Note

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Construction of 1,3-Oxazolidines through a Three-component [3 + 2] Cycloaddition of Tetrahydroisoquinolines, Aldehydes and Ethyl Ketomalonate

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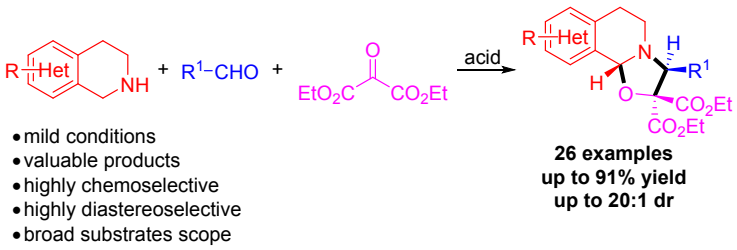


Abstract

A chemoselective and diastereoselective synthesis of fused oxazolidines was achieved by a three-component cascade reaction of tetrahydroisoquinolines (THIQs), α,β-unsaturated aldehydes and diethyl 2-oxomalonate. Probably due to the reactivity difference between the aldehyde and the ketone, the reaction proceeded through the condensation of THIQs with α,β-unsaturated aldehydes and 1,3-dipolar cycloaddition of the generated azomethine ylide intermediate with 2-oxomalonate. The key features are easily available starting materials, mild reaction conditions, broad substrate scope and high chemo- and diastereoselectivity.

1,3-Oxazolidines are a unique class of five-membered heterocycles,[1] distributed widely in natural products and synthetic complex compounds which are utilized as drugs, dyes and agrochemicals[2] and useful as synthetic intermediates, auxiliaries, ligands and catalysts for organic transformations.[3] Therefore, extensive effort has been devoted to the development of efficient and versatile synthetic

methods for their construction.[4] Among these methodologies, the 1,3-dipolar cycloaddition reaction of azomethine ylides with carbonyl dipolarophiles has emerged as one of the most powerful and atom economy strategies.[5] Azomethine ylides **1** are usually generated *in situ* from amines, imines, aziridines and silylmethylamines, and most frequently prepared *via* the direct condensation of amines with aldehydes (Figure 1A).[6] Of the carbonyl dipolarophiles **2**, aldehydes and ketones are most well studied (Figure 1A). Interestingly, aldehydes not only serve as the carbonyl dipolarophiles in the cycloaddition but also act as the precursors for the generation of azomethine ylides (Figure 1B). For example, Grigg and co-workers studied the reaction of two equivalents of pyridine-2-carbaldehyde with 1,2,3,4-tetrahydroisoquinoline (THIQ) in warm acetonitrile. One equivalent of pyridine-2-carbaldehyde reacted with THIQ to give the azomethine ylide, and the subsequent cycloaddition with another equivalent of the aldehyde afforded the dipyridyl oxazolo[2,3-*a*]tetrahydroisoquinoline.[7] Recently, Houk and Seidel,[8] Mantelingu and Rangappa[9] also described the similar results respectively. However, when the two different carbonyl compounds such as an aldehyde and a ketone exist simultaneously in the reaction system, the problem of how to improve the chemoselectivity of the reaction is still challenging and has rarely been addressed (Figure 1C). Therefore, since we are interested in *in situ* generated azomethine ylide followed by the intermolecular [3 + 2]-cycloaddition reaction for the synthesis of heterocyclic compounds,[10] we describe herein an efficient three-component cascade reaction of tetrahydroisoquinolines, aldehydes and ketone to access 1,3-oxazolidine compounds diastereoselectively and chemoselectively under mild conditions.

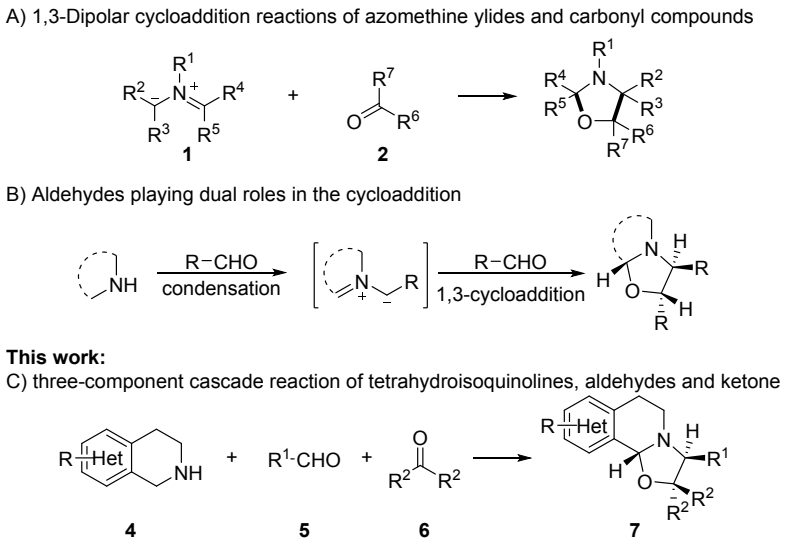
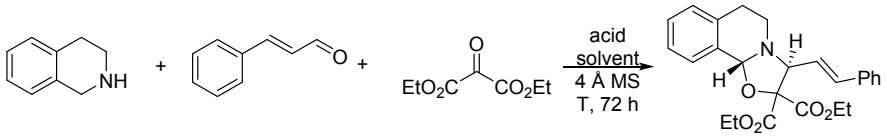


Figure 1. 1,3-Dipolar cycloaddition reactions of azomethine ylides and carbonyl compounds to give 1,3-oxazolidines

Using THIQ **4a**, cinnamaldehyde **5a** and diethyl 2-oxomalonate **6** as model substrates, optimization of the reaction conditions using acid as the catalyst was firstly carried out in the presence of 4 Å MS in THF at rt for 72 h (entries 1–6, Table 1). Strong acid such as CF_3CO_2H failed to render the desired cascade reaction (entry 1). Fortunately, benzoic acid and derivatives facilitate the formation of azomethine ylide intermediate *via* the condensation of THIQ **4a** and cinnamaldehyde **5a**, giving the 1,3-oxazolidine **7aa** in good yields (entries 2-5). Among them, 2,6-$(CF_3)_2$-$PhCO_2H$ turned out to be the best of choice, delivering the product **7aa** in 78% yield with 16:1 dr (entry 5). The relative configuration of the major diastereomer was confirmed by single X-ray crystal studies.[11] Lewis acid $Cu(OAc)_2$ could also afford the product but was quite less effective (entry 6). The solvents screened included toluene, EtOAc, DCE,1,4-dioxane and THF, among which THF was found to be the preferred solvent (entries 5, 7–10). A lower amount of the desired product was obtained when the reaction was conducted at 0 and 50 ºC, and room temperature was found to be the most suitable operation temperature (entries 5 vs 11 and 12).

Table 1. Optimization of the reaction conditions[a]



