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PAPER

A one-pot asymmetric organocatalytic tandem reaction for the synthesis of oxazine derivatives†

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An easy one-pot tandem reaction catalyzed by a chiral secondary amine for the synthesis of optically active oxazine derivatives has been performed and the corresponding substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives were afforded in generally high yields (up to 99%) and excellent enantioselectivities (up to >99%).

Introduction

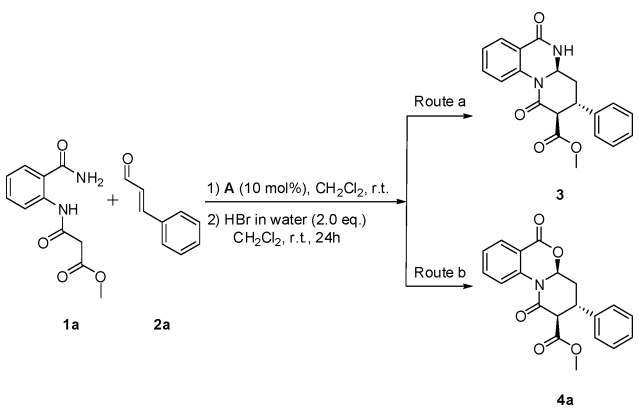
Heterocyclic compounds have always been one of the most popular structures in almost every discipline in chemistry.[1] Most of them have diverse biological or medical activities and are very common in natural and non-natural compounds.[2] The synthesis of them has drawn the attention of many organic chemists for over a century and it is still a challenging subject today both in the total synthesis of natural products and organic synthetic methodologies.[3]

Among the large numbers of heterocyclic compounds, fused heterocycles are a family of the most important ones, which are considered as "privileged structures" and contribute greatly to both the pharmaceutical and agrochemical industries.[4] Therefore, great efforts have been made in order to develop efficient approaches for the preparations of various fused heterocyclic compounds.[5] Of these well established strategies, asymmetric organocatalytic tandem reaction has been one of the most attractive methods mainly due to its high stereoselectivities, easy operation and "environmental friendliness".[6]

Substituted oxazine derivatives have emerged as a challenging synthetic structure recently and have appealed to the interests of several scientists.[7] For example, Liu[8] and coworkers reported an efficient one-pot gold-catalyzed tandem coupling/cyclization reaction for the synthesis of pyrrolo/pyrido[2,1-*a*][1,3]benzoxazinones and pyrrolo/pyrido [2,1-*a*]quinazolinones recently, and Eycken[9] *et al.* previously described a solvent-free procedure for the synthesis of different pyridopyridazines and quinolines under both MW and conventional heating conditions. However, to the best of our knowledge, no reports have presented efficient protocols for the enantioselective synthesis of this kind of fused benzopyrido-oxazine derivatives. Asymmetric organocatalytic tandem reactions, especially those catalyzed by proline and its derivatives, have resulted in the success of the synthesis of many complicated heterocyclic compounds in a highly enantioselective manner.[10] For example, an enantioselective secondary-amine-catalyzed conjugate addition for the synthesis of optically active quinolizidine derivatives has been performed by Franzén *et al*.[11] recently, and a similar structure which has been accomplished by Zhao[12] and coworkers also represents an elegant example of this methodology. Herein, we wish to describe an enantioselective tandem reaction catalyzed by a simple secondary amine to afford a series of substituted benzo[*d*]pyrido[2,1-*b*][1,3] oxazine derivatives.

Results and discussion

Initially, the rationally designed aryl amide **1a** was applied in the tandem reaction with cinnamyl aldehyde **2a** in order to prepare the pyrido[1,2-*a*]quinazoline derivative **3** as shown in Scheme 1 (Route a). The model reaction was firstly carried out using Jørgensen–Hayashi catalyst **A** for the Michael addition under reported conditions.[13] As we expected, the process went smoothly and the aryl amide **1a** vanished within 1 h. Then excess aqueous HBr solution was added into the reaction mixture to promote the annulation step of the tandem reaction. To our great surprise,



Scheme 1 Two possible processes for the tandem reaction of aryl amide **1a** and cinnamyl aldehyde **2a**.

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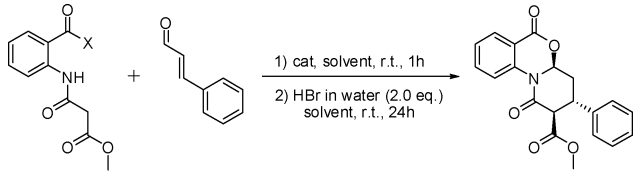
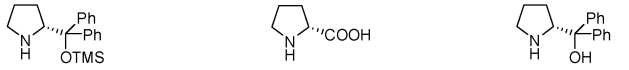
Table 1 Optimization of the reaction conditions for the Michael addition of the tandem reaction



X = NH_2, **1a**; OH, **1b**. **2a** **4a**

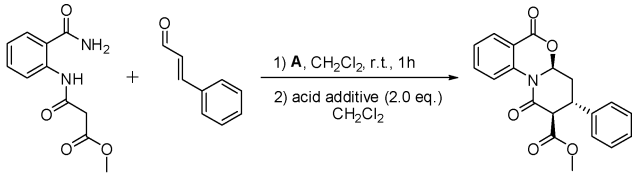


A **B** **C**

Entry[a]	**1**	Cat.	Equiv.[b]	Solvent	Conv. (%)[c]	ee(%)[d]
1	**1a**	**A**	0.1	CH_2Cl_2	Full	96
2	**1b**	**A**	0.1	CH_2Cl_2	Full[e]	92
3	**1a**	**B**	0.1	CH_2Cl_2	13	—[f]
4	**1a**	**C**	0.1	CH_2Cl_2	38	72
5	**1a**	**A**	0.1	DMF	Full	96
6	**1a**	**A**	0.1	THF	63	92
7	**1a**	**A**	0.1	Toluene	64	92
8	**1a**	**A**	0.1	CH_3CN	Full	95
9	**1a**	**A**	0.1	1,4-Dioxane	79	91
10	**1a**	**A**	0.1	EtOAc	64	90
11	**1a**	**A**	0.1	2-Propanol	92	—[f]
12	**1a**	**A**	0.1	CH_3Cl	Full	94
13	**1a**	**A**	0.05	CH_2Cl_2	Full	97
14	**1a**	**A**	0.02	CH_2Cl_2	50	97

[a] Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1** (0.20 mmol), 1.5 equiv of **2a**, 0.5 mL solvent, and 2.0 equiv of HBr aq. [b] The amount of catalyst used in each reaction. [c] Determined by ^{1}H NMR on the crude reaction mixture before the addition of HBr in water. [d] Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. [e] 4 days was needed for the Michael addition step of the tandem reaction. [f] No annulation product was isolated in 24 h after aqueous HBr had been added.

