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Diastereoselective synthesis of oxazolo[3,4-*b*] tetrahydroisoquinolin-3-ones via Lewis acid TMSOTf-mediated Pictet–Spengler reaction

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ABSTRACT

An alternative and efficient method to stereoselectively synthesize oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones via a Pictet–Spengler reaction promoted by Lewis acid TMSOTf from readily available (*S*)-4-benzyl-2-oxazolidinone with various aromatic, aliphatic, and cyclic aldehydes under room temperature is described.

1. Introduction

Tetrahydroisoquinolines are important *N*-containing heterocycles that are present in a variety of natural and synthetic therapeutic products with a wide range of biological and pharmacological activities.[1] Among the various tetrahydroisoquinoline derivatives, oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones have attracted special attention. On the one hand, as analogues of strong antitumor agents such as podophyllotoxin,[2,3] many of them have been found to exhibit potent cytotoxicity and inhibition to KB cells in vivo against P-388 in mice[4] and cells derived from human carcinoma of the nasopharynx,[5] as well as inhibitors of DNA topoisomerase II.[6] On the other hand, the transformation of these compounds into β-amino alcohols through hydrolysis, means that not only can they be used as useful intermediates in the synthesis of naturally occurring alkaloids and synthetic biologically active molecules,[1,7] but it also allows them to be used as precursors of ligands,[8] chiral auxiliaries,[9] and catalysts[10] in organic synthesis (Fig. 1).

Therefore, efficient syntheses of 2-azapodophyllotoxin analogues, oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones, are of interest. The well-known Bischler–Napieralski[11] or Pictet–Spengler[12] reactions are powerful and classic tools for constructing the corresponding *N*-containing heterocyclic derivatives via the ring closure of iminium intermediates. Vandewalle et al. reported the Bischler–Napieralski method to obtain 2-azapodophyllotoxins.[13] The C1-substituted dihydroisoquinoline precursor structure was built first, after which the reaction afforded the target products through reduction and condensation, respectively. At almost the same time, Pictet–Spengler reactions promoted by a Bronsted acid, such as H_2SO_4, CF_3SO_3H, and CF_3COOH, were reported by Tomioka et al., which provided the corresponding derivatives in a more straightforward and efficient manner.[4,5,14] Katritzky developed a benzotriazole methodology to stereospecifically synthesize oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones.[15] In contrast with the above methods, Katritzky's method produced single diastereomers in two steps, that is the PTSA-catalyzed intramolecular reaction of (*S*)-4-benzyl-2-oxazolidinone with benzotriazole and diverse aldehydes, followed by treating the formed benzotriazole Mannich intermediates with a Lewis acid, $TiCl_4$ or $AlCl_3$, to give the final products as pure stereoisomers. In addition, another similar approach was also established to obtain pure stereoisomers via the Lewis acid-treatment of (phenylsulfonyl)alkyl oxazolidin-2-ones, which were generated from the reaction of (*S*)-4-benzyl-1,3-oxazolidin-2-one with diverse aldehydes in the presence of benzenesulfinic acid.[16] Despite these advances, the development of new and direct methodologies for the Lewis acid catalyzed synthesis of oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones remains largely unrealized. Herein we describe a facile, straightforward, and efficient procedure to obtain highly diastereoselective 5-substituted oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones through the Pictet–Spengler reaction of (*S*)-4-benzyl-2-oxazolidinone with various aldehydes in the presence of Lewis acid trimethylsilyl trifluoromethanesulfonate (TMSOTf).[17]

2. Results and discussion

We began our study by investigating the condensation reaction of commercially available (*S*)-4-benzyl-2-oxazolidinone **1** with benzaldehyde **2a**. Different Lewis acids including $ZnCl_2$, $FeCl_3$, $SnCl_5{\cdot}5H_2O$, $AlCl_3$, $TiCl_4$, $BF_3{\cdot}Et_2O$, TMSCl, and TMSOTf were employed to screen the reaction in dry toluene at room temperature as shown in Table 1. We found that when the reaction was