4a **5a** **6** **7aa**

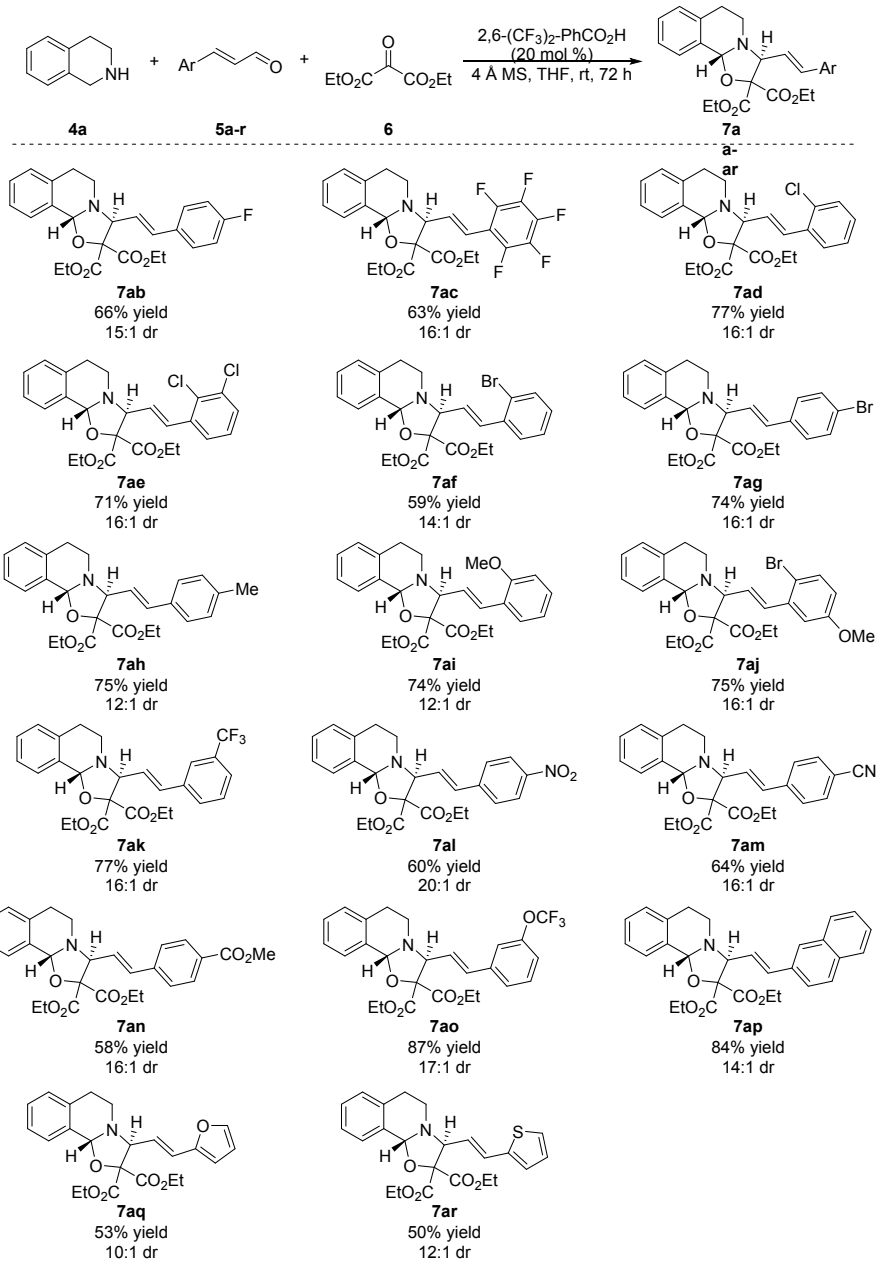
entry	acid	solvent	T (ºC)	yield (%)[b]
1	CF_3CO_2H	THF	rt	NR
2	$PhCO_2H$	THF	rt	63
3	2,6-$(NO_2)_2$-$PhCO_2H$	THF	rt	71
4	2,6-F_2-$PhCO_2H$	THF	rt	70
5[b]	2,6-$(CF_3)_2$-$PhCO_2H$	THF	rt	78
6	$Cu(OAc)_2$	THF	rt	52
7	2,6-$(CF_3)_2$-$PhCO_2H$	toluene	rt	56
8	2,6-$(CF_3)_2$-$PhCO_2H$	EtOAc	rt	64
9	2,6-$(CF_3)_2$-$PhCO_2H$	DCE	rt	74
10	2,6-$(CF_3)_2$-$PhCO_2H$	1,4-dioxane	rt	73
11	2,6-$(CF_3)_2$-$PhCO_2H$	THF	0	66
12	2,6-$(CF_3)_2$-$PhCO_2H$	THF	50	70

[a]Unless indicated otherwise, the reaction of **4a** (0.4 mmol), **5a** (0.2 mmol), **6** (0.22 mmol), acid (0.04 mmol) and 4 Å MS (150 mg) was carried out in solvent (2.0 mL) at rt for 72 h. NR = No Reaction. [b]Dr value was determined by ^{1}H NMR analysis of the product.

With the optimal conditions in hand, the generality of α,β-unsaturated aldehydes **5** was then investigated (Scheme 1). A variety of substituents on the phenyl ring of the cinnamaldehyde, including halogens (F, Cl, Br), electron-donating (Me, MeO) and -withdrawing (CF_3, NO_2, CN,

CO_2Me) groups, had no substantial differences in the diastereoselectivities (all > 10:1) and afforded the corresponding products **7aa-an** in moderate yields. An interesting observation was made in the case of a trifluoromethoxy group (F_3CO) located at the meta-position (**5j**), which lead to high yield (87%) and diastereoselectivity (17:1) of the corresponding product **7ao**. Moreover, β-(2-naphthyl) substituted enal substrate gave the product **7ap** in 84% yield. Notably, the thiophene and furan ring of substrates were well tolerated and delivered the products **7aq** and **7ar** in moderate yields.

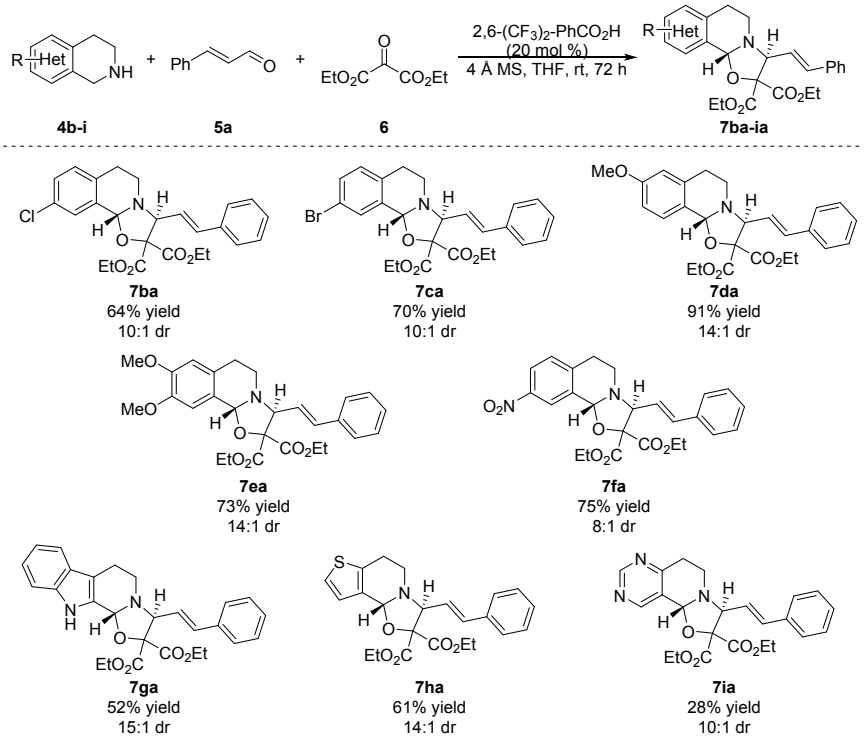
Scheme 1. Scope of α,β-Unsaturated Aldehydes[a]



[a]Reaction conditions: the reaction of **4a** (0.4 mmol), **5** (0.2 mmol), **6** (0.22 mmol), 2,6-$(CF_3)_2$-$PhCO_2H$ (0.04 mmol) and 4 Å MS (150 mg) was carried out in THF (2.0 mL) at rt for 72 h.

A variety of substituents on the phenyl moiety of the 1,2,3,4-tetrahydroisoquinoline were also well tolerated (Scheme 2). Regardless of the position and electronic character of the substituents, reactions proceeded smoothly under the optimal conditions, furnishing 1,3-oxazolidines **7ba-ia** in moderate to high yields. The scope of the reaction was successfully extended to other heteroaromatic ring fused piperidine substrates such as tetrahydro-β-carboline **4g**, tetrahydrothieno[3,2-c]pyridine **4h** and tetrahydropyrido[4,3-d]pyrimidine **4i**, which also underwent the title reaction under equally mild conditions to afford the corresponding products **7ga-ia** smoothly albeit in relatively lower yields (Scheme 2).

