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Highly Diastereo and Enantioselective Synthesis of α-spiro-δ-lactams *via* Organocascade Reaction

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Abstract: An asymmetric synthesis of α-spiro-δ-lactam via organocascade reaction from easily accessible starting materials is reported. The catalytic sequence undergoes enantioselective Michael addition of β-ketoamide to α,β-unsaturated aldehyde catalysed by a secondary amine catalyst, followed by hemiaminal annulation. Optically enantiopure compounds with three stereogenic centres are obtained in good yields and excellent selectivities (up to >20:1 dr and up to >99% *ee*).

Keywords: Spiro lactams · Organocatalysis · Asymmetric synthesis · Michael addition · Enantioselective

Introduction

Cascade reactions are a useful methodology for the synthesis of chemical compounds.[1] Starting from easily accessible substrates, without modifying the reaction conditions, two or more new bonds are sequentially formed in only one-step. This avoids the process of purification after each step and protection-deprotection of functional groups. It increases the efficiency of the procedures, addressing the problems of the handling of waste and the quest for environmentally tolerable procedures. Since the renaissance of organocatalysis, asymmetric organocascade reactions allowed for a direct access to complex frameworks.[2]

The unique skeleton of bicyclic α-spiro-δ-lactam is common among natural products, showing considerable potential in drug discovery[3] and new ligands[4] (Figure 1). In previous researches, the preparation of bicyclic spiro-lactam compounds was disclosed *via* rearrangement,[5] gold catalyzed reactions,[6] Mn(III)-radical cyclization[7] and organocatalytic conjugate addition,[8] while an asymmetric version, catalyzed by non-covalent H-bonding activation was reported by Rodriguez.[8b] Therefore, the high stereocontrol o spirocyclic lactam compounds bearing several stereogenic centres *vi* new approaches remains a challenging and important objective.

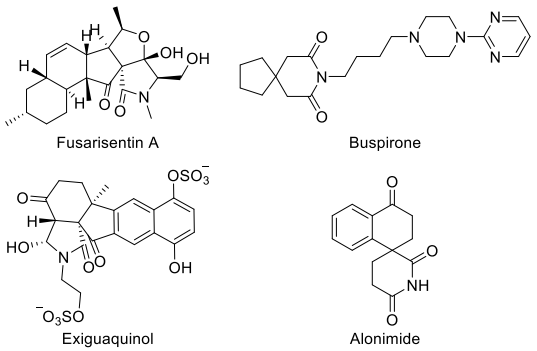

Figure 1. Natural and pharmaceutical products containing the spiro lactam scaffold

The diarylprolinol silyl ether chiral secondary amine catalyst play a crucial role in one-pot asymmetric organocascade reactions. They were employed in previously reported doubl Michael/hemiaminalization organocascade reactions for th construction of diverse optically active molecules from simple achira materials. These C-C, C-N consecutive bond-forming reactions hav attracted considerable attention in the past decade.[10]

For these reasons, we planned an asymmetric synthesis of α-spiro-δ-lactam compounds *via* an organocatalyzed one-pot Michael/hemiaminalization cascade reaction, based on our knowledge in the synthesis of hetereocycles[11] and aza-spirocyclic compounds.[12] Therefore, we envisioned the enantioselective spirocyclization between a β-ketoamide with two nucleophilic sites and an α,β-unsaturated aldehyde with two electrophilic sites. c.[13]

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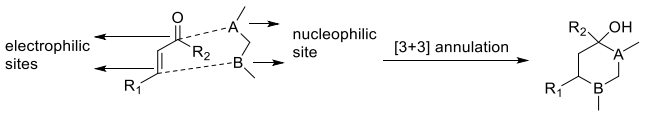
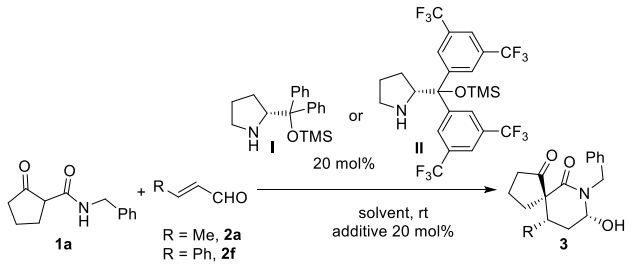


Scheme 1. General scheme of the reaction developed

Results and Discussion

We first tested the conjugate addition of *N*-benzyl-2-oxocyclopentane-1-carboxamide **1a** to crotonaldehyde **2a**, catalyzed by the secondary amine Jørgensen-Hayashi catalyst **I**.

Table 1. Screening of the reaction conditions between *N*-benzyl-2-oxocyclopentane-1-carboxamide and enal **2a** or **2f**[a]



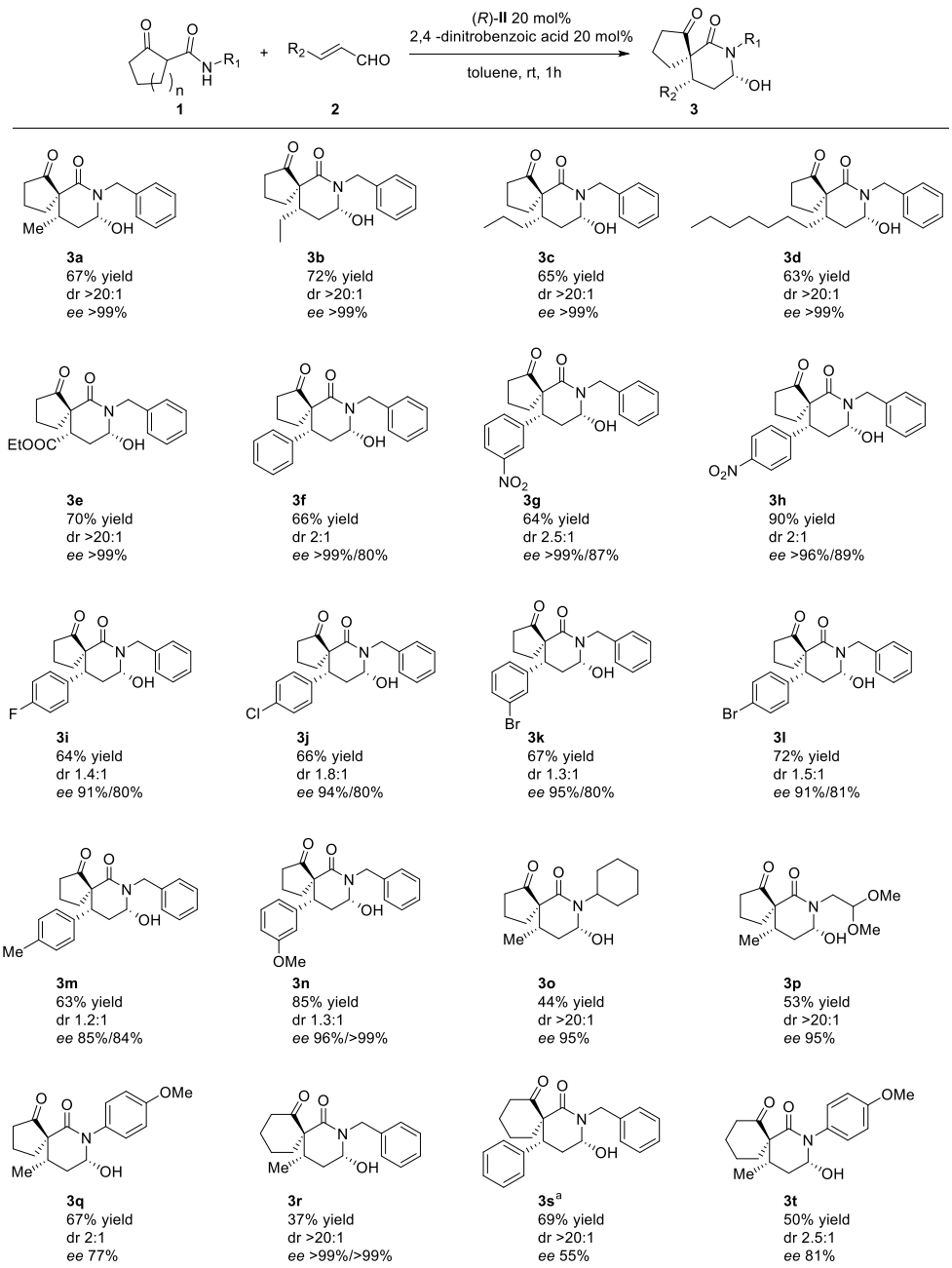
Entry	Cat.	R	Additive	Time (h)	Conversion[b] (yield %[c])	dr[b]	*ee* %[d]
1	I	Me	-	24	67 (47)	>20:1	n.d.
2	I	Me	NaOAc	14	99 (69)	>20:1	82
3	I	Me	BA	14	99 (79)	>20:1	92
4[e]	I	Me	BA	14	99	>20:1	77
5[f]	I	Me	BA	14	99 (80)	>20:1	81
6	I	Me	3,5-CF_3-BA	14	86 (52)	>20:1	97
7	I	Me	4-CN-BA	14	99 (66)	>20:1	94
8	I	Me	2,4-NO_2-BA	14	99 (66)	>20:1	95
9	I	Ph	BA	14	(70)	>20:1	6
10	I	Ph	BA	1	(59)	>20:1	82
11	II	Ph	BA	1	(60)	>20:1	82
12	II	Ph	2,4-NO_2-BA	1	(66)	2:1	99
13	I	Ph	2,4-NO_2-BA	1	(65)	2:1	87