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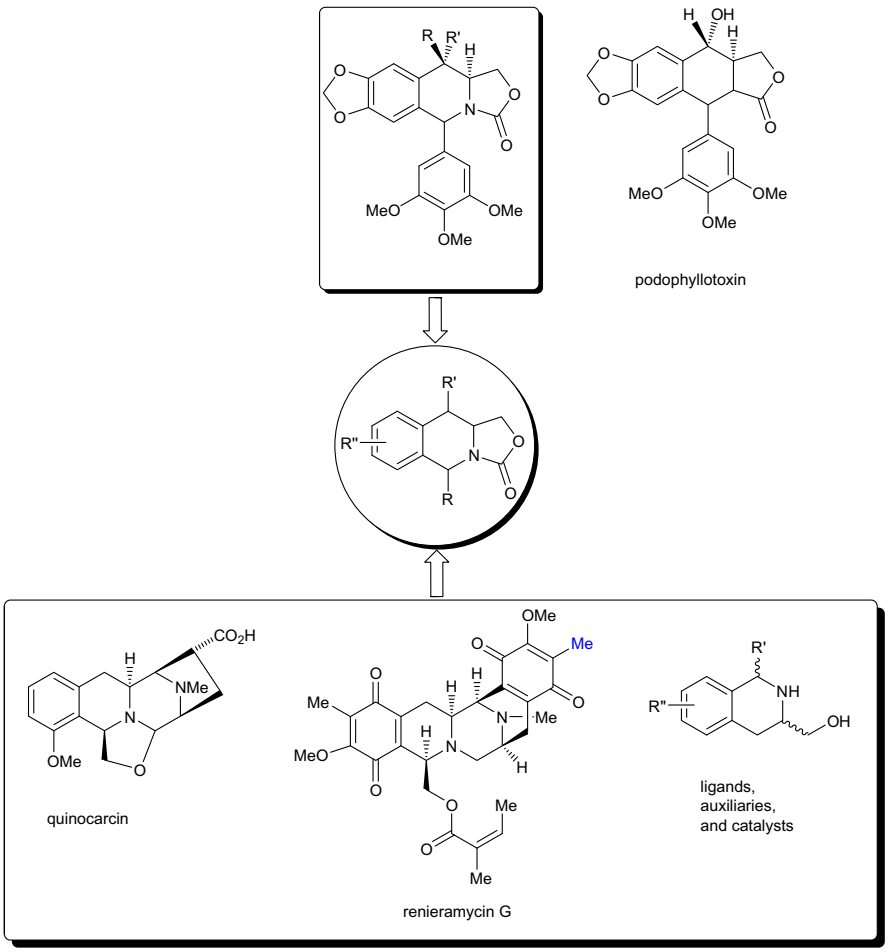
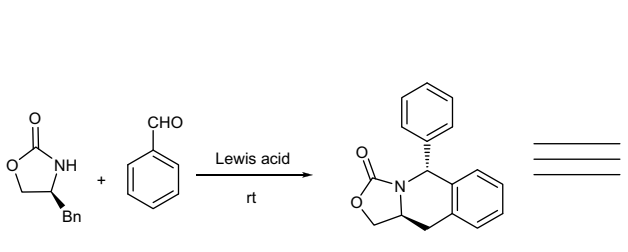
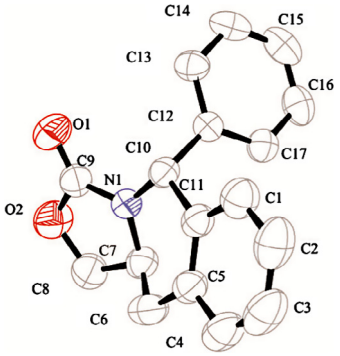


Figure 1. Oxazolo[3,4-*b*]tetrahydroisoquinolin-3-one compounds and their application.

Table 1
Optimization of the reaction conditions for the synthesis of oxazolo[3,4-*b*]tetrahydroisoquinolin-3-one **3a** from (*S*)-4-benzyl-2-oxazolidinone **1** with benzaldehyde **2a**[a]



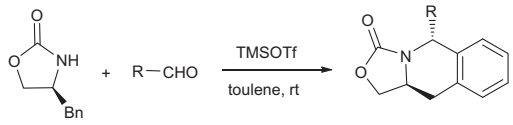


Entry	Lewis acid	Solvent	Time (h)	Yield[b] (%)	de[c] (%)
1	$ZnCl_2$	Toulene	6, 12	Trace, trace	/
2	$FeCl_3$	Toulene	6, 12	37, 42	99
3	$SnCl_5{\cdot}5H_2O$	Toulene	6, 12	27, 51	98
4	$AlCl_3$	Toulene	6, 12	23, 28	99
5	$TiCl_4$	Toulene	6, 12	Trace, trace	/
6	TMSCl	Toulene	6, 12	Trace, 9	/
7	$BF_3{\cdot}Et_2O$	Toulene	6, 12	46, 49	97
8	TMSOTf	Toulene	6	89[d]	98
9	TMSOTf	CH_2Cl_2	23	81	79
10	TMSOTf	$CHCl_3$	19	52	80

