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Diastereoselective Construction of Tetrahydropyridine Fused Bicyclic Structures via Three-Component Domino Reaction

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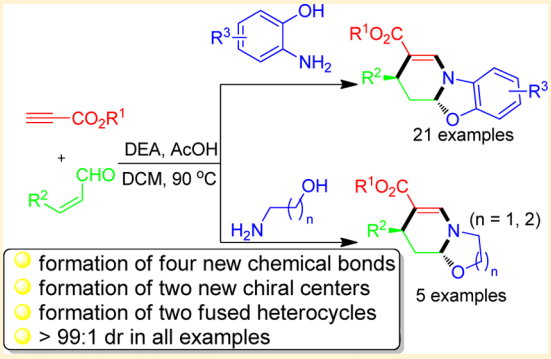
Supporting Information

ABSTRACT: The three-component reactions of enals, electron-deficient alkynes, and hydroxyl-functionalized primary amines for the highly diastereoselective construction of dihydro-3*H*-benzo[4,5]oxazolo-[3,2-*a*]pyridines, hexahydropyrido[2,1-*b*][1,3]oxazines, and tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines have been achieved. Domino formation of one C−C, two C−N, and one C−O bonds are furnished in these reactions. This bis-annulation protocol allows for the synthesis of fused heterocyclic products of high structural diversity with variation not only of appended fragments but also the ring size of the central backbone.



One major challenge in current organic chemistry is achieving the synthesis of architecturally complex and diverse molecules with minimum cost. In order to solve the problems of low efficiency, large amount production of organic wastes, as well as time consumption in traditional step-by-step synthesis, an efficient tactic known as domino (also known as cascade or tandem) reaction has rapidly emerged as a frontier concept. These reactions, according to the definition, complete the generation and/or cleavage of multiple chemical bonds in one pot via a one-step operation.[1] The inherent advantages of domino reaction-based synthesis lie in the unique step economics,[2] including the simplicity of operation, low comsuption of volatile chemicals, and short synthetic period. These advantages unsurprisingly make the cascade reaction one of the most frequently consulted strategies in the synthesis of numerous organic molecules, including natural products, fine chemicals, agrochemicals and materials, etc. As a particular class of examples of domino reaction, multicomponent reactions (MCRs) utilize three or more reactants to assemble a product containing structural contributions of all starting materials in the fashion of a one-step, one-pot operation. These reactions notably are even more powerful because they are able to reach extended molecular complexity and diversity more easily by employing simpler starting materials.[3]

The past several decades have witnessed an unprecedented bloom of multicomponent chemistry. MCRs have been now recognized and employed as one of the most powerful tools in orgnaic synthesis and numerous other related research areas. Following the extensive exploration and understanding of MCRs, their application in the synthesis of polycyclic structured molecules has attracted significant attention and become an issue of high contemporary interest since the molecules of fused, bridged, or spiro polycyclic structures are the common feature of numerous natural products. It is believed that synthesis of polycyclic molecules can significantly enhance the possibility of discovering lead compounds possessing improved biological activity or therapeutic function.[4] However, due to their inherent structural complexity, synthesis of these target molecules has been found as rather tough work. As an unconventional synthetic tactic making use of the flexible assembly of starting materials *in situ*, MCRs have been found amazingly efficient in the synthesis of polycyclic scaffolds. An exceptional example of the type has actually been known for almost 100 years ago in Robinson's landmark tropinone synthesis.[5] Although the superiority of MCRs-based polycycle synthesis has not been realized as a general feature for a long period, renewed interest has been attracted to this issue since the beginning of the new century following the occurrence of many excellent examples of MCRs-based polycyclic synthesis wherein at least two new rings are constructed via direct MCRs or simple post treatment on MCR adducts.[6]

Polycyclic molecules containing tetrahydropyridine fused structures such as 3,7,8,8a-tetrahydro-2*H*-oxazolo[3,2-*a*]-pyridines **4** and 2,3,4,8,9,9a-hexahydropyrido [2,1-*b*][1,3]-oxazines **5** are valuable scaffolds that occur in many natural products, biologically functional molecules, and precursors of peptidominetic compounds.[7] Not surprisingly, the research work towards the synthesis of these fused heterocyclic scaffolds has been a topic of considerable interest and longstanding effort. During the past decades, different methodologies targeting on tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines and hexahydropyrido[2,1-*b*][1,3]oxazines have been developed, including both step-by-step and one-pot cascade versions.[8]

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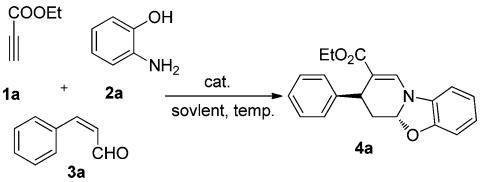
Inarguably, these decent approaches contributed enormously to the synthesis of these fused moieties, but on the other hand, the limits present with those known methods, such as the unfavorable chemical and time consumption in the step-by-step process, the unsatisfactory diastereoselectivity for those products containing two or more chiral centers, the restricted product diversity, etc., demonstrate that there is still abundant space to improve. Therefore, designing new sythetic methods possessing the advantages of high product diversity, excellent stereoselectivity, and facile operation using simple starting materials to access tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines and hexahydropyrido[2,1-*b*][1,3]oxazines is highly demanding. Herein, we report a multicomponent protocol for the synthesis of these products with excellent diastereoselectivity using readily available electron-deficient alkynes, enals, and hydroxy amines as staring materials and the cheapest AcOH as catalyst.

