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Stereospecific Synthesis of 3,4-Dihydro-2*H*-naphtho-1,4-oxazin-2-ones by Unification of Benzoxepine-4-carboxylates with Chiral Amino Acid Ethyl Esters

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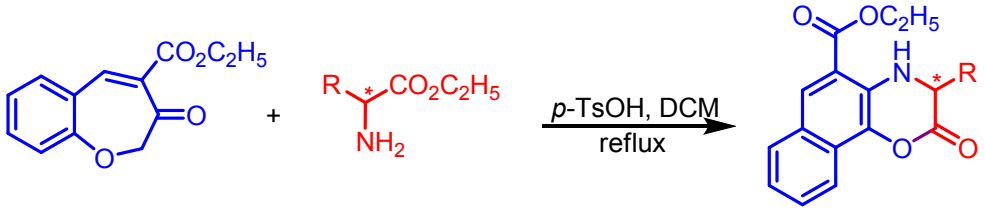
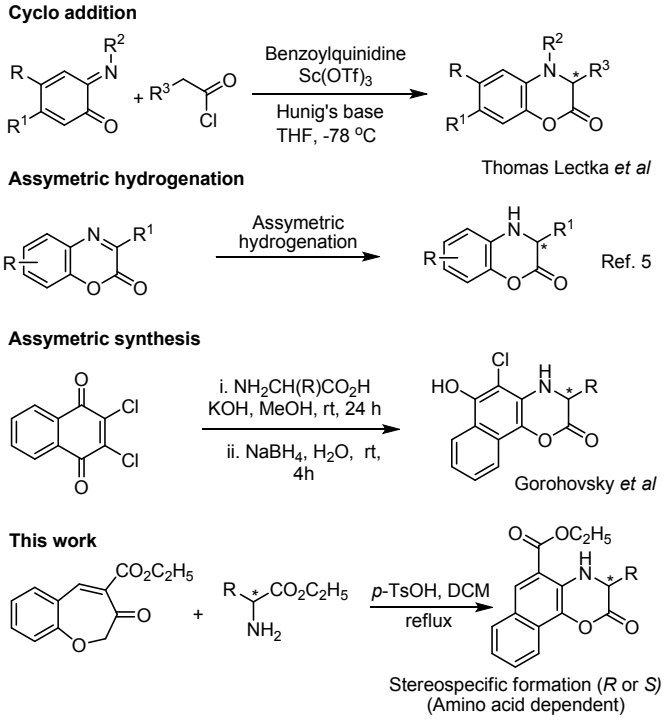


ABSTRACT: A novel and efficient stereocontrolled method has been developed for the preparation of chiral 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-2-ones by the reaction of benzoxepine-4-carboxylates with chiral amino acid ethyl esters for the first time. The chiral 3,4-dihydro-2*H*-naphtho-1,4-oxazinones have been achieved in one step by the formation of C-N, C-C and C-O bonds.

INTRODUCTION

Naphthoxazinones and benzoxazinones constitute an important class of bio-active compounds and useful intermediates for the preparation of pharmaceuticals.[1] These heterocyclic compounds particularly benzoxazinones are synthetic building blocks and present in a variety of natural products.[2] Further, these compounds are photo active molecules which possess fluorescent, photophysical and photochemical properties.[3] Similarly, chiral 3,4-dihydro-1,4-naphthoxazin-2-ones and 3,4-dihydro-1,4-benzoxazin-2-ones represent the structural motif of several natural products with interesting biological properties. Hence, the preparations of these heterocyclic compounds have attracted much attention to synthetic organic and medicinal chemists. To the best of our knowledge only two approaches are available for the preparation of chiral dihydrobenzoxazinones (Scheme 1). The enantioselective cycloaddition of *ortho*-benzoquinone imides with chiral ketene enolates furnished the chiral dihydrobenzoxazinones.[4] Asymmetric reduction of benzoxazinones is the another approach to access the dihydrobenzoxazinones.[5] Interestingly, there is only one method reported by Gorohovsky et al[6] for the preparation of chiral dihydronaphthoxazinones by the reaction of 2,3-dichloro-1,4-naphthoquinones with natural amino acids as chiral source (Scheme 1). Therefore, the development of new general strategies for the synthesis of enantiopure dihydronaphthoxazinone framework has become attractive and challenging.



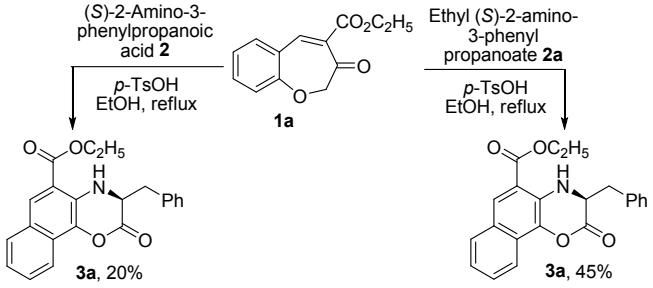
Scheme 1. Previous approaches for the preparation of chiral dihydro[1,4]benzoxazinones and naphthoxazinone

Our research group is interested in the development of novel methods for the preparation of heterocyclic compounds.[7] The research work on benzoxepine-4-carboxylates have produced novel heterocyclic compounds.[8] In continuation of our work on benzoxepine-4-carboxylates, recently we have prepared useful oxygenated heterocycles.[9] The present work envision to develop a stereospecific method for the construction of 3,4-dihydro-2*H*-1,4-naphtho-1,4-oxazin-2-ones by the reaction of benzoxepine-4-carboxylates with chiral amino acid ethyl esters.

RESULTS AND DISCUSSION

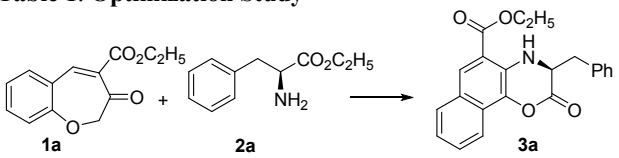
In an initial experiment, we have carried out the reaction of benzoxepine-4-carboxylate (**1a**, 1 equiv. Prepared as per our previous reported method) with (*S*)-2-amino-3-phenylpropanoic acid (**2**, 1 equiv.) in the presence of *p*-TsOH (30 mol %) with ethanol under reflux conditions (Scheme 2). A pale yellow solid was obtained after column chromatography (20% yield). The compound was identified as ethyl (*S*)-3-benzyl-2-oxo-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-5-carboxylate **3a** based on spectral data. The reaction is stereocontrolled and specifically obtained compound **3a**. This work represents the first example for the stereospecific construction of 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-2-one by the formation of C-N, C-C and C-O bonds in one-pot starting from benzoxepine-4-carboxylate.

Scheme 2. Preparation of compound 3a



We observed that the above reaction is very slow and produced compound **3a** in low quantity. The unreacted starting materials were recovered even after prolonged reaction time. This may be due to the amino acid is not reacted well under these conditions. We thought the amino acid ethyl ester is better species when compared to its acid. Therefore, the ethyl (*S*)-2-amino-3-phenylpropanoate **2a** was prepared from **2** by standard esterification protocol.[10] Thus obtained ester **2a** (1 equiv.) was reacted with **1a** (1 equiv.) in the presence of *p*-TsOH (30 mol %) with ethanol under reflux conditions (Scheme 2). This furnished compound **3a** with improved yield (45%, Table 1, entry 2). Other solvents such as MeOH, toluene, xylene, diethyl ether, DCM, DCE, MeCN and THF (Table 1, entry 3-10) were also studied to see the effect of solvents. We observed that DCM and DCE solvents are superior when compared to other tested solvents and produced compound **3a** in good yields (69%, 58%, Table 1, entry 7-8). The reaction at room temperature with DCM is inferior when compared to reflux condition (**3a**, 36% yield, Table 1, entry 11). A similar result was obtained with both low (20 mol %) and high (50 mol %) equivalents of *p*-TsOH (Table 1, entry 12-13) when we tested the reaction of **1a** with **2a** in DCM under reflux conditions.

Table 1. **Optimization Study**



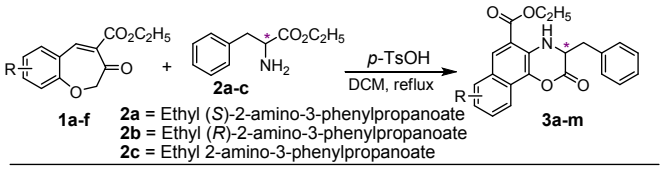
Entry	Catalyst (equiv)	Solvent	Time[h]	Yield[d]
01[a,b]	*p*-TsOH (0.3)	EtOH	16	20
02[b]	*p*-TsOH (0.3)	EtOH	16	45
03[b]	*p*-TsOH (0.3)	MeOH	18	31
04[b]	*p*-TsOH (0.3)	toluene	18	20
05[b]	*p*-TsOH (0.3)	xylene	18	38
06[b]	*p*-TsOH (0.3)	ether	32	42
07[b]	***p*-TsOH (0.3)**	**DCM**	**24**	**69**
08[b]	*p*-TsOH (0.3)	1,2-DCE	18	58
09[b]	*p*-TsOH (0.3)	MeCN	18	47
10[b]	*p*-TsOH (0.3)	THF	18	43
11[c]	*p*-TsOH (0.3)	DCM	48	36
12[b]	*p*-TsOH (0.2)	DCM	32	62
13[b]	*p*-TsOH (0.5)	DCM	22	68
14[b]	HCl (1.0)	DCM	15	31
15[b]	AcOH (0.3)	DCM	18	37
16[b]	TFA (0.3)	DCM	16	30
17[b]	$AlCl_3$ (0.3)	DCM	07	34
18[b]	$FeCl_3$ (0.3)	DCM	16	33
19[b]	$Cu(OAc)_2$ (0.3)	DCM	16	Trace
20[b]	CuI (0.3)	DCM	18	Trace
21[b]	$Bi(OTf)_3$ (0.3)	DCM	10	49
22[b]	$La(OTf)_3$ (0.3)	DCM	10	46

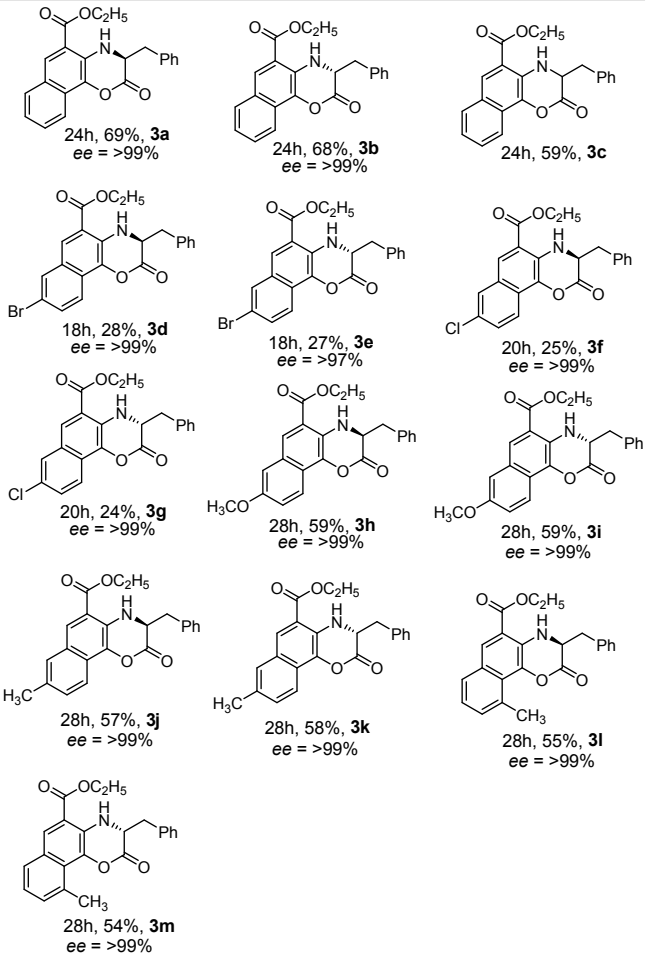
[a](*S*)-2-Amino-3-phenylpropanoic acid used as reactant, [b] reflux, [c] room temperature, [d]isolated yield.

Having optimized the reaction conditions, next, the reaction of **1a** with **2a** was tested with various catalysts such as protic acids (Table 1, entry 14-16), Lewis acids (Table 1, entry

17-20) and triflates (Table 1, entry 21-22) in DCM under reflux conditions. All these reactions have produced compound **3a** in moderate yields. No product formation was observed when the reaction was carried out in absence of catalyst. The above results revealed that 30 mol % *p*-TsOH is sufficient to promote the reaction in DCM under reflux conditions to produce the compound **3a** (69% yield, Table 1, entry 7). The compound **3a** was obtained stereospecifically and this was confirmed by chiral HPLC analysis (Table 2, enantiomeric purity = 99.89%, see SI). Then we have carried out the reaction of **1a** with ethyl (*R*)-2-amino-3-phenylpropanoate **2b** under our optimized reaction conditions to obtain **3b** (Table 2, enantiomeric purity = 99.95%, see SI). Further, we also carried out the reaction of **1a** with ethyl 2-amino-3-phenylpropanoate **2c** (Table 2) to furnish racemic (±) naphthoxazinone compound **3c** (*S* = 50.61%; *R* = 49.39%, see SI). The HPLC analysis of the chiral compounds **3a-b** was compared with the racemic compound **3c**. The present protocol was found to be stereocontrolled and specifically formed the chiral compounds.

Table 2. Preparation of 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-5-carboxylates 3a-m



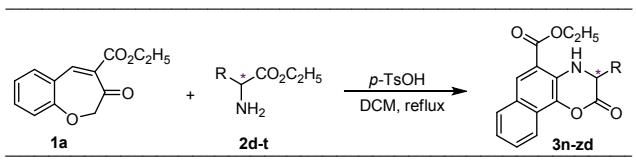


Further to explore the present protocol, we have investigated the reaction with substrates present on benzoxepine-4-carboxylates. Accordingly, the electron withdrawing (bromo **1b**, chloro **1c**) and electron donating (methoxy **1d**, methyl **1e-f**) groups present on benzoxepine-4-carboxylates were prepared as per our earlier reported method.[8a] The benzoxepines **1b-f** were reacted with ethyl (*S*)-2-amino-3-phenylpropanoate **2a** and ethyl (*R*)-2-amino-3-phenylpropanoate **2b** under our optimized conditions. All these reactions proceeded smoothly and produced the corresponding chiral naphthoxazinones **3b-m** (Table 2). The electron donating groups produced the compounds with better yields when compared to electron withdrawing groups. All the compounds were characterized by spectral data and the enantiomeric purity of the compounds were analyzed by chiral HPLC (>97-99%, see SI).

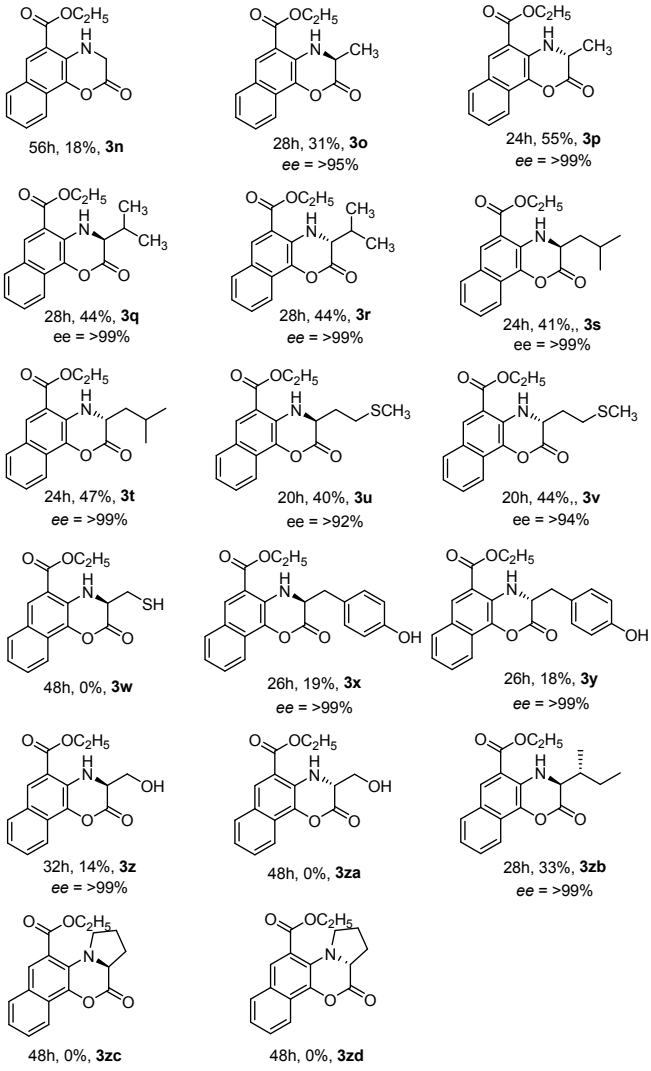
To broaden the scope of the present stereospecific reaction, the following amino acid ethyl esters **2d-v** have been prepared from their corresponding amino acids (see SI).[10] Accordingly, **1a** was reacted with **2d-t** under our optimized reaction conditions (Table 3).[11] The reactions underwent smoothly with amino acid ethyl esters such as **2d-l**, **2n-p** and **2r** provided the corresponding chiral naphthoxazinones **3n-v**, **3x-z** and **3zb** with >92-99% enantiomeric purity (Table 3). Whereas, the amino acid ethyl esters such as **2m, 2q** and **2s-t** could not provide the target compounds under these reaction conditions and the starting materials were recovered. The reaction of **1a** with ethyl (*R*)-2-amino-2-phenylacetate **2u** and ethyl (*S*)-2-amino-2-phenylacetate **2v** provided the compounds **3ze** and **3zf** (Table 4). The compound **3ze** afforded with low enantiomeric purity (*R* isomer = 16.25%, *S* isomer = 83.75% see SI) and compound **3zf** obtained in racemic (±) mixture (*R* isomer = 46.46%, *S* isomer = 53.54%, see SI). As the α-

hydrogen is more acidic in case of 2-amino-2-phenylacetic acid this type of recemization is possible. 2D NMR spectra were recorded for the compounds **3zb**, **3ze** and **3zg** and incorporated in the SI.

Table 3. **Preparation of 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-5-carboxylates 3n-zd**

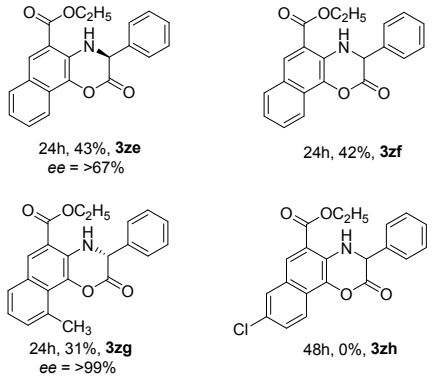


1a 2d-t 3n-zd



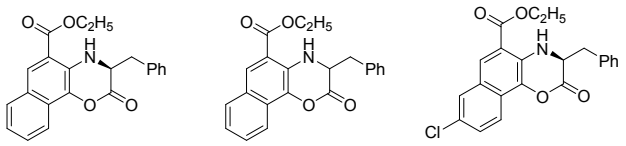
Since we obtained racemic target compound **3zf** from ethyl (*S*)-2-amino-2-phenylacetate **2v**, then we sought to conduct the reaction with electron withdrawing and electron donating group present on benzoxepine-4-carboxyltes in order to check the racemization. Accordingly, we have carried out the reaction of benzoxepine-4-carboxylates **1c** and **1f** with **2v** under our optimized conditions (Table 4). Interestingly, the electron donating group present on benzoxepine produced chiral compound **3zg** (enantiomeric purity for *R* isomer = > 99%, see SI) and electron withdrawing group present on benzoxepine could not provided the compound **3zh** (Table 4, see SI). This result indicated that the racemization has not been observed when electron donating group present on benzoxepine. All the obtained compounds were characterized by spectroscopy and enantiomeric purity analyzed by chiral HPLC (see SI).

Table 4. Preparation of compounds 3ze-zh



To further demonstrate the present protocol, chiral 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-2-ones **3a**, **3c** and **3f** have been prepared in gram scale by the reaction of benzoxepine compounds **1a** (2.5 g) with **2a**, **1a** (2.2 g) with **2c**, and **1c** (1.2 g) with **2a** under our optimized conditions and the results were depicted in Scheme 3.

Scheme 3. Gram scale preparation of compounds 3a, 3c & 3f

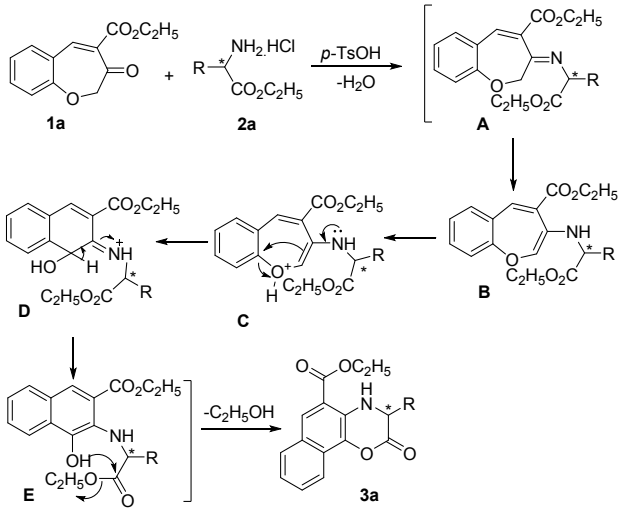


3a, 67.35% (2.62 g) **3c**, 57.60% (1.97 g) **3f**, 23.59% (0.42 g)

A plausible reaction pathway for the preparation of **3a** was depicted in Scheme 4. The benzoxepine-4-carboxylate **1a** with ethyl (*S*)-2-amino-3-phenylpropanoate **2a** under acidic medium forms the Schiff base **A**. The imine (Schiff base) upon rearrangement provides enamine intermediate **B**. The

rearrangement of intermediate **B** and subsequent intramolecular cyclization through **C-E** furnish the compound **3a** with the elimination of ethanol.

Scheme 4. Plausible Reaction Mechanism



CONCLUSIONS

In conclusion, a facile stereospecific method has been developed for the preparation of chiral 3,4-dihydro-1,4-naphthoxazin-2-ones by the reaction of benzoxepine-4-carboxylates with chiral amino acid ethyl esters for the first time. The present protocol is efficient and practical one-step process to construct the chiral naphthoxazinones. The synthesized compounds can be utilized as lead compounds in the area of pharmaceuticals, agrochemicals and material science.

EXPERIMENTAL SECTION

General Information. Salicylaldehydes, ethyl 4-chloro-3-oxobutanoate and amino acids such as glycine, phenylglycine, alanine, phenylalanine, valine, serine, tyrosine, methionine, leucine, isoleucine and cystein were procured from Sigma-Aldrich. Triphenylphosphine, *p*-TsOH, thionyl chloride and solvents were obtained from local suppliers. All the reactions were carried out under reflux conditions using oil bath. The reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (mesh) and spots were visualized under UV light. Merck silica gel (60-120 mesh) was used for chromatography. Melting points were determined in open glass capillary tubes on a Stuart melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Avance 400 MHz and 500 MHz spectrometers in $CDCl_3$ using TMS as internal standard. FT-IR spectra were recorded on a Thermo Nicollet Nexus 670 spectrometer. Mass spectra were obtained on Agilent LCMS instrument. HRMS were measured on Agilent Technologies 6510, Q-TOFLC/MS ESI-Technique. Optical rotations were recorded on Anton Paar, MCP-200 polarimeter with 1 mL cell. Chiral HPLC analysis was carried out by Shimadzu SPD-M20A, PDA detector using Chiral column: CHIRALPAK IC-3, 250 mm. Eluent: *n*-hexane/isopropyl alcohol = 85:15; flow rate: 0.6 mL/min; 200-500 nm. The Chiral HPLC analyses for the amino acid ethyl esters **2e-f** and **2p-q** have been analyzed by CHIRALPAK IC-G, 250 mm. Eluent: *n*-hexane/isopropyl alcohol = 85:15; flow rate: 0.5 mL/min using RID detector.

General procedure for the preparation of ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates 1a-f: The benzoxepine-4-carboxylates **1a-f** have been prepared from ethyl 2-(chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylates by Wittig homologation as per our previous reported method and the compounds were compared with our reported compounds.[8a,c,9]

Typical procedure for the preparation of 3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazin-2-ones: *p*-TsOH (0.057 g, 0.3 mmol) was added to the stirred solution of ethyl (*S*)-2-amino-3-phenylpropanoate (**2a**, 0.229 g, 1.0 mmol) and ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate (**1a**, 0.232 g, 1.0 mmol) in DCM at room temperature. The contents were refluxed. After completion of the reaction (TLC, 24h), the solvent was removed under reduced pressure. The crude product was purified by column chromatography using silica gel (60:120, hexane: ethyl acetate, 98:2) as eluent afforded ethyl (*S*)-3-benzyl-2-oxo-3,4-dihydro-2*H*-naphtho[1,2-*b*][1,4]oxazine-5-carboxylate **3a** as pale yellow solid in 69% yield. The target compounds **3b-v, 3x-z, 3zb** and **3ze-zg** were prepared by the reaction of ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates **1a-f** with amino acid ethyl esters **2b-l, 2n-p, 2r** and **2u-v** under similar conditions.

*Ethyl (S)-3-benzyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (**3a**)*. Pale yellow solid (108 mg, 69% Yield); $[\alpha]_D^{20}$ = +20.12 (*c* = 0.33, $CHCl_3$); mp: 168-170 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.06 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.78 (d, *J* = 8.3 Hz, 1H), 7.58-7.54 (m, 1H), 7.36-7.31 (m, 3H), 7.27 (dd, *J* = 9.5, 3.4 Hz, 1H), 7.21-7.18 (m, 2H), 7.11 (s, 1H), 4.38-4.25 (m, 3H), 3.35 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H}

NMR (126 MHz, $CDCl_3$): δ 166.8, 165.5, 135.9, 134.1, 129.6, 129.4, 129.1, 128.9, 128.8, 127.3, 126.3, 126.0, 124.2, 119.2, 115.1, 61.3, 55.6, 37.3, 14.3. FT-IR (KBr): 3332, 2990, 1768, 1688, 1466, 1298, 1211, 1154, 1047, 740 cm^{-1}. MS-ESI: *m/z* 362 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{20}NO_4$ $[M+H]^+$ 362.1392; found 362.1386. HPLC analysis: enantiomeric purity = 99.89%.

Ethyl (R--3-benzyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3b***). Pale yellow solid (106 mg, 68% Yield); $[\alpha]_D^{20}$ = -19.52 (*c* = 0.33, $CHCl_3$); mp: 167-169 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.58-7.54 (m, 1H), 7.37-7.31 (m, 3H), 7.27 (dd, *J* = 9.5, 3.4 Hz, 1H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.11 (s, 1H), 4.37-4.26 (m, 3H), 3.35 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 10.1 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.8, 165.2, 135.9, 134.1, 129.6, 129.4, 129.1, 128.9, 128.8, 127.3, 126.3, 126.0, 124.2, 119.2, 115.1, 61.3, 55.6, 37.3, 14.3. FT-IR (KBr): 3331, 2989, 1768, 1688, 1465, 1298, 1210, 1154, 1047, 740 cm^{-1}. MS-ESI: *m/z* 362 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}NNaO_4$ $[M+Na]^+$ 384.1206; found 384.1229. HPLC analysis: enantiomeric purity = 99.95%.

Ethyl 3-benzyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3c***). Pale yellow solid (93 mg, 59% Yield); mp: 152-154 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.06 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.79 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.60-7.52 (m, 1H), 7.37-7.26 (m, 4H), 7.22-7.17 (m, 2H), 7.11 (s, 1H), 4.38-4.25 (m, 3H), 3.35 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.7, 10.1 Hz, 1H), 1.40-1.35 (m, 3H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.7, 165.5, 135.8, 134.0, 129.6, 129.3, 129.1, 128.6, 128.8, 127.3, 126.3, 125.7, 124.1, 119.1, 115.1, 61.3, 55.5, 37.2, 14.3. FT-IR (KBr): 3563, 3371, 3328, 1766, 1702, 1641, 1520, 1475, 1382, 1304, 1212 cm^{-1}. MS-ESI: *m/z* 362 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{20}NO_4$ $[M+H]^+$ 362.1392; found 362.1392. HPLC analysis: enantiomeric purity = 50.61% for (*S*) and 49.39% for (*R*).

Ethyl (S)-3-benzyl-8-bromo-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3d***). Pale yellow solid (40 mg, 28% Yield) ; $[\alpha]_D^{20}$ = +6.91 (*c* = 0.33, $CHCl_3$); mp: 170-172 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.93 (dd, *J* = 7.9, 5.3 Hz, 2H), 7.60 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.16 (s, 1H), 4.38-4.27 (m, 3H), 3.36 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 9.9 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.5, 165.1, 135.7, 134.1, 132.5, 130.8, 130.1, 129.3, 128.9, 127.6, 127.4, 127.2, 124.3, 121.0, 117.7, 115.9, 61.5, 55.4, 37.5, 14.3. FT-IR (KBr): 3336, 2992, 1772, 1690, 1465, 1330, 1277, 1159, 1048, 810 cm^{-1}. MS-ESI: *m/z* 440 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}BrNO_4$ $[M+H]^+$ 440.0497; found 440.0500. HPLC analysis: enantiomeric purity = 99.76%.

Ethyl (R)-3-benzyl-8-bromo-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3e***). Pale yellow solid (38 mg, 27% Yield); $[\alpha]_D^{20}$ = -8.60 (*c* = 0.2, $CHCl_3$); mp: 168-170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.92 (d, *J* = 9.7 Hz, 2H), 7.60 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.27 (d, *J* = 7.4 Hz, 1H), 7.19 (d, *J* = 6.9 Hz, 2H), 7.16 (s, 1H), 4.38-4.26 (m, 3H), 3.35 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.7, 9.9 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.5, 165.1, 135.7, 134.1, 132.5, 130.8, 130.1, 129.4, 128.9, 127.6, 127.4, 127.2, 124.3, 121.0, 117.7, 115.9, 61.5, 55.4, 37.5, 14.3. FT-IR (KBr): 3335, 2990, 1772, 1690, 1464, 1330, 1276, 1159, 1048, 810 cm^{-1}. MS-ESI: *m/z* 440 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}BrNO_4$ $[M+H]^+$ 440.0497; found 440.0479. HPLC analysis: enantiomeric purity = 98.63%.

Ethyl (S)-3-benzyl-8-chloro-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3f***). Pale yellow solid (36 mg, 25% Yield); $[\alpha]_D^{20}$ = +7.55 (*c* = 0.05, $CHCl_3$); mp: 168-170 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.76 (d, *J* = 1.9 Hz, 1H), 7.48 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.15 (s, 1H), 4.38-4.27 (m, 3H), 3.36 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 9.9 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.5, 165.1, 135.7, 134.1, 130.1, 129.9, 129.8, 129.4, 128.9, 127.7, 127.5, 127.4, 126.7, 124.2, 121.0, 116.1, 61.5, 55.4, 37.5, 14.3. FT-IR (KBr): 3337, 2925, 1770, 1690, 1465, 1333, 1279, 1153, 1046, 809 cm^{-1}. MS-ESI: *m/z* 396 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}ClNO_4$ $[M+H]^+$ 396.1003; found 396.0965. HPLC analysis: enantiomeric purity = 99.99%.

Ethyl (R)-3-benzyl-8-chloro-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3g***). Pale yellow solid (33 mg, 24% Yield); $[\alpha]_D^{20}$ = -7.0 (*c* = 0.2, $CHCl_3$); mp: 167-169 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.99 (d, *J* = 9.1 Hz, 1H), 7.76 (d, *J* = 1.9 Hz, 1H), 7.48 (dd, *J* = 9.1, 2.0 Hz, 1H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.15 (s, 1H), 4.38-4.27 (m, 3H), 3.36 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.8, 9.9 Hz, 1H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.5, 165.1, 135.7, 134.1, 130.1, 129.9, 129.8, 129.3, 128.9, 127.7, 127.5,

127.4, 126.7, 124.1, 120.9, 116.0, 61.5, 55.4, 37.5, 14.3. FT-IR (KBr): 3336, 2924, 1770, 1690, 1464, 1333, 1279, 1152, 1046, 809 cm^{-1}. MS-ESI: *m/z* 396 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}ClNO_4$ $[M+H]^+$ 396.1003; found 396.0971. HPLC analysis: enantiomeric purity = >99%.

Ethyl (S)-3-benzyl-8-methoxy-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3h***). Pale yellow solid (99 mg, 59% Yield); $[\alpha]_D^{20}$ = +26.23 (*c* = 0.33, $CHCl_3$); mp: 166-168 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.29-7.22 (m, 2H), 7.19 (d, *J* = 6.9 Hz, 2H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.95 (s, 1H), 4.36-4.27 (m, 2H), 4.26-4.21 (m, 1H), 3.90 (s, 3H), 3.34 (dd, *J* = 13.8, 3.7 Hz, 1H), 3.00 (dd, *J* = 13.7, 10.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.8, 165.7, 156.4, 136.0, 134.8, 129.4, 128.9, 128.2, 127.5, 127.3, 127.0, 122.6, 121.7, 120.9, 115.6, 106.5, 61.3, 55.6, 55.4, 37.2, 14.3. FT-IR (KBr): 3320, 2969, 2935, 1757, 1686, 1517, 1339, 1289, 1160, 1024, 826, 698 cm^{-1}. MS-ESI: *m/z* 392 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{22}NO_5$ $[M+H]^+$ 392.1498; found 392.1495. HPLC analysis: enantiomeric purity = >99%.

Ethyl (R)-3-benzyl-8-methoxy-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3i***). Pale yellow solid (99 mg, 59% Yield); $[\alpha]_D^{20}$ = -24.92 (*c* = 0.33, $CHCl_3$); mp: 165-167 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.30-7.23 (m, 2H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.09 (d, *J* = 2.4 Hz, 1H), 6.95 (s, 1H), 4.36-4.28 (m, 2H), 4.24 (ddt, *J* = 10.0, 3.6, 1.8 Hz, 1H), 3.90 (s, 3H), 3.34 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.01 (dd, *J* = 13.8, 10.1 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.8, 165.7, 156.5, 135.9, 134.8, 129.4, 128.9, 128.2, 127.5, 127.3, 127.0, 122.6, 121.7, 120.9, 115.6, 106.5, 61.3, 55.7, 55.4, 37.2, 14.3. FT-IR (KBr): 3319, 2967, 2934, 1757, 1686, 1517, 1338, 1287, 1160, 1024, 824, 698 cm^{-1}. MS-ESI: *m/z* 392 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{22}NO_5$ $[M+H]^+$ 392.1492; found 392.1500. HPLC analysis: enantiomeric purity = 99.98%.

Ethyl (S)-3-benzyl-8-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3j***). Pale yellow solid (87 mg, 57% Yield); $[\alpha]_D^{20}$ = +18.32 (*c* = 0.33, $CHCl_3$); mp: 186-188 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.96 (d, *J* = 8.7 Hz, 1H), 7.55 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 1H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 -7.24 (m, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 7.02 (s, 1H), 4.35-4.27 (m, 2H), 4.27-4.22 (m, 1H), 3.34 (dd, *J* = 13.8, 3.7 Hz, 1H), 3.00 (dd, *J* = 13.7, 10.2 Hz, 1H), 2.47 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.9, 165.7, 135.9, 134.3, 133.8, 131.8, 129.4, 128.9, 128.8, 128.1, 127.8, 127.3, 126.7, 124.3, 119.1, 115.1, 61.3, 55.6, 37.2, 21.4, 14.3. FT-IR (KBr): 3331, 2973, 2927, 1757, 1689, 1488, 1337, 1292, 1158, 1049, 809 cm^{-1}. MS-ESI: *m/z* 376 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{22}NO_4$ $[M+H]^+$ 376.1543; found 376.1554. HPLC analysis: enantiomeric purity = 99.56%.

Ethyl (R)-3-benzyl-8-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3k***). Pale yellow solid (85 mg, 58% Yield); $[\alpha]_D^{20}$ = -18.12 (*c* = 0.33, $CHCl_3$); mp: 183-185 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.56 (s, 1H), 7.43-7.39 (m, 1H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.30-7.24 (m, 2H), 7.19 (d, *J* = 6.9 Hz, 2H), 7.03 (s, 1H), 4.32 (qd, *J* = 7.1, 3.6 Hz, 2H), 4.25 (dd, *J* = 10.8, 3.2 Hz, 1H), 3.34 (dd, *J* = 13.7, 3.7 Hz, 1H), 3.01 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.47 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.9, 165.7, 135.9, 134.3, 133.8, 131.7, 129.4, 128.9, 128.8, 128.1, 127.8, 127.3, 126.7, 124.3, 119.1, 115.1, 61.3, 55.6, 37.2, 21.4, 14.3. FT-IR (KBr): 3330, 2972, 2927, 1757, 1689, 1488, 1336, 1292, 1158, 1049, 808 cm^{-1}. MS-ESI: *m/z* 376 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{21}NNaO_4$ $[M+Na]^+$ 398.1363; found 398.1386. HPLC analysis: enantiomeric purity = 99.59%.

Ethyl (S)-3-benzyl-10-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3l***). Pale yellow solid (79 mg, 55% Yield); $[\alpha]_D^{20}$ = +19.02 (*c* = 0.33, $CHCl_3$); mp: 189-191 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.32 (dd, *J* = 13.2, 5.9 Hz, 3H), 7.27 (d, *J* = 8.1 Hz, 1H), 7.18 (dd, *J* = 6.9, 5.0 Hz, 4H), 4.37-4.28 (m, 2H), 4.19 (ddd, *J* = 9.8, 3.7, 1.5 Hz, 1H), 3.34 (dd, *J* = 13.8, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.7, 9.9 Hz, 1H), 2.93 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.7, 165.6, 136.2, 135.9, 132.2, 131.9, 130.8, 129.8, 129.4, 128.9, 127.8, 127.7, 127.3, 125.8, 123.8, 114.7, 61.3, 54.9, 36.9, 24.4, 14.3. FT-IR (KBr): 3333, 2989, 2930, 1759, 1688, 1448, 1325, 1292, 1163, 1047, 785 cm^{-1}. MS-ESI: *m/z* 376 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{22}NO_4$ $[M+H]^+$ 376.1549; found 376.1545. HPLC analysis: enantiomeric purity = 99.30%.

Ethyl (R)-3-benzyl-10-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3m***). Pale yellow solid (76 mg, 54% Yield); $[\alpha]_D^{20}$ = -18.92 (*c* = 0.33, $CHCl_3$); mp: 187-189 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.61 (d, *J* = 8.1 Hz, 1H), 7.32 (dd, *J* = 13.9, 6.4 Hz, 3H), 7.27 (d, *J* = 8.6 Hz, 1H), 7.22-7.16 (m, 4H), 4.37-4.28 (m, 2H), 4.19 (ddd, *J* = 9.9, 3.9, 1.6 Hz, 1H), 3.34 (dd, *J* = 13.8, 3.9 Hz, 1H), 3.03 (dd, *J* = 13.8, 9.9 Hz, 1H), 2.93 (s, 3H), 1.37 (t, *J* = 7.1 Hz, 3H). ^{13}C $\{^1H\}$

NMR (126 MHz, $CDCl_3$): δ 166.7, 165.6, 136.2, 135.9, 132.2, 131.9, 130.8, 129.7, 129.4, 128.9, 127.8, 127.7, 127.3, 125.8, 123.8, 114.7, 61.3, 54.9, 36.9, 24.4, 14.3. FT-IR (KBr): 3332, 2987, 2929, 1759, 1688, 1448, 1324, 1291, 1163, 1047, 784 cm^{-1}. MS-ESI: *m/z* 376 $[M+H]^+$; HRMS-ESI: calcd for $C_{23}H_{21}NNaO_4$ $[M+Na]^+$ 398.1363; found 398.1389. HPLC analysis: enantiomeric purity = 99.83%.

Ethyl 2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3n***). Pale yellow solid (21 mg, 18% Yield); mp: 127-129 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.21 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.17 (d, *J* = 1.5 Hz, 2H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ 167.4, 163.9, 134.2, 130.9, 129.5, 129.1, 128.8, 126.3, 126.3, 124.2, 119.1, 114.7, 61.4, 44.5, 14.3. FT-IR (KBr): 3364, 2924, 2854, 1777, 1695, 1461, 1376, 1300, 1042, 786 cm^{-1}. MS-ESI: *m/z* 272 $[M+H]^+$. HRMS-ESI: calcd for $C_{15}H_{14}NO_4$ $[M+H]^+$ 272.0923; found 272.0920.

Ethyl (S)-3-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3o***). Pale yellow solid (38 mg, 31% Yield); $[\alpha]_D^{20}$ = +9.01 (*c* = 0.2, $CHCl_3$); mp: 102-104 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.09-8.03 (m, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.56 (m, 1H), 7.38-7.32 (m, 1H), 7.17 (s, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.09 (m, 1H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.47 (t, *J* = 7.1 Hz, 3H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$): δ 167.4, 166.5, 134.4, 130.8, 129.4, 129.1, 128.6, 126.3, 126.2, 124.2, 119.2, 114.7, 61.4, 49.8, 17.3, 14.3. FT-IR (KBr): 3330, 2980, 2925, 1772, 1692, 1466, 1377, 1298, 1212, 1042, 784 cm^{-1}. MS-ESI: *m/z* 286 $[M+H]^+$; HRMS-ESI: calcd for $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1074; found 286.1090. HPLC analysis: enantiomeric purity = 97.84%.

Ethyl (R)-3-methyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3p***). Pale yellow solid (68 mg, 55% Yield); $[\alpha]_D^{20}$ = -8.81 (c = 0.3818, $CHCl_3$); mp: 124-126 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.06 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.83-7.75 (m, 1H), 7.61-7.51 (m, 1H), 7.35 (m, 1H), 7.19 (s, 1H), 4.48-4.40 (m, 2H), 4.13-4.06 (m, 1H), 1.63 (d, *J* = 6.7 Hz, 3H), 1.50-1.44 (m, 3H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$): δ 167.4, 166.5, 134.3, 130.8, 129.3, 129.1, 128.5, 126.3, 126.1, 124.1, 119.2, 114.7, 61.4, 49.7, 17.2, 14.2. FT-IR (KBr): 3363, 3023, 1174, 1696, 1471, 1381, 1304, 1215 cm^{-1}. MS-ESI: *m/z* 286 $[M+H]^+$; HRMS-ESI: calcd for $C_{16}H_{16}NO_4$ $[M+H]^+$ 286.1079; found 286.1094. HPLC analysis: enantiomeric purity = 99.63%.

Ethyl (S)-3-isopropyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3q***). Pale yellow solid (60 mg, 44% Yield); $[\alpha]_D^{20}$ = +65.16 (*c* = 0.33, $CHCl_3$); mp: 72-74 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.57-7.51 (m, 1H), 7.45 (s, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 4.45 (tt, *J* = 7.2, 3.6 Hz, 2H), 3.94 (dd, *J* = 6.1, 1.8 Hz, 1H), 2.28 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$): δ 167.5, 165.0, 133.5, 130.2, 129.3, 129.1, 128.6, 125.9, 123.8, 119.1, 114.3, 61.4, 59.9, 30.3, 19.0, 17.8, 14.3. FT-IR (KBr): 3327, 2963, 2928, 1764, 1692, 1475, 1342, 1296, 1156, 1046, 783 cm^{-1}. MS-ESI: *m/z* 314 $[M+H]^+$; HRMS-ESI: calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1392; found 314.1391. HPLC analysis: enantiomeric purity = >99%.

Ethyl (R)-3-isopropyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3r***). Pale yellow solid (60 mg, 44% Yield); $[\alpha]_D^{20}$ = -60.66 (*c* = 0.33, $CHCl_3$); mp: 70-72 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.2 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 4.45 (dd, *J* = 13.2, 6.7 Hz, 2H), 3.94 (d, *J* = 5.0 Hz, 1H), 2.28 (m, 1H), 1.47 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.7 Hz, 3H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$): δ 167.5, 165.0, 133.5, 130.2, 129.3, 129.1, 128.6, 125.9, 123.8, 119.1, 114.4, 61.4, 59.9, 30.3, 19.0, 17.8, 14.4. FT-IR (KBr): 3326, 2962, 2928, 1764, 1692, 1474, 1342, 1295, 1156, 1045, 783 cm^{-1}. MS-ESI: *m/z* 314 $[M+H]^+$; HRMS-ESI: calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$ 314.1387; found 314.1376. HPLC analysis: enantiomeric purity = 99.88%.

Ethyl (S)-3-isobutyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3s***). Pale yellow solid (58 mg, 41% Yield); $[\alpha]_D^{20}$ = +4.76 (c = 0.4181, $CHCl_3$); mp: 76-78 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.36 (s, 1H), 8.08-8.02 (m, 1H), 7.82-7.76 (m, 1H), 7.58-7.52 (m, 1H), 7.33 (dd, *J* = 9.2, 5.1, 1.7 Hz, 2H), 4.48-4.40 (m, 2H), 4.11 (dd, *J* = 8.8, 4.9, 1.6 Hz, 1H), 1.91-1.73 (m, 3H), 1.49-1.45 (m, 3H), 1.00 (dd, *J* = 6.2, 5.3 Hz, 6H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$): δ 167.4, 166.2, 133.9, 130.2, 129.3, 129.1, 128.6, 126.2, 126.0, 124.0, 119.1, 114.7, 61.4, 52.2, 39.6, 24.3, 23.1, 21.3, 14.3. FT-IR (KBr): 3324, 3053, 2978, 2928, 1728, 1652, 1490, 1316, 1232, 1101, 1047 cm^{-1}. MS-ESI: *m/z* 328 $[M+H]^+$; HRMS-ESI: calcd for $C_{19}H_{22}NO_4$ $[M+H]^+$ 328.1549; found 328.1557. HPLC analysis: enantiomeric purity = >99%.

Ethyl (R)-3-isobutyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3t***). Pale yellow solid (66 mg,

47% Yield); $[\alpha]_D^{20}$ = -2.24 (c = 0.6454, $CHCl_3$); mp: 90-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 6.9 Hz, 1H), 7.98 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.71 (t, *J* = 6.3 Hz, 1H), 7.52-7.45 (m, 1H), 7.30-7.23 (m, 2H), 4.40-4.33 (m, 2H), 4.06-4.00 (m, 1H), 1.84-1.67 (m, 3H), 1.42-1.38 (m, 3H), 0.92 (dd, *J* = 6.2, 5.2 Hz, 6H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.4, 165.2, 133.0, 129.2, 128.3, 128.1, 127.6, 125.2, 125.0, 123.0, 118.1, 113.7, 60.4, 51.2, 38.6, 23.4, 22.1, 20.3, 13.3. FT-IR (KBr): 3355, 2964, 1776, 1697, 1640, 1525, 1476, 1382, 1306, 1210 cm^{-1}. MS-ESI: *m/z* 328 $[M+H]^+$; HRMS-ESI: calcd for $C_{19}H_{22}NO_4$ $[M+H]^+$ 328.1531; found 328.1549. HPLC analysis: enantiomeric purity = >99%.

Ethyl (S)-3-(2-(methylthio)ethyl)-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3u***). Pale yellow solid (60 mg, 40% Yield); $[\alpha]_D^{20}$ = +9.18 (c = 0.4636, $CHCl_3$); mp: 111-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.05 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.84-7.75 (m, 1H), 7.56 (m, 1H), 7.40-7.32 (m, 2H), 4.49-4.40 (m, 2H), 4.29 (m, 1H), 2.80-2.65 (m, 2H), 2.35-2.23 (m, 1H), 2.20-2.15 (m, 4H), 1.50-1.44 (m, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.3, 165.7, 133.9, 129.9, 129.4, 129.1, 128.7, 126.3, 126.0, 124.1, 119.1, 114.7, 61.9, 61.4, 52.7, 30.2, 29.7, 15.4, 14.3. FT-IR (KBr): 3601, 3358, 3012, 2555, 1777, 1699, 1641, 1526, 1480, 1382, 1301, 1215 cm^{-1}. MS-ESI: *m/z* 346 $[M+H]^+$; HRMS-ESI: calcd for $C_{18}H_{20}NO_4S$ $[M+H]^+$ 346.1113; found 346.1104. HPLC analysis: enantiomeric purity = 96.11%.

Ethyl (R)-3-(2-(methylthio)ethyl)-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3v***). Pale yellow solid (56 mg, 44% Yield); $[\alpha]_D^{20}$ = -9.70 (c = 0.2909, $CHCl_3$); mp: 102-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.05 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.56 (dd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.37 (d, *J* = 1.1 Hz, 1H), 7.36-7.32 (m, 1H), 4.48-4.41 (m, 2H), 4.29 (dd, *J* = 7.4, 5.0, 1.4 Hz, 1H), 2.80-2.65 (m, 2H), 2.34-2.23 (m, 1H), 2.20-2.10 (m, 4H), 1.50-1.44 (m, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.4, 165.7, 133.9, 129.9, 129.4, 129.1, 128.7, 126.3, 126.0, 124.1, 119.1, 114.7, 61.4, 52.7, 30.2, 29.8, 15.4, 14.3. FT-IR (KBr): 3684, 3022, 2405, 1773, 1695, 1215 cm^{-1}. MS-ESI: *m/z* 346 $[M+H]^+$; HRMS-ESI: calcd for $C_{18}H_{20}NO_4S$ $[M+H]^+$ 346.1113; found 346.1102. HPLC analysis: enantiomeric purity = 97.28%.

Ethyl (S)-3-(4-hydroxybenzyl)-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3x***). Pale yellow solid (33 mg, 19% Yield); $[\alpha]_D^{20}$ = +2.0 (*c* = 0.3, $CHCl_3$); mp: 158-160 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.12 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 4.34 (qd, *J* = 7.1, 3.6 Hz, 2H), 4.26-4.19 (m, 1H), 3.27 (dd, *J* = 13.9, 3.8 Hz, 1H), 2.95 (dd, *J* = 13.9, 10.0 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.9, 165.7, 155.0, 134.0, 130.6, 129.7, 129.4, 129.13, 128. 9, 127.8, 126.3, 126.0, 124.2, 119.2, 115.8, 114.9, 61.4, 55.6, 36.5, 14.3. FT-IR (KBr): 3446, 3332, 2985, 1765, 1687, 1511, 1471, 1332, 1298, 1210, 1158, 1046, 783 cm^{-1}. MS-ESI: *m/z* 378 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{20}NO_5$ $[M+H]^+$ 378.1341; found 378.1346. HPLC analysis: enantiomeric purity = 99.79%.