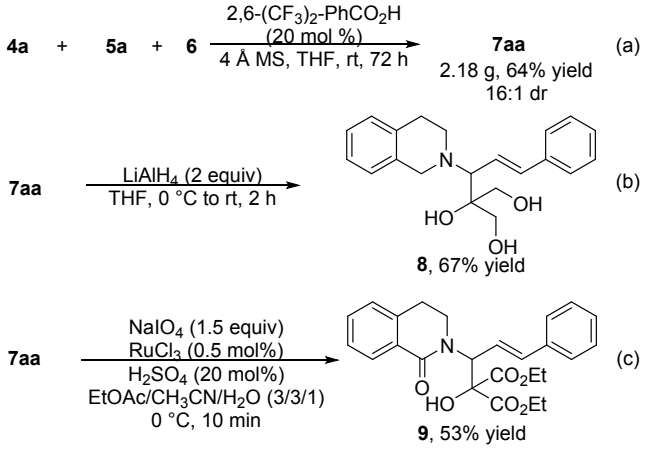
Scheme 2. Scope of Tetrahydroisoquinolines and Arene fused Piperidine[a]



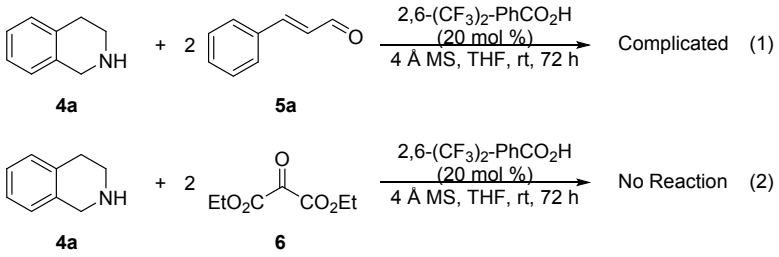
[a]Reaction conditions: the reaction of **4b-i** (0.4 mmol), **5a** (0.2 mmol), **6** (0.22 mmol), 2,6-$(CF_3)_2$-$PhCO_2H$ (0.04 mmol) and 4 Å MS (150 mg) was carried out in THF (2.0 mL) at rt for 72 h.

As indicated in Scheme 3a, a gram-scale reaction of model substrates was conducted. A slightly lower but still satisfactory yield of **7aa** was obtained (vs entry 5, Table 1). Reduction of **7aa** *via* $LiAlH_4$ was then carried out. The oxazolidine ring was opened and both of the ester groups were reduced to give the triol **8**. Under oxidative conditions, the oxazolidine ring could also be opened to form the dihydroisoquinolinone **9** in moderate yield.

Scheme 3 Gram-scale synthesis and synthetic transformation

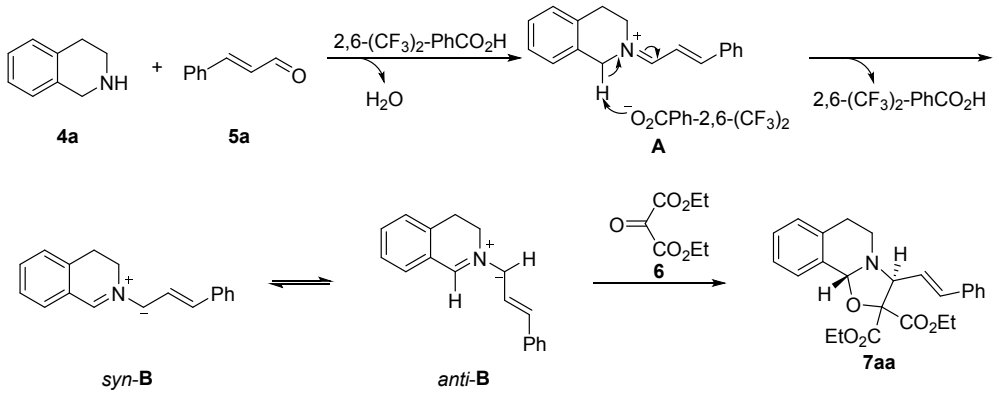


To explore the reaction mechanism, control experiments were performed. Under the standard conditions, the reaction of THIQ **4a** and two equivalents of cinnamaldehyde **5a** was conducted. Although the starting materials were consumed, the reaction was complicated and no desired 1,3-oxazolidine product was obtained (eq 1). Moreover, THIQ **4a** and two equivalents of diethyl 2-oxomalonate **6** were unreactive under the identical conditions (eq 2).



On the basis of the experimental observations, we proposed that the reaction is highly chemoselective probably due to the reactivity difference between the aldehyde and the ketone (Scheme 4). When an aldehyde (cinnamaldehyde **5a**) and a ketone (diethyl 2-oxomalonate **6**) exist simultaneously in the reaction system, THIQ reacted only with cinnamaldehyde **5a** firstly to give the iminium salt **A** with the assistance of 2,6-$(CF_3)_2$-$PhCO_2H$. Then α-deprotonation of the intermediate iminium ion **A** afford the azomethine ylide **B** by the carboxylate anion. Cases involving azomethine ylide formation from aldehydes and secondary amines showed that anti-dipole (anti-**B**) was formed at a faster rate and was thermodynamically more stable than syn-dipole (syn-**B**).[7a] Therefore, finally, only diethyl 2-oxomalonate **6** participated in the 1,3-dipolar cycloaddition with azomethine ylide anti-**B** to diastereoselectively generate the corresponding 1,3-oxazolidine **7aa** in good yield.

Scheme 4. Proposed Mechanism



In summary, we have developed an efficient and highly diastereoselective three-component one-pot [3 + 2] cycloaddition of 1,2,3,4-tetrahydroisoquinolines, α,β-unsaturated aldehydes and diethyl 2-oxomalonate, which afforded a wide range of useful 1,3-oxazolidine in moderate yields. Easily available starting materials, mild reaction conditions and broad substrate scope are the attractive features of this methodology. Importantly, the reaction is highly chemoselective propably due to the reactivity difference between the aldehyde and the ketone. Moreover, a gram-scale experiment and some chemical transformations were conducted to highlight the synthetic utility of this approach.

Experimental Section

General Methods. NMR spectra were recorded on Bruker-600 MHz or Brucker-400 MHz spectrometer. The high resolution mass spectra were recorded on a Thermo LTQ Orbitrap XL (ESI+). Column chromatography was performed on silica gel or basic alumina (200-300 mesh) eluting with ethyl acetate and petroleum ether. TLC was performed on glass-backed silica plates. All chemicals were used without purification as commercially available unless otherwise noted.

General Procedure for the Synthesis of 1,3-oxazolidine compounds. Tetrahydroisoquinoline **4** (0.4 mmol), aldehydes **5** (0.2 mmol) and diethyl ketomalonate **6** (0.22 mmol, 38 mg) were added in an oven-dried Schlenk tube. Then the catalyst 2,6-$(CF_3)_2$-$PhCO_2H$ (0.04 mmol, 10 mg) and 4 Å MS (150 mg) were added and the reaction was carried out in solvent THF (2.0 mL) at rt for 72 h. Solvents were evaporated under reduced pressure. The residue was directed purified by column chromatography on silica gel (petroleum ether/EtOAc) to afford product **7**. However, if the conjugated aldehydes are replaced by saturated aldehydes or nonaromatic aldehydes, the reaction could not occur.

Diethyl(3S,10bR)-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7aa**: 66 mg was obtained as a white solid in 78% yield after flash chromatography

(petroleum ether/EtOAc = 30 : 1). Mp 93-96 °C. Dr: 10:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 – 7.54 (m, 1H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.32 – 7.26 (m, 4H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.17 (d, *J* = 6.9 Hz, 1H), 6.73 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.92 (s, 1H), 4.94 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (ddd, *J* = 14.3, 8.9, 5.4 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.09 – 4.02 (m, 1H), 3.11 – 3.04 (m, 1H), 2.99 (ddd, *J* = 10.6, 5.1, 2.2 Hz, 1H), 2.92 (ddd, *J* = 12.6, 10.8, 3.1 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.2, 136.3, 135.2, 133.0, 130.5, 129.5, 128.8, 128.5, 128.1, 127.9, 126.5, 126.4, 123.9, 93.3, 87.4, 73.8, 62.4, 61.8, 45.9, 29.5, 14.2, 13.88. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{28}NO_5$: 422.1962, observed: 422.1963.

