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Synthesis of Six-Membered Spirocyclic Oxindoles with Five Consecutive Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence

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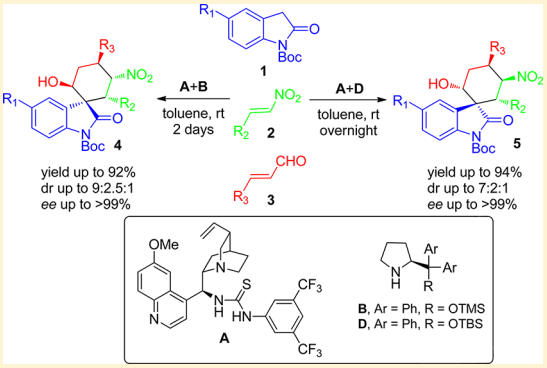
Supporting Information

ABSTRACT: An asymmetric organocatalytic one-pot synthesis of six-membered spirocyclic oxindoles has been successfully developed through a relay Michael/Michael/aldol addition reaction catalyzed by the combination of readily available diphenylprolinol silyl ether and bifunctional quinine thiourea. The one-pot protocol affords the highly substituted spirocyclic oxindoles in high yields and perfect enantioselectivities. More importantly, through judicious choice of the organocatalysts employed, this reaction could be readily adapted to predominantly afford an alternative major diastereomer of the product.



INTRODUCTION

Oxindoles bearing a quaternary stereocenter at the 3-position are versatile and useful building blocks and are commonly present in a number of synthetic and naturally occurring bioactive compounds.[1] In particular, spirocyclic oxindoles are fascinating subunits for bioactive alkaloids and medicinally relevant compounds.[2] Therefore, various synthetic protocols have been developed for the stereoselective synthesis of multistereogenic spirocyclic oxindoles.[3] Although great progress has been made in the synthesis of diversely structured spirocyclic oxindoles, enantioselective methods for construction of spirocyclic oxindoles have been relatively less exploited, and there are even fewer using organocatalysis.[4]

Oxindole incorporating a six-membered spirocyclic moiety is a fascinating subset with potential bioactivity and is featured in a number of natural products, as exemplified by gelsemine (**I**)[2a] as well as pharmacologically important compounds (**II** and **III**) (Figure 1).[5] Stereocontrolled installation of a spiro-quaternary chiral carbon center, together with their medicinal relevance, makes the asymmetric synthesis of this family of molecules an attractive but challenging task. In 2009, Melchiorre and co-workers developed the first example of a one-step synthesis of multistereogenic spiro[cyclohexane-1,3′-indoline]-2′,4-diones via a tandem iminium and enamine catalytic sequence.[6] Subsequently, a bifunctional organocatalytic asymmetric formal [4 + 2] cycloaddition reaction of Nazarov's reagents and methyleneindolinones also gave access to this class of molecules,[7] as did Diels–Alder reactions,[8] an amine-catalyzed formal [2 + 2 + 2] annulation strategy,[9] a primary amine-catalyzed formal [4 + 2] cycloaddition reaction,[10] formal [5 + 1] annulation,[11] and an amine-catalyzed cascade Michael/Michael/aldol reaction.[12] In this context, considering the profile between the potential bioactivities and molecular diversities, the development of new approaches to chiral spirooxindolic cyclohexane derivatives with functional diversity is still highly desirable, particularly with regard to the controlled preparation of different stereoisomers through routine changes to the reaction conditions and/or catalysts.

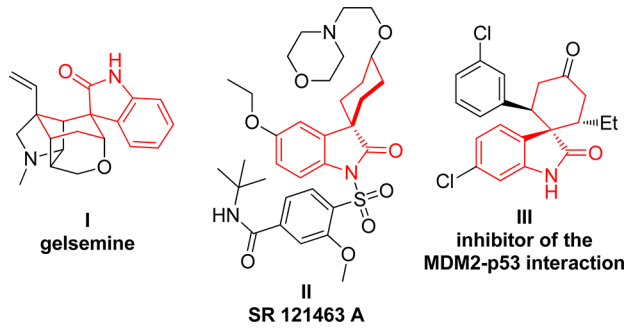


Figure 1. Natural products and biologically active six-membered spirocyclic oxindoles.

In addition to the often used enamine/iminium activation modes via Lewis base catalysis, bifunctional base/Brønsted acid catalysis is another fundamental activation mode in organocatalysis.[13] Recently, the combination of two organocatalysts or of metal and organocatalyst has been elegantly employed in

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one-pot reactions as an efficient route in asymmetric catalysis.[14] Encouraged by these results, we designed a Michael/Michael/aldol process to construct highly substituted carbocyclic spiro-[cyclohexane-1,3′-indoline] core units catalyzed by the combination of two different organocatalysts in one pot (Figure 2).

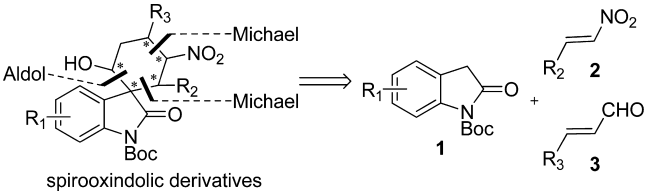


Figure 2. Retrosynthetic analysis for the construction of spiro-[cyclohexane-1,3′-indoline].

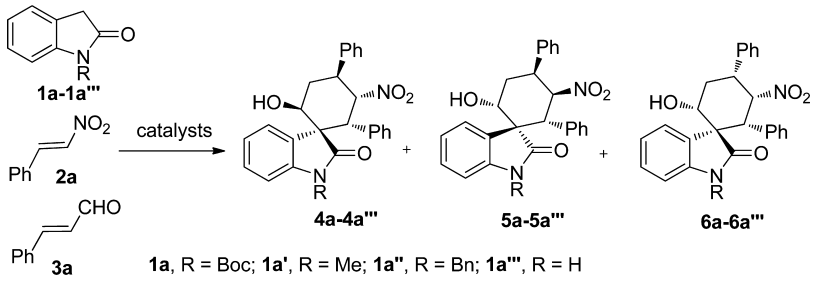
Successfully executed, this strategy would allow three new bonds and five contiguous stereogenic centers, including one quaternary spirocarbon center, to be set in a simple-to-perform, single-operation cascade sequence. Herein, we report this organocatalytic synthesis of spiro[cyclohexane-1,3′-indoline] in excellent yield and perfect enantioselectivity.

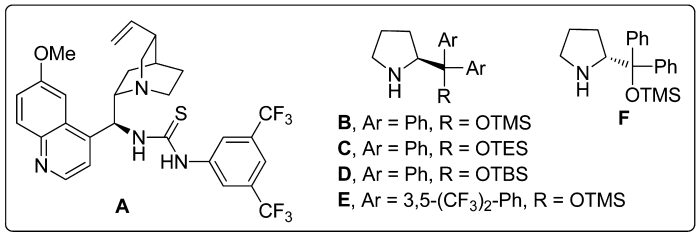
RESULTS AND DISCUSSION

We initiated our investigation by exploring the reactions of a variety of *N*-substituted oxindoles **1a**−**1a‴** and nitrostyrene (**2a**) with *trans*-cinnamaldehyde (**3a**) (Table 1). The choice of indole protecting group was found to be crucial (Table 1, entries 1−4), with the Boc group being optimal (entry 1). *N*-Boc-oxindoles **1a**−**3a** reacted smoothly in the presence of two organocatalysts, **A** (15 mol %) and **B** (15 mol %), in toluene at room temperature to furnish the main product **4a** in 31% yield and 96% ee (entry 1). Following a screen of various catalyst combinations (entries 5−8), we found that this cascade reaction could be readily adapted to predominantly afford another major diastereomer, **5a**, in 40% yield and 99% ee, when **A** and **D** were used as a catalyst pair for the reaction (entry 6). A screen of solvents (entries 6, 9, and 10) and additives (entries 11−14) revealed toluene to be the preferred solvent and that addition of 2.0 equiv of NaOAc could lead to higher yield and diastereoselectivity, without a drop in ee (entries 14 and 15).

After the reaction conditions were optimized, the substrate scope and limitations were explored under the optimized reaction conditions (Table 2). Overall, the reaction proceeded

Table 1. Catalyst Screening and Optimization of Reaction Conditions[a]





entry	R	catalysts	solvent	major product	yield (%)[b]	dr[c]	ee (%)[d]
1	Boc	**A** + **B**	toluene	**4a**	62	4.5:3.5:1	96
2	Me	**A** + **B**	toluene	**4a′**	<5	n.d.	n.d.
3	Bn	**A** + **B**	toluene	**4a″**	<5	n.d.	n.d.
4	H	**A** + **B**	toluene	**4a‴**	<5	n.d.	n.d.
5	Boc	**A** + **C**	toluene	**5a**	50	4:3:1	98
6	Boc	**A** + **D**	toluene	**5a**	70	4:2:1	>99
7	Boc	**A** + **E**	toluene	**5a**	54	3:3:1	97
8	Boc	**A** + **F**	toluene	**5a**	<25	n.d.	82
9	Boc	**A** + **D**	THF	**5a**	<10	n.d.	n.d.
10	Boc	**A** + **D**	CH_2Cl_2	**5a**	32	3:2:1	98
11[e]	Boc	**A** + **D**	toluene	**5a**	34	3:3:1	99
12[f]	Boc	**A** + **D**	toluene	**5a**	<10	n.d.	n.d.
13[g]	Boc	**A** + **D**	toluene	**5a**	<10	n.d.	n.d.
14[h]	Boc	**A** + **D**	toluene	**5a**	85	6.5:2.5:1	>99
15[h]	Boc	**A** + **B**	toluene	**4a**	77	7:3:1	97

[a]Unless otherwise noted, all the reactions were performed with **1a**−**1a‴** (0.2 mmol), **2a** (0.4 mmol), **3a** (0.3 mmol), and a pair of organocatalysts (0.03 mmol of each) in solvent (2.0 mL) at room temperature. n.d. = not detected. [b]Combined yield of the three isolated stereoisomers. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The ee values for the isolated major product were determined by HPLC on a chiral stationary phase. [e]0.015 mmol of AcOH was added. [f]0.015 mmol of Et_3N was added. [g]0.4 mmol of K_2CO_3 was added. [h]0.4 mmol of NaOAc was added.

