Synthesis of 2-Oxazolone-4-carboxylates from 3-Nosyloxy- and 3-Bromo-2-ketoesters

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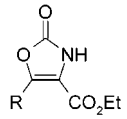
New methods for the synthesis of 2-oxazolone-4-carboxylates from 3-nosyloxy- and 3-bromo-2-ketoesters are described. Condensation of 3-nosyloxy-2-ketoesters with methyl carbamate in refluxing toluene in the presence of *p*-TSA provided 2-oxazolone-4-carboxylates in good yields (41−80%). Alternatively, bromination of α-ketoesters with $CuBr_2$ provided 3-bromo-2-ketoesters which condensed with methyl carbamate in the presence of *p*-TSA and AgOTf under similar conditions to provide 2-oxazolone-4-carboxylates in comparable yields (30−79%). The 2-oxazolone-4-carboxylates bear functionality that can be elaborated to a variety of potentially useful compounds. For example, some of these heterocycles were readily *N*-acylated, reduced to alcohols, or saponified and coupled with amino acids.

Introduction

We recently reported that 4-oxazolin-2-one-4-carboxylates (also referred to as 2-[3*H*]-oxazolone-4-carboxylates, **1**)[1] could be prepared by the cyclocondensation of 3-nosyloxy-2-ketoesters **2** with methyl carbamate.[2]



2-Oxazolone-4-carboxylates, **1**

Oxazolones with a carboxyl group at the 4- or 5-position are relatively uncommon,[3] which is somewhat surprising considering that the oxazolone moiety incorporates dense functionality that could find great utility in synthesis. For example, oxazolones provide a template for the construction of *vicinal*-amino alcohols. This feature has indeed been exploited by additions to the olefinic function of oxazolones,[4] by [4 + 2] cycloadditions of oxazolones with azidocarboxylates,[5] and by asymmetric catalytic hydrogenations of oxazolones.[6] Analogous transformations of 2-oxazolone-4-carboxylates (**1**) could provide access to biologically important *β*-hydroxy-α-amino acid derivatives. Furthermore, oxazolone-4-carboxylates bear functionality that can allow them to be incorporated in peptides and proteins and can, as a consequence of their planarity and rigidity, impart conformational constraints in peptide and protein backbones. The great potential that these heterocycles offer led us to pursue methods for their synthesis.

The synthesis of oxazolone-5-carboxylates has been accomplished by treatment of chloropyruvic acid derivatives with KO-*t*-Bu and carbamates[3f] and by the treatment of diazopyruvates with isocyanates in the presence of catalytic $Rh_2(OAc)_4$.[3e] The regioisomeric oxazolone-4-carboxylates were reported to be prepared by oxidation of *N*-alkoxycarbonyl-α-didehyroamino acids derivatives with $SOCl_2$,[3a] NBS,[3b] or $Pb(OAc)_4$,[3d] followed by intramolecular cyclization. Earlier we communicated a synthesis of oxazolone-4-carboxylates **1**[2] by the cyclocondensation of 3-nosyloxy-2-ketoesters with carbamates, in which the regiochemical and mechanistic aspects of the transformation were described. Herein we describe the experimental details for the preparation of oxazolone-4-carboxylates **1**[2] from 3-nosyloxy-2-ketoesters, as well as a new synthesis of these heterocyles from more readily available 3-bromo-2-ketoesters. In addition, some transformations which demonstrate the synthetic potential of oxazolone-4-carboxylates are also reported.

Results and Discussion

3-Nosyloxy-2-ketoesters **2** are accessible via 2-ketoesters.[7] The synthetic utility of **2** for the synthesis of 1,2,3-trifunctionalized derivatives is compromised by the high electrophilicity of the ketone carbonyl group and the base sensitivity of the nosylate group. This reactivity pattern led us to explore acid-catalyzed additions of weak, nonbasic nucleophiles to **2**. We were pleased to find that

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(7) Hoffman, R. V.; Johnson, C. M.; Okonya, J. F. *J. Org. Chem.* **1997**, *62*, 2458−2465. An alternative method that may potentially offer easy access to 3-nosyloxy-2-ketoesters has recently been described: Lee, J. C.; Choi, Y. *Tetrahedron Lett.* **1998**, *39*, 3171−3172.

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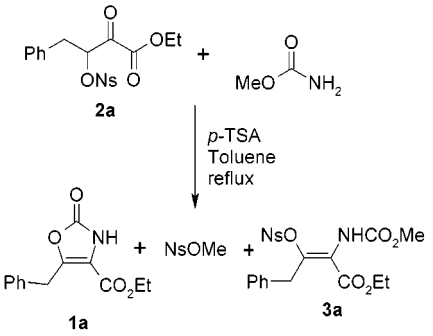
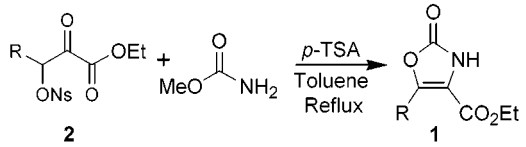
Scheme 1



Scheme 2



R	1	%Yield
Bn	**a**	80
H (Me ester)	**b**	51
Pentyl	**c**	84
i-Bu	**d**	70
i-Pr	**e**	41
Me	**f**	56
Ph	**g**	46

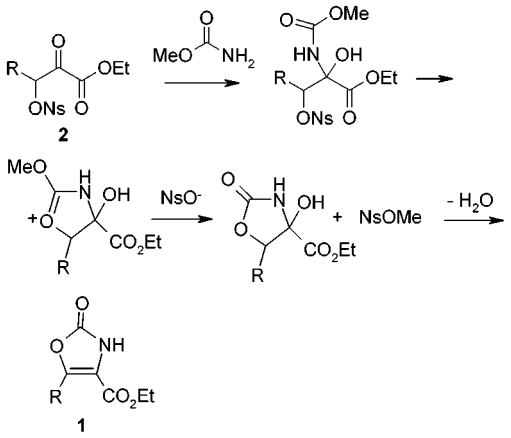
condensation of 3-nosyloxy-2-ketoester **2a** with methyl carbamate and *p*-TSA in refluxing toluene generated oxazolone **1a** as the major product in greater than 60% yield (Scheme 1).[7] The formation of **1a** was accompanied by the formation of methyl nosylate (NsOMe) in an identical yield and nosyloxyenamide **3a** as a minor product (<10%).