[a] Reaction conditions: **1** (0.30 mmol), **2a** (0.45 mmol), and Lewis acid (0.36 mmol) in solvent (1.0 mL) under room temperature.
[b] LC–MS yields.
[c] Determined by HPLC analysis.
[d] Isolated yield.

promoted by $FeCl_3$, $SnCl_5{\cdot}5H_2O$, or $AlCl_3$, it afforded the desired product in a lower yield along with most of the starting materials after 6 h, although with high diastereoselectivity (Table 1, entries 2–4), while $ZnCl_2$, $TiCl_4$, and TMSCl were ineffective in promoting

Table 2
Synthesis of oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones **3a–o** from (*S*)-4-benzyl-2-oxazolidinone **1** with various aldehydes **2a–o**[a]



1 **2a-o** **3a-o**

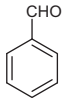
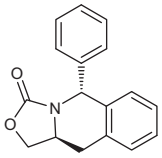
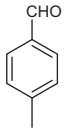
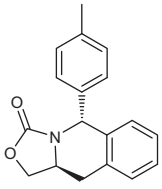
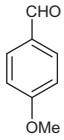
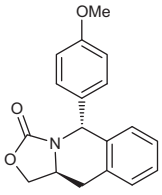
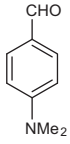
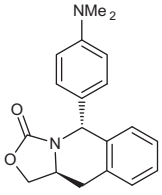
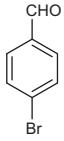
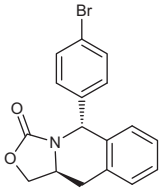
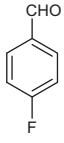
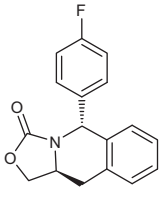
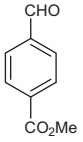
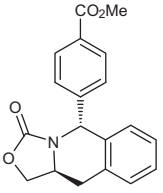
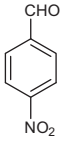
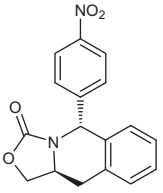
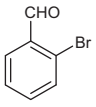
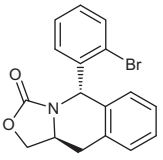
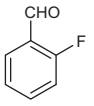
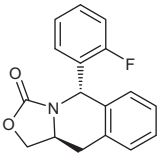
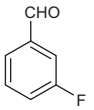
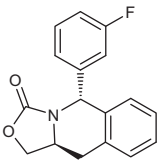
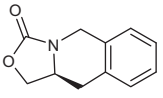
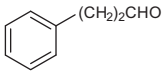
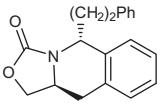
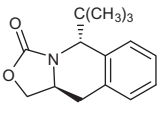
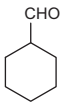
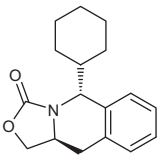
Aldehyde **2**	Time (h)	Product **3**	Yield[b] (%)	de[c] (%)
 **2a**	6	 **3a**	89	98
 **2b**	28	 **3b**	90	>99
 **2c**	35	 **3c**	83	>99
 **2d**	19[d]	 **3d**	83	>99
 **2e**	22	 **3e**	99	93
 **2f**	5	 **3f**	97	>99

Table 2 (*continued*)

Aldehyde **2**	Time (h)	Product **3**	Yield[b] (%)	de[c] (%)
 **2g**	27	 **3g**	95	97
 **2h**	22	 **3h**	98	98
 **2i**	22	 **3i**	99	99
 **2j**	22	 **3j**	97	>99
 **2k**	22	 **3k**	97	>99
$(HCHO)_n$ **2l**	6	 **3l**	94	/
 **2m**	6	 **3m**	91	>99
$(CH_3)_3CCHO$ **2n**	72	 **3n**	48	99
 **2o**	28	 **3o**	91	99