[a] The reactions were performed, unless otherwise noted, between **1a** (0.2 mmol, 1 equiv), **2a** or **2f** (1.5 equiv), catalyst **I** or **II** (20 mol%), additive (20 mol%) and 1 ml of toluene at room temperature. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Isolated yield after flash column chromatography. [d] The *ee* was determined by chiral HPLC. [e] CF_3CH_2OH was used as solvent. [f] CH_2Cl_2 was used as solvent.

The absence of additive (Table 1, entry 1) led to the corresponding product **3a**, in low yield but high dr. The addition of benzoic acid (BA) or NaOAc as additives gave full conversion and excellent dr, while higher *ee* and yields were obtained with BA (Table 1, entries 2 and 3). Then we tested different solvents and toluene gave the highest enantioselectivity (Table 1, entry 3) compared with other protic or aprotic solvents (Table 1, entries 4 and 5), therefore, toluene was chosen as the best solvent. The screening of different benzoic acids showed that in the presence of stronger benzoic acids derivatives (Table 1, entries 6-8), the enantioselectivity is slightl improved, but lower yields were obtained. To our surprise, when th optimal reaction conditions were tested with cinnamaldehyde **2f**, low enantioselectivity was obtained (Table 1, entry 9). We discovere that the enantioselectivity is time dependent (as previously reporte in the synthesis of DABCO derivatives by Rodriguez an coworkers)[14], probably due to the existence of a racemic non catalyti pathway in conjunction with a retro Michael reaction. When th reaction was stopped after 1 h, the *ee* significantly increased to 82% maintaining high dr and the same results were obtained with catalys **II** (Table 1, entries 10 and 11). Finally, combining th trifluoromethyl-substituted diarylprolinolsilyl ether secondary amin catalyst **II** with 2,4-dinitrobenzoic acid (Table 1, entries 11-13) rendered the final product in an almost enantiopure form (>99% *ee* while the dr were lowered to 2:1.

With the optimal conditions in hand, we investigated the reactio scope (Scheme 2), testing the reaction of *N*-benzyl-2-oxocyclopentane-1-carboxamide **1a** with different α,β-unsaturate aldehydes. All the alkyl substituted enals (**2a-d**) performed wel rendering the final hemiaminal products **3a-d** in good yields an excellent stereoselectivities (>99% *ee*, >20:1 dr). Also when an este substituent was present, similar results were observed in the produc **3e**. Next, various aromatic enals were tested. A range of differen electron withdrawing (**3g,h**), electron donating (**3m,n**) and halogen (**3i-l**) substituents were well tolerated, in both *ortho*, *meta* and *par* positions, rendering the final products **3f-n** in good yields, exceller enantioselectivities but low diastereoselectivities compared to th aliphatic aldehydes. Then we turned our attention to the scope of th β-ketoamide substrate. To our delight, when we employed alky substituted β-ketoamide (**1b,c**), the final products **3o,p** were obtaine in excellent stereoselectivities although in slightly lower yields. Th introduction of an electron donating methoxy group on the pheny substituted amide (**1d**) afforded the product **3q** in higher yield bu lower dr and *ee*. Moreover, the reaction also worked with *N*-benzyl 2-oxocyclohexane-1-carboxamide **1e**, rendering the final products **3** and **3s** in lower yields, excellent dr and *ee* when crotonaldehyde wa used (**3r**) while lower *ee* when cinnamaldehyde was used (**3s**). Thi can be attributed to the longer reaction time needed for **3s**, due to the steric hindrance of the aromatic ring. When a methoxy substituent was present on the phenyl ring of the β-ketoamide **1f**, the product **3t** was obtained in lower dr and good *ee*.

The absolute configuration of **3a** catalyzed by (*S*)-**II** catalyst was determined by X-ray analysis and the other products were assigned by analogy (Figure 2).



Scheme 2. Scope of the reaction between β-ketoamides **1a,f** (1 equiv) and α,β-unsaturated aldehydes **2a,n** (1.5 equiv). The reactions were performed on 0.2 mmol scale. [a] The reaction was performed for 14 h.

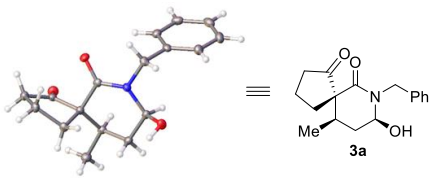
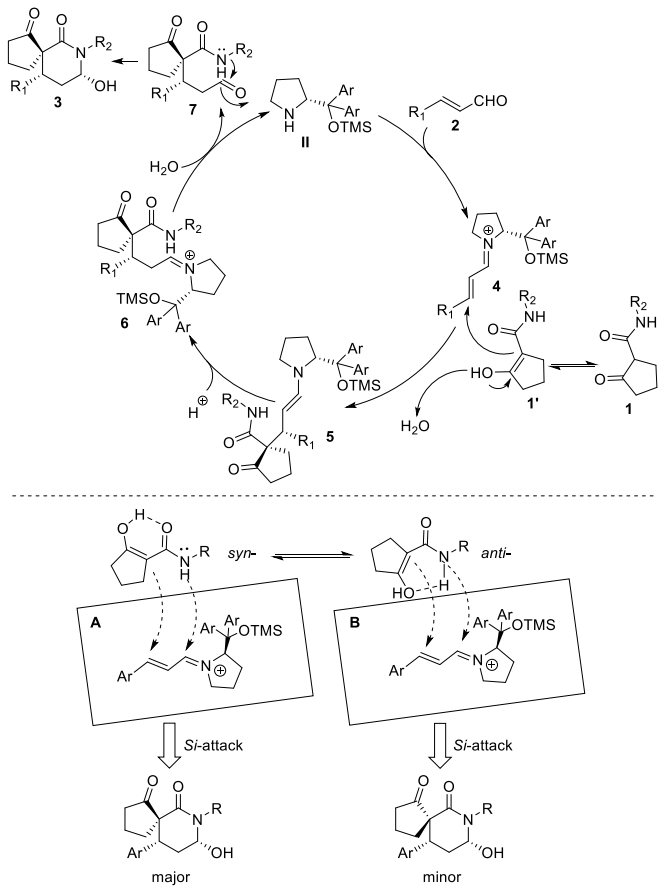


Figure 2. X-ray crystal structure of **3a** obtained with the (*S*)-**II** catalyst.[15]