Table 2 Screening of the acid additives for the hydrolyzation/annulation step of the tandem reaction



1a **2a** **4a**

Entry[a]	Acid additive	T/°C[b]	t[c]	Yield(%)[d]	d.r.[e]
1	40% HBr aq	r.t.	12 h	nd	63 : 37
2	40% HBr aq	–20	7 d	12	65 : 35
3	37% HCl aq	r.t.	12 h	nd	64 : 36
4	TFA	r.t.	12 h	16	75 : 25
5	diphenyl phosphate	r.t.	3 d	79	70 : 30
6	$TsOH·H_2O$	r.t.	3 d	74	80 : 20
7	$TsOH·H_2O$	4	3 d	61	71 : 29

[a] Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1a** (0.20 mmol), 1.5 equiv of **2a**, 0.5 mL CH_2Cl_2, and 2.0 equiv of the certain acid additive. [b] The temperature under which the hydrolyzation/annulation step of the tandem reaction was carried out. [c] The reaction time taken for the hydrolyzation/annulation step. [d] Isolated yield. [e] Determined by ^{1}H NMR on the crude reaction mixture.

the product we got upon isolation by column chromatography was the oxazine derivative **4a** instead of the predicted quinazoline derivative **3**! Obviously, a hydrolyzation process had occurred on the addition of the aqueous acid solution before the annulation step took place (Scheme 1, Route b). This unexpected result prompted us to examine the direct synthesis of **4a** from the carboxylic acid **1b**. Results showed that neither the reactivity nor the enantioselectivity of the reaction could be as good as that of the reaction in which **1a** was applied as the nucleophilic reagent (Table 1, entries 1 and 2), which was most probably because of the serious hindrance against the Michael addition step by the interactions between the carboxylic group in **1b** and the aminocatalyst **A**.

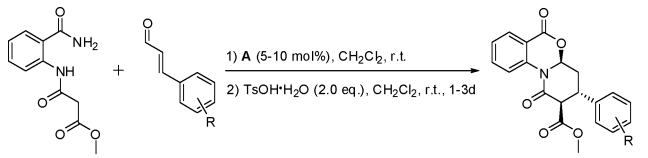
The reaction conditions for the Michael addition of the tandem sequence were then firstly optimized using the aryl amide **1a** as the nucleophilic reagent based on both the conversion of **1a** and the ee value of the final product **4a**. After screening of a number of different catalysts and solvents, it was found that the tandem reaction proceeded very well in a wide scope of solvents with both high enantioselectivities and reactivities when **A** was applied as the catalyst at room temperature. It appeared that the reaction failed to complete in protonic solvents such as 2-propanol while in non-protonic solvents, regardless of the polarities of them, the product could be obtained with excellent ee values ranging from 90% to 96%. A slight increase of enantioselectivity was observed when the reaction was carried out using 5.0 mol% of catalyst **A** in CH_2Cl_2. When the loading of catalyst **A** was decreased to 2.0 mol%, the same level of ee value could also be obtained while the reaction rate was found to be subject to an obvious decrease.

Having established the best reaction conditions for the Michael addition, the hydrolyzation/annulation step catalyzed by acid additives was subsequently investigated, mainly based on the total yield and the diastereomeric ratio of the final product **4a** (Table 2). Experimental data showed that the type of the acid used had a significant influence on both the d.r. value and the total yield of **4a**, while the temperature under which the hydrolyzation/annulation step was carried out contributed little to the diastereoselectivity of the final product. After a series of investigations, the oxazine derivative **4a** could be obtained as two separable diastereoisomers with a 4 : 1 ratio in 74% yield.

With the optimized conditions for both the Michael addition and the hydrolyzation/annulation steps at hand, the scope of this approach was next examined by synthesizing a series of substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives (Table 3). To our delight, all the main products were obtained with excellent enantioselectivities in moderate to good yields, regardless of the properties of the substituents on the cinnamyl aldehydes, albeit with generally moderate diastereoselectivities for the two separable diastereoisomers. It could be inferred that the reaction time for the hydrolyzation/annulation step affected the total yields of the final products greatly. For example, the product **4a** could be afforded in a yield of 58% after stirring for 1 day after the acid $TsOH·H_2O$ was added, but when the reaction time of the second step was prolonged to 3 days, the yield of the final product **4a** could be raised to 74%.

Having successfully extended the scope of the tandem reaction of **1a** and a variety of cinnamyl aldehydes **2** in an enantioselective manner, we next tried to apply this approach further to include

Table 3 Expanding of the scope of the tandem reaction

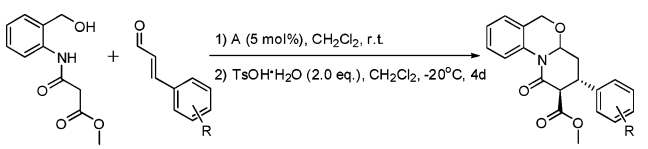


1a 2 4

Entry[a]	R	t_1[b]	t_2[c]	Yield(%)[d]	Product	ee(%)[e]	d.r.[f]
1	H	1.5 h	1 d (3 d)	58 (74)	**4a**	97	80 : 20
2	3-CH_3	6 h	1 d	57	**4b**	97	79 : 21
3	2- OCH_3	1 d	3 d	63	**4c**	93	80 : 20
4	4-CH_3	1.5 h	1 d	52	**4d**	95	79 : 21
5	4- OCH_3	2.5 h	1 d	48	**4e**	95	79 : 21
6	2-Cl	1 d	3 d[i]	69	**4f**	97	81 : 19
7	3-Cl	3 d[g,h]	3 d	35	**4g**	95	83 : 17
8	4-Cl	3 h	3 d	84	**4h**	93	84 : 16
9	2-F	2 d[i]	3d	84	**4i**	95	85 : 15
10	4-F	2 d	3 d	76	**4j**	94	82 : 18
11	2-Br	9 h	3 d	85	**4k**	94	81 : 19
12	4-Br	3 h	3 d	78	**4l**	>99	81 : 19
13	4-NO_2	1 d	3 d	89	**4m**	94	81 : 19

