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SYNTHESES OF NOVEL 1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACID (ACC)-CONTAINING β-LACTAMS

Francine Farouz-Grant and Marvin J. Miller*
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556

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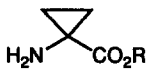
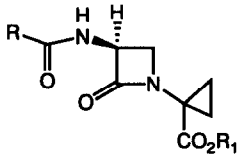
Abstract: Direct cyclization of an Ox-protected seryl-1-aminocyclopropane-1-carboxylic acid derivative to a β-lactam was accomplished by the Mitsunobu reaction. However, preparation of related, more functionalized β-lactams required development of a novel Staudinger reaction based on Ox-glycine.

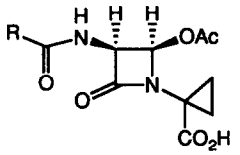
1-Aminocyclopropane-1-carboxylic acid (**1**, ACC) has been of considerable interest to both chemists and biologists. Reviews[1] have described some of its chemistry and biochemistry and summarized the investigations that led to the discovery of its role as a biosynthetic intermediate in the conversion to ethylene in plants. Recently, cyclopropane-containing peptides synthesized from the coupling of the benzamides of ACC with phenylalanine and proline methyl esters have been shown to exhibit irreversible inhibition of carboxypeptidase.[2] Because of the unique structure and considerable biological activity of ACC, we thought that it would be interesting to incorporate this unusual amino acid into a β-lactam. Here, we describe the synthesis of two ACC-based monocyclic β-lactams **2** and **3**, in which the nitrogen of the 2-azetidinone ring is derived from ACC.