To optimize the yield of **1a**, we investigated the effect of concentration, catalyst, substrate equivalency, and reaction time on the course of the condensation reaction. The reaction was found to tolerate a wide range of conditions. For example, the oxazolone **1a** was formed in good yields when from 1 to 13 equiv of methyl carbamate was used and when the reaction was run in the presence or absence of *p*-TSA or 2,6-lutidine as catalyst. The concentration of the reactants was also found to have minimal effect on the course of the reaction. *tert*-Butyl and benzyl carbamate were also suitable for the cyclocondensation reaction, but in these cases the product was more difficult to purify. Optimal conditions for the reaction were found to be reaction of 5 equiv of methyl carbamate with 3-nosyloxy-2-ketoester **2a** in refluxing toluene in the presence of catalytic amounts of *p*-TSA over a period of 16 h. A series of 3-nosyloxy-2-ketoesters (**2a**−**g**) subjected to these reaction conditions gave the corresponding oxazolones **1a**−**g** in 41−84% yield (Scheme 2).

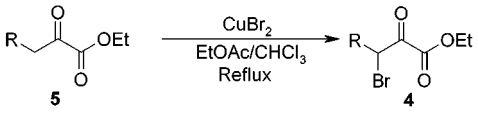
The mechanism for the formation of oxazolones from 3-nosyloxy-2-ketoesters **2** and methyl carbamate is shown in Scheme 3.[2] The evidence indicates that initial addition of the carbamate nitrogen to the C-2 ketone must be followed by the displacement of the leaving group at C-3 *prior* to dehydration to the enamide. The excellent leaving ability of the nosylate group ensures that the intramolecular displacement is rapid.

Since bromide is also a good leaving group, it is possible that 3-bromo-2-ketoesters **4** might undergo a similar process with carbamates to produce **1**. In fact, oxazole-

Scheme 3



Scheme 4



R	4	%Yield
Bn	**a**	89
H	**b**	commercial
Pentyl	**c**	88
i-Bu	**d**	82
i-Pr	**e**	83
Me	**f**	80
Ph	**g**	70
MeO_2CCH_2 (Me ester)	**h**	90

4-carboxylates have previously been prepared by the condensation of 3-bromo-2-ketoesters with acetamides.[8] 3-Bromo-2-ketoesters **4** are attractive substrates for this purpose as they can readily be prepared by bromination of α-ketoesters using a variety of methods.[8a,9] In particular, our attention was drawn to a report by Weinreb of the bromination of an α-ketoester with $CuBr_2$.[9] Because of its simplicity, this method was chosen for the bromination of a series α-ketoesters **5**. Refluxing α-ketoesters **5a**,**c**−**h**[10] with $CuBr_2$ in $EtOAc/CHCl_3$ overnight provided the corresponding 3-bromo-2-ketoesters **4a**,**c**−**h** in excellent yields (Scheme 4).

$CuBr_2$ selectively brominates the *β*-position of an α-ketoester in the presence of a benzyl group (substrate **5a**) or a methylene group proximal to an ester (substrate **5h**). Some transesterification with EtOAc was observed in the $CuBr_2$ bromination of methyl ester **5h**. Attempts to extend this methodology to the bromination *β*-ketoesters were futile. Treatment of *β*-ketoester **6f** with $CuBr_2$ led to a mixture of products, with bromination occurring at both the 2-position and the 4-position. α-Bromination of *β*-ketoester **6f** was ultimately carried out by enolizing the *β*-ketoester with NaH and rapidly

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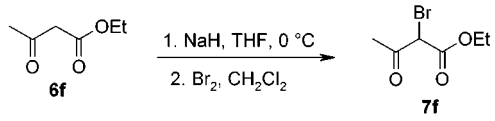
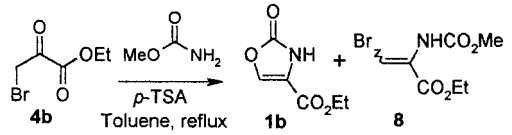
(10) α-Ketoesters **5a**,**b**,**h** were obtained commercially from Aldrich. α-Ketoesters **5c**−**g** were prepared by the reaction of Grignard reagents with diethyl oxalate according to literature precedence: (a) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026−5030. (b) Weinstock, L. M.; Currie, R. B.; Lovell, A. V. *Synth. Commun.* **1981**, *11*, 943−946. (c) Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143−5150.

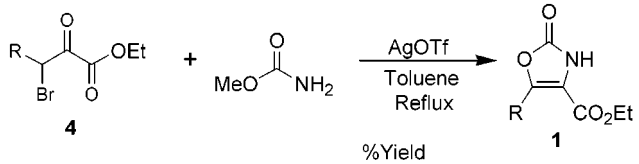
Scheme 5



Scheme 6



Scheme 7



R	1	%Yield	%Yield With *p*-TSA
Bn	**a**	64	75
H (Me ester)	**b**	43	54
Pentyl	**c**	63	79
i-Bu	**d**	68	75
i-Pr	**e**	30	-
Me	**f**	60	60
Ph	**g**	64	-
$MeOCCH_2$ (Me ester)	**h**	-	49

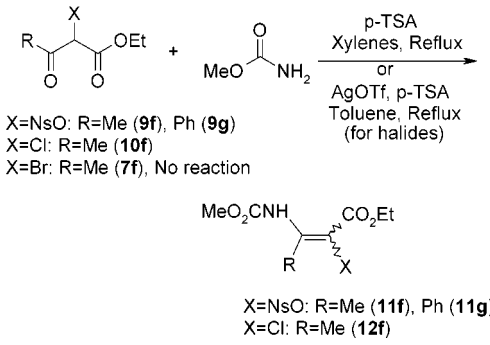
quenching the resulting enolate with Br_2 in CH_2Cl_2 (Scheme 5).[11] Recent work has provided an improved method for the monobromination of *β*-ketoesters.[12]

With 3-bromo-2-ketoesters **4** in hand, we evaluated their suitability as substrates for reaction with methyl carbamate. Reaction of ethyl bromopyruvate (**4b**) with methyl carbamate and catalytic *p*-TSA in refluxing toluene yielded a mixture containing oxazolone **1b** as a minor product and bromoenamide **8b** as the major product in a combined yield of <30% (Scheme 6).

