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Highly enantioselective organocatalytic cascade reaction for the synthesis of piperidines and oxazolidines

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ABSTRACT

The synthesis of piperidines and piperidines derivatives in enantiopure fashion has been a challenging goal for organic chemists. In this report we developed a nice cascade reaction for piperidine derivatives based in an amidomalonate Michael addition to enals followed by an intramolecular hemiaminal formation with good yields and enantioselectivities. Moreover we studied the 'in situ' intramolecular cyclization of this hemiaminals with alcohols forming fused piperidine–oxazolidines.

1. Introduction

In the last decades, the development of new asymmetric methodologies that allow building complex structures has been a highly pursued target for organic chemists.

With the renaissance of organocatalysis in 2000,[1] new and powerful cascade or tandem reactions have emerged for the synthesis of heterocycles.[2] In these processes, highly complex and functionalized organic scaffolds are easily accessed from simple starting materials by combining two or more reaction steps, where at least one involves an asymmetric process, to take place in the same reaction mixture. These processes are commonly environmentally friendly, since the generation of chemical waste is reduced and avoids time-consuming and costly processes, including the purification of intermediates and steps involving the protection and deprotection of functional groups in addition to high efficiency.[3]

Heterocycles, and more concretely, aza-heterocycles, such as piperidines, have a great importance in biological and pharmaceutical chemistry due to its presence as structural motif in numerous natural alkaloids, such as the fire ant toxin solenopsin, the nicotine analog anabasine, or the famous Socrates' poison coniine.

The importance of piperidine analogs in medicinal chemistry is well established due to the blockbuster drug paroxetine and the related analog femoxetine (Fig. 1).[4]

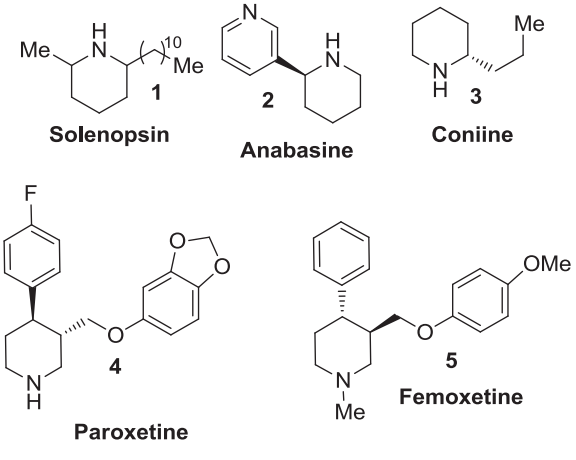

Fig. 1. Examples of biologically active piperidines.

Aza-heterocycles have attracted much attention from several research groups. For example the synthesis of pyrrolidines has been achieved via [3+2] cycloadditions of azomethine ylides with enals,[5]

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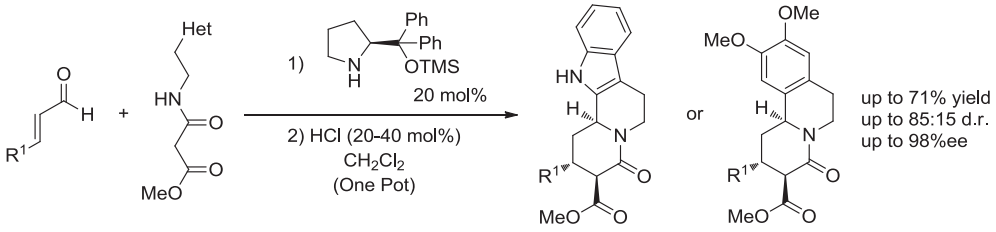
nitroalkenes[6] or other activated alkenes;[7] a different approximation was made by Rios and Cordova consisting on the addition of 2-aminomalonates to enals.[8] Soon after, Carter and Fustero reported the highly enantioselective synthesis of pyrrolidines via an intramolecular aza-Michael addition.[9]

Despite all these efforts the synthesis of piperidine moieties has been limited to few examples of intramolecular aza-Michael reactions described by Fustero and Carter,[9] and aza-Diels–Alder reaction reported by Bode,[10] Cordova,[11] Chen,[12] and others…[13]

In 2009, based on the previous synthesis of pyrrolidines via a malonate addition followed by an intramolecular aminal formation, Franzen,[14] and soon after us[15] developed a similar strategy to the synthesis of highly substituted piperidines (Scheme 1). During the preparation of this manuscript, several research groups have found similar results base on similar strategies.[16]



Scheme 1. Reaction reported by Franzén.

Here we wish to present our work in the synthesis of piperidines and related bicycles and the application of this methodology to the formal synthesis of blockbuster drug paroxetine and its related analog femoxetine.

2. Results and discussion

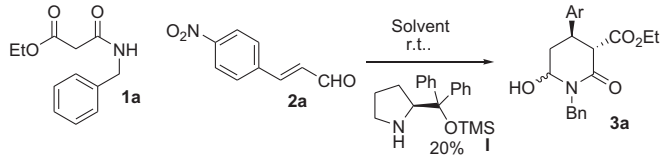
Based in our previous experience in organocatalysis,[17] we selected the TMS-protected diphenylprolinol **I** as the catalyst in our initial experiments (Table 1), and we screened different solvents and additives in order to achieve high enantioselectivities and yields in the addition of amidomalonate **6a** to 4-nitrocinnamaldehyde (**7a**).

To our delight, when polar protic solvents, such as MeOH or EtOH were used (entries 6 and 8), the reaction performed well but with moderate enantioselectivities. Interestingly, when non-polar or non-protic solvents were used (entries 2, 3, 9, and 10), no reaction was observed. The reaction is simply catalyzed by secondary amines, but it requires an additional base, such as KOAc to afford high yields. Surprisingly when 2,2,2-trifluoroethanol, which is more acidic, was used as a solvent (entry 11), we achieved very high enantioselectivities and yields.

This effect could probably be explained by the increment in the nucleophilicity of the amidomalonate in more acidic solvents.

Once we determined the optimal conditions to perform the reaction, we screened several secondary amines as catalysts. As it is shown in Table 2, catalyst **I** gave us the best enantioselectivities, while proline (**II**) or catalysts **III** or **IV** afforded worse enantioselectivities and yields.

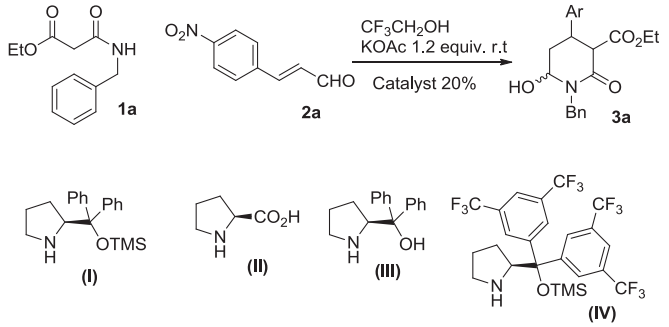
Table 1
Solvent and additive screening[a]



Entry	Solvent	Additive	Yield[b] (%)	dr[c]	ee[d] (%)
1	$CHCl_3$	—	0	—	—
2	$CHCl_3$	Et_3N	0	—	—
3	$CHCl_3$	KOAc	Traces	—	—
4	MeOH	—	0	—	—
5	MeOH	Et_3N	67	5:1	57
6	MeOH	KOAc	86	5:1	74
7	MeOH[e]	KOAc	72	5:1	96
8	EtOH	KOAc	75	5:1	62
9	AcOEt	Et_3N	0	—	—
10	Toluene	Et_3N	0	—	—
11	CF_3CH_2OH	KOAc	92	5:1	95

[a] Experimental conditions: A mixture of **1a** (0.30 mmol), catalyst **I** (20 mol %, 0.05 mmol), **2a** (0.25 mmol), and additive (0.30 mmol) in the corresponding solvent (1 mL) was stirred at rt overnight. Crude product **3a** was purified by column chromatography.
[b] Isolated yield.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis.
[e] Reaction run at 0 °C.

Table 2
Catalyst screening[a]

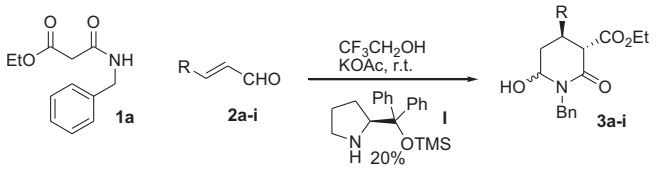


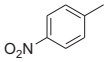
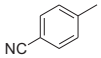
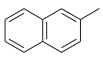
Entry	Catalyst	Yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	92	5:1	95
2	**II**	76	5:1	22
3	**III**	0	—	—
4	**IV**	56	5:1	58

[a] Experimental conditions: A mixture of **1a** (0.30 mmol), catalyst **I** (20 mol %, 0.05 mmol), **2a** (0.25 mmol), and additive (0.30 mmol) in solvent (1 mL) was stirred at rt overnight. Crude product **3a** was purified by column chromatography.
[b] Isolated yield.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis.

