{13}C NMR (125.7 MHz) δ_C 52.6 (CH), 52.8 (CH_3), 64.2 (CH_2), 64.5 (CH_2), 117.8 (CH), 121.4 (CH), 122.0 (CH), 125.3 (C), 127.2 (2 × CH), 128.5 (2 × CH), 131.7 (CH), 134.0 (C), 141.5 (C), 143.8 (C), 166.6 (C), 171.4 (C); MS *m*/*z* (rel intensity) 327 (M^+, 9), 295 (M^+ − CH_3OH, 6), 268 (M^+ − $COOCH_3$, 74), 222 (M^+ − COPh, 21), 105 (COPh, 100), 77 (Ph, 47); HRMS *m*/*z* calcd for $C_{18}H_{17}NO_5$, 327.1107; found, 327.1105; calcd for C_7H_5O, 105.0340; found, 105.0343. Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.23; N, 4.28. Found: C, 66.31; H, 5.38; N, 4.34.

Methyl 2-Benzamido-2-(3-methyl-2-oxo-2,3-dihydrobenzo[*d*]-oxazol-6-yl)acetate (27). The one-step fragmentation−arylation procedure, using 3-methylbenzo[*d*]oxazol-2(3*H*)-one as the nucleophile, afforded compound **27** (59%) as a white solid: mp 144−145 °C (from EtOAc/*n*-hexane); IR 3431, 3022, 1778, 1739, 1664 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.38 (3H, s), 3.78 (3H, s), 5.77 (1H, d, J = 6.8 Hz), 6.95 (1H, d, J = 8.0 Hz), 7.28 (1H, br d, J = 6.5 Hz), 7.30 (1H, d, J = 2.0 Hz), 7.32 (1H, dd, J = 1.5, 8.0 Hz), 7.45 (2H, dd, J = 7.0, 8.0 Hz), 7.52 (1H, dd, J = 7.5, 7.5 Hz), 7.82 (2H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz) δ_C 28.2 (CH_3), 53.1 (CH_3), 56.6 (CH), 108.2 (CH), 109.0 (CH), 123.3 (CH), 127.1 (2 × CH), 128.7 (2 × CH), 131.7 (2 × C), 132.0 (CH), 133.4 (C), 142.9 (C), 154.6 (C), 166.5 (C), 171.2 (C); MS *m*/*z* (rel intensity) 340 (M^+, 9), 281 (M^+ − COOMe, 12), 235 (M^+ − COPh, 90), 175 (M^+ − H − $COOCH_3$ − COPh, 40), 105 (COPh, 100); HRMS *m*/*z* calcd for $C_{18}H_{16}N_2O_5$, 340.1059; found, 340.1057; calcd for C_7H_5O, 105.0340; found, 105.0339. Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.51; H, 4.72; N, 8.45.

Methyl 2-Benzoylamino-2-[5-(methoxycarbonyl)methyl-2-methoxyphenyl]acetate (28). The one-step fragmentation−arylation procedure, using methyl 4-methoxyphenylacetate as the nucleophile, afforded compound **28** (82%): syrup; IR 3448, 1740, 1662, 1510, 1484, 1326, 1257 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.56 (2H, s), 3.66 (3H, s), 3.70 (3H, s), 3.83 (3H, s), 5.93 (1H, d, J = 8.2 Hz), 6.86 (1H, d, J = 8.4 Hz), 7.23 (1H, dd, J = 2.2, 8.4 Hz), 7.31 (1H, d, J = 8.0 Hz), 7.32 (1H, d, J = 2.3 Hz), 7.39 (2H, dd, J = 7.5, 7.7 Hz), 7.47 (1H, dd, J = 7.3, 7.4 Hz), 7.78 (2H, d, J = 7.5 Hz); ^{13}C NMR (125.7 MHz) δ_C 39.9 (CH_2), 51.9 (CH_3), 52.6 (CH_3), 53.5 (CH), 55.7 (CH_3), 111.3 (CH), 125.3 (C), 126.5 (C), 127.1 (2 × CH), 128.4 (2 × CH), 130.5 (CH), 131.6 (2 × CH), 133.9 (C), 156.2 (C), 166.5 (C), 171.3 (C), 171.9 (C); MS *m*/*z* (rel intensity) 371 (M^+, 4), 339 (M^+ − MeOH, 6), 312 (M^+ − COOMe, 67), 266 (M^+ − COPh, 23), 105 (COPh, 100); HRMS calcd for $C_{20}H_{21}NO_6$, 371.1369; found, 371.1402; calcd for C_7H_5O, 105.0340; found, 105.0349. Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.64; H, 5.57; N, 3.87.