Didiethyl(3S,10bR)-3-((E)-4-fluorostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ab**: 57 mg was obtained as a white solid in 66% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 112-115 ℃. Dr: 15:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.33 – 7.25 (m, 4H), 7.17 (d, *J* = 7.0 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 15.7 Hz, 1H), 6.10 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.90 (s, 1H), 4.92 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.37 – 4.31 (m, 1H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 – 4.09 (m, 1H), 4.06 (dq, *J* = 10.8, 7.3 Hz, 1H), 3.10 – 3.02 (m, 1H), 2.98 (ddd, *J* = 10.6, 5.1, 2.2 Hz, 1H), 2.95 – 2.89 (m, 1H), 2.76 (d, *J* = 16.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (564 MHz, $CDCl_3$) δ -109.65. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.1, 162.4 (d, *J* = 247.3 Hz), 135.1, 132.5 (d, *J* = 3.3 Hz), 131.8, 130.4, 129.5, 128.8, 128.1, 128.0, 126.4, 123.7, 115.5 (d, *J* = 21.6 Hz), 93.3, 87.4, 73.8, 62.5, 61.8, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}FNO_5$: 440.1868, observed: 440.1865.

Diethyl(3S,10bR)-3-((E)-2-(perfluorophenyl)vinyl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ac**: 64 mg was obtained as a white solid in 63% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 129-130 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.33 – 7.25 (m, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 16.2 Hz, 1H), 6.52 (dd, *J* = 16.2, 6.7 Hz, 1H), 5.81 (s, 1H), 4.97 (d, *J* = 6.6 Hz, 1H), 4.39 – 4.33 (m, 1H), 4.30 (dd, *J* = 10.7, 7.1 Hz, 1H), 4.14 (ddd, *J* = 14.3, 10.7, 7.2 Hz, 2H), 3.13 – 3.04 (m, 1H), 3.01 – 2.90 (m, 2H), 2.78 (d, *J* = 16.1 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 6H). ^{19}F NMR (564 MHz, $CDCl_3$) δ -138.43, -151.3, -158.39. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 167.9, 135.1, 133.4, 130.2, 129.4, 128.9, 128.1, 126.4, 116.6, 93.3, 87.1, 74.0, 62.6, 62.0, 46.0, 29.5, 14.0, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{23}F_5NO_5$: 512.1491, observed: 512.1493.

Diethyl(3S,10bR)-3-((E)-2-chlorostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ad**: 70 mg was obtained as a white solid in 77% yield after flash chromatography (petroleum ether/EtOAc = 30 : 1). Mp 72-75℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58–7.54 (m, 1H), 7.47 (dd, *J* = 7.4, 2.0 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.30–7.25 (m, 2H), 7.18 (td, *J* = 7.0, 1.8 Hz, 3H), 7.11 (d, *J* = 15.7 Hz, 1H), 6.18 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.93 (s, 1H), 4.98 (dd, *J* = 8.2, 0.8 Hz, 1H), 4.36 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.22 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.12–2.97 (m, 2H), 2.96–2.89 (m, 1H), 2.79–2.73 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.16 (dd, *J* = 8.7, 5.6 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.1, 135.2, 134.5, 133.1, 130.4, 129.7, 129.5, 129.1, 128.9, 128.8, 128.1, 127.0, 126.9, 126.8, 126.4, 93.3, 87.3, 73.7, 62.4, 61.9, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}ClNO_5$: 456.1573, observed: 456.1578 .

Diethyl(3S,10bR)-3-((E)-2,3-dichlorostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ae**: 66 mg was obtained as a white solid in 71% yield after flash chromatography (petroleum ether/EtOAc = 30 : 1). Mp 115-116 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.36 (ddd, *J* = 12.0, 7.9, 1.4 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.16 (dd, *J* = 18.8, 7.5 Hz, 2H), 7.13 – 7.09 (m, 1H), 6.17 (dd, *J* = 15.7, 8.1 Hz, 1H), 5.91 (s, 1H), 4.98 (dd, *J* = 8.0, 1.1 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.93 (dd, *J* = 12.9, 2.4 Hz, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.0, 136.9, 135.2, 133.4, 131.3, 130.3, 129.5, 129.5, 129.1, 128.9, 128.4, 128.1, 127.2, 126.4, 125.1, 93.4, 87.3, 73.6, 62.5, 61.9, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{26}Cl_2NO_5$: 490.1183, observed: 490.1182.

Diethyl(3S,10bR)-3-((E)-2-bromostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7af**: 59 mg was obtained as a white solid in 59% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 89-92 ℃. Dr: 14:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 2H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.25 – 7.15 (m, 3H), 7.12 – 7.07 (m, 1H), 7.06 – 6.96 (m, 2H), 6.06 (dd, *J* = 15.7, 8.2 Hz, 1H), 5.86 (s, 1H), 4.91 (d, *J* = 8.2 Hz, 1H), 4.28 (dt, *J* = 14.1, 7.1 Hz, 1H), 4.15 (dt, *J* = 14.0, 7.1 Hz, 1H), 4.10–3.93 (m, 2H), 2.98 (dd, *J* = 26.7, 11.5 Hz, 2H), 2.88 – 2.79 (m, 1H), 2.70 (d, *J* = 15.5 Hz, 1H), 1.18 (t, *J* = 6.9 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 168.6, 168.1, 136.3, 135.2, 133.0, 131.7, 130.4, 129.6, 129.2, 128.9, 128.1, 127.5, 127.1, 127.1, 126.4, 123.7, 93.4, 87.3, 73.6, 62.5, 61.9, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$

calculated for $C_{25}H_{27}BrNO_5$: 500.1067, observed: 500.1066.

Diethyl(3S,10bR)-3-((E)-4-bromostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ag**: 74 mg was obtained as a white solid in 74% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 83-85 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 –7.55 (m, 1H), 7.53 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.46 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.31 – 7.23 (m, 3H), 7.17 (d, *J* = 6.9 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.14 (dd, *J* = 15.7, 8.2 Hz, 1H), 5.93 (s, 1H), 4.98 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.10 – 2.99 (m, 2H), 2.96 – 2.90 (m, 1H), 2.80 – 2.74 (m, 1H), 1.25 (dd, *J* = 8.3, 5.9 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.1, 136.3, 135.2, 132.9, 131.6, 130.4, 129.5, 129.1, 128.8, 128.1, 127.5, 127.1, 127.1, 126.4, 123.6, 93.3, 87.3, 73.6, 62.4, 61.9, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}BrNO_5$: 500.1067, observed: 500.1069.

Diethyl(3S,10bR)-3-((E)-4-methylstyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ah**: 66 mg was obtained as a white solid in 75% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 87-90 ℃. Dr: 12:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 1H), 7.21 – 7.13 (m, 4H), 7.10 – 7.06 (m, 1H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.05 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.84 (s, 1H), 4.84 (d, *J* = 8.2 Hz, 1H), 4.32 – 4.20 (m, 1H), 4.15 – 3.90 (m, 3H), 3.04 – 2.77 (m, 3H), 2.67 (d, *J* = 15.8 Hz, 1H), 2.23 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.5, 167.2, 136.7, 134.2, 132.5, 132.0, 129.4, 128.5, 128.2, 127.8, 127.4, 125.4, 125.4, 121.8, 92.3, 86.4, 72.9, 61.4, 60.8, 44.9, 28.5, 20.2, 13.2, 12.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{30}NO_5$: 436.2119, observed: 436.2114.

Diethyl(3S,10bR)-3-((E)-2-methoxystyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ai**: 67 mg was obtained as a white solid in 74% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 87-90 ℃. Dr: 12:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 1H), 7.37 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.21 (td, *J* = 8.4, 1.6 Hz, 1H), 7.16 (d, *J* = 6.8 Hz, 1H), 7.03 (d, *J* = 15.8 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.22 (dd, *J* = 15.9, 8.3 Hz, 1H), 5.93 (s, 1H), 4.96 (dd, *J* = 8.3, 0.9 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.11 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.83 (s, 3H), 3.07 (s, 1H), 2.99 (dd, *J* = 5.0, 2.2 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.76 (dd, *J* = 10.5, 8.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 168.3, 156.8, 135.3, 130.6, 129.5, 128.9, 128.7, 128.1, 128.0, 127.1, 126.3, 125.3,

124.5, 120.5, 110.7, 93.3, 87.4, 74.3, 62.3, 61.7, 55.3, 45.9, 29.5, 14.3, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{30}NO_6$: 452.2068, observed: 452.2066.