Next, we screened different α,β-unsaturated aldehydes in order to study the scope of the process (Table 3). In all the examples screened, the reaction furnished the desired piperidines in moderate to excellent yields and excellent enantioselectivities (90–99%). When electron-withdrawing substituents were used on the aromatic ring, the yields and enantioselectivies were excellent (entries 1 and 2; Table 3) and the reaction times were shorter. The reaction also works fine with halogen substituents on the aromatic ring, such as chloro, bromo or fluoro in 4-position (entries 3, 5, and 7; Table 3) or in 2-position (entry 6; Table 3). It should be noticed

Table 3
Enal screening[a]

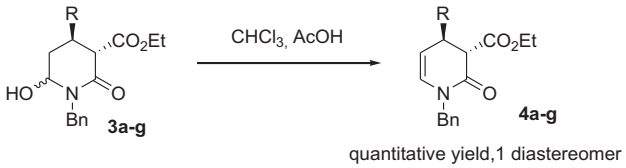


Entry	Compound	R	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	**2a**		**3a**	92	5:1	95
2	**2b**		**3b**	94	5:1	94[e]
3	**2c**		**3c**	84	4:1	90[e]
4	**2d**		**3d**	90	3:1	98
5	**2e**		**3e**	93	5:1	94[e]
6	**2f**		**3f**	71	5:1	96[e]
7	**2g**		**3g**	84	5:1	90[e]
8	**2h**		**3h**	86	3:1	99
9	**2i**	Me	**3i**	0	—	—

[a] Experimental conditions: A mixture of **1a** (0.30 mmol), catalyst **I** (20 mol %, 0.05 mmol), **2a**–**i** (0.25 mmol), and AcONa (0.30 mmol) in CF_3CH_2OH (1 mL) was stirred at rt overnight. Crude product **3a** was purified by column chromatography.
[b] Isolated yield.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis.
[e] Determined by chiral HPLC analysis of dehydrated compound.

that the reaction with aliphatic aldehydes, such as crotonaldehyde did not render the final compound in any of the conditions tested, probably due to the presence of side reactions.

In all the examples we obtained a mixture of diastereomers with 3:1 to 5:1 ratio. This diastereoselectivity corresponds to the equatorial or axial position of the hemiaminal hydroxyl group of the piperidine. This can be easily confirmed by elimination of the hydroxyl to furnish compounds **4** in acid media. In all the cases we obtained only one product in quantitative yield and without loss of enantioselectivity, as shown in Scheme 2.



Scheme 2. Dehydration of compounds **3a**–**g**.

In order to elucidate the structure of the major diastereomer of compound **3d**, we performed an X-ray diffraction analysis as shown in Fig. 2.

Next, we focused our efforts on the reaction between amidomalonates bearing different substituents in the nitrogen of the

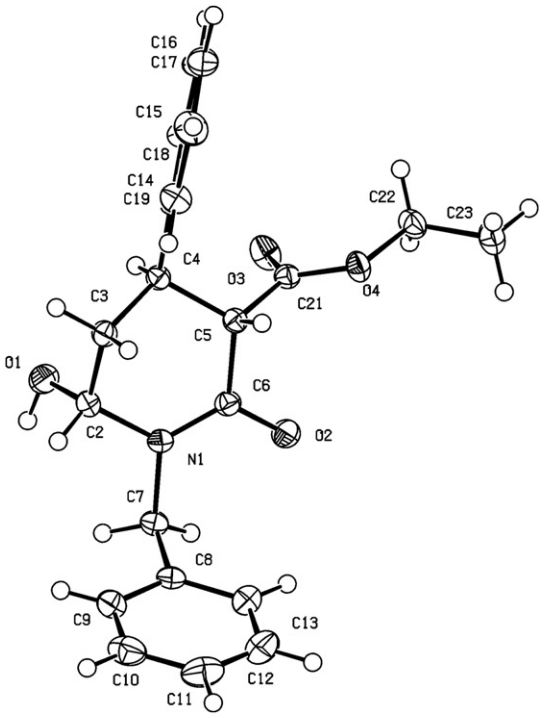
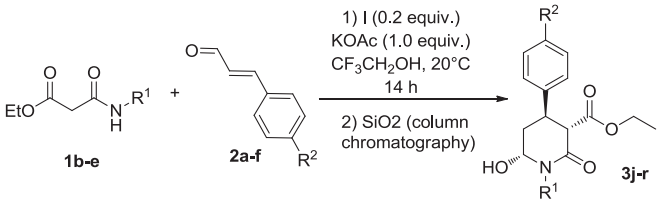


Fig. 2. X-ray ORTEP of compound **3d**.[18]

amidomalonate and enals. Thus, when we use ethyl 3-(methylamino)-3-oxopropanoate (**1b**) this reaction will render us a direct access to femoxetine (**5**).

To our delight the reaction renders the final piperidine derivatives with good yields and enantioselectivities as it is shown in Table 4. Only when bulky substituents like *tert*-butyl or isopropyl were used the yield decreases dramatically probably due to the steric hinderance that avoids the hemiaminal forming reaction. Remarkably, these compounds are quite unstable and during slow purification by column chromatography dehydrates to furnish compound **4**.

Table 4
Amidomalonate screening[a]

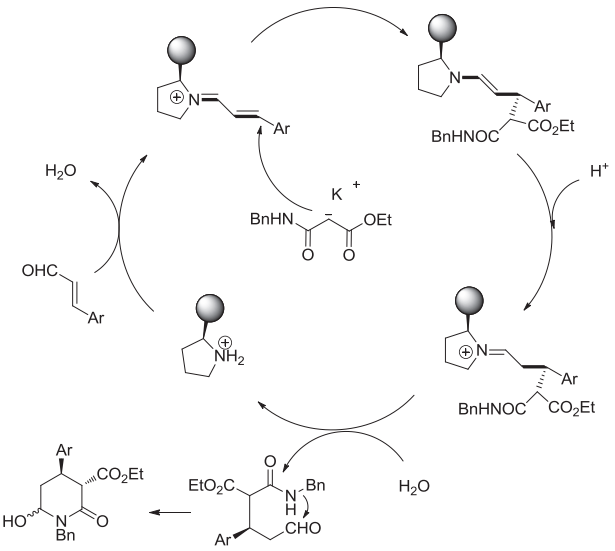


Entry	1	R^1	R^2	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1[e]	**1b**	Me	H	**3j**	66	19:1	95
2	**1b**	Me	Me	**3k**	66	9:1	92
3	**1b**	Me	F	**3l**	52	9:1	69
4	**1b**	Me	Cl	**3m**	82	9:1	94
5	**1b**	Me	Br	**3n**	68	9:1	94
6	**1b**	Me	No_2	**3o**	95	19:1	95
7	**1c**	Et	H	**3p**	14	19:1	89
8	**1d**	*i*-Pr	H	**3q**	10	10:7	91
9	**1e**	*t*-Bu	H	**3r**	—	—	—

[a] Experimental conditions: A mixture of **1b**–**e** (0.30 mmol), catalyst **I** (20 mol %, 0.05 mmol), **2a**–**f** (0.25 mmol), and AcOK (0.30 mmol) in CF_3CH_2OH (1 mL) was stirred at rt overnight. Crude product **3** was purified by column chromatography that dehydrates during the column to furnish product **4**.
[b] Isolated yield of **4**.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis of **4**.
[e] Reaction run with the opposite enantiomer of **I**.