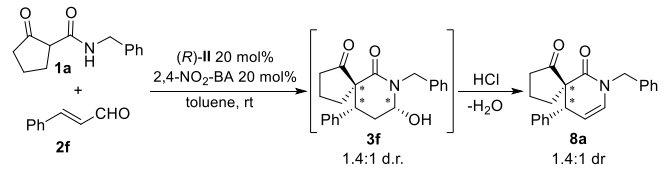
The mechanism of the reaction (Scheme 3, top) starts with a Michael addition of the ketoamide, in its enol form **1'**, to the enal **2**, catalyzed by the secondary amine **II**, followed by the intramolecular hemiacetalization between the amide and the aldehyde to generate the corresponding spiro compound **3**. In the Michael addition step th catalyst efficiently controls the enantioselectivity of the reaction a the bulky group blocks the bottom face of the iminium io intermediate **4**. For this reason the nucleophile **1** attacks from the *Si* face forming a new C-C bond in a highly enantioselective fashion. The pronucleophile **1'** can attack the iminium ion **4** following two different trajectories (Scheme 3, bottom). Trajectory **A** where the bulky ketoamide is far away of the catalyst will render the major diastereomer. In the case of aliphatic enals, the steric hindrance between the enal and the ketoamide is small, thus affording excellent diastereoselectivities. When bigger aromatic enals are used, the steric hindrance of both trajectories **A** and **B** have similar energies, explaining the lower diastereoselectivity. The last step of the cascade reaction is the hemiaminal cyclization. We suppose that this step occurs after the hydrolysis of the catalyst. Considering that this

reaction is under thermodynamic control, this will generate the most stable six membered ring **3**, where both substituents R and OH are in equatorial positions.



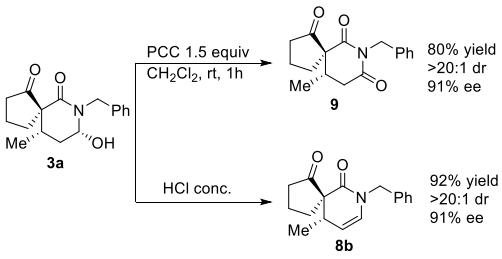
Scheme 3. Proposed mechanism of the 3+3 cycloaddition and rationalization of the diastereoselectivity.

This is suggested also by the treatment of the crude mixture of **3f**, consisting of 2 diastereomers in a ratio of 1.4:1, with HCl to obtain the dehydrated compound **8a** (Scheme 4). The isolated product **8a** consisted of a mixture of diastereomers in the same ratio as for **3f**, suggesting that the diastereoselectivity of this reaction is due to the different face from which the pronucleophile attacks the enal.



Scheme 4. One-pot synthesis of **3f** and subsequent dehydration

We also investigated some derivatizations of the product **3a** (Scheme 5): oxidation of hydroxyl group (**9**) and dehydration (**8b**). Excellent yields (92 and 80% respectively) and stereoselectivities (>20:1 dr, 91% *ee*) were obtained.



Scheme 5. Derivatizations of **3a**

Conclusion

In summary, we developed an organocascade reaction betwee ketoamides and enals, leading to a diastereoselective an enantioselective synthesis of α-spiro-δ-lactam compounds bearin three stereogenic centres. The reaction goes through a [3+3 cyclization. The combination of trifluoromethyl-substitute Jørgensen-Hayashi catalyst and 2,3-dinitrobenzoic acid enable excellent enantioselectivities with both aromatic and aliphatic α,β unsaturated aldehydes, while lower diastereoselectivities wer obtained with aromatic enals. Remarkably, in all the examples th final hemiaminals were stables at r.t., and were analysed withou problems in contrast with previously reported methodologies.[8,1] Probably, the use of non electron-withdrawing protecting groups o the nitrogen, increase the stability of the compounds. Whe employing TMS-substituted Jørgensen-Hayashi catalyst with benzoi acid, only one diastereomer was obtained with both aryl and alky enals but only aliphatic products maintained exceller enantioselectivities.

Experimental Section

General procedure: in a small vial, β-ketoamide **1** (0.2 mmol, 1.0 equiv), α,β unsaturated aldehyde **2** (0.3 mmol, 1.5 equiv), additive (0.04 mol, 0.2 equiv) an organocatalyst (0.04 mol, 0.2 equiv) were added in 1 ml of solvent, stirred at roo temperature. The crude mixture was purified by flash column chromatography (EtOA hexane = 4:1 gradient to 1:1) to obtain the hemiaminal products **3**.

Compound 3a: IR (CH_2Cl_2 liquid film): 3400, 2962, 1739, 1640, 1496, 1453, 1385, 126 1152, 733 cm^{-1}. mp: 152-163 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.20 (m, 5H), 4.9 (d, *J* = 14.9 Hz, 1H), 4.77 (d, *J* = 6.7 Hz, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 2.66 – 2.54 (m 1H), 2.33 – 2.08 (m, 7H), 1.84 (dd, *J* = 12.6, 7.0 Hz, 1H), 1.50 – 1.42 (m, 1H), 0.81 (d, = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8, 172.4, 137.1, 128.7, 128.0, 127. 78.9, 59.7, 45.0, 39.8, 36.7, 29.4, 29.3, 19.9, 16.0. HRMS m/z (ESI) calculated fo $C_{17}H_{21}NO_3Na$ $[M+Na]^+$ 310.1417, found 310.1414. The enantiomeric excess wa determined by HPLC using Chiralpak IB column (hexane/iPrOH = 95:5, flow rate = 0. ml/min, 230 nm); t_{major} = 42.3 min, t_{minor} = 47 min. $[\alpha]_D^{22}$ = +61.4° (c = 0.6 in $CHCl_3$).

Compound 3b: IR (CH_2Cl_2 liquid film): 3385, 2957, 2871, 1741, 1608, 1496, 1451, 131 1162, 732, 699 cm^{-1}. mp: 135-141 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.14 (m, 5H 4.92 (d, *J* = 14.8 Hz, 1H), 4.70 (dd, *J* = 14.8, 7.4 Hz, 1H), 4.32 – 4.26 (m, 1H), 2.77 2.50 (m, 2H), 2.28 – 2.05 (m, 5H), 2.00 – 1.91 (m, 1H), 1.85 – 1.76 (m, 1H), 1.31 (td, = 13.3, 8.8 Hz, 1H), 1.13 – 1.01 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3, 172.5, 137.1, 128.7, 128.0, 127.8, 79.1, 60.0, 44.8, 40.0, 36.5, 33.3, 30.0, 23.2, 19.9, 11.9. HRMS m/z (ESI) calculated for $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.1570, found 324.1570. The enantiomeric excess was determined by HPLC using Chiralpak IB column (hexane/iPrOH = 95:5, flow rate = 0.7 ml/min, 230 nm); t_{major} = 35.0 min, t_{minor} = 39.7 min. $[\alpha]_D^{22}$ = +100.0° (c = 0.6 in $CHCl_3$).

Compound 3c: IR (CH_2Cl_2 liquid film): 3386, 2925, 2854, 1741, 1606, 1496, 1451, 1285, 1120, 730, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 12.0, 8.8 Hz, 5H), 5.03 (d, *J* = 14.8 Hz, 1H), 4.80 (s, 1H), 4.40 (d, *J* = 14.8 Hz, 1H), 2.74 – 2.61 (m, 1H), 2.42 – 2.12 (m, 6H), 2.05 (ddd, *J* = 13.0, 7.5, 3.9 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.58 (s, 1H), 1.39 (td, *J* = 13.3, 8.7 Hz, 1H), 1.28 – 1.12 (m, 3H), 0.89 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3, 172.7, 137.1, 128.6, 127.9, 127.2, 79.0, 59.9, 44.8, 40.0, 34.5, 33.9, 32.6, 30.0, 20.5, 19.9, 14.1. HRMS m/z (ESI) calculated for $C_{19}H_{25}NO_3Na$ $[M+Na]^+$

338.1726, found 338.1727. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 97:3, flow rate = 1.0 ml/min, 230 nm); t_{major} = 41.3 min, t_{minor} = 44.9 min. $[\alpha]_D^{22}$ = +56.6° (c = 0.4 in $CHCl_3$).