1, R = H



2, R = Ph, R_1 = H

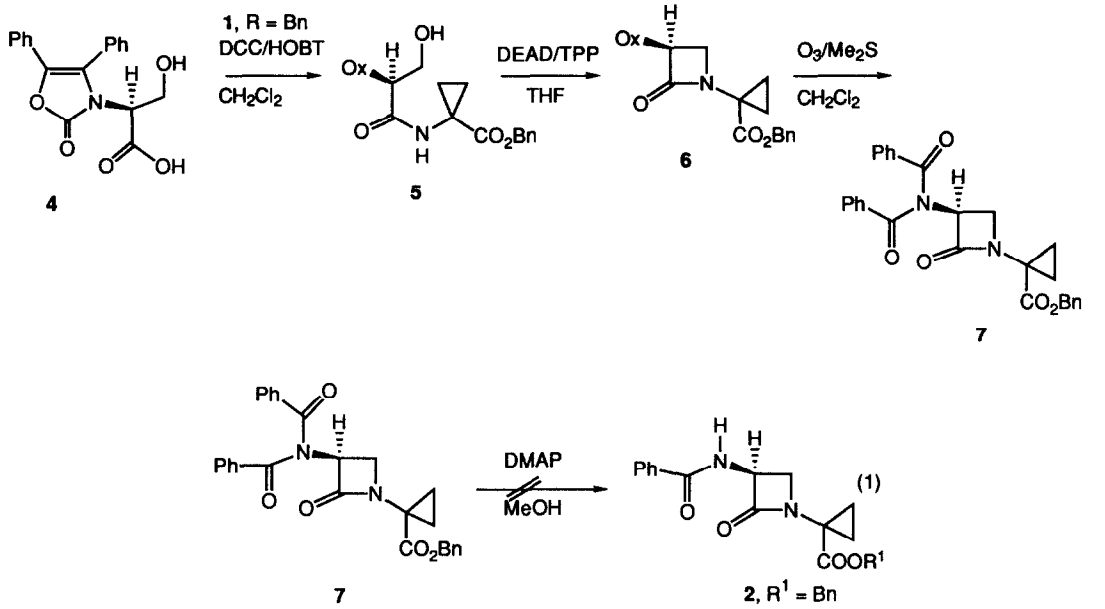


3, R = Ph

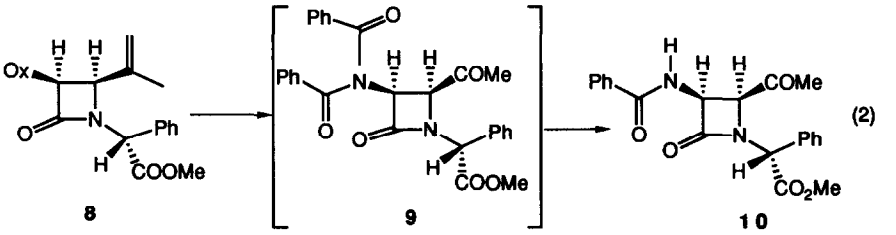
The synthesis of a 4-unsubstituted monocyclic β-lactam, **2**, was based on previous cyclizations of β-hydroxy amide derivatives to β-lactams mediated by the Mitsunobu reaction.[3] As has been clearly established in these laboratories and others,[4] such peptide cyclizations are facilitated by double protection of the seryl nitrogen, in order to prevent competing aziridine or oxazoline formation in the cyclodehydration step. The 4,5-diphenyloxazolin-2-one (Ox) group[5] is one of the few protecting groups, other than a phthalimido group, which masks both hydrogens of a primary amine function and seems to be perfectly suited for a Mitsunobu cyclization. Quite simply, **2** was derived from the suitably protected amino acids L-serine and 1-amino-1-cyclopropane carboxylic acid (ACC) as shown in Scheme 1. First, ACC was converted to the corresponding benzyl ester **1** (R = Bn) in 67% yield, in the presence of benzyl alcohol, in dry benzene with a catalytic amount of *p*-toluenesulfonic acid. The amino acid ester was then coupled to Ox-L-serine[6] **4**, under standard procedures

(dicyclohexylcarbodiimide/1-hydroxybenzotriazole), to give the desired dipeptide **5** in 35% yield. Cyclization of **5** to β-lactam **6** proceeded in 55% yield under Mitsunobu conditions, but only when an excess (4.0 equivalents) of triphenylphosphine and di-*tert*-butylazodicarboxylate[7] was used. The outcome of this reaction paralleled earlier results[8] on the cyclization of unsaturated peptides. Apparently, the unusual hybridization of the α-carbon of the cyclopropyl glycine component of **5** reduced the pK of the peptide bond and facilitated formation of β-lactam **6** without dehydration of the serine residue to a dehydroalanine. Removal of the oxazolidinone protecting group constituted the next step. Reductive conditions such as lithium or sodium in liquid ammonia[5,9] were briefly considered, however reductive opening of a cyclopropane derivative activated by a carbonyl group has precedent.[10] Consequently, a method was selected which in earlier studies on similar substrates had proved valuable.[11] Ozonolysis of **6** in dichloromethane at -78°C, followed by reductive work-up in the presence of dimethylsulfide (5.0 eq) gave **7**. The formation of dibenzoylimide **7** resulted from a Chapman rearrangement.[12] The characteristic ^{1}H NMR of this β-lactam nucleus included a double doublet at 5.64 ppm (H_3), a triplet at 3.87 ppm (H_4) and a double doublet at 3.64 ppm (H_4). Attempted removal of one of the benzoyl protecting groups to provide **2** by treatment of **7** under solvolytic conditions, including a catalytic amount of DMAP in methanol, failed and only led to decomposition of the β-lactam ring (Eq 1).

Scheme 1



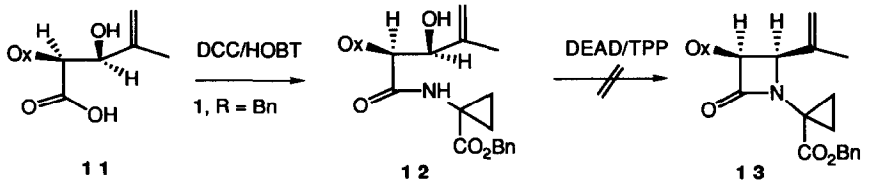
In a previous communication,[11] we reported that ozonolysis of a 3-Ox-4-substituted-2-azetidinone of type **8** (Eq 2) led to the isolation of the corresponding α-benzamido-β-acyl-2-azetidinone, **10**. Presumably, the imide intermediate, **9**, resulting from a Chapman rearrangement, was rendered very labile because of the anchimeric assistance of the methyl ketone at C_4 and readily hydrolyzed to the monobenzylated product **10**.