Methyl 2-Benzamido-2-(4-[2-methoxy-2-oxoethoxy]phenyl)-acetate (29) and Methyl 2-Benzamido-2-(2-[2-methoxy-2-oxo-ethoxy]phenyl)acetate (30). The one-step fragmentation−arylation procedure, using methyl 2-phenoxyacetate as the nucleophile, afforded compounds **29** (61%) and **30** (31%). Compound **29**: white solid; mp 130−131 °C (from EtOAc/*n*-hexane); IR 3441, 3013, 1742, 1663 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.77 (3H, s), 3.80 (3H, s), 4.62 (2H, s), 5.71 (1H, d, J = 7.0 Hz), 6.89 (2H, d, J = 9.0 Hz), 7.09 (1H, br d, J = 7.0 Hz), 7.37 (2H, d, J = 8.5 Hz, Ar), 7.44 (2H, dd, J = 7.5, 7.5 Hz, Ar), 7.51 (1H, dd, J = 7.0, 7.5 Hz, Ar), 7.81 (2H, d, J = 7.5 Hz, Ar); ^{13}C NMR (125.7 MHz) δ_C 52.3 (CH_3), 52.9 (CH_3), 56.2 (CH), 65.3 (CH_2), 115.1 (2 × CH), 127.1 (2 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 129.9 (C), 131.9 (CH), 133.6 (C), 158.0 (C), 166.5 (C), 169.2 (C), 171.6 (C); MS *m*/*z* (rel intensity) 357 (M^+, 3), 325 (M^+ − CH_3OH, 13), 298 (M^+ − $COOCH_3$, 18), 252 (M^+ − COPh, 47), 192 (M^+ − $COOCH_3$ − COPh, 19), 105 (COPh, 100), 77 (Ph, 35); HRMS *m*/*z* calcd for $C_{19}H_{19}NO_6$, 357.1212; found, 357.1211; calcd for C_7H_5O, 105.0340; found, 105.0344. Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.88; H, 5.37; N, 4.05. Compound **30**: white solid; mp 122−123 °C (from dryness); IR 3433, 3020, 1748, 1662 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.72 (3H, s), 3.77 (3H, s), 4.64 (1H, d, J = 16.0 Hz), 4.73 (1H, d, J = 16.0 Hz), 6.00 (1H, d, J = 8.5 Hz), 6.81 (1H, d, J = 8.0 Hz), 7.04 (1H, dd, J = 7.5, 8.0 Hz), 7.30 (1H, ddd, J = 2.0, 7.5, 8.0 Hz), 7.41 (2H, dd, J = 7.0, 7.5 Hz), 7.48 (1H, dd, J = 7.5, 7.5 Hz), 7.49 (1H, dd, J = 2.0, 7.5 Hz), 7.91 (2H, d, J = 7.8 Hz), 8.01 (1H, br d, J = 8.5 Hz); ^{13}C NMR (125.7 MHz) δ_C 52.4 (CH_3), 52.7 (CH_3), 54.4 (CH), 65.0 (CH_2), 111.6 (CH), 122.4 (CH), 126.4 (C), 127.5 (2 × CH), 128.3 (2 × CH), 129.8 (CH), 131.5 (CH), 131.8 (CH), 134.1 (C), 155.3 (C), 166.7 (C), 169.2 (C), 171.2 (C); MS *m*/*z* (rel intensity) 357 (M^+, 1), 325 (M^+ − CH_3OH, 3), 298 (M^+ − $COOCH_3$, 71), 252 (M^+ − COPh, 18), 192 (M^+ − $COOCH_3$ − COPh, 5), 105 (COPh, 100), 77 (Ph, 44); HRMS *m*/*z* calcd for $C_{19}H_{19}NO_6$, 357.1212; found, 357.1196; calcd for C_7H_5O, 105.0340; found, 105.0337. Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.47; H, 5.74; N, 4.01.