Compound 3d: IR (CH_2Cl_2 liquid film): 3378, 2957, 1738, 1641, 1436, 1386, 1247, 1120, 732, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (ddd, *J* = 14.2, 7.3, 3.5 Hz, 5H), 4.91 (d, *J* = 14.9 Hz, 1H), 4.69 (dd, *J* = 14.1, 7.6 Hz, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 2.66 – 2.51 (m, 2H), 2.27 – 1.99 (m, 7H), 1.86 – 1.77 (m, 1H), 1.33 (td, *J* = 13.3, 8.8 Hz, 1H), 1.25 – 1.10 (m, 10H), 0.98 – 0.89 (m, 1H), 0.80 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.2, 172.7, 137.1, 128.7, 128.0, 127.3, 79.1, 60.0, 44.9, 40.0, 34.7, 34.0, 31.7, 30.4, 30.0, 29.6, 29.1, 27.4, 22.6, 19.9, 14.1. HRMS m/z (ESI) calculated for $C_{23}H_{33}NO_3Na$ $[M+Na]^+$ 394.2351, found 394.2351. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 97:3, flow rate = 1.0 ml/min, 230 nm); t_{major} = 30.9 min, t_{minor} = 33.7 min. $[\alpha]_D^{22}$ = +51.4° (c = 1.3 in $CHCl_3$).

Compound 3e: IR (CH_2Cl_2 liquid film): 3372, 2982, 1735, 1498, 1451, 1368, 1239, 1096, 732, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5H), 5.18 (d, *J* = 15.0 Hz, 1H), 4.87 – 4.79 (m, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 4.22 – 4.14 (m, 2H), 3.75 (d, *J* = 9.9 Hz, 1H), 3.07 (dd, *J* = 8.2, 4.3 Hz, 1H), 2.70 (ddd, *J* = 14.5, 5.5, 4.4 Hz, 1H), 2.59 (dddd, *J* = 18.8, 11.4, 6.0, 2.9 Hz, 2H), 2.49 – 2.36 (m, 1H), 2.32 – 2.21 (m, 1H), 1.95 (qdd, *J* = 13.7, 7.9, 4.3 Hz, 3H), 1.27 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.4, 172.9, 169.2, 136.8, 128.7, 127.8, 127.3, 78.1, 61.8, 56.6, 45.7, 41.6, 38.0, 32.3, 29.4, 19.7, 14.0. HRMS m/z (ESI) calculated for $C_{19}H_{23}NO_5Na$ $[M+Na]^+$ 368.1469, found 368.1468. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 56.1 min, t_{minor} = 61.6 min. $[\alpha]_D^{22}$ = +66.3° (c = 0.8 in $CHCl_3$).

Compound 3f, minor diastereomer: IR (CH_2Cl_2 liquid film): 3386, 2928, 2853, 1740 (C=O), 1627, 1529, 1450, 1278, 1156, 1078, 730, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.20 (m, 8H), 7.09 – 7.03 (m, 2H), 5.09 (d, *J* = 14.7 Hz, 1H), 4.87 (t, *J* = 6.7 Hz, 1H), 4.36 (d, *J* = 14.7 Hz, 1H), 3.63 (s, 1H), 2.96 – 2.83 (m, 2H), 2.70 (td, *J* = 14.2, 6.0 Hz, 1H), 2.43 – 2.33 (m, 1H), 2.21 (dt, *J* = 15.3, 8.0 Hz, 1H), 1.82 (dddd, *J* = 18.7, 14.5, 10.2, 6.5 Hz, 3H), 0.96 – 0.84 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.0, 169.3, 139.4, 137.6, 128.9, 128.6, 128.2, 128.2, 127.9, 127.3, 78.6, 61.0, 46.8, 46.6, 40.8, 35.2, 32.5, 19.9. The enantiomeric excess was determined by HPLC using Chiralpak IB column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 12.0 min, t_{minor} = 13.4 min. HRMS m/z (ESI) calculated for $C_{22}H_{23}NO_3Na$ $[M+Na]^+$ 372.1575, found 372.1570. $[\alpha]_D^{22}$ = -10.6° (c = 0.6 in $CHCl_3$).

Compound 3f, major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.44 (m, 8H), 7.35 – 7.29 (m, 2H), 5.33 (d, *J* = 14.8 Hz, 1H), 5.13 (d, *J* = 5.2 Hz, 1H), 4.63 (d, *J* = 14.8 Hz, 1H), 3.75 (dd, *J* = 13.4, 2.4 Hz, 1H), 2.94 (dd, *J* = 10.4, 6.6 Hz, 1H), 2.58 (dddd, *J* = 28.3, 20.8, 14.5, 8.1 Hz, 3H), 2.43 – 2.29 (m, 2H), 2.16 – 1.98 (m, 2H), 1.16 – 1.03 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.2, 172.5, 138.5, 136.9, 128.8, 128.6, 128.3, 128.0, 127.5, 127.4, 79.0, 61.0, 44.8, 40.0, 39.4, 34.3, 30.7, 19.8. HRMS m/z (ESI) calculated for $C_{22}H_{23}NO_3Na$ $[M+Na]^+$ 372.1575, found 372.1570. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 33.0 min, t_{minor} = 35.3 min. $[\alpha]_D^{22}$ = +59.0° (c = 1.0 in $CHCl_3$).

Compound 3g, minor diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 1H), 7.96 (d, *J* = 1.8 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.31 – 7.21 (m, 5H), 5.11 (d, *J* = 14.6 Hz, 1H), 4.94 – 4.84 (m, 1H), 4.36 (d, *J* = 14.6 Hz, 1H), 3.45 (d, *J* = 11.5 Hz, 1H), 3.06 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.97 – 2.87 (m, 1H), 2.77 (td, *J* = 14.1, 6.0 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.34 – 2.25 (m, 1H), 1.98 – 1.84 (m, 2H), 1.78 (dt, *J* = 13.3, 6.8 Hz, 1H), 1.02 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2, 168.6, 148.5, 141.7, 137.3, 134.0, 130.1, 128.7, 128.5, 127.5, 123.5, 123.0, 78.3, 60.5, 46.8, 46.0, 40.7, 35.1, 32.6, 20.1. HRMS m/z (ESI) calculated for $C_{22}H_{22}N_2O_5Na$ $[M+Na]^+$ 417.1425, found 417.1421. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 26.3 min, t_{minor} = 39.5 min. $[\alpha]_D^{22}$ = -35.8° (c = 0.3 in $CHCl_3$).

Compound 3g, major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dt, *J* = 5.1, 2.3 Hz, 1H), 7.97 (s, 1H), 7.39 (d, *J* = 2.7 Hz, 1H), 7.32 – 7.15 (m, 6H), 5.06 (d, *J* = 14.8 Hz, 1H), 4.96 – 4.83 (m, 1H), 4.36 (d, *J* = 14.9 Hz, 1H), 3.63 (dd, *J* = 13.7, 2.4 Hz, 1H), 2.77 (d, *J* = 7.8 Hz, 1H), 2.51 – 2.39 (m, 1H), 2.38 – 2.26 (m, 2H), 2.16 (td, *J* = 13.5, 8.9 Hz, 1H), 2.02 – 1.89 (m, 2H), 1.81 – 1.70 (m, 1H), 1.05 – 0.92 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.2, 171.7, 148.4, 140.7, 136.6, 135.3, 129.9, 128.9, 128.0, 127.6, 122.8, 122.6, 78.6, 60.8, 44.9, 39.7, 39.0, 34.1, 30.2, 19.8. HRMS m/z (ESI) calculated for $C_{22}H_{22}N2O_5Na$ $[M+Na]^+$ 417.1411, found 417.1421. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 36.0 min, t_{minor} = 44.3 min. $[\alpha]_D^{22}$ = +21.1° (c = 1.0 in $CHCl_3$).