(2)

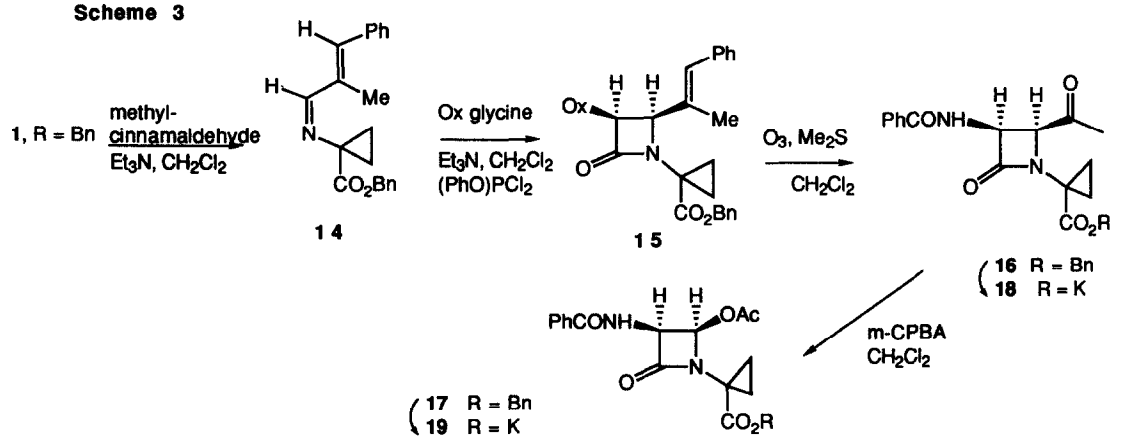
To take advantage of such a precedent for the current studies, a substituent was purposely introduced at the C_4 position of the azetidinone ring in order to transform the oxazolidine protecting group into a benzamide functionality (Scheme 3). Thus, 4-acetyl monocyclic β-lactam **16** (Scheme 3) was considered a viable precursor of both **2** and **3**. Ozonolysis of **13** was anticipated to provide **16** directly. As shown in Scheme 2, the first attempt to prepare **13** involved coupling of Ox-β-hydroxy amino acid[13] **11** with ACC derivative **3** in the presence of dicyclohexylcarbodiimide and N-hydroxybenzotriazole (1.0 eq) to give **12** in 57% yield. However, subsequent attempted ring closure of **12** under Mitsunobu conditions failed.

Scheme 2

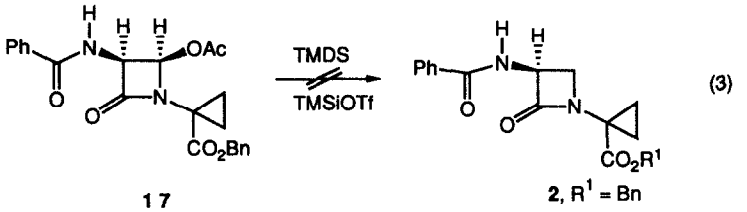


An alternative strategy for the synthesis of **16**, and eventually **3**, involved formation of the azetidinone ring by a [2+2] reaction of a ketene derived from an activated form of Ox-glycine with Schiff base **14**.[14] This is the first time, to the best of our knowledge, that the oxazolidinone (Ox) protecting group has been used for amine protection in a Staudinger reaction.[9] The introduction of a C_3 amino group on the 2-azetidinone ring system is of particular interest in β-lactam chemistry. Until now, common precursors of the 3-amino group from the Staudinger reaction have been either azido or phthalimido groups.[15] However, caution must often be used in handling the azides and the phthalimides are often difficult to remove.[4b] Schiff base **14** was prepared in 43% yield by condensation of the amino acid ester **3** with α-methylcinnamaldehyde (Scheme 3). Compound **14** proved to be quite unstable and moisture sensitive. Thus, immediately upon generation, **14** was treated with Ox-glycine in the presence of phenyl dichlorophosphate[16] and triethylamine (3.0 eq), to yield β-lactam **15** as an oil in 57% yield. Only the *cis* β-lactam[17] was produced, as indicated by NMR analysis of the coupling constant between H_3 and H_4 (J = 5.4 Hz) of both the crude and purified reaction product. As anticipated, ozonolysis of **15** provided mono benzamide substituted β-lactam **16** in 48% yield. These results were consistent with the ones obtained in the case of 3-aminonocardicinic acid derivative, **8** (eq 2). Conversion of 4-acetyl-2-azetidinone **16** into 4-acetoxy-2-azetidinone **17** was accomplished in 80% yield with a Baeyer-Villiger reaction using an excess of *m*-chloroperbenzoic acid in dichloromethane for 2 days at room temperature. Retention of configuration was noted at the C_4 position (J = 4.12 Hz), as expected.