Methyl 2-Benzamido-2-(3-bromo-4-(2-methoxy-2-oxoethoxy)-phenyl)acetate (31). The one-step fragmentation−arylation procedure, using methyl 2-(2-bromophenoxy)acetate as the nucleophile, afforded compound **31** (63%) as a white solid: mp 128−129 °C (from EtOAc/*n*-hexane); IR 3440, 3022, 1741, 1664 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.78 (3H, s), 3.80 (3H, s), 4.70 (2H, s), 5.69 (1H, d, J = 7.0 Hz), 6.78 (1H, d, J = 8.5 Hz), 7.18 (1H, br d, J = 6.5 Hz), 7.34 (1H, dd, J = 2.0, 8.0 Hz), 7.45 (2H, dd, J = 7.5, 8.0 Hz), 7.53 (1H, dd, J = 7.5, 7.5 Hz), 7.63 (1H, d, J = 2.5 Hz), 7.81 (2H, d, J = 7.8 Hz); ^{13}C NMR (125.7 MHz) δ_C 52.4 (CH_3), 53.1

(CH_3), 55.7 (CH), 66.2 (CH_2), 112.9 (C), 113.6 (CH), 127.1 (2 × CH), 127.7 (CH), 128.7 (2 × CH), 131.5 (C), 132.0 (CH), 132.4 (CH), 133.4 (C), 154.6 (C), 166.5 (C), 168.8 (C), 171.1 (C); MS (FAB) *m*/*z* (rel intensity) 437/435 (M^+, 2/2), 405/403 ($M^+ - CH_3OH$, 6/5), 376 ($M^+ - COOCH_3$, 5), 332/330 ($M^+ - COPh$, 28/28), 105 (COPh, 100), 77 (Ph, 26); HRMS *m*/*z* calcd for $C_{19}H_{18}{}^{81}BrNO_6$/$C_{19}H_{18}{}^{79}BrNO_6$, 437.0297/435.0317; found, 437.0295/435.0304; calcd for $C_{18}H_{14}{}^{81}BrNO_5$/$C_{18}H_{14}{}^{79}BrNO_5$, 405.0035/403.0055; found, 405.0025/403.0060; calcd for C_7H_5O, 105.0340; found, 105.0343. Anal. Calcd for $C_{19}H_{18}BrNO_6$: C, 52.31; H, 4.16; N, 3.21. Found: C, 52.44; H, 4.13; N, 3.37.

Methyl (4-Allyloxy-3-iodophenyl)-(benzoylamino)acetate (32). The one-step fragmentation−arylation procedure, using 1-allyloxy-2-iodobenzene as the nucleophile, gave compound **32** (86%): crystalline solid; mp 161.5−162.5 °C (from EtOAc/*n*-hexane); IR 3432, 1740, 1663, 1510, 1484 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.72 (3H, s), 4.52 (2H, d, J = 4.9 Hz), 5.26 (1H, dd, J = 1.4, 10.7 Hz), 5.47 (1H, dd, J = 1.6, 17.3 Hz), 5.64 (1H, d, J = 6.9 Hz), 5.98 (1H, m), 6.71 (1H, d, J = 8.5 Hz), 7.34 (1H, dd, J = 2.3, 8.5 Hz), 7.35 (2H, dd, J = 7.8, 8.1 Hz), 7.38 (1H, d, J = 6.5 Hz), 7.46 (1H, dd, J = 7.3, 7.5 Hz), 7.78 (2H, dd, J = 1.3, 7.2 Hz), 7.82 (1H, d, J = 2.3 Hz); ^{13}C NMR (100.6 MHz) δ_C 52.8 (CH_3), 55.4 (CH), 69.5 (CH_2), 86.8 (C), 112.2 (CH), 117.5 (CH_2), 127.0 (2 × CH), 128.3 (2 × CH), 128.6 (CH), 130.6 (C), 131.7 (CH), 132.1 (CH), 133.2 (C), 137.9 (CH), 157.1 (C), 166.4 (C), 171.1 (C); MS *m*/*z* (rel intensity) 451 (M^+, <1), 419 ($M^+ - MeOH$, 7), 392 ($M^+ - COOMe$, 5), 346 ($M^+ - COPh$, 28), 105 (COPh, 100); HRMS calcd for $C_{19}H_{18}INO_4$, 451.0281; found, 451.0273; calcd for C_7H_5O, 105.0340; found, 105.0332. Anal. Calcd for $C_{19}H_{18}INO_4$: C, 50.57; H, 4.02; N, 3.10. Found: C, 50.32; H, 4.14; N, 3.20.