Compound 3h, minor diastereomer: IR (CH_2Cl_2 liquid film): 3378, 2960, 1738, 1606, 1519, 1451, 1347, 1159, 1073, 857, 733, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.8 Hz, 2H), 7.30 – 7.20 (m, 7H), 5.08 (d, *J* = 14.7 Hz, 1H), 4.88 (d, *J* = 6.1 Hz, 1H), 4.37 (d, *J* = 14.7 Hz, 1H), 3.53 (d, *J* = 10.9 Hz, 1H), 3.04 (dd, *J* = 13.9, 4.7 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.77 (td, *J* = 14.1, 6.3 Hz, 1H), 2.40 – 2.24 (m, 2H), 1.94 – 1.84 (m, 2H), 1.80 – 1.72 (m, 1H), 1.02 (ddd, *J* = 14.2, 9.1, 5.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.1, 167.6, 146.5, 145.9, 136.3, 128.3, 127.7, 127.2, 126.4, 123.1, 77.3, 59.4, 45.7, 44.9, 39.7, 33.8, 31.7, 19.1. HRMS m/z (ESI) calculated for $C_{22}H_{22}N2O_5Na$ $[M+Na]^+$ 417.1428, found 417.1421. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 85:15, flow rate = 1.0 ml/min, 230 nm); t_{major} = 19.4 min, t_{minor} = 40.1 min. $[\alpha]_D^{22}$ = -8.7° (c = 0.6 in $CHCl_3$).

Compound 3h, major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.26 – 7.17 (m, 7H), 5.01 (d, *J* = 14.9 Hz, 1H), 4.86 (s, 1H), 4.34 (d, *J* = 14.9 Hz, 1H), 3.59 (dd, *J* = 13.6, 2.1 Hz, 1H), 3.28 (s, 1H), 2.41 (dt, *J* = 17.9, 8.1 Hz, 1H), 2.27 (ddd, *J* = 12.3, 7.9, 3.0 Hz, 2H), 2.12 (td, *J* = 13.4, 9.0 Hz, 1H), 1.98 – 1.82 (m, 2H), 1.81 – 1.67 (m, 1H), 0.92 (dt, *J* = 15.7, 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4, 171.8, 147.2, 146.0, 136.5, 129.5, 128.8, 127.9, 127.6, 123.7, 78.6, 60.9, 44.8, 39.8, 39.3, 33.9, 30.3, 19.8. HRMS m/z (ESI) calculated for $C_{22}H_{22}N2O_5Na$ $[M+Na]^+$ 417.1434, found 417.1421. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 82:18, flow rate = 1.0 ml/min, 230nm); t_{major} = 16.8 min, t_{minor} = 32.2 min. $[\alpha]_D^{22}$ = +94.1° (c = 1.3 in $CHCl_3$).

Compound 3i, minor diastereomer: IR (CH_2Cl_2 liquid film): 3387, 2923, 1730, 160 1509, 1449, 1227, 1162, 1117, 1053, 839, 732 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.3 – 7.19 (m, 5H), 7.08 – 6.99 (m, 2H), 6.98 – 6.90 (m, 2H), 5.09 (d, *J* = 14.7 Hz, 1H), 4.9 – 4.81 (m, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 3.47 (d, *J* = 12.3 Hz, 1H), 2.97 – 2.84 (m, 2H 2.66 (td, *J* = 14.2, 5.9 Hz, 1H), 2.37 (ddd, *J* = 14.4, 8.0, 5.0 Hz, 1H), 2.30 – 2.17 (m, 1H 1.95 – 1.75 (m, 3H), 0.97 (ddd, *J* = 12.0, 8.5, 4.7 Hz, 1H). ^{13}C NMR (101 MHz, CDCl δ 219.9, 169.1, 137.5, 129.7, 129.7, 128.7, 128.3, 127.4, 116.0, 115.8, 78.5, 61.0, 46.9 45.7, 40.8, 35.4, 32.5, 20.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.09. HRMS m/z (ES calculated for $C_{22}H_{22}FNO_3Na$ $[M+Na]^+$ 390.1485, found 390.1476. The enantiomeri excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:1(flow rate = 1.0 ml/min, 230 nm); t_{major} = 13.0 min, t_{minor} = 22.4 min. $[\alpha]_D^{22}$ = -5.3° (c = 0. in $CHCl_3$).

Compound 3i, major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H 7.01 (dd, *J* = 8.4, 5.4 Hz, 2H), 6.91 (t, *J* = 8.6 Hz, 2H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.87 (*J* = 5.9 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 3.48 (d, *J* = 13.1 Hz, 1H), 2.59 (s, 1H), 2.3 (s, 1H), 2.34 – 2.20 (m, 2H), 2.03 (ddd, *J* = 13.3, 10.1, 6.8 Hz, 2H), 1.88 (dt, *J* = 19.8, 6. Hz, 1H), 1.82 – 1.71 (m, 1H), 0.98 – 0.85 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.(172.4, 136.8, 129.9, 129.8, 128.8, 128.0, 127.5, 115.6, 115.4, 78.9, 61.0, 44.9, 40.0, 38.7 34.5, 30.5, 19.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.88. HRMS m/z (ESI) calculated fo $C_{22}H_{22}FNO_3Na$ $[M+Na]^+$ 390.1487, found 390.1476. The enantiomeric excess wa determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate 1.0 ml/min, 230 nm); t_{major} = 14.2 min, t_{minor} = 17.8 min. $[\alpha]_D^{22}$ = +42.3° (c = 0.9 in $CHCl_3$

Compound 3j, minor diastereomer: IR (CH_2Cl_2 liquid film): 3371, 2958, 1738, 160 1492, 1450, 1293, 1160, 1031, 833, 734, 699, 616, 587 cm^{-1}. ^1H NMR (400 MHz, CDCl δ 7.45 – 7.35 (m, 7H), 7.15 (d, *J* = 8.5 Hz, 2H), 5.23 (d, *J* = 14.7 Hz, 1H), 5.01 (t, *J* = 6. Hz, 1H), 4.51 (d, *J* = 14.7 Hz, 1H), 3.71 (s, 1H), 3.10 – 2.96 (m, 2H), 2.82 (td, *J* = 14. 6.1 Hz, 1H), 2.50 (ddd, *J* = 14.3, 7.8, 4.8 Hz, 1H), 2.44 – 2.34 (m, 1H), 2.10 – 1.91 (m 3H), 1.23 – 1.12 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7, 169.0, 137.9, 137. 133.8, 129.5, 129.1, 128.7, 128.3, 127.4, 78.4, 60.8, 46.8, 45.9, 40.8, 35.2, 32.5, 20.(HRMS m/z (ESI) calculated for $C_{22}H_{22}ClNO_3Na$ $[M+Na]^+$ 406.1187, found 406.118(The enantiomeric excess was determined by HPLC using Chiralpak OD-H colum (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 19.9 min, t_{minor} = 38.8 mi $[\alpha]_D^{22}$ = +16.1° (c = 0.7 in $CHCl_3$).

Compound 3j, major diastereomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 7H 6.97 (d, *J* = 8.5 Hz, 2H), 5.02 (d, *J* = 14.8 Hz, 1H), 4.84 (s, 1H), 4.34 (d, *J* = 14.9 H 1H), 3.46 (dd, *J* = 13.6, 2.2 Hz, 1H), 2.87 (s, 1H), 2.39 (dt, *J* = 16.7, 8.0 Hz, 1H), 2.31 2.17 (m, 2H), 2.09 – 1.94 (m, 2H), 1.93 – 1.82 (m, 1H), 1.82 – 1.71 (m, 1H), 0.93 (dt, = 12.0, 7.5 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.9, 172.3, 137.0, 136.7, 133.4 129.7, 128.8, 128.8, 128.0, 127.5, 78.8, 60.9, 44.8, 39.9, 38.8, 34.3, 30.4, 19.8. HRM m/z (ESI) calculated for $C_{22}H_{22}ClNO_3Na$ $[M+Na]^+$ 406.1189, found 406.1180. Th enantiomeric excess was determined by HPLC using Chiralpak OD-H colum (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 33.5 min, t_{minor} = 47.8 mi $[\alpha]_D^{22}$ = +41.7° (c = 2.3 in $CHCl_3$).

