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Five- and Six-Membered Lactones and Lactams by Tandem Dealkoxycarbonylation-Michael Addition Reactions

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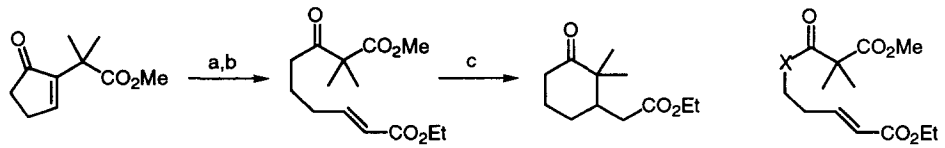
Introduction

We recently reported a tandem dealkoxycarbonylation-Michael addition-based ring expansion sequence (**1** → **3**) for the preparation of 2,2-dialkyl-3-oxocyclohexaneacetic esters.[1,2] The current study sought to extend this methodology[3,4] to the preparation of heterocyclic systems by applying this reaction tandem to readily accessible esters and amides related to **4**. We present here our results on the use of the dealkoxycarbonylation-Michael addition sequence for the preparation of lactones and lactams that could prove useful as building blocks for organic synthesis.



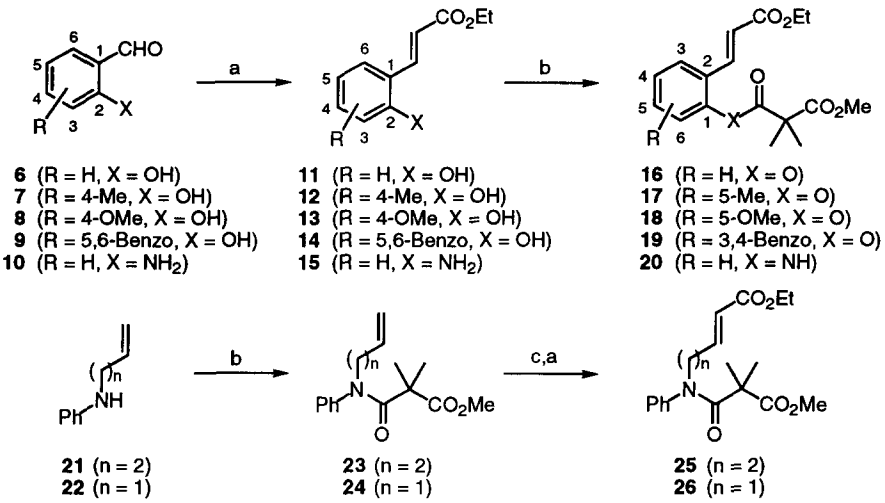
1 **2** **3** **4** (X = O, N-R)

a) O_3, -78 °C, CH_2Cl_2; then Me_2S, -78 °C → rt; b) $Ph_3P{=}CHCO_2Et$, PhH, Δ;
c) LiCl, HMPA, Δ

Synthesis of the Cyclization Substrates

Lactone precursors were prepared from salicylaldehyde derivatives **6**, **8** and **9**. Installation of the acrylate moiety was accomplished by Wittig olefination to give **11**, **13** and **14** in 63-76% yields; compound **12** was prepared in 52% overall yield via **7** as previously described.[5] Esterification of **11-14** with methyl dimethylmalonyl chloride[6] gave cyclization substrates **16-19** in yields ranging from 70-80%. Aryl-fused lactam precursor **20** was prepared similarly from 2-aminobenzaldehyde[7] (**10**) in 52% overall yield. Substrates **25** and **26** were prepared from *N*-(3-butenyl)aniline[8] (**21**) and *N*-allylaniline (**22**) by acylation with methyl dimethylmalonyl chloride followed by ozonolysis (reductive workup) and Wittig olefination in yields of 44% and 38%, respectively. The syntheses are summarized in Scheme 1.

Scheme 1. Synthesis of the Cyclization Substrates



6 (R = H, X = OH)
7 (R = 4-Me, X = OH)
8 (R = 4-OMe, X = OH)
9 (R = 5,6-Benzo, X = OH)
10 (R = H, X = NH_2)

11 (R = H, X = OH)
12 (R = 4-Me, X = OH)
13 (R = 4-OMe, X = OH)
14 (R = 5,6-Benzo, X = OH)
15 (R = H, X = NH_2)

16 (R = H, X = O)
17 (R = 5-Me, X = O)
18 (R = 5-OMe, X = O)
19 (R = 3,4-Benzo, X = O)
20 (R = H, X = NH)

21 (n = 2)
22 (n = 1)

23 (n = 2)
24 (n = 1)

25 (n = 2)
26 (n = 1)

a) $Ph_3P{=}CHCO_2Et$, PhH, Δ; b) $ClCOC(CH_3)_2CO_2Me$, pyridine, DMAP, CH_2Cl_2, 0 °C → rt; c) O_3, CH_2Cl_2, -78 °C; then Me_2S, -78 °C → rt.

Results and Discussion

The results of our tandem dealkoxycarbonylation-Michael synthesis of lactones and lactams are shown in Scheme 2 and Table 1. Our previous work,[1,9] using this strategy, was run with lithium chloride in anhydrous HMPA, a hazardous solvent. The procedure has now been adapted to use the less toxic solvent DMEU (1,3-dimethyl-2-imidazolidinone); in this medium, the conversion proceeded best when iodide was used to initiate the sequence. The optimized reaction conditions involved treating 1 equivalent of the substrate with 4 equivalents of lithium iodide in DMEU at a temperature of 100 °C. Substrate concentrations of 0.10 - 0.12 M and scales up to 5 mmol were used.