[a] Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1a** (0.40 mmol), 1.5 equiv of **2**, 0.05 equiv of catalyst **A**, 1.0 mL CH_2Cl_2, and 2.0 equiv of. $TsOH{\cdot}H_2O$. [b] The time needed for the first step of Michael addition, which was determined by TLC evidence of the disappearance of the nucleophilic reagent. [c] The time needed for the cyclization step of the tandem reaction. [d] Isolated yield of both diastereoisomers. [e] Enantiomeric excess of the major diastereoisomer, which was determined by chiral HPLC. The value within parentheses represents the ee value of the minor diastereoisomer. [f] Determined by ^{1}H NMR on the crude reaction mixture. [g] Without full conversion of **1a**. [h] 10 mmol% catalyst was used. [i] 0.5 mL CH_2Cl_2 was added.

Table 4 Further expanding of the scope of the tandem reaction



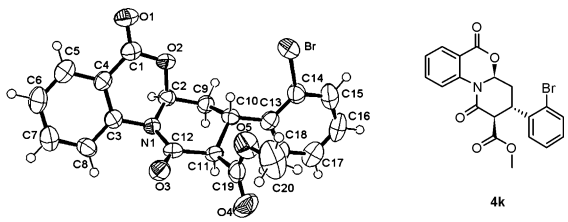
1c 2 4

Entry[a]	R	Time[b]	Yield(%)[c]	Product	ee(%)[d]	d.r.[e]
1	H	1.5 h	86	**4n**	94/97	67 : 33
2	3-CH_3	1.5 h	97	**4o**	97/97	52 : 48
3	4-CH_3	1.5 h	89	**4p**	99/94	61 : 39
4	4-OCH_3	1.5 h	98	**4q**	92/93	62 : 38
5	3-Cl	3 d[f,g]	76	**4r**	97/97	56 : 44
6	4-Cl	1.5 h	99	**4s**	93/93	59 : 41
7	2-F	1.5 h	99	**4t**	95/94	60 : 40
8	4-F	1.5 h	63	**4u**	99/94	67 : 33
9	4-Br	1.5 h	86	**4v**	99/96	57 : 43

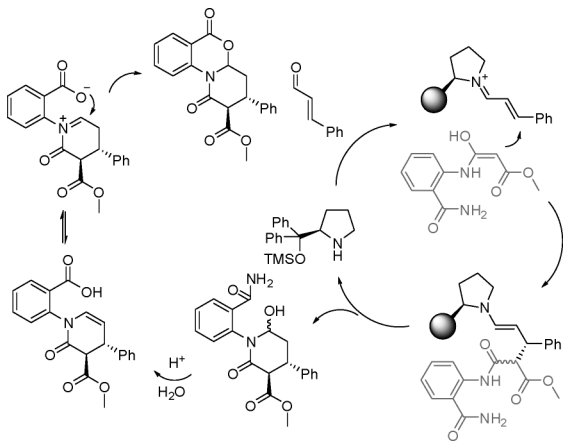
[a] Unless otherwise indicated, all reactions were carried out using 1.0 equiv of **1c** (0.40 mmol), 1.5 equiv of **2**, 0.05 equiv of catalyst **A**, 1.0 mL CH_2Cl_2, and 2.0 equiv of. $TsOH{\cdot}H_2O$. [b] The time needed for the first step of Michael addition, which was determined by TLC evidence of the disappearance of the nucleophilic reagent. [c] Isolated yield of the product mixture **4** of both diastereoisomers. [d] Enantiomeric excess of both diastereoisomers, which was determined by chiral HPLC. [e] Determined by ^{1}H NMR on the product mixture. [f] Without full conversion of **1c**. [g] 0.7 mL CH_2Cl_2 was added.

reaction of the newly designed aryl amide **1c** under similar conditions (Table 4). These reactions proceeded well with high enantioselectivities in good to excellent yields even with 5.0 mol% of catalyst **A** at room temperature for the Michael addition. Unfortunately, the diastereomeric ratios failed to increase conspicuously after a number of attempts at the annulation step of the sequences, probably due to the flexibility of the methylene group in the aryl amide.

The absolute configuration of the isolated major diastereoisomer **4k** was determined by an X-ray analysis on the single crystal (Scheme 2),[14] which was identical to that produced by our assumed process summarized in Scheme 3, based on previous work by Jørgensen *et al.*,[15] Franzén *et al.*[11] and Rios *et al.*,[16] as well as other related reports.[17]



Scheme 2 X-ray crystal structure of **4k**.



Scheme 3 Assumed process of the tandem reaction.

Conclusions

In conclusion, an easy one-pot tandem reaction catalyzed by a chiral secondary amine which afforded a series of oxazine derivatives has been developed. This approach could prepare the required substituted benzo[*d*]pyrido[2,1-*b*][1,3]oxazine derivatives in generally high yields and excellent enantioselectivities. Further investigations towards this methodology are currently being studied well and will be presented in the near future.

Experimental

General methods

Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker AV-400 spectrometer (400 MHz and 100 MHz). Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the

NMR solvent ($CDCl_3$: δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($CDCl_3$: δ 77.16). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz). Mass spectra (ESI) were measured on a Waters Micromass LCT spectrometer. High performance liquid chromatography (HPLC) was performed on an Agilent 1100 Series chromatographs using a Daicel Chiralpak IA and IC column (0.46 cm × 25 cm) as noted.

General procedure for the asymmetric tandem reaction of 1a and 2

To a solution of aryl amide **1a** (0.4 mmol) in CH_2Cl_2 (0.6 mL) was added the solution of the catalyst **A** (0.02 mmol) and cinnamyl aldehyde (0.6 mmol) in CH_2Cl_2 (0.4 mL) and the reaction mixture was stirred at room temperature for 1.5 h (determined by TLC evidence of the disappearance of **1a**). Then $TsOH\cdot H_2O$ (0.8 mmol) was added into the mixture in one portion and the solution was stirred for 1 day. Lastly the reaction mixture was separated by column chromatography with petrol ether : ethyl acetate = 9 : 1 to 4 : 1 as eluant to give the product of both diastereoisomers as a white solid with a yield of 53%.