Diethyl(3S,10bR)-3-((E)-2-bromo-5-methoxystyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7aj**: 80 mg was obtained as a white solid in 75% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 118-120 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 15.7, 0.8 Hz, 1H), 6.98 (d, *J* = 3.0 Hz, 1H), 6.68 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.12 (dd, *J* = 15.6, 8.2 Hz, 1H), 5.93 (s, 1H), 4.97 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.09 – 4.02 (m, 1H), 3.78 (d, *J* = 5.8 Hz, 3H), 3.10 – 3.03 (m, 1H), 3.01 (ddd, *J* = 10.5, 4.9, 2.0 Hz, 1H), 2.95 – 2.89 (m, 1H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.0, 158.9, 136.9, 135.2, 133.5, 131.8, 130.4, 129.5, 128.8, 128.1, 127.1, 126.4, 115.6, 114.3, 111.9, 93.3, 87.3, 73.6, 62.5, 61.9, 55.5, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{29}BrNO_6$: 530.1173, observed: 530.1175.

Diethyl(3S,10bR)-3-((E)-3-(trifluoromethyl)styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ak**: 76 mg was obtained as a white solid in 77% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 101-102 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.57 – 7.54 (m, 1H), 7.50 (dd, *J* = 15.1, 7.7 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.31 – 7.26 (m, 2H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.78 (d, *J* = 15.8 Hz, 1H), 6.26 (dd, *J* = 15.8, 7.7 Hz, 1H), 5.91 (s, 1H), 4.96 (d, *J* = 7.7 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.21 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.16 – 4.11 (m, 1H), 4.11 – 4.06 (m, 1H), 3.07 (s, 1H), 2.98 (dd, *J* = 5.1, 2.2 Hz, 1H), 2.94 (dd, *J* = 12.4, 2.9 Hz, 1H), 2.81 – 2.73 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.16 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (564 MHz, $CDCl_3$) δ -58.63. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.0, 137.1, 135.1, 131.4, 130.9 (t, *J* = 32.1 Hz), 130.3, 129.6, 129.6, 129.5, 129.1, 128.9, 128.1, 126.4, 126.2, 124.4 (q, *J* = 3.6 Hz), 123.1 (q, *J* = 3.9 Hz), 93.4, 87.3, 73.6, 62.5, 61.9, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{27}F_3NO_5$: 490.1836, observed: 490.1835.

Diethyl(3S,10bR)-3-((E)-4-nitrostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7al**: 56 mg was obtained as a white solid in 60% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 126-128 ℃. Dr: 20:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 2H), 7.56 – 7.53 (m, 1H), 7.49 – 7.46 (m, 2H), 7.29 (ddd, *J* = 18.7, 9.8, 6.7 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.83 (d, *J* = 15.7 Hz, 1H), 6.36 (dd, *J* = 15.8, 7.6 Hz, 1H), 5.89 (s, 1H), 4.97 (dd,

J = 7.6, 1.1 Hz, 1H),4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16 – 4.11 (m, 1H), 4.11 – 4.05 (m, 1H), 3.07 (ddt, *J* = 21.6, 14.2, 7.1 Hz, 1H), 2.97 (dd, *J* = 14.1, 2.6 Hz, 2H), 2.78 (d, *J* = 16.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, CDCl3) δ 168.4, 167.9, 147.1, 142.8, 135.1, 130.5, 130.2, 129.5, 129.2, 128.9, 128.1, 127.0, 126.5, 124.1, 93.4, 87.3, 73.5, 62.6, 61.9, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}N_2O_7$: 467.1813, observed: 467.1818.

Diethyl(3S,10bR)-3-((E)-4-cyanostyryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7am**: 57 mg was obtained as a white solid in 64% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 61-63 ℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 – 7.56 (m, 2H), 7.55 – 7.52 (m, 1H), 7.42 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.26 (m, 2H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.76 (d, *J* = 15.7 Hz, 1H), 6.30 (dd, *J* = 15.8, 7.7 Hz, 1H), 5.88 (s, 1H), 4.95 (dd, *J* = 7.7, 1.1 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.07 (dq, *J* = 10.8, 7.2 Hz, 1H), 3.12 – 3.01 (m, 1H), 3.00 – 2.88 (m, 2H), 2.77 (d, *J* = 16.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 168.4, 167.9, 140.8, 135.1, 132.5, 131.0, 130.2, 129.5, 128.9, 128.3, 128.1, 126.9, 126.5, 118.8, 111.2, 93.4, 87.3, 73.5, 62.6, 61.9, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{27}N_2O_5$: 447.1915, observed: 447.1918.

Diethyl(3S,10bR)-3-((E)-4-(methoxycarbonyl)styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7an**: 56 mg was obtained as a white solid in 58% yield after flash chromatography (petroleum ether/EtOAc = 30 : 1). Mp 79-81℃. Dr: 16:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.57 – 7.53 (m, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.31 – 7.25 (m, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 6.77 (d, *J* = 15.8 Hz, 1H), 6.29 (dd, *J* = 15.8, 7.9 Hz, 1H), 5.91 (s, 1H), 4.95 (d, *J* = 7.9 Hz, 1H), 4.35 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.90 (s, 3H), 3.11 – 3.02 (m, 1H), 3.02 – 2.89 (m, 2H), 2.80 – 2.73 (m, 1H), 1.25 (dd, *J* = 8.2, 6.0 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 168.5, 168.0, 166.8, 140.8, 135.1, 131.9, 130.3, 130.0, 129.5, 129.3, 128.9, 128.1, 126.8, 126.4, 126.3, 93.4, 87.3, 73.7, 62.5, 61.9, 52.1, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{27}H_{30}NO_7$: 480.2017, observed: 480.2022.

Diethyl(3S,10bR)-3-((E)-3-(trifluoromethoxy)styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ao**: 88 mg was obtained as a white solid in 87% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 112-114 ℃. Dr: 17:1. ^{1}H NMR (600

MHz, $CDCl_3$) δ 7.57 – 7.53 (m, 1H), 7.32 – 7.30 (m, 1H), 7.29 – 7.24 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.10 – 7.06 (m, 1H), 6.73 (d, *J* = 15.4 Hz, 1H), 6.20 (dd, *J* = 15.8, 7.7 Hz, 1H), 5.90 (s, 1H), 4.94 (dd, *J* = 7.8, 1.1 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.20 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.11 – 3.02 (m, 1H), 3.01 – 2.89 (m, 2H), 2.80 – 2.73 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (564 MHz, $CDCl_3$) δ -53.57. $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.5, 168.0, 149.6, 138.5, 135.1, 131.4, 130.3, 129.9, 129.5, 1285.9 (q, *J* = 271.8 Hz), 128.9, 128.1, 126.4, 126.0, 124.9, 120.2, 118.7, 93.3, 87.3, 73.6, 62.5, 61.9, 46.0, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{27}F_3NO_6$: 506.1785, observed: 506.1782.

Diethyl(3S,10bR)-3-((E)-2-(naphthalen-2-yl)vinyl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ap**: 79 mg was obtained as a white solid in 84% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 137-139℃. Dr: 14:1. ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 3H), 7.72 (s, 1H), 7.59 – 7.53 (m, 2H), 7.47 – 7.42 (m, 2H), 7.32 – 7.27 (m, 2H), 7.18 (d, *J* = 6.8 Hz, 1H), 6.89 (d, *J* = 15.7 Hz, 1H), 6.32 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.97 (s, 1H), 5.00 (dd, *J* = 8.2, 0.9 Hz, 1H), 4.37 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.15 (dq, *J* = 25.0, 10.7, 7.1 Hz, 2H), 4.05 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.14 – 3.05 (m, 1H), 3.02 (ddd, *J* = 10.6, 5.0, 2.1 Hz, 1H), 2.98 – 2.92 (m, 1H), 2.81 – 2.74 (m, 1H), 1.26 (dd, *J* = 8.4, 5.9 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.6, 168.2, 135.2, 133.8, 133.5, 133.1, 133.1, 130.4, 129.5, 128.8, 128.2, 128.1, 128.0, 127.6, 126.7, 126.4, 126.3, 126.0, 124.3, 123.4, 93.4, 87.5, 74.0, 62.5, 61.9, 46.0, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{29}H_{30}NO_5$: 472.2119, observed: 472.2115.