Scheme 3

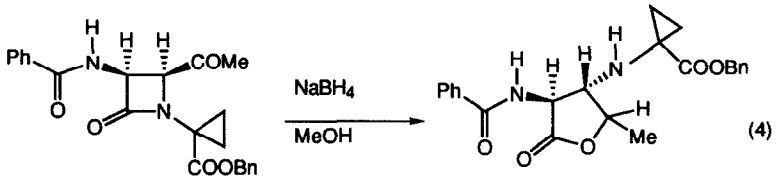


Attempted reductive removal of the acetate of **17** to give a derivative of **2** with a variety of reagents, including a precedented[18] sixfold excess of 1,1,3,3-tetramethyldisiloxane (TMDS), used as a hydride transfer reagent, and trimethylsilyl trifluoromethanesulfonate, used as a catalyst, either in benzene for two days, under reflux, or at room temperature in dichloromethane, resulted in decomposition (Eq 3).



(3)

Finally, we briefly investigated the reactivity of 4-acetyl-2-azetidinone **16** towards borohydride reduction. Treatment of **16** at -78°C, under N_2, in methanol with $NaBH_4$ (1.0 eq) produced γ-lactone **20** (Eq 4). Apparently, the hydride reduction occurred very selectively on the less hindered side of the molecule and consequently, the generated alkoxide was properly oriented to attack the carbonyl of the β-lactam ring.[11,19] The potential utility of **20**, and its precursor **16**, for the preparation of novel α,β-diamino acids and peptide analogs is under consideration.



(4)

In order to test compounds derived from **16** and **17**, they were hydrogenated in 95% ethanol or pure methanol, respectively, in the presence of 1.0 equivalent of K_2CO_3 and a catalytic amount of 10% palladium on carbon. The corresponding carboxylates, **18** and **19**, were isolated in good yields. Preliminary biological tests

of **18** indicated that this compound possesses weak antibacterial activity and inhibits β-lactamase enzymes only at 50mM concentration or higher. Replacement of the benzoyl side chain with more physiologically effective groups is being considered.

In conclusion, the Mitsunobu reaction has been shown to be effective for the cyclization of Ox-protected seryl-ACC peptide **5**, but not for the cyclization of a more complex β-hydroxy amino acid-containing ACC peptide **12**. An alternative Staudinger reaction led to the formation of **15** and demonstrated the potential utility of the Ox protecting group in this important reaction for the preparation of β-lactams.[20]

Acknowledgment. We wish to thank Professor G. Stammer, who kindly provided a sample of 1-amino-1-cyclopropane carboxylic acid hydrochloride salt. Mass spectral determinations were performed by Dr. Bruce Plashko at the University of Notre Dame. Preliminary biological testing was performed at Eli Lilly and Company. Financial support of this work by the National Institute of Health and Eli Lilly and Company is gratefully acknowledged.

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17. No trace of trans β-lactam could be identified in a ^{1}H NMR spectrum of the crude material.
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19. The use of $NaCNBH_3$ in methanol-glacial acetic acid (9:1) still led to the formation of the lactone as the dominant product in the reaction.
20. Representative characterization data includes the following: **1** (R = Bn): 67%; mp 129-133°C; ^{1}H NMR (300 MHz, D_2O) δ 7.64 (d, *J* = 8.5 Hz, 2H, aromatic), 7.42 (s, 5H, aromatic), 7.35 (d, *J* = 8.5 Hz, 2H, aromatic), 5.23 (s, 2H, $COOCH_2Ph$), 3.32 (s, 3H, NH_3^+), 2.36 (s, 3H, Ph-Me), 1.61 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (75 MHz) δ 169.47, 140.38, 134.89, 128.83, 128.31, 128.50, 128.07, 125.98, 67.64, 34.50, 21.63,14.40; IR (KBr pellet) 2900, 1745 cm^{-1}; MS (FAB) M^+ 192 (cation); Anal Calcd for $C_{17}H_{19}NO_4S$: C, 62.24; H, 6.05. Found: C, 62.31; H, 5.96. **5**: 35%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94-7.21 (m, 15H, aromatic), 5.10 (s, 2H, $COOCH_2Ph$), 4.16 (m, 1H, CHOx), 4.07 (m, 2H, CH_2OH), 1.59 (m, 2H), 1.21 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.84, 168.22, 154.88, 135.47, 135.38, 130.99, 130.43, 129.58, 128.48, 128.41, 128.15, 127.96, 127.82, 127.23,