General procedure for the asymmetric tandem reaction of 1c and 2

To a solution of methyl 3-(2-(hydroxymethyl)phenylamino)-3-oxopropanoate **1c** (0.4 mmol) in CH_2Cl_2 (0.6 mL) was added the solution of the catalyst **A** (0.02 mmol) and cinnamyl aldehyde (0.6 mmol) in CH_2Cl_2 (0.4 mL) and the reaction mixture was stirred at room temperature for 1.5 h (determined by TLC evidence of the disappearance of **1c**). Then the reaction mixture was cooled down to –20 °C and stirred for about an hour. After that $TsOH\cdot H_2O$ (0.8 mmol) was added into the mixture in one portion and the solution was stirred at –20 °C for 4 days. Lastly the reaction mixture was separated by column chromatography with petrol ether : ethyl acetate = 9 : 1 as eluant to give the product mixture of both diastereoisomers as a white solid with a yield of 86%.

Methyl 3-(2-carbamoylphenylamino)-3-oxopropanoate (1a). Mp 120–121 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.79 (br s, 1H), 8.42–8.40 (d, J = 8.4 Hz, 1H), 8.28 (br s, 1H), 7.82–7.80 (d, J = 7.2 Hz, 1H), 7.75 (br s, 1H), 7.52–7.48 (t, J = 14.8 Hz, 1H), 7.17–7.13 (t, J = 14.8 Hz, 1H), 3.68 (s, 3H), 3.57 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 171.0, 168.3, 164.4, 139.4, 132.5, 129.0, 123.4, 121.0, 52.5, 44.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{12}N_2O_4$) requires m/z 236.0797, found m/z 236.0799.

2-(3-Methoxy-3-oxopropanamido)benzoic acid (1b). Mp 112–114 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 11.39 (br s, 1H), 8.75 (br s, 1H), 8.72–8.70 (d, J = 8.4 Hz, 1H), 8.16–8.13 (dd, J = 7.6 Hz, 0.8 Hz, 1H), 7.64–7.60 (td, J = 15.6 Hz, 0.8 Hz, 1H), 7.19–7.16 (t, J = 15.2 Hz, 1H), 3.83 (s, 3H), 3.61 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 171.7, 168.2, 164.6, 140.9, 135.3, 131.7, 123.5, 121.0, 115.2, 52.7, 44.3. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{11}NO_5$) requires m/z 237.0637, found m/z 237.0633.

Methyl 3-(2-(hydroxymethyl)phenylamino)-3-oxopropanoate (1c). Mp 75–76 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 9.61 (br s, 1H), 7.54–7.52 (d, J = 8.0 Hz, 1H), 7.48–7.47 (d, J = 7.2 Hz, 1H), 7.28–7.18 (m, 2H), 5.29 (br s, 1H), 4.55 (s, 2H), 3.69 (s, 3H), 3.55 (s, 2H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 168.8, 164.6, 135.7, 135.2, 127.8, 127.4, 125.6, 124.6, 60.3, 52.4, 43.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{11}H_{13}NO_4$) requires m/z 223.0845, found m/z 223.0846.

(2*R*,3*S*,4a*S*)-Methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4a). The product was obtained in 58% yield, white solid. Mp 72–74 °C; $[\alpha]_D^{22}$ = +46.3° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17–8.14 (dd, J = 8.0, 1.2 Hz, 1H), 7.87–7.85 (d, J = 8.4 Hz, 1H), 7.71–7.67 (td, J = 15.6, 1.6 Hz, 1H), 7.46–7.37 (m, 3H), 7.34–7.28 (m, 3H), 5.75–5.74 (d, J = 2.4 Hz, 1H), 4.05–3.98 (td, J = 25.2, 2.8 Hz, 1H), 3.90–3.87 (d, J = 12.4 Hz, 1H), 3.61 (s, 3H), 2.63–2.58 (m, 1H), 2.53–2.45 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.7, 163.3, 140.7, 139.2, 134.4, 130.4, 129.2, 128.0, 127.0, 126.9, 124.4, 119.8, 84.6, 57.0, 52.5, 37.7, 34.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{17}NO_5$) requires m/z 351.1107, found m/z 351.1105. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 9.0 min (major), 16.0 min (minor), ee = 97%.

(2*R*,3*S*,4a*S*)-Methyl 1,6-dioxo-3-*m*-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4b). The product was obtained in 57% yield, white solid. Mp 97–101 °C; $[\alpha]_D^{22}$ = +70.6° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16–8.14 (dd, J = 8.0, 0.8 Hz, 1H), 7.87–7.85 (d, J = 8.4 Hz, 1H), 7.71–7.66 (td, J = 15.6, 1.2 Hz, 1H), 7.45–7.41 (t, J = 15.2 Hz, 1H), 7.28–7.25 (t, J = 14.0 Hz, 1H), 7.13–7.00 (m, 3H), 5.74–5.73 (d, J = 2.4 Hz, 1H), 4.01–3.94 (td, J = 25.2, 3.2 Hz, 1H), 3.89–3.86 (d, J = 12.4 Hz, 1H), 3.61 (s, 3H), 2.60–2.56 (m, 1H), 2.51–2.44 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 140.7, 139.1, 138.8, 134.4, 130.4, 129.0, 128.7, 127.7, 127.0, 124.4, 123.8, 119.8, 84.7, 56.9, 52.5, 37.6, 34.1, 21.5. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_5$) requires m/z 365.1263, found m/z 365.1259. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 8.3 min (major), 14.4 min (minor), ee = 97%.