As an initial study, the reaction of ethyl propiolate **1a**, *o*-aminophenol **2a**, and cinnamaldehyde **3a** was tentatively run in the presentce of *p*-tolsulfonic acid (*p*-TSA), in 1,2-dichloroethane (DCE); however, no expected reaction was observed (entry 1, Table 1). Altering the acid catalyst to the basic

Table 1. Optimization of Reaction Conditions[a]



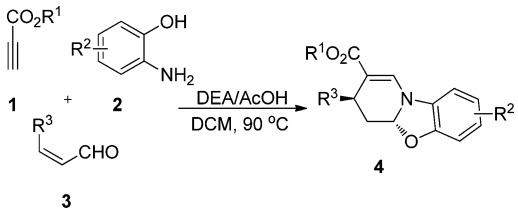
entry	catalyst (equiv)	solvent	yield (%)[b]
1	*p*-TSA	DCE	NR[c]
2	PPZ	DCE	trace
3	PPZ/*p*-TSA	DCE	48
4	PPZ/*p*-TSA	CH_3CN	33
5	PPZ/*p*-TSA	toluene	31
6	PPZ/*p*-TSA	EtOH	27
7	PPZ/AcOH	DCE	58
8	PPZ/$FeCl_3$	DCE	33
9[d]	PPZ/AcOH	DCE	61
10[e]	PPZ/AcOH	DCE	47
11[d]	morpholine/AcOH	DCE	54
12[d]	DEA/AcOH	DCE	71
13[d,f]	DEA/AcOH	DCE	87
14[d,g]	DEA/AcOH	DCE	56
15[d,f,h]	DEA/AcOH	DCE	67

[a]General conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), **3a** (0.3 mmol), secondary amine (0.12 mmol) and acid (0.24 mmol) in 2 mL solvent, stirred at 90 °C for 12 h. [b]Yield of isolated product. [c]NR = no reaction. [d]AcOH was 0.18 mmol. [e]AcOH was 0.12 mmol. [f]DEA was 0.06 mmol. [g]DEA was 0.03 mmol. [h]The temperature was 80 °C.

secondary amine piperazine (PPZ) did not give the target molecule either (entry 2, Table 1). Because we previously found that a secondary amine was able to activate electron-deficient alkynes and initiate cascade reactions together with an acid catalyst,[9] we then attempted to employ both PPZ and *p*-TSA in the reaction. As expected, the amine−acid bicatalytic system successfully promoted the three-component reaction to give **4a** (entry 3, Table 1). This result inspired us to conduct systematic optimization experiments. The original comparison of different solvents such as acetonitrile, toluene, and EtOH implied the superior function of DCE as the medium (entries 4−6, Table 1). Subsequently, a brief examination on different Brønsted and Lewis acids disclosed that AcOH was an even better acid catalyst (entries 7−10, Table 1). Interestingly, the variation on secondary amine species revealed that diethanolamine (DEA) was able to promote the reaction to give significantly higher yield of **4a** than other secondary amines (entries 11 and 12, Table 1). Moreover, further optimization proved that 20 mol % loading DEA was most proper (entries 13 and 14, Table 1). Finally, it was also found that lowering the temperature was not farvorable (entry 15, Table 1). Notably, the product provided by the optimized conditions possessed an excellent diastereoselectivity of >99:1 dr. Even in the ^{1}H NMR of crude product (direct evaporation of the extracted solution, see Supporting Information for the ^{1}H NMR spectrum of crude **4a**), only the diastereoisomer showing *trans* relative configuration on C2 and C4 was observed.

Following the efforts in optimization, we then turned to investigate the application scope of the catalytic method. First, different *o*-aminophenols **2** were selected to incorporate alkynes **1** and enals **3**. As outlined in Table 2, excellent tolerance was

Table 2. Three-Component Synthesis of Dihydro-3*H*-benzo[4,5]oxazolo[3,2-*a*]pyridines



R^1	R^2	R^3	product	yield (%)[a]
Et	H	Ph	**4a**	87
Et	H	2-$MeOC_6H_4$	**4b**	79
Et	H	3-MeC_6H_4	**4c**	80
Et	H	4-$MeOC_6H_4$	**4d**	82
Et	H	4-$NO_2C_6H_4$	**4e**	85
Et	4-Me	Ph	**4f**	75
Et	4-Me	2-$MeOC_6H_4$	**4g**	79
Et	4-Me	3-MeC_6H_4	**4h**	82
Et	5-Cl	Ph	**4i**	75
Et	5-Cl	3-MeC_6H_4	**4j**	79
Et	5-Cl	4-$MeOC_6H_4$	**4k**	74
Et	4-Me	Et	**4l**	64
Et	5-Cl	Et	**4m**	67
Me	H	2-ClC_6H_4	**4n**	76
Me	H	3-MeC_6H_4	**4o**	76
Me	H	4-$NO_2C_6H_4$	**4p**	82
Me	4-Me	2-ClC_6H_4	**4q**	85
Me	4-Me	2-$MeOC_6H_4$	**4r**	77
Me	5-Cl	4-$MeOC_6H_4$	**4s**	81
t-Bu	4-Me	H	**4t**	79
t-Bu	5-Cl	H	**4u**	80

[a]Yield of isolated product.

exhibited with this synthetic method, and various functional groups such as alkyl, alkoxyl, halide, and nitro were found compatible to provided the corresponding ring-fused products. The property of functional groups in alkyne and *o*-aminophenol components did not show evident impact on the results, and most fused heterocyclic products **4** were provided in good to excellent yields. However, for the enal component, an alkyl-substituted enal such as pent-2-enal gave relatively lower yield

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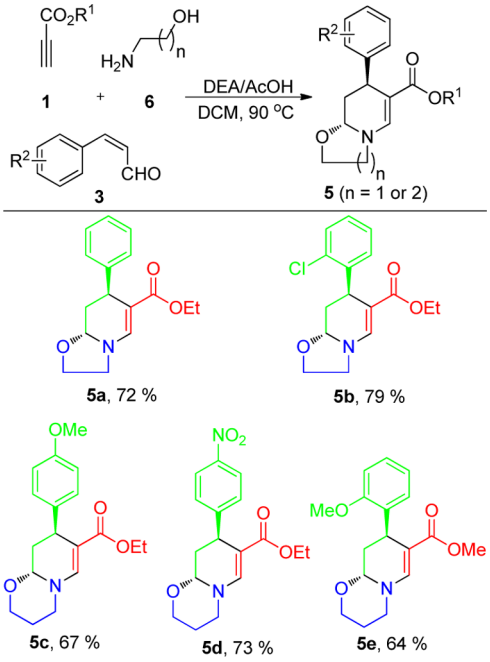
of corresponding products than those entries using aryl-functionalized and nonsubstituted enals (**4l** and **4m**, Table 2). Notably, all products **4**, according the their ^{1}H NMR results and the X-ray single crystal analysis of **4p**,[10] were obtained as *trans*- configured diastereoisomers.