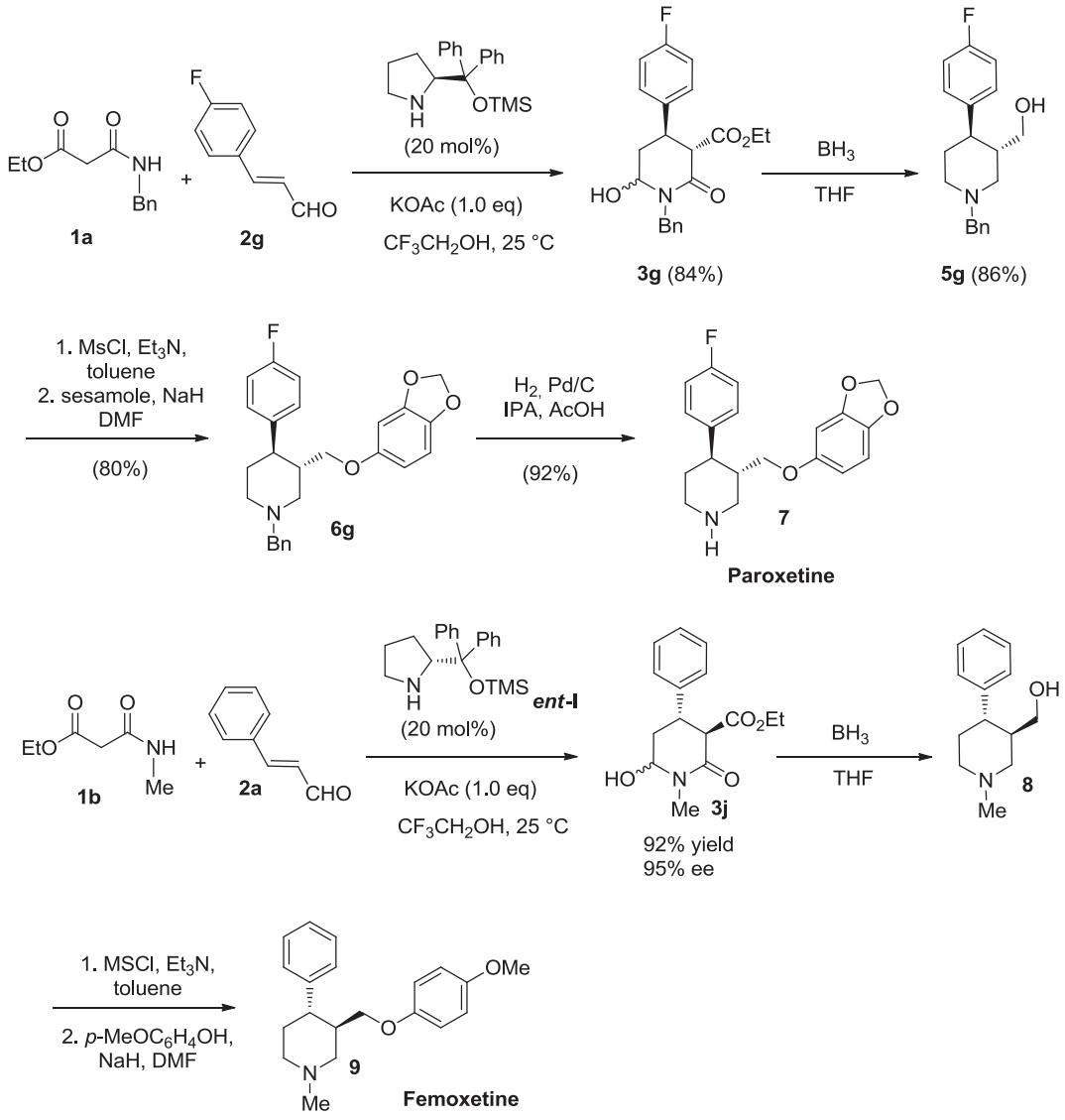
In order to show the broad utility of this reaction and to ascertain the absolute configuration of the compounds obtained we decided to do a formal synthesis of (−)-paroxetine[19] and femoxetine. As it is shown in Scheme 3, reduction of compound **3g**, gave the corresponding piperidine **5g**. Comparison with the literature data revealed that the absolute configuration of compound **5g** is (3*R*,4*S*) $[\alpha]_D^{25}$ −23.4 (*c* 1.2, $CHCl_3$), $[\alpha]_D^{25}$ −21.2 (*c* 0.5, $CHCl_3$).[20] This compound **5g** is described as a chiral intermediate in the synthesis of (−)-paroxetine, a blockbuster antidepressive drug. In a similar way, femoxetine unit was synthesized starting from amidomalonate **1b** and cinnamaldehyde. The reaction catalyzed by *ent*-**I** render the compound **3j** in 92% yield and 95% ee. Next **3j** was reduced with BH_3 in THF to render the piperidine **8** that should be further transformed to femoxetine (**9**) as shown in Scheme 3.[20]

The stereochemical outcome could be rationalized by the mechanistic proposal outlined in Scheme 4. Thus, efficient shielding of the *Re*-face of the chiral iminium intermediate by the bulky aryl groups of **I** leads to stereoselective *Si*-facial nucleophilic conjugate attack on the β-carbon of **2**. This is in accordance with other amine-catalyzed reactions between malonates and enals. Next, intermediate **7** cyclizes spontaneously via a favored 6-*exo*-*trig* ring closure to afford the hemiacetal **3**. It should be noticed that epimerization of the stereochemically labile stereocenter at C3 will establish the thermodynamically more stable (3*S*,4*R*) *trans*-configuration.



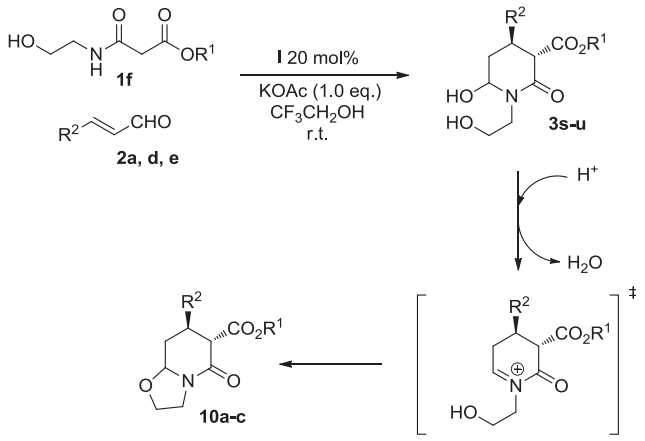
Scheme 4. Proposed mechanism.

Next, we decided to study the formation of oxazolidines via a cascade reaction taking advantage of the easy imine formation of



Scheme 3. Synthesis of paroxetine and femoxetine.

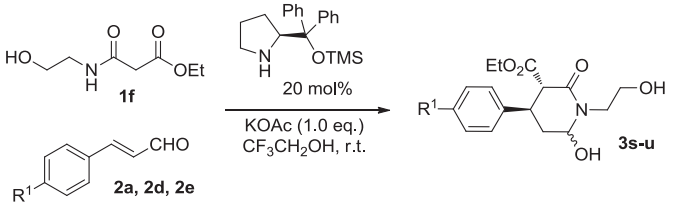
the resulting pyridines **3** in acid media. As it is shown in Scheme 5, initially, the cascade reaction of the rationally designed hydroxyamide **1f** and enal (**2**) was carried out at room temperature by using catalysts **I**, to form the desired piperidine. Next the piperidine was treated in acid media to furnish the desired oxazolidine via an intramolecular acetal formation through the formed 'in situ' imine (Scheme 5).



Scheme 5. Proposed mechanism for the oxazolidine formation.

The first step works fine in exactly the same reaction conditions that were used previously. The reaction rendered the final piperidine **3s**–**u** in good yields, enantio and diastereoselectivities as it is illustrated in Table 5.

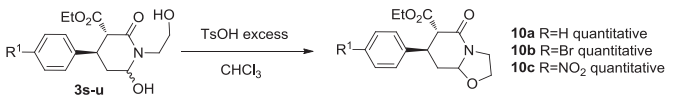
Table 5
Cascade reaction[a]



Entry	R^1	Compound	Yield[b] (%)	dr[c]	ee[d] (%)
1	H	**3s**	73	9:1	98
2	Br	**3t**	44	9:1	90
3	No_2	**3u**	56	9:1	95

[a] The experimental conditions: A mixture of **1f** (0.30 mmol), catalyst **I** (20 mol %, 0.05 mmol), **2a**–**c** (0.25 mmol), and AcOK (0.30 mmol) in CF_3CH_2OH (1 mL) was stirred at rt overnight. Crude product **3s**–**u** was purified by column chromatography.
[b] Isolated yield.
[c] Determined by NMR analysis of crude reaction.
[d] Determined by chiral HPLC analysis.

Next, the addition of acid to the reaction media rendered the final oxazolidines in quantitative yields as it is shown in Scheme 6.



Scheme 6. Oxazolidine formation.

Interestingly, the cascade reaction can also proceed in a 'one pot' fashion, rendering the final compounds in good yields and with slightly lower enantioselectivities (**10a** 93% ee, **10b** and **10c**<90% ee).

The relative configuration of these products was determined by X-ray analysis of compound **10a**. As shown in Fig. 3, the relative configuration will be (6*S*,7*R*,8*aS*).