(2*R*,3*S*,4a*S*)-Methyl 3-(2-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4c). The product was obtained in 63% yield, white solid. Mp 99–101 °C; $[\alpha]_D^{22}$ = +69.7° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17–8.15 (dd, J = 8.0, 1.2 Hz, 1H), 7.89–7.87 (d, J = 8.0 Hz, 1H), 7.71–7.66 (td, J = 15.6, 1.6 Hz, 1H), 7.45–7.41 (t, J = 15.2 Hz, 1H), 7.31–7.28 (m, 1H), 7.22–7.19 (dd, J = 7.6, 1.2 Hz, 1H), 6.98–6.93 (m, 1H), 5.71–5.70 (d, J = 2.8 Hz, 1H), 4.39–4.35 (d, J = 12.4 Hz, 1H), 4.20–4.12 (td, J = 25.2, 3.2 Hz, 1H), 3.91 (s, 3H), 3.59 (s, 3H), 2.88–2.80 (m, 1H), 2.54–2.50 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.4, 166.4, 163.6, 157.7, 140.9, 134.3, 130.4, 129.4, 129.1, 126.8, 126.5, 124.3, 121.0, 119.8, 111.3, 85.1, 55.4, 54.4, 52.4, 35.6, 31.6. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_6$) requires m/z 381.1212, found m/z 381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 8.9 min (major), 30.9 min (minor), ee = 93%.

(2*R*,3*S*,4a*S*)-Methyl 1,6-dioxo-3-*p*-tolyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4d). The product was obtained in 52% yield, white solid. Mp 174–175 °C;

$[\alpha]_D^{22}$ = +149.4° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15–8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.86–7.84 (d, *J* = 8.4 Hz, 1H), 7.70–7.66 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44–7.41 (t, *J* = 15.2 Hz, 1H), 7.18 (s, 4H), 5.73–5.73 (d, *J* = 2.4 Hz, 1H), 4.00–3.93 (td, *J* = 25.2, 3.2 Hz, 1H), 3.87–3.84 (d, *J* = 12.4 Hz, 1H), 3.60 (s, 3H), 2.59–2.54 (m, 1H), 2.51–2.43 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 140.7, 137.7, 136.2, 134.4, 130.4, 129.8, 126.9, 126.7, 124.4, 119.8, 84.7, 57.1, 52.5, 37.3, 34.1, 21.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_5$) requires *m*/*z* 365.1263, found *m*/*z* 365.1260. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 8.9 min (major), 12.6 min (minor), ee = 95%.

(2*R*,3*S*,4a*S*)-Methyl 3-(4-methoxyphenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4e). The product was obtained in 48% yield, white solid. Mp 194–196 °C; $[\alpha]_D^{22}$ = +89.2° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15–8.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.85–7.83 (d, *J* = 8.0 Hz, 1H), 7.70–7.65 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44–7.40 (t, *J* = 15.2 Hz, 1H), 7.22–7.20 (m, 2H), 6.91–6.89 (m, 2H), 5.73–5.72 (d, *J* = 2.4 Hz, 1H), 3.98–3.91 (td, *J* = 25.2, 3.2 Hz, 1H), 3.83–3.80 (m, 4H), 3.60 (s, 3H), 2.58–2.53 (m, 1H), 2.49–2.41 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 168.0, 165.8, 163.3, 159.1, 140.7, 134.4, 131.2, 130.4, 128.0, 126.9, 124.4, 119.8, 114.5, 84.7, 57.3, 52.3, 52.5, 36.9, 34.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{19}NO_6$) requires *m*/*z* 381.1212, found *m*/*z* 381.1213. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 15.4 min (major), 25.1 min (minor), ee = 95%.

(2*R*,3*S*,4a*S*)-Methyl 3-(2-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4f). The product was obtained in 69% yield, white solid. Mp 186–188 °C; $[\alpha]_D^{22}$ = +115.2° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13–8.11 (d, *J* = 7.6 Hz, 1H), 7.85–7.83 (d, *J* = 8.0 Hz, 1H), 7.68–7.64 (t, *J* = 16.0 Hz, 1H), 7.46–7.39 (m, 2H), 7.32–7.23 (m, 3H), 5.72–5.71 (d, *J* = 2.8 Hz, 1H), 4.55–4.48 (td, *J* = 25.6, 2.4 Hz, 1H), 4.15–4.12 (d, *J* = 12.4 Hz, 1H), 3.60 (s, 3H), 2.62–2.59 (m, 1H), 2.48–2.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.6, 163.2, 140.6, 136.3, 134.4, 133.9, 130.6, 130.4, 129.1, 127.6, 127.0, 124.3, 119.8, 84.6, 55.0, 52.6, 34.7, 33.0, 26.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires *m*/*z* 385.0717, found *m*/*z* 385.0709. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min^{-1}]: 5.6 min (minor), 6.6 min (major), ee = 97%.

(2*R*,3*S*,4a*S*)-Methyl 3-(3-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4g). The product was obtained in 35% yield, white solid. Mp 190–192 °C; $[\alpha]_D^{22}$ = +81.2° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16–8.14 (d, *J* = 7.6 Hz, 1H), 7.86–7.84 (d, *J* = 8.4 Hz, 1H), 7.71–7.67 (t, *J* = 15.6 Hz, 1H), 7.46–7.42 (t, *J* = 15.2 Hz, 1H), 7.35–7.28 (m, 3H), 7.22–7.18 (m, 1H), 5.75–5.74 (d, *J* = 2.4 Hz, 1H), 4.03–3.96 (td, *J* = 25.6, 2.8 Hz, 1H), 3.86–3.83 (d, *J* = 12.4 Hz, 1H), 3.63 (s, 3H), 2.60–2.57 (m, 1H), 2.51–2.44 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.3, 163.1, 141.2, 140.6, 135.0, 134.5, 130.5, 128.3, 127.1, 127.1, 125.3, 124.4, 119.7, 84.4, 56.8, 52.7, 37.4, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires *m*/*z* 385.0717, found *m*/*z* 385.0721. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 7.7 min (major), 8.9 min (minor), ee = 95%.

(2*R*,3*S*,4a*S*)-Methyl 3-(4-chlorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4h). The product was obtained in 84% yield, white solid. Mp 188–190 °C; $[\alpha]_D^{22}$ = +89.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11–8.10 (d, *J* = 6.8 Hz, 1H), 7.82–7.80 (d, *J* = 8.0 Hz, 1H), 7.68–7.63 (td, *J* = 15.6, 1.2 Hz, 1H), 7.43–7.39 (t, *J* = 15.2 Hz, 1H), 7.35–7.33 (d, *J* = 8.4 Hz, 2H), 7.24–7.22 (d, *J* = 8.4 Hz, 2H), 5.73–5.73 (d, *J* = 2.0 Hz, 1H), 4.00–3.93 (td, *J* = 24.8, 3.2 Hz, 1H), 3.85–3.82 (d, *J* = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55–2.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.8, 165.4, 163.2, 140.6, 137.7, 134.5, 133.8, 130.4, 129.4, 128.4, 127.0, 124.3, 119.7, 84.5, 56.9, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Cl$) requires *m*/*z* 385.0717, found *m*/*z* 385.0719. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min^{-1}]: 5.9 min (minor), 7.1 min (major), ee = 93%.