[a] Reaction conditions: Compound **1** (0.30 mmol), Aldehyde **2** (0.45 mmol), TMSOTf (0.36 mmol), Toulene (3.0 mL), Room temperature.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The reaction was carried out at −10 °C.

the reaction (Table 1, entries 1, 5, and 6). These Lewis acids had low efficiency for this reaction, even if prolonging the reaction time to 12 h (Table 1, entries 1–6). Further screening of the conditions showed that $BF_3{\cdot}Et_2O$ was also less effective in producing oxazolo[3,4-*b*]tetrahydroisoquinolin-3-one **3a** (Table 1, entry 7), which was consistent with the previous report.[14] When the reaction was carried out for 6 h in the presence of TMSOTf under the same conditions, **3a** was obtained with high yield and diastereoselectivity in an efficient manner (Table 1, entry 8). The *trans*-structure of **3a** as the major diastereomer was confirmed by the NOE effect as illustrated in a previous example,[4] and the absolute configuration of the newly formed stereogenic center in compound **3a** was unequivocally determined as (*R*) by X-ray single-crystal analysis,[18] which was in agreement with the observations obtained by Katritzky[15] and Marino Petrini.[16a] Further solvent screening showed CH_2Cl_2 and $CHCl_3$ to not be the best choice for the reaction, because the reaction time needed to be prolonged significantly, while the diastereoselectivity of product decreased (Table 1, entries 9 and 10).

Under the optimized conditions, we proceeded to explore the scope of the TMSOTf-mediated Pictet–Spengler reaction of (*S*)-4-benzyl-2-oxazolidinone **1** with various aldehydes. The results are shown in Table 2. It was found that the reactions proceeded smoothly to afford the desired products in good yields and with high diastereoselectivity, when different aldehydes including aromatic, aliphatic, and cyclic **2a**–**o** were employed. A wide range of substituted aromatic aldehydes with electron donating and electron withdrawing groups **2b**–**k**, even the sterically hindered *ortho*-substituted aldehydes **2i** and **2j**, also reacted efficiently to give the target products **3** in good to high yields and high selectivity, which did not show the obvious effects on the yield, except for the reaction time. According to LC–MS analysis of the reaction mixtures for **2c** and **2d**, a small amount of unknown by-products was observed in the reaction, which might be due to the lower electrophilicity arising from the existence of a strong electron-rich substituent (OMe and NMe_2). The reactivity of aliphatic aldehydes, such as **2l** and **2m**, was similar to aromatic aldehydes **2a** and **2f**, and gave the corresponding annulated products **3l** and **3m** in 94% and 91% yields, respectively. However, in the case of pivalaldehyde **2n**, because of the large steric hindrance of the *tert*-butyl group, it only afforded **3n** in moderate yield after 72 h, along with most of the starting materials. Cyclic aldehyde cyclohexanecarbaldehyde **2o** was also compatible, efficiently providing the desired **3o**.

In order to establish a rational reaction mechanism, a control experiment was carried out. Treatment of (*S*)-4-benzyl-2-oxazolidinone **1** and benzaldehyde **2a** with 1.2 equiv of TfOH under otherwise identical conditions gave only **3a** in 40% isolated yield (93% de) with 50% recovery of **1** after 6 h, thus implying that the Bronsted acid TfOH generated from TMSOTf in the reaction was not responsible for the actual catalysis.

Based on the above control experiment, a plausible formation mechanism of compounds **3** was proposed as shown in Scheme 1. First, intermediate **A** was generated in the presence of TMSOTf, followed by a loss of TMSOH to afford *N*-acyliminium ion intermediate **B**.[15,16a,19] Next, the ring closure reaction proceeded to give compound **3** by an attack of the phenyl ring nucleus on the $C{=}N^+$ double bond of the *N*-acyliminium intermediate **B**. With regard to the diastereoselectivity in the reaction, we thought it was favorable for an *Re* attack of the phenyl ring over the course of the nucleophilic cyclization, that is **B** to **3**, due to the substrate-induced effect of optically active (*S*)-4-benzyl-2-oxazolidinone, which made the final compound **3** adopt a more stable *trans*-configuration.[20] Accordingly, the newly-formed stereocenter has an (*R*)-configuration, thus avoiding unfavorable steric interactions. In addition, there might be an equilibration of the *cis*/*trans* products under these conditions. However, the C—N bond of **3** could be cleaved to give a benzyl cation intermediate, especially in the presence of Bronsted acid TfOH generated in the reaction, thus a *cis*-product could also transform to a *trans*-isomer via epimerization.

