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Efficient and stereoselective one-pot synthesis of benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-ones†

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An efficient and mild one-pot convergent synthesis protocol has been developed for benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one derivatives through the Mitsunobu reaction and sequential cyclization. Various tricyclic fused benzoxazinyl-oxazolidinones (20 examples) were obtained in good to excellent yields and high enantioselectivities with facile operation. Furthermore, four stereoisomers were afforded respectively in high ee values (>97.8%) *via* using different chiral 2,3-epoxy-4-trityloxybutanol. This methodology has been applied to the synthesis of key intermediates of drug candidates.

Introduction

Oxazolidinone was a key scaffold for some pharmaceuticals. As shown in Fig. 1, Linezolid (1)¹ was the first approved (2000) oxazolidinone antibacterial drug for the treatment of Gram-positive bacterial infection with the off-label use to treat complicated MDR-TB and XDR-TB. Another oxazolidinone drug Tedizolid phosphate was approved by FDA in June 2014 for the treatment of MRSA skin infections.² Furthermore, Rivaroxaban launched in 2011 is a FXa inhibitor as an anticoagulant drug containing the oxazolidinone moiety.³ Benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one, a [6,6,5] tricyclic fused benzoxazinyl-oxazolidinone, was developed based on the oxazolidinone scaffold and is the essential structural framework of several bioactive compounds with antibacterial,⁴ anticoagulant,⁵ and antituberculosis⁶ activities (Fig. 2).

To the best of our knowledge, four synthetic routes for the synthesis of benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one derivatives have been reported (Scheme 1). Nicolaou's group reported the synthesis of tricyclic fused benzoxazinyl-oxazolidinone *via* Dess–Martin periodinane-mediated cascade cyclization of γ,δ -unsaturated urethanes in moderate yields (36–50%).⁷ Yang's group disclosed the synthesis of tricyclic fused oxazolidinone *via* *n*-BuLi mediated intramolecular cyclization reaction in

linear synthetic routes (6–7 steps).^{4b,8} Chen *et al.* reported the synthesis of FXa inhibitors exemplified by 6 from substituted benzyl(2-hydroxyphenyl)carbamate and methyl 3-(bromomethyl)oxirane-2-carboxylate in the presence of Cs₂CO₃, which gave a moderate cyclization yield (54%).⁹ Malhotra *et al.* provided an approach for the synthesis of chiral benzoxazinyl-oxazolidinone from benzo[*b*][1,4]-oxazine-3-carboxylic acid *via* 3–5 steps of derivatization including acylation, reduction, Grignard reaction and cyclization reaction.¹⁰ Although these methods provided access to benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one analogues, the reported routes suffered from limitations to some extent such as ineffective stereoselectivity, limited substrates scope, unsatisfactory yields, harsh reaction conditions or tedious synthesis steps. Therefore, the development of a practical and efficient approach to benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one is still required.

In recent years, our group have developed a series of benzoxazinyl-oxazolidinones as anti-TB agents.^{6,11} To improve the efficiency of synthesis and avoid oxidation of the sulfide in the thiomorpholine, a convergent protocol has been developed,¹¹ however, tedious column purification and harsh cyclization conditions posed a hurdle for further derivatization and large-scale preparation. As our continuing efforts toward the

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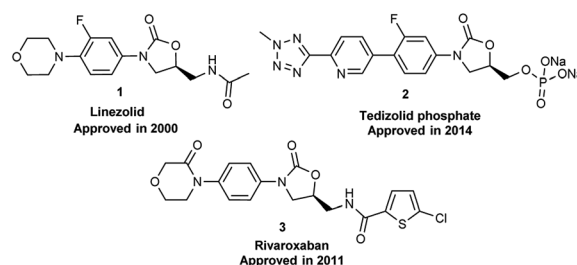


Fig. 1 Chemical structure of oxazolidinone drugs.



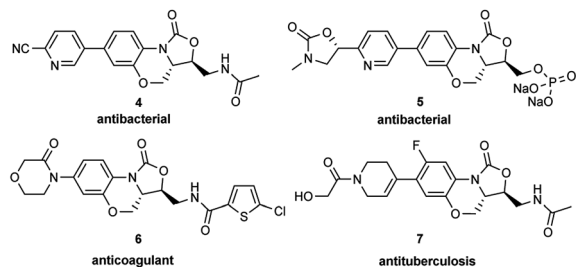


Fig. 2 Bioactive compounds containing benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one scaffold.

development of novel benzoxazinyl-oxazolidinones as anti-TB agents, herein, we report the first efficient protocol for one-pot and convergent synthesis of tricyclic fused benzoxazinyl-oxazolidinone compounds by the reaction of benzyl(2-hydroxyphenyl)carbamate with 2,3-epoxy-4-trityloxybutanol through the Mitsunobu reaction and sequential cyclization in mild conditions (Scheme 1).

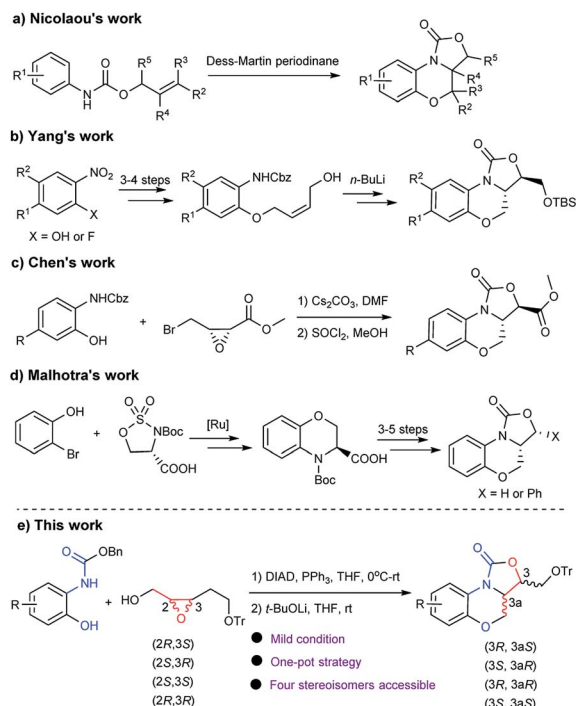
Results and discussion

As the key substrate in the Mitsunobu reaction, ((2*R*,3*S*)-3-((trityloxy)methyl)oxiran-2-yl)methanol **9a** could be synthesized easily from (*Z*)-4-(trityloxy)but-2-en-1-ol by Sharpless epoxidation in excellent yield with high ee value according to the reported procedure,^{5a} and the trityl protection group could be removed smoothly under acid condition as well. Thus, at the outset of our attempt, *N*-Boc or *N*-Cbz substituted 2-aminophenol derivatives **8a** and **8b**, compound **9a** were chosen as

model substrates to optimize the Mitsunobu reaction conditions (Table 1). When *R* is Boc of **8a**, the reaction furnished **10a** in good yield (81%) in the presence of DEAD and PPh₃ in anhydrous THF (entry 1). Employment of DIAD resulted in a similar yield (entry 2).

However, this reaction did not work when TMAD or ADDP was used (entries 3 and 4). When *R* is Cbz of **8b**, only a trace product was observed in the presence of ADDP (entry 5). DEAD and DIAD could promote the reaction of **8b** and **9a** efficiently to afford the desired product **10b** in 94% and 90% yields (entries 6 and 7), respectively, which was superior to the corresponding *N*-Boc substrate **8a**. Another polar aprotic solvent, MeCN, was also tested and the yields for **10b** using DEAD or DIAD as azo agent were found to be similar with THF (entries 8 and 9). Based on the above results and the safety consideration of dialkyl azodicarboxylates,¹² the combination of DIAD and PPh₃ was selected to be the optimized conditions and *N*-Cbz-2-aminophenol was a privilege substrate.

Next, we examined the optimization of the cyclization reaction conditions (Table 2). **11aa** was obtained in 69% yield, when **10b** was treated with *n*-BuLi (1.3 equiv.) from −78 °C to room temperature (entry 1). Consideration of danger of *n*-BuLi and harsh reaction condition, this reaction was not suitable for scale-up preparation. We noted that the lithium ion plays a very important role in region-chemical control and cyclization in the synthesis of Linezolid.¹³ It prompted us to replace dangerous *n*-BuLi by other lithium salts such as LiOH·H₂O, Li₂CO₃ and *t*-BuOLi. As depicted in Table 2, LiOH·H₂O and Li₂CO₃ failed to produce the expected product (entries 2 and 3). To our delight, *t*-BuOLi was found very effective for this reaction (entry 4), generating **11aa** in an excellent yield (86%) at room temperature. However, the annulation process did not occur in the presence of Cs₂CO₃ and K₂CO₃ (entries 5 and 6). Although *t*-BuOLi could also promote the cyclization in the solvent of MeCN with the desired product **11aa** obtained in 85% yield after 12 h at room temperature, it was difficult to stir the reaction



Scheme 1 Synthetic approaches to benzo[b]oxazolo[3,4-d][1,4]oxazin-1-ones.

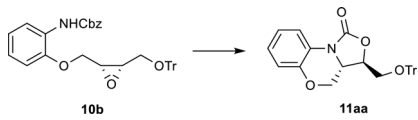
Table 1 Optimization of Mitsunobu reaction conditions^a

Entry	R	Azo agents	Phosphine	Solvent	Yield ^b (%)
1	Boc	DEAD	PPh ₃	THF	81
2	Boc	DIAD	PPh ₃	THF	80
3	Boc	TMAD	PPh ₃	THF	Trace
4	Boc	ADDP	PPh ₃	THF	Trace
5	Cbz	ADDP	PPh ₃	THF	Trace
6	Cbz	DEAD	PPh ₃	THF	94
7	Cbz	DIAD	PPh ₃	THF	90
8	Cbz	DEAD	PPh ₃	MeCN	82
9	Cbz	DIAD	PPh ₃	MeCN	91

^a Reaction conditions: **8a** or **8b** (1 mmol), **9a** (1.35 mmol), azo agent (1.5 mmol), PPh₃ (1.5 mmol), solvent (8 mL), 0 °C–rt, 4 h. ^b Isolated yields.



Table 2 Optimization of cyclization reaction conditions^a

				
Entry	Base	Solvent	Temp.	Yield ^b (%)
1	<i>n</i> -BuLi	THF	−78 °C–rt	69
2	LiOH·H ₂ O	THF	rt	—
3	Li ₂ CO ₃	THF	rt	—
4	<i>t</i> -BuOLi	THF	rt	86
5	Cs ₂ CO ₃	THF	rt	—
6	K ₂ CO ₃	THF	rt	—
7 ^c	<i>t</i> -BuOLi	MeCN	rt	85

^a Reaction conditions: **10b** (1 mmol), base (1.3 mmol), solvent (8 mL), rt, 6 h. ^b Isolated yields. ^c Reaction time was 12 h.

mixture due to the solid precipitation formed (entry 7). The results displayed that *t*-BuOLi was an excellent base for the annulation process given the stability and mild condition compared with *n*-BuLi. Thus, 1.3 equiv. of *t*-BuOLi in THF at room temperature was identified as the optimal cyclization condition.

Considering the tedious column chromatography purification after the Mitsunobu reaction, we wonder if one-pot strategy could be applied to simplify the process. Since the reaction solvent (THF) was not only suitable for the Mitsunobu reaction (step 1), but also for the cyclization reaction (step 2), we explored the possibility of cyclization reaction by adding *t*-BuOLi directly into the mixture when the Mitsunobu reaction was completed without any purified treatment (Table 3). When 1.3 or 1.5 equiv. of *t*-BuOLi was used, no product was detected (entries 1 and 2). We were pleased to find that the target compound **11aa** was obtained in 60% yield using 2.0 equiv. of *t*-BuOLi. The yield of **11aa** was further improved (83%) when 2.5 equiv. of *t*-BuOLi was employed. It indicated that diisopropyl hydrazine-1,2-dicarboxylate, the byproduct of the Mitsunobu reaction, may form the complex with Li⁺ to cause the

consumption of the base. The result demonstrated that the desired product **11aa** can be synthesized by simple one-pot operation with higher isolated yield (83%) compared to the stepwise process (77%).

Encouraged by the success of one-pot protocol, subsequently, the generality of this one-pot process leading to the benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one skeleton using various combinations of substrates was investigated. As summarized in

Table 4 Scope of one-pot synthesis of benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-ones^b

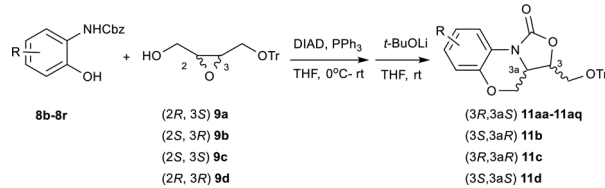
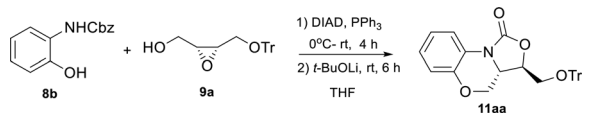
		
8b-8r	(2 <i>R</i> , 3 <i>S</i>) 9a (2 <i>S</i> , 3 <i>R</i>) 9b (2 <i>S</i> , 3 <i>S</i>) 9c (2 <i>R</i> , 3 <i>R</i>) 9d	(3 <i>R</i> , 3 <i>aS</i>) 11aa-11aq (3 <i>S</i> , 3 <i>aR</i>) 11b (3 <i>R</i> , 3 <i>aR</i>) 11c (3 <i>S</i> , 3 <i>aS</i>) 11d
11aa^b	11b^b	11c^c
83%, 98.9%ee	67%, 97.8%ee	73%, >99%ee
11d^c	11ab^b	11ac^c
80%, >99%ee	77%, 96.2%ee	82%, >99%ee
11ad^b	11ae^b	11af^c
81%, 99.2%ee	85%, 96.3%ee	79%, >99%ee
11ag^b	11ah^b	11ai^b
84%, 95.2%ee	88%, 95.6%ee	85%, 97.2%ee
11aj^b	11ak^b	11al^b
84%, 96.4%ee	86%, 95.1%ee	85%, 97.9%ee
11am^b	11an^c	11ao^c
83%, 97.2%ee	81%, >99%ee	80%, >99%ee
11ap^c	11aq^c	
74%, >99%ee	62%, >99%ee	

Table 3 Optimization of one-pot reaction conditions^a

		
Entry	Equiv. of <i>t</i> -BuOLi	Yield ^b (%)
1	1.3	—
2	1.5	—
3	2.0	60
4	2.5	83

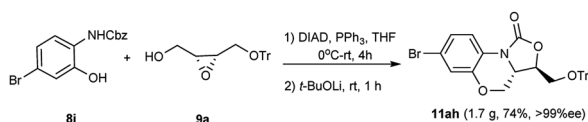
^a Reaction conditions: **8b** (1 mmol), **9a** (1.35 mmol), DIAD (1.5 mmol), PPh₃ (1.5 mmol), THF (8 mL), 0 °C–rt, 4 h; then *t*-BuOLi, THF, rt, 6 h. ^b Isolated yields.

^a Reaction conditions: **8b-8r** (1 mmol), **9a-9d** (1.35 mmol), DIAD (1.5 mmol), PPh₃ (1.5 mmol), THF (8 mL), 0 °C–rt, 8 h for **11ab** and **11ac**, 6 h for **11ad** and **11ae**, 4 h for the others; then *t*-BuOLi (2.5 mmol), THF, rt, 1–3 h. ^b Isolated yields *via* column chromatography. ^c Isolated yields *via* trituration with MeOH and filtration.

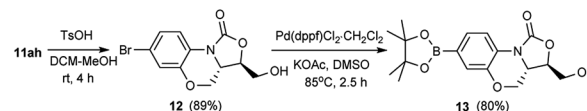
Table 4, first, the reaction of benzyl(2-hydroxyphenyl)carbamate **8b** with different chiral 2,3-epoxy-4-trityloxybutanol was explored. Delightfully, four isomers were afforded smoothly in good to excellent yields and high ee values ((3*R*,3*aS*)-**11aa**: 83% yield, 98.9% ee; (3*S*,3*aR*)-**11b**: 67% yield, 97.8% ee; (3*R*,3*aR*)-**11c**: 73% yield, >99% ee; (3*S*,3*aS*)-**11d**: 80% yield, >99% ee).

Benzyl(2-hydroxyphenyl)carbamate substituted with electron-donating groups such as methyl and methoxy delivered the corresponding target compounds **11ab–11ae** in 77–85% yields with excellent enantioselectivities (96.2 to >99% ee). Halogenated benzyl(2-hydroxyphenyl)carbamates furnished the halogenated target compounds **11af–11an** in 79–88% yields with high enantiomeric purity (95.1 to >99% ee). As anticipated, the electron-deficient benzyl(2-hydroxyphenyl)carbamates bearing nitro group performed efficiently to deliver the corresponding target compounds **11ao** and **11ap** in 80% yield, >99% ee and 74% yield, >99% ee respectively. In addition, the reaction was also efficient when benzyl(2-hydroxyphenyl)carbamate bearing morpholin-3-one group, leading to the desired product **11aq** in 62% yield and >99% ee, a key intermediate for the synthesis of anticoagulant agent **6** shown in Fig. 1. It was worth noting that the reaction time of the Mitsunobu reaction was different depending on different substrate. When the substrate **8** containing electron-withdrawing substituent on the phenyl ring or non-substituted, 4 hours was sufficient for the Mitsunobu reaction (**11aa**, **11b–11d** and **11af–11ap**), while benzyl(2-hydroxyphenyl)carbamate containing electron-donating groups, the reaction took 6–8 hours (**11ab–11ae**). It is apparently that the electron-withdrawing group is beneficial to speed up the reaction due to increasing the acidity of the phenol hydroxyl, exemplified by 4 h for **11ap** (R is 4-NO₂) vs. 8 h for **11ac** (R is 4-MeO). Taking the advantage of some rigid tricyclic fused oxazolidinones with low solubility in MeOH, we simplified the purification only *via* trituration with MeOH and then by filtration to afford the pure products. Notably, the excellent enantioselectivity (>99% ee) was observed after the simple operation, represented by **11c**, **11d**, **11ac**, **11af**, and **11an–11aq**.

To further explore the scalability and potential synthetic application of the present method, the gram-scale reaction and application were carried out. As displayed in Schemes 2 and 3, **11ah** was obtained in good yield (1.7 g, 74%, >99% ee) after trituration in MeOH. Next, the deprotection of the triphenylmethyl group of **11ah** was performed well under mild condition. After aqueous workup and trituration with DCM/PE (1/1), compound **12** was obtained in 89% yield, and then the Suzuki–Miyaura reaction of **12** and bis(pinacolato)diboron provided the corresponding borate ester **13** (80%) which was an important intermediate to synthesize the clinical candidate **5** (Fig. 1) as an antibacterial agent.^{4c,14}



Scheme 2 Gram-scale synthesis of compound **11ah**.



Scheme 3 Application of the methodology.

Conclusion

In summary, we have developed a practical, efficient and operationally simple one-pot convergent protocol to afford the tricyclic fused benzoxazinyl-oxazolidinones through the Mitsunobu reaction and sequential cyclization. The present methodology is a stereoselective process which was controlled by the chiral 2,3-epoxy-4-trityloxybutanol, delivering a series of benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-ones in good to excellent yields (62–88%) with high ee values (95.1 to >99% ee). In addition, this one-pot strategy was suitable for large-scale preparation, which has been successfully employed to afford the important intermediates of some promising candidate compounds such as **5** and **6**.

Experimental

General

Unless otherwise stated, all the solvents and reagents were purchased from commercial suppliers and were used without further purification. All melting points were measured with a micro melting point apparatus (MP-J3, Yanaco) and were uncorrected. ¹H NMR or ¹³C NMR spectra were recorded on Varian 400 MHz or 500 MHz spectrometer using CDCl₃, DMSO-*d*₆ or acetone-*d*₆ as solvents and tetramethylsilane (TMS) as an internal standard. HR-MS spectra were obtained on a ThermoFisher Exactive Plus mass spectrometer (ESI, ThermoFisher Scientific, Bremen, Germany). Optical rotations were measured with a Rudolph Research Analytical (Autopol IV-T).

General procedure for the synthesis of target compounds

To a mixture of **8** (1.0 equiv.), **9** (1.35 equiv.), PPh₃ (1.5 equiv.) in anhydrous THF (8 mL) at 0 °C was added dropwise a solution of DIAD (1.5 equiv.) in anhydrous THF (0.3 mL). The reaction mixture was stirred at 0 °C for 30 min. Then, the reaction was allowed to warm to room temperature and monitored by TLC. Upon the completion of reaction, *t*-BuOLi (2.5 equiv.) was added, and the reaction mixture was stirred at room temperature for 1–3 h. After the reaction completed, water (20 mL) was added to quench the reaction, the reaction mixture was extracted with EtOAc (15 mL × 3). The combined organic phase was washed with brine (15 mL), dried over anhydrous Na₂SO₄, and evaporated in vacuum. The residue was purified by column chromatography or trituration with MeOH to give the products **11**.

((3*R*,3*aS*)-3-((Trityloxy)methyl)-3*a*,4-dihydro-1*H*,3*H*-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (**11aa**). White solid (385 mg, 83% yield); mp: 175–177 °C. The product was analyzed by chiral HPLC (IC, 5 μm, 4.6 mm × 250 mm; eluent: hexane/isopropanol, 80/20; flow rate: 1 mL min^{−1}; λ



= 220 nm; $T = 20\text{ }^{\circ}\text{C}$): $t_R = 12.06\text{ min}$ (99.46%), $t_R = 14.30\text{ min}$ (0.54%). The enantiomeric purity of **11aa** was determined to be 98.9% ee. $[\alpha]_D^{21} = -33.9$ ($c = 1$, CHCl_3). ^1H NMR (400 MHz, acetone- d_6) δ : 7.98–7.94 (m, 1H), 7.53–7.48 (m, 6H), 7.39–7.32 (m, 6H), 7.31–7.26 (m, 3H), 7.07–6.96 (m, 2H), 6.95–6.90 (m, 1H), 4.66–4.59 (m, 1H), 4.54 (dd, $J = 2.8$, 10.4 Hz, 1H), 4.14–4.08 (m, 1H), 4.02 (t, $J = 10.0$ Hz, 1H), 3.61 (dd, $J = 4.0$, 10.4 Hz, 1H), 3.46 (dd, $J = 4.4$, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 154.7, 145.7, 144.7, 129.5, 128.9, 128.2, 125.2, 124.9, 122.1, 120.4, 117.7, 87.8, 75.5, 67.2, 64.9, 53.7. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676; found: 486.1670.

(3S,3aR)-3-((Trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11b). White solid (310 mg, 67% yield); mp: 184–186 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 80/20; flow rate: 1 mL min^{-1} ; $\lambda = 220\text{ nm}$; $T = 20\text{ }^{\circ}\text{C}$): $t_R = 12.05\text{ min}$ (1.10%), $t_R = 14.23\text{ min}$ (98.90%). The enantiomeric purity of **11b** was determined to be 97.8% ee. $[\alpha]_D^{21} = +33.1$ ($c = 1$, CHCl_3). ^1H NMR (500 MHz, acetone- d_6) δ : 7.96 (dd, $J = 1.0$, 7.5 Hz, 1H), 7.56–7.44 (m, 6H), 7.40–7.32 (m, 6H), 7.32–7.24 (m, 3H), 7.08–6.96 (m, 2H), 6.94 (dd, $J = 1.5$, 8.0 Hz, 1H), 4.66–4.58 (m, 1H), 4.53 (dd, $J = 3.0$, 10.5 Hz, 1H), 4.16–4.06 (m, 1H), 4.02 (t, $J = 10.5$ Hz, 1H), 3.61 (dd, $J = 4.0$, 10.5 Hz, 1H), 3.46 (dd, $J = 4.0$, 10.5 Hz, 1H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 154.7, 145.8, 144.7, 129.5, 128.9, 128.2, 125.2, 124.9, 122.1, 120.4, 117.7, 87.8, 75.5, 67.2, 64.9, 53.7. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676; found: 486.1663.

(3R,3aR)-3-((Trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11c). White solid (340 mg, 73% yield); mp: 249–251 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 85/15; flow rate: 0.7 mL min^{-1} ; $\lambda = 220\text{ nm}$; $T = 20\text{ }^{\circ}\text{C}$): $t_R = 20.17\text{ min}$ (100.00%). The enantiomeric purity of **11c** was determined to be >99% ee. $[\alpha]_D^{25} = -32.6$ ($c = 1$, DMSO). ^1H NMR (400 MHz, acetone- d_6) δ : 8.28–8.24 (m, 1H), 7.48–7.42 (m, 6H), 7.33–7.22 (m, 9H), 7.09–6.98 (m, 2H), 6.95–6.90 (m, 1H), 5.06–5.00 (m, 1H), 4.56–4.49 (m, 1H), 4.40 (dd, $J = 3.2$, 10.4 Hz, 1H), 4.11 (t, $J = 10.0$ Hz, 1H), 3.60 (dd, $J = 4.4$, 11.2 Hz, 1H), 3.09 (dd, $J = 2.8$, 10.8 Hz, 1H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 154.3, 145.2, 144.4, 129.4, 128.9, 128.2, 125.6, 124.5, 122.5, 118.5, 117.9, 88.1, 74.6, 64.3, 63.0, 54.2. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676; found: 486.1666.

(3S,3aS)-3-((Trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11d). White solid (371 mg, 80% yield); mp: 250–252 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 85/15; flow rate: 0.7 mL min^{-1} ; $\lambda = 220\text{ nm}$; $T = 20\text{ }^{\circ}\text{C}$): $t_R = 21.88\text{ min}$ (100.00%). The enantiomeric purity of **11d** was determined to be >99% ee. $[\alpha]_D^{25} = +35.8$ ($c = 1$, DMSO). ^1H NMR (400 MHz, acetone- d_6) δ : 8.28–8.24 (m, 1H), 7.48–7.42 (m, 6H), 7.33–7.22 (m, 9H), 7.09–6.98 (m, 2H), 6.95–6.90 (m, 1H), 5.06–5.00 (m, 1H), 4.56–4.49 (m, 1H), 4.40 (dd, $J = 3.2$, 10.4 Hz, 1H), 4.11 (t, $J = 10.0$ Hz, 1H), 3.60 (dd, $J = 4.4$, 11.2 Hz, 1H), 3.09 (dd, $J = 2.8$, 10.8 Hz, 1H). ^{13}C NMR (100

MHz, acetone- d_6) δ : 154.4, 145.2, 144.4, 129.4, 128.9, 128.2, 125.6, 124.5, 122.5, 118.5, 117.9, 88.1, 74.6, 64.3, 63.0, 54.2. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{30}\text{H}_{25}\text{NNaO}_4$: 486.1676; found: 486.1672.

(3R,3aS)-8-Methoxy-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ab). White solid (379 mg, 77% yield); mp: 145–147 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 70/30; flow rate: 1 mL min^{-1} ; $\lambda = 210\text{ nm}$; $T = 25\text{ }^{\circ}\text{C}$): $t_R = 12.82\text{ min}$ (98.09%), $t_R = 15.68\text{ min}$ (1.91%). The enantiomeric purity of **11ab** was determined to be 96.2% ee. $[\alpha]_D^{21} = -17.8$ ($c = 1$, CHCl_3). ^1H NMR (500 MHz, acetone- d_6) δ : 7.61 (d, $J = 2.5$ Hz, 1H), 7.56–7.46 (m, 6H), 7.42–7.32 (m, 6H), 7.32–7.25 (m, 3H), 6.85 (d, $J = 9.0$ Hz, 1H), 6.62 (dd, $J = 2.5$, 9.0 Hz, 1H), 4.65–4.57 (m, 1H), 4.47 (dd, $J = 3.0$, 10.5 Hz, 1H), 4.14–4.04 (m, 1H), 3.95 (t, $J = 10.5$ Hz, 1H), 3.77 (s, 3H), 3.60 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.46 (dd, $J = 4.5$, 10.5 Hz, 1H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 155.1, 154.6, 144.7, 139.6, 129.5, 128.9, 128.2, 125.1, 118.1, 111.0, 105.3, 87.9, 75.5, 67.0, 64.8, 56.0, 54.0. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{27}\text{NNaO}_5$: 516.1781; found: 516.1762.

(3R,3aS)-7-Methoxy-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ac). White solid (403 mg, 82% yield); mp: 220–222 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 70/30; flow rate: 1 mL min^{-1} ; $\lambda = 210\text{ nm}$; $T = 25\text{ }^{\circ}\text{C}$): $t_R = 13.88\text{ min}$ (100.00%). The enantiomeric purity of **11ac** was determined to be >99% ee. $[\alpha]_D^{21} = -27.1$ ($c = 1$, CHCl_3). ^1H NMR (400 MHz, acetone- d_6) δ : 7.78 (d, $J = 9.2$ Hz, 1H), 7.51–7.44 (m, 6H), 7.36–7.30 (m, 6H), 7.28–7.22 (m, 3H), 6.58 (dd, $J = 2.8$, 8.8 Hz, 1H), 6.48 (d, $J = 2.8$ Hz, 1H), 4.58–4.53 (m, 1H), 4.49 (dd, $J = 1.6$, 9.2 Hz, 1H), 4.06–3.93 (m, 2H), 3.73 (s, 3H), 3.56 (dd, $J = 3.6$, 10.4 Hz, 1H), 3.40 (dd, $J = 4.4$, 10.4 Hz, 1H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 157.8, 154.9, 146.6, 144.7, 129.5, 128.9, 128.2, 121.4, 118.1, 108.3, 103.0, 87.8, 75.4, 67.0, 65.0, 55.9, 53.6. HR-MS (ESI): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{27}\text{NNaO}_5$: 516.1781; found: 516.1780.

(3R,3aS)-8-Methyl-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ad). White solid (388 mg, 81% yield); mp: 155–157 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1 mL min^{-1} ; $\lambda = 220\text{ nm}$; $T = 25\text{ }^{\circ}\text{C}$): $t_R = 14.86\text{ min}$ (99.62%), $t_R = 20.00\text{ min}$ (0.38%). The enantiomeric purity of **11ad** was determined to be 99.2% ee. $[\alpha]_D^{21} = -26.9$ ($c = 1$, CHCl_3). ^1H NMR (500 MHz, acetone- d_6) δ : 7.80 (s, 1H), 7.56–7.45 (m, 6H), 7.41–7.32 (m, 6H), 7.32–7.24 (m, 3H), 6.85 (d, $J = 9.0$ Hz, 1H), 6.81 (d, $J = 9.0$ Hz, 1H), 4.64–4.56 (m, 1H), 4.47 (d, $J = 10.5$ Hz, 1H), 4.13–4.04 (m, 1H), 3.97 (t, $J = 10.5$ Hz, 1H), 3.60 (d, $J = 10.0$ Hz, 1H), 3.46 (dd, $J = 3.5$, 10.5 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, acetone- d_6) δ : 154.7, 144.7, 143.6, 131.5, 129.5, 128.9, 128.2, 125.8, 124.5, 120.5, 117.4, 87.8, 75.4, 67.2, 64.9, 53.9, 21.0. HR-MS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_4$: 478.2013; found: 478.2005.

(3R,3aS)-7-Methyl-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ae). White solid (407 mg, 85% yield); mp: 237–239 $^{\circ}\text{C}$. The product was analyzed by chiral HPLC (IC, 5 μm , 4.6 mm \times 250 mm; eluent: hexane/



isopropanol, 80/20; flow rate: 1 mL min⁻¹; λ = 220 nm; T = 25 °C): t_R = 11.75 min (98.15%), t_R = 14.16 min (1.85%). The enantiomeric purity of **11ae** was determined to be 96.3% ee. $[\alpha]_D^{21}$ = -27.0 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.81 (d, J = 8.0 Hz, 1H), 7.52–7.46 (m, 6H), 7.39–7.31 (m, 6H), 7.31–7.25 (m, 3H), 6.84–6.78 (m, 1H), 6.76 (d, J = 0.8 Hz, 1H), 4.62–4.56 (m, 1H), 4.50 (dd, J = 2.8, 10.0 Hz, 1H), 4.10–4.03 (m, 1H), 3.99 (t, J = 10.0 Hz, 1H), 3.60 (dd, J = 4.0, 10.4 Hz, 1H), 3.44 (dd, J = 4.4, 10.4 Hz, 1H), 2.26 (s, 3H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.8, 145.6, 144.7, 135.1, 129.5, 128.9, 128.2, 122.8, 122.3, 120.2, 118.0, 87.8, 75.4, 67.3, 64.9, 53.8, 21.0. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₁H₂₇NNaO₄: 500.1832; found: 500.1808.

(3R,3aS)-9-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11af). Off-white solid (427 mg, 79% yield); mp: 234–236 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 80/20; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 14.85 min (99.51%), t_R = 19.54 min (0.49%). The enantiomeric purity of **11af** was determined to be 99.0% ee. $[\alpha]_D^{21}$ = -85.4 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.59–7.51 (m, 6H), 7.39–7.31 (m, 6H), 7.31–7.24 (m, 4H), 7.11 (t, J = 8.4 Hz, 1H), 6.94 (dd, J = 1.6, 8.4 Hz, 1H), 4.64–4.54 (m, 2H), 4.04 (t, J = 10.8 Hz, 1H), 3.99–3.93 (m, 1H), 3.62 (dd, J = 3.6, 10.8 Hz, 1H), 3.38 (dd, J = 4.0, 10.8 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.5, 149.6, 144.7, 129.6, 128.9, 128.3, 128.1, 126.7, 123.8, 119.4, 117.0, 87.8, 75.5, 67.5, 64.8, 52.0. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄BrNNaO₄: 564.0781; found: 564.0778.

(3R,3aS)-8-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11ag). Pink solid (454 mg, 84% yield); mp: 207–209 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 16.33 min (97.61%), t_R = 21.17 min (2.39%). The enantiomeric purity of **11ag** was determined to be 95.2% ee. $[\alpha]_D^{21}$ = -9.0 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 8.14 (d, J = 2.4 Hz, 1H), 7.53–7.46 (m, 6H), 7.40–7.32 (m, 6H), 7.32–7.25 (m, 3H), 7.18 (dd, J = 2.8, 8.8 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.69–4.63 (m, 1H), 4.57 (dd, J = 3.2, 10.4 Hz, 1H), 4.18–4.11 (m, 1H), 4.06 (t, J = 10.4 Hz, 1H), 3.62 (dd, J = 4.0, 10.8 Hz, 1H), 3.48 (dd, J = 4.4, 10.4 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.6, 145.0, 144.6, 129.5, 128.9, 128.2, 127.8, 126.3, 122.5, 119.6, 113.5, 87.9, 75.8, 67.1, 64.7, 53.4. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄BrNNaO₄: 564.0781; found: 564.0756.

(3R,3aS)-7-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11ah). White solid (478 mg, 88% yield); mp: 208–210 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 0.6 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 27.91 min (2.21%), t_R = 29.96 min (97.79%). The enantiomeric purity of **11ah** was determined to be 95.6% ee. $[\alpha]_D^{21}$ = -12.9 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.90 (d, J = 8.8 Hz, 1H), 7.52–7.47 (m, 6H), 7.39–7.32 (m, 6H), 7.32–7.25 (m, 3H), 7.18 (dd, J = 2.0, 8.4 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 4.68–4.63 (m, 1H), 4.57 (dd, J = 2.4, 9.6 Hz, 1H),

4.16–4.10 (m, 1H), 4.07 (t, J = 9.6 Hz, 1H), 3.62 (dd, J = 3.6, 10.4 Hz, 1H), 3.46 (dd, J = 4.4, 10.8 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.6, 146.6, 144.6, 129.5, 128.9, 128.2, 125.1, 124.4, 121.7, 120.6, 116.7, 87.9, 75.7, 67.3, 64.8, 53.4. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄BrNNaO₄: 564.0781; found: 564.0772.

(3R,3aS)-6-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11ai). White solid (460 mg, 85% yield); mp: 213–215 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 95/5; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 29.35 min (1.38%), t_R = 31.89 min (98.62%). The enantiomeric purity of **11ai** was determined to be 97.2% ee. $[\alpha]_D^{21}$ = -34.8 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.98 (dd, J = 1.6, 8.0 Hz, 1H), 7.55–7.46 (m, 6H), 7.40–7.32 (m, 6H), 7.32–7.25 (m, 4H), 6.96 (t, J = 8.0 Hz, 1H), 4.74–4.62 (m, 2H), 4.24–4.09 (m, 2H), 3.63 (dd, J = 3.6, 10.4 Hz, 1H), 3.46 (dd, J = 4.0, 10.4 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.6, 144.6, 142.9, 129.5, 128.9, 128.7, 128.2, 126.3, 122.8, 119.8, 111.1, 87.8, 75.4, 67.8, 64.8, 53.5. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄BrNNaO₄: 564.0781; found: 564.0757.

(3R,3aS)-8-Fluoro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11aj). White solid (405 mg, 84% yield); mp: 180–182 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1 mL min⁻¹; λ = 220 nm; T = 25 °C): t_R = 16.99 min (98.18%), t_R = 19.75 min (1.82%). The enantiomeric purity of **11aj** was determined to be 96.4% ee. $[\alpha]_D^{21}$ = -26.9 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.76 (dd, J = 3.2, 10.4 Hz, 1H), 7.54–7.47 (m, 6H), 7.40–7.32 (m, 6H), 7.32–7.26 (m, 3H), 6.95 (dd, J = 5.2, 8.8 Hz, 1H), 6.84–6.78 (m, 1H), 4.68–4.62 (m, 1H), 4.54 (dd, J = 3.2, 10.4 Hz, 1H), 4.18–4.10 (m, 1H), 4.02 (t, J = 10.4 Hz, 1H), 3.62 (dd, J = 4.0, 10.8 Hz, 1H), 3.48 (dd, J = 4.4, 10.4 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 157.8 (d, J = 235 Hz), 154.6, 144.6, 141.9 (d, J = 3 Hz), 129.5, 128.9, 128.2, 125.4 (d, J = 12 Hz), 118.6 (d, J = 9 Hz), 111.4 (d, J = 24 Hz), 106.6 (d, J = 28 Hz), 87.9, 75.8, 67.0, 64.7, 53.7. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄FNNaO₄: 504.1582; found: 504.1570.

(3R,3aS)-7-Fluoro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (11ak). White solid (412 mg, 86% yield); mp: 178–180 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 0.7 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 23.65 min (97.54%), t_R = 25.39 min (2.46%). The enantiomeric purity of **11ak** was determined to be 95.1% ee. $[\alpha]_D^{21}$ = -29.5 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.94 (dd, J = 5.6, 8.8 Hz, 1H), 7.54–7.45 (m, 6H), 7.41–7.32 (m, 6H), 7.32–7.24 (m, 3H), 6.87–6.78 (m, 1H), 6.74 (dd, J = 2.8, 10.0 Hz, 1H), 4.67–4.60 (m, 1H), 4.60–4.53 (m, 1H), 4.16–4.00 (m, 2H), 3.61 (dd, J = 4.0, 10.8 Hz, 1H), 3.45 (dd, J = 4.4, 10.8 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 160.1 (d, J = 240 Hz), 154.9, 146.7 (d, J = 12 Hz), 144.6, 129.5, 128.9, 128.2, 121.6 (d, J = 10 Hz), 121.4 (d, J = 2 Hz), 108.8 (d, J = 22 Hz), 104.9 (d, J = 26 Hz), 87.8, 75.5, 67.5, 64.9, 53.3. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄FNNaO₄: 504.1582; found: 504.1578.



(3R,3aS)-6,8-Dichloro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11al). Off-white solid (449 mg, 85% yield); mp: 205–207 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 12.24 min (98.95%), t_R = 14.46 min (1.05%). The enantiomeric purity of **11al** was determined to be 97.9% ee. $[\alpha]_D^{21}$ = -15.1 (c = 1, CHCl₃). ¹H NMR (500 MHz, acetone-*d*₆) δ : 7.99 (s, 1H), 7.55–7.45 (m, 6H), 7.42–7.32 (m, 6H), 7.32–7.24 (m, 3H), 7.21 (s, 1H), 4.77–4.65 (m, 2H), 4.29–4.10 (m, 2H), 3.64 (dd, J = 3.5, 10.5 Hz, 1H), 3.50 (dd, J = 4.0, 10.5 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.4, 144.6, 141.0, 129.5, 128.9, 128.2, 127.1, 126.2, 124.9, 123.1, 118.4, 88.0, 75.8, 67.6, 64.6, 53.3. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₃Cl₂NNaO₄: 554.0896; found: 554.0880.

(3R,3aS)-7,8-Difluoro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11am). White solid (413 mg, 83% yield); mp: 222–224 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 0.7 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 20.21 min (98.59%), t_R = 22.95 min (1.40%). The enantiomeric purity of **11am** was determined to be 97.2% ee. $[\alpha]_D^{21}$ = -24.6 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 7.88 (dd, J = 8.4, 12.0 Hz, 1H), 7.52–7.47 (m, 6H), 7.39–7.32 (m, 6H), 7.32–7.25 (m, 3H), 6.96 (dd, J = 7.6, 11.6 Hz, 1H), 4.70–4.63 (m, 1H), 4.58 (dd, J = 2.8, 10.4 Hz, 1H), 4.17–4.10 (m, 1H), 4.06 (t, J = 10.4 Hz, 1H), 3.62 (dd, J = 3.6, 10.4 Hz, 1H), 3.47 (dd, J = 4.4, 10.4 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 153.7, 145.5 (dd, J = 13, 240 Hz), 143.5 (dd, J = 13, 237 Hz), 143.2, 140.7 (dd, J = 2, 10 Hz), 128.2, 128.0, 127.2, 119.6 (dd, J = 3, 9 Hz), 107.2 (d, J = 23 Hz), 106.0 (d, J = 21 Hz), 86.2, 74.6, 65.8, 63.6, 51.5. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₃F₂NNaO₄: 522.1487; found: 522.1474.

(3R,3aS)-7-Bromo-8-fluoro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11an). Off-white solid (185 mg, 81% yield); mp: 221–223 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 80/20; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 9.87 min (100.00%). The enantiomeric purity of **11an** was determined to be >99% ee. $[\alpha]_D^{21}$ = -9.7 (c = 1, CHCl₃). ¹H NMR (500 MHz, acetone-*d*₆) δ : 7.88 (d, J = 10.0 Hz, 1H), 7.55–7.41 (m, 6H), 7.41–7.32 (m, 6H), 7.32–7.25 (m, 3H), 7.22 (d, J = 6.5 Hz, 1H), 4.74–4.63 (m, 1H), 4.57 (dd, J = 3.0, 10.5 Hz, 1H), 4.22–4.11 (m, 1H), 4.06 (t, J = 10.5 Hz, 1H), 3.63 (dd, J = 4.0, 11.0 Hz, 1H), 3.49 (dd, J = 4.0, 10.5 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.4, 154.2 (d, J = 236 Hz), 144.6, 142.6 (d, J = 2 Hz), 129.5, 128.9, 128.2, 125.2 (d, J = 10 Hz), 121.6, 107.4 (d, J = 30 Hz), 102.6 (d, J = 23 Hz), 88.0, 76.0, 67.1, 64.6, 53.4. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₃BrFNNaO₄: 582.0687; found: 582.0682.

(3R,3aS)-8-Nitro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ao). Yellow solid (405 mg, 80% yield); mp: 235–237 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 60/40; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 20.31 min (100.00%). The

enantiomeric purity of **11ao** was determined to be >99% ee. $[\alpha]_D^{21}$ = +5.3 (c = 1, CHCl₃). ¹H NMR (500 MHz, acetone-*d*₆) δ : 8.88 (d, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.5, 9.0 Hz, 1H), 7.55–7.46 (m, 6H), 7.40–7.32 (m, 6H), 7.32–7.24 (m, 3H), 7.17 (d, J = 9.0 Hz, 1H), 4.78–4.67 (m, 2H), 4.30–4.19 (m, 2H), 3.66 (dd, J = 3.5, 10.5 Hz, 1H), 3.55 (dd, J = 4.5, 10.5 Hz, 1H). ¹³C NMR (100 MHz, acetone-*d*₆) δ : 154.6, 151.0, 144.6, 142.7, 129.5, 128.9, 128.3, 125.2, 120.8, 118.3, 115.6, 88.0, 76.0, 67.7, 64.7, 53.0. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄N₂NaO₆: 531.1527; found: 531.1525.

(3R,3aS)-7-Nitro-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ap). Yellow solid (374 mg, 74% yield); mp: 220–222 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 60/40; flow rate: 1 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 21.46 min (100.00%). The enantiomeric purity of **11ap** was determined to be >99% ee. $[\alpha]_D^{21}$ = +34.0 (c = 1, CHCl₃). ¹H NMR (400 MHz, acetone-*d*₆) δ : 8.23 (d, J = 8.8 Hz, 1H), 7.94 (dd, J = 2.8, 10.2 Hz, 1H), 7.78 (d, J = 2.8 Hz, 1H), 7.53–7.48 (m, 6H), 7.39–7.33 (m, 6H), 7.32–7.26 (m, 3H), 4.78–4.72 (m, 1H), 4.68 (dd, J = 2.8, 10.4 Hz, 1H), 4.31–4.24 (m, 1H), 4.19 (t, J = 10.4 Hz, 1H), 3.67 (dd, J = 3.6, 10.4 Hz, 1H), 3.52 (dd, J = 4.4, 10.8 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 153.3, 144.1, 143.2, 142.9, 129.8, 128.2, 128.0, 127.2, 118.6, 116.9, 112.1, 86.3, 74.9, 65.7, 63.4, 51.8. HR-MS (ESI): m/z [M + Na]⁺ calcd for C₃₀H₂₄N₂NaO₆: 531.1527; found: 531.1524.

(3R,3aS)-7-(3-Oxomorpholino)-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11aq). Off-white solid (1.6 g, 62% yield). Mp: 211–213 °C. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/ethyl acetate, 50/50; flow rate: 0.5 mL min⁻¹; λ = 254 nm; T = 25 °C): t_R = 26.30 min (100.00%). The enantiomeric purity of **11aq** was determined to be >99% ee. $[\alpha]_D^{25}$ = -11.6 (c = 1, CHCl₃). ¹H NMR (400 MHz, DMSO-*d*₆) δ : 7.85 (d, J = 9.2 Hz, 1H), 7.54–7.19 (m, 15H), 7.16–6.91 (m, 2H), 4.66–4.57 (m, 1H), 4.53–4.42 (m, 1H), 4.18 (s, 2H), 4.05–3.90 (m, 4H), 3.70 (t, J = 5.2 Hz, 2H), 3.48 (dd, J = 3.2, 10.8 Hz, 1H), 3.37–3.25 (m, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ : 165.9, 153.8, 144.3, 143.3, 137.8, 128.2, 128.0, 127.2, 121.6, 119.2, 118.4, 114.2, 86.2, 74.4, 67.7, 65.9, 63.6, 63.4, 51.9, 49.0. HR-MS (ESI): m/z [M + H]⁺ calcd for C₃₄H₃₁N₂O₆: 563.2177; found: 563.2201.

Gram-scale synthesis and application

(3R,3aS)-7-Bromo-3-((trityloxy)methyl)-3a,4-dihydro-1H,3H-benzo[b]oxazolo[3,4-d][1,4]oxazin-1-one (11ah). Compound **11ah** was prepared from **8i** (1.4 g, 4.36 mmol) and compound **9a** (2.0 g, 5.89 mmol) following the general procedure. After workup, MeOH was added to the residue. The mixture was stirred for 1 h, and then the slurry was filtered, the filter cake was washed with MeOH to give the product (1.7 g, 74%) as an off-white solid. The product was analyzed by chiral HPLC (IC, 5 μ m, 4.6 mm \times 250 mm; eluent: hexane/isopropanol, 90/10; flow rate: 0.6 mL min⁻¹; λ = 210 nm; T = 25 °C): t_R = 29.71 min (100.00%). The enantiomeric purity of **11ah** was determined to be >99% ee.



(3*R*,3*aS*)-7-Bromo-3-(hydroxymethyl)-3*a*,4-dihydro-1*H*,3*H*-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (12). To a solution of compound 11*ah* (1.6 g, 3 mmol) in MeOH (1.6 mL) and DCM (16 mL) was added TsOH·H₂O (1.14 g, 6 mmol). The reaction mixture was stirred at room temperature for 4 h. Saturated NaHCO₃ (6 mL) was added and stirred vigorously for 10 min. The mixture was extracted with DCM. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated in vacuum. The residue was stirred in a mixture of DCM (10 mL) and PE (10 mL) for 10 min. After filtration, the filter cake was dried to give compound 12 (0.8 g, 89%) as an off-white solid. Mp: 148–150 °C; $[\alpha]_D^{25} = -25.4$ (*c* = 0.22, DMSO). ¹H NMR (400 MHz, CDCl₃) δ: 7.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.15–7.09 (m, 2H), 4.50 (dd, *J* = 3.2, 10.4 Hz, 1H), 4.41–4.33 (m, 1H), 4.22–4.12 (m, 1H), 4.03 (dd, *J* = 4.0, 12.4 Hz, 1H), 3.96–3.82 (m, 2H), 2.18 (brs, 1H). ¹³C NMR (100 MHz, CDCl₃) δ: 153.4, 144.9, 125.0, 122.2, 120.4, 120.2, 117.0, 75.9, 66.6, 62.1, 52.1. HR-MS (ESI): *m/z* [*M* + *H*]⁺ calcd for C₁₁H₁₁BrNO₄: 299.9866; found: 299.9876.

(3*R*,3*aS*)-3-(Hydroxymethyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3*a*,4-dihydro-1*H*,3*H*-benzo[*b*]oxazolo[3,4-*d*][1,4]oxazin-1-one (13). To a mixture of compound 12 (100 mg, 0.33 mmol), bis(pinacolato)diboron (168 mg, 0.66 mmol), KOAc (98 mg, 1 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (14 mg) was added DMSO (3 mL) under argon. The reaction mixture was heated at 85 °C for 2.5 h. The mixture was cooled to room temperature and water was added. The resulting mixture was extracted with ethyl acetate and the organic phase was washed with water and brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluted with EtOAc/PE (1 : 1) to give 13 (91 mg, 80%) as a white solid. Mp: 184–186 °C. ¹H NMR (400 MHz, CDCl₃) δ: 8.02 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.40 (d, *J* = 1.2 Hz, 1H), 4.48 (dd, *J* = 3.2, 10.4 Hz, 1H), 4.39–4.32 (m, 1H), 4.23–4.15 (m, 1H), 4.02 (dd, *J* = 3.6, 12.4 Hz, 1H), 3.95–3.81 (m, 2H), 1.34 (s, 12H). ¹³C NMR (100 MHz, CDCl₃) δ: 153.3, 143.6, 128.4, 125.6, 123.1, 118.3, 83.9, 76.0, 66.4, 62.1, 52.5, 24.9, 24.8. HR-MS (ESI): *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₃BNO₆: 348.1613; found: 348.1630.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 K. J. Shaw and M. R. Barbachyn, *Ann. N. Y. Acad. Sci.*, 2011, **1241**, 48.
- 2 W. B. Im, S. H. Choi, J.-Y. Park, S. H. Choi, J. Finn and S.-H. Yoon, *Eur. J. Med. Chem.*, 2011, **46**, 1027.
- 3 S. Roehrig, A. Straub, J. Pohlmann, T. Lampe, J. Pernerstorfer, K.-H. Schlemmer, P. Reinemer and E. Perzborn, *J. Med. Chem.*, 2005, **48**, 5900.
- 4 (a) Q.-S. Xin, H.-X. Fan, B. Guo, H.-L. He, S. Gao, H. Wang, Y. Q. Huang and Y.-S. Yang, *J. Med. Chem.*, 2011, **54**, 7493; (b) B. Guo, H.-X. Fan, Q.-S. Xin, W.-J. Chu, H. Wang and Y.-S. Yang, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 3697; (c) B. Guo, H.-X. Fan, Q.-S. Xin, W.-J. Chu, H. Wang, Y.-Q. Huang, X.-Y. Chen and Y.-S. Yang, *J. Med. Chem.*, 2013, **56**, 2642.
- 5 (a) T. Xue, S. Ding, B. Guo, Y.-R. Zhou, P. Sun, H.-Y. Wang, W.-J. Chu, G.-Q. Gong, Y.-Y. Wang, X.-Y. Chen and Y.-S. Yang, *J. Med. Chem.*, 2014, **57**, 7770; (b) C. Xu and Y.-J. Ren, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 4522.
- 6 H.-Y. Zhao, Y. Lu, L. Sheng, Z.-S. Yuan, B. Wang, W.-P. Wang, Y. Li, C. Ma, X.-L. Wang, D.-F. Zhang and H.-H. Huang, *ACS Med. Chem. Lett.*, 2017, **8**, 533.
- 7 K. C. Nicolaou, P. S. Baran, Y.-L. Zhong and K. Sugita, *J. Am. Chem. Soc.*, 2002, **124**, 2212.
- 8 Y.-J. Cui, Y.-X. Dang, Y.-S. Yang and R.-Y. Ji, *J. Heterocycl. Chem.*, 2006, **43**, 1071.
- 9 S.-H. Chen, Z.-Z. Ding, G.-L. Gong, X.-B. Yan, W. Huang, F. Guo, B.-L. Duan, R.-L. Gao, P.-F. Zhou, X.-H. Lu and G.-M. Dong, *CN Pat.*, 105503903B, New Drug Research and Development Co., Ltd. of North China Pharmaceutical Corporation, 2019.
- 10 R. Malhotra, T. K. Dey, S. Basu and S. Hajra, *Org. Biomol. Chem.*, 2015, **13**, 3211.
- 11 H.-H. Huang, D.-F. Zhang and H.-Y. Zhao, *WO Pat.*, 2018177302A1, Institute of Materia Medica, Chinese Academy of Medical Sciences, 2018.
- 12 A. Berger and K. D. Wehrstedt, *J. Loss Prev. Process Ind.*, 2010, **23**, 734.
- 13 M. R. Barbachyn and C. W. Ford, *Angew. Chem., Int. Ed.*, 2003, **42**, 2010.
- 14 P. Chen, Y.-Y. Zhang, C.-H. Shi, X. Meng, Y.-S. Yang, X.-L. Zhou and B. Guo, *J. Chem. Res.*, 2019, **43**, 380.