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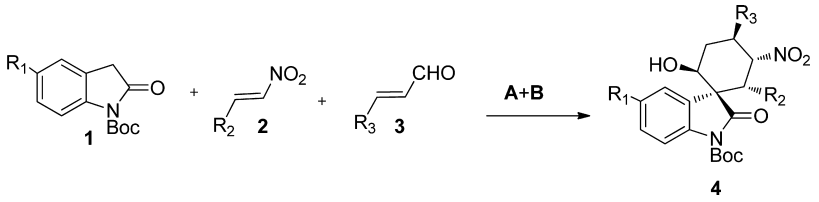
Table 2. Investigating the Scope of the Cascade Reaction[a]



entry	R_1	R_2	R_3	4	yield (%)[b]	dr[c]	ee (%)[d]
1	H	Ph	Ph	**4a**	77	7:3:1	97
2	H	4-Me-Ph	Ph	**4b**	84	4.7:2:1	95
3	H	4-MeO-Ph	Ph	**4c**	80	6:3:1	>99
4	H	3-MeO-Ph	Ph	**4d**	84	5.5:2:1	>99
5	H	2-MeO-Ph	Ph	**4e**	92	7:3:1	97
6	H	4-CN-Ph	Ph	**4f**	45	5:2:1	>99
7	H	4-Cl-Ph	Ph	**4g**	80	8:2:1	98
8	H	3-Cl-Ph	Ph	**4h**	80	5:2.5:1	>99
9	H	2-Cl-Ph	Ph	**4i**	90	5:3:1	95
10	H	2-thienyl	Ph	**4j**	87	4:3:1	96
11	H	Ph	4-MeO-Ph	**4l**	74	4.5:2.5:1	>99
12	H	Ph	4-Cl-Ph	**4n**	65	3.5:2:1	91
13	H	Ph	2-furyl	**4p**	77	4:3:1	92
14	MeO	Ph	Ph	**4r**	87	7:3:1	97
15	Cl	Ph	Ph	**4s**	90	9:2.5:1	90

[a]Unless otherwise noted, all the reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), **A** (0.03 mmol), **B** (0.03 mmol), and NaOAc (0.4 mmol) in toluene (2.0 mL) for 2 days at room temperature. [b]Combined yield of the three isolated stereoisomers. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The ee values for the isolated major product **4** were determined by HPLC on a chiral stationary phase.

smoothly to give desired products in high yields and was found to be broad in scope, with perfect enantioselectivity obtained for all products. First, different nitroalkenes **2** were tested under the optimized reaction conditions. These modifications of the substrates **2** were well tolerated and gave the corresponding products **4a−i** with excellent enantioselectivities irrespective of the electronic nature or position of the substituents on the phenyl ring (entries 1−9). Moreover, heteroaromatic groups could be accommodated in the reaction, giving high yields and excellent enantioselectivity (entry 10). The variation of R_3 in the aromatic α,β-unsaturated aldehydes **3** to electron-donating and electron-withdrawing groups as well as to heterocycles led to moderate yields while still keeping the excellent ee values (entries 11−13). Oxindoles with electron-donating and -withdrawing groups could be used well in this reaction (entries 14 and 15).

More importantly, through judicious choice of the organocatalysts employed, this reaction could be readily adapted to predominantly afford an alternative major diastereomer of the product (Table 3). For example, with **A** and **D** as the catalyst pair, this relay cascade resulted in the formation of **5** as the major diastereomers. The nitroalkenes **2** allowed incorporation of a wide range of functionalizations in the spirocyclic oxindole products; aromatic groups bearing electron-donating or -withdrawing groups at the para, meta. or ortho position were tolerated and excellent enantioselectivities were observed, irrespective of the electronic nature or position of the substituents on the phenyl ring (entries 1−9). In contrast, the diastereoselection was to some degree sensitive to the electronic properties of aryl substituents and benefited from electron-donating groups. Furthermore, heteroaromatic groups, such as thiophene, could be accommodated in the reaction, giving high yields and excellent enantioselectivity (entry 10). Alkyl substrates could also be successfully employed to afford the corresponding product with excellent enantioselectivity (entry 11). The α,β-unsaturated aldehydes were also examined under our standard conditions. For substituted cinnamaldehyde derivatives, perfect enantioselectivities (>99% ee) were obtained regardless of the electronic nature or position of the substituents on the aryl moiety (entries 12−15). Significantly, furyl- and methyl-substituted acroleins were also shown to be compatible in the reaction and provided the corresponding products **5p,q** with perfect enantioselectivity (entries 16 and 17). The current reaction system was also applicable to oxindoles with different substituents on the aromatic ring, including electron-donating and -withdrawing groups, and high chemical yields and excellent enantioselectivities were obtained (entries 18−20). It should be noted that all products can be effectively purified just by column chromatography.

While the relative configuration of the products of the cascade was assigned by NOE analyses of compounds **4a−6a**, **4t**, and **5t**, the absolute configuration of the major diastereomeric product was identified unambiguously through X-ray crystallographic analysis of **5g-1**, derived from the corresponding adduct **5g** (Figure 3).[15]

To study the mechanism of the reaction, we conducted a series of control experiments (Scheme 1). Initially, reactions were carried out using **1a−3a** in the presence of either **A** or **D** as catalyst. However, the product **5a** was not observed when either catalyst was used. The adduct **7** was afforded by the Michael reaction of **1a** and **2a** in the presence of **A** for 2 h in good yield with low diastereoselectivity (1.8:1 dr). With compound **7** in hand, we next examined the second stage of the cascade reaction. In the presence of **D** (15 mol %; Scheme 1, path A), **5a** was formed in excellent enantioselectivity (>99% ee, 12 h), but in only low 24% conversion with respect to Michael adduct **7**. In the presence of **D** (15 mol %) and NaOAc (2 equiv), **5a** was obtained in excellent enantioselectivity (>99% ee, 12 h) and in 35% conversion with respect to **7**

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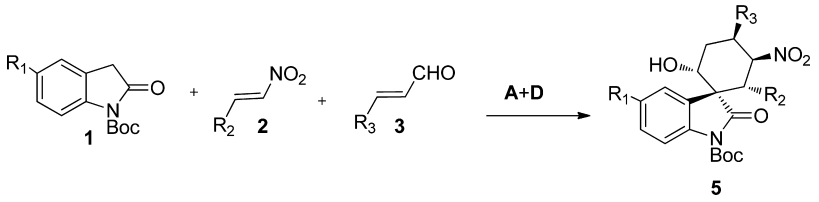
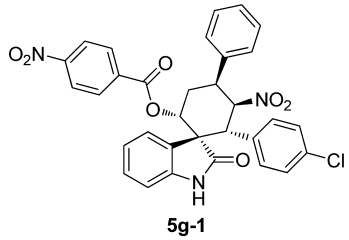
Table 3. Investigating the Scope of the Cascade Reaction[a]



entry	R_1	R_2	R_3	5	yield (%)[b]	dr[c]	ee (%)[d]
1	H	Ph	Ph	**5a**	85	6:2.5:1	>99
2	H	4-Me-Ph	Ph	**5b**	90	5:3:1	>99
3	H	4-MeO-Ph	Ph	**5c**	80	5:3:1	>99
4	H	3-MeO-Ph	Ph	**5d**	78	5.5:3:1	>99
5	H	2-MeO-Ph	Ph	**5e**	92	7:4:1	>99
6	H	4-CN-Ph	Ph	**5f**	53	2:2:1	>99
7	H	4-Cl-Ph	Ph	**5g**	84	4.5:3:1	>99
8	H	3-Cl-Ph	Ph	**5h**	93	4:3:1	>99
9	H	2-Cl-Ph	Ph	**5i**	94	4.5:3.1:1	>99
10	H	2-thienyl	Ph	**5j**	87	3.5:3.5:1	>99
11	H	*i*-Pr	Ph	**5k**	32	2.2:1:0	>99
12	H	Ph	4-MeO-Ph	**5l**	62	6:3:1	>99
13	H	Ph	4-Me-Ph	**5m**	72	6.2:3:1	>99
14	H	Ph	4-Cl-Ph	**5n**	50	6:1.3:1	>99
15	H	Ph	2-Br-Ph	**5o**	45	7:2:1	>99
16	H	Ph	2-furyl	**5p**	85	2.7:1.1:1	>99
17	H	Ph	Me	**5q**	50	2.3:1.5:1	>99
18	MeO	Ph	Ph	**5r**	94	6.7:5:1	>99
19	Cl	Ph	Ph	**5s**	92	3:3:1	>99
20	Cl	4-MeO-Ph	4-Me-Ph	**5t**	53	4:2.8:1	>99

[a]Unless otherwise noted, all the reactions were performed with **1** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), **A** (0.03 mmol), **D** (0.03 mmol) and NaOAc (0.4 mmol) in toluene (2.0 mL) overnight at room temperature. [b]Combined yield of the three isolated stereoisomers. [c]Determined by ^{1}H NMR analysis of the crude reaction mixture. [d]The ee values for the isolated major product **5** were determined by HPLC on a chiral stationary phase.



5g-1

Figure 3. Structure of **5g-1**.