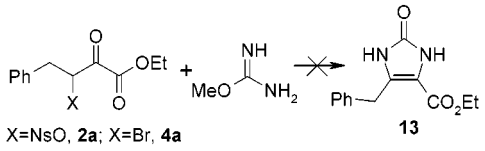
Apparently the leaving group ability of bromide is insufficient to promote intramolecular cyclization of the carbinolamide intermediate prior to dehydration. Silver salts are known to activate halides toward displacement reactions; thus reaction of **4b** with methyl carbamate in the presence of stoichiometric amounts of AgOTf led to the clean formation of oxazolone **1b**. This result provided a new, general method for the synthesis of oxazolone-4-carboxylates **1**. 3-Bromo-2-ketoesters **4a**−**h** were refluxed with methyl carbamate in toluene in the presence of AgOTf to provide oxazolones **1a**−**h** in 30−68% yield. Addition of catalytic amounts of *p*-TSA to the reaction was found improve the yields so that **1a**−**d**,**f**,**h** could be isolated in 49−79% yield (Scheme 7).

It was of interest to see if 2-nosyloxy- or 2-halo-3-ketoesters could be used as substrates since analogous condensation with carbamates would provide the regioisomeric 2-oxazolone-5-carboxylates. However, no reaction was seen when 2-nosyloxy-3-ketoesters **9f** and **9g**, methyl carbamate, and *p*-TSA were refluxed in toluene for 24 h. Reaction at higher temperature in refluxing xylenes gave only a mixture of *Z*- and *E*-nosyloxy enamides **11f**,**g** (Scheme 8). The same behavior was seen

Scheme 8



Scheme 9



with 2-halo-3-ketoesters. Refluxing 2-chloro-3-ketoester **10f**, methyl carbamate, AgOTf, and *p*-TSA in toluene for 24 h provided a mixture of *Z*- and *E*-bromoenamides **12f** as the major condensation products. 2-Bromo-3-ketoester **7f** was inert to condensation with methyl carbamate in refluxing toluene or xylenes.

β-Ketoester derivatives **7**, **9**, and **10** and α-ketoester derivatives **2** and **4** differ only by the transposition of functional groups and yet **7**, **9**, and **10** show remarkably different reactivity with carbamates. Apparently, the diminished electrophilicity of the *β*-ketone carbonyl and the enhanced acidity of the α-proton in the α-substituted *β*-ketoesters **7f**, **9f**,**g**, and **10f** combine to thwart cyclocondensation to oxazolones and favor the formation enamides. Marked differences in reactivity between *β*-nosyloxy-α-ketoesters and regioisomeric α-nosyloxy-*β*-ketoesters have previously been observed.[7]

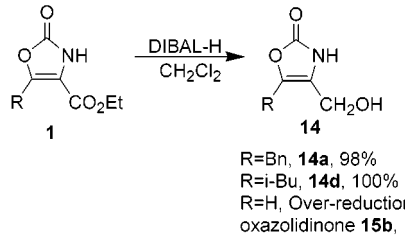
The structural similarity between *O*-methylisourea and methyl carbamate suggested that reaction of the former with **2** or **4** could produce 2-imidazolone-4-carboxylates **13** (Scheme 9). Surprisingly, attempts to prepare 2-imidazolone-4-carboxylates by this method were unsuccessful. Treatment of either **2a** or **4a** with *O*-methylisourea under typical condensation conditions resulted in either no reaction or decomposition of starting materials.

Transformations of oxazolone-4-carboxylates to other densely functionalized compounds will necessarily involve functionalization of nitrogen, manipulation of the olefinic function, and/or elaboration of the ester group. Three transformations of the ester functionality of the oxazolones of **1** were explored: reduction, saponification, and amidation. DIBAL-H was found to be a good reagent for the reduction of oxazolone-4-carboxylates to the corresponding alcohols. As an example, oxazolones **1a**,**d** were reduced with DIBAL-H to the alcohols **14a**,**d** in quantitative yields (Scheme 10). Oxazolone **1b**, on the other hand, was over-reduced to 4-hydroxymethyl-2-oxazolidinone **15b**, which was isolated in 13% yield.

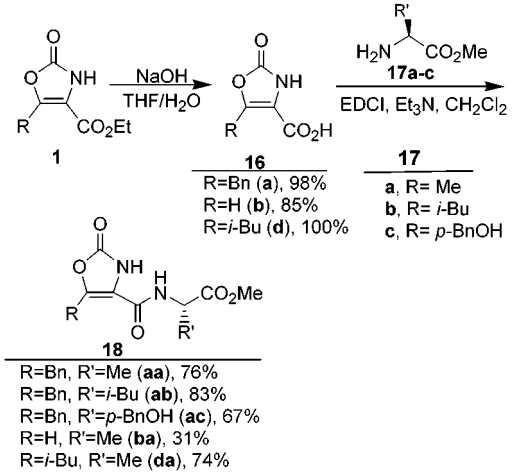
The oxazolone ester groups of **1a**,**b**,**d** were saponified by treatment with NaOH in a mixture of THF/H_2O to obtain the corresponding acids **16a**,**b**,**d** in excellent yields (Scheme 11). When acids **16a**,**b**,**d** were coupled to amino esters **17a**−**c** using EDCI.HCl as coupling reagent and

(11) Stotter, P. L.; Hill, K. A. *Tetrahedron Lett.* **1972**, 4067−4070.
(12) Hoffman, R. H.; Weiner, W. S.; Maslouh, N. *J. Org. Chem.* **2001**, *66*, 5790.

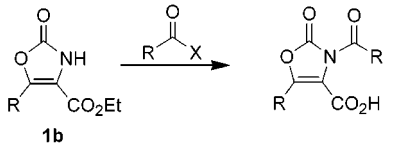
Scheme 10



Scheme 11



Scheme 12



Acylation Conditions	Product
Ac_2O, 120 °C or Ac_2O or AcCl, EtN, DMAP, THF	*N*-Acetyloxazolone
Boc_2O, EtN, DMAP, THF	*N*-Boc-oxazolone
BzlCl, EtN, DMAP, CH_2Cl_2	*N*-Benzoyloxazolone
$(CF_3CO)_2O$	No reaction
Protected Amino Acids	No reaction

CH_2Cl_2 or CH_3CN as solvent, the dipeptide analogues **18** were isolated in good yields (31−83%, Scheme 11).

N-Acylation of oxazolone **1b** proved to be more challenging than anticipated. Acylation of **1b** with Ac_2O, Boc_2O, and benzoyl chloride under standard conditions went smoothly and quantitatively (Scheme 12). However, attempts to acylate **1b** with trifluoroacetic anhydride or amino acids, under a variety of coupling conditions, failed.

Despite their potential as synthetic intermediates for the preparation of densely functionalized compounds, 2-oxazolone-4-carboxylates **1** have received very little attention in the literature.[3] This work now provides reliable access to these compounds so that their potential can be developed. Conversion of **1** to the corresponding alcohols, acids, dipeptide analogues, and *N*-acyl derivatives represents a beginning of their development.