3. Conclusion

In conclusion, we have developed a facile and alternative method for the synthesis of oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones **3** via a Pictet–Spengler reaction promoted by Lewis acid TMSOTf. This condensation between (*S*)-4-benzyl-2-oxazolidinone and aldehydes represents a straightforward and efficient procedure for the construction of this type of products in organic synthesis. It is also associated with a wide range of substrates, excellent yields and high diastereoselectivity.

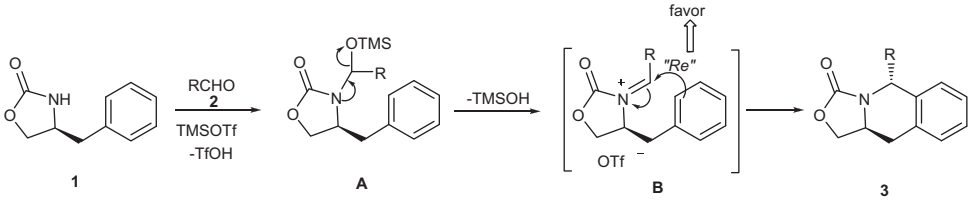
4. Experimental

4.1. General

All reagents were obtained from commercial sources and used without further purification, unless otherwise noted. All reactions were monitored by TLC with GF254 silica gel coated plates. Flash column chromatography was carried out by using 200−300 mesh silica gel at increased pressure. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in solutions of $CDCl_3$ using tetramethylsilane as the internal standard, δ values are given in ppm and coupling constants (J) in Hz. The high resolution mass spectra were measured on a MicroTOF mass spectrometer. Melting points were measured on a melting point apparatus equipped with a thermometer and are uncorrected. Diastereoisomer ratios were determined by HPLC analysis with Extend-C18 columns (0.46 × 15 cm) with a mixture of water and acetonitrile as mobile phase.

4.2. General procedure for the Pictet–Spengler reaction of (*S*)-4-benzyl-2-oxazolidinone with various aldehydes in the presence of TMSOTf

A mixture of (*S*)-4-benzyloxazolidin-2-one **1** (53.1 mg, 0.30 mmol) and aldehyde **2** (0.45 mmol) was first added to a dry round-bottom flask (25 mL), and then dissolved in dry toluene (1.0 mL). Next, TMSOTf (65 μL, 0.36 mmol) was added to the mixture dropwise in approximately 1 min, after which the resulting solution was stirred vigorously at room temperature (monitored



Scheme 1. Proposed reaction mechanism.

by TLC). Water (25 mL) was then added to the mixture when the reaction was completed. The aqueous layer was extracted with 3 × 15 mL of DCM. The combined organic layer was dried over anhydrous $MgSO_4$, after which the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel using petroleum ether and ethyl acetate (10:1) as the eluent to afford the desired product **3**.

4.2.1. (5*R*,10a*S*)-5-Phenyl-1,5,10,10a-tetrahydro[1,3]oxazolo [3,4-*b*]isoquinolin-3-one 3a[15]

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), benzaldehyde (0.45 mmol, 46 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 6 h (71.0 mg, 89%); R_f = 0.38 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -261$ (*c* 0.68, $CHCl_3$); White solid; mp: 157–159 °C; 98% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.15 (m, 8H), 6.98 (d, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 4.43 (t, *J* = 8.0 Hz, 1H), 4.13–4.04 (m, 2H), 3.04 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.96 (dd, *J* = 10.6, 15.6 Hz, 1H); HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}NO_2$ $[M+H]^+$ 266.1176, found: 266.1172.

4.2.2. (5*R*,10a*S*)-5-(*p*-Tolyl)-1,5,10,10a-tetrahydro[1,3]oxazolo [3,4-*b*]isoquinolin-3-one 3b

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), *p*-tolualdehyde (0.45 mmol, 53.0 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 28 h (75.2 mg, 90%); R_f = 0.33 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -238$ (*c* 0.08, $CHCl_3$); White solid; mp: 150–152 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.13 (m, 7H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.04 (s, 1H), 4.47 (t, *J* = 8.0 Hz, 1H), 4.16–4.07 (m, 2H), 3.07 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.99 (dd, *J* = 10.4, 15.6 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 139.3, 137.8, 134.2, 132.4, 129.31, 129.26, 128.8, 128.6, 127.3, 126.9, 68.5, 56.1, 48.1, 34.4, 21.1; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{17}NO_2$ 280.1332, found: 280.1332.