Ethyl (R)-3-(4-hydroxybenzyl)-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3y***). Pale yellow solid (31 mg, 18% Yield); $[\alpha]_D^{20}$ = -1.67 (*c* = 0.3, $CHCl_3$); mp: 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 6.79 (d, *J* = 8.2 Hz, 2H), 4.40-4.30 (m, 2H), 4.23 (d, *J* = 7.4 Hz, 1H), 3.27 (dd, *J* = 13.9, 3.6 Hz, 1H), 2.96 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.9, 165.7, 154.9, 134.0, 130.6, 129.7, 129.4, 129.13, 128.9, 127.9, 126.3, 126.0, 124.2, 119.2, 115.8, 115.0, 61.4, 55.6, 36.5, 14.3. FT-IR (KBr): 3445, 3330, 2986, 1766, 1687, 1510, 1471, 1330, 1298, 1211, 1155, 1044, 820 cm^{-1}. MS-ESI: *m/z* 378 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{19}NNaO_5$ $[M+Na]^+$ 400.1155; found 400.1149. HPLC analysis: enantiomeric purity = 99.79%.

Ethyl (S)-3-(hydroxymethyl)-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3z***). Pale yellow solid (19 mg, 14% Yield); $[\alpha]_D^{20}$ = +3.86 (*c* = 0.23, $CHCl_3$); mp: 152-154 °C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.47 (s, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 4.44 (q, *J* = 7.1 Hz, 2H), 4.20 (dd, *J* = 13.0, 8.4 Hz, 2H), 4.08 (d, *J* = 5.7 Hz, 1H), 2.38 (s, 1H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.4, 165.1, 133.8, 130.2, 129.5, 129.2, 128.9, 126.3, 126.1, 124.2, 119.1, 114.7, 62.6, 61.5, 55.3, 14.3. FT-IR (KBr): 3335, 2981, 1769, 1693, 1471, 1377, 1300, 1176, 1041, 786 cm^{-1}. MS-ESI: *m/z* 324 $[M+Na]^+$; HRMS-ESI: calcd for $C_{16}H_{15}NNaO_5$ $[M+Na]^+$ 324.0827; found 324.0842. HPLC analysis: enantiomeric purity = >99%.

Ethyl (S)-3-sec-butyl-2-oxo-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3zb***). Pale yellow liquid (47 mg, 33% Yield); $[\alpha]_D^{20}$ = +2.63 (c = 0.5727, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.49-7.43 (m, 1H), 7.34 (s, 1H), 7.22 (dd, *J* = 6.3,

4.6, 0.7 Hz, 1H), 4.40-4.33 (m, 2H), 3.95 (dd, *J* = 6.0, 1.9 Hz, 1H), 1.99-1.90 (m, 1H), 1.62-1.45 (m, 2H), 1.41-1.37 (m, 3H), 1.07-0.97 (m, 3H), 0.82 (t, *J* = 7.4 Hz, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): *δ* 166.4, 163.9, 132.3, 129.2, 128.2, 128.1, 127.6, 124.9, 124.8, 122.7, 117.9, 113.2, 60.3, 58.0, 35.8, 23.6, 13.3, 10.2. FT-IR (KBr): 3735, 3594, 3374, 2972, 1778, 1698, 1526, 1476, 1383, 1339, 1302, 1207 cm^{-1}. MS-ESI: *m/z* 328 $[M+H]^+$; HRMS-ESI: calcd for $C_{19}H_{22}NO_4$ $[M+H]^+$ 328.1549; found 328.1553. HPLC analysis: enantiomeric purity = >99%.

Ethyl (S)-2-oxo-3-phenyl-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3ze***). Pale yellow solid (64 mg, 43% Yield); $[\alpha]_D^{20}$ = -24.26 (c = 0.1909, $CHCl_3$); mp: 138-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.40 (s, 1H), 8.06 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.79 (t, *J* = 8.6 Hz, 1H), 7.72 (s, 1H), 7.56 (dd, *J* = 8.3, 6.8, 1.1 Hz, 1H), 7.47-7.40 (m, 2H), 7.39-7.30 (m, 4H), 5.30 (d, *J* = 1.5 Hz, 1H), 4.48-4.41 (m, 2H), 1.49-1.44 (m, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$): *δ* 167.4, 164.2, 136.2, 133.8, 130.0, 129.4, 129.1, 128.9, 128.8, 127.0, 126.3, 126.1, 124.2, 119.2, 114.5, 61.4, 58.2, 14.3. FT-IR (KBr): 3307, 3022, 1779, 1698, 1636, 1525, 1383, 1300, 1214, 1049 cm^{-1}. MS-ESI: *m/z* 348 $[M+H]^+$; HRMS-ESI: calcd for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1236; found 348.1240. HPLC analysis: enantiomeric purity = 83.75%.

Ethyl-2-oxo-3-phenyl-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3zf***). Pale yellow solid (62 mg, 42% Yield); mp: 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.40 (s, 1H), 8.06 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.72 (s, 1H), 7.60-7.53 (m, 1H), 7.46-7.41 (m, 2H), 7.39-7.31 (m, 4H), 5.30 (d, *J* = 1.7 Hz, 1H), 4.49-4.40 (m, 2H), 1.50-1.44 (m, 3H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$): *δ* 167.5, 164.3, 136.3, 133.8, 130.1, 129.5, 129.2, 129.0, 128.9, 128.8, 127.1, 126.3, 126.2, 124.2, 119.3, 114.6, 61.5, 58.3, 14.3. FT-IR (KBr): 3364, 3075, 2928, 2341, 1774, 1706, 1387, 1216, 1153 cm^{-1}. MS-ESI: *m/z* 348 $[M+H]^+$; HRMS-ESI: calcd for $C_{21}H_{18}NO_4$ $[M+H]^+$ 348.1236; found 348.1240. HPLC analysis: enantiomeric purity of *R* isomer = 46.46%, *S* isomer = 53.54%.

Ethyl (R)-10-methyl-2-oxo-3-phenyl-3,4-dihydro-2H-naphtho[1,2-b][1,4]oxazine-5-carboxylate (***3zg***). Pale yellow solid (45 mg, 31% Yield); $[\alpha]_D^{20}$ = +0.69 (c = 0.7272, $CHCl_3$); mp: 108-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.36 (s, 1H), 7.81 (s, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 6.6 Hz, 2H), 7.36-7.29 (m, 4H), 7.19 (t, *J* = 7.6 Hz, 1H), 5.21 (s, 1H), 4.45 (q, *J* = 7.0 Hz, 2H), 2.91 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H). ^{13}C {1H} NMR (101 MHz, $CDCl_3$): *δ* 166.3, 151.3, 147.7, 145.4, 136.3, 134.4, 134.1, 131.9, 131.5, 129.5, 129.0, 128.5, 128.3, 127.9, 127.5, 126.2, 123.0, 61.8, 60.3, 24.6, 14.5. FT-IR (KBr): 3697, 3021, 2407, 1763, 1524, 1312, 1215, 1026 cm^{-1}. MS-ESI: *m/z* 362 $[M+H]^+$; HRMS-ESI: calcd for $C_{22}H_{20}NO_4$ $[M+H]^+$ 362.1392; found 362.1400. HPLC analysis: enantiomeric purity = >99%.

ASSOCIATED CONTENT

Supporting Information

The copies of ^{1}H, ^{13}C NMR spectras, structures of the amino acid ethyl esters 2a-v, HPLC chromatograms and HRMS spectra were provided in SI. This material is available free of charge via the internet at http://pubs.acs.org.

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Notes

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