(2*R*,3*S*,4a*S*)-Methyl 3-(2-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4i). The product was obtained in 84% yield, white solid. Mp 180–182 °C; $[\alpha]_D^{22}$ = +70.9° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12–8.10 (d, *J* = 7.6 Hz, 1H), 7.84–7.82 (d, *J* = 8.4 Hz, 1H), 7.68–7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.42–7.38 (t, *J* = 15.2 Hz, 1H), 7.32–7.26 (m, 2H), 7.15–7.06 (m, 2H), 5.73–5.72 (d, *J* = 2.4 Hz, 1H), 4.18–4.03 (m, 2H), 3.57 (s, 3H), 2.75–2.68 (td, *J* = 26.8, 4.0 Hz, 1H), 2.57–2.53 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.5, 163.3, 140.7, 134.4, 130.3, 129.8, 129.6, 127.0, 125.7, 124.8, 124.4, 119.8, 116.5, 116.3, 84.7, 55.1, 52.5, 34.2, 32.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5F$) requires *m*/*z* 369.1013, found *m*/*z* 369.1010. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 7.8 min (major), 14.9 min (minor), ee = 95%.

(2*R*,3*S*,4a*S*)-Methyl 3-(4-fluorophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4j). The product was obtained in 76% yield, colorless oil. $[\alpha]_D^{22}$ = +72.5° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13–8.11 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.84–7.82 (d, *J* = 8.0 Hz, 1H), 7.69–7.64 (td, *J* = 15.6, 1.2 Hz, 1H), 7.44–7.40 (t, *J* = 15.2 Hz, 1H), 7.29–7.25 (m, 2H), 7.09–7.04 (m, 2H), 5.74–5.73 (d, *J* = 2.4 Hz, 1H), 4.02–3.95 (td, *J* = 24.8, 3.2 Hz, 1H), 3.84–3.81 (d, *J* = 12.4 Hz, 1H), 3.59 (s, 3H), 2.57–2.53 (m, 1H), 2.51–2.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.9, 165.5, 163.5, 163.2, 161.0, 140.6, 135.0, 134.4, 130.4, 128.6, 128.6, 127.0, 124.3, 119.7, 116.2, 116.0, 84.5, 57.1, 52.6, 37.0, 34.0. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5F$) requires *m*/*z* 369.1013, found *m*/*z* 369.1014. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 7.7 min (major), 9.7 min (minor), ee = 94%.

(2*R*,3*S*,4a*S*)-Methyl 3-(2-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4k). The product was obtained in 85% yield, white solid. Mp 190–192 °C; $[\alpha]_D^{22}$ = +82.6° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12–8.10 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.84–7.82 (d,

J = 8.0 Hz, 1H), 7.70–7.60 (m, 2H), 7.43–7.11 (m, 4H), 5.70-5.70 (d, J = 2.4 Hz, 1H), 4.56–4.49 (td, J = 25.2, 2.4 Hz, 1H), 4.12–4.09 (d, J = 12.8 Hz, 1H), 3.60 (s, 3H), 2.63–2.59 (m, 1H), 2.41–2.32 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.7, 165.6, 163.2, 140.6, 138.0, 134.4, 134.0, 130.4, 129.3, 128.2, 127.2, 126.9, 124.4, 124.3, 119.8, 84.6, 55.2, 52.6, 36.9, 33.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Br$) requires m/z 429.0212, found m/z 429.0213. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, DCM, 0.7 mL min^{-1}]: 5.6 min (minor), 6.8 min (major), ee = 94%.

(2*R*,3*S*,4a*S*)-Methyl 3-(4-bromophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4l). The product was obtained in 78% yield, white solid. Mp 120–122 °C; $[\alpha]_D^{22}$ = +95.7° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12–8.10 (d, J = 6.8 Hz, 1H), 7.83–7.81 (d, J = 8.0 Hz, 1H), 7.68–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.51–7.49 (t, J = 8.4 Hz, 2H), 7.43–7.39 (t, J = 15.2 Hz, 1H), 7.19–7.16 (d, J = 8.4 Hz, 2H), 5.73–5.72 (d, J = 2.4 Hz, 1H), 4.00–3.93 (td, J = 24.8, 3.2 Hz, 1H), 3.85–3.82 (d, J = 12.4 Hz, 1H), 3.59 (s, 3H), 2.55–2.52 (m, 1H), 2.50–2.42 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.8, 165.4, 163.2, 140.6, 138.2, 134.5, 132.3, 130.4, 128.7, 127.1, 124.3, 121.9, 119.7, 84.5, 56.8, 52.6, 37.2, 33.8. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}NO_5Br$) requires m/z 429.0212, found m/z 429.0214. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 0.6 mL min^{-1}]: 13.4 min (major), 15.2 min (minor), ee >99%.

(2*R*,3*S*,4a*S*)-Methyl 3-(4-nitrophenyl)-1,6-dioxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4m). The product was obtained in 89% yield, yellow solid. Mp 84–86 °C; $[\alpha]_D^{22}$ = +59.3° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.23–8.21 (d, J = 8.4 Hz, 2H), 8.11–8.09 (d, J = 6.8 Hz, 1H), 7.82–7.80 (d, J = 8.0 Hz, 1H), 7.68–7.64 (td, J = 15.6, 1.2 Hz, 1H), 7.52–7.49 (d, J = 8.4 Hz, 2H), 7.44–7.40 (t, J = 15.0 Hz, 1H), 5.77 (m, 1H), 4.16–4.07 (m, 1H), 3.95–3.92 (d, J = 12.4 Hz, 1H), 3.58 (s, 3H), 2.58–2.56 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 167.5, 164.9, 163.0, 147.6, 146.5, 140.5, 134.6, 130.4, 128.2, 127.2, 124.4, 124.4, 119.7, 84.3, 56.4, 52.7, 37.6, 33.4. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{16}N_2O_7$) requires m/z 396.0958, found m/z 396.0961. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, n-hexane/DCM = 1/1, 1.0 mL min^{-1}]: 19.8 min (minor), 31.3 min (major), ee = 94%.