4.2.3. (5*R*,10a*S*)-5-(4-Methoxyphenyl)-1,5,10,10a-tetrahydro [1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3c

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), *p*-methoxybenzaldehyde (0.45 mmol, 55.3 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 35 h (73.5 mg, 83%); R_f = 0.26 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -214$ (*c* 0.10, $CHCl_3$); White solid; mp: 124–125 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.08 (m, 5H), 6.93 (d, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8.4 Hz, 2H), 5.94 (s, 1H), 4.40 (t, *J* = 8.4 Hz, 1H), 4.05 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.02–3.96 (m, 2H), 3.71 (s, 3H), 2.97 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.89 (dd, *J* = 10.4, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 134.5, 134.3, 132.3, 129.9, 129.2, 128.8, 127.3, 126.9, 113.9, 68.5, 55.7, 55.3, 48.0, 34.4; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{17}NO_3$ 296.1281, found: 296.1278.

4.2.4. (5*R*,10a*S*)-5-(4-(Dimethylamino)phenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3d

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), *p*-dimethylaminobenzaldehyde (0.45 mmol, 67.1 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was carried out at −10 °C. The reaction was completed in 19 h (77.5 mg, 83%); R_f = 0.26 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -263$ (*c* 0.56, $CHCl_3$); Yellow solid; mp: 163–164 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 3H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.02 (s, 1H), 4.47 (t, *J* = 8.0 Hz, 1H), 4.14–4.07 (m, 2H), 3.06 (dd, *J* = 4.4, 15.6 Hz, 1H), 3.01–2.95 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 150.1, 134.7, 132.3, 129.9, 129.5, 129.1, 128.8, 127.1, 126.7, 112.1, 68.4, 55.8, 47.9, 40.4, 34.3; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{20}N_2O_2$ 309.1598, found: 309.1598.

4.2.5. (5*R*,10a*S*)-5-(4-Bromophenyl)-1,5,10,10a-tetrahydro [1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3e

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), 4-bromobenzaldehyde (0.45 mmol, 83.3 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 22 h (102.9 mg, 99%); R_f = 0.41 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -178$ (*c* 0.28, $CHCl_3$); White solid; mp: 170–172 °C; 93% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 2H), 7.33–7.17 (m, 4H), 7.13 (d, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 5.99 (s, 1H), 4.47 (t, *J* = 8.4 Hz, 1H), 4.13 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.04 (dq, *J* = 4.4, 8.4 Hz, 1H), 3.05 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.96 (dd, *J* = 10.8, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 141.1, 133.4, 132.4, 131.8, 130.4, 129.4, 128.7, 127.6, 127.1, 122.2, 68.6, 55.7, 48.1, 34.3; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}BrNO_2$ 344.0281, found: 344.0268.

4.2.6. (5*R*,10a*S*)-5-(4-Fluorophenyl)-1,5,10,10a-tetrahydro [1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3f

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), 4-fluorobenzaldehyde (0.45 mmol, 47.4 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 5 h (82.4 mg, 97%); R_f = 0.34 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -219$ (*c* 0.15, $CHCl_3$); Yellow solid; mp: 135–138 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.19 (m, 5H), 7.03–6.97 (m, 3H), 6.04 (s, 1H), 4.49 (t, *J* = 8.4 Hz, 1H), 4.15 (dd, *J* = 4.4, 8.4 Hz, 1H), 4.07 (dq, *J* = 4.4, 8.4 Hz, 1H), 3.07 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.98 (dd, *J* = 10.8, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, *J* = 245.4 Hz), 156.6, 138.1 (d, *J* = 3.0 Hz), 133.8, 132.4, 130.4 (d, *J* = 8.2 Hz), 129.4, 128.7, 127.6, 127.0, 115.5 (d, *J* = 21.3 Hz), 68.6, 55.6, 48.0, 34.4; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}FNO_2$ 284.1081, found: 284.1076.