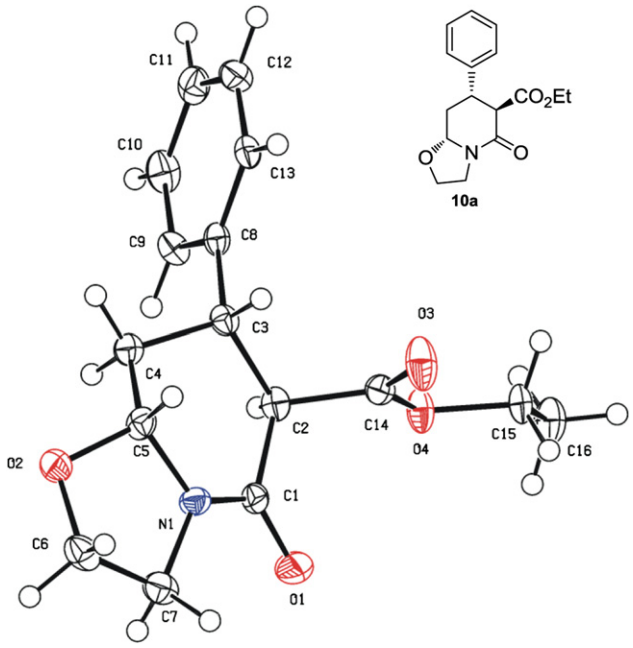


Fig. 3. X-ray of **10a**.[21]

This configuration corresponds to the thermodynamic product where all the substituents of the cyclohexyl ring are in equatorial position.

3. Conclusions

In summary, we have reported an organocatalytic, highly enantioselective conjugate addition of amidomalonates to α,β-unsaturated aldehydes, that furnishes chiral piperidines after hemiaminal formation in excellent yields and enantioselectivities. Furthermore, we have developed a simple synthesis of (−)-paroxetine and femoxetine in only three steps from commercially starting materials in high yields and enantioselectivities. This new synthesis improves the reported procedures by the reduced number of steps and the high levels of enantioselectivity achieved.[22] Moreover, we have expanded the scope of the reaction developing a new cascade reaction that renders highly interesting oxazolidines in excellent yields and enantioselectivities in two-step processes or even in one-pot procedure.

4. Experimental section

4.1. General

Chemicals and solvents were either purchased *puriss p.A.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F_{254} were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), Ce(SO4)2·H2O(10 g) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.063–0.200 mm), ^{1}H NMR, ^{13}C NMR spectra were recorded on Varian $_{UNITY}$ INOVA-300. Chemical shifts for protons are given in δ relative to tetramethylsilane (TMS) and are referenced to residual protium in the NMR solvent ($CDCl_3$: δ=7.26 ppm). Chemical shifts

for carbon are given in δ relative to tetramethylsilane (TMS) and are referenced to the carbon resonances in the solvent ($CDCl_3$: δ=77.0 ppm). The coupling constants *J* are given in hertz. Chiral HPLC was carried out using an LCP 5020 Ignos liquid chromatography pump with LCD 5000 spectrophotometric detector. High-resolution mass spectroscopic data were obtained at the University of Barcelona, Department of Organic Chemistry.

4.2. General procedure for the preparation of 3

In a round bottom flask, unsaturated aldehyde **2** (0.25 mmol, 1 equiv), amidomalonate 1 (0.3 mmol, 1.2 equiv), catalyst (0.05 mmol, 20% mol), and KOAc (0.3 mmol, 1.2 equiv) were added sequentially in 1 mL of 2,2,2-trifluoroethanol. The reaction was stirred at room temperature overnight. Then the crude was purified by column chromatography to furnish piperidine adducts **3**.

4.3. General procedure for the one-pot cyclization reactions

To a stirred solution of (*S*)-2,2-diphenyl-2-trimethylsilanoxymethylpyrrolidine (0.05 mmol, 0.2 equiv, 16 mg) in 2,2,2-trifluoroethanol (1 mL) was added *E*-arylprop-2-enal (0.3 mmol, 1.2 equiv), amidomalonate (0.25 mmol, 1 equiv), and potassium acetate (0.25 mmol, 1 equiv, 21 mg). Reaction mixture was allowed to stir at room temperature for 14 h. After that, *p*-toluenesulfinic acid (0.5 mmol, 2 equiv, 95 mg) was added. After 1 h, crude mixture was purified by column chromatography (EtOAc) to give the final product.

*4.3.1. (3S,4R,6R)-Ethyl 1-benzyl-6-hydroxy-4-(4-nitrophenyl)-2-oxopiperidine-3-carboxylate (**3a**).* Colorless oil (92%). ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}) δ (ppm)=8.26 (d, *J*=8.8 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 2H), 7.44–7.37 (m, 5H), 4.43 (d, *J*=15.0 Hz, 1H), 4.30–4.10 (m, 2H), 3.72–3.66 (m, 2H), 2.30–2.12 (m, 2H), 1.19 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=169.6, 165.5, 148.1, 136.6, 129.0, 128.8, 128.3, 128.2, 128.1, 127.8, 124.3, 78.0, 61.8, 56.7, 48.0, 37.1, 37.0, 14.2. $[\alpha]_D^{25}$ +5.3 (*c* 1.1, CH_2Cl_2). HRMS (ESI): calcd for $[C_{21}H_{22}N_2O_6Na]^+$ 421.1370, found 421.1372. The enantiomeric excess (95%) was determined by HPLC with an IA column (*n*-hexane/*i*-PrOH=90:10, λ=220), 1.0 mL/min; t_R=minor enantiomer 19.3 min, major enantiomer 35.4 min.

*4.3.2. (3S,4R,6R)-Ethyl 1-benzyl-4-(4-cyanophenyl)-6-hydroxy-2-oxopiperidine-3-carboxylate (**3b**).* Colorless oil (94%). ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.60 (d, *J*=8.1 Hz, 2H), 7.36–7.26 (m, 7H), 5.16 (d, *J*=14.8 Hz, 1H), 5.06–5.03 (m, 1H), 4.47 (d, *J*=5.8 Hz, 1H), 4.32 (d, *J*=14.8 Hz, 1H), 4.20–3.90 (m, 4H), 3.57 (d, *J*=11.8 Hz, 1H), 2.18–2.10 (m, 1H) 4.30–4.10 (m, 2H), 3.72–3.66 (m, 2H), 2.30–2.12 (m, 2H), 1.09 (t, 3H, *J*=7.2 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=170.1, 166.1, 146.7, 137.2, 133.2, 129.3, 129.2, 128.7, 128.6, 128.3, 118.9, 78.2, 62.2, 57.0, 48.2, 37.5, 37.2, 14.5. $[\alpha]_D^{25}$ +16.7 (*c* 0.6 CH_2Cl_2, 94% ee).

*4.3.3. (3S,4R,6R)-Ethyl 1-benzyl-4-(4-chlorophenyl)-6-hydroxy-2-oxopiperidine-3-carboxylate (**3c**).* Colorless oil (84%). ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.40–7.16 (m, 9H), 5.12–5.02 (m, 2H), 4.46–4.02 (m, 5H), 3.80–3.60 (m, 1H), 2.20–2.00 (m, 2H), 1.13 (t, 3H, *J*=8.0 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=169.8, 166.2, 139.6, 138.0, 137.1, 133.4, 129.8, 129.6, 128.9, 128.8, 128.5, 128.3, 127.9, 78.2, 61.9, 56.3, 49.5, 41.2, 36.8, 14.2. $[\alpha]_D^{25}$ +7.1 (*c* 1.1, CH_2Cl_2, 90% ee).

*4.3.4. (3S,4R,6R)-Ethyl 1-benzyl-6-hydroxy-2-oxo-4-phenylpiperidine-3-carboxylate (**3d**).* White solid (90%). Mp: 167 °C $[\alpha]_D^{25}$ 14.2 (*c* 0.8 CH_2Cl_2) IR (KBr): 3338, 3056, 3032, 2981, 2955, 2908, 1735, 1617, 1478, 1454, 1321, 1167, 1152, 1037, 748, 702, 644, 531 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm)=7.37–7.22 (m, 10H), 5.13 (d, *J*=14.4 Hz, 1H), 5.06 (dt, *J*=7.2, 6.3 Hz, 1H), 4.45 (d, *J*=15 Hz, 1H), 4.12 (q, *J*=9.9 Hz, 2H), 3.85 (dt, *J*=11.7, 3.9 Hz, 1H), 3.63 (d, *J*=11.7 Hz, 1H), 2.78 (t, *J*=7.2 Hz, 1H), 2.06–2.23 (m, 2H), 1.12 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.46 MHz): δ (ppm)=170.06, 166.25, 140.71, 137.01, 128.85, 128.42, 127.78, 127.47, 127.04, 78.34, 77.22, 61.46, 57.11, 47.48, 37.11, 13.97. HRMS (ESI): calcd for $[C_{21}H_{23}NO_4Na]^+$ 376.1525, found 376.1525. The enantiomeric excess (98%) was determined by HPLC with an AD-H column. (*n*-heptane/*i*-PrOH=90:10, λ=220 nm), 1.0 mL/min; t_R=minor enantiomer 22.46 min, major enantiomer 32.81 min.