Experimental Section

General Methods. Descriptions of instruments, general procedures, and chromatographic procedures have been published previously.[7] β-Nosyloxy-α-ketoesters **2** were prepared as described previously.[7] β-Bromo-α-ketoesters **4a**,[13] **4f**,[14] and **4h**[15] have been reported in the literature. Their characterizations were not complete and are given in detail here.

Ethyl 3-Bromo-2-oxo-4-phenylbutanoate (4a). To a suspension of $CuBr_2$ (9.48 g, 42.4 mmol) in EtOAc (150 mL) was added a solution of ethyl 2-oxo-4-phenylbutanoate (**5a**, 2.94 g, 14.3 mmol) in 75 mL of $CHCl_3$. The mixture was refluxed for 18h, cooled, and filtered through a short pad of silica gel, eluting with EtOAc/hexanes (1:1). The solvent was removed in vacuo to obtain a light green liquid which was further purified by bulb-to-bulb distillation (165 °C, 0.07 mmHg) to provide bromoketoester **4a** (3.60 g, 89%) as a clear yellow liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, J = 7.0 Hz, 3H), 3.24 (dd, J = 14.5 and 7.5 Hz, 1H), 3.54 (dd, J = 14.5 and 7.5 Hz, 1H), 4.35 (q, J = 7.0 Hz, 2H), 5.27 (t, J = 7.3 Hz, 1H), 7.28 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 38.1, 47.5, 63.1, 127.3, 128.7, 129.3, 136.4, 160.1, 185.2; IR (neat) 3100−2850, 1734, 1605 cm^{-1}. Anal. Calcd for $C_{12}H_{13}O_3Br$: C, 50.55; H, 4.6. Found: C, 50.80; H, 4.80.

Ethyl 3-Bromo-2-oxooctanoate (4c). This compound was prepared by the same procedure from $CuBr_2$ (4.74 g, 21.2 mmol) and ethyl 2-oxooctanoate (**5c**, 1.33 g, 7.13 mmol) to provide bromoketoester **4c** (1.67 g, 88%) as a clear yellow liquid after bulb-to-bulb distillation (130 °C, 0.07 mmHg): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, J = 6.2 Hz, 3H), 1.25−1.65 (m, 6H), 1.40 (t, J = 7.2 Hz, 3H), 2.05 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 5.04 (dd, J = 8.2 and 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.92, 13.96, 22.3, 26.7, 31.0, 31.8, 48.4, 63.0, 160.6, 185.9; IR (neat) 2959, 2950, 2861, 1733 cm^{-1}. Anal. Calcd for $C_{10}H_{17}O_3Br$: C, 45.30; H, 6.46. Found: C, 45.12; H, 6.60.

Ethyl 3-Bromo-5-methyl-2-oxohexanoate (4d). This compound was prepared by the same procedure from $CuBr_2$ (4.74 g, 21.2 mmol) and ethyl 5-methyl-2-oxohexanoate (**5d**, 1.23 g, 7.13 mmol) to provide bromoketoester **4d** (1.50 g, 82%) as a clear yellow liquid after bulb-to-bulb distillation (95 °C, 0.07 mmHg): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, J = 6.1 Hz, 3H), 0.99 (d, J = 6.1 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.70−2.05 (m, 3H), 4.39 (q, J = 7.2 Hz, 2H), 5.11 (dd, J = 8.7 and 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.4, 22.6, 26.1, 40.3, 46.9, 63.0, 160.7, 185.9; IR (neat) 2961−2873, 1733 cm^{-1}. Anal. Calcd for $C_9H_{15}O_3Br$: C, 43.05; H, 6.02. Found: C, 43.22; H, 6.05.

Ethyl 3-Bromo-4-methyl-2-oxopentanoate (4e). This compound was prepared by the same procedure from $CuBr_2$ (4.74 g, 21.2 mmol) and ethyl 4-methyl-2-oxohexanoate (**5e**, 1.02 g, 7.13 mmol) to provide bromoketoester **4e** (1.27 g, 83%) as a clear yellow liquid after bulb-to-bulb distillation (70 °C, 0.07 mmHg): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 6.6 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H), 2.36 (m, 3H), 4.38 (q, J = 7.1 Hz, 2H), 4.86 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 20.1, 20.3, 29.8, 56.6, 63.0, 160.7, 185.9; IR (neat) 2970−2876, 1733 cm^{-1}. Anal. Calcd for $C_8H_{13}O_3Br$: C, 40.53; H, 5.53. Found: C, 40.63; H, 5.70.

Ethyl 3-Bromo-2-oxobutanoate (4f). This compound was prepared by the same procedure from $CuBr_2$ (4.74 g, 21.2 mmol) and ethyl 2-oxobutanoate (**5f**, 95% purity, 0.930 g, 7.13 mmol) to provide bromoketoester **4f** (95% purity, 1.20 g, 80%) as a clear yellow liquid after bulb-to-bulb distillation (50 °C, 0.07 mmHg): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (t, J = 7.1 Hz, 3H), 1.82 (d, J = 6.8 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 5.18 (q, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 18.4, 42.3, 63.0, 160.5, 186.0; IR (neat) 2982−2800, 1733 cm^{-1}.

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Because of an impurity, elemental analysis was not obtained for **4f**. The impurity did not affect subsequent reactions and was removed in the next step.

Ethyl 3-Bromo-3-phenyl-2-oxopropanoate (4g). This compound was prepared by the same procedure from $CuBr_2$ (4.74 g, 21.2 mmol) and ethyl 3-phenyl-2-oxopropanoate (**5g**, 1.37 g, 7.13 mmol) to provide bromoketoester **4g** (1.36 g, 70%) as a clear yellow liquid upon purification by flash chromatography eluting with EtOAc/hexanes (1:4): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 4.34 (q, J = 7.1 Hz, 2H), 6.21 (s, 1H), 7.38−7.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 49.8, 63.2, 129.0, 129.6, 129.7, 133.1, 160.0, 184.0; IR (neat) 3100−2850, 1735, 1660, 1605 cm^{-1}. Anal. Calcd for $C_{11}H_{11}O_3Br$: C, 48.73; H, 4.09. Found: C, 48.89; H, 4.19.