The cyclized product structures were characterized by spectroscopic methods. IR indicated the loss of the conjugated double bond. ^1H NMR showed the presence of diastereotopic methyl groups and confirmed the loss of the acrylate and methoxycarbonyl moieties. ^{13}C NMR exhibited the correct number of carbons and corroborated the IR and ^1H NMR assignments. Finally, exact molecular weights and elemental analyses agreed with those expected for the lactone and lactam products.

The mechanism of the reaction involves chemoselective attack by iodide ion at the methyl ester[10] in an S_N2-type reaction. This generates methyl iodide and an activated carboxylate anion which spontaneously loses carbon dioxide to produce an enolate that cyclizes on the pendant acrylate group. Ring formation proceeded most favorably through a 6-[*enol-endo*]-*exo-trig* transition state, but one case of a five-membered ring closure by a disfavored 5-[*enol-endo*]-*exo-trig* process was also observed.[11] As discovered in our earlier work,[1,9] the best results are achieved with cyclization substrates that decarboxylate to give tertiary enolates.

In the current reaction, lactone and lactam products were produced in moderate to good isolated yields. It was found that only aryl-fused lactones could be generated while both fused and simple lactams could

Scheme 2. Lactones and Lactams by Tandem Dealkoxycarbonylation-Michael Addition Reactions

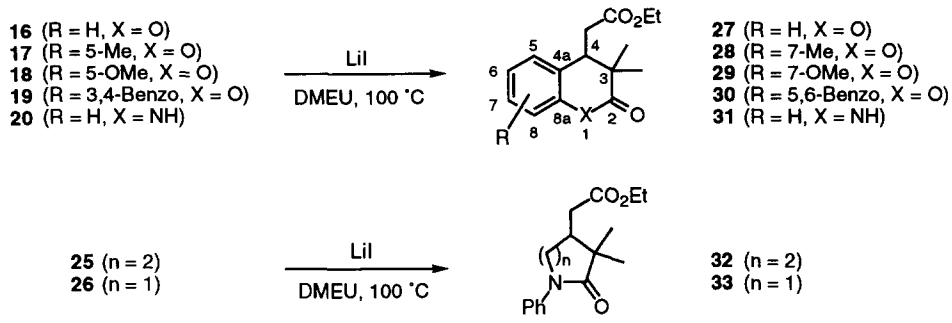
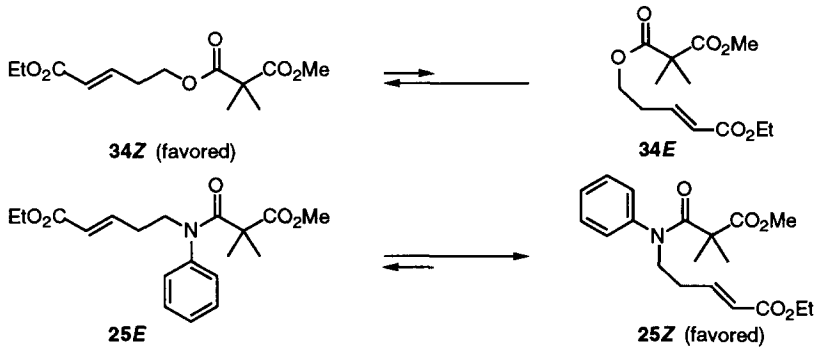


Table 1. Lactone and Lactam Formation by Dealkoxycarbonylation-Michael Addition Reaction

Substrate	Product	Isolated Yield (%)
16	**27**	62
17	**28**	48
18	**29**	50
19	**30**	52
20	**31**	76
25	**32**	82
26	**33**	34

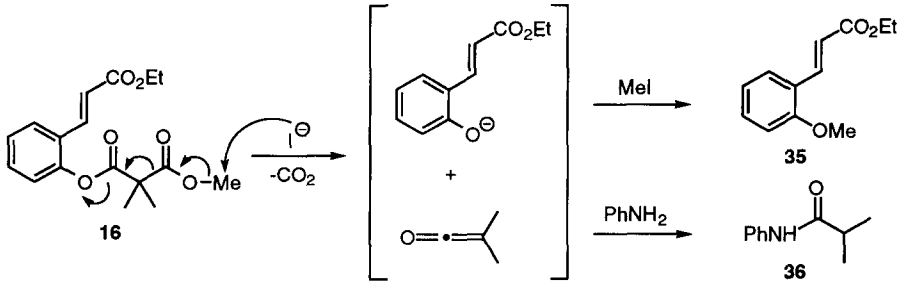
be prepared. Critical to the success of the reaction was the aryl substitution on the heteroatom in the cyclization substrates. In the aryl-fused precursors, cyclization was facilitated by the enforced proximity of the reacting centers resulting from ortho substitution on the planar aromatic framework. Attempts to close simple lactones from methyl 4-ethoxycarbonyl-3-butenyl dimethylpropanedioate (**34**),[12] however,



resulted in decarboxylation but no cyclization. This outcome can be rationalized in terms of the strong preference for conformation **34Z** (*Z* about the ester CO-O partial π bond)[13] which would tend to disfavor ring closure. Nitrogen substrates lacking *N*-phenyl substitution also failed to give cyclized products; with

the exception of *o*-substituted aromatic substrate **20**, secondary amides and *N*-benzyl tertiary amides reacted to give complex mixtures with no lactam formation. In the closure of monocyclic lactams **32** and **33**, the *N*-phenyl group should shift the conformational equilibrium to favor **25Z** (*Z* about the amide CO-N partial π bond).[13] Assuming the phenyl ring in **25Z** is nearly coplanar with the amide moiety, steric interactions would then push the reacting sites closer together and facilitate ring closure.