Compound 3k, minor diastereomer: IR (CH_2Cl_2 liquid film): 3376, 2960, 1730, 1616, 1567, 1449, 1327, 1294, 1169, 885, 788, 734, 698, 542 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (ddd, *J* = 8.0, 1.9, 1.0 Hz, 1H), 7.25 (ddd, *J* = 12.8, 4.2, 2.2 Hz, 6H), 7.12 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 6.5, 1.3 Hz, 1H), 5.10 (d, *J* = 14.7 Hz, 1H), 4.86 (ddd, *J* = 12.3, 7.9, 5.9 Hz, 1H), 4.34 (d, *J* = 14.7 Hz, 1H), 3.49 (d, *J* = 12.3 Hz, 1H), 2.93 – 2.82 (m, 2H), 2.65 (td, *J* = 14.2, 5.9 Hz, 1H), 2.37 (ddd, *J* = 14.4, 8.0, 5.0 Hz, 1H), 2.30 – 2.20 (m, 1H), 1.96 – 1.77 (m, 3H), 1.07 – 0.98 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7, 168.9, 141.8, 137.5, 131.5, 131.1, 130.5, 128.7, 128.2, 127.4, 126.7, 123.0, 78.4, 60.8, 46.8, 46.2, 40.8, 35.2, 32.5, 20.0. HRMS m/z (ESI) calculated for $C_{22}H_{22}BrNO_3Na$ $[M+Na]^+$ 450.0668, found 450.0675. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 93:7, flow rate = 1.0 ml/min, 230 nm); t_{major} = 22.5 min, t_{minor} = 28.7 min. $[\alpha]_D^{22}$ = +9.8° (c = 0.7 in $CHCl_3$).

Compound 3k, major diastereomer: mp: 133-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (ddd, *J* = 33.3, 17.1, 8.7 Hz, 7H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 14.8 Hz, 1H), 4.85 (td, *J* = 8.7, 5.7 Hz, 1H), 4.34 (d, *J* = 14.8 Hz, 1H), 3.46 (dd, *J* = 13.6, 2.1 Hz, 1H), 2.70 (d, *J* = 7.9 Hz, 1H), 2.49 – 2.34 (m, 1H), 2.34 – 2.18 (m, 2H), 2.10 – 1.95 (m, 2H), 1.84 (dtd, *J* = 18.1, 14.2, 6.4 Hz, 2H), 0.95 (dt, *J* = 11.9, 7.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.7, 172.2, 140.9, 136.7, 131.2, 130.7, 130.1, 128.8, 128.0, 127.5, 127.3, 122.8, 78.8, 60.9, 44.9, 39.9, 39.1, 34.2, 30.5, 19.8. HRMS m/z (ESI) calculated for $C_{22}H_{22}BrNO_3Na$ $[M+Na]^+$ 450.0685, found 450.0675. The enantiomeric excess was determined by HPLC using Chiralpak IB column (hexane/iPrOH = 97:3, flow rate = 1.0 ml/min, 230 nm); t_{major} = 58.2 min, t_{minor} = 61.5 min. $[\alpha]_D^{22}$ = +54.2° (c = 1.7 in $CHCl_3$).

Compound 3l, minor diastereomer: IR (CH_2Cl_2 liquid film): 3369, 2938, 1752, 1608, 1492, 1450, 1293, 1160, 823, 733, 700, 650 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.5 Hz, 2H), 7.29 – 7.20 (m, 5H), 6.94 (d, *J* = 8.5 Hz, 2H), 5.08 (d, *J* = 14.7 Hz, 1H), 4.85 (ddd, *J* = 12.3, 7.8, 6.1 Hz, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 3.52 (d, *J* = 12.3 Hz, 1H), 2.93 – 2.81 (m, 2H), 2.66 (td, *J* = 14.2, 6.0 Hz, 1H), 2.35 (ddd, *J* = 14.3, 7.9, 4.9 Hz, 1H), 2.29 – 2.18 (m, 1H), 1.95 – 1.83 (m, 2H), 1.83 – 1.74 (m, 1H), 1.07 – 0.97 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.7, 169.0, 138.5, 137.5, 132.1, 129.9, 128.7, 128.2, 127.4, 121.9, 78.4, 60.7, 46.8, 45.9, 40.8, 35.2, 32.5, 20.0. HRMS m/z (ESI) calculated for $C_{22}H_{22}BrNO_3Na$ $[M+Na]^+$ 450.0686, found 450.0675. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 12.1 min, t_{minor} = 21.4 min. $[\alpha]_D^{22}$ = -1.8° (c = 0.6 in $CHCl_3$).

Compound 3l, major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.31 – 7.19 (m, 5H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.04 (d, *J* = 14.8 Hz, 1H), 4.85 (dd, *J* = 8.9, 5.6 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.45 (dd, *J* = 13.6, 2.3 Hz, 1H), 2.40 (dt, *J* = 16.4, 8.0 Hz, 1H), 2.32 – 2.20 (m, 2H), 2.11 – 1.72 (m, 5H), 1.01 – 0.89 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.8, 172.2, 137.5, 136.7, 131.7, 130.1, 128.8, 128.0, 127.5, 121.6, 78.8, 60.8, 44.9, 39.9, 38.9, 34.2, 30.4, 19.8. HRMS m/z (ESI) calculated for $C_{22}H_{22}BrNO_3Na$ $[M+Na]^+$ 450.0685, found 450.0675. The enantiomeric excess was determined by HPLC using OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 15.7 min, t_{minor} = 21.9 min. $[\alpha]_D^{22}$ = +50.0° (c = 0.8 in $CHCl_3$).

Compound 3m, minor diastereomer: IR (CH_2Cl_2 liquid film): 3361, 2956, 1738, 1607, 1492, 1450, 1137, 1091, 1031, 823, 734, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.19 (m, 5H), 7.04 (d, *J* = 7.9 Hz, 2H), 6.94 (d, *J* = 8.1 Hz, 2H), 5.09 (d, *J* = 14.7 Hz, 1H), 4.85 (s, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 2.92 – 2.80 (m, 2H), 2.66 (td, *J* = 14.2, 5.9 Hz, 1H), 2.36 (ddd, *J* = 14.3, 8.0, 5.0 Hz, 1H), 2.26 (d, *J* = 3.8 Hz, 3H), 2.19 (dd, *J* = 12.9, 5.2 Hz, 1H), 1.85 (dddd, *J* = 18.4, 15.4, 12.5, 7.5 Hz, 3H), 0.99 – 0.90 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.1, 169.4, 137.7, 136.3, 129.6, 128.6, 128.2, 128.0, 127.3, 126.2, 78.6, 61.1, 46.8, 46.3, 40.8, 35.4, 32.5, 21.0, 20.0. HRMS m/z (ESI) calculated for $C_{23}H_{25}NO_5Na$ $[M+Na]^+$ 386.1733, found 386.1727. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 9.3 min, t_{minor} = 16.2 min. $[\alpha]_D^{22}$ = +10.5° (c = 0.9 in $CHCl_3$).

Compound 3m, major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 5H), 7.01 (d, *J* = 8.1 Hz, 2H), 6.92 (d, *J* = 8.1 Hz, 2H), 5.04 (d, *J* = 14.9 Hz, 1H), 4.84 (d, *J* = 5.8 Hz, 1H), 4.35 (d, *J* = 14.8 Hz, 1H), 3.43 (d, *J* = 12.1 Hz, 1H), 2.42 – 2.18 (m, 6H), 2.10 – 2.01 (m, 2H), 1.87 – 1.70 (m, 2H), 1.63 (s, 1H), 0.88 (dd, *J* = 12.6, 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.3, 172.6, 137.1, 136.9, 135.4, 129.3, 128.7, 128.2, 128.0, 127.4, 126.2, 79.0, 61.0, 44.8, 39.0, 39.1, 34.4, 30.7, 21.0, 19.8. HRMS m/z (ESI) calculated for $C_{23}H_{25}NO_5Na$ $[M+Na]^+$ 386.1729, found 386.1727. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 12.5 min, t_{minor} = 15.2 min. $[\alpha]_D^{22}$ = +42.9° (c = 1.8 in $CHCl_3$).

Compound 3n, minor diastereomer: IR (CH_2Cl_2 liquid film): 3376, 2959, 1738, 1605, 1520, 1493, 1452, 1268 (aromatic OCH_3), 1154, 858, 789, 734, 699 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 7.18 – 7.12 (m, 1H), 6.75 (ddd, *J* = 8.3, 2.5, 0.8 Hz, 1H), 6.64 (d, *J* = 7.7 Hz, 1H), 6.62 – 6.57 (m, 1H), 5.10 (d, *J* = 14.7 Hz, 1H), 4.86 (ddd, *J* = 12.4, 8.0, 5.8 Hz, 1H), 4.35 (d, *J* = 14.7 Hz, 1H), 3.71 (s, 3H), 3.57 (d, *J* = 12.3 Hz, 1H), 2.88 (ddd, *J* = 14.0, 7.9, 4.8 Hz, 2H), 2.66 (td, *J* = 14.2, 5.8 Hz, 1H), 2.39 (ddd, *J* = 14.4, 8.1, 5.0 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.02 – 1.91 (m, 1H), 1.89 – 1.76 (m, 2H), 1.05 – 0.93 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 220.0, 169.2, 159.9, 141.0, 137.6, 130.0, 128.6, 128.3, 127.3, 120.4, 114.2, 113.0, 78.5, 61.0, 55.2, 46.9, 46.7, 40.9, 35.3, 32.5, 20.0. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 17.9 min, t_{minor} = 28.3 min. HRMS m/z (ESI) calculated for $C_{23}H_{25}NO_4Na$ $[M+Na]^+$ 402.1676, found 402.1676. $[\alpha]_D^{22}$ = +83.3° (c = 0.6 in $CHCl_3$).

Compound 3n, major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 7.13 (t, *J* = 7.9 Hz, 1H), 6.72 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.67 – 6.56 (m, 2H), 5.08 (d, *J* = 14.8 Hz, 1H), 4.87 (dd, *J* = 14.0, 8.5 Hz, 1H), 4.36 (d, *J* = 14.8 Hz, 1H), 3.70 (s, 3H), 3.47 (dd, *J* = 13.3, 2.4 Hz, 1H), 2.47 – 2.31 (m, 3H), 2.31 – 2.22 (m, 1H), 2.12 – 2.00 (m, 2H), 1.93 – 1.77 (m, 2H), 0.99 – 0.87 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.0, 172.4, 159.7, 140.2, 136.9, 129.7, 128.8, 128.1, 127.5, 120.6, 114.3, 112.6, 79.0, 60.9, 55.2, 45.0, 40.0, 39.5, 34.4, 30.9, 19.8. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm); t_{major} = 17.4 min, t_{minor} = 19.8 min. HRMS m/z (ESI) calculated for $C_{23}H_{25}NO_4Na$ $[M+Na]^+$ 402.1673, found 402.1676. $[\alpha]_D^{22}$ = +35.4° (c = 0.5 in $CHCl_3$).

Compound 3o: mp: 134-143 °C. IR (CH_2Cl_2 liquid film): 3386, 2929, 2853, 1739 (C=O), 1627, 1529, 1450, 1347, 1296, 1145, 1059 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (d, *J* = 5.8 Hz, 1H), 4.14 – 4.01 (m, 1H), 2.75 (ddt, *J* = 11.7, 9.7, 6.4 Hz, 1H), 2.42 (ddd, *J* = 9.7, 8.8, 5.0 Hz, 3H), 2.33 (ddd, *J* = 12.3, 6.8, 3.2 Hz, 2H), 2.06 – 1.95 (m, 4H), 1.93 – 1.76 (m, 5H), 1.64 (ddd, *J* = 20.1, 9.5, 4.2 Hz, 1H), 1.57 – 1.39 (m, 3H), 1.36 – 1.27 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.0, 172.4, 78.2, 60.1, 55.7, 39.7, 37.2, 31.9, 29.9, 29.5, 29.3, 26.3, 26.3, 25.6, 19.8, 16.0. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 97:3, flow rate = 0.7 ml/min, 230 nm); t_{major} = 32.4 min, t_{minor} = 34.6 min. HRMS m/z (ESI) calculated for $C_{16}H_{25}NO_3Na$ $[M+Na]^+$ 302.1732, found 302.1727. $[\alpha]_D^{22}$ = +20.3° (c = 0.3 in $CHCl_3$).

Compound 3p: IR (CH_2Cl_2 liquid film): 3370, 3002, 2951, 1741 (C=O), 1617, 151(1461, 1292(aliphatic OCH_3), 1067 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (td, *J* = 6.7 4.1 Hz, 1H), 4.45 (dd, *J* = 6.4, 3.8 Hz, 1H), 4.25 (d, *J* = 4.0 Hz, 1H), 3.78 (dd, *J* = 14.3 3.7 Hz, 1H), 3.38 (d, *J* = 1.5 Hz, 6H), 3.35 – 3.29 (m, 1H), 3.14 (dd, *J* = 14.2, 6.4 H 1H), 2.51 (ddd, *J* = 15.3, 9.0, 5.7 Hz, 1H), 2.26 (ddd, *J* = 12.2, 6.8, 3.7 Hz, 1H), 2.22 2.11 (m, 4H), 1.85 – 1.78 (m, 1H), 1.47 (ddd, *J* = 13.8, 12.4, 7.1 Hz, 1H), 0.82 (d, *J* = 6. Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.6, 172.9, 103.0, 81.2, 59.9, 55.9, 55.5, 47.9 39.6, 35.7, 29.6, 29.4, 19.8, 16.1. The enantiomeric excess was determined by HPL using Chiralpak OD-H column (hexane/iPrOH = 90:10, flow rate = 1.0 ml/min, 230 nm t_{major} = 13.1 min, t_{minor} = 13.6 min. HRMS m/z (ESI) calculated for $C_{14}H_{23}NO_5Na$ [M+Na 308.1467, found 308.1468. $[\alpha]_D^{22}$ = +1.6° (c = 0.6 in $CHCl_3$).

Compound 3q: mp: 163-167 °C. IR (CH_2Cl_2 liquid film): 3378, 2962, 1740 (C=O), 162 1509, 1443, 1245, 1181(aromatic OCH3), 1064, 830 cm^{-1}. ^{1}H NMR (400 MHz, CDCl δ 7.07 (d, *J* = 8.8 Hz, 2H), 6.92 – 6.88 (m, 2H), 5.15 (dt, *J* = 8.0, 5.7 Hz, 1H), 3.78 (3H), 2.91 (d, *J* = 5.0 Hz, 1H), 2.50 (tdd, *J* = 9.7, 8.6, 4.8 Hz, 2H), 2.33 (dd, *J* = 11.0, 4. Hz, 1H), 2.28 – 2.09 (m, 4H), 1.92 – 1.80 (m, 1H), 1.68 – 1.60 (m, 1H), 0.92 (d, *J* = 6. Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.4, 172.3, 159.0, 130.9, 129.8, 114.7, 81. 59.9, 55.5, 39.7, 35.4, 29.5, 29.3, 19.7, 16.1. The enantiomeric excess was determined b HPLC using Chiralpak OD-H column (hexane/iPrOH = 88:12, flow rate = 1.0 ml/mi 230 nm); t_{major} = 18.7 min, t_{minor} = 31.1 min. HRMS m/z (ESI) calculated for $C_{17}H_{21}NO_4N$ $[M+Na]^+$ 326.1358, found 326.1363. $[\alpha]_D^{22}$ = +61.4° (c = 0.6 in $CHCl_3$).