Under the inspiration of the reactions using *o*-aminophenol, we evisioned that linear amino alcohols of type **6** would also undergo similar transformation to give fused heterocyclic products **5** with different ring sizes. Upon identical treatment, we delightfully found that the desired reactions ran smoothly to give corresponding **5** with generally good yields. According to the typical results given in Scheme 1, the substrates with

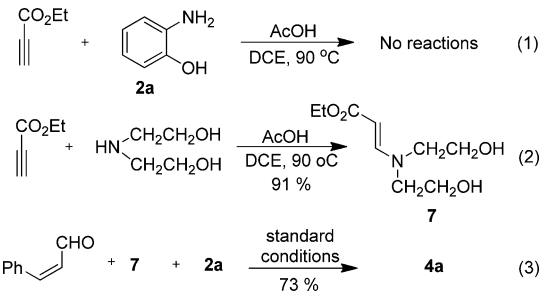
Scheme 1. Synthesis of Ring-Fused Products Using Linear Amino Alcohols



different chain length (n = 1 or 2) provided satisfactory results without showing evident influence from the chain. The tetrahydro-2*H*-oxazolo[3,2-*a*]pyridines and hexahydropyrido-[2,1-*b*][1,3]oxazines **5** were also produced with excellent diastereoselectivity, which proved the excellent tolerance of this protocol in retaining diastereoselectivity even using substrates of evident distinction. Considering the structural similarity of the linear hydroxyl amines **6** with DEA, we also conducted a control experiment for synthesizing **5a** in the absence of DEA to investigate the possibility of self-catalysis via the amine substrate. In this entry, the target product **5a** was obtained in 16% yield, which demonstrated that linear hyroxyl amines **6** were able to undergo this domino transformaton without DEA, but with remarkably lower yield than the entry employing a secondary amine catalyst.

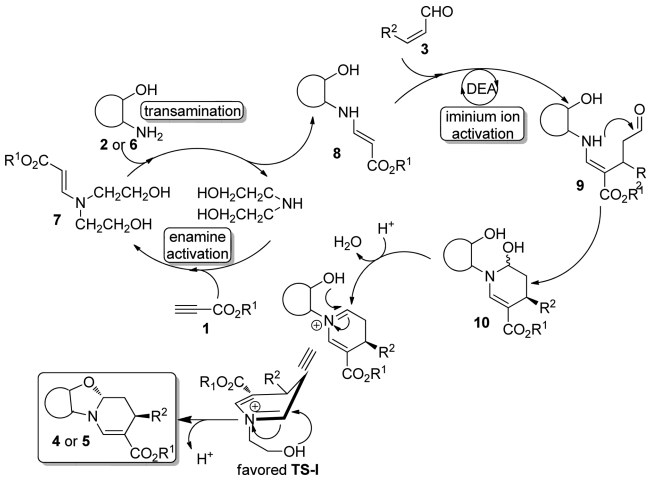
In order to probe the possible reaction mechanism, we then performed some control experiments that were expected to provide useful clues to elucidate the reaction process. First, in order to compare the reactivity of a primary amine and a secondary amine to that of an electron-deficient alkyne, we conducted the reactions of of *o*-aminophenol **2a** and DEA with ethyl propiolate, respectively. By running both entries under the standard catalytic conditions, it was found that no reaction took place with **2a** (eq 1, Scheme 2), while DEA gave electron-

Scheme 2. Control Experiment in Elucidating Reaction Mechanism



deficient enamine **7** with 91% yield (eq 2, Scheme 2). The results suggested that species **7** provided by the addition of the secondary amine to the electron-deficient alkyne may be a key intermediate of the reaction. Following this assumption, **7** was then directly subjected with cinnamaldehyde and *o*-amino-phenol **2a** to standard reaction conditions. As expected, this entry provided target product **4a** with good yield (eq 3, Scheme 2). The results from the control experiments, together with the previously known transamination of a *N*,*N*-disubstituted, electron-deficient enamine with a primary amine,[11] were able to help in deducing the general reaction mechanism. As displayed in Scheme 3, the mechanism of the reactions

Scheme 3. Postulated Mechanism for the Cascade Reaction Towards Fused Scaffolds



consisted of generally the main domino transformations of Michael addition-based enamine activation, transamination, iminium ion activation initiated Michael addition, aza-adolization, and intramolecular dehydrative annulation. First, the addition of secondary amine DEA to the alkynes led to generation of the reactive enamine intermediate **7**,[12] which was proposed to undergo transamination with amino alcohols to provide **8** *in situ* and release DEA. In the presence of the enal component, intermediates **8** were immediately captured by the iminium ion activated enal[13] to form intermediates **9** via Michael addition.

Subsequently, the intramolecular aza-adolization on **9** led to the production of hydroxylated tetrahydropyridine intermediates **10**. In the presence of a proton acid, the dehydration on **10** proceeded to iminium ion transition state **TS-I**, which quickly transformed to target products **4** or **5** through the addition of

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hydroxyl in the structure. The attack of hydroxyl from the reverse side of R^2 in farvored **TS-I** might be the key factor in determining the selective formation of the *trans*-C2 and C4 diastereoisomer.

Conclusion. In conclusion, we have established a three-component protocol for the disatereoselective synthesis of diverse tetrahydropyridine ring-fused heterocycles. The products bearing two newly formed chiral centers were obtained with generally >99:1dr, which demonstrates the excellent diastereoselectivity of the method. Therefore, the present work provides a valuable and economical new method for the synthesis of these highly useful small molecules.

EXPERIMENTAL SECTION

General Proceudure for the Synthesis of Tetrahydropyridine Fused Heterocycles 4 and 5. Alkyl propionate **1** (0.3 mmol), cinnamaldehyde **3** (0.3 mmol), amino alcohol **2** or **6** (0.3 mmol), DEA (0.06 mmol), and AcOH (0.18 mmol) were charged in a 25 mL round-bottom flask equipped with stirring bar. DCM (2 mL) was added, and the mixture was refluxed at 90 °C for 12 h (TLC) at open air with a condenser. After cooling down to room temperature, 5 mL of water was added, and the resulting mixture was extracted with ethyl acetate (3 × 8 mL). The organic phases were collected and dried with anhydrous Na_2SO_4. After filtration and removal of the solvent from the solution under reduced pressure, the residue was subjected to flash silica gel column chromatography to provide pure products with elution of mixed petroleum ether/ethyl acetate (v/v = 15:1).

2-Phenyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Enthyl Ester (4a). Yield: 84 mg, 87%; white solid; mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1 H), 7.28 (t, 2 H, J = 8.0 Hz), 7.17 (d, 3 H, J = 7.6 Hz), 6.90 (d, 1 H, J = 6.0 Hz), 6.86−6.78 (m, 2 H), 6.71 (d, 1 H, J = 7.2 Hz), 5.57 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.20 (d, 1 H, J = 4.0 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 2.49 (d, 1 H, J = 10.4 Hz), 2.12−2.05 (m, 1 H), 1.17 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.2, 144.0, 135.3, 132.2, 128.6, 127.5, 126.6, 122.9, 121.7, 109.3, 108.3, 103.1, 90.3, 59.8, 36.5, 33.1, 14.4; IR (KBr, cm^{-1}) 3061, 1972, 1680, 1599,1500, 1254; ESI-HRMS calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1438, found 322.1451.

2-(2-Methoxy-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4b). Yield: 83 mg, 79%; white solid; mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.18 (t, 1 H, J = 7.6 Hz), 6.96−6.78 (m, 6 H), 6.72 (d, 1H, J = 7.6 Hz), 5.56 (dd, 1 H, J = 3.6 Hz, 7.6 Hz), 4.58 (d, 1 H, J = 4.8 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 3.88 (s, 3 H), 2.59 (d, 1 H, J = 12.4 Hz), 2.04−1.97 (m, 1 H), 1.18 (t, 3 H, J = 7.2 Hz) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 156.4, 151.3, 135.6, 132.4, 131.7, 128.6, 127.7, 122.6, 121.6, 120.2, 110.6, 109.2, 108.1, 103.1, 91.1, 59.7, 55.4, 30.9, 30.5, 14.4; IR (KBr, cm^{-1}) 3063, 1972, 1680, 1592, 1498, 1256; ESI-HRMS calcd for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.1543, found 352.1555.

2-*m*-Tolyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4c). Yield: 80 mg, 80%; pale yellow solid; mp 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92 (s, 1 H), 7.13 (t, 1 H, J = 7.2 Hz), 6.97−6.88 (m, 4 H), 6.83−6.76 (m, 2 H), 6.69 (d, 1 H, J = 7.6 Hz), 5.57 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.13−4.06 (m, 3 H), 2.44 (d, 1 H, J = 10.8 Hz), 2.27 (s, 3 H), 2.08−2.01 (m, 1 H), 1.15 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.3, 144.0, 138.1, 135.2, 132.3, 128.4, 128.2, 127.4, 124.6, 122.8, 121.6, 109.3, 108.3, 103.3, 90.4, 59.8, 36.4, 33.1, 21.5, 14.4; IR (KBr, cm^{-1}) 3055, 1975, 1680, 1599,1503, 1254; ESI-HRMS calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1594, found 336.1600.

2-(4-Methoxy-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4d). Yield: 86 mg, 82%; white solid; mp128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.09 (d, 2 H, J = 7.6 Hz), 6.93 (d, 1 H, J = 7.2 Hz), 6.88−6.82 (m, 4 H), 6.74 (d, 1 H, J = 7.2 Hz), 5.60 (d, 1 H, J = 9.2 Hz), 4.15−4.10 (m, 3 H), 3.76 (s, 3 H), 2.46 (d, 1 H, J = 11.6 Hz), 2.11−2.04 (m, 1 H), 1.19 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 158.3, 151.3, 136.2, 135.0, 132.3, 128.4, 122.8, 121.6, 114.0, 109.3, 108.3, 103.5, 90.4, 59.8, 55.3, 35.6, 33.3, 14.4; IR (KBr, cm^{-1}) 3062, 1975, 1681, 1599, 1500, 1254; ESI-HRMS calcd for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.1543, found 352.1548.

2-(4-Nitro-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4e). Yield: 93 mg, 85%; yellow solid; mp 153−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ8.27 (d, 2 H, J = 8.0 Hz), 8.12 (s, 1 H), 7.48 (d, 2 H, J = 8.0 Hz), 7.09 (d, 1 H, J = 6.8 Hz), 7.02−6.96 (m, 2 H), 6.87 (d, 1 H, J = 7.2 Hz), 5.65 (d, 1 H, J = 9.2 Hz), 4.04 (d, 1 H, J = 2.8 Hz), 4.23 (q, 2 H, J = 7.2 Hz), 2.62 (d, 1 H, J = 12.4 Hz), 2.35−2.28 (m, 1 H), 1.30 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 151.7, 151.1, 146.8, 135.9, 131.7, 128.4, 123.9, 123.3, 121.9, 109.5, 108.5, 101.6, 89.6, 60.0, 36.5, 32.6, 14.4; IR (KBr, cm^{-1}) 3061, 1685, 1601, 1502, 1254; ESI-HRMS calcd for $C_{20}H_{19}N_2O_5$ $[M + H]^+$ 367.1288, found 367.1285.

6-Methyl-2-phenyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4f). Yield: 75 mg, 75%; white solid; mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.95 (s, 1 H), 7.30−7.24 (m, 2 H), 7.21−7.17 (m, 3 H), 6.78 (s, 1 H), 6.63 (s, 2 H), 5.58 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.20 (d, 1 H, J = 4.0 Hz), 4.12 (q, 2 H, J = 7.2 Hz), 2.49 (d, 1 H, J = 11.2 Hz), 2.30 (s, 3 H), 2.14−2.07 (m, 1 H), 1.19 (t, 1 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.2, 144.1, 135.3, 132.1, 131.4, 128.5, 127.5, 126.6, 122.9, 109.1, 108.7, 102.8, 90.4, 59.8, 36.5, 33.2, 21.2, 14.4; IR (KBr, cm^{-1}) 3046, 1669, 1599, 1500, 1244; ESI-HRMS calcd for $C_{21}H_{22}NO_3$ $[M + H]^+$ 336.1594, found 336.1593.

2-(2-Methoxy-phenyl)-6-methyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4g). Yield: 87 mg, 79%; colorless crystal; mp 140−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1 H), 7.17 (t, 1 H, J = 8.0 Hz), 6.94 (dd, 1 H, J = 1.6 Hz, 6.0 Hz), 6.89−6.81 (m, 2 H), 6.76 (s, 1 H), 6.60 (s, 2 H), 5.53 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.48 (d, 1 H, J = 4.0 Hz), 4.11 (q, 2 H, J = 7.2 Hz), 3.88 (s, 3 H), 2.57 (d, 1 H, J = 10.4 Hz), 2.28 (s, 3 H), 2.02−1.96 (m, 1 H), 1.18 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 156.4, 149.3, 135.5, 132.3, 131.8, 131.3, 128.6, 127.6, 122.8, 120.2, 110.6, 109.0, 108.7, 102.9, 91.2, 59.7, 55.3, 30.9, 30.5, 21.2, 14.5; IR (KBr, cm^{-1}) 3047, 1678, 1600,1500, 1244; ESI-HRMS calcd for $C_{22}H_{24}NO_4$ $[M + H]^+$ 366.1700, found 366.1706.

6-Methyl-2-*m*-tolyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4h). Yield: 86 mg, 82%; white solid; mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.17 (t, 1 H, J = 7.2 Hz), 7.01−6.95 (m, 3 H), 6.77 (s, 1 H), 6.62 (s, 2 H), 5.59 (dd, 1 H, J = 3.6 Hz, 7.2 Hz), 4.16−4.09 (m, 3 H), 2.47 (d, 1 H, J = 12.0 Hz), 4.60 (d, 6 H, J = 7.2 Hz), 2.11−2.04 (m, 1 H), 1.20 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 149.2, 144.1, 138.1, 135.2, 132.2, 131.4, 128.4, 128.2, 127.4, 124.6, 122.8, 109.1, 108.8, 103.0, 90.5, 59.8, 36.4, 33.1, 21.5, 21.2, 14.4; IR (KBr, cm^{-1}) 3054, 1681, 1599, 1500, 1254; ESI-HRMS calcd for $C_{22}H_{24}NO_3$ $[M + H]^+$ 350.1751, found 350.1749.

7-Chloro-2-phenyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4i). Yield: 80 mg, 75%; pale yellow solid; mp 154−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.39 (t, 2 H, J = 7.6 Hz), 7.31−7.25 (m, 3 H), 6.94−6.89 (m, 2 H), 6.82 (s, 1 H), 5.71 (dd, 1 H, J = 3.6 Hz, 7.2 Hz), 4.30 (d, 1 H, J = 4.0 Hz), 4.21 (q, 2 H, J = 7.2 Hz), 2.59 (d, 1 H, J = 14.0 Hz), 2.23−2.16 (m, 1 H), 1.27 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.0, 143.7, 134.9, 131.3, 128.7, 127.5, 127.4, 126.7, 121.4, 110.2, 108.4, 103.9, 91.4, 59.9, 36.3, 33.1, 14.4; IR (KBr, cm^{-1}) 3061, 1683, 1599, 1504, 1242; ESI-HRMS calcd for $C_{20}H_{19}ClNO_3$ $[M + H]^+$ 356.1048, found 356.1053.

7-Chloro-2-*m*-tolyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4j). Yield: 87 mg, 79%; yellow solid; mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1 H), 7.18 (t, 1 H, J = 7.6 Hz), 7.02 (d, 1 H, J = 7.2 Hz), 6.95 (d, 2 H, J = 8.4 Hz), 6.84−6.73 (m, 2 H), 6.73 (s, 1 H), 5.64 (dd, 1 H, J = 4.0 Hz, 6.4 Hz), 4.17−4.10 (m, 3 H), 2.49 (d, 1 H, J = 14.0 Hz), 2.32 (s, 3 H), 2.13−2.05 (m, 1 H), 1.19 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 152.0, 143.6, 138.2, 134.8, 131.4, 128.5, 128.2, 127.5, 127.4, 124.5, 121.4, 110.2, 108.4, 104.0, 91.4, 59.9, 36.2, 33.1, 21.5, 14.4; IR (KBr, cm^{-1}) 3052, 1677, 1597, 1500, 1254; ESI-HRMS calcd for $C_{21}H_{21}ClNO_3$ $[M + H]^+$ 370.1204, found 370.1192.

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7-Chloro-2-(4-Methoxy-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4k). Yield: 85 mg, 74%; white solid; mp 113−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.88 (s, 1 H), 7.08 (d, 2 H, J = 8.0 Hz), 6.84−6.80 (m, 4 H), 6.73 (s, 1 H), 5.63 (dd, 1 H, J = 3.2 Hz, 7.2 Hz), 4.16−4.09 (m, 3 H), 3.77 (s, 3 H), 2.47 (d, 1 H, J = 13.2 Hz), 2.11−2.04 (m, 1 H), 1.19 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 158.4, 152.0, 135.9, 134.7, 131.4, 128.4, 127.3, 121.5, 114.0, 110.2, 108.4, 104.2, 91.4, 59.9, 55.2, 35.5, 33.3, 14.4; IR (KBr, cm^{-1}) 3061, 1680, 1600,1502, 1233; ESI-HRMS calcd for $C_{21}H_{21}ClNO_4$ $[M + H]^+$ 386.1154, found 386.1147

2-Ethyl-6-methyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4l). Yield: 55 mg, 64%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 6.70 (s, 1 H), 6.64 (dd, 2 H, J = 8.0 Hz, 6.0 Hz), 5.79 (dd, 1 H, J = 3.6 Hz, 7.2 Hz), 4.20−4.16 (m, 2 H), 2.80−2.76 (m, 1 H), 2.45 (d, 1 H, J = 12.8 Hz), 2.28 (s, 3 H), 1.75−1.68 (m, 2 H), 1.32−1.22 (m, 4 H), 0.99 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 149.1, 133.6, 132.4, 131.4, 122.6, 109.0, 108.6, 105.9, 90.6, 59.6, 32.4, 28.1, 28.0, 21.1, 14.5, 11.7; IR (KBr, cm^{-1}) 3053, 2975, 1680, 1598, 1503, 1238; ESI-HRMS calcd for $C_{17}H_{22}NO_3$ $[M + H]^+$ 288.1594, found 288.1599.

7-Chloro-2-ethyl-1,9a-dihydro-2H-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4m). Yield: 62 mg, 67%; brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1 H), 6.82 (d, 1 H, J = 10.0 Hz), 6.75 (d, 2 H, J = 8.4 Hz), 5.85 (dd, 1 H, J = 3.6 Hz, 7.2 Hz), 4.24−4.18 (m, 2 H), 2.81−2.77 (m, 1 H), 2.46 (d, 1 H, J = 12.8 Hz), 1.77−1.68 (m, 2 H), 1.32−1.21 (m, 4 H), 0,99 (t, 3 H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 151.9, 133.3, 131.5, 127.2, 121.3, 110.1, 108.3, 106.9, 91.5, 59.8, 32.3, 28.0, 18.4, 14.5, 11.6; IR (KBr, cm^{-1}) 3055, 2975, 1680, 1598, 1503, 1238;ESI-HRMS calcd for $C_{16}H_{19}ClNO_3$ $[M + H]^+$ 308.1048, found 308.1043.

2-(2-Chloro-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Methyl Ester (4n). Yield: 78 mg, 76%; white solid; mp 140−143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.40 (t, 1 H, J = 4.0 Hz), 7.17−7.15 (m, 2 H), 7.06 (d, 1 H, J = 4.4 Hz), 6.95 (d, 1 H, J = 6.8 Hz), 6.90−6.83 (m, 2 H), 6.76 (d, 1 H, J = 7.2 Hz), 5.56 (dd, 1 H, J = 3.2 Hz, 7.6 Hz), 4.61 (d, 1 H, J = 4.8 Hz), 3.64 (s, 3 H), 2.63 (d, 1 H, J = 12.4 Hz), 2.12−2.04 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 151.2, 140.7, 136.1, 133.1, 131.2, 129.1, 128.1, 126.6, 123.1, 121.7, 109.5, 108.4, 102.0, 90.4, 51.3, 33.7, 30.5; IR (KBr, cm^{-1}) 3050, 1683, 1599, 1504, 1255; ESI-HRMS calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.0891, found 342.0883.

2-*m*-Tolyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Methyl Ester (4o). Yield: 73 mg, 76%; white solid; mp 147−148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.13 (t, 1 H, J = 7.2 Hz), 6.97−6.88 (m, 4 H), 6.84−6.76 (m, 2 H), 6.69 (d, 1 H, J = 7.2 Hz), 5.55 (d, 1 H, J = 10.0 Hz), 4.12 (d, 1 H, J = 3.2 Hz), 3.61 (s, 3 H), 2.43 (d, 1 H, J = 12.0 Hz), 2.27 (s, 3 H), 2.07−1.98 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 151.3, 143.9, 138.2, 135.5, 132.2, 128.4, 128.2, 127.5, 124.6, 122.9, 121.7, 109.3, 108.3, 102.8, 90.3, 51.3, 36.4, 33.2, 21.5; IR (KBr, cm^{-1}) 3063, 1681, 1599,1500, 1254; ESI-HRMS calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1438, found 322.1436.

2-(4-Nitro-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Methyl Ester (4p). Yield: 87 mg, 82%; red solid; mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 2 H, J = 8.4 Hz), 8.03 (s, 1 H), 7.38 (d, 2 H, J = 8.8 Hz), 6.98 (d, 1 H, J = 6.8 Hz), 6.93−6.86 (m, 2 H), 6.77 (d, 1 H, J = 8.4 Hz), 5.54 (dd, 1 H, J = 3.6 Hz, 6.8 Hz), 4.30 (d, 1 H, J = 4.4 Hz), 3.67 (s, 3 H), 2.52 (d, 1 H, J = 12.8 Hz), 2.25−2.18 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 151.6, 151.1, 146.9, 136.1, 131.7, 128.5, 123.9, 123.4, 121.9, 109.5, 108.6, 101.3, 89.6, 51.4, 36.4, 32.6; IR (KBr, cm^{-1}) 3056, 1687, 1599, 1505, 1244; ESI-HRMS calcd for $C_{19}H_{17}N_2O_5$ $[M + H]^+$ 353.1132, found 353.1138

2-(2-Chloro-phenyl)-6-methyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Ethyl Ester (4q). Yield: 91 mg, 85%; pale yellow solid; mp 190−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.39 (t, 1 H, J = 4.8 Hz), 7.14 (dd, 2 H, J = 3.6 Hz, 2.0 Hz), 7.06−7.03 (m, 1 H), 6.78 (s, 1 H), 6.63 (s, 2 H), 5.52 (dd, 1 H, J = 3.6 Hz, 7.2 Hz), 4.59 (d, 1 H, J = 4.4 Hz), 3.64 (s, 3 H), 2.60 (d, 1 H, J = 11.2 Hz), 2.29 (s, 3 H), 2.09−2.03 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 149.2, 140.8, 136.1, 133.1, 131.9, 131.5, 130.1, 129.2, 128.0, 126.7, 123.1, 109.2, 108.9, 101.8, 90.5, 51.3, 33.7, 30.6, 21.2; IR (KBr, cm^{-1}) 3050, 1681, 1599, 1500, 1254; ESI-HRMS calcd for $C_{20}H_{19}ClNO_3$ $[M + H]^+$ 356.1048, found 356.1040.

2-(2-Methoxy-phenyl)-6-methyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Methyl Ester (4r). Yield: 81 mg, 77%; white solid; mp191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.19 (t, 1 H, J = 8.0 Hz), 6.95−6.82 (m, 3 H), 6.77 (s, 1 H), 6.62 (s, 2 H), 5.52 (dd, 1 H, J = 3.2 Hz, 7.6 Hz), 4.55 (d, 1 H, J = 5.2 Hz), 3.90 (s, 3 H), 3.65 (s, 3 H), 2.58 (d, 1 H, J = 12.4 Hz), 2.30 (s, 3 H), 2.04−1.96 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 156.4, 149.3, 135.8, 132.2, 131.6, 131.3, 128.6, 127.8, 122.8, 120.2, 110.6, 109.1, 108.7, 102.4, 91.1, 55.4, 51.2, 30.8, 30.5, 21.1; IR (KBr, cm^{-1}) 3061, 1682, 1599, 1500, 1234; ESI-HRMS calcd for $C_{21}H_{22}NO_4$ $[M + H]^+$ 352.1543, found 352.1548.

7-Chloro-2-(4-methoxy-phenyl)-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid Methyl Ester (4s). Yield: 90 mg, 81%; pale yellow solid; mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.08 (d, 2 H, J = 8.8 Hz), 6.84−6.80 (m, 4 H), 6.73 (s, 1 H), 5.61 (dd, 1 H, J = 4.0, 6.8 Hz), 4.15 (d, 1 H, J = 3.6 Hz), 3.77 (s, 3 H), 3.66 (s, 3 H), 2.47 (d, 1 H, J = 12.4 Hz), 2.10−2.03 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 158.4, 152.0, 135.6, 135.0, 131.3, 128.4, 127.5, 121.4, 114.1, 110.2, 108.4, 103.8, 91.4, 55.2, 51.3, 35.5, 33.3; IR (KBr, cm^{-1}) 3051, 1672, 1597, 1503, 1254; ESI-HRMS calcd for $C_{20}H_{19}ClNO_4$ $[M + H]^+$ 372.0997, found 372.0985.

6-Methyl-2-phenyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid *tert*-Butyl Ester (4t). Yield: 86 mg, 79%; pale yellow solid; mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.28 (t, 2 H, J = 7.2 Hz), 7.20−7.16 (m, 3 H), 6.72 (s,. One H), 6.60 (s, 2 H), 5.57 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.13 (d, 1 H, J = 4.0 Hz), 2.46 (d, 1 H, J = 11.2 Hz), 2.28 (s, 3 H), 2.13−2.06 (m, 1 H), 1,36 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 149.2, 144.6, 134.5, 132.4, 131.4, 128.5, 127.5, 126.4, 122.6, 108.9, 108.7, 104.5, 90.4, 79.4, 36.8, 33.3, 28.3, 21.2; IR (KBr, cm^{-1}) 3033, 2975, 1692, 1611, 1373; ESI-HRMS calcd for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1907, found 364.1896.

7-Chloro-2-phenyl-1,9a-dihydro-2*H*-9-oxa-4a-aza-fluorene-3-carboxylic Acid *tert*-Butyl Ester (4u). Yield: 92 mg, 80%; pale yellow solid; mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1 H), 7.29 (t, 2 H, J = 7.6 Hz), 7.22−7.15 (m, 3 H), 6.83 (d, 1 H, J = 10.0 Hz), 6.77 (d, 1 H, J = 8.0 Hz), 6.71 (d, 1 H, J = 1.6 Hz), 5.62 (dd, 1 H, J = 4.0 Hz, 6.8 Hz), 4.14 (d, 1 H, J = 5.6 Hz), 2.48 (d, 1 H, J = 12.0 Hz), 2.14−2.07 (m, 1 H), 1.35 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 151.9, 144.1, 134.2, 131.4, 128.5, 127.4, 127.1, 126.6, 121.4, 110.1, 108.1, 105.6, 91.3, 79.7, 36.6, 33.3,28.2; IR (KBr, cm^{-1}) 3030, 2975, 1692, 1610, 1371; ESI-HRMS calcd for $C_{22}H_{23}ClNO_3$ $[M + H]^+$ 384.1361, found 384.1349.

7-Phenyl-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]pyridine-6-carboxylic Acid Ethyl Ester (5a). Yield: 59 mg, 72%; pale yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1 H), 7.26 (t, 2 H, J = 7.6 Hz), 7.16 (d, 3 H, J = 8.4 Hz), 4.46 (dd, 1 H, J = 4.0 Hz, 6.0 Hz), 4.13−4.05 (m, 4 H), 3.84 (dd, 1 H, J = 8.4 Hz, 7.2 Hz), 3.65−3.60 (m, 1 H), 3.46 (dd, 1 H, J = 8.4, 7.2 Hz), 2.30 (d, 1 H, J = 13.6 Hz), 1.69−1.62 (m, 1 H), 1.17 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.5, 142.5, 128.4, 127.4, 126.2, 99.5, 84.5, 65.3, 59.2, 48.6, 36.3, 33.7, 14.6; IR (KBr, cm^{-1}) 3054, 2976, 1684, 1603, 1282; ESI-HRMS calcd for $C_{16}H_{20}NO_3$ $[M + H]^+$ 274.1438, found 274.1439.