(2*R*,3*S*)-Methyl 1-oxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4n). The product was obtained as a mixture of both diastereoisomers in 86% yield, colorless oil. $[\alpha]_D^{22}$ = +11.0° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16–7.80 (m, 1H), 7.36–7.34 (m, 2H), 7.32–7.24 (m, 4H), 7.21–7.15 (m, 1H), 7.07–7.03 (m, 1H), 5.21–4.93 (m, 3H), 3.97–3.42 (m, 5H), 2.59–2.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.8, 169.0, 166.0, 165.5, 140.5, 139.9, 137.1, 135.3, 129.0, 129.0, 127.7, 127.6, 127.2, 127.0, 126.9, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.4, 37.6, 35.2, 35.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{19}NO_4$) requires m/z 337.1314, found m/z 337.1313. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 13.9 min (major), 18.3 min (minor), ee = 94%; 15.9 min (major), 51.4 min (minor), ee = 97%.

(2*R*,3*S*)-Methyl 1-oxo-3-*m*-tolyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4o). The product was obtained as a mixture of both diastereoisomers in 97% yield, colorless oil. $[\alpha]_D^{22}$ = −5.4° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16–7.81 (m, 1H), 7.28–7.04 (m, 7H), 5.21–4.93 (m, 3H), 3.94–3.42 (m, 5H), 2.58–2.10 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.0, 166.1, 165.5, 140.5, 139.9, 138.6, 138.5, 137.2, 135.3, 128.9, 128.8, 128.5, 128.3, 127.8, 127.7, 127.2, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.9, 123.8, 123.7, 84.0, 82.8, 67.8, 67.2, 58.4, 57.5, 52.4, 52.2, 38.2, 37.5, 35.3, 35.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_4$) requires m/z 351.1471, found m/z 351.1468. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 11.6 min (major), 25.0 min (minor), ee = 97%; 14.6 min (major), 48.3 min (minor), ee = 97%.

(2*R*,3*S*)-Methyl 1-oxo-3-*p*-tolyl-1,2,3,4,4a,6-hexahydrobenzo-[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4p). The product was obtained as a mixture of both diastereoisomers in 89% yield, white solid. Mp 124–126 °C; $[\alpha]_D^{22}$ = +9.1° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.16–7.81 (m, 1H), 7.28–7.03 (m, 7H), 5.20–4.93 (m, 3H), 3.93–3.42 (m, 5H), 2.57–2.06 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.0, 166.1, 165.5, 137.5, 137.3, 137.2, 137.1, 137.0, 135.3, 129.7, 129.6, 127.2, 126.8, 126.8, 126.4, 126.1, 125.7, 125.3, 125.2, 124.5, 124.4, 123.7, 84.0, 82.8, 67.8, 67.2, 58.5, 57.6, 52.4, 52.2, 37.9, 37.2, 35.4, 35.2, 21.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_4$) requires m/z 351.1471, found m/z 351.1469. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 11.3 min (minor), 12.9 min (major), ee = 99%; 16.1 min (major), 31.6 min (minor), ee = 94%.

(2*R*,3*S*)-Methyl 3-(4-methoxyphenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4q). The product was obtained as a mixture of both diastereoisomers in 98% yield, yellow solid. Mp 75–77 °C; $[\alpha]_D^{22}$ = +11.4° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.14–7.78 (m, 1H), 7.28–7.13 (m, 4H), 7.05–7.02 (m, 1H), 6.89–6.86 (m, 2H), 5.19–4.92 (m, 3H), 3.90–3.39 (m, 8H), 2.55–2.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 169.1, 166.0, 165.5, 159.0, 158.8, 137.2, 135.3, 132.6, 132.0, 128.0, 127.9, 127.2, 126.8, 126.4, 126.1, 125.6, 125.3, 125.2, 124.5, 124.4, 123.7, 114.3, 114.3, 84.0, 82.8, 67.8, 67.2, 58.7, 57.9, 55.2, 52.4, 52.2, 37.6, 36.8, 35.5, 35.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{21}H_{21}NO_5$) requires m/z 367.1420, found m/z 367.1423. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 15.0 min (major), 24.2 min (minor), ee = 92%; 17.0 min (major), 39.9 min (minor), ee = 93%.

(2*R*,3*S*)-Methyl 3-(3-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4r). The product was obtained as a mixture of both diastereoisomers in 76% yield, yellow solid. Mp 78–80 °C; $[\alpha]_D^{22}$ = +4.5° (c = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13–7.78 (m, 1H), 7.43–7.04 (m, 7H), 5.30–4.94 (m, 3H), 3.95–3.44 (m, 5H), 2.59–2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.7, 165.6, 165.0, 142.5, 142.0, 137.0, 135.1, 134.8, 134.7, 130.3, 130.3, 130.2, 128.0, 127.8, 127.3, 127.1, 126.9, 126.5,

126.1, 125.8, 125.3, 125.2, 125.1, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.6, 52.4, 38.0, 37.3, 35.0, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Cl$) requires m/z 371.0924, found m/z 371.0921. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 2/1, 1.0 mL min^{-1}]: 12.9 min (minor), 28.3 min (major), ee = 97%; 15.0 min (minor), 17.7 min (major), ee = 97%.

(2*R*,3*S*)-Methyl 3-(4-chlorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4s). The product was obtained as a mixture of both diastereoisomers in 99% yield, white solid. Mp 129–132 °C; $[\alpha]_D^{22}$ = +4.3° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12–7.77 (m, 1H), 7.33–7.30 (m, 2H), 7.26–7.14 (m, 4H), 7.06–7.02 (m, 1H), 5.20–4.92 (m, 3H), 3.93–3.41 (m, 5H), 2.55–2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.8, 165.7, 165.1, 139.0, 138.5, 137.0, 135.2, 133.5, 133.3, 129.2, 129.1, 128.4, 128.4, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 83.8, 82.6, 67.8, 67.2, 58.2, 57.4, 52.5, 52.3, 37.8, 37.0, 35.1, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Cl$) requires m/z 371.0924, found m/z 371.0916. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 2/1, 1.0 mL min^{-1}]: 13.5 min (minor), 41.1 min (major), ee = 93%; 14.1 min (minor), 24.1 min (major), ee = 93%.