Diethyl(3S,10bR)-3-((E)-2-(furan-2-yl)vinyl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7aq**: 43 mg was obtained as a white solid in 53% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 89-92 ℃. Dr: 10:1. ^1H NMR (600 MHz, $CDCl_3$) δ 7.50 – 7.43 (m, 1H), 7.21 – 7.20 (m, 1H), 6.26 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.15 (d, *J* = 3.2 Hz, 1H), 6.04 (dd, *J* = 15.6, 7.5 Hz, 1H), 5.78 (s, 1H), 4.83 (d, *J* = 7.4 Hz, 1H), 4.26 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 – 4.00 (m, 3H), 3.04 – 2.93 (m, 1H), 2.92 – 2.78 (m, 2H), 2.68 (d, *J* = 15.9 Hz, 1H), 1.15 (dt, *J* = 15.4, 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 168.5, 168.2, 152.1, 142.3, 135.2, 130.5, 129.5, 128.8, 128.1, 126.4, 122.5, 121.0, 111.3, 108.6, 93.3, 87.4, 73.5, 62.5, 61.9, 45.9, 29.5, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{23}H_{26}NO_6$: 412.1755, observed: 412.1758.

Diethyl(3S,10bR)-3-((E)-2-(thiophen-2-yl)vinyl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ar**: 42 mg was obtained as a white solid in 50% yield after flash

chromatography (petroleum ether/EtOAc = 20 : 1). Mp 123-127 ℃. Dr: 12:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 1H), 7.31 – 7.25 (m, 2H), 7.17 (d, *J* = 7.1 Hz, 1H), 7.14 (dd, *J* = 4.2, 1.9 Hz, 1H), 6.93 (dd, *J* = 4.9, 2.8 Hz, 2H), 6.88 (d, *J* = 15.5 Hz, 1H), 6.00 (dd, *J* = 15.5, 7.6 Hz, 1H), 5.87 (s, 1H), 4.90 (dd, *J* = 7.6, 1.1 Hz, 1H), 4.34 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.13 (dq, *J* = 14.3, 10.8, 7.1 Hz, 2H), 3.12 – 3.02 (m, 1H), 2.99 – 2.88 (m, 2H), 2.76 (dt, *J* = 15.9, 2.5 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 168.1, 141.4, 135.2, 130.4, 129.5, 128.8, 128.1, 127.3, 126.4, 126.2, 125.9, 124.6, 123.4, 93.3, 87.4, 73.6, 62.5, 62.0, 45.9, 29.5, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{23}H_{26}NO_5S$: 428.1526, observed: 428.1522.

Diethyl(3S,10bR)-9-chloro-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ba**: 58 mg was obtained as a white solid in 64% yield after flash chromatography (petroleum ether/EtOAc = 30 : 1). Mp 52-55 ℃. Dr: 10:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, *J* = 1.8 Hz, 1H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.24 (dt, *J* = 16.2, 5.3 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 15.8 Hz, 1H), 6.15 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.85 (s, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.36 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.22–4.17 (m, 1H), 4.14 (ddd, *J* = 14.2, 10.9, 7.2 Hz, 1H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.04 – 2.96 (m, 2H), 2.89 (dd, *J* = 18.1, 8.1 Hz, 1H), 2.76 – 2.71 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 168.0, 136.2, 133.6, 133.2, 132.2, 132.1, 129.4, 129.3, 129.0, 128.6, 127.9, 126.5, 123.6, 92.5, 87.4, 73.6, 62.5, 61.9, 45.7, 28.9, 14.2, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}ClNO_5$: 456.1573, observed: 456.1576.

Diethyl(3S,10bR)-9-bromo-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ca**: 70 mg was obtained as a white solid in 70% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 73-76 ℃. Dr: 10:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 15.7 Hz, 1H), 6.15 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.85 (s, 1H), 4.91 (dd, *J* = 8.1, 0.9 Hz, 1H), 4.36 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.23–4.17 (m, 1H), 4.14 (ddd, *J* = 14.2, 10.9, 7.3 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.2 Hz, 1H), 2.98 (dt, *J* = 20.0, 6.6 Hz, 2H), 2.90 – 2.85 (m, 1H), 2.72 (dd, *J* = 14.3, 3.5 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 168.0, 136.2, 134.2, 133.2, 132.5, 132.2, 131.9, 129.7, 128.6, 127.9, 126.5, 123.6, 119.9, 92.4, 87.4, 73.6, 62.5, 61.9, 45.6, 28.9, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}BrNO_5$: 500.1067, observed: 500.1066.

Diethyl(3S,10bR)-8-methoxy-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7da**: 83 mg was obtained as a white solid in 91% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 56-57 ℃. Dr: 14:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 2H), 7.28 (dd, *J* = 15.2, 7.4 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 6.82 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.70 (dd, *J* = 19.3, 9.0 Hz, 2H), 6.17 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.89 (s, 1H), 4.92 (d, *J* = 8.2 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.05 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.80 (s, 3H), 3.08 – 3.01 (m, 1H), 2.98 – 2.88 (m, 2H), 2.72 (d, *J* = 16.1 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 168.2, 159.8, 136.7, 136.3, 133.0, 130.8, 128.5, 127.8, 126.5, 124.0, 122.9, 112.7, 112.6, 93.3, 87.4, 73.8, 62.4, 61.8, 55.2, 45.9, 29.8, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{26}H_{30}NO_6$: 452.2068, observed: 452.2063.

Diethyl(3S,10bR)-8,9-dimethoxy-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7ea**: 71 mg was obtained as a white solid in 73% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 101-103 ℃. Dr: 14:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 7.5 Hz, 2H), 7.27 (dd, *J* = 13.3, 5.6 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.00 (s, 1H), 6.71 (d, *J* = 15.8 Hz, 1H), 6.63 (s, 1H), 6.16 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.86 (s, 1H), 4.91 (d, *J* = 8.2 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.18 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.04 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 2.95 (dt, *J* = 28.9, 12.0 Hz, 3H), 2.66 (d, *J* = 16.2 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.6, 168.1, 149.4, 147.7, 136.3, 133.0, 128.5, 127.9, 127.8, 126.5, 124.0, 122.4, 111.7, 110.5, 93.4, 87.4, 73.6, 62.4, 61.8, 56.1, 55.9, 46.0, 29.1, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{27}H_{32}NO_7$: 482.2174, observed: 482.2170.

Diethyl(3S,10bR)-9-nitro-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[2,3-a]isoquinoline-2,2(3H)-dicarboxylate **7fa**: 70 mg was obtained as a white solid in 75% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 94-97 ℃. Dr: 8:1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.3 Hz, 1H), 8.08 (dd, *J* = 8.4, 2.3 Hz, 1H), 7.29 – 7.21 (m, 5H), 7.20 – 7.14 (m, 1H), 6.66 (d, *J* = 15.8 Hz, 1H), 6.09 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.88 (s, 1H), 4.88 (d, *J* = 8.1 Hz, 1H), 4.29 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.14 (ddd, *J* = 10.7, 9.0, 5.3 Hz, 1H), 4.11–3.97 (m, 2H), 3.02 (tdd, *J* = 9.6, 7.6, 3.8 Hz, 2H), 2.90 – 2.78 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 4H), 1.08 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.1, 166.8, 145.6, 141.9, 135.1, 132.4, 131.0, 128.2, 127.6, 127.1, 125.5,

123.8, 122.7, 122.2, 91.0, 86.4, 72.5, 61.7, 61.1, 44.1, 28.6, 13.1, 12.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{27}N_2O_7$: 467.1813, observed: 467.1812.