The methyl iodide by-product in the current reaction was not volatilized from the reaction mixture as readily as the methyl chloride generated in earlier versions of the reaction run in HMPA. The presence of this powerful alkylating agent resulted in one notable side reaction. In the lactone ring closures, each product was accompanied by *ca.* 25% of the methyl ether corresponding to **35** resulting from loss of the methyl dimethylmalonyl group. This process presumably occurred by (1) iodide-initiated demethoxycarbonylation, (2) loss of dimethyl ketene and (3) alkylation of the resulting alkoxide by the methyl iodide produced in step 1. This hypothesis was substantiated by running the reaction in the presence of aniline



which trapped the ketene as *N*-phenylisobutyramide (**36**).[14] A control experiment run under identical conditions without lithium iodide, produced neither **35** nor **36**, demonstrating that aniline was not directly attacking either ester group. The formation of **35** (plus **36** with added aniline) and the absence of simple demethoxycarbonylated product in the oxygen cases are manifestations of the relatively high aptitude of phenoxide ion as a leaving group. Similar products were not produced during lactam closures in accordance with the poor leaving group properties of the anilide moiety.[15]

In summary, we have developed a novel route to aryl-fused lactones and lactams as well as simple monocyclic lactams using a tandem dealkoxycarbonylation-Michael addition strategy. The starting substrates are easily prepared, and the final cyclizations proceed in generally good yield. The procedure is novel in providing highly substituted systems which would be difficult to prepare by conventional methods. It has also been demonstrated that five-ring lactams can be prepared in modest yield via a disfavored cyclization process. Efforts are continuing to extend the scope of this methodology.

Experimental Section

Solvents / reagents were purified in the following manner: DMF and DMEU were vacuum distilled from BaO and stored under N_2 over 4-Å molecular sieves, THF was distilled from $LiAlH_4$ and Et_3N was distilled from CaH_2. All other reagents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The saturated NH_4Cl, saturated $NaHCO_3$, saturated NaCl, 5% $Na_2S_2O_3$ and 0.5-

1.0 M HCl used in workup procedures refer to aqueous solutions. Reactions were monitored by one of the following methods: (1) TLC on hard-layer silica gel GF plates (Analtech) visualized using UV light, phosphomolybdic acid, or I_2 vapor or (2) capillary GC with FI detection (SE-30 column, 6-m x 0.25-mm i.d., 0.25 μm film thickness) programmed between 50-300 °C. Preparative separations were performed using one of the following methods: (1) PTLC on 20-cm x 20-cm silica gel GF plates (Analtech), (2) flash chromatography[16] on silica gel (Grace, grade 62, 60-200 mesh) containing UV-active phosphor (Sylvania no. 2282), or (3) flash vacuum chromatography[17] on silica gel (60-200 mesh). Band elution, where appropriate, was monitored using a hand-held UV lamp. Melting points are uncorrected. IR spectra are referenced to polystyrene. ^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ at 400 MHz and 100 MHz, respectively, and are referenced to internal $(CH_3)_4Si$. High resolution mass spectra (HRMS, EI/DP) were obtained at 70 eV. Elemental analyses are ± 0.3%.

Representative Procedure for Wittig Olefination of Hydroxy Aldehydes: Ethyl (*E*)-3-(2-Hydroxyphenyl)propenoate (11). A mixture of 5.25 g (43.0 mmol) of **6** and 31.3 g (90.0 mmol) of ethyl (triphenylphosphoranylidene)acetate[18] in 300 mL of benzene was heated under reflux for 12 h. The reaction was cooled and concentrated to afford a tan semisolid mass. This residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude hydroxy ester as a yellow oil which crystallized on standing. Final purification by flash chromatography on a 100-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 6.27 g (32.7 mmol, 76%) of the hydroxy ester as a white solid, mp 81-82 °C. IR (thin film) 3440, 1685, 1630, 1608, 1510, 1375, 758 cm^{-1}; ^{1}H NMR δ 8.06 (d, 1 H, J = 16.2 Hz), 7.46 (d, 1 H, J = 7.8 Hz), 7.24 (m, 1 H), 7.13 (br s, 1 H), 6.89 (m, 2 H), 6.66 (d, 1 H, J = 16.2 Hz), 4.29 (q, 2 H, J = 7.1 Hz), 1.35 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 168.7, 155.6, 140.9, 131.4, 129.2, 121.7, 120.6, 118.2, 116.4, 60.7, 14.3; HRMS *m/e* Calcd for $C_{11}H_{12}O_3$: 192.0787. Found: 192.0788.

Ethyl 3-(2-Hydroxy-4-methylphenyl)propenoate (12): This compound was prepared via **7** in 52% overall yield using the method of Bunce and Moore.[5] The spectral data matched those reported.

Ethyl 3-(2-Hydroxy-4-methoxyphenyl)propenoate (13): 5.25 g (25.0 mmol, 76%) from **8** as a viscous oil; IR (thin film) 3340, 2842, 1678, 1619, 1590, 1377, 981 cm^{-1}; ^{1}H NMR δ 8.01 (d, 1 H, J = 15.9 Hz), 7.63 (s, 1 H), 7.38 (d, 1 H, J = 8.6 Hz), 6.55 (d, 2 H, J = 15.9 Hz), 6.48-6.43 (m, 1 H), 4.28 (q, 2 H, J = 7.1 Hz), 3.78 (s, 3 H), 1.34 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 169.2, 162.5, 157.3, 140.9, 130.5, 115.2, 115.0, 106.8, 101.8, 60.6, 55.3, 14.3; HRMS *m/e* Calcd for $C_{12}H_{14}O_4$: 210.0892. Found: 210.0890.

Ethyl 3-(2-Hydroxy-1-naphthyl)propenoate (14): 4.43 g (18.3 mmol, 63%) from **9** as a viscous oil; IR (thin film) 3325, 1678, 1619, 1597, 1509, 1378, 975 cm^{-1}; ^{1}H NMR δ 8.35 (d, 1 H, J = 16.2 Hz), 8.05 (d, 1 H, J = 8.6 Hz), 7.76 (t, 2 H, J = 8.1 Hz), 7.52 (t, 1 H, J = 8.2 Hz), 7.37 (t, 1 H, J = 8.2 Hz), 7.17 (d, 1 H, J = 8.9 Hz), 6.84 (d, 1 H, J = 16.2 Hz), 6.80 (s, 1 H), 4.36 (q, 2 H, J = 7.2 Hz), 1.40 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 168.0, 153.3, 138.5, 132.7, 131.6, 128.9, 128.6, 127.4, 123.8, 123.2, 122.9, 118.1, 113.8, 60.9, 14.4; HRMS *m/e* Calcd for $C_{15}H_{14}O_3$: 242.0943. Found: 242.0935.

Ethyl (*E*)-3-(2-Aminophenyl)propenoate (15): 3.78 g (19.8 mmol, 66%) from **10**[7] as a yellow solid, mp 68-69 °C; IR ($CHCl_3$) 3469, 3370, 3233, 1693, 1622, 1602, 1488, 1374, 756 cm^{-1}; ^1H NMR δ 7.82 (d, 1 H, *J* = 15.7 Hz), 7.37 (d, 1 H, *J* = 7.7 Hz), 7.16 (t, 1 H, *J* = 7.5 Hz), 6.75 (t, 1 H, *J* = 7.5 Hz), 6.68 (d, 1 H, *J* = 7.7 Hz), 6.34 (d, 1 H, *J* = 15.7 Hz), 4.25 (q, 2 H, *J* = 7.2 Hz), 4.01 (br s, 2 H), 1.33 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR δ 167.3, 145.6, 140.0, 131.2, 128.0, 119.8, 118.8, 118.0, 116.6, 60.4, 14.2; HRMS *m/e* Calcd for $C_{11}H_{13}NO_2$: 191.0983. Found: 191.0979.

Representative Procedure for Acylations with Methyl Dimethylmalonyl Chloride: (*E*)-2-(2-Ethoxycarbonylethenyl)phenyl Methyl Dimethylpropanedioate (16). To a stirred 0 °C solution of 4.00 g (20.8 mmol) of **11**, 3.16 g (4.35 mL, 31.3 mmol) of Et_3N and 0.15 g of DMAP in 50 mL of CH_2Cl_2 was added a solution of 3.95 g (24.0 mmol) of methyl dimethylmalonyl chloride[6] in 15 mL of CH_2Cl_2. The mixture was warmed to rt over 1 h and stirred overnight. The reaction mixture was poured into saturated NH_4Cl and extracted with ether (3x). The combined ether extracts were washed with 1 M HCl (2x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by flash chromatography on a 50-cm x 2-cm silica gel column eluted with increasing concentrations of ether in hexanes. Concentration of the major band gave 4.79 g (15.0 mmol, 72%) of the triester as a light yellow solid, mp 39-41 °C. IR (thin film) 1770, 1745, 1715, 1640, 1603, 1488, 1390, 1369, 986, 759 cm^{-1}; ^1H NMR δ 7.75 (d, 1 H, *J* = 16.1 Hz), 7.66 (d, 1 H, *J* = 8.0 Hz), 7.40 (t, 1 H, *J* = 7.4 Hz), 7.27 (t, 1 H, *J* = 7.5 Hz), 7.07 (d, 1 H, *J* = 8.1 Hz), 6.44 (d, 1 H, *J* = 16.1 Hz), 4.25 (q, 2 H, *J* = 7.1 Hz), 3.89 (s, 3 H), 1.63 (s, 6 H), 1.33 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 172.8, 171.2, 166.4, 149.1, 137.3, 131.1, 127.4, 127.1, 126.5, 122.6, 120.4, 60.5, 52.9, 50.1, 22.9 (2), 14.2; HRMS *m/e* Calcd for $C_{17}H_{20}O_6$: 320.1260. Found 320.1257. Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.75; H, 6.25. Found: C, 63.69; H, 6.23.

(*E*)-2-(2-Ethoxycarbonylethenyl)-5-methylphenyl Methyl Dimethylpropanedioate (17): 2.64 g (7.90 mmol, 79%) from **12** as a light yellow solid, mp 38-40 °C; IR (thin film) 1772, 1751, 1722, 1641, 1612, 1509, 1392, 1369, 982 cm^{-1}; ^1H NMR δ 7.72 (d, 1 H, *J* = 16.1 Hz), 7.54 (d, 1 H, *J* = 7.9 Hz), 7.07 (dd, 1 H, *J* = 8.0, 1.8 Hz), 6.88 (d, 1 H, *J* = 1.8 Hz), 6.39 (d, 1 H, *J* = 16.1 Hz), 4.24 (q, 2 H, *J* = 7.2 Hz), 3.89 (s, 3 H), 2.36 (s, 3 H), 1.63 (s, 6 H), 1.32 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 172.7, 171.2, 166.6, 149.0, 142.0, 137.2, 127.4, 126.8, 124.4, 122.9, 119.1, 60.3, 52.8, 50.0, 22.8 (2), 21.2, 14.2; HRMS *m/e* Calcd for $C_{18}H_{22}O_7$: 334.1416. Found: 334.1411. Anal. Calcd for $C_{18}H_{22}O_7$: C, 64.67; H, 6.59. Found: C, 64.75; H, 6.63.

(*E*)-2-(2-Ethoxycarbonylethenyl)-5-methoxyphenyl Methyl Dimethylpropanedioate (18): 6.16 g (17.6 mmol, 78%) from **13** as a yellow oil; IR (thin film) 2843, 1767, 1743, 1722, 1634, 1612, 1509, 1392, 1370, 982 cm^{-1}; ^1H NMR δ 7.69 (d, 1 H, *J* = 15.9 Hz), 7.59 (d, 1 H, *J* = 8.9 Hz), 6.81 (dd, 1 H, *J* = 8.9, 2.5 Hz), 6.59 (d, 1 H, *J* = 2.5 Hz), 6.32 (d, 1 H, *J* = 15.9 Hz), 4.23 (q, 2 H, *J* = 7.1 Hz), 3.89 (s, 3 H), 3.81 (s, 3 H), 1.64 (s, 6 H), 1.32 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 172.6, 170.9, 166.7, 161.8, 150.2, 137.1, 127.6, 119.7, 117.8, 113.6, 107.1, 60.2, 55.5, 55.3, 50.0, 22.8 (2), 14.2; HRMS *m/e* Calcd for $C_{18}H_{22}O_7$: 350.1365. Found: 350.1369. Anal. Calcd for $C_{18}H_{22}O_7$: C, 61.71; H, 6.29. Found: C, 61.86; H, 6.33.

(*E*)-1-(2-Ethoxycarbonylethenyl)-2-naphthyl Methyl Dimethylpropanedioate (19): 4.29 g (11.6 mmol, 70%) from **14** as a yellow oil; IR (thin film) 1766, 1743, 1722, 1648, 1392, 1370, 989

cm^{-1}; ^1H NMR δ 8.09 (d, 1 H, *J* = 7.6 Hz), 8.03 (d, 1 H, *J* = 16.4 Hz), 7.85 (m, 2 H), 7.54 (m, 2 H), 7.19 (d, 1 H, *J* = 8.9 Hz), 6.38 (d, 1 H, *J* = 16.4 Hz), 4.31 (q, 2 H, *J* = 7.1 Hz), 3.85 (s, 3 H), 1.62 (s, 6 H), 1.36 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 172.8, 171.1, 166.2, 146.1, 137.0, 131.7, 130.5, 128.5, 127.3, 126.2, 126.1, 126.0, 124.5, 123.8, 120.9, 60.6, 52.8, 50.1, 22.8 (2), 14.2; HRMS *m/e* Calcd for $C_{21}H_{22}O_6$: 370.1416. Found: 370.1405. Anal. Calcd for $C_{21}H_{22}O_6$: C, 68.11; H, 5.95. Found: C, 68.29; H, 6.02.

Methyl (*E*)-2-(*N*-(2-(2-Ethoxycarbonylethenyl) phenyl) carbamoyl)-2-methylpropanoate (20): 3.26 g (10.2 mmol, 78%) from **15** as a light yellow oil; IR (thin film) 3307, 1741, 1715, 1689, 1636, 1394, 1372, 765 cm^{-1}; ^1H NMR δ 8.68 (br s, 1 H), 7.80 (d, 1 H, *J* = 15.8 Hz), 7.76 (d, 1 H, *J* = 8.0 Hz), 7.57 (d, 1 H, *J* = 7.8 Hz), 7.39 (t, 1 H, *J* = 7.8 Hz), 7.21 (t, 1 H, *J* = 7.7 Hz), 6.40 (d, 1 H, *J* = 15.8 Hz), 4.27 (q, 2 H, *J* = 7.1 Hz), 3.87 (s, 3 H), 1.60 (s, 6 H), 1.34 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 175.6, 170.3, 166.5, 138.9, 135.7, 130.5, 128.0, 126.9, 125.9, 124.9, 120.6, 60.4, 53.0, 50.3, 23.8 (2), 14.1; HRMS *m/e* Calcd for $C_{17}H_{21}NO_5$: 319.1448. Found 319.1448. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.95; H, 6.58. Found: C, 63.82; H, 6.55.

Methyl 2-(*N*-(3-Butenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (23): 2.17 g (7.93 mmol, 79%) from **21**[8] as a light yellow oil; IR (thin film) 1734, 1650, 1596, 1488, 1389, 990, 913, 767, 706 cm^{-1}; ^1H NMR δ 7.37 (m, 3 H), 7.16 (m, 2 H), 5.76 (ddt, 1 H, *J* = 16.8, 10.3, 7.0 Hz), 5.06 (d, 1 H, *J* = 16.8 Hz), 5.02 (d, 1 H, *J* = 10.3 Hz), 3.71 (t, 2 H, *J* = 7.3 Hz), 3.45 (br s, 3 H), 2.29 (q, 2 H, *J* = 7.3 Hz), 1.34 (s, 6 H); ^{13}C NMR δ 174.1, 171.4, 140.7, 135.1, 130.3, 129.0, 128.5, 116.6, 52.5, 51.9, 50.1, 31.8, 25.4 (2); HRMS *m/e* Calcd for $C_{16}H_{21}NO_3$: 275.1521. Found: 275.1509. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.64. Found: C, 69.91; H, 7.76.

Methyl 2-(*N*-Phenyl-*N*-(2-propenyl)carbamoyl)-2-methylpropanoate (24): 5.52 g (21.1 mmol, 70%) from **22** as a light yellow oil; IR (thin film) 1734, 1676, 1602, 1504, 1392, 1374, 993, 918, 754, 698 cm^{-1}; ^1H NMR δ 7.36 (m, 3 H), 7.14 (m, 2 H), 5.87 (ddt, 1 H, *J* = 17.1, 10.2, 5.0 Hz), 5.12 (d, 1 H, *J* = 10.2 Hz), 5.06 (d, 1 H, *J* = 17.1 Hz), 4.23 (d, 2 H, *J* = 5.0 Hz), 3.46 (s, 3 H), 1.36 (s, 6 H); ^{13}C NMR δ 174.1, 171.4, 140.7, 132.7, 130.2, 128.9, 128.6, 117.9, 55.0, 51.9, 50.0, 25.3 (2); HRMS *m/e* Calcd for $C_{15}H_{19}NO_3$: 261.1402. Found 261.1403. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.28. Found: C, 69.04; H, 7.30.

Representative Ozonolysis-Wittig Procedure: **Methyl (*E*)-2-(*N*-(3-Ethoxycarbonyl-3-butenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (25)**. A solution of 2.00 g (13.6 mmol) of **23** in 200 mL of CH_2Cl_2 was cooled to -78 °C and treated with ozone until the solution turned light blue. The reaction was quenched at -78 °C with 5.00 g (5.91 mL, 80.6 mmol) of dimethyl sulfide, warmed to rt, stirred for 3 h, and concentrated under vacuum. To the resulting yellow oil was added 200 mL of benzene and 10.4 g (29.8 mmol) of ethyl (triphenylphosphoranylidene)acetate.[18] The solution was heated under reflux for 12 h, then cooled to rt, and concentrated under vacuum to give a tan semisolid mass. The residue was loaded onto a 10-cm x 10-cm plug of silica gel in a sintered glass frit and 2 L of 20-25% ether in hexanes was poured through under aspirator vacuum. Concentration of the filtrate afforded the crude product as a yellow oil. Final purification by flash chromatography on an 80-cm x 2.5-cm silica gel column eluted with increasing concentrations of ether in hexanes gave 3.89 g (10.7 mmol, 58%) of the amido diester as a light yellow oil. IR (thin film) 1734, 1715, 1652, 1596, 1396, 1370, 982, 767, 706

cm^{-1}; ^1H NMR δ 7.38 (m, 3 H), 7.16 (m, 2 H), 6.87 (dt, 1 H, *J* = 15.7, 7.0 Hz), 5.85 (d, 1 H, *J* = 15.7 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.77 (t, 2 H, *J* = 7.0 Hz), 3.45, (br s, 3 H), 2.47 (q, 2 H, *J* = 7.0 Hz), 1.33 (s, 6 H), 1.27 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 174.0, 171.5, 166.2, 145.1, 140.6, 130.1, 129.1, 128.7, 123.1, 60.2, 51.9, 50.6, 50.1, 30.2, 25.3 (2), 14.2; HRMS *m/e* Calcd for $C_{19}H_{25}NO_5$: 347.1732. Found: 347.1729. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.71; H, 7.20. Found: C, 65.96; H, 7.27.

Methyl (*E*)-2-(*N*-(3-Ethoxycarbonyl-2-propenyl)-*N*-phenylcarbamoyl)-2-methylpropanoate (26): 3.59 g (10.8 mmol, 55%) from **24** as a light yellow oil; IR (thin film) 1738, 1713, 1680, 1604, 1502, 1390, 1372, 751, 696 cm^{-1}; ^1H NMR δ 7.38 (m, 3 H), 7.15 (m, 2 H), 6.91 (dt, 1 H, *J* = 15.7, 5.8 Hz), 5.89 (d, 1 H, *J* = 15.7 Hz), 4.38 (dd, 2 H, *J* = 5.8, 1.6 Hz), 4.18 (q, 2 H, *J* = 7.1 Hz), 3.48 (s, 3 H), 1.36 (s, 6 H), 1.28 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 174.0, 171.6, 166.0, 142.2, 140.7, 129.9, 129.3, 128.9, 123.2, 60.4, 53.3, 52.0, 50.0, 25.3 (2), 14.1; HRMS *m/e* Calcd for $C_{18}H_{23}NO_5$: 333.1613. Found 333.1605. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.86; H, 6.91. Found: C, 64.98; H, 6.94.