Methyl 4-Carbomethoxy-3-bromo-2-oxobutanoate (4h). This compound was prepared by the same procedure from $CuBr_2$ (7.90 g, 35.4 mmol) and dimethyl 2-oxoglutarate (**5h**, 96% from Aldrich, 2.11 g, 11.9 mmol) to provide bromoketoester **4h** (2.70 g, 90%, contaminated with ∼5% trans esterified product) as a clear yellow liquid upon purification by bulb-to-bulb distillation (150 °C, 0.07 mmHg). An analytical sample of **4h** was obtained upon further purification by flash chromatography, eluting with EtOAc/hexanes (1:4): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.07 (dd, J = 17.6 and 5.9 Hz, 1H), 3.35 (dd, J = 17.6 and 9.1 Hz, 1H), 3.72 (s, 3H), 3.96 (s, 3H), 5.09 (dd, J = 9.0 and 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 39.6, 52.3, 53.5, 159.8, 170.0, 184.4; IR (neat) 2957, 1736 (br) cm^{-1}. Anal. Calcd for $C_7H_9O_5Br$: C, 33.23; H, 3.58. Found: C, 33.41; H, 3.55.

Ethyl 2-Bromo-3-oxobutanoate (7f). Method A.[10] Ethyl acetoacetate (**6f**, 2.60 g, 2.60 mL, 20.0 mmol) was added dropwise to NaH (50% suspension in oil, 1.15 g, 24.0 mmol) in THF (30 mL) under N_2 at 0 °C. The mixture was stirred at room temperature for 30 min. The mixture was then cooled to 0 °C, rapidly quenched with Br_2 (3.52 g, 1.20 mL, 22.0 mmol) in CH_2Cl_2 (10 mL), and filtered through a thin pad of silica gel. The filtrate was concentrated under reduced pressure to provide 2-bromo-3-ketoester **7f** as a light yellow liquid (4.18 g, 100%): ^{1}H NMR (400 MHz, $CDCl_3$, keto−enol tautomers) δ 1.30 (two overlapping t, 3H), 2.43 (s, 1.2H, ketoform), 2.60 (s, 1.8H enol form), 4.33 (two overlapping q, 2H), 4.76 (s, 0.4H, ketoform).

Ethyl 2-Bromo-3-oxobutanoate (7f). Method B. To a solution of ethyl acetoacetate (**6f**, 0.39 g, 3.0 mmol) in CH_2Cl_2 (15 mL) at rt was added NBS (0.54 g, 3.0 mmol). The solution was stirred at rt for 24 h, washed with 1 N HCl (50 mL), dried ($MgSO_4$), and then passed through a short pad of silica gel. The filtrate was concentrated under reduced pressure to give a yellow liquid. Further purification by bulb-to-bulb distillation (55 °C, 0.07 mmHg) provided the 2-bromo-3-ketoester **7f** as a light yellow liquid (0.50 g, 80%): ^{1}H NMR was identical with that reported above (method A).

General Procedure for the Preparation of Oxazolone-4-carboxylates 1 from 3-Nosyloxy-2-ketoesters. Method C. 5-Benzyl-4-carboethoxy-4-oxazolin-2-one, 1a. A mixture of ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-4-phenylbutanoate (**2a**, 1.60 g, 4.00 mmol), methyl carbamate (1.50 g, 20.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.400 mmol) in 80 mL of toluene was refluxed overnight. The reaction was monitored by TLC (EtOAc/CH_2Cl_2,1:9). The reaction mixture was cooled to rt, 80 mL of EtOAc was added, and the mixture was washed with water (2 × 60 mL) and brine (60 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow solid. The crude product was chromatographed on a silica gel column eluting with hexanes/EtOAc (gradient of 4:1 then 2:1) and recrystallized from EtOAc/hexanes to provide oxazolone **1a** as a white crystalline solid (0.780 g, 80%): mp 141−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (t, J = 7.2 Hz, 3H), 4.11 (s, 2H), 4.37 (q, J = 7.2 Hz, 2H), 7.25−7.34 (m, 5H), 8.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 32.0, 61.8, 114.3, 127.3, 128.82, 128.84, 135.3, 148.1, 153.4, 158.8; IR (KBr) 3440, 1762, 1718, 1670 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.91; H, 5.12; N, 5.31.

General Method for the Preparation of Oxazolone-4-carboxylates from 3-Bromo-2-ketoesters. Method D. 5-Benzyl-4-carboethoxy-4-oxazolin-2-one 1a. To ethyl 3-bromo-2-oxo-4-phenylbutanoate (**4a**, 1.71 g, 6.00 mmol) in toluene (100 mL) were added methyl carbamate (2.25 g, 30.0 mmol) and AgOTf (1.54 g, 6.00 mmol) [with or without *p*-toluenesulfonic acid monohydrate (0.110 g, 0.600 mmol)]. The mixture was refluxed overnight. The reaction was monitored by TLC using EtOAc/CH_2Cl_2 (1:9). The reaction mixture was cooled to rt, 100 mL of EtOAc was added, and the mixture was then washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated in vacuo to provide a yellow solid. The crude product was chromatographed on a silica gel column eluting with EtOAc/CH_2Cl_2 (1:9) and recrystallized from EtOAc/hexanes to provide oxazolone **1a** as a white crystalline solid (0.950 g, 64% without *p*-TSA or 1.11 g, 75% with *p*-TSA).

4-Carbomethoxy-4-oxazolin-2-one (1b). Using method C, methyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxopropanoate (**2b**, 0.30 g, 0.99 mmol) was condensed with methyl carbamate (0.37 g, 5.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.019 g, 0.10 mmol) in 20 mL of toluene to provide oxazolone **1b** as a white crystalline solid (0.15 g, 51%): mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.43 (d, J = 1.5 Hz, 1H), 9.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 119.9, 134.6, 154.6, 158.4; IR (KBr) 3322, 1783 (br), 1723, 1624 cm^{-1}. Anal. Calcd for $C_5H_5NO_4$: C, 41.97; H, 3.52; N, 9.79. Found: C, 41.97; H, 3.79; N, 9.75.

4-Carboethoxy-4-oxazolin-2-one (1b). Using method D, ethyl 3-bromopyruvate (**4b**, Aldrich, 90% purity, 1.08 g, 5.00 mmol) was reacted with methyl carbamate (1.88 g, 25.0 mmol), and AgOTf (1.28 g, 5.00 mmol) [with or without *p*-toluenesulfonic acid monohydrate (0.100 g, 0.500 mmol)] to give oxazolone **1b** as a white crystalline solid (0.330 g, 43% without *p*-TSA or 0.430 g, 54% with *p*-TSA): mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 7.41 (d, J = 1.5 Hz, 1H), 9.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 62.0, 120.3, 134.4, 155.0, 158.1; IR (KBr) 3300, 1760, 1710, 1640 cm^{-1}. Anal. Calcd for $C_6H_7NO_4$: C, 45.87; H, 4.49; N, 8.91. Found: C, 46.08; H, 4.47; N, 8.90.

5-Pentyl-4-carboethoxy-4-oxazolin-2-one (1c). Using method C, ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxooctanoate (**2c**, 1.55 g, 4.00 mmol) was condensed with methyl carbamate (1.50 g, 20.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.400 mmol) in 80 mL of toluene to provide oxazolone **1c** as a white crystalline solid (0.760 g, 84%): mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 6.6 Hz, 3H),1.32−1.38 (m, 7H), 1.65 (m, J = 7.1 Hz, 2H), 2.79 (t, J = 7.3 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 8.55 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.2, 25.7, 26.7, 31.0, 61.5, 114.1, 150.5, 153.9, 159.0; IR (KBr) 3199, 1759, 1717, 1675 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.27; H, 7.47; N, 5.96.

Using method D, ethyl 3-bromo-2-oxooctanoate (**4c**, 1.06 g, 4.00 mmol) was reacted with methyl carbamate (1.50 g, 20.0 mmol) and AgOTf (1.03 g, 4.00 mmol) [with or without *p*-toluenesulfonic acid monohydrate (0.080 g, 0.40 mmol)] to provide oxazolone **1c** as a white crystalline solid (0.580 g, 63% without *p*-TSA or 0.720 g, 79% with *p*-TSA).

5-Isobutyl-4-carboethoxy-4-oxazolin-2-one (1d). Using method C, ethyl 5-methyl-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxohexanoate (**2d**, 1.72 g, 4.61 mmol) was condensed with methyl carbamate (1.73 g, 23.1 mmol) and *p*-toluenesulfonic acid monohydrate (0.10 g, 0.500 mmol) in 80 mL of toluene to provide oxazolone **1d** as a white crystalline solid (0.690 g, 70%): mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.36 (t, J = 7.1 Hz, 3H), 2.04 (m, J = 7.0 Hz, 1H), 2.67 (d, J = 7.0, 2H), 4.33 (q, J = 7.1 Hz, 2H), 8.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.1, 27.4, 34.5, 61.5, 114.5, 149.6, 154.1, 159.0; IR (KBr) 3205, 1750, 1717, 1672 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.49; H, 6.89; N, 6.59.

Using method D, ethyl 3-bromo-5-methyl-2-oxohexanoate (**4d**, 1.26 g, 5.00 mmol) was reacted with methyl carbamate (1.88 g, 25.0 mmol) and AgOTf (1.28 g, 5.00 mmol) [with or without *p*-toluenesulfonic acid monohydrate (0.10 g, 0.500

mmol) to provide oxazolone **1d** as a white crystalline solid (0.720 g, 68% without *p*-TSA or 0.80 g, 75% with *p*-TSA).

5-Isopropyl-4-carboethoxy-4-oxazolin-2-one (1e). Using method C, ethyl 4-methyl-3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxopentanoate (**2e**, 1.42 g, 3.95 mmol) was condensed with methyl carbamate (1.50 g, 20.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.40 mmol) in 80 mL of toluene. The reaction was run for 48 h, and fresh methyl carbamate was added midway through the reaction. Oxazolone **1e** was obtained as a white crystalline solid (0.320 g, 41%): mp 123−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, J = 7.9 Hz, 6H), 1.36 (t, J = 7.1 Hz, 3H), 3.54 (m, J = 7.0, 1H), 4.36 (q, J = 7.1 Hz, 2H), 8.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 20.0, 25.8, 61.5, 112.5, 154.0, 154.5, 158.9; IR (KBr) 3199, 1762, 1720, 1669 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.29; H, 6.38; N, 7.10.

Using method D, ethyl 3-bromo-4-methyl-2-oxopentanoate (**4e**, 0.95 g, 4.00 mmol) was reacted with methyl carbamate (1.50 g, 20.0 mmol) and AgOTf (1.03 g, 4.00 mmol) to provide oxazolone **1e** as a white crystalline solid (0.110 g, 14% for a reaction time of 24 h, and 0.24 g, 30% for a reaction time of 48 h).

5-Methyl-4-carboethoxy-4-oxazolin-2-one (1f). Using method C, ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxobutanoate (**2f**, 1.33 g, 4.00 mmol) was condensed with methyl carbamate (1.50 g, 20.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.400 mmol) in 80 mL of toluene to provide oxazolone **1f** as a white crystalline solid (0.380 g, 56%): mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J = 7.1 Hz, 3H), 2.41 (s, 3H), 4.34 (q, J = 7.1 Hz, 2H), 8.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 14.2, 61.6, 114.4, 146.5, 153.8, 158.9; IR (KBr) 3200, 1762, 1717, 1675 cm^{-1}. Anal. Calcd for $C_7H_9NO_4$: C, 49.12; H, 5.3; N, 8.18. Found: C, 49.04; H, 5.46; N, 8.13.

Using method D, ethyl 3-bromo-2-oxobutanoate (**4f**, 0.840 g, 4.00 mmol) was reacted with methyl carbamate (1.50 g, 20.0 mmol) and AgOTf (1.03 g, 4.00 mmol) [with or without *p*-toluenesulfonic acid monohydrate (0.080 g, 0.400 mmol)] to provide oxazolone **1f** as a white crystalline solid (0.410 g, 60% with or without TSA).

5-Phenyl-4-carboethoxy-4-oxazolin-2-one (1g). Using method C, ethyl 3-[(*p*-nitrobenzenesulfonyl)oxy]-2-oxo-3-phenylpropanoate (**2g**, 1.57 g, 4.00 mmol) was condensed with methyl carbamate (1.50 g, 20.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.080 g, 0.400 mmol) in 80 mL of toluene to provide oxazolone **1g** as a white crystalline solid (0.520 g, 46%): mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 7.45 (m, 3H), 8.03 (m, 2H), 9.22 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.0, 113.7, 126.0, 127.9, 128.4, 130.5, 145.9, 153.3, 158.3; IR (KBr) 3187, 1768, 1720, 1630 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.8; H, 4.75; N,

Using method D, ethyl 3-bromo-2-oxo-3-phenylpropanoate (**4g**, 1.08 g, 4.00 mmol) was reacted with methyl carbamate (1.50 g, 20.0 mmol) and AgOTf (1.03 g, 4.00 mmol) to provide oxazolone **1g** as a white crystalline solid (0.600 g, 64%).