Diethyl(3S,11bR)-3-((E)-styryl)-5,6,11,11b-tetrahydrooxazolo[3',2':1,2]pyrido[3,4-b]indole-2,2(3H)-dicarboxylate **7ga**: 48 mg was obtained as a white solid in 52% yield after flash chromatography (petroleum ether/EtOAc = 15 : 1). Mp 101-103 ℃. Dr: 15:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 6.5 Hz, 3H), 7.29 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.19 (m, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 15.7 Hz, 1H), 6.19 (dd, *J* = 15.8, 8.2 Hz, 1H), 6.13 (s, 1H), 4.91 (d, *J* = 8.2 Hz, 1H), 4.29 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.19 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.13–4.06 (m, 2H), 3.22 – 3.13 (m, 1H), 3.12 – 3.04 (m, 1H), 2.93 – 2.85 (m, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.2, 167.8, 136.8, 136.3, 133.6, 128.6, 128.4, 127.9, 126.5, 125.8, 123.8, 122.9, 119.7, 119.1, 111.9, 111.5, 89.0, 88.2, 71.6, 62.5, 62.0, 46.6, 20.9, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{27}H_{29}N_2O_5$: 461.2071, observed: 461.2073.

Diethyl(3S,9bR)-3-((E)-styryl)-6,9b-dihydro-5H-oxazolo[3,2-a]thieno[3,2-c]pyridine-2,2(3H)-dicarboxylate **7ha**: 52 mg was obtained as a white solid in 61% yield after flash chromatography (petroleum ether/EtOAc = 20 : 1). Mp 105-107 ℃. Dr: 14:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 – 7.32 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.15 (s, 2H), 6.72 (d, *J* = 15.7 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.89 (s, 1H), 4.88 (dd, *J* = 8.1, 1.0 Hz, 1H), 4.35 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.21–4.16 (m, 1H), 4.16–4.10 (m, 1H), 4.05 (dq, *J* = 10.7, 7.1 Hz, 1H).), 3.09 – 3.05 (m, 1H), 3.03 (dd, *J* = 10.6, 3.0 Hz, 1H), 3.01 – 2.96 (m, 1H), 2.90 – 2.82 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.4, 168.0, 138.2, 136.3, 133.2, 130.9, 128.5, 127.9, 126.5, 126.5, 123.9, 123.5, 90.6, 88.0, 72.1, 62.5, 61.9, 46.3, 25.2, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{23}H_{26}NO_5S$: 428.1526, observed: 428.1525.

Diethyl(3S,10bR)-3-((E)-styryl)-6,10b-dihydro-5H-oxazolo[3',2':1,2]pyrido[4,3-d]pyrimidine-2,2(3H)-dicarboxylate **7ia**: 24 mg was obtained as a white solid in 28% yield after flash chromatography (petroleum ether/EtOAc = 10 : 1). Mp 99-100 ℃. Dr: 10:1. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.5 Hz, 1H), 8.85 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 1H), 6.73 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 15.7, 8.0 Hz, 1H), 5.92 (s, 1H), 4.92 (d, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 10.8, 7.1 Hz, 1H), 4.23 – 4.13 (m, 2H), 4.11 – 4.03 (m, 1H), 3.13 (dddd, *J* = 23.1, 10.3, 5.3, 2.4 Hz, 2H), 3.01 (td, *J* = 11.4, 2.8 Hz, 1H), 2.93 (dd, *J* = 17.2, 2.3 Hz, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.9,

167.6, 164.3, 158.6, 157.4, 136.0, 133.6, 128.7, 128.1, 126.5, 124.5, 123.0, 90.3, 87.9, 73.2, 62.7, 62.1, 44.9, 31.8, 14.1, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{23}H_{26}N_3O_5$: 424.1867, observed: 424.1866.

Gram-Scale Procedure for the Synthesis of 7aa. Tetrahydroisoquinoline **4a** (16 mmol, 2.129 g), cinnamaldehyde **5a** (8 mmol, 1.056 g) and diethyl ketomalonate **6** (8.8 mmol, 1.532 g) were added in an oven-dried Schlenk tube. Then the catalyst 2,6-$(CF_3)_2$-$PhCO_2H$ (1.6 mmol, 0.412 g) and 4 Å MS (6.00 g) were added and the reaction was carried out in solvent THF (80.0 mL) at rt for 72 h. After the reaction was completed the mixture was filtered and the filtrate were evaporated under reduced pressure. The residue was directed purified by column chromatography on silica gel (petroleum ether/EtOAc = 30 : 1) to afford product **7aa** as a white solid (2.18 g, 64% yield).

Method for crystal growth. Put a certain amount of pure product **7aa** into a clean glass bottle, dissolve it with mixed solvent (hexane/EtOAc = 50 : 1), volatilize it at room temperature until the solvent volatilizes completely, and then crystal particles can be obtained.

Procedure for the Synthesis of 8. To a flame-dried and N_2-purged flask (50 mL) were added **7aa** (84.6 mg, 0.2 mmol), THF (10 mL) and a stirring bar. The flask was cooled down to 0 °C by low temperature reactor and then $LiAlH_4$ (2 equiv) was added. After the resulting reaction mixture was stirred for 2 h at 0 ºC, the reaction was quenched by the addition of 1 g $Na_2SO_4 \cdot 10H_2O$. The reaction mixture was diluted with Et_2O, and then filtered through celite with the aid of Et_2O. The solution was concentrated under the reduced pressure. The residue was directed purified by column chromatography on silica gel to afford product **8**.

(E)-2-(1-(3,4-dihydroisoquinolin-2(1H)-yl)-3-phenylallyl)propane-1,2,3-triol **8**: 34 mg was obtained as a white solid in 67% yield after flash chromatography (petroleum ether/EtOAc = 2 : 1). Mp 84-87℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 4.7 Hz, 1H), 7.14 – 7.09 (m, 2H), 7.09 – 7.05 (m, 1H), 7.03 – 6.99 (m, 1H), 6.58 (d, *J* = 15.9 Hz, 1H), 6.49 (dd, *J* = 15.9, 9.8 Hz, 1H), 4.03 (d, *J* = 14.6 Hz, 1H), 3.78 (q, *J* = 11.6 Hz, 3H), 3.61 (d, *J* = 11.4 Hz, 1H), 3.48 – 3.42 (m, 1H), 3.40 (d, *J* = 11.4 Hz, 1H), 3.34 (d, *J* = 9.8 Hz, 1H), 3.03 – 2.94 (m, 1H), 2.85 (d, *J* = 16.5 Hz, 1H), 2.72 (t, *J* = 8.1 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 136.5, 136.2, 134.5, 133.9, 128.7, 128.1, 126.6, 126.5, 126.3, 125.7, 121.8, 75.2, 71.5, 66.5, 64.8, 29.5. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{21}H_{26}NO_3$: 340.1907, observed: 340.1902.

Procedure for the Synthesis of 9. An oven-dried Schlenk tube with magnetic stirring bar $NaIO_4$ (64.2 mg, 0.3 mmol) was stirred in 0.15 mL of H_2O and 40 μL of H_2SO_4 (2M). After all solids were

dissolved the solution was cooled to 0 °C by low temperature reactor. Aqueous solution of $RuCl_3$ (10 μL, 0.001 mmol, 0.1 M) was added and the mixture was stirred until the color turned bright yellow. Ethyl acetate (0.6 mL) was added and stirring was continued for 5 min. Acetonitrile (0.6 mL) was added and stirring was continued for further 5 min. The **7aa** (0.2 mmol) was added in one portion and the resulting slurry was stirred until all starting material was consumed. The residue was directed purified by column chromatography on silica gel to afford product **9**.