*4.3.5. (3S,4R,6R)-Ethyl 1-benzyl-4-(4-bromophenyl)-6-hydroxy-2-oxopiperidine-3-carboxylate (**3e**).* White solid (93%). Mp: 167 °C. IR (KBr): 3338, 3032, 2981, 2908, 1735, 1617, 1477, 1454, 1166, 1152, 1037, 763, 748, 701 cm^{-1}. ^{1}H NMR ($CDCl_3$, 299.94 MHz): δ (ppm)= 7.22–7.37 (m, 10H), 5.13 (d, *J*=15 Hz, 1H), 5.03–5.08 (m, 1H), 4.45 (d, *J*=15 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 3.85 (dt, *J*=11.6, 3.9 Hz, 1H), 3.62 (d, *J*=11.7 Hz, 1H), 2.78 (br d, 1H), 2.06–2.23 (m, 2H), 1.12 (t, *J*=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.43 MHz): δ (ppm)=170.1, 166.3, 140.7, 137.0, 128.9, 128.4, 127.8, 127.5, 127.0, 78.3, 61.5, 57.1, 47.8, 37.1, 37.0, 14.0. $[\alpha]_D^{25}$ +20.0 (*c* 0.8, CH_2Cl_2, 94% ee). HRMS (ESI): calcd for $[M+H]^+$ $C_{21}H_{23}NO_4$ 354.1627, found 354.1632.

*4.3.6. (3S,4R,6R)-Ethyl 1-benzyl-4-(2-bromophenyl)-6-hydroxy-2-oxopiperidine-3-carboxylate (**3f**).* Colorless oil (71%). mixture of diastereomers ^{1}H NMR (400 MHz, $CDCl_3$, TMS_{int}): δ (ppm)=7.60 (dd, *J*=8.2, 1.5 Hz, 1H), 7.39–7.26 (m, 7H), 7.15 (m, 1H), 5.39–5.19 (d, *J*=15.5 Hz, 1H), 5.03 (m, 1H), 4.49–4.33 (m, 1H), 4.15 (q, *J*=7.0 Hz, 2H), 3.86–3.76 (m, 1H), 3.64–3.56 (sample, 1H (OH)), 2.28–1.92 (m, 2H), 1.32–1.15 (t, *J*=7.3 Hz, 3H). $[\alpha]_D^{25}$ +16.1 (*c* 0.6, CH_2Cl_2, 96% ee). HRMS (ESI): calcd for $[M+H]^+$ $C_{21}H_{22}BrNO_4$ 432.0804, found 432.0802.

*4.3.7. (3S,4R,6R)-Ethyl 1-benzyl-4-(4-fluorophenyl)-6-hydroxy-2-oxopiperidine-3-carboxylate (**3g**).* Colorless oil (84%). ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.36–7.10 (m, 9H), 5.10–5.00 (m, 1H), 4.50–4.00 (m, 5H), 3.90–3.80 (m, 1H), 3.53 (d, 1H, *J*=11.7 Hz), 2.20–2.00 (m, 2H), 1.11 (t, *J*=7.9 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=169.2, 164.6, 137.2–128.5, 62.6, 57.6, 50.0, 41.9, 14.7. ^{19}F NMR (100 MHz $CDCl_3$): δ (ppm)=−114.1. $[\alpha]_D^{25}$ +4.0 (*c* 0.7, $CHCl_3$). HRMS (ESI): calcd for $[C_{21}H_{21}FNO_4]^+$: 371.1500; found: 371.1498. (3*S*,4*R*,6*S*)-*Ethyl* 1-*benzyl*-4-(4-*fluoroophenyl*)-6-*hydroxy*-2-*oxopiperidine*-3-*carboxylate* (3**g**′ (*minor diastereomer*)) ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.36–7.10 (m, 9H), 5.10–5.00 (m, 1H), 4.50–4.00 (m, 5H), 3.90–380 (m, 1H), 3.64 (d, *J*=11.3 Hz, 1H)2.20–2.00 (m, 2H), 1.36 (t, *J*=7.3 Hz, 3H). ^{19}F NMR (100 MHz $CDCl_3$): δ (ppm)=−110.0.

*4.3.8. (3S,4R,6R)-Ethyl 1-benzyl-6-hydroxy-4-(naphthalen-1-yl)-2-oxopiperidine-3-carboxylate (**3h**).* White solid (86%). Mp: 174 °C $[\alpha]_D^{25}$ +20.0. IR (KBr): 3307, 3047, 2987, 2937, 1741, 1618, 1482, 1321, 1153, 1035, 750, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300.13 MHz): δ (ppm)= 7.83–7.30 (m, 12H), 5.17 (d, *J*=15 Hz, 1H), 5.08 (m, 1H), 4.20 (br d, *J*=15 Hz, 1H), 4.14–3.98 (m, 3H), 3.75 (d, *J*=11.4 Hz, 1H), 3.18 (br s, 1H), 2.28–2.14 (m, 2H), 1.05 (t, *J*=6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75.46 MHz): δ (ppm)=170.13, 166.24, 138.13, 136.98, 133.45, 132.72, 128.87, 128.73, 128.43, 127.81, 127.77, 127.64, 126.33, 125.97, 125.93, 124.95, 78.34, 77.23, 61.54, 56.91, 47.88, 37.11, 13.96. $[\alpha]_D^{25}$ +54.3 (*c* 0.8, CH_2Cl_2, 99% ee). HRMS (ESI): calcd for $[C_{21}H_{23}NO_4Na]^+$ 426.1681, found 426.1680. The enantiomeric excess (99%) was determined by HPLC with an AD-H column. (*n*-heptane/*i*-PrOH=90:10, λ=254 nm), 1.0 mL/min; t_R=minor enantiomer 35.41 min, major enantiomer 58.24 min.

*4.3.9. (3R,4S,6S)-Ethyl 6-hydroxy-1-methyl-2-oxo-4-phenylpiperidine-3-carboxylate (**3j**).* Yellowish oil (66%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.20–7.33 (m, 5H), 5.00 (t,

J=3 Hz, 1H), 4.01–4.16 (q, *J*=7.2 Hz, 2H), 3.71–3.89 (m, 1H), 3.53 (d, *J*=12 Hz, 1H), 3.06 (s, 3H), 2.18–2.22 (m, 2H) 1.05 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=170.18, 166.38, 140.69, 128.78, 127.37, 126.99, 80.84, 61.34, 56.82, 56.48, 37.17, 37.09, 33.16, 13.92.

*4.3.10. (3S,4R,6R)-Ethyl 6-hydroxy-1-methyl-2-oxo-4-p-tolylpiperidine-3-carboxylate (**3k**).* Yellowish oil (66%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.07–7.13 (m, 4H), 5.0 (t, *J*=3 Hz, 1H), 4.02–4.15 (m, 2H), 3.68–3.80 (m, 1H), 3.49 (d, *J*=11.7 Hz, 1H), 3.05 (s, 3H), 2.31 (s, 3H), 2.15–2.18 (m, 2H), 1.07 (t, *J*=7.2 Hz, 3H).

*4.3.11. (3S,4R,6R)-Ethyl 4-(4-fluorophenyl)-6-hydroxy-1-methyl-2-oxopiperidine-3-carboxylate (**3l**).* Dark red oil (45%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.16–7.20 (m, 2H), 6.96–7.02 (m, 2H), 5.00 (br s, 1H), 4.04 (q, *J*=7.2 Hz, 2H), 3.75–3.84 (m, 1H), 3.46 (d, *J*=12 Hz, 1H), 3.04 (s, 3H), 2.13–2.17 (m, 2H), 1.05 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz $CDCl_3$, 25 °C): δ (ppm)=170.09, 166.28, 163.72, 160.03, 136.41, 128.56 (d, *J*=30.6 Hz, 1C), 115.63 (d, *J*=83.7 Hz, 1C), 80.69, 61.40, 57.00, 37.24, 36.40, 33.16, 13.89.

*4.3.12. (3S,4R,6R)-Ethyl 4-(4-chlorophenyl)-6-hydroxy-1-methyl-2-oxopiperidine-3-carboxylate (**3m**).* Colorless oil (82%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.29 (d, *J*=8.4 Hz, 2H), 7.16 (d, *J*=8.4 Hz, 2H), 5.02 (t, *J*=3 Hz, 1H), 4.02–4.13 (m, 2H), 3.73–3.83 (m, 1H), 3.47 (d, *J*=11.7 Hz, 1H), 3.06 (s, 3H), 2.15–2.18 (m, 2H), 1.09 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (300 MHz $CDCl_3$, 25 °C): δ (ppm)=169.86, 166.00, 139.18, 133.25, 129.02, 128.40, 80.83, 61.53, 56.70, 37.08, 36.55, 33.22, 14.00.

*4.3.13. (3S,4R,6R)-Ethyl 4-(4-bromophenyl)-6-hydroxy-1-methyl-2-oxopiperidine-3-carboxylate (**3n**).* Colorless oil (58%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.44 (d, *J*=8.1 Hz, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 5.00 (t, *J*=3.3 Hz, 1H), 3.98–4.12 (m, 2H), 3.73–3.83 (m, 1H), 3.50 (d, *J*=12 Hz, 1H), 3.05 (s, 3H), 2.14–2.17 (m, 2H), 1.11 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz $CDCl_3$, 25 °C): δ (ppm)=169.99, 166.14, 139.75, 131.92, 131.51, 129.13, 128.76, 121.24, 80.68, 61.52, 56.58, 37.04, 36.57, 33.22, 13.82.

*4.3.14. (3S,4R,6R)-Ethyl 6-hydroxy-1-methyl-4-(4-nitrophenyl)-2-oxopiperidine-3-carboxylate (**3o**).* Pale yellow oil (95%). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=8.19 (d, *J*=7.2 Hz, 2H), 7.42 (d, *J*=7.2 Hz, 2H), 5.05 (t, *J*=2.7 Hz, 1H), 3.92–4.17 (m, 3H), 3.54 (d, *J*=12 Hz, 1H), 3.07 (s, 3H), 2.19–2.24 (m, 2H), 1.09 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz $CDCl_3$, 25 °C): δ (ppm)=169.53, 165.62, 148.13, 147.29, 128.10, 127.67, 124.13, 80.53, 61.71, 56.20, 36.98, 36.85, 33.29, 13.97.

*4.3.15. (3S,4R,6R)-Ethyl 6-hydroxy-1-(2-hydroxyethyl)-2-oxo-4-phenylpiperidine-3-carboxylate (**3s**).* Yellowish oil (73%). ^{1}H NMR (300 MHz, DMSO, 25 °C): δ (ppm)=7.20–7.34 (m, 5H), 6.34 (d, *J*=4.5 Hz, 1H), 5.04 (br s, 1H), 4.95 (t, *J*=4.5 Hz, 1H), 3.90 (q, *J*=7.2 Hz, 2H), 3.57–3.73 (m, 2H), 3.52 (br s, 3H), 3.29–3.40 (m, 1H), 2.27 (dt, *J*=13.2, 3.3 Hz, 1H), 1.85 (br d, *J*=13.2 Hz, 1H), 0.93 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (300 MHz DMSO, 25 °C): δ (ppm)=169.35, 165.65, 141.71, 128.52, 127.16, 126.95, 78.68, 59.97, 58.58, 56.57, 54.49, 47.63, 36.78, 13.86.

*4.3.16. (3S,4R,6R)-Ethyl 4-(4-bromophenyl)-6-hydroxy-1-(2-hydroxyethyl)-2-oxopiperidine-3-carboxylate (**3t**).* Colorless oil (44%). ^{1}H NMR (300 MHz, DMSO, 25 °C): δ (ppm)=7.50 (d, *J*=8.4 Hz, 2H), 7.23 (d, *J*=8.4 Hz, 2H), 6.35 (d, *J*=4.5 Hz, 1H), 5.03 (br s, 1H), 4.94 (t, *J*=4.8 Hz, 1H), 3.92 (q, *J*=7.2 Hz, 2H), 3.62–3.72 (m, 2H), 3.46–3.56 (m, 3H), 3.29–3.36 (m, 1H), 2.26 (t, *J*=12 Hz, 1H), 1.83 (d, *J*=13.5 Hz, 1H), 0.96 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, DMSO, 25 °C): δ (ppm)=169.22, 165.39, 141.12, 131.43, 129.50, 120.03, 78.59, 60.10, 58.56, 56.29, 47.61, 36.36, 13.88.

*4.3.17. (3S,4R,6R)-Ethyl 6-hydroxy-1-(2-hydroxyethyl)-4-(4-nitrophenyl)-2-oxopiperidine-3-carboxylate (**3u**).* Yellow oil (56%). ^{1}H NMR (300 MHz, DMSO, 25 °C): δ (ppm)=8.19 (d, *J*=8.7 Hz, 2H), 7.58 (d, *J*=8.7 Hz, 2H), 6.42 (d, *J*=4.5 Hz, 1H), 5.07 (br s, 1H), 4.95 (t, *J*=4.8 Hz, 1H), 3.92 (q, *J*=6.9 Hz, 2H), 3.72–3.85 (m, 2H), 3.48–3.53 (m, 3H), 2.33 (dt, *J*=12.9, 2.7 Hz, 1H), 1.88 (br d, *J*=13.8 Hz, 1H), 0.95 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, DMSO, 25 °C): δ (ppm)= 169.06, 165.10, 149.46, 146.61, 128.73, 123.76, 78.53, 60.26, 58.57, 55.78, 47.62, 36.90, 36.09, 13.88.

*4.3.18. (3S,4R)-Ethyl 1-benzyl-4-(4-cyanophenyl)-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**4b**).* Colorless oil. ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.56 (d, *J*=8.5 Hz, 2H), 7.37–7.26 (m, 7H), 6.26 (dd, *J*=7.8 Hz, *J′*=1.7 Hz, 1H), 5.19 (dd, *J*=7.8 Hz, *J′*=4.2 Hz, 1H), 4.75 (m, 2H), 4.28–4.12 (m, 3H), 3.64 (d, *J*=8.3 Hz, 1H), 1.20 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=169.0, 164.6, 146.2, 136.7, 133.2, 130.5, 129.4, 129.3, 128.9, 128.7, 128.5, 119.0, 112.0, 108.3, 62.4, 56.1, 49.9, 42.1, 14.5. $[\alpha]_D^{25}$ +13.8 (*c* 0.82 CH_2Cl_2, 94% ee). HRMS (ESI): calcd for $[C_{22}H_{21}N_2O_3]^+$: 361.1546; found: 361.1545. $[\alpha]_D^{25}$ +13.8 (*c* 0.8, CH_2Cl_2). The enantiomeric excess (94%) was determined by HPLC with an IA column. (*n*-hexane/*i*-PrOH=90:10, λ=254 nm), 1.0 mL/min; t_R=minor enantiomer 26.3 min, major enantiomer 42.1 min.

*4.3.19. (3S,4R)-Ethyl 1-benzyl-4-(4-chlorophenyl)-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**4c**).* Colorless oil. ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.36–7.10 (m, 9H), 6.20 (dd, *J*=7.9 Hz, *J′*=1.8 Hz, 1H), 5.19 (dd, *J*=7.9 Hz, *J′*=4.8 Hz, 1H), 4.75 (m, *J*=5.6 Hz, 2H), 4.22–4.10 (m, 3H), 3.63 (d, *J*=8.7 Hz, 1H), 1.19 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=169.2, 164.5, 130.1, 129.8, 129.7, 129.6, 129.5128.7, 128.5, 109.8, 62.5, 56.8, 50.1, 41.8, 14.8. $[\alpha]_D^{25}$ +8.2 (*c* 1.1, CH_2Cl_2, 90% ee). HRMS (ESI): calcd for $[C_{21}H_{21}NO_3Cl]^+$: 370.1204, found: 370.1212. The enantiomeric excess (90%) was determined by HPLC with an IA column. (*n*-hexane/*i*-PrOH=90:10, λ=254 nm), 1.0 mL/min; t_R=minor enantiomer 16.1 min, major enantiomer 18.21 min.