4.2.7. Methyl 4-((5*R*,10a*S*)-3-Oxo-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-5-yl)benzoate 3g

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), methyl *p*-formylbenzoate (0.45 mmol, 73.8 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 27 h (92.1 mg, 95%); $[\alpha]_D^{23} = -230$ (*c* 0.25, $CHCl_3$); R_f = 0.21 (Petroleum ether/EtOAc 2:1); White solid; mp: 184–185 °C; 97% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.27–7.17 (m, 3H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.07 (s, 1H), 4.49 (t, *J* = 8.4 Hz, 1H), 4.17–4.06 (m, 2H), 3.90 (s, 3H), 3.10–2.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.1, 166.7, 156.7, 146.9, 133.2, 132.4, 130.0, 129.8, 129.5, 128.7, 127.7, 127.1, 68.6, 56.0, 52.2, 48.3, 34.3; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{17}NO_4$ 324.1230, found: 324.1228.

4.2.8. (5*R*,10a*S*)-5-(4-Nitrophenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3h[15]

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), *p*-nitrobenzaldehyde (0.45 mmol, 68 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 22 h (91.2 mg, 98%); R_f = 0.23 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -240$ (*c* 0.25, $CHCl_3$); Yellow solid; mp: 153–156 °C; 98% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.22–7.11 (m, 3H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.01 (s, 1H), 4.44 (t, *J* = 8.4 Hz, 1H), 4.10 (dd, *J* = 4.4, 8.4 Hz, 1H), 4.04–3.97 (m, 1H), 3.02 (dd, *J* = 4.0, 15.6 Hz, 1H), 2.90 (dd, *J* = 11.2, 15.6 Hz, 1H); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}N_2O_4$ 311.1026, found: 311.1025.

4.2.9. (5*R*,10a*S*)-5-(2-Bromophenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3i

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), 2-bromobenzaldehyde (0.45 mmol, 83 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 22 h (101.8 mg, 99%); R_f = 0.29 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -223$ (*c* 0.66, $CHCl_3$); Yellow solid; mp: 147–149 °C; 99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.6 Hz, 1H), 7.28–7.14 (m, 5H), 7.03 (dd, *J* = 1.2, 7.6 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.42 (s, 1H), 4.49 (t, *J* = 8.0 Hz, 1H), 4.26–4.15 (m, 2H), 3.07–2.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 141.7, 134.3, 133.5, 132.3, 130.7, 129.4, 129.3, 128.0, 127.8, 127.5, 127.2, 124.2, 68.3, 56.4, 49.7, 34.0; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}BrNO_2$ 344.0281, found: 344.0273.

4.2.10. (5*R*,10a*S*)-5-(2-Fluorophenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3j

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), 2-fluorobenzaldehyde (0.45 mmol, 47.4 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 22 h (82.4 mg, 97%); R_f = 0.32 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -268$ (*c* 0.30, $CHCl_3$); White solid; mp: 153–155 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.02 (m, 7H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.12 (s, 1H), 4.50 (t, *J* = 8.4 Hz, 1H), 4.24 (dq, *J* = 4.0, 8.0 Hz, 1H), 4.17 (dd, *J* = 3.6, 8.4 Hz, 1H), 3.04 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.97 (dd, *J* = 10.8, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (d, *J* = 246.9 Hz), 157.0, 134.1, 132.1, 131.2 (d, *J* = 4.1 Hz), 130.0 (d, *J* = 8.1 Hz), 129.3, 129.2 (d, *J* = 13.9 Hz), 127.6, 127.3, 127.1, 124.2 (d, *J* = 3.4 Hz), 116.2 (d, *J* = 21.5 Hz), 68.4, 52.7, 49.3 (d, *J* = 3.3 Hz), 34.5; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}FNO_2$ 284.1081, found: 284.1081.

4.2.11. (5*R*,10a*S*)-5-(3-Fluorophenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3k

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), *m*-fluorobenzaldehyde (0.45 mmol, 47.5 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 22 h (81.5 mg, 96%); R_f = 0.35 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -250$ (*c* 0.37, $CHCl_3$); White solid; mp: 160–163 °C; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (m, 4H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.03–6.97 (m, 2H), 6.90 (d, *J* = 2.0, 9.6 Hz 1H), 6.04 (s, 1H), 4.50 (t, *J* = 8.4 Hz, 1H), 4.15 (dd, *J* = 4.4, 8.8 Hz, 1H), 4.07 (dq, *J* = 4.4, 8.4 Hz, 1H), 3.06 (dd, *J* = 4.4, 15.6 Hz, 1H), 2.98 (dd, *J* = 10.8, 15.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, *J* = 245.6 Hz,), 156.6, 144.4 (d, *J* = 6.4 Hz), 133.3, 132.4, 130.2 (d, *J* = 8.1 Hz), 129.4, 128.7, 127.7, 127.1, 124.5 (d, *J* = 2.7 Hz), 115.5 (d, *J* = 21.8 Hz), 115.0 (d, *J* = 21.1 Hz), 68.6, 55.8, 48.2, 34.3; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{14}FNO_2$ 284.1081, found: 284.1083.