5-Carbomethoxy-4-carbomethoxy-4-oxazolin-2-one (1h). Using method D, methyl 4-carbomethoxy-3-bromo-2-oxobutanoate (**4h**, 1.52 g, 6.00 mmol) was reacted with methyl carbamate (2.25 g, 30.0 mmol), AgOTf (1.54 g, 6.00 mmol), and *p*-toluenesulfonic acid monohydrate (0.110 g, 0.60 mmol) to provide oxazolone **1h** as a white crystalline solid (0.630 g, 49%): mp 93−95 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.88 (s, 2H), 3.89 (s, 3H), 8.54 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8, 52.6, 52.8, 116.3, 141.9, 153.3, 158.6, 167.5; IR (KBr) 3216, 2965, 1760 (br), 1710, 1670 cm^{-1}. Anal. Calcd for $C_8H_9NO_6$: C, 44.66; H, 4.22; N, 6.51. Found: C, 44.84; H, 4.19; N, 6.49.

5-Benzyl-4-hydroxymethyl-4-oxazolin-2-one(14a).DIBAL-H (1.5 M in toluene, 2.5 mL, 3.8 mmol) was added dropwise to a solution of 5-benzyl-4-carboethoxy-4-oxazolin-2-one (**1a**, 0.25 g, 1.0 mmol) in dry CH_2Cl_2 (2.5 mL) at 0 °C under N_2. The reaction mixture was stirred for 4 h at 0 °C and then poured into ice-cooled 2 M HCl (15 mL). The product was extracted with EtOAc, the EtOAc extracts were washed with brine, dried ($MgSO_4$), and filtered, and the filtrate was evaporated under reduced pressure. The product was triturated with EtOAc/hexanes to provide the alcohol **14a** as a white solid (0.20 g, 98%): mp 210−212 °C; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 3.65 (s, 2H), 4.12 (t, J = 5.6 Hz, 1H), 4.31 (d, J = 5.6 Hz, 2H), 7.13 (m, 5H), 9.12 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 30.4, 53.0, 122.1, 126.8, 128.67, 128.74, 135.5, 137.8, 155.4; IR (KBr) 3256 (br), 3100−2850 (br), 1750, 1719, 1700 cm^{-1}.

5-Isobutyl-4-hydroxymethyl-4-oxazolin-2-one (14d). By the same procedure 5-isobutyl-4-carboethoxy-4-oxazolin-2-one (**1d**, 0.21 g, 1.0 mmol) was reduced with DIBAL-H (1.5 M in toluene, 2.5 mL, 3.8 mmol). Alcohol **14d** was obtained as a white solid following recrystallization from EtOAc/hexanes (0.17 g, 100%): mp 70−71 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.03 (d, J = 6.6 Hz, 6H), 1.98 (m, 1H), 2.41 (d, J = 7.0 Hz, 2H), 4.30 (t, J = 5.3 Hz, 1H), 4.46 (d, J = 4.4 Hz, 2H), 9.36 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 21.7, 27.3, 33.1, 52.9, 122.0, 136.2, 155.6; IR (KBr) 3380, 3269, 3130, 2959−2850, 1752, 1700, 1650 cm^{-1}.

4-Hydroxymethyl-2-oxazolidinone (15b). By the same procedure, 4-carboethoxy-4-oxazolin-2-one (**1b**, 0.31 g, 2.0 mmol) was reduced with DIBAL-H (1.5 M in toluene, 5.0 mL, 7.5 mmol) for 30 min. Over-reduced oxazolidinone **15b** was obtained as a white solid following recrystallization from EtOAc/hexanes (0.030 g, 13%): ^{1}H NMR (200 MHz, $(CD_3)_2SO$) δ 2.50 (s, 1H), 3.77 (d, J = 11.8 Hz, 1H), 3.95 (d, J = 12.1 Hz, 1H), 4.09 (d, J = 9.9 Hz, 1H), 4.17 (d, J = 9.2 Hz, 1H), 4.26 (m, 1H), 9.45 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 65.0, 70.6, 84.2, 157.4.

4-Carboxy-5-benzyl-4-oxazolin-2-one (16a). To a solution of 4-carboethoxy-5-benzyl-4-oxazolin-2-one (**1a**, 1.00 g, 4.04 mmol) in THF (5 mL) and H_2O (5 mL) was added NaOH (1.00 g, 25 mmol) The mixture was stirred at rt for 24 h. The reaction mixture was acidified with 1 N HCl to pH 3 and extracted with EtOAc. The EtOAc extracts were washed with H_2O and brine, dried ($MgSO_4$), and evaporated in vacuo. Trituration of the residue with EtOAc/hexanes provided the acid **16a** as a white solid (0.870 g, 98%): mp 210−212 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 4.28 (s, 2H), 7.38 (m, 5H), 9.95 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 31.6, 115.1, 127.2, 128.9, 136.6, 147.7, 153.3, 159.7; IR (KBr) 3500−2500 (br), 1741, 1710, 1650 cm^{-1}.

4-Carboxy-4-oxazolin-2-one (16b). By the same procedure, 4-carboethoxy-4-oxazolin-2-one (**1b**, 1.00 g, 6.36 mmol) in THF (5 mL) and H_2O (5 mL) was treated with NaOH (1.00 g, 25 mmol). The acid **16b** was obtained as a white solid following trituration with EtOAc/hexanes (0.700 g, 85%): mp 200−201 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 7.72 (d, J = 1.2, 1H), 10.12 (br s, 1H), 11.00 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO_3$) δ 120.7, 135.2, 154.6, 158.9; IR (KBr) 3500−2500 (br), 1757, 1700, 1650 cm^{-1}.

4-Carboxy-5-isobutyl-4-oxazolin-2-one (16d). By the same procedure, 4-carboethoxy-5-isobutyl-4-oxazolin-2-one (**1d**, 0.50 g, 2.3 mmol) in THF (5 mL) and H_2O (5 mL) was treated with NaOH (0.50 g, 13 mmol). The acid **16d** was obtained as a white solid (0.43 g, 100%): mp 212−213 °C; ^{1}H NMR (200 MHz, $(CD_3)_2CO$) δ 1.13 (d, J = 6.8 Hz, 6H), 2.17 (m, 1H), 2.86 (d, J = 7.1 Hz, 2H), 9.88 (br s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO_3$) δ 21.8, 27.6, 34.3, 115.5, 149.0, 153.5, 159.8; IR (KBr) 3500−2500 (br), 2954, 1736, 1700, 1650 cm^{-1}.