Methyl 2-Benzoylamino-2-(3-methylene-2,3-dihydro-[benzofuran-5-yl])acetate (33). To a solution of $Pd(OAc)_2$ (11 mg, 0.05 mmol) in DMF (1 mL) was added triphenylphosphine (26 mg, 0.1 mmol). After stirring for 15 min, the solution was added to a mixture of the iodoarylglycine **32** (225 mg, 0.5 mmol) and silver carbonate (1.35 g, 5 mmol) in dry DMF (5 mL). The reaction mixture was stirred at room temperature under nitrogen for 30 min, and then it was heated at 80 °C for 18 h. Additional $Pd(OAc)_2$ (10 mg) was added after the first 12 h. The mixture was cooled to room temperature, filtered through celite, diluted with water, and extracted twice with ether. The combined organic layers were washed with water, dried, and evaporated under vacuum. The residue was purified by column chromatography (hexanes/EtOAc, 95:5), giving compound **33** (114.5 mg, 71%): crystalline solid; mp 105.0−107.0 °C (from EtOAc/*n*-hexane); IR 3433, 1740, 1662, 1510, 1483 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.77 (3H, s), 5.02 (1H, dd, J = 2.7, 2.8 Hz), 5.10 (2H, dd, J = 3.0, 3.0 Hz), 5.43 (1H, dd, J = 3.2, 3.2 Hz), 5.71 (1H, d, J = 6.8 Hz), 6.83 (1H, d, J = 8.3 Hz), 7.16 (1H, d, J = 6.4 Hz), 7.27 (1H, dd, J = 2.0, 8.4 Hz), 7.43 (2H, dd, J = 7.4, 7.4 Hz), 7.46 (1H, d, J = 2.0 Hz), 7.51 (1H, dd, J = 7.4, 7.4 Hz), 7.82 (2H, d, J = 7.5 Hz); ^{13}C NMR (100.6 MHz) δ_C 52.9 (CH_3), 56.4 (CH), 75.4 (CH_2), 100.6 (CH_2), 111.1 (CH), 120.1 (CH), 126.6 (C), 127.1 (2 × CH), 128.5 (2 × CH), 129.0 (C), 129.7 (CH), 131.8 (CH), 133.5 (C), 143.0 (C), 163.9 (C), 166.5 (C), 171.7 (C); MS *m*/*z* (rel intensity) 323 (M^+, 14), 291 ($M^+ - MeOH$, 17), 264 ($M^+ - COOMe$, 10), 218 ($M^+ - COPh$, 32), 158 ($M^+ - [AcOH + COOMe]$, 43), 105 (COPh, 100); HRMS calcd for $C_{19}H_{17}NO_4$, 323.1158; found, 323.1179; calcd for C_7H_5O, 105.0340; found, 105.0337. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.37; H, 5.68; N, 4.26.

Methyl 2-Benzoylamino-2-(2-furyl)acetate (34). The one-step fragmentation−arylation procedure, using furan as the nucleophile, gave compound **34** (79%). This compound was previously synthesized by another method[35] but the spectroscopic data were poorly described: IR 3436, 1747, 1666, 1513, 1483 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.80 (3H, s), 5.97 (1H, d, J = 8.0 Hz), 6.38 (1H, d, J = 3 Hz), 6.44 (1H, d, J = 3 Hz), 7.07 (1H, d, J = 8.0 Hz), 7.39 (1H, s), 7.44 (2H, dd, J = 8.0, 8.0 Hz), 7.52 (1H, dd, J = 8.0, 8.0 Hz), 7.82 (2H, d, J = 8.0 Hz); ^{13}C NMR (100.6 MHz) δ_C 50.6 (CH), 53.1 (CH_3), 109.0 (CH), 110.8 (CH), 127.2 (2 × CH), 128.6 (2 × CH), 132.0 (CH), 133.4 (C), 142.9 (CH), 148.5 (C), 166.7 (C), 169.4 (C); MS *m*/*z* (rel intensity) 259 (M^+, 4), 227 ($M^+ - MeOH$, 6), 200 ($M^+ - COOMe$, 12), 154 ($M^+ - COPh$, 75), 105 (COPh, 100); HRMS calcd for $C_{14}H_{13}NO_4$, 259.0845; found, 259.0839; calcd for C_7H_5O, 105.0340; found, 105.0351. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.79; H, 5.18; N, 5.32.

Methyl 3-(1-Benzamido-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (35) and Methyl 2-(1-Benzamido-2-methoxy-2-oxoethyl)-1*H*-indole-1-carboxylate (36). The one-step fragmentation−arylation procedure, using methyl 1*H*-indole-1-carboxylate as the nucleophile, afforded compounds **35** (43%) and **36** (20%). Compound **35**: white solid; mp 162−163 °C (from dryness); IR 3440, 3022, 1740, 1664 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.77 (3H, s), 4.04 (3H, s), 6.06 (1H, d, J = 7.0 Hz), 7.03 (1H, br d, J = 7.0 Hz), 7.29 (1H, dd, J = 7.5, 8.0 Hz), 7.38 (1H, dd, J = 7.0, 8.0 Hz), 7.43 (2H, dd, J = 7.5, 8.0 Hz), 7.51 (1H, dd, J = 7.5, 7.5 Hz), 7.70 (1H, s), 7.71 (1H, d, J = 7.5 Hz), 7.80 (2H, d, J = 7.0 Hz), 8.20 (1H, br d, J = 8.0 Hz); ^{13}C NMR (125.7 MHz) δ_C 49.5 (CH), 53.0 (CH_3), 54.0 (CH_3), 115.5 (CH), 116.8 (C), 119.4 (CH), 123.5 (CH), 124.5 (CH), 125.2 (CH), 127.2 (2 × CH), 128.1 (C), 128.6 (2 × CH), 132.0 (CH), 133.5 (C), 135.7 (C), 151.1 (C), 166.8 (C), 171.1 (C); MS *m*/*z* (rel intensity) 366 (M^+, 12), 334 ($M^+ - CH_3OH$, 15), 307 ($M^+ - COOCH_3$, 15), 261 ($M^+ - COPh$, 81), 201 ($M^+ - H - COOCH_3 - COPh$, 15), 105 (COPh, 100), 77 (Ph, 34); HRMS *m*/*z* calcd for $C_{20}H_{18}N_2O_5$, 366.1216; found, 366.1210; calcd for C_7H_5O, 105.0340; found, 105.0348. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.36; H, 5.14; N, 7.40. Compound **36**: colorless oil; IR 3421, 3022, 1742 cm^{-1}; ^1H NMR (500 MHz) δ_H 3.76 (3H, s), 4.10 (3H, s), 6.46 (1H, d, J = 9.0 Hz), 6.89 (1H, br s), 7.26 (1H, dd, J = 7.7, 7.9 Hz), 7.33 (1H, dd, J = 7.5, 7.8 Hz), 7.44 (2H, dd, J = 7.5, 7.5 Hz), 7.51 (1H, dd, J = 7.5, 7.5 Hz), 7.55 (1H, d, J = 8.0 Hz), 7.63 (1H, br d, J = 9.0 Hz), 7.81 (2H, d, J = 7.5 Hz), 7.97 (1H, d, J = 8.0 Hz); ^{13}C NMR (125.7 MHz) δ_C 51.5 (CH), 52.9 (CH_3), 54.2 (CH_3), 113.9 (CH), 115.8 (CH), 121.4 (CH), 123.6 (CH), 125.2 (CH), 127.2 (2 × CH), 128.6 (2 × CH), 128.8 (C), 131.8 (CH), 133.8 (C), 134.6 (C), 135.8 (C), 153.2 (C), 166.5 (C), 169.8 (C); MS *m*/*z* (rel intensity) 366 (M^+, 8), 334 ($M^+ - CH_3OH$, 12), 307 ($M^+ - COOCH_3$, 12), 261 ($M^+ - COPh$, 72), 201 ($M^+ - H - COOCH_3 - COPh$, 9), 105 (COPh, 100), 77 (Ph, 34); HRMS *m*/*z* calcd for $C_{20}H_{18}N_2O_5$, 366.1216; found, 366.1227; calcd for C_7H_5O, 105.0340; found, 105.0345. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.62; H, 5.04; N, 7.69.

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Supporting Information Available: The ^1H and ^{13}C NMR spectra for compounds **8**, **11**, **12**, **14**−**19**, **21**−**36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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