(2*R*,3*S*)-Methyl 3-(2-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4t). The product was obtained as a mixture of both diastereoisomers in 99% yield, yellow solid. Mp 106–111 °C; $[\alpha]_D^{22}$ = −3.4° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13–7.79 (m, 1H), 7.28–7.04 (m, 7H), 5.21–4.91 (m, 3H), 4.19–3.40 (m, 5H), 2.58–2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.9, 165.8, 165.3, 137.1, 135.3, 129.3, 129.3, 129.2, 129.0, 129.0, 128.4, 128.3, 127.2, 127.1, 127.0, 126.8, 126.7, 126.6, 126.4, 126.1, 125.7, 125.3, 125.3, 124.7, 124.7, 124.6, 124.6, 124.5, 124.4, 123.7, 116.3, 116.1, 116.1, 116.0, 83.9, 82.8, 67.8, 67.2, 56.4, 55.6, 52.5, 52.3, 34.2, 33.5, 33.2, 32.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4F$) requires m/z 355.1220, found m/z 355.1219. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 1/1, 1.0 mL min^{-1}]: 6.3 min (minor), 9.5 min (major), ee = 95%; 7.3 min (minor), 8.0 min (major), ee = 94%.

(2*R*,3*S*)-Methyl 3-(4-fluorophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4u). The product was obtained as a mixture of both diastereoisomers in 63% yield, yellow solid. Mp 144–149 °C; $[\alpha]_D^{22}$ = +16.2° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13–7.78 (m, 1H), 7.28–7.02 (m, 7H), 5.30–4.94 (m, 3H), 3.95–3.45 (m, 5H), 2.58–2.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 168.9, 165.8, 165.2, 163.3, 160.8, 137.1, 136.3, 136.2, 128.6, 128.5, 127.1, 126.8, 126.4, 125.8, 125.3, 124.5, 124.4, 123.7, 116.0, 115.9, 115.8, 115.7, 83.8, 82.7, 67.8, 67.2, 58.5, 57.7, 52.5, 52.3, 37.7, 36.9, 35.3, 35.1. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4F$) requires m/z 355.1220, found m/z 355.1215. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 3/1, 1.0 mL min^{-1}]: 23.1 min (minor), 78.5 min (major), ee = 99%; 25.8 min (minor), 50.2 min (major), ee = 94%.

(2*R*,3*S*)-Methyl 3-(4-bromophenyl)-1-oxo-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4v). The product was obtained in 86% yield, white solid. Mp 146–148 °C; $[\alpha]_D^{22}$ = +15.9° (*c* = 1.00 in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.12–7.77 (m, 1H), 7.48–7.46 (m, 2H), 7.27–7.23 (m, 1H), 7.20–7.11 (m, 3H), 7.06–7.02 (m, 1H), 5.20–4.92 (m, 3H), 3.92–3.42 (m, 5H), 2.55–2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.6, 168.8, 165.6, 165.1, 139.5, 139.0, 137.0, 135.2, 132.1, 132.1, 128.8, 128.7, 127.1, 126.8, 126.4, 126.1, 125.8, 125.3, 124.5, 124.4, 123.7, 121.6, 121.4, 83.8, 82.6, 67.8, 67.2, 58.1, 57.3, 52.5, 52.4, 37.8, 37.1, 35.0, 34.9. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{18}NO_4Br$) requires m/z 415.0419, found m/z 415.0416. The enantiomeric excess was determined by HPLC. [IA column, 254 nm, *n*-hexane/DCM = 3/1, 1.0 mL min^{-1}]: 27.4 min (minor), 102.3 min (major), ee = 99%; 30.4 min (minor), 54.5 min (major), ee = 96%.

(2*R*,3*S*,4a*R*)-Methyl 1,6-dioxo-3-phenyl-1,2,3,4,4a,6-hexahydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine-2-carboxylate (4a1). White solid. Mp 181–183 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ (ppm) 8.15–8.13 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.07–8.05 (d, *J* = 8.4 Hz, 1H), 7.70–7.67 (td, *J* = 15.6, 1.2 Hz, 1H), 7.42–7.38 (m, 3H), 7.35–7.32 (m, 1H), 7.27–7.26 (m, 2H), 5.89–5.85 (dd, *J* = 8.4, 6.8 Hz, 1H), 3.82–3.79 (d, *J* = 12.0 Hz, 1H), 3.65 (s, 3H), 3.59–3.52 (td, *J* = 26.0, 2.8 Hz, 1H), 2.79–2.73 (m, 1H), 2.53–2.44 (m, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ (ppm) 169.0, 165.3, 162.2, 139.8, 138.8, 134.8, 130.3, 129.2, 128.1, 126.9, 126.5, 123.0, 118.5, 84.4, 57.8, 52.7, 38.1, 34.2. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{17}NO_5$) requires m/z 351.1107, found m/z 351.1106. The enantiomeric excess was determined by HPLC. [IC column, 254 nm, DCM, 1.0 mL min^{-1}]: 12.6 min (major), 18.1 min (minor), ee = 98%.

(3*R*,4*S*,6*S*)-Methyl 1-(2-carbamoylphenyl)-6-hydroxy-2-oxo-4-phenyl piperidine-3-carboxylate (4a2). The intermediate product was isolated as a mixture of two diastereomers by column chromatography after full conversion of **1a** using ethyl acetate and then 1,4-dioxane as the eluent. White solid. Mp 198–199 °C; ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): δ (ppm) 8.15–6.89 (m, 9H), 6.46–5.18 (m, 1H), 3.95–3.81 (m, 1H), 3.57–3.24 (m, 4H), 2.58–2.37 (m, 1H), 2.03–1.37 (m, 1H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): δ (ppm) 174.9, 174.4, 174.0, 173.9, 170.9, 170.6, 146.9, 144.2, 143.7, 140.8, 139.7, 136.9, 136.0, 135.4, 134.2, 134.0, 133.6, 133.2, 132.9, 132.8, 132.5, 132.4, 132.3, 132.1, 87.0, 86.0, 62.5, 61.8, 56.9, 42.9, 42.2, 41.8, 41.7, 35.7. HRMS (EI): exact mass calculated for $[M]^+$ ($C_{20}H_{20}N_2O_5$) requires m/z 368.1372, found m/z 368.1378.

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