4.2.12. (*S*)-1,5,10,10a-Tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3l[7a]

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), paraformaldehyde (0.45 mmol, 13.5 mg), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 6 h (53.3 mg, 94%); R_f = 0.16 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -18$ (*c* 0.04, $CHCl_3$); White solid; mp: 135–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.13 (m, 4H), 4.83 (d, *J* = 16.8 Hz, 1H), 4.59 (t, *J* = 8.4 Hz, 1H), 4.38 (d, *J* = 16.8 Hz, 1H), 4.15 (dd, *J* = 4.8, 8.4 Hz, 1H), 4.02–3.94 (m, 1H), 2.95 (dd, *J* = 4.4, 15.2 Hz, 1H), 2.87 (dd, *J* = 10.8, 15.2 Hz, 1H); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{11}H_{11}NO_2$ 190.0863, found: 190.0863.

4.2.13. (5*R*,10a*S*)-5-Phenethyl-1,5,10,10a-tetrahydro[1,3]xazolo[3,4-*b*]isoquinolin-3-one 3m[16a]

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), phenylpropyl aldehyde (0.45 mmol, 59.7 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 6 h (80.0 mg, 91%); R_f = 0.37 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -200$ (*c* 0.65, $CHCl_3$); Oil; >99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.12 (m, 8H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.98 (dd, *J* = 3.2, 10.0 Hz, 1H), 4.32 (t, *J* = 8.4 Hz, 1H), 4.08 (dd, *J* = 2.8, 8.4 Hz, 1H), 3.93 (dq, *J* = 2.4, 7.6 Hz, 1H), 2.89–2.72 (m, 4H), 2.30–2.21 (m, 1H), 2.13–2.02 (m, 1H); HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{19}NO_2$ 294.1489, found: 294.1489.

4.2.14. (5*R*,10a*S*)-5-(*tert*-Butyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3n

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), pivaldehyde (0.45 mmol, 48.8 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 72 h (36.2 mg, 48%); R_f = 0.46 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -70$ (*c* 0.30, $CHCl_3$); White solid; mp: 174–176 °C; 99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.16 (m, 3H), 7.13 (d, *J* = 7.2 Hz, 1H), 4.67 (s, 1H), 4.59 (t, *J* = 8.0 Hz, 1H), 4.54–4.46 (m, 1H), 4.02 (dd, *J* = 5.2, 8.4 Hz, 1H), 3.15 (dd, *J* = 6.8, 16.8 Hz, 1H), 2.84 (dd, *J* = 8.0, 16.8 Hz, 1H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 134.3, 131.9, 129.3, 128.7, 127.3, 125.7, 69.3, 61.3, 49.4, 38.0, 32.7, 28.3; HRMS (ESI) *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{19}NO_2$ 246.1489, found: 246.1487.

4.2.15. (5*R*,10a*S*)-5-Cyclohexyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one 3o[15]

(*S*)-4-Benzyloxazolidin-2-one (53.1 mg, 0.30 mmol), cyclohexanecarboxaldehyde (0.45 mmol, 54.4 μL), and TMSOTf (0.36 mmol, 65 μL) were used according to the general procedure. The reaction was completed in 28 h (73.6 mg, 91%); R_f = 0.44 (Petroleum ether/EtOAc 2:1); $[\alpha]_D^{23} = -151$ (*c* 0.24, $CHCl_3$); White solid; mp: 139–141 °C; 99% de; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.17 (m, 3H), 7.11 (d, *J* = 7.6 Hz, 1H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.57 (t, *J* = 8.0 Hz, 1H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.12–4.05 (m, 1H), 2.91 (dd, *J* = 5.2, 15.6 Hz, 1H), 2.85 (dd, *J* = 10.0, 15.6 Hz, 1H), 2.00–1.64 (m, 5H), 1.46–0.95 (m, 6H); HRMS (ESI), *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{21}NO_2$ 272.1645, found: 272.1644.

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