(Scheme 1, path B). The improved conversion suggests that base promotion is beneficial to the iminium-catalyzed Michael addition. In the presence of **A** (15 mol %) and **D** (15 mol %), **5a** was formed in excellent enantioselectivity (>99% ee, 7 h) and at 90% conversion (Scheme 1, path C). This indicates that both organocatalysts are working cooperatively in the iminium-catalyzed nitro-Michael addition. Actually, the final base-promoted intramolecular aldol reaction was so quick that intermediate **8a** could not be detected in pathway A, B, or C.

On the basis of these experiments, a plausible mechanism was proposed, as shown in Scheme 2. Activation of the nitrostyrene was achieved by intermolecular H-bonding of the thiourea moiety on catalyst **A**; simultaneously, the tertiary amine portion of the catalyst, acting as the Brønsted base, assisted in the enolization of the amide and triggered the Michael addition to the nitrostyrene, giving the intermediate **7**, as depicted in Scheme 2. Then the coordination of the thiourea catalyst to the nitro group allows the pendant tertiary amine to deprotonate the α-proton to generate the nitronate. Alternatively, the nitronate can also be formed by the deprotonation of nitroalkanes by NaOAc. Finally, an iminium-catalyzed nitro-Michael addition, followed by a rapid base-promoted aldol reaction, provides the two main products **4a** and **5a**.

■ CONCLUSIONS

In summary, we have developed an efficient and convenient one-pot, three-component tandem reaction for the assembly of highly substituted spirocyclic oxindoles in high yields and with perfect enantioselectivities. Under optimal conditions, this reaction could furnish a series of spirooxindolic carbocyclic derivatives with versatile molecular complexity from very simple starting materials in a one-pot fashion. Three new C−C bonds and five adjacent stereogenic centers, including one quaternary spirocarbon center, are formed by combining bifunctional Brønsted acid/base and amine catalysis. More importantly, through a judicious choice of the organocatalysts employed, this reaction could be readily adapted to predominantly afford an alternative major diastereomer of the product. We believe that the strategy demonstrated here may be utilized in the further synthesis of natural products and potential bioactive compounds. More results will be reported in due course.

■ EXPERIMENTAL SECTION

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer in $CDCl_3$. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, m = multiplet), J = coupling constant in

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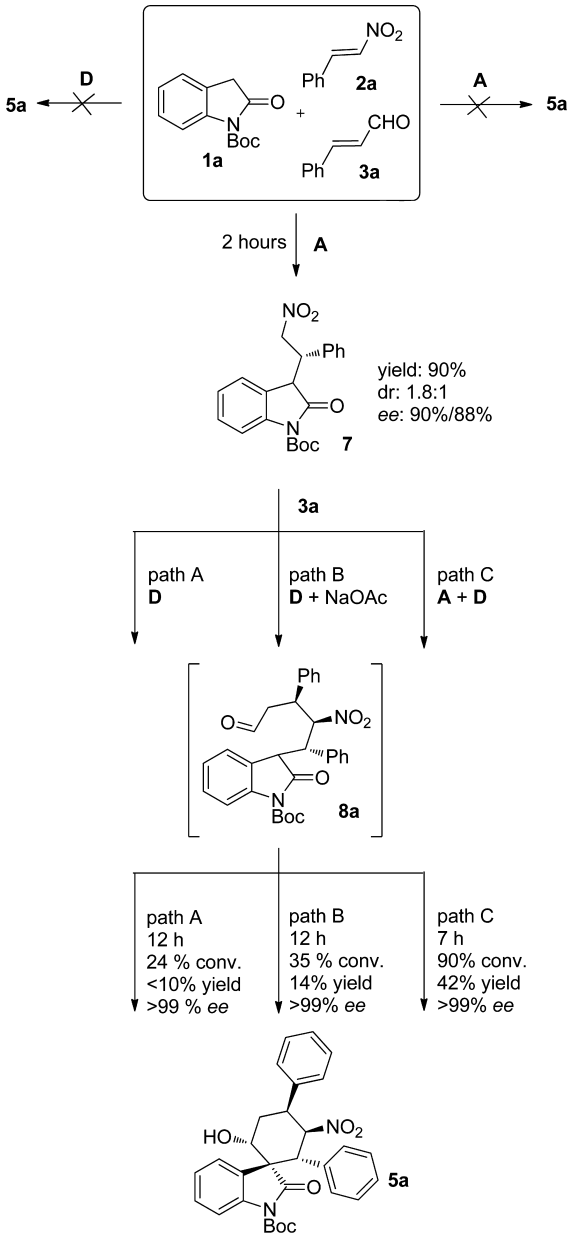
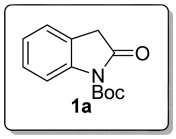
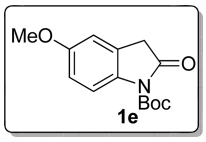
Scheme 1. Probing the Mechanism



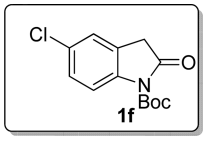
hertz (Hz). Optical rotations were recorded on a polarimeter. IR spectra were recorded with an FT-IR spectrophotometer and are reported as cm^{-1}. HRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. Silica gel 60H (200–300 mesh) was used for general chromatography. Solvent, substrate **2**, and substrate **3** were commercially available and were used without further purification. Organocatalysts were prepared according to literature procedures.[16] Oxindoles **1** were synthesized according to published procedures.[17] Spectroscopic data are reported below.



^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (d, J = 7.8 Hz, 1H), 7.33–7.23 (m, 2H), 7.14 (t, J = 7.2 Hz, 1H), 3.65 (s, 2H), 1.65 (s, 9H). MS (ESI, m/z): 256.1 $[M + Na]^+$.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 9.6 Hz, 1H), 6.83–6.81 (m, 2H), 3.80 (s, 3H), 3.63 (s, 2H), 1.64 (s, 9H). MS (ESI, m/z): 286.3 $[M + Na]^+$.



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.7 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.23 (s, 1H), 3.63 (s, 2H), 1.60 (s, 9H). MS (ESI, m/z): 290.4 $[M + Na]^+$.

General Procedures for Synthesis of Compounds 4 and 5. *General Procedure A.* To a solution of organocatalyst **A** (0.03 mmol, 15 mol %), **B** (0.03 mmol, 15 mol %), NaOAc (32.8 mg, 0.4 mmol, 2.0 equiv), and nitroalkene **2** (0.4 mmol) in toluene (1.0 mL) were added subsequently with stirring **1** (0.2 mmol) and α,β-unsaturated aldehyde **3** (0.3 mmol) at room temperature. After 2 days, the reaction was complete (as judged by TLC analysis). The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (DCM/EA = 80/1) to give the main diastereomeric product **4**.

General Procedure B. To a solution of organocatalyst **A** (0.03 mmol, 15 mol %), **D** (0.03 mmol, 15 mol %), NaOAc (32.8 mg, 0.4 mmol, 2.0 equiv), and nitroalkene **2** (0.4 mmol) in toluene (1.0 mL) were added subsequently with stirring **1** (0.2 mmol) and α,β-unsaturated aldehyde **3** (0.3 mmol) at room temperature. After 6–12 h, the reaction was complete (as judged by TLC analysis). The reaction mixture was concentrated, and the residue was purified by flash chromatography on silica gel (DCM/EA = 80/1) to give the main diastereomeric product **5**.

4a: the product was prepared according to general procedure A as an amorphous solid in 49% yield (51.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 18.866 min, t_{minor} = 14.619 min, 97% ee. $[\alpha]_D^{20}$ = +88.0° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 7.5 Hz, 2H), 7.35–7.08 (m, 7H), 6.62 (t, J = 7.6 Hz, 1H), 6.48 (s, 1H), 6.19 (dd, J = 12.2, 6.6 Hz, 1H), 5.77 (d, J = 7.6 Hz, 1H), 4.66 (d, J = 11.1 Hz, 1H), 4.14 (td, J = 12.9, 5.5 Hz, 1H), 3.82 (d, J = 6.5 Hz, 1H), 2.77 (q, J = 13.3 Hz, 1H), 2.39–2.22 (m, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 148.6, 140.9, 140.3, 133.9, 128.9, 128.8, 128.7, 127.8, 127.4, 126.4, 124.6, 123.8, 114.6, 87.0, 85.1, 70.0, 56.9, 51.9, 40.8, 35.3, 28.0. IR (thin film): 3501, 2931, 1779, 1552, 1370, 1149, 757, 701, 612 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{30}N_2NaO_6$) requires m/z 537.1996, found m/z 537.2001.

5a: the product was prepared according to the general procedure B as an amorphous solid in 53% yield (54.0 mg, 0.106 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 9.481 min, t_{minor} = 11.397 min, >99% ee. $[\alpha]_D^{20}$ = −34.3° (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 9.0 Hz, 2 H), 7.45–7.22 (m, 7 H), 7.05–6.90 (m, 5 H), 6.43 (dd, J = 12.5, 6.5 Hz, 1 H), 4.90 (m, 1 H), 4.25 (t, J = 5.0 Hz, 1 H), 4.05 (d, J = 13.0 Hz, 1 H), 3.21 (td, J = 12.8, 6.5 Hz, 1 H), 2.40 (dd, J = 13.2, 5.0 Hz, 1 H), 1.67(d, J = 4.5 Hz, 1 H), 1.57 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 148.3, 140.4, 138.6, 133.9, 129.1, 129.0, 128.7, 128.1, 128.0, 127.7, 124.6, 121.9, 115.0, 85.5, 84.3, 71.3, 59.5, 47.3, 43.9, 33.4, 28.0. IR (thin film): 3479, 2927, 1779, 1552, 1369, 1149, 699, 679, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{30}N_2NaO_6$) requires m/z 537.1996, found m/z 537.2000.