*4.3.20. (3S,4R)-Ethyl 1-benzyl-4-(4-bromophenyl)-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**4e**).* White solid. ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ (ppm)=7.41–7.27 (m, 7H), 7.05 (d, *J*=8.5 Hz, 2H), 6.20 (dd, *J*=7.9, 1.8 Hz, 1H), 5.19 (dd, *J*=7.9, 4.1 Hz, 1H), 5.21–5.17 (dd, *J*=7.9, 1.8 Hz 1H), 4.75 (m, 2H), 4.20–4.15 (m, 3H), 3.63 (d, *J*=8.8 Hz, 1H), 1.20 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$, TMS_{int}): δ (ppm)=169.1, 164.6, 139.6, 136.6, 132.1, 129.6, 129.4, 129.0, 128.3, 128.1, 121.5, 109.1, 61.9, 56.1, 49.5, 41.3, 14.3. HRMS (ESI): $[M+H]^+$ $C_{21}H_{20}BrNO_3$ calcd 414.0699, found: 414.0693. $[\alpha]_D^{25}$ +3.5, (*c* 0.92, $CHCl_3$, 94% ee). The enantiomeric excess (94%) was determined by HPLC with an IA column. (*n*-hexane/*i*-PrOH=90:10, λ=254 nm), 1.0 mL/min; t_R=minor enantiomer 15.2 min, major enantiomer 17.9 min.

*4.3.21. (3S,4R)-Ethyl 1-benzyl-4-(2-bromophenyl)-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**4f**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, TMS_{int}): δ (ppm)=7.50 (dd, *J*=7.0, 2.3 Hz, 1H), 7.31–7.23 (m, 5H), 7.09–6.99 (m, 2H), 6.94 (dd, *J*=7.3, 2.3 Hz, 1H), 6.21 (d, *J*=7.6 Hz, 1H), 6.20 (dd, *J*=7.9, 1.8 Hz, 1H), 5.19 (dd, *J*=7.6, 5.6 Hz, 1H), 4.78–4.62 (m, 1H), 4.54 (m, 1H), 4.16 (q, *J*=7.0 Hz, 2H), 3.73 (d, *J*=4.4 Hz, 1H), 1.18 (t, *J*=7.0 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$, TMS_{int}): δ (ppm)=168.6, 164.4, 137.9, 136.5, 133.6, 130.1, 129.0, 128.7, 128.5, 128.3, 127.9, 127.8, 124.2, 107.8, 61.9, 53.8, 49.3, 40.6, 14.1. HRMS (ESI): $[M+Na]^+$ calcd for $C_{21}H_{20}BrNO_3$ 436.0518, found: 436.0521. $[\alpha]_D^{25}$ +4.5, (*c* 0.99, $CHCl_3$, 96% ee). The enantiomeric excess (96%) was determined by HPLC with an IA column (*n*-hexane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 13.3 min, minor enantiomer 15.4 min.

*4.3.22. (3S,4R)-Ethyl 1-benzyl-4-(4-fluorophenyl)-1,2,3,4-tetrahydro-2-oxopyridine-3-carboxylate (**4g**).* Colorless oil. ^{1}H NMR (400 MHz $CDCl_3$, TMS_{int}): δ (ppm)=7.36–7.10 (m, 9H), 6.19 (dd, *J*=7.9, 1.7 Hz, 1H), 5.20 (dd, *J*=7.9, 4.1 Hz, 1H), 4.75 (m, 2H), 4.22–4.10 (m, 3H), 3.64 (d, *J*=8.8 Hz, 1H), 1.19 (t, 3H, *J*=7.1 Hz). ^{13}C NMR (100 MHz $CDCl_3$): δ (ppm)=169.2, 164.57, 160.1, 159.8, 137.2, 130.1, 128.4, 129.8, 129.7, 129.6, 129.5128.7, 128.5, 109.6, 62.6, 56.7, 50.0, 41.9, 14.7. ^{19}F NMR (100 MHz $CDCl_3$): δ (ppm)=−115.1. HRMS (ESI): Calcd for $[C_{21}H_{22}FNO_3]^+$: 354.1500; found: 354.1498. $[\alpha]_D^{25}$ +12.2 (*c* 1.02, $CHCl_3$, 90% ee). The enantiomeric excess (90%) was determined by HPLC with an IA column (*n*-hexane/*i*-PrOH=95:5, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 25.5 min, minor enantiomer 29.7 min.

*4.3.23. (3R,4S)-Ethyl 1,2,3,4-tetrahydro-1-methyl-2-oxo-4-phenylpyridine-3-carboxylate (**4j**).* Colorless oil (54%). IR (KBr): 2980, 1739, 1661, 1453, 1372, 1154, 1031, 761, 700, 526 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.21–7.31 (m, 5H), 6.15 (dd, *J*=7.8, 2.1 Hz, 1H), 5.21 (dd, *J*=7.8, 3.9 Hz, 1H), 4.08–4.22 (m, 3H), 3.62 (d, *J*=10.2 Hz, 1H), 3.14 (s, 3H), 1.16 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.2, 165.0, 140.7, 130.4, 128.8, 127.4, 127.0, 109.2, 61.4, 56.0, 41.9, 34.0, 14.0. $[\alpha]_D^{25}$ −20.0 (*c* 0.05, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{15}H_{17}NO_3)$ requires 282.1106, found 282.1101. The enantiomeric excess (95%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 32.2 min, minor enantiomer 49.2 min.

*4.3.24. (3S,4R)-Ethyl 1,2,3,4-tetrahydro-1-methyl-2-oxo-4-p-tolylpyridine-3-carboxylate (**4k**).* Pale yellow oil (66%). IR (KBr): 2976, 1728, 1623, 14,920, 1326, 1154, 1027, 814, 634, 535 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.11 (br s, 4H), 6.13 (dd, *J*=8.1, 2.1 Hz, 1H), 5.20 (dd, *J*=8.1, 3.9 Hz, 1H), 4.09–4.20 (m, 3H), 3.60 (d, *J*=10.2 Hz, 1H), 3.13 (s, 3H), 2.31 (s, 3H), 1.18 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.3, 165.0, 137.6, 137.0, 130.2, 129.5, 127.2, 109.5, 61.4, 56.0, 41.5, 34.0, 21.0, 14.0. $[\alpha]_D^{25}$ +29.4 (*c* 0.55, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{16}H_{19}NO_3)$ requires 296.1263, found 296.1257. The enantiomeric excess (92%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 33.6 min, minor enantiomer 56.7 min.

*4.3.25. (3S,4R)-Ethyl 4-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyridine-3-carboxylate (**4l**).* Reddish oil (85%). IR (KBr): 2977, 1737, 1639, 1510, 1321, 1158, 1028, 817 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.13–7.21 (m, 2H), 6.94–7.01 (m, 2H), 6.14 (dd, *J*=7.8, 2.1 Hz, 1H), 5.17 (dd, *J*=7.8, 3.6 Hz, 1H), 4.02–4.22 (m, 3H), 3.56 (d, *J*=10.2 Hz, 1H), 3.12 (s, 3H), 1.15 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.0, 164.8, 136.4, 130.5, 129.0, 128.9, 115.8, 115.5, 109.0, 61.4, 56.1, 41.1, 33.9, 14.0. $[\alpha]_D^{25}$ +5.4 (*c* 0.19, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{15}H_{16}FNO_3)$ requires *m*/*z* 300.1012, found 300.1007. The enantiomeric excess (69%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=190 nm), 1.0 mL/min; t_R=major enantiomer 42.5 min, minor enantiomer 47.6 min.

*4.3.26. (3S, 4R)-Ethyl 4-(4-chlorophenyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyridine-3-carboxylate (**4m**).* Pale yellow oil (80%). IR (KBr): 2980, 1736, 1638, 1490, 1325, 1174, 1091, 823, 657, 533 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.28 (d, *J*=8.7 Hz, 2H), 7.17 (d, *J*=8.7 Hz, 2H), 6.16 (dd, *J*=8.1, 2.1 Hz, 1H), 5.16 (dd, *J*=7.8, 3.6 Hz, 1H), 4.06–4.21 (m, 3H), 3.57 (d, *J*=10.2 Hz, 1H), 3.14 (s, 3H), 1.18 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)= 169.0, 164.7, 139.2, 133.2, 130.7, 129.0, 128.8, 108.7, 61.6, 55.9, 41.2, 34.0, 14.0. $[\alpha]_D^{25}$ +46.3 (*c* 0.27, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{15}H_{16}ClNO_3)$ requires 316.0716, found 316.0709. The enantiomeric excess (94%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=230 nm), 1.0 mL/min; t_R=major enantiomer 27.33 min, minor enantiomer 39.2 min.

*4.3.27. (3S,4R)-Ethyl 4-(4-bromophenyl)-1,2,3,4-tetrahydro-1-methyl-2-oxopyridine-3-carboxylate (**4n**).* Pale yellow oil (86%). IR (KBr): 2977, 1737, 1640, 1486, 1324, 1174, 1011, 820 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.43 (d, *J*=8.7 Hz, 2H), 7.11 (d, *J*=8.7 Hz, 2H), 6.16 (dd, *J*=7.8, 2.1 Hz, 1H), 5.16 (dd, *J*=8.1, 3.9 Hz, 1H), 4.12–4.21 (m, 3H), 3.57 (d, *J*=10.2 Hz, 1H), 3.14 (s, 3H), 1.19 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.0, 164.7, 139.8, 132.0, 130.8, 129.2, 121.3, 108.6, 61.6, 55.9, 41.3, 34.1, 14.1. $[\alpha]_D^{25}$ +43.9 (*c* 0.29, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{15}H_{16}BrNO_3)$ requires 360.0211, found 360.0204. The enantiomeric excess (94%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=221 nm), 1.0 mL/min; t_R=major enantiomer 28.4 min, minor enantiomer 40.18 min.

*4.3.28. (3S,4R)-Ethyl 1,2,3,4-tetrahydro-1-methyl-4-(4-nitrophenyl)-2-oxopyridine-3-carboxylate (**4o**).* Pale yellow oil (72%). IR (KBr): 2978, 1736, 1657, 1518, 1348, 1250, 1034, 852, 699 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3, 25 °C): δ (ppm)=8.18 (d, *J*=9 Hz, 2H), 7.42 (d, *J*=9 Hz, 2H), 6.23 (dd, *J*=7.5, 2.1 Hz, 1H), 5.17 (dd, *J*=7.5, 3.3 Hz, 1H), 4.31–4.36 (m, 1H), 4.07–4.25 (m, 2H), 3.61 (d, *J*=10.5 Hz, 1H), 3.16 (s, 3H), 1.19 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=168.6, 164.3, 148.1, 147.3, 131.5, 128.5, 124.1, 107.3, 61.8, 55.4, 41.6, 34.1, 14.0. $[\alpha]_D^{25}$ −69.1 (*c* 0.47, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{15}H_{16}N_2O_5)$ requires 327.0957, found 327.0950. The enantiomeric excess (94%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 79.1 min, minor enantiomer 98.7 min.

*4.3.29. (3S,4R)-Ethyl 1-ethyl-1,2,3,4-tetrahydro-2-oxo-4-phenylpyridine-3-carboxylate (**4p**).* White solid (92%). IR (KBr): 2980, 1712, 1643, 1420, 1365, 1176, 1095, 840, 690, 533 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3, 25 °C): δ (ppm)=7.22–7.32 (m, 5H), 6.19 (dd, *J*=7.5, 1.8 Hz, 1H), 5.24 (dd, *J*=7.5 Hz, 3.6 Hz, 1H), 4.12–4.21 (m, 3H), 3.51–3.72 (m, 3H), 1.15–1.24 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.3, 164.3, 140.7, 129.1, 128.8, 127.4, 127.4, 109.3, 61.4, 56.1, 41.7, 41.4, 14.0, 13.5 $[\alpha]_D^{25}$ +77.3 (*c* 0.06, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{16}H_{19}NO_3)$ requires *m*/*z* 274.1438, found 274.1437. The enantiomeric excess (89%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 20.3 min, minor enantiomer 31.9 min.

*4.3.30. (3R,4S)-Ethyl 1,2,3,4-tetrahydro-1-isopropyl-2-oxo-4-phenylpyridine-3-carboxylate (**4q**).* White solid (92%). IR (KBr): 2978, 1740, 1660, 1403, 1369, 1147, 1045, 886, 702, 533 cm^{-1}. ^{1}H NMR (300 MHz, CDCl3, 25 °C): δ (ppm)=7.22–7.33 (m, 5H), 6.29 (dd, *J*=8.1, 1.8 Hz, 1H), 5.30 (dd, *J*=7.8, 4.2 Hz, 1H), 4.90 (sep, *J*=6.6 Hz, 1H), 4.07–4.22 (m, 3H), 3.61 (d, *J*=9 Hz, 1H), 1.15–1.25 (m, 9H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.4, 164.2, 140.6, 128.8, 127.4, 127.3, 124.5, 109.6, 61.4, 56.5, 44.0, 41.2, 20.5, 20.5, 14.0. $[\alpha]_D^{25}$ −190.8 (*c* 0.49, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{17}H_{21}NO_3)$ requires *m*/*z* 310.1419, found 310.1413. the enantiomeric excess (91%) was determined by HPLC with an IC column (*n*-heptane/*i*-PrOH=80:20, λ=230 nm), 1.0 mL/min; t_R=major enantiomer 13.8 min, minor enantiomer 20.8 min.

*4.3.31. (6S,7R,8aS)-Ethyl hexahydro-5-oxo-7-phenyl-2H-oxazolo [3,2-a]pyridine-6-carboxylate (**10a**).* White solid (95%). IR (KBr): 2960, 1730, 1627, 1487, 1334, 1174, 1061, 866, 758, 513 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.18–7.35 (m, 5H), 4.95 (dd, *J*=9.9, 4.5 Hz, 1H), 4.18–4.26 (m, 1H), 4.08 (q, *J*=9 Hz, 2H), 3.86–3.99 (m, 2H), 3.44–3.50 (m, 3H), 2.44–2.50 (m, 1H), 1.85–1.96 (m, 1H), 1.08 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C):

δ (ppm)=169.7, 164.0, 140.5, 129.0, 127.6, 126.9, 86.7, 65.0, 61.4, 56.8, 42.8, 39.8, 34.7, 14.0. $[\alpha]_D^{25}$ −40 (*c* 0.1, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{16}H_{19}NO_4)$ requires *m*/*z* 290.1387, found 290.1385. The enantiomeric excess (98%) was determined by HPLC with an IA column (*n*-heptane/*i*-PrOH=80:20, λ=198 nm), 1.0 mL/min; t_R=major enantiomer 8.5 min, minor enantiomer 17.7 min.

*4.3.32. (6S,7R,8aS)-Ethyl 7-(4-bromophenyl)-hexahydro-5-oxo-2H-oxazolo[3,2-a]pyridine-6-carboxylate (**10b**).* White solid (95%). IR (KBr): 2975, 1734, 1638, 1489, 1313, 1155, 988, 834, 681, 517 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=7.45 (d, *J*=8.4 Hz, 2H), 7.07 (d, *J*=8.7 Hz, 2H), 4.93 (dd, *J*=9.6, 4.2 Hz, 1H), 4.17–4.25 (m, 1H), 4.04–4.15 (m, 2H), 3.82–3.98 (m, 2H), 3.38–3.52 (m, 3H), 2.40–2.46 (m, 1H), 1.80–1.92 (m, 1H), 1.12 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.4, 163.6, 142.4, 139.6, 132.1, 128.6, 86.5, 65.0, 61.6, 56.6, 42.9, 39.2, 34.6, 14.0. $[\alpha]_D^{25}$ −37.4 (*c* 0.46, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{16}H_{18}N_2O_4)$ requires *m*/*z* 390.0317, found 390.0311. The enantiomeric excess (90%) was determined by HPLC with an IA column (*n*-heptane/*i*-PrOH=80:20, λ=230 nm), 1.0 mL/min; t_R=major enantiomer 13.0 min, minor enantiomer 24.0 min.

*4.3.33. (6S,7R,8aS)-Ethyl hexahydro-7-(4-nitrophenyl)-5-oxo-2H-oxazolo[3,2-a]pyridine-6-carboxylate (**10c**).* Yellowish solid (95%). IR (KBr): 2981, 1734, 1639, 1520, 1354, 1188, 1054, 864, 756, 616 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=8.21 (d, *J*=8.7 Hz, 2H), 7.39 (d, *J*=9 Hz, 2H), 4.96 (dd, *J*=9.6, 4.2 Hz, 1H), 4.18–4.29 (m, 1H), 4.04–4.17 (m, 2H), 3.84–4.02 (m, 2H), 3.54–3.68 (m, 1H), 3.44–3.51 (m, 2H), 2.45–2.51 (m, 1H), 1.87–1.99 (m, 1H), 1.12 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ (ppm)=169.1, 163.0, 147.8, 128.4, 128.0, 124.3, 86.3, 65.1, 61.8, 56.1, 42.9, 39.5, 34.3, 14.0. $[\alpha]_D^{25}$ −10 (*c* 0.05, $CHCl_3$). HRMS (ESI): calcd for $[M^+Na]^+(C_{16}H_{18}N_2O_6)$ requires *m*/*z* 357.1063, found 357.1056. The enantiomeric excess (95%) was determined by HPLC with an IB column (*n*-heptane/*i*-PrOH=80:20, λ=254 nm), 1.0 mL/min; t_R=major enantiomer 43.9 min, minor enantiomer 64.8 min.

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