Diethyl(E)-2-hydroxy-2-(1-(1-oxo-3,4-dihydroisoquinolin-2(1H)-yl)-3-phenylallyl)malonate **9**: 46 mg was obtained as a white solid in 53% yield after flash chromatography (petroleum ether/EtOAc = 6 : 1). Mp 109-111℃. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.41 (td, *J* = 7.4, 1.0 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 2H), 7.31 (dt, *J* = 19.7, 7.7 Hz, 3H), 7.24 (dd, *J* = 15.1, 7.8 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 15.9 Hz, 1H), 6.51 (dd, *J* = 15.9, 8.0 Hz, 1H), 5.98 (d, *J* = 8.0 Hz, 1H), 5.46 (s, 1H), 4.34 – 4.23 (m, 2H), 4.23 – 4.13 (m, 2H), 3.95 (ddd, *J* = 12.5, 7.7, 4.8 Hz, 1H), 3.68 – 3.59 (m, 1H), 2.97 (ddd, *J* = 13.5, 8.6, 4.8 Hz, 1H), 2.90 (ddd, *J* = 15.8, 7.6, 4.8 Hz, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 169.3, 168.5, 165.4, 138.5, 136.2, 135.7, 132.0, 129.2, 128.6, 128.5, 128.1, 127.0, 126.8, 126.7, 121.0, 83.0, 62.8, 61.8, 45.7, 28.5, 14.0, 13.9. HRMS (ESI) m/z $(M+H)^+$ calculated for $C_{25}H_{28}N_3O_6$: 438.1911, observed: 438.1913.

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General and characterization data, ^{1}H and ^{13}C NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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REFERENCES:

(1) (a) Bergmann, E. D., The Oxazolidines. *Chem. Rev.* **1953,** *53*, 309-352. (b) Cordero, F. M.; Lascialfari, L.; Machetti F. *Progress in Heterocyclic Chemistry*, 2020, Vol. 31, pp 399-429.

(2) (a) Scott, J. D.; Williams, R. M., Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. *Chem. Rev.* **2002,** *102*, 1669-730; (b) Yu, L.; Zhou, W.; Wang, Z., Synthesis and in vitro Antibacterial Activity of Oxazolidine LBM-415 Analogs as Peptide Deformylase Inhibitors. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 1541-4; (c) Ii, K.; Ichikawa, S.; Al-Dabbagh, B.; Bouhss, A.; Matsuda, A., Function-Oriented Synthesis of Simplified Caprazamycins: Discovery of Oxazolidine-Containing Uridine Derivatives as Antibacterial Agents against Drug-Resistant Bacteria. *J. Med. Chem.* **2010,** *53*, 3793-813.

(3) (a) Saleem, A.; Kobielska, P. A.; Harms, K.; Katsikogianni, M. G.; Telford, R.; Novitchi, G.; Nayak, S., Transition Metal Complexes of a Versatile Polyalkoxy Oxazolidine-Based Ligand Derived from *in situ* Cyclization. *Dalton Trans* **2018,** *47*, 6156-6165; (b) Raghavan, S.; Senapati, P., Oxazolidines as Intermediates in the Asymmetric Synthesis of 3-Substituted and 1,3-Disubstituted Tetrahydroisoquinolines. *J. Org. Chem.* **2016,** *81*, 6201-6210; (c) Wolf, C.; Xu, H., Asymmetric Catalysis with Chiral Oxazolidine Ligands. *Chem. Commun.* **2011,** *47*, 3339-3350; (d) Nakano, H.; Okuyama, Y.; Kwon, E., Chiral Oxazolidine Catalyst for Asymmetric Synthesis. *Heterocycles* **2014,** *89*, 1-26; (e) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y., A Novel Chiral Oxazolidine Organocatalyst for the Synthesis of An Oseltamivir Intermediate Using a Highly Enantioselective Diels-Alder Reaction of 1,2-Dihydropyridine. *Chem. Commun.* **2010,** *46*, 4827-9; (f) Agami, C.; Couty, F., The Use of *N*-Boc-1,3-Oxazolidines as Chiral Auxiliaries in Asymmetric Synthesis. *Eur. J. Org. Chem.* **2004,** *2004*, 677-685; (g) Arai, T.; Ogino, Y.; Sato, T., Development of a Tailor-Made Bis(oxazolidine)pyridine-Metal Catalyst for the [3+2] Cycloaddition of Azomethine Imines with Propiolates. *Chem. Commun.* **2013,** *49*, 7776-8.

(4) (a) Teranishi, S.; Maeda, K.; Kurahashi, T.; Matsubara, S., Diastereoselective Synthesis of 1,3-Oxazolidines via Cationic Iron Porphyrin-catalyzed Cycloaddition of Aziridines with Aldehydes. *Org. Lett.* **2019,** *21*, 2593-2596; (b) Singh, N.; Dar, A. A.; Kumar, A., A Simple and Efficient Approach for the Synthesis of 1,3-Oxazolidines from

β-Amino Alcohols Using Grinding Technique. *Chemistryselect* **2018,** *3*, 13675-13681; (c) Kondoh, A.; Akahira, S.; Oishi, M.; Terada, M., Enantioselective Formal [3+2] Cycloaddition of Epoxides with Imines under Brønsted Base Catalysis: Synthesis of 1,3-Oxazolidines with Quaternary Stereogenic Center. *Angew. Chem. Int. Ed.* **2018,** *57*, 6299-6303; (d) Satheesh, V.; Vivek Kumar, S.; Punniyamurthy, T., Expedient Stereospecific Co-catalyzed Tandem C-N and C-O Bond Formation of N-methylanilines with Styrene Oxides. *Chem. Commun.* **2018,** *54*, 11813-11816; (e) Wu, X.; Zhou, W.; Wu, H. H.; Zhang, J., Enantioselective [3+2] Cycloaddition of Azomethine Ylides and Aldehydes via Ni/bis(oxazoline)-catalyzed Ring Opening of N-tosylaziridines through a Chirality Transfer Approach. *Chem. Commun.* **2017,** *53*, 5661-5664; (f) Liao, Y.; Liu, X.; Zhang, Y.; Xu, Y.; Xia, Y.; Lin, L.; Feng, X., Asymmetric [3 + 2] Cycloaddition of Donor–Acceptor Aziridines with Aldehydes via Carbon–carbon Bond Cleavage. *Chem. Sci.* **2016,** *7*, 3775-3779.

(5) Meyer, A. G.; Ryan, J. H., 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides with Carbonyl Dipolarophiles Yielding Oxazolidine Derivatives. *Molecules* **2016,** *21*.

(6) (a) Coldham, I.; Hufton, R., Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005,** *105*, 2765-810; (b) Pandey, G.; Banerjee, P.; Gadre, S. R., Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3+2]-Cycloaddition of Azomethine Ylides. *Chem. Rev.* **2006,** *106*, 4484-517.

(7) (a) Ardill, H.; Fontaine, X. L. R.; Grigg, R.; Henderson, D.; Montgomery, J.; Sridharan, V.; Surendrakumar, S., X=Y-ZH Compounds as Potential 1,3-dipoles. Part 29. The Iminium Ion Route to Azomethine Ylides. Reaction of Cyclic Secondary Amines with Mono- and Bi-Functional Aldehydes. *Tetrahedron* **1990,** *46*, 6449-6466; (b) Aly, M. F.; Ardill, H.; Grigg, R.; Leong-Ling, S.; Rajviroongit, S.; Surendrakumar, S., The Reaction of Secondary α-Amino Acids with Carbonyl Compounds. Properties of the Intermediate Azomethine Ylides. Oxazolidine Formation versus 1.4-Prototropy. *Tetrahedron Lett.* **1987,** *28*, 6077-6080; (c) Ardill, H.; Grigg, R.; Sridharan, V.; Surendrakumar, S.; Thianpatanagul, S.; Kanajun, S., Iminium Ion Route to Azomethine Yields from Primary and Secondary Amines. *J. Chem. Soc., Chem. Commun.* **1986**, 602.

(8) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D., Redox-Neutral α-Oxygenation of Amines: Reaction Development and Elucidation of the Mechanism. *J. Am. Chem. Soc.* **2014,** *136*, 6123-35.

(9) Pavan Kumar, C. S.; Harsha, K. B.; Mantelingu, K.; Rangappa, K. S., Diastereoselective Synthesis of Fused Oxazolidines and Highly Substituted 1H-pyrrolo [2,1-c][1,4] oxazines via C–H Functionalization. *RSC Adv.* **2015,** *5*, 61664-61670.

(10) Wang, H. J.; Guo, L.; Zhu, C. F.; Luo, Y. F.; Li, Y. G.; Wu, X., Pd/C-Catalyzed Dehydrogenative [3+2] Cycloaddition for the Synthesis of Functionalized Tropanes. *Eur. J. Org. Chem.* **2018,** *2018*, 5456-5459.

(11) CCDC 1948964 (**7aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre