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Asymmetric Conjugate Addition of Malonate Esters to α,β-Unsaturated *N*-Sulfonyl Imines: An Expeditious Route to Chiral δ-Aminoesters and Piperidones

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Abstract: The asymmetric conjugate addition of malonate esters to α,β-unsaturated *N*-sulfonyl imines is catalyzed by PyBOX/La(OTf)$_3$ complexes in the presence of 4 Å MS. The reaction gives the corresponding *E* enamines bearing a stereogenic center at the allylic position with good yields and enantiomeric ratios up to 97:3. This reaction provides a synthetic entry to chiral δ-aminoesters and piperidones.

Keywords: amino acids · asymmetric catalysis · carbanions · conjugate addition · imino compounds

Introduction

Conjugate addition reactions have played a crucial role in organic synthesis. The research on this transformation has been boosted by the wide diversity of compounds that can serve as nucleophiles and electrophiles to generate a varied array of products.[1] Such reactions often result in the generation of a new stereocenter, and consequently a considerable effort has been devoted to the development of asymmetric catalytic versions of 1,4-addition reactions. Unsaturated carbonyl compounds,[2] nitroalkenes,[3] and less frequently unsaturated sulfones[4] have been used as electrophilic partners in asymmetric conjugate additions of easily enolizable nucleophiles, such as 1,3-dicarbonyl and related compounds. In this context, α,β-unsaturated imines (1-azabutenes), readily prepared through condensation of *N*-substituted amines with the parent unsaturated ketones, have emerged as an interesting family of compounds with important applications in the synthesis of nitrogen-containing molecules. Thus, numerous applications of 1-azabutenes as heterodienes in asymmetric cycloaddition reactions have been reported in the literature.[5]

In contrast to carbonyl substrates and nitroalkenes, the asymmetric conjugate addition to α,β-unsaturated imines has been scarcely explored probably due to the lower electrophilicity of these substrates. Furthermore, α,β-unsaturated imines are ambidented electrophiles that can either undergo 1,2- or 1,4-nucleophilic addition processes.[6] However, generally, the control of the regioselectivity is difficult and dependent on the nucleophile and reaction conditions, often 1,2-addition is preferred,[7] or double nucleophilic addition products are obtained.[8] On the other hand, only a much reduced number of examples regarding the enantioselective 1,4-nucleophilic addition of carbon nucleophiles to unsaturated imines have been reported.[9] In 2005, Ellman's group reported the asymmetric conjugate addition of organocuprates to chiral *N*-*tert*-butylsulfinylimines with good yields and diastereomeric ratios (d.r.) of up to 93:7.[10] The first example of catalytic enantioselective conjugate addition was reported by Tomioka's group in 2005. These authors carried out the addition of diethylzinc to *N*-sulfonyl aldimines bearing a bulky group on the azomethinic nitrogen atom in the presence of a phosphine/Cu^{I} complex to give the corresponding 1,4-alkylation products with *ee* values in the 75–91% range. The group of Carretero reported the conjugate addition of diethylzinc to unsaturated *N*-sulfonyl ketimines by using a Cu^{I}/phosphorimidite complex, obtaining the alkylated products with moderate enantioselectivity (*ee* = 70–80%).[11] Later, Palacios described the Cu^{I}-catalyzed conjugate addition of diethylzinc to a reduced number of *N*-aryl imines derived from α-ketoesters, by using a different phosphorimidite ligand with enantiomeric excesses in the 76–88% range.[12] Besides these examples, a conjugate addition of malonate esters or related 1,3-dicarbonyl compounds to unsaturated imines in an enantioselective fashion has not been reported so far, to the best of our knowledge (Scheme 1).[13] In this paper, we describe the first example of asymmetric conjugate addition of methyl malonate to unsaturated *N*-tosyl imines as an efficient procedure to access chiral δ-amino acid derivatives.

Results and Discussion

In this investigation we have used *N*-tosyl imines **2** as electrophiles since the reactivity of imines toward nucleophilic attack is significantly increased by the presence of strong electron-withdrawing groups on the azomethinic nitrogen

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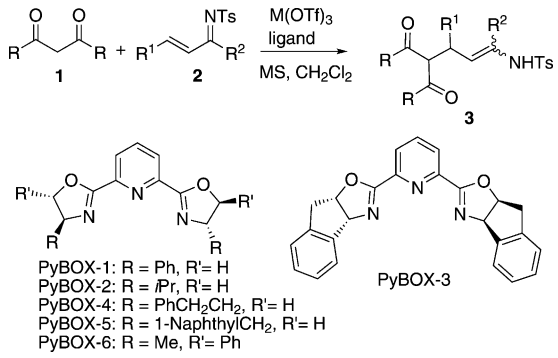


Scheme 1. Conjugate addition of 1,3-dicarbonyl compounds to unsaturated *N*-sulfonyl imines and catalysts used in this study.

atom. For the optimization of the reaction conditions, we studied the addition of dimethyl malonate (**1**, R = OMe) to *N*-tosyl imine **2a** ($R^1 = R^2 = Ph$) by using complexes of trivalent metals and PyBOX ligands (Scheme 1, Table 1).[14]

Table 1. Enantioselective addition of 1,3-dicarbonyl compounds **1** to unsaturated imine **2a** ($R^1 = R^2 = Ph$) according to Scheme 1.[a]

Entry	M	Ligand	R	*T*	*t* [h]	Yield [%][b]	e.r.[c]
1[d]	La	PyBOX-1	MeO	RT	48	–[e]	–
2	La	PyBOX-1	MeO	RT	24	81	93:7
3	Yb	PyBOX-1	MeO	RT	48	–[e]	–
4	Sc	PyBOX-1	MeO	RT	48	–[e]	–
5	In	PyBOX-1	MeO	RT	48	–[e]	–
6	La	PyBOX-2	MeO	RT	24	65	46:54
7	La	PyBOX-3	MeO	RT	106	25	56:44
8	La	PyBOX-4	MeO	RT	16	60	47:53
9	La	PyBOX-5	MeO	RT	42	59	56:44
10	La	PyBOX-6	MeO	RT	24	86	78:22
11	La	PyBOX-1	MeO	0 °C	64	63	96:4
12	La	PyBOX-1	EtO	RT	48	73	91.5:8.5
13	La	PyBOX-1	*i*PrO	RT	120	16	–
14	La	PyBOX-1	Me	RT	170	69	68:32
15	La	PyBOX-1	–[f]	RT	48	–[e]	–

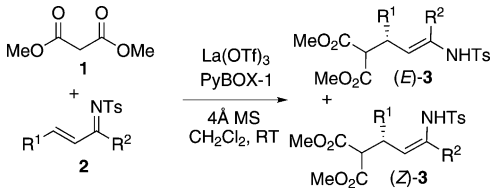
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.12 mmol), ligand (0.012 mmol), $M(OTf)_3$ (0.012 mmol), 4 Å MS (20 mg), CH_2Cl_2 (0.8 mL). [b] Yield of isolated product. [c] Only for the major (*E*)-diastereomer. Determined by HPLC analysis with chiral stationary phases. [d] Reaction carried out without MS. [e] No reaction observed after 48 h. [f] Malononitrile was used as the nucleophile.

When the reaction was carried out in the presence of the $La(OTf)_3$/PyBOX-1 in dichloromethane we did not observe any advance of the reaction after 24 h. However, after addition of 4 Å molecular sieves (MS)[15] the reaction proceeded smoothly to give compound **3a** (R = OMe, $R^1 = R^2 = Ph$) as an approximately 9:1 mixture of diastereomers with a 93:7 enantiomeric ratio (e.r.) for the major *E* diastereomer (Table 1, entry 1). The geometry of the double bond was assigned as *E* for the major diastereomer and *Z* for the minor one by NOESY experiments.[16] These results contrast with those reported for the Cu^I-catalyzed addition of diethylzinc to related unsaturated imines, which gave the *Z* isomers as the major products.[11] On the other hand, no cyclization to the corresponding lactam was observed under the reaction conditions. Yb^{III}, Sc^{III}, and In^{III} triflates in combination with PyBOX-1 were also tested (entries 3–5) although we did not observe any advance of the reaction. We also tested different PyBOX ligands with $La(OTf)_3$ (entries 6–10), although none of them provided better results than PyBOX-1. The use of toluene, hexane, or THF was prevented due to the low solubility of the imine in these solvents. Finally, the enantioselectivity of the reaction could be increased up to 96:4 e.r. by carrying out the reaction at 0 °C, although with a loss of yield (entry 11). The effect of the substituent R attached to the carbonyl group of the nucleophile was also tested. First we tested the use of other malonate esters. Diethyl malonate (**1**, R = OEt) performed similarly to dimethyl malonate providing the expected addition product (**3**, R = OEt, $R^1 = R^2 = Ph$) with 73% yield and 91.5:8.5 e.r. (entry 12). However, increasing the bulk of the alkoxy group as in diisopropyl malonate (**1**, R = O*i*Pr) produced a serious decrease on the reaction rate and the conjugate addition product was obtained in only 16% yield after 120 h. On the other hand, 2,4-pentanedione (**1**, R = Me) reacted slowly with imine **2a** to give the corresponding product (**3**, R = Me, $R^1 = R^2 = Ph$) in 59% yield, but with low diastereo- and enantioselectivity (entry 14). Finally, malononitrile did not react under the optimized conditions.

Next, we studied the scope of the addition of dimethyl malonate (**1**, R = OMe) to different imines **2** under the optimized conditions (Table 2). The reaction can be carried out with imines bearing an aromatic ring attached to the β-carbon atom substituted with either electron-donating or -withdrawing substituents (Table 2, entries 1–8), to give the expected products with good diastereoselectivities (from 71:29 to 97:3) favoring the *E* diastereomer and high enantiomeric ratios (from 84.4:15.5 to 96:4). R^1 can be also a heterocyclic furanyl ring (entries 9, 10). When R^1 was a phenyl group substituted with electron-withdrawing groups, good yields of the addition products could be obtained after 24 h. However, when R^1 was an aromatic ring substituted with an electron-donating group, or an electron-rich heterocycle (entries 8–10), the reaction required longer times and the corresponding products were obtained with slightly lower yields. Finally, the reaction allowed imines with R^1 as an aliphatic group. Imine **2i** ($R^1 = Me$) reacted with dimethyl malonate to give the expected product with almost quantitative yield, good diastereoselectivity, and 87.5:12.5 e.r. for the major diastereomer (entry 11). However, imine **2j** bearing a bulky *tert*-butyl group did not react under similar conditions (entry 12). The R^2 group attached to the imine was also amenable to variation (entries 13–18). Aromatic rings bearing either electron-donating or -withdrawing groups were permitted without much influence on the enantioselectivity of the reaction. The study with unsaturated imines **2** in which R^2 is aliphatic (Me) was not possible because of enolization of the *N*-sulfonyl imine during the preparation of the starting materials.

The absolute stereochemistry of compound **3a** was established by chemical correlation with compound **4** of known stereochemistry. A sample of compound (*E*)-**3a** (e.r. = 91:9)

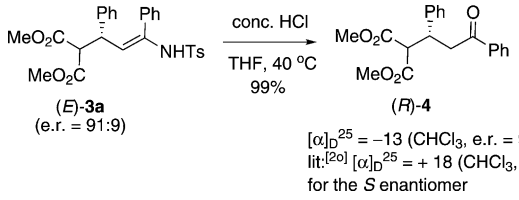
Table 2. Enantioselective addition of dimethyl malonate to unsaturated imines catalyzed by $La(OTf)_3$/PyBOX-1.[a]



Entry	2	R^1	R^2	t [h]	3	Yield [%][b]	d.r. (E/Z)	e.r. (E/Z)[c,d]
1	**a**	Ph	Ph	24	**a**	81	89:11	93:7/nd
2[e]	**a**	Ph	Ph	64	**a**	63	95:5	96:4/nd
3	**b**	4-FC_6H_4	Ph	24	**b**	88	90:10	93:7/nd
4[e]	**b**	4-FC_6H_4	Ph	64	**b**	66	97:3	95:5/nd
5	**c**	4-ClC_6H_4	Ph	24	**c**	93	88:12	93:7/nd
6	**d**	4-BrC_6H_4	Ph	24	**d**	99	77:23	92.5:7.5/nd
7	**e**	4-$NO_2C_6H_4$	Ph	24	**e**	97	87:13	95:5/nd
8	**f**	4-$MeOC_6H_4$	Ph	72	**f**	80	71:29	84.5:15.5/nd
9	**g**	2-furanyl	Ph	45	**g**	78	79:21	97:3/76:24
10	**h**	3-furanyl	Ph	45	**h**	66	84:16	92.5:7.5/80:20
11	**i**	Me	Ph	24	**i**	98	88:12	87.5:12.5/77:23
12	**j**	*t*Bu	Ph	64	**j**	–[f]	–	–
13	**k**	Ph	4-FC_6H_4	24	**k**	67	88:12	93:7/77.5:22.5
14	**l**	Ph	4-ClC_6H_4	24	**l**	80	84:16	90:10/73:27
15	**m**	Ph	4-$NO_2C_6H_4$	24	**m**	84	80:20	91:9/74.5:25.5
16	**n**	Ph	4-$MeOC_6H_4$	24	**n**	86	71:29	90:10/71:29
17	**o**	Ph	2-FC_6H_4	24	**o**	84	76:24	91:9/64:36
18	**p**	Ph	3-$NO_2C_6H_4$	24	**p**	99	82:18	92:8/74:26

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.12 mmol), PyBOX-1 (0.012 mmol), $La(OTf)_3$ (0.012 mmol), 4 Å MS (20 mg), CH_2Cl_2 (0.8 mL), RT. [b] Yield of isolated product. [c] Determined by HPLC analysis with chiral stationary phases. [d] nd = not determined. [e] Reaction carried out at 0 °C. [f] No reaction was observed after 64 h.

was hydrolyzed upon treatment with HCl in THF at 40 °C to give ketone **4** in quantitative yield without loss of optical purity (Scheme 2). By comparison of the optical rotation



Scheme 2. Hydrolysis and determination of the absolute stereochemistry of compound (*E*)-**3a**.

sign and chiral HPLC retention times of compound **4** obtained in this way with those described in the literature for its *S* enantiomer,[2o] we established the configuration of the stereogenic center of (*E*)-**3a** (Table 2, entry 1) to be *R*.[17] For the rest of compounds **3b**–**p**, the stereochemistry was assigned upon the assumption of a common stereochemical mechanism. These results indicate the preference of methyl malonate to attack from the *Si* face of the double bond of the unsaturated imine **2**. Taking into account previous studies on La^{III}/PyBOX-catalyzed reactions,[14a,18] we propose the participation of an octa-coordinated La^{III} species with both the 1,3-dicarbonyl compound and the imine coordinated to the metal center (Figure 1).[19] In this complex, the unsaturated imine **2**, in its s-*trans* conformation would be oriented to avoid the steric interaction of the R^2 and tosyl groups with the phenyl group of the ligand, thus leading to the conjugate addition product **3** with the *R* configuration at the stereogenic center and the *E* geometry at the double bond.

Enamines **3** can be used as starting materials for the synthesis of optically active nitrogenated compounds, such as δ-aminoesters and piperidones (Scheme 3). Thus, hydrogenation of (*E*)-**3a** over Pd/C gave a 95% yield of a 75:25 mixture of two diastereomeric δ-aminodiesters **5** and **6**, favoring the (*R*,*S*)-diastereomer **5**. Both diastereomers **5** and **6** could be separated after column chromatography and subjected to chemical transformations separately. Decarboxylation of either **5** or **6** upon treatment with tetraethylammonium hydroxide[20] in DMSO gave the monoesters **7** and **8** in 70 and