Representative Procedure for Dealkoxycarbonylation-Michael Addition: Ethyl 3,4-Dihydro-3,3-dimethylcoumarin-4-acetate (27). A solution of 320 mg (1.00 mmol) of **16** and 535 mg (4.00 mmol) of anhydrous LiI in 8.5 mL of DMEU was heated in an oil bath at 100 °C (± 2 °C). After 48 h, GC analysis indicated that the reaction was complete. The crude reaction mixture was cooled, added to saturated NH_4Cl, and extracted with ether (3x). The combined organic layers were washed with NH_4Cl (2x), 5% $Na_2S_2O_3$ (1x), H_2O (1x), and NaCl (1x), then dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by PTLC, eluting with increasing concentrations of ether in hexanes to afford 162 mg (0.62 mmol, 62%) of **27** as a light yellow oil. IR (thin film) 1767, 1733, 1616, 1593, 1490, 1395, 1377, 761 cm^{-1}; ^1H NMR δ 7.27 (t, 1 H, *J* = 7.8 Hz), 7.20 (d, 1 H, *J* = 7.6), 7.08 (t, 1 H, *J* = 7.5 Hz), 7.02 (d, 1 H, *J* = 8.0 Hz), 4.05 (m, 2 H), 3.19 (dd, 1 H, *J* = 9.4, 4.9 Hz), 2.75 (dd, 1 H, *J* = 15.4, 4.9 Hz), 2.35 (dd, 1 H, *J* = 15.4, 9.4 Hz), 1.37 (s, 3 H), 1.21 (s, 3 H), 1.16 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 173.0, 171.4, 150.5, 128.7 (2), 125.2, 124.4, 116.4, 60.8, 43.7, 40.7, 37.1, 25.2, 21.7, 14.0; HRMS *m/e* Calcd for $C_{15}H_{18}O_4$: 262.1205. Found 262.1204. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.70; H, 6.87. Found: C, 68.62; H, 6.86.

Ethyl 3,4-Dihydro-3,3,7-trimethylcoumarin-4-acetate (28): 132 mg (0.48 mmol, 48%) from **17** as a yellow oil; IR (thin film) 1765, 1734, 1626, 1580, 1504, 1390, 1373, 805 cm^{-1}; ^1H NMR δ 7.07 (d, 1 H, *J* = 7.7 Hz), 6.89 (d, 1 H, *J* = 7.7 Hz), 6.84 (s, 1 H), 4.06 (m, 2 H), 3.14 (dd, 1 H, *J* = 9.5, 4.8 Hz), 2.72 (dd, 1 H, *J* = 15.4, 4.8 Hz), 2.33 (s, 3 H), 2.32 (dd, 1 H, *J* = 15.4, 9.5 Hz), 1.36 (s, 3 H), 1.20 (s, 3 H), 1.17 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 173.2, 171.5, 150.3, 138.9, 128.3, 125.1, 122.1, 116.8, 60.7, 43.4, 40.8, 37.3, 25.3, 21.8, 21.1, 14.0; HRMS *m/e* Calcd for $C_{16}H_{20}O_4$: 276.1361. Found 276.1356. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.57; H, 7.25. Found: C, 69.66; H, 7.28.

Ethyl 3,4-Dihydro-7-methoxy-3,3-dimethylcoumarin-4-acetate (29): 147 mg (0.50 mmol, 50%) from **18** as a yellow oil; IR (thin film) 2840, 1767, 1733, 1626, 1590, 1509, 1391, 1375, 844, 813 cm^{-1}; ^1H NMR δ 7.10 (d, 1 H, *J* = 8.4 Hz), 6.64 (dd, 1 H, *J* = 8.4, 2.6 Hz), 6.58 (d, 1 H, *J* = 2.6 Hz), 4.06 (m, 2 H), 3.79 (s, 3 H), 3.12 (dd, 1 H, *J* = 9.6, 4.8 Hz), 2.72 (dd, 1 H, *J* = 15.3, 4.8 Hz),

2.31 (dd, 1 H, J = 15.3, 9.6 Hz), 1.36 (s, 3 H), 1.21 (s, 3 H), 1.17 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 172.9, 171.4, 159.8, 151.2, 129.2, 117.0, 110.2, 101.9, 60.6, 55.3, 43.0, 40.7, 37.3, 25.2, 21.7, 14.0; HRMS *m/e* Calcd for $C_{16}H_{20}O_5$: 292.1310. Found: 292.1304. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.75; H, 6.85. Found: C, 65.93; H, 6.91.