4-Carboxy-5-benzyl-4-oxazolin-2-onyl-L-alanine Methyl Ester (18aa). To a stirred solution of 4-carboxy-5-benzyl-4-oxazolin-2-one (**16a**, 0.22 g, 1.0 mmol) and L-Ala·OMe·HCl (**17a**, 0.14 g 1.0 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.14 mL, 0.11 g, 1.1 mmol) and 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (EDCI·HCl, 0.21 g, 1.1 mmol). The mixture was stirred for 12 h at rt. The mixture was then washed with H_2O (2 × 10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, eluting with EtOAc/hexanes (1:1) and recrystallized from EtOAc/hexanes to provide the dipeptide analogue **18aa** as a white solid (0.23 g, 76%): mp 116−118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.42 (d, J = 7.3 Hz, 3H), 3.71 (s, 3H), 4.12 (d, J = 15.2 Hz, 1H), 4.28 (d, J = 15.2 Hz, 1H), 4.63 (m, J = 7.3

Hz, 1H), 7.23 (m, 5H), 7.50 (d, J = 6.8 Hz, 1H), 10.00 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 31.5, 48.2, 52.4, 116.1, 127.0, 128.6, 128.8, 135.6, 147.1, 154.7, 157.4, 172.8; IR (KBr) 3345, 3100−2850, 1752 (br), 1677, 1650 cm^{-1}. Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.3; N, 9.21. Found: C, 59.15; H, 5.46; N, 9.47.

4-Carboxy-5-benzyl-4-oxazolin-2-onyl-L-leucine Methyl Ester (18ab). By the same procedure 4-carboxy-5-benzyl-4-oxazolin-2-one (**16a**, 0.33 g, 1.5 mmol) in 10 mL of CH_2Cl_2 was reacted with L-Leu·OMe·HCl (**17b**, 0.27 g 1.5 mmol), Et_3N (0.23 mL, 0.17 g, 1.7 mmol), and EDCI·HCl (0.36 g, 1.7 mmol) to provide dipeptide analogue **18ab** as a pale yellow oil (0.43 g, 83%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, J = 6.0 Hz, 3H), 0.91 (d, J = 6.0 Hz, 3H), 1.64 (m, 3H), 3.71 (s, 3H), 4.16 (d, J = 15.4 Hz, 1H), 4.28 (d, J = 15.4 Hz, 1H), 4.66 (m, J = 7.7 Hz, 1H), 7.28 (m, 5H), 7.34 (d, J = 7.7 Hz, 1H), 10.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.7, 24.8, 31.6, 40.4, 51.1, 52.4, 116.4, 127.1, 128.7, 128.8, 135.6, 147.1, 154.8, 157.6, 172.9; IR (neat) 3349, 3100−2850, 1747 (br), 1677, 1681, 1640 cm^{-1}. Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.4; N, 8.09. Found: C, 62.24; H, 6.47; N, 8.27.

4-Carboxy-5-benzyl-4-oxazolin-2-onyl-L-tyrosine Methyl Ester (18ac). By the same procedure 4-carboxy-5-benzyl-4-oxazolin-2-one (**16a**, 0.33 g, 1.5 mmol) in CH_2Cl_2 (10 mL) was reacted with L-Tyr·OMe·HCl (**17c**, 0.35 g 1.5 mmol), Et_3N (0.23 mL, 0.17 g, 1.7 mmol), and EDCI·HCl (0.36 g, 1.7 mmol) to provide the dipeptide analogue **18ac** as a white solid (0.40 g, 67%): mp 99.5−101 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.40 (br s, 1H), 2.93 (dd, J = 13.9 and 6.7 Hz, 1H), 3.07 (dd, J = 13.9 and 5.1 Hz, 1H), 3.68 (s, 3H), 4.05 (s, 2H), 4.93 (m, 1H), 6.60 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 7.7 Hz, 1H), 7.21 (m, 5H), 9.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 36.6, 52.7, 53.7, 115.5, 116.2, 126.9, 127.2, 128.7, 128.8, 130.2, 135.3, 146.4, 154.5, 155.2, 157.8, 172.2; IR (KBr) 3344, 3100−2850, 1757, 1676, 1650, cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.68; H, 5.06; N, 7.19.

4-Carboxy-4-oxazolin-2-onyl-L-alanine Methyl Ester (18ba). By the same procedure 4-carboxy-4-oxazolin-2-one (**16b**, 0.19 g, 1.5 mmol) in CH_3CN (10 mL) was reacted with l-Ala·OMe·HCl (**17a**, 0.21 g 1.5 mmol), Et_3N (0.23 mL, 0.17 g, 1.7 mmol), and EDCI·HCl (0.36 g, 1.7 mmol) to provide the dipeptide analogue **18ba** as a white solid (0.10 g, 31%): mp broad and undefined; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.47 (d, J = 7.3 Hz, 3H), 3.78 (s, 3H), 4.71 (m, J = 7.3 Hz, 1H), 7.50 (s, 1H), 7.59 (d, J = 7.3 Hz, 1H), 9.86 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.0, 47.6, 52.1, 122.0, 131.1, 154.8, 156.5, 172.9; IR (KBr) 3500−2600, 1762 (br), 1672, 1610, cm^{-1}. Anal. Calcd for $C_8H_{10}N_2O_5$: C, 44.86; H, 4.71; N, 13.08. Found: C, 45.00; H, 4.83; N, 12.86.

4-Carboxy-5-isobutyl-4-oxazolin-2-onyl-L-alanine Methyl Ester (18da). By the same procedure 4-carboxy-5-isobutyl-4-oxazolin-2-one (**16d**, 0.28 g, 1.5 mmol) in 10 mL of CH_2Cl_2 was reacted with L-Ala·OMe·HCl (**17a**, 0.21 g 1.5 mmol), Et_3N (0.23 mL, 0.17 g, 1.7 mmol), and EDCI·HCl (0.36 g, 1.7 mmol) to provide the dipeptide analogue **18da** as a white solid (0.30 g, 74%): mp 96−97 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, J = 6.6 Hz, 6H), 1.52 (d, J = 7.3 Hz, 3H), 2.01 (m, 1H), 2.75 (dd, J = 7.2 and 4.1 Hz, 2H), 3.77 (s, 3H), 4.66 (m, J = 7.3 Hz, 1H), 7.38 (d, J = 7.0 Hz, 1H), 9.99 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.6, 22.2, 27.5, 34.3, 48.3, 52.7, 116.9, 148.1, 154.9, 157.7, 173.3; IR (KBr) 3353, 3069, 2955, 2870, 1762, 1705, 1678, 1650, cm^{-1}. Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.39; H, 6.60; N, 10.50.

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Supporting Information Available: ^{13}C NMR spectra of **14a, 14d, 15b, 16a, 16b**, and **16d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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