6a: the product was prepared according to the general procedure B as an amorphous solid in 8.5% yield (8.7 mg, 0.017 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK

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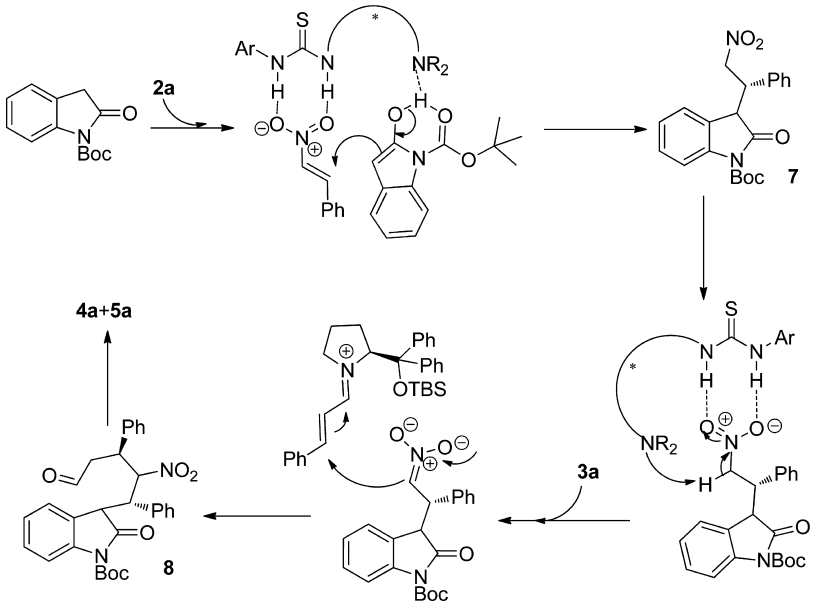
Scheme 2. Plausible Reaction Mechanism



QD-AX column, hexane/2-propanol 97/3, 1.0 mL/min). Retention time: t_{major} = 61.292 min, t_{minor} = 57.525 min, >99% ee. $[\alpha]_D^{20}$ = −47.5° (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 7.1 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.40−7.30 (m, 7H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 2H), 5.15 (t, *J* = 5.4 Hz, 1H), 4.48 (dd, *J* = 12.1, 4.0 Hz, 1H), 3.89 (d, *J* = 5.9 Hz, 1H), 3.61 (dt, *J* = 13.4, 4.0 Hz, 1H), 3.40 (q, *J* = 12.8 Hz, 1H), 2.38 (dt, *J* = 13.1, 3.6 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 147.9, 141.2, 137.3, 132.6, 129.3, 129.0, 128.8, 128.4, 128.1, 127.9, 127.3, 124.2, 124.1, 115.0, 89.9, 84.3, 73.6, 60.0, 53.0, 43.5, 30.2, 27.8. IR (thin film): 3485, 2930, 1783, 1556, 1371, 1150, 755, 700, 574 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{30}N_2NaO_6$) requires *m*/*z* 537.1996, found *m*/*z* 537.1998.

4b: the product was prepared according to the general procedure A as an amorphous solid in 51% yield (51.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 14.860 min, t_{minor} = 13.274 min, 95.0% ee. $[\alpha]_D^{20}$ = +115° (*c* = 1.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.27−7.19 (m, 3H), 6.93 (br s, 1H), 6.76 (t, *J* = 7.6 Hz, 1H), 6.47 (br s, 1H), 6.28 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.97 (d, *J* = 7.6 Hz, 1H), 4.77 (dd, *J* = 11.8, 5.2 Hz, 1H), 4.22 (td, *J* = 12.9, 5.4 Hz, 1H), 3.89 (d, *J* = 6.5 Hz, 1H), 2.86 (q, 13.3 Hz, 1H), 2.40 (dt, *J* = 13.7, 5.4 Hz, 1H), 2.34 (s, 3H), 1.71 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 148.6, 141.0, 140.3, 138.6, 133.5, 130.8, 128.9, 128.7, 127.8, 127.4, 126.6, 124.8, 123.9, 114.5, 87.1, 85.1, 70.1, 56.9, 51.6, 40.7, 35.3, 28.0, 21.0. IR (thin film): 3490, 2980, 1780, 1747, 1552, 1370, 1286, 1252, 1149, 701, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_6$) requires *m*/*z* 551.2152, found *m*/*z* 551.2153.

5b: the product was prepared according to the general procedure B as an amorphous solid in 50% yield (53.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 8.812 min, t_{minor} = 10.445 min, >99% ee. $[\alpha]_D^{20}$ = −23.6° (*c* = 2.4, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54−7.50 (m, 2H), 7.42−7.23 (m, 7H), 6.77 (m, 4H), 6.39 (dd, *J* = 12.4, 6.4 Hz, 1H), 4.88 (m, 1H), 4.23 (t, *J* = 5.8 Hz, 1H), 4.02 (d, *J* = 12.8 Hz, 1H), 3.19 (td, *J* = 13.2, 6.4 Hz, 1H), 2.39 (dd, *J* = 13.4, 4.2 Hz, 1H), 2.11 (s, 3 H), 1.74 (d, *J* = 4.8 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 148.5, 140.6, 138.9, 137.5, 131.0, 129.2, 129.1, 128.8, 128.4, 128.1, 127.9, 124.7, 122.0, 115.2, 85.9, 84.4, 71.5, 59.7, 47.1, 44.1, 33.6, 28.1, 21.0. IR (thin film): 3484, 2980, 1781, 1735, 1552, 1369, 1290, 1248, 1149, 754, 699, 610 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_6$) requires *m*/*z* 551.2152, found *m*/*z* 551.2153.

4c: the product was prepared according to the general procedure A as an amorphous solid in 52% yield (56.0 mg, 0.103 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 23.667 min, t_{minor} = 18.344 min, >99% ee. $[\alpha]_D^{20}$ = +75.0° (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 3H), 7.26−7.19 (m, 2H), 7.01 (br s, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.69 − 6.44 (m, 2H), 6.27 (dd, *J* = 12.2, 6.5 Hz, 1H), 5.97 (d, *J* = 7.5 Hz, 1H), 4.80 − 4.63 (m, 1H), 4.19 (td, *J* = 12.9, 5.5 Hz, 1H), 3.87 (d, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 2.85 (q, *J* = 13.4 Hz, 1H), 2.38 (dt, *J* = 13.4, 5.3 Hz, 1H), 1.70 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 159.7, 148.7, 141.1, 140.3, 135.0, 128.9, 128.7, 127.8, 127.4, 126.7, 125.9, 124.9, 123.9, 114.6, 113.9, 87.1, 85.1, 70.1, 57.2, 55.2, 51.2, 40.7, 35.4, 28.1. IR (thin film): 3495, 2980, 1780, 1746, 1552, 1370, 1287, 1252, 1149, 751, 701, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires *m*/*z* 567.2101, found *m*/*z* 567.2106.

5c: the product was prepared according to the general procedure B as an amorphous solid in 48% yield (52.2 mg, 0.096 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 11.826 min, t_{minor} = 14.709 min, >99% ee. $[\alpha]_D^{20}$ = −33.3° (*c* = 2.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.44−7.22 (m, 7H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 6.36 (dd, *J* = 12.8, 6.4 Hz, 1H), 4.87 (m, 1H), 4.22 (t, *J* = 5.7 Hz, 1H), 4.00 (d, *J* = 12.6 Hz, 1H), 3.61 (s, 3H), 3.18 (td, *J* = 13.2, 6.4 Hz, 1H), 2.38 (dd, *J* = 13.6, 4.0 Hz, 1H), 1.75 (d, *J* = 4.8 Hz, 1H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 158.9, 148.5, 140.6, 138.9, 129.2, 129.1, 128.8, 128.4, 128.1, 126.1, 124.7, 122.0, 115.2, 113.5, 86.0, 84.5, 71.4, 59.8, 55.1, 46.7, 44.1, 33.5, 28.2; IR (thin film): 3482, 2980, 1780, 1732, 1552, 1369, 1289, 1251, 1149, 755, 699, 610 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires *m*/*z* 567.2101, found *m*/*z* 567.2104.

4d: the product was prepared according to the general procedure A as an amorphous solid in 54% yield (59.0 mg, 0.109 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 21.008 min, t_{minor} = 16.366 min, >99% ee. $[\alpha]_D^{20}$ = +74.0° (*c* = 3.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.2 Hz, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 3H),

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7.30 − 7.17 (m, 3H), 6.88 (d, J = 6.7 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 6.29 (dd, J = 12.2, 6.6 Hz, 1H), 6.17 − 5.93 (m, 2H), 4.76 (dd, J = 11.8, 5.2 Hz, 1H), 4.23 (td, J = 12.9, 5.4 Hz, 1H), 3.55 (m, 1 H), 2.85 (q, J = 13.3 Hz, 1H), 2.38 (dt, J = 13.5, 5.3 Hz, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 148.6, 141.0, 140.2, 135.3, 129.0, 128.7, 127.8, 127.4, 126.4, 124.7, 123.9, 114.5, 86.9, 85.1, 70.0, 56.8, 55.2, 51.8, 40.8, 35.3, 28.0. IR (thin film): 3500, 2980, 1780, 1731, 1552, 1369, 1289, 1262, 1149, 750, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2104.

5d: the product was prepared according to the general procedure B as an amorphous solid in 49% yield (54.4 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 11.617 min, t_{minor} = 14.203 min, >99% ee. $[\alpha]_D^{20}$ = −30.3° (c = 2.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.6 Hz, 1H), 7.84 (d, J = 7.0 Hz, 1H), 7.90−7.56 (m, 7H), 7.23 (t, J = 7.6 Hz, 1H), 6.88 (dd, J = 13.6, 7.6 Hz, 2H), 6.74 (dd, J = 12.4, 6.4 Hz, 2H), 5.23 (d, J = 11.4 Hz, 1H), 4.58 (t, J = 5.6 Hz, 1H), 4.35 (d, J = 12.8 Hz, 1H), 3.88 (s, 3H), 3.54 (td, J = 13.2, 6.4 Hz, 1H), 2.74 (dd, J = 13.2, 4.4 Hz, 1H), 2.16 (s, 1H), 1.90 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 158.6, 147.9, 140.1, 138.2, 135.0, 128.7, 128.6, 128.5, 128.3, 127.8, 127.5, 124.1, 121.4, 114.6, 113.5, 85.1, 84.0, 70.9, 59.0, 54.5, 46.8, 43.5, 33.0, 27.5. IR (thin film): 3489, 2980, 1781, 1735, 1552, 1369, 1289, 1262, 1149, 754, 699, 633 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2100.

4e: The product was prepared according to the general procedure A as an amorphous solid in 58% yield (63.6 mg, 0.12 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 18.203 min, t_{minor} = 15.436 min, 97% ee. $[\alpha]_D^{20}$ = +64.0° (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.32−7.24 (m, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 6.4 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 6.22 (dd, J = 12.3, 7.4 Hz, 1H), 5.72 (d, J = 6.8 Hz, 1H), 4.91 (d, J = 6.2 Hz, 1H), 4.59 (d, J = 7.4 Hz, 1H), 4.32 (td, J = 12.5, 5.2 Hz, 1H), 3.18 (s, 3H), 2.90 (q, J = 13.0 Hz, 1H), 2.49−2.26 (m, 1H), 1.72 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 158.5, 148.8, 141.3, 140.5, 129.7, 129.5, 128.7, 127.8, 127.3, 126.8, 123.6, 123.5, 122.8, 120.0, 114.3, 111.8, 86.5, 84.9, 69.7, 56.4, 55.4, 41.7, 40.1, 35.1, 28.1. IR (thin film): 3456, 2929, 1773, 1550, 1370, 1286, 1247, 1149, 753, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2106.

5e: the product was prepared according to the general procedure B as an amorphous solid in 54% yield (58.3 mg, 0.107 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 11.279 min, t_{minor} = 12.865 min, >99% ee. $[\alpha]_D^{20}$ = −58.0° (c = 3.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.17 (m, 10H), 6.98 (t, J = 7.6 Hz, 1H), 6.71 (m, 1H), 6.44 (d, J = 8.0 Hz, 1H), 6.35 (m, 1H), 5.01 (d, J = 12.4 Hz, 1H), 4.84 (m, 1H), 4.24 (t, J = 5.6 Hz, 1H), 3.47 (s, 3H), 3.19 (td, J = 12.8, 6.4 Hz, 1H), 2.37 (d, J = 9.6 Hz, 1H), 1.74 (d, J = 4.4 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 156.8, 148.6, 140.3, 139.2, 129.0, 128.8, 127.9, 127.6, 125.7, 123.6, 123.5, 120.3, 114.4, 110.6, 86.0, 84.4, 71.8, 59.6, 55.3, 44.2, 36.8, 33.7, 28.2. IR (thin film): 3489, 2979, 1780, 1731, 1552, 1369, 1291, 1249, 1149, 754, 699, 613 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2103.

4f: the product was prepared according to the general procedure A as an amorphous solid in 28% yield (30.3 mg, 0.056 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 40.035 min, t_{minor} = 35.450 min, >99% ee. $[\alpha]_D^{20}$ = +101° (c = 1.8, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 7.4 Hz, 3H), 7.36 (t, J = 7.5 Hz, 2H), 7.32−7.20 (m, 2H), 6.79 (t, J = 7.6 Hz, 2H), 6.30 (dd, J = 12.3, 6.6 Hz, 1H), 5.85 (d, J = 7.6 Hz, 1H), 4.70 (dd, J = 11.8, 5.2 Hz, 1H), 4.16 (td, J = 13.0, 5.4 Hz, 1H), 3.99 (d, J = 6.6 Hz, 1H), 2.90 (q, J = 13.3 Hz, 1H), 2.42 (dt, J = 13.5, 5.2 Hz, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 148.4, 140.4, 140.2, 139.5, 132.1, 131.8, 129.4, 128.8, 127.7, 127.6, 125.7, 124.1, 124.0, 117.8, 115.0, 112.9, 86.7, 85.4, 69.8, 56.3, 51.7, 40.9, 35.1, 28.0. IR (thin film): 3485, 2981, 1782, 1747, 1552, 1370, 1286, 1252, 1149, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{29}N_3NaO_6$) requires m/z 562.1948, found m/z 562.1946.

5f: the product was prepared according to the general procedure B as an amorphous solid in 21% yield (23 mg, 0.042 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 17.295 min, t_{minor} = 22.985 min, >99% ee. $[\alpha]_D^{20}$ = −20.0° (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.50 (m, 2H), 7.41−7.29 (m, 9H), 7.06 (d, J = 7.6 Hz, 2H), 6.42 (dd, J = 12.4, 6.4 Hz, 1H), 4.91 (dd, J = 12.2, 5.1 Hz, 1H), 4.28 (t, J = 5.8 Hz, 1H), 4.11 (d, J = 12.4 Hz, 1H), 3.18 (td, J = 13.4, 6.6 Hz, 1H), 2.44 (dd, J = 13.8, 3.8 Hz, 1H), 1.66 (s, 1H), 1.59 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 148.1, 140.4, 140.0, 138.2, 131.9, 129.8, 129.3, 128.7, 128.4, 127.4, 125.1, 122.0, 118.2, 115.4, 112.0, 85.2, 85.1, 71.5, 59.3, 47.3, 44.0, 33.4, 28.1. IR (thin film): 3483, 2980, 1782, 1736, 1552, 1370, 1289, 1248, 1148, 699, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{29}N_3NaO_6$) requires m/z 562.1948, found m/z 562.1945.

4g: the product was prepared according to the general procedure A as an amorphous solid in 58% yield (63.7 mg, 0.12 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 17.645 min, t_{minor} = 16.168 min, 98% ee. $[\alpha]_D^{20}$ = +52° (c = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.2 Hz, 2H), 7.53 (t, J = 14.7 Hz, 2H), 7.35 (t, J = 7.5 Hz, 3H), 7.28−7.10 (m, 3H), 6.81 (t, J = 7.5 Hz, 1H), 6.60−6.40 (br s, 1H), 6.28 (dd, J = 12.3, 6.6 Hz, 1H), 5.96 (d, J = 7.4 Hz, 1H), 4.70 (dd, J = 11.8, 5.2 Hz, 1H), 4.16 (td, J = 13.0, 5.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 2.87 (q, J = 13.4 Hz, 1H), 2.39 (dt, J = 13.6, 5.3 Hz, 1H), 1.67 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 148.5, 140.6, 140.3, 134.9, 132.5, 129.1, 128.7, 127.7, 127.5, 126.2, 124.5, 124.0, 114.7, 86.8, 85.2, 69.9, 56.6, 51.2, 40.7, 35.2, 28.0. IR (thin film): 3505, 2980, 1780, 1745, 1552, 1370, 1288, 1252, 1149, 700 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1613.

5g: the product was prepared according to the general procedure B as an amorphous solid in 45% yield (49.0 mg, 0.09 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 9.417 min, t_{minor} = 11.697 min, >99% ee. $[\alpha]_D^{20}$ = −23.0° (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.48 (m, 2H), 7.41−7.25 (m, 7H), 6.96 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 7.6 Hz, 2H), 6.37 (dd, J = 12.6, 6.4 Hz, 1H), 4.88 (m, 1H), 4.24 (t, J = 5.6 Hz, 1H), 4.03 (d, J = 12.4 Hz, 1H), 3.17 (td, J = 13.2, 6.4 Hz, 1H), 2.40 (dd, J = 13.2, 4.4 Hz, 1H), 1.76 (d, J = 4.8 Hz, 1H), 1.59 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 148.3, 140.5, 138.5, 133.8, 132.9, 129.5, 129.2, 128.8, 128.4, 128.2, 127.9, 124.9, 121.9, 115.3, 85.6, 84.8, 71.4, 59.5, 46.8, 44.0, 33.5, 28.1. IR (thin film): 3493, 2981, 1780, 1738, 1553, 1370, 1289, 1248, 1149, 699, 609 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1609.

4h: the product was prepared according to the general procedure A as an amorphous solid in 47% yield (51.0 mg, 0.094 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 17.861 min, t_{minor} = 14.550 min, >99% ee. $[\alpha]_D^{20}$ = +105.8° (c = 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.2 Hz, 2H), 7.57 (d, J = 7.4 Hz, 2H), 7.35 (t, J = 6.5 Hz, 3H), 7.30−7.02 (m, 3H), 6.80 (t, J = 7.6 Hz, 1H), 6.60 (br s, 1H), 6.29 (dd, J = 12.3, 6.6 Hz, 1H), 5.93 (s, 1H), 4.71 (dd, J = 11.8, 5.2 Hz, 1H), 4.17 (dd, J = 12.3, 7.5 Hz, 1H), 3.90 (d, J = 5.3 Hz, 1H), 2.87 (q, J = 13.3 Hz, 1H), 2.50−2.31 (m, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 148.5, 140.6, 140.3, 136.0, 129.2, 129.0, 128.7, 127.7, 127.5, 126.0, 124.5, 124.0, 114.8, 86.7, 85.3, 69.9, 56.6, 51.5, 40.8, 35.2,

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28.0. IR (thin film): 3504, 2981, 1781, 1747, 1553, 1369, 1285, 1252, 1149, 757, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1613.

5h: the product was prepared according to the general procedure B as an amorphous solid in 46.5% yield (51.0 mg, 0.093 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 10.055 min, t_{minor} = 12.134 min, >99% ee. $[\alpha]_D^{20}$ = −21.5° (c = 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59−7.49 (m, 2H), 7.42−7.25 (m, 7H), 7.02−6.78 (m, 4H), 6.37 (dd, J = 12.8, 6.4 Hz, 1H), 4.89 (dt, J = 12.0, 5.2 Hz, 1H), 4.25 (t, J = 5.6 Hz, 1H), 4.02 (d, J = 12.8 Hz, 1H), 3.20 (td, J = 12.8, 6.8 Hz, 1H), 2.41 (m, 1H), 1.78 (d, J = 4.8 Hz, 1H), 1.60 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 148.5, 140.5, 138.5, 136.4, 134.1, 129.6, 129.3, 129.2, 128.8, 128.2, 127.8, 124.9, 122.0, 115.2, 85.4, 84.8, 71.4, 59.4, 47.1, 44.1, 33.5, 28.1. IR (thin film): 3480, 2981, 1780, 1738, 1553, 1370, 1289, 1249, 1149, 696, 620 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1610.

4i: the product was prepared according to the general procedure A as an amorphous solid in 50% yield (55.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 19.327 min, t_{minor} = 17.580 min, 95% ee. $[\alpha]_D^{20}$ = +76.5° (c = 1.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 7.7 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.45−7.15 (m, 7H), 6.75 (t, J = 7.5 Hz, 1H), 6.26 (dd, J = 12.3, 7.2 Hz, 1H), 5.70 (d, J = 7.5 Hz, 1H), 4.95 (d, J = 7.2 Hz, 1H), 4.62 (dd, J = 11.9, 5.0 Hz, 1H), 4.31 (td, J = 12.9, 5.6 Hz, 1H), 2.92 (q, J = 13.2 Hz, 1H), 2.40 (dt, J = 10.9, 5.2 Hz, 1H), 1.72 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 148.6, 141.0, 140.7, 137.8, 131.8, 130.5, 130.0, 129.7, 129.1, 128.8, 127.8, 127.5, 126.5, 125.8, 123.9, 123.4, 114.7, 86.2, 85.2, 69.5, 56.1, 44.7, 41.5, 34.9, 28.0. IR (thin film): 3479, 2982, 1778, 1552, 1370, 1149, 755, 679 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1610.

5i: the product was prepared according to the general procedure B as an amorphous solid in 50% yield (55.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 10.020 min, t_{minor} = 12.054 min, >99% ee. $[\alpha]_D^{20}$ = −50.0° (c = 1.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, J = 5.6, 3.0 Hz, 1H), 7.52−7.34 (m, 7H), 7.23−7.19 (m, 2H), 7.06−6.95 (m, 3H), 6.34 (dd, J = 12.4, 6.0 Hz, 1H), 5.03 (d, J = 12.8 Hz, 1H), 4.88 (dd, J = 12.0, 5.2 Hz, 1H), 4.25 (t, J = 5.8 Hz, 1H), 3.22 (td, J = 12.8, 6.8 Hz, 1H), 2.39 (dd, J = 13.4, 4.4 Hz, 1H), 1.62 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 148.5, 140.0, 138.8, 135.5, 133.0, 130.0, 129.4, 129.1, 129.1, 128.8, 128.1, 126.8, 126.7, 124.3, 123.7, 114.5, 86.3, 84.7, 71.9, 59.5, 44.3, 41.2, 33.7, 28.2. IR (thin film): 3484, 2980, 1778, 1737, 1553, 1369, 1289, 1248, 1149, 699, 612 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1604.

4j: the product was prepared according to the general procedure A as an amorphous solid in 43% yield (45 mg, 0.087 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 18.814 min, t_{minor} = 15.296 min, 96% ee. $[\alpha]_D^{20}$ = +88.0° (c = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 7.3 Hz, 2H), 7.45 − 7.23 (m, 5H), 6.86 (t, J = 7.5 Hz, 2H), 6.48 (br s, 1H), 6.32 (dd, J = 12.1, 5.7 Hz, 1H), 6.10 (d, J = 7.6 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 4.35−4.10 (m, 2H), 2.83 (dd, J = 25.5, 13.2 Hz, 1H), 2.50 − 2.23 (m, 1H), 1.71 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 148.6, 140.6, 140.2, 134.1, 133.1, 129.3, 128.8, 127.8, 127.5, 126.4, 124.2, 114.7, 86.2, 85.2, 70.5, 56.9, 48.2, 40.6, 35.3, 28.1. IR (thin film): 2979, 1780, 1732, 1555, 1370, 1148, 699, 620 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{28}H_{28}N_2NaO_6S$) requires m/z 543.1560, found m/z 543.1565.

5j: the product was prepared according to the general procedure B as an amorphous solid in 38% yield (40.0 mg, 0.076 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 10.935 min, t_{minor} = 13.620 min, >99% ee. $[\alpha]_D^{20}$ = −46.3° (c = 2.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64−7.62 (m, 1H), 7.52−7.50 (m, 1H), 7.41−7.31 (m, 7H), 6.91 (d, J = 4.8 Hz, 1H), 6.75−6.66 (m, 2H), 6.32 (dd, J = 12.4, 6.4 Hz, 1H), 4.85 (dd, J = 12.2, 5.0 Hz, 1H), 4.36 (d, J = 12.4 Hz, 1H), 4.21 (t, J = 5.7 Hz, 1H), 3.17 (td, J = 13.2, 6.4 Hz, 1H), 2.36 (dd, J = 13.4, 4.0 Hz, 1H), 1.59 (s, 9H). ^1H NMR (400 MHz, $CDCl_3$): δ 174.5, 148.6, 141.0, 138.6, 136.7, 129.6, 129.2, 128.8, 128.5, 128.2, 126.3, 125.5, 125.0, 121.9, 115.3, 86.9, 84.6, 71.4, 60.0, 44.2, 42.9, 33.4, 28.1. IR (thin film): 3493, 2980, 1780, 1732, 1555, 1370, 1289, 1249, 1149, 700, 622 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{28}H_{28}N_2NaO_6S$) requires m/z 543.1560, found m/z 543.1562.

5k: the product was prepared according to the general procedure B as an amorphous solid in 22% yield (21.0 mg, 0.044 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 90/10, 1.0 mL/min). Retention time: t_{major} = 12.567 min, t_{minor} = 13.936 min, >99% ee. $[\alpha]_D^{20}$ = −33.3° (c = 0.6, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 1H), 7.42−7.30 (m, 8 H), 5.68 (dd, J = 9.9, 6.4 Hz, 1H), 4.64 (dd, J = 9.8, 5.9 Hz, 1H), 4.29 (q, J = 6.0 Hz, 1H), 2.97 (dd, J = 10.0, 2.0 Hz, 1H), 2.65 (ddd, J = 14.0, 9.9, 6.6 Hz, 1H), 2.43−2.36 (m, 1H), 1.65 (s, 9 H), 1.44 (m, 1 H), 0.82 (d, J = 7.1 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3): δ 174.8, 148.7, 140.9, 139.2, 129.8, 129.1, 128.7, 128.4, 127.7, 124.9, 121.8, 115.0, 86.8, 84.6, 77.2, 76.9, 76.6, 72.7, 58.6, 46.6, 43.4, 32.1, 28.7, 28.0, 23.5, 17.7. IR (thin film): 3488, 2979, 1783, 1731, 1551, 1371, 1290, 1249, 1149, 755, 699, 619 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{27}H_{32}N_2NaO_6$) requires m/z 503.2152, found m/z 503.2154.

4l: the product was prepared according to the general procedure A as an amorphous solid in 42% yield (45.2 mg, 0.083 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 24.004 min, t_{minor} = 20.948 min, >99% ee. $[\alpha]_D^{20}$ = +57.5° (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (br s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.41−7.15 (m, 4H), 6.88 (d, J = 8.5 Hz, 2H), 6.74 (t, J = 7.6 Hz, 1H), 6.58 (br s, 1H), 6.23 (dd, J = 12.2, 6.5 Hz, 1H), 5.88 (d, J = 7.6 Hz, 1H), 4.83−4.71 (m, 1H), 4.20 (td, J = 13.0, 5.6 Hz, 1H), 3.91 (d, J = 6.5 Hz, 1H), 3.79 (s, 3H), 2.86 (q, J = 13.3 Hz, 1H), 2.45−2.29 (m, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.5, 158.9, 148.7, 140.4, 134.1, 133.0, 128.9, 128.8, 126.5, 124.7, 123.9, 114.7, 114.1, 87.4, 85.2, 70.1, 57.0, 55.2, 52.0, 40.1, 35.4, 28.1. IR (thin film): 3495, 2933, 1779, 1746, 1552, 1370, 1285, 1251, 1149, 835, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2106.

5l: the product was prepared according to the general procedure B as an amorphous solid in 37% yield (40.4 mg, 0.074 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 15.091 min, t_{minor} = 18.562 min, >99% ee. $[\alpha]_D^{20}$ = −33.6° (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 7.6 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H), 7.31−7.22 (m, 3H), 7.02−6.87 (m, 6H), 6.40 (dd, J = 12.8, 6.4 Hz, 1H), 4.93−4.87 (m, 1H), 4.20 (t, J = 5.6 Hz, 1H), 4.00 (d, J = 12.8 Hz, 1H), 3.82 (s, 3H), 3.19 (td, J = 12.8, 6.4 Hz, 1H), 2.39 (dd, J = 13.6, 4.4 Hz, 1H), 1.69 (d, J = 4.4 Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 159.3, 148.5, 140.6, 134.2, 130.7, 129.9, 129.3, 128.3, 128.1, 127.9, 124.8, 122.0, 115.1, 114.4, 85.8, 84.5, 71.5, 59.7, 55.3, 47.3, 43.4, 33.7, 28.2. IR (thin film): 3489, 2979, 1781, 1736, 1552, 1370, 1289, 1251, 1149, 744, 701, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2104.

5m: the product was prepared according to the general procedure B as an amorphous solid in 44% yield (46.6 mg, 0.088 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 90/10, 1.0 mL/min). Retention time: t_{major} = 17.145 min, t_{minor} = 20.309 min, >99% ee. $[\alpha]_D^{20}$ = −38.3° (c = 0.9, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52−7.50

(m, 2H), 7.33−7.19 (m, 6H), 7.05−6.90 (m, 5H), 6.41 (dd, J = 12.4, 6.4 Hz, 1H), 4.90 (dd, J = 12.4, 5.2 Hz, 1H), 4.21 (t, J = 5.8 Hz, 1H), 4.02 (d, J = 12.4 Hz, 1H), 3.19 (td, J = 13.2, 6.6 Hz, 1H), 2.40 (m, 1H), 2.36 (s, 3H), 1.64 (s, 1H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 148.5, 140.6, 137.9, 135.7, 134.2, 129.8, 129.3, 128.7, 128.3, 128.1, 127.9, 124.8, 122.0, 115.1, 85.8, 84.5, 71.5, 59.7, 47.4, 43.8, 33.7, 28.1, 21.1. IR (thin film): 3479, 2981, 1782, 1737, 1553, 1370, 1290, 1248, 1149, 744, 700, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_6$) requires m/z 551.2152, found m/z 551.2153.

4n: the product was prepared according to the general procedure A as an amorphous solid in 35% yield (38.5 mg, 0.07 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 17.310 min, t_{minor} = 14.242 min, 91% ee. $[\alpha]_D^{20}$ = +49.2° (c = 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.1 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 7.44 − 7.15 (m, 6H), 6.74 (t, J = 7.5 Hz, 1H), 6.61 (br s, 1H), 6.23 (dd, J = 12.1, 6.5 Hz, 1H), 5.87 (d, J = 7.6 Hz, 1H), 4.86−4.67 (m, 1H), 4.24 (td, J = 12.8, 4.8 Hz, 1H), 3.92 (d, J = 6.4 Hz, 1H), 2.84 (q, J = 13.2 Hz, 1H), 2.49 − 2.27 (m, 1H), 1.71 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 148.6, 140.4, 139.6, 133.8, 133.3, 129.3, 129.1, 129.0, 128.5, 126.3, 124.7, 124.0, 114.7, 87.0, 85.3, 69.9, 56.9, 51.9, 40.4, 35.1, 28.1. IR (thin film): 2981, 1780, 1738, 1552, 1370, 1250, 1149, 700 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1602.

5n: the product was prepared according to the general procedure B as an amorphous solid in 36% yield (40.0 mg, 0.072 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 10.188 min, t_{minor} = 13.857 min, >99% ee. $[\alpha]_D^{20}$ = −32.7° (c = 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.47 (m, 2H), 7.42−7.22 (m, 6H), 7.16−6.90 (m, 5H), 6.42 (dd, J = 12.6, 6.6 Hz, 1H), 4.84 (dd, J = 12.2, 5.0 Hz, 1H), 4.23 (t, J = 5.6 Hz, 1H), 3.96 (d, J = 12.4 Hz, 1H), 3.21 (td, J = 13.6, 6.6 Hz, 1H), 2.38 (dd, J = 13.8, 3.4 Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 148.4, 140.5, 137.2, 134.2, 133.9, 130.1, 129.4, 129.3, 128.2, 128.0, 124.8, 122.0, 115.2, 85.6, 84.6, 71.3, 59.6, 47.4, 43.4, 33.3, 28.1. IR (thin film): 3491, 2981, 1782, 1738, 1553, 1370, 1289, 1248, 1149, 743, 700, 610 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1604.

5o: the product was prepared according to the general procedure B as an amorphous solid in 32% yield (37.0 mg, 0.063 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 90/10, 1.0 mL/min). Retention time: t_{major} = 28.437 min, t_{minor} = 31.546 min, >99% ee. $[\alpha]_D^{20}$ = +1.3° (c = 0.45, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 7.7 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 6.8 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.31−7.23 (m, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.07−6.96 (m, 5H), 6.34 (dd, J = 12.4, 7.0 Hz, 1H), 5.04 (dd, J = 9.6, 6.4 Hz, 1H), 4.63 (dd, J = 10.8, 4.8 Hz, 1H), 4.34 (d, J = 12.5 Hz, 1H), 3.20−3.05 (m, 1H), 2.38 (dt, J = 14.0, 4.0 Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 148.2, 140.3, 137.9, 134.2, 133.7, 129.1, 129.0, 128.1, 128.0, 128.0, 127.9, 127.4, 126.0, 124.6, 121.7, 115.0, 84.9, 84.3, 70.8, 59.2, 48.8, 41.1, 32.4, 27.9. IR (thin film): 3477, 2980, 1781, 1738, 1553, 1369, 1290, 1250, 1149, 752, 700, 611 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}BrN_2NaO_6$) requires m/z 615.1101, found m/z 615.1100.

4p: the product was prepared according to the general procedure A as an amorphous solid in 39% yield (39.0 mg, 0.077 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 18.528 min, t_{minor} = 16.925 min, 92% ee. $[\alpha]_D^{20}$ = +60.0° (c = 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J = 8.1 Hz, 1H), 7.50 − 7.04 (m, 7H), 6.72 (t, J = 7.5 Hz, 1H), 6.40 − 6.11 (m, 3H), 5.88 (d, J = 7.5 Hz, 1H), 4.74 (dd, J = 11.9, 4.9 Hz, 1H), 4.54 − 4.31 (m, 1H), 3.89 (d, J = 6.4 Hz, 1H), 2.91 (q, J = 13.2 Hz, 1H), 2.60 − 2.38 (m, 1H), 1.69 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 153.7, 148.8, 141.7, 140.4, 133.9, 129.0, 128.9, 128.7, 126.3, 124.7, 123.9, 114.6, 110.4, 106.0, 85.1, 85.0, 69.9, 56.8, 51.7, 34.7, 32.6, 28.1. IR (thin film): 2982, 1781, 1552, 1250, 1150, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{28}H_{28}N_2NaO_7$) requires m/z 527.1788, found m/z 527.1783.

5p: the product was prepared according to the general procedure B as an amorphous solid in 48% yield (48.0 mg, 0.096 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 8.780 min, t_{minor} = 10.075 min, >99% ee. $[\alpha]_D^{20}$ = −43.8° (c = 1.9, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56−7.49 (m, 3H), 7.30−7.21 (m, 2H), 7.04−6.78 (m, 5H), 6.37 (m, 1H), 6.27 (dd, J = 12.6, 5.4 Hz, 1H), 6.22 (d, J = 2.8 Hz, 1H), 5.02 (dd, J = 12.0, 4.8 Hz, 1H), 4.21 (t, J = 4.4 Hz, 1H), 4.13 (d, J = 12.4 Hz, 1H), 3.14 (td, J = 12.8, 5.8 Hz, 1H), 2.32 (m, 1H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.0, 152.2, 148.5, 143.2, 140.6, 134.1, 129.2, 128.4, 128.1, 127.9, 124.8, 122.3, 115.0, 110.7, 109.7, 85.4, 84.4, 71.4, 59.6, 47.7, 38.4, 32.1, 28.1. IR (thin film): 3505, 2981, 1782, 1736, 1554, 1370, 1289, 1249, 1149, 743, 700, 610 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{28}H_{28}N_2NaO_7$) requires m/z 527.1788, found m/z 527.1785.

5q: the product was prepared according to the general procedure B as an amorphous solid in 23% yield (21.0 mg, 0.046 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 8.648 min, t_{minor} = 10.297 min, >99% ee. $[\alpha]_D^{20}$ = +15.0° (c = 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 6.6 Hz, 1H), 7.28−7.21 (m, 2H), 7.05−6.85 (m, 5H), 6.15 (dd, J = 12.4, 5.0 Hz, 1H), 4.47 (dd, J = 12.0, 4.6 Hz, 1H), 3.84 (d, J = 12.4 Hz, 1H), 3.10−2.96 (m, 2H), 2.02 (d, J = 13.5 Hz, 1H), 1.55 (s, 9H), 1.27 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 148.2, 140.3, 133.6, 129.0, 127.9, 127.8, 127.7, 124.5, 121.7, 114.9, 85.6, 84.2, 70.2, 59.7, 46.0, 33.7, 32.4, 27.9, 13.8. IR (thin film): 3500, 2976, 1780, 1738, 1548, 1370, 1289, 1250, 1149, 741, 700, 610 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{25}H_{28}N_2NaO_6$) requires m/z 475.1839, found m/z 475.1835.

4r: the product was prepared according to the general procedure A as an amorphous solid in 55% yield (60.0 mg, 0.11 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 21.810 min, t_{minor} = 19.634 min, 97% ee. $[\alpha]_D^{20}$ = +93° (c = 2.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (br s, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 7.3 Hz, 2H), 7.51−7.10 (m, 6H), 6.74 (dd, J = 9.0, 2.5 Hz, 1H), 6.63 (br s, 1H), 6.31 (dd, J = 12.2, 6.6 Hz, 1H), 5.45 (d, J = 2.5 Hz, 1H), 4.74 (dd, J = 11.8, 5.2 Hz, 1H), 4.25 (td, J = 12.9, 5.4 Hz, 1H), 3.94 (d, J = 6.6 Hz, 1H), 3.31 (s, 3H), 2.87 (q, J = 13.3 Hz, 1H), 2.40 (dt, J = 13.4, 5.3 Hz, 1H), 1.70 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 156.0, 148.7, 141.0, 134.1, 133.6, 128.8, 128.7, 127.8, 127.7, 127.5, 115.6, 115.3, 109.8, 87.0, 85.0, 70.1, 57.0, 55.2, 51.9, 40.9, 35.4, 28.1. IR (thin film): 3500, 2981, 1778, 1731, 1552, 1494, 1370, 1277, 1250, 1150, 737, 701 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2105.

5r: the product was prepared according to the general procedure B as an amorphous solid in 50% yield (54.0 mg, 0.1 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 11.807 min, t_{minor} = 13.309 min, >99% ee. $[\alpha]_D^{20}$ = +16.0° (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45−7.34 (m, 6H), 7.06−6.94 (m, 6H), 6.74 (dd, J = 9.0, 2.6 Hz, 1H), 6.41 (dd, J = 12.8, 6.4 Hz, 1H), 4.85 (dd, J = 12.4, 5.2 Hz, 1H), 4.23 (t, J = 5.8 Hz, 1H), 4.00 (d, J = 12.4 Hz, 1H), 3.87 (s, 3H), 3.19 (td, J = 13.0, 6.4 Hz, 1H), 2.39 (dd, J = 14.0, 3.6 Hz, 1H), 1.56 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 157.1, 148.5, 138.8, 134.1, 133.9, 129.7, 129.1, 128.8, 128.1, 127.9, 116.0, 112.8, 109.3, 85.7, 84.3, 71.5, 59.8, 55.9, 47.4, 44.1, 33.6, 28.1. IR (thin film): 3483, 2977, 1779, 1735, 1552, 1490, 1369, 1280, 1249, 1151, 735, 699 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{31}H_{32}N_2NaO_7$) requires m/z 567.2101, found m/z 567.2103.

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4s: the product was prepared according to the general procedure A as an amorphous solid in 65% yield (71.0 mg, 0.13 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 22.145 min, t_{minor} = 15.527 min, 90% ee. $[\alpha]_D^{20}$ = +87.0° (c = 2.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.72 (d, J = 8.7 Hz, 1H), 7.56 (d, J = 7.3 Hz, 2H), 7.50−7.22 (m, 6H), 7.18 (dd, J = 8.7, 2.0 Hz, 1H), 6.60 (br s, 1H), 6.25 (dd, J = 12.2, 6.6 Hz, 1H), 5.72 (d, J = 1.9 Hz, 1H), 4.68 (dd, J = 11.7, 5.1 Hz, 1H), 4.25 (td, J = 12.9, 5.4 Hz, 1H), 3.91 (d, J = 6.5 Hz, 1H), 2.83 (q, J = 13.3 Hz, 1H), 2.36 (dt, J = 13.4, 5.2 Hz, 1H), 1.70 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 148.4, 140.8, 138.7, 133.6, 129.3, 129.1, 128.7, 128.5, 127.7, 127.5, 125.1, 115.7, 86.8, 85.5, 69.9, 57.0, 51.7, 40.8, 35.4, 28.0. IR (thin film): 3498, 1782, 1751, 1552, 1475, 1370, 1295, 1253, 1149, 739, 700 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1601.

5s: the product was prepared according to the general procedure B as an amorphous solid in 40% yield (43.3 mg, 0.08 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 9.800 min, t_{minor} = 10.996 min, >99% ee. $[\alpha]_D^{20}$ = +21.9° (c = 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.36 (m, 7H), 7.20 (dd, J = 8.6, 1.8 Hz, 1H), 7.07−6.92 (m, 5H), 6.38 (dd, J = 12.4, 6.4 Hz, 1H), 4.86 (dd, J = 12.0, 5.2 Hz, 1H), 4.24 (t, J = 5.6 Hz, 1H), 3.99 (d, J = 12.8 Hz, 1H), 3.19 (td, J = 13.2, 6.4 Hz, 1H), 2.41 (dd, J = 13.2, 4.4 Hz, 1H), 1.57 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.0, 148.3, 139.0, 138.5, 133.8, 130.4, 130.2, 129.2, 128.8, 128.3, 128.2, 128.1, 122.3, 116.4, 85.5, 84.9, 71.3, 59.8, 47.4, 44.0, 33.7, 28.1. IR (thin film): 3498, 2981, 1783, 1736, 1553, 1475, 1370, 1294, 1249, 1150, 736, 699 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{30}H_{29}ClN_2NaO_6$) requires m/z 571.1606, found m/z 571.1604.

5t: the product was prepared according to the general procedure B as an amorphous solid in 27% yield (32.0 mg, 0.054 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 10.324 min, t_{minor} = 11.949 min, >99% ee. $[\alpha]_D^{20}$ = +20.0° (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 1.6 Hz, 1H), 7.30−7.21 (m, 5H), 6.84 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.4 Hz, 2H), 6.31 (dd, J = 12.8, 6.4 Hz, 1H), 4.85 (dd, J = 12.0, 5.2 Hz, 1H), 4.18 (t, J = 5.8 Hz, 1H), 3.92 (d, J = 12.4 Hz, 1H), 3.63 (s, 3H), 3.15 (td, J = 13.8, 6.4 Hz, 1H), 2.40−2.31 (m, 4H), 1.58 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 159.1, 148.3, 139.1, 138.0, 135.5, 130.6, 130.2, 129.9, 129.2, 128.6, 125.8, 122.3, 116.5, 113.7, 85.8, 84.8, 71.4, 59.9, 55.1, 46.6, 43.7, 33.8, 28.1, 21.1. IR (thin film): 3491, 2980, 1783, 1738, 1554, 1514, 1476, 1371, 1296, 1253, 1150, 759, 617 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{32}H_{33}ClN_2NaO_7$) requires m/z 615.1868, found m/z 615.1864.

4t: the product was prepared according to the general procedure B as an amorphous solid in 19% yield (22.0 mg, 0.038 mmol). The enantiomeric excess was determined by HPLC analysis (CHIRALPAK QD-AX column, hexane/2-propanol 80/20, 1.0 mL/min). Retention time: t_{major} = 26.907 min, t_{minor} = 17.085 min, 95% ee. $[\alpha]_D^{20}$ = +51.6° (c = 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.7 Hz, 2H), 7.45 (d, J = 7.9 Hz, 2H), 7.23−6.90 (m, 4H), 6.69 (br s, 1H), 6.54 (br s, 1H), 6.19 (dd, J = 12.2, 6.6 Hz, 1H), 5.80 (d, J = 1.8 Hz, 1H), 4.68 (dd, J = 11.8, 5.2 Hz, 1H), 4.18 (td, J = 12.8, 5.3 Hz, 1H), 3.85 (d, J = 6.5 Hz, 1H), 3.82 (s, 3H), 2.84 (q, J = 13.3 Hz, 1H), 2.45−2.25 (m, 4H), 1.70 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 160.0, 148.4, 138.7, 137.8, 137.1, 129.4, 128.7, 128.6, 127.6, 125.4, 125.3, 115.6, 87.0, 85.4, 70.0, 57.3, 55.3, 51.0, 40.3, 35.5, 28.0, 20.9. IR (thin film): 3505, 2928, 1783, 1753, 1552, 1514, 1478, 1370, 1298, 1253, 1150, 703 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{32}H_{33}ClN_2NaO_7$) requires m/z 615.1868, found m/z 615.1870.

Synthesis of 5g-1. To a solution of **5g** (54.8 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) was added 4-nitrobenzoyl chloride (22.0 mg, 0.11 mmol), Et_3N (30.0 mg, 0.3 mmol), and DMAP (1.2 mg, 0.01 mmol). After the reaction mixture had been stirred for 2 h at 0 °C, aqueous NaCl was added and the organic materials were extracted twice with CH_2Cl_2. The combined organic extracts were washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to give a crude product which was dissolved in CH_2Cl_2 (2 mL) and TFA (0.2 mL). The reaction mixture had been stirred for 3 h at room temperature, aqueous NaCl was added, and the organic materials were extracted twice with CH_2Cl_2. The combined organic extracts were washed three times with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by neutral silica gel column chromatography (hexane/AcOEt 1/1) gave the product **5g-1** (50.0 mg, 85%) as a white solid. Mp: 283−285 °C. $[\alpha]_D^{20}$ = −18.0° (c = 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.54−7.39 (m, 7H), 7.11−6.99 (m, 5H), 6.60−6.51 (m, 2H), 6.38 (dd, J = 12.4, 5.0 Hz, 1H), 4.33 (t, J = 5.3 Hz, 1H), 4.11 (d, J = 12.5 Hz, 1H), 3.32 (m, 1H), 2.64 (ddd, J = 13.6, 5.0, 2.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.3, 163.2, 150.6, 140.0, 137.5, 134.2, 133.8, 132.5, 130.4, 129.3, 129.2, 128.5, 128.4, 128.3, 128.2, 123.5, 123.1, 122.9, 109.6, 85.2, 73.6, 56.9, 46.0, 43.4, 29.8. IR (thin film): 3405, 1720, 1554, 1529, 1268, 1101, 864, 752, 717, 607 cm^{-1}. HRMS (ESI+): exact mass calculated for $[M + Na]^+$ ($C_{32}H_{24}ClN_3NaO_7$) requires m/z 620.1194, found m/z 620.1197.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures and a CIF file giving X-ray crystallographic data for compound **5g-1** (CCDC 899914) and ^{1}H and ^{13}C NMR, HPLC data, and NOE spectra of **4a**−**6a**, **4t**, and **5t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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