Ethyl 5,6-Benzo-3,4-dihydro-3,3-dimethylcoumarin-4-acetate (30): 162 mg (0.52 mmol, 52%) from **19** as a viscous yellow oil; IR (thin film) 1770, 1732, 1627, 1516, 1396, 1378, 816, 750 cm^{-1}; ^{1}H NMR δ 8.00 (d, 1 H, J = 8.5 Hz), 7.85 (d, 1 H, J = 8.2 Hz), 7.78 (d, 1 H, J = 8.9 Hz), 7.59 (t, 1 H, J = 7.1 Hz), 7.47 (t, 1 H, J = 7.1 Hz), 7.21 (d, 1 H, J = 8.9 Hz), 4.12-3.98 (complex, 2 H), 3.95 (m, 1 H), 2.72 (dd, 1 H, J = 16.1, 7.8 Hz), 2.49 (dd, 1 H, J = 16.1, 4.3 Hz), 1.47 (s, 3 H), 1.24 (s, 3 H), 1.12 (t, 3 H, J = 7.2 Hz); ^{13}C NMR δ 172.8, 171.7, 148.1, 131.0, 130.6, 129.4, 128.8, 127.4, 125.0, 122.5, 118.5, 116.8, 60.9, 41.0, 40.0, 36.9, 25.6, 21.6, 13.8; HRMS *m/e* Calcd for $C_{19}H_{20}O_4$: 312.1361. Found: 312.1365. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.08; H, 6.41. Found: C, 73.26; H, 6.49.

Ethyl 3,4-Dihydro-3,3-dimethyl-2(1*H*)-quinolinone-4-acetate (31): 199 mg (0.76 mmol, 76%) from **20** as a light yellow solid, mp 110-112 °C; IR ($CHCl_3$) 3235, 1733, 1677, 1394, 1379, 758 cm^{-1}; ^{1}H NMR δ 8.93 (br s, 1 H), 7.16 (m, 2 H), 6.96 (t, 1 H, J = 7.6 Hz), 6.83 (d, 1 H, J = 7.7 Hz), 4.02 (m, 2 H), 3.14 (dd, 1 H, J = 10.2, 4.8 Hz), 2.71 (dd, 1 H, J = 14.8, 4.8 Hz), 2.32 (dd, 1 H, J = 14.8, 10.2 Hz), 1.30 (s, 3 H), 1.15 (s, 3 H), 1.13 (t, 3 H, J = 7.1 Hz); ^{13}C NMR δ 176.1, 172.1, 135.7, 128.6, 127.8, 126.1, 123.0, 115.2, 60.5, 45.2, 40.6, 36.3, 25.2, 20.8, 14.0; HRMS *m/e* Calcd for $C_{15}H_{19}NO_3$: 261.1402. Found 261.1399. Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.97; H, 7.28. Found: C, 68.84; H, 7.24.

Ethyl 3,3-Dimethyl-1-phenyl-2-piperidinone-4-acetate (32): 236 mg (0.82 mmol, 82%) from **25** as a light yellow oil; IR (thin film) 1732, 1651, 1595, 1493, 1382, 764, 697 cm^{-1}; ^{1}H NMR δ 7.37 (t, 2 H, J = 7.5 Hz), 7.23 (t, 1 H, J = 6.9 Hz), 7.20 (d, 2 H, J = 7.3 Hz), 4.17 (q, 2 H, J = 7.0 Hz), 3.72 (m, 1 H), 3.52 (ddd, 1 H, J = 13.9, 5.5, 1.8 Hz), 2.57 (dd, 1 H, J = 15.4, 2.8 Hz), 2.35 (tt, 1 H, J = 10.6, 2.8 Hz), 2.23 (dd, 1 H, J = 15.4, 10.6 Hz), 2.02 (dm, 1 H, J = 13.9 Hz), 1.93-1.81 (complex, 1 H), 1.35 (s, 3 H), 1.28 (t, 3 H, J = 7.0 Hz), 1.20 (s, 3 H); ^{13}C NMR δ 175.3, 172.7, 143.5, 128.9, 126.5, 126.1, 60.5, 49.9, 42.1, 39.5, 35.3, 25.5, 24.6, 21.7, 14.1; HRMS *m/e* Calcd for $C_{17}H_{23}NO_3$: 289.1678. Found: 289.1673. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.59; H, 7.96. Found: C, 70.69; H, 7.99.

Ethyl 3,3-Dimethyl-1-phenyl-2-pyrrolidinone-4-acetate (33): 124 mg (0.45 mmol, 34%) from **26** as a light yellow oil; IR (thin film) 1736, 1707, 1597, 1494, 1392, 1377, 761, 696 cm^{-1}; ^{1}H NMR δ 7.64 (d, 2 H, J = 7.7 Hz), 7.35 (t, 2 H, J = 7.5 Hz), 7.13 (t, 1 H, J = 7.6 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 3.99 (dd, 1 H, J = 9.9, 7.3 Hz), 3.48 (dd, 1 H, J= 9.9, 8.8 Hz), 2.56 (m, 2 H), 2.38 (dd, 1 H, J = 16.5, 11.5 Hz), 1.29 (t, 3 H, J = 7.1 Hz), 1.25 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR δ 178.1, 172.0, 139.4, 128.7, 124.3, 119.6, 60.7, 50.5, 44.1, 39.3, 33.2, 23.7, 18.7, 14.1; HRMS *m/e* Calcd for $C_{16}H_{21}NO_3$: 275.1558. Found 275.1775. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.82; H, 7.64. Found: C, 69.72; H, 7.62.

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