7-(2-Chloro-phenyl)-2,3,8,8a-tetrahydro-7*H*-oxazolo[3,2-*a*]-pyridine-6-carboxylic Acid Ethyl Ester (5b). Yield: 73 mg, 79%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1 H), 7.35 (t, 1 H, J = 4.0 Hz), 7.12 (t, 2 H, J = 4.4 Hz), 7.03 (t, 1 H, J = 4.4 Hz), 4.50 (d, 1 H, J = 4.0 Hz), 4.33 (dd, 1 H, J = 4.0 Hz, 6.4 Hz), 4.14−4.09 (m, 1 H), 4.05 (q, 2 H, J = 7.2 Hz),3.89−3.83 (m, 1 H), 3.67−3.62 (m, 1 H), 3.50−3.46 (m, 1 H), 2.40 (d, 1 H, J = 10.8 Hz), 1.66−1.59 (m, 1 H), 1.15 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.0, 141.3, 133.3, 129.8, 129.0, 127.6, 126.4, 98.9, 84.6, 65.3, 59.2, 48.4, 33.7, 31.1, 14.4; IR (KBr, cm^{-1}) 3055, 2975, 1689, 1609, 1286; ESI-HRMS calcd for $C_{16}H_{19}ClNO_3$ $[M + H]^+$ 308.1048, found 308.1053.

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8-(4-Methoxy-phenyl)-3,4,9,9a-tetrahydro-2*H*,8*H*-pyrido-[2,1-*b*][1,3]oxazine-7-carboxylic Acid Ethyl Ester (5c). Yield: 64 mg, 67%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1 H), 7.08 (d, 2 H, J = 8.4 Hz), 6.82 (d, 2 H, J = 8.8 Hz), 4.23 (dd, 1 H, J = 4.0 Hz, 4.8 Hz), 4.06−4.00 (m, 3 H), 3.91−3.89 (m, 1 H), 3.77 (s, 3 H), 3.59−3.42 (m, 2 H), 3.33−3.26 (m, 1 H), 2.17−1.96 (m, 3 H), 1.52 (d, 1 H, J = 12.8 Hz), 1.11 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 157.9, 145.3, 137.9, 128.2, 113.1, 100.0, 81.9, 66.9, 59.1, 55.2, 49.9, 36.5, 35.2, 25.6, 14.4; IR (KBr, cm^{-1}) 3053, 2975, 1687, 1605, 1286; ESI-HRMS calcd for $C_{18}H_{24}NO_4$ $[M + H]^+$ 318.1700, found 318.1700.

8-(4-Nitro-phenyl)-3,4,9,9a-tetrahydro-2*H*,8*H*-pyrido[2,1-*b*]-[1,3]oxazine-7-carboxylic Acid Ethyl Ester (5d). Yield: 73 mg, 73%; pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 2 H, J = 8.8 Hz), 7.42 (s, 1 H), 7.35 (d, 2 H, J = 8.4 Hz), 4.27 (dd, 1 H, J = 4.0 Hz, 4.4 Hz), 4.09−3.97 (m, 4 H), 3.63−3.53 (m, 2 H), 3.42−3.35(m, 1 H), 2.26−2.19 (m, 1 H), 2.06−2.00 (m, 2 H), 1.57 (d, 1 H, J = 13.2 Hz), 1.09 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ167.3, 153.9, 146.5, 145.9, 128.2, 123.6, 99.0, 81.5, 67.1, 59.3, 50.3, 36.0, 35.9, 25.6, 14.3; IR (KBr, cm^{-1}) 3053, 2975, 1686, 1603, 1283; ESI-HRMS calcd for $C_{17}H_{21}N_2O_5$ $[M + H]^+$: 333.1445, found 333.1446.

8-(2-Methoxy-phenyl)-3,4,9,9a-tetrahydro-2*H*,8*H*-pyrido-[2,1-*b*][1,3]oxazine-7-carboxylic Acid Methyl Ester (5e). Yield: 58 mg, 64%; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1 H), 7.16 (t, 1 H, J = 8.4 Hz), 6.95 (d, 1 H, J = 4.8 Hz), 6.84 (d, 2 H, J = 8.8 Hz), 4.30 (q, 1 H, J = 2.8 Hz), 4.12 (dd, 1 H, J = 4.0 Hz, 6.0 Hz), 4.00 (d, 1 H, J = 16 Hz), 3.84 (s, 3 H), 3.55 (s, 3 H), 3.49−3.42 (m, 2 H), 3.29−3.22 (m, 1 H), 2.20−2.15 (m, 1 H), 2.08−1.95 (m, 2 H), 1.50 (d, 1 H, J = 14.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 156.7, 146.2, 133.3, 128.0, 127.2, 120.0, 110.5, 98.8, 82.4, 66.8, 55.3, 50.7, 49.6, 33.9, 29.9, 25.5; IR (KBr, cm^{-1}) 3053, 2975, 1684, 1603, 1284; ESI-HRMS calcd for $C_{17}H_{22}NO_4$ $[M + H]^+$ 304.1543, found 304.1550.

(*E*)-Ethyl 3-(bis(2-hydroxyethyl)amino)acrylate (7).[12] Yield: 55 mg, 91%; yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6), 7.40 (d, 1 H, J = 13.2 Hz), 4.77 (t, 2 H, J = 5.2 Hz), 4.52 (d, 1 H, J = 13.2 Hz), 3.99 (q, 2 H, J = 7.2 Hz), 3.53 (t, 4 H, J = 5.2 Hz), 3.27 (brs, 4 H), 1.16 (t, 3 H, J = 7.2 Hz).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental information, copies of ^{1}H and ^{13}C NMR spectra of all products, and cif file containing crystallographic data of **4p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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