126.09, 124.43, 123.94, 67.10, 60.58, 59.02, 33.72, 17.65, 17.50; IR ($CHCl_3$) 3400, 1760, 1730. 1680 cm^{-1}; MS (EI) m/z 498 (M^+), exact mass calcd 498.1790, found 498.1786. **6**: 55%; mp 138-140°C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.56-7.29 (m, 15H, aromatic), 5.15 (dd, J = 6.56, 12.30 Hz, 2H, -$COOCH_2$ Ph), 4.96 (dd, J = 2.92, 5.32 Hz, 1H, -CHOx), 3.73 (t, J = 5.30 Hz, 1H, -CH-N), 3.63 (dd, J = 2.91, 5.30 Hz, 1H, -CH-N), 1.42 (m, 2H), 1.15 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 170.90, 164.50, 153.10, 135.29, 135.21, 131.04, 130.55, 129.57, 128.63, 128.48, 128.41, 128.04, 124.51, 122.33, 67.25, 57.21, 46.66, 35.11, 17.30, 15.91; IR ($CHCl_3$) 1770, 1740 cm^{-1}; MS (EI) m/z 480 (M^+), exact mass calcd 480.1685, found 480.1682. **7**: 30%; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.21 (m, 15H, aromatic), 5.54 (dd, J = 2.92, 5.12 Hz, 1H, -CONCH), 5.06 (dd, J= 6.45, 12.3 Hz, 2H, $COOCH_2Ph$), 3.76 (t, J = 5.13 Hz, 1H, -CHN), 3.55 (dd, J = 2.90, 5.13 Hz, 1H, -CHN),1.87 (m, 2H), 1.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.25, 171.39, 166.32, 135.69, 132.30, 128.87, 128.62, 128.53, 128.37, 128.09, 67.26, 60.93, 47.07, 35.43, 17.27, 16.18; IR (neat) 1770, 1730, 1700 cm^{-1}; MS (CI, isobutane) m/z 469 ($M+H^+$), 363 (M+-105); exact mass calcd for (M+-105) 363. 1345, found 363.1342. **14**: 43%; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 1H, CH=N), 7.40-7.23 (m, 10H, aromatic), 6.76 (s, 1H, CH=CMe), 5.18 (s, 2H, $COOCH_2Ph$), 2.14 (d, J = 1.25 Hz, 3H, Me), 1.68 (m, 2H), 1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.54, 140.17, 137.13, 136.50, 129.40, 128.40, 128.33, 128, 127.8, 66.56, 48.84, 18.71, 12.93; IR ($CDCl_3$) 1725 cm^{-1}; MS (EI) m/z 319 (M^+), exact mass calcd 319.1572, found 319.1566. **15**: 57%; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.22 (m, 20H, aromatic), 6.65 (s, 1H, CH=CMe), 5.06 (s, 2H, -$COOCH_2Ph$), 4.84 (d, J = 5.58 Hz, 1H, CHOx), 4.37 (d, J = 5.58Hz, 1H, CH-N), 1.81 (s, 3H), 1.55 (m, 2H), 1.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.08, 164.95, 152.94,136.48, 135.30, 135.08, 131.99, 130.73, 130.46, 130.43, 129.61, 129.58, 128.79, 128.57, 128.39, 128.29, 127.97, 127.94, 127.22, 127.16, 126.18, 124.51, 122.55, 67.42, 67.07, 62.15, 35.32, 16.85, 15.95, 14.34; IR ($CHCl_3$) 1750, 1735 cm^{-1}; MS (EI) m/e 596 (M^+), exact mass calcd 596.2311, found 596.2305. **16**: 48%; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62-7.13 (m, 10H, aromatic), 6.59 (d, J = 8.54 Hz, 1H, NHCH), 5.74 (dd, J = 5.63, 8.55 Hz, 1H, NHCHCH), 5.13 (s, 2H, $COOCH_2Ph$), 4.99 (d, J = 5.62 Hz, 1H, CHCHCO), 2.14 (s, 3H, COMe), 1.88 (m, 2H, CH_2), 1.21 (m, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.78, 171.25, 168.09, 166.66, 135.56, 133.97, 132.92, 132.84,130.55, 129.17, 129.15, 129.03, 128.85, 128.53, 127.59, 67.99, 66.85, 59.81, 35.8, 29.13, 17.53, 16.22; IR (neat) 3300, 1760, 1720, 1650 cm^{-1}; MS (EI).m/z 406 (M+), exact mass calcd 406.1528, found 406.1537; Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 65.02; H, 5.41. Found: C, 64.98; H, 5.34. **18**: 77%; oil; ^1H NMR (300 MHz, CD_3OD) δ 8.00-7.44 (m, 5H, aromatic), 5.65 (d, J = 5.79 Hz, 1H, CH-NH), 5.05 (d, J = 5.82 Hz, 1H, CHCOMe), 2.06 (s, 3H, COMe), 1.57 (m, 2H), 1.3 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 205.47, 170.56, 169.01, 134.33, 133.92, 133.32, 130.67, 129.65, 128.53, 67.97, 60.25, 27.97, 16.85, 15.99; IR (neat) 3400, 1750, 1710, 1650 cm^{-1}; MS (CI, isobutane) negative ion 316 ($M+H^+$). **17**: 80%; oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.83-7.26 (m, 10H, aromatic), 6.77 (d, J = 8.99 Hz, 1H, NH), 6.31 Hz (d, J = 4.14 Hz, 1H, CHOAc), 5.61 (dd, J = 4.14, 8.89 Hz, 1H, CHNH), 5.15 (s, 2H, $COOCH_2Ph$), 1.98 (s, 3H, COMe), 1.59 (m, 4H, CH_2-CH_2); ^{13}C NMR (75 MHz) δ 170.61, 169.98, 167.05, 167.00, 135.24, 133.63, 133.16, 132.20, 130.21, 129.78, 128.72, 128.70, 128.50,128.23, 128.02, 127.17, 79.98, 67.62, 59.57, 34.58, 20.59, 16.86, 16.58; IR ($CDCl_3$) 1785, 1735, 1660 cm^{-1}; MS (CI, isobutane) 423 ($M+H^+$), 363 (M^+-60), exact mass calcd on (M^+-60) 362.1266, found 362.1271. **19**: 62%; foam; ^1H NMR (300 MHz, CD_3OD) δ 7.83-7.24 (m, 5H, aromatic), 6.31 (d, J = 3.78 Hz, 1H, CHOCOMe), 5.53 (d, J = 3.78 Hz, 1H, CHNHCOPh), 2.02 (s, 3H, COMe), 1.42-1.23 (m, 4H, CH_2); ^{13}C NMR (75 MHz, CD_3OD) δ 171.65, 169.96, 169.92, 169.34, 134.72, 133.24, 129.72, 128.45, 81.84, 60.70, 36.78, 20.70, 15.62, 15.15; IR (neat) 3300, 1740-1710, 1685 cm^{-1}, MS (CI, isobutane) 332 ($M+H^+$). **20**: 91.5%; oil (9:1 mixture of diastereomers); ^1H NMR (300 MHz, $CDCl_3$) δ 7.85-7.21 (m, 10H, aromatic), 5.71 (dd, 1H, J = 5.32, 10.19 Hz, CHNHCO, major diastereomer), 5.63 (dd, 1H, J = 5.49, 10.20 Hz, CHNHCO, minor diastereomer), 5.13 (s, 2H, $COOCH_2Ph$), 4.23 (1H, q, OCHMe, J = 6.90 Hz, major diastereomer), 3.72 (dd, 1H, CHCHNHCO, J = 0.68, 5.49 Hz, minor diastereomer), 3.62 (dd, 1H, J = 0.64, 5.28 Hz, CHCHNHCO, major diastereomer), 1.7-1.3 (4H, m, CH_2-CH_2), 1.23 (d, 3H, J = 6.91 Hz, Me, major diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.56, 168.33, 166.46, 134.58, 133.54, 131.82, 128.80, 128.63, 128.41, 128.31, 127.20, 68.15, 65.07, 62.13, 58.82, 33.63, 18.66, 17.30, 16.29; IR ($CDCl_3$) 3460, 1770, 1715, 1670 cm^{-1}; MS (EI) m/e 408 (M^+) exact mass calcd 408.1685, found 408.1673.