Compound 3r: mp: 123-134 °C. IR (CH_2Cl_2 liquid film): 3369, 2940, 1661, 1525, 145 1371, 1278, 700, 682 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 6.8, 4.2 Hz, 5H 5.05 (d, *J* = 15.0 Hz, 1H), 4.81 – 4.75 (m, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 2.78 – 2.68 (m 1H), 2.63 (ddd, *J* = 10.3, 6.8, 3.6 Hz, 1H), 2.47 (dt, *J* = 15.9, 5.9 Hz, 2H), 2.39 – 2.24 (m 2H), 1.93 (ddd, *J* = 21.4, 9.9, 5.8 Hz, 3H), 1.67 (ddd, *J* = 19.9, 10.4, 5.5 Hz, 3H), 0.98 (*J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.6, 170.8, 137.2, 128.7, 127.9, 127. 78.5, 59.8, 46.0, 40.5, 34.3, 29.3, 29.0, 25.3, 20.4, 16.3. HRMS m/z (ESI) calculated fo $C_{18}H_{23}NO_3Na$ $[M+Na]^+$ 324.1564, found 324.1570. The enantiomeric excess wa determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 97:3, flow rate 1.0 ml/min, 230 nm); t_{major} = 49.8 min, t_{minor} = 54.1 min. $[\alpha]_D^{22}$ = +40.2° (c = 0.9 in $CHCl_3$

Compound 3s: IR (CH_2Cl_2 liquid film): 3377, 2933, 2865, 1656, 1451, 1309, 1233, 118(730, 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.44 (m, 8H), 7.39 – 7.35 (m, 2H 5.39 (d, *J* = 14.9 Hz, 1H), 5.07 (dd, *J* = 13.9, 6.8 Hz, 1H), 4.65 – 4.59 (d, *J* = 14.9 H 1H), 4.12 (dd, *J* = 10.5, 4.2 Hz, 1H), 2.93 – 2.77 (m, 2H), 2.56 – 2.38 (m, 4H), 2.14 (dd *J* = 16.3, 9.7, 5.3 Hz, 1H), 2.07 – 1.97 (m, 2H), 1.74 – 1.58 (m, 2H). ^{13}C NMR (101 MH $CDCl_3$) δ 210.9, 171.6, 139.3, 137.1, 129.1, 128.8, 128.7, 128.6, 128.1, 127.3, 78.8, 59.9 45.3, 40.4, 40.0, 33.5, 29.5, 23.6, 20.4. HRMS m/z (ESI) calculated for $C_{23}H_{25}NO_3N$ $[M+Na]^+$ 386.1730, found 372.1727. The enantiomeric excess was determined by HPL using Chiralpak IB column (hexane/iPrOH = 95:5, flow rate = 0.5 ml/min, 230 nm); t_{maj} = 48.1 min, t_{minor} = 53.2 min. $[\alpha]_D^{22}$ = +29.4° (c = 0.8 in $CHCl_3$).

Compound 3t: IR (CH_2Cl_2 liquid film): 3405, 2931, 1669, 1607, 1510, 1441, 1381, 129 1254, 1178, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.12 (m, 2H), 6.84 – 6.81 (m, 2H), 5.21 (t, *J* = 2.4 Hz, 1H), 3.72 (s, 3H), 2.53 (ddd, *J* = 13.1, 9.6, 2.0 Hz, 1H), 2.40 (tdd, *J* = 13.1, 8.5, 4.6 Hz, 2H), 2.32 – 2.25 (m, 1H), 1.78 – 1.70 (m, 2H), 1.58 – 1.52 (m, 2H), 1.45 (ddd, *J* = 6.8, 5.0, 2.6 Hz, 3H), 1.27 (td, *J* = 13.4, 4.3 Hz, 1H), 0.92 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 157.9, 132.0, 125.7, 114.3, 98.4, 84.6, 55.5, 52.2, 39.1, 36.8, 27.0, 26.2, 22.6, 22.0, 18.1. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{minor} = 28.3 min, t_{major} = 37.0 min. HRMS m/z (ESI) calculated for $C_{18}H_{24}NO_4$ $[M+H]^+$ 318.1695, found 318.1700. $[\alpha]_D^{22}$ = +12.8° (c = 0.5 in $CHCl_3$).

c: To a stirring mixture of **3a** (0.2 mmol, 1 equiv) in 1 ml of toluene, 0.2 equiv of concentrated HCl were added. The reaction was allowed to stir for 30 minutes, monitored by TLC. The crude mixture was purified by flash column chromatography (EtOAc: hexane = 1:1) to render the product **8b**.

Compound 8b: IR (CH_2Cl_2 liquid film): 2964, 1764, 1663, 1496, 1381, 1252, 731, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 15.3, 10.5, 1.5 Hz, 5H), 5.88 (dd, *J* = 7.7, 2.5 Hz, 1H), 4.87 (dd, *J* = 7.7, 3.2 Hz, 1H), 4.66 (d, *J* = 15.0 Hz, 1H), 4.52 (d, *J* = 15.0 Hz, 1H), 3.04 – 2.94 (m, 1H), 2.56 – 2.45 (m, 1H), 2.21 – 2.12 (m, 1H), 2.08 – 1.96 (m, 3H), 1.87 – 1.77 (m, 1H), 0.87 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 216.4, 170.2, 136.9, 128.7, 127.6, 127.6, 127.3, 112.0, 59.1, 48.9, 39.3, 31.7, 28.0, 19.1, 14.7. HRMS m/z (ESI) calculated for $C_{17}H_{19}NO_2Na$ $[M+Na]^+$ 292.1300, found 292.1308. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 17.4 min, t_{minor} = 21.5min. $[\alpha]_D^{22}$ = +111.3° (c = 0.6 in $CHCl_3$).

Procedure for the synthesis of 9: To a stirring mixture of hemiaminal product **3a** (0.2 mmol, 1.0 equiv) in 2 ml of CH_2Cl_2, DCC (0.3 mmol, 1.5 equiv) was added. The reaction was allowed to stir for 3 h, monitored by TLC. The crude mixture was purified by flash column chromatography (EtOAc: hexane = 1:1) to render the oxidation product **9**.

Compound 9: IR (CH_2Cl_2 liquid film): 2939, 1726, 1666, 1496, 1269, 1023, 733, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, *J* = 5.4, 4.4 Hz, 5H), 4.86 (d, *J* = 6.1 Hz, 2H), 2.99 – 2.92 (m, 1H), 2.50 – 2.18 (m, 5H), 2.05 (dddd, *J* = 20.4, 17.0, 9.2, 5.3 Hz, 2H), 1.94 – 1.85 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.4, 172.5, 171.1, 137.0, 128.5, 128.3, 127.4, 60.4, 43.2, 38.8, 37.0, 29.6, 29.1, 19.4, 16.2. HRMS m/z (ESI) calculated for $C_{17}H_{20}NO_3$ $[M+Na]^+$ 286.1430, found 286.1438. The enantiomeric excess was determined by HPLC using Chiralpak OD-H column (hexane/iPrOH = 95:5, flow rate = 1.0 ml/min, 230 nm); t_{major} = 15.6 min, t_{minor} = 17.9 min. $[\alpha]_D^{22}$ = +43.7° (c = 0.7 in $CHCl_3$).

For ^1H-NMR, ^{13}C-NMR, ^{19}F-NMR spectra and HPLC traces see Supporting Information.

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Organocascade Reaction

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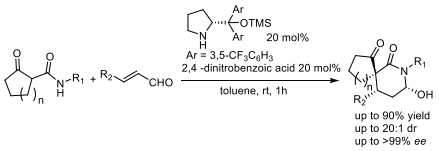
Highly Diastereo and Enantioselective Synthesis of α-spiro-δ-lactams Bearing Three Contiguous Stereogenic Centers *via* Organocascade Reaction



An asymmetric synthesis of α-spiro-δ-lactam via organocascade reaction from easily accessible starting materials is reported. The catalytic sequence undergoes enantioselective Michael addition of β-ketoamide to α,β-unsaturated aldehyde catalysed by a secondary amine catalyst, followed by hemiaminal annulation. Optically enantiopure compounds with three stereogenic centres are obtained in good yields and excellent selectivities (up to >20:1 dr and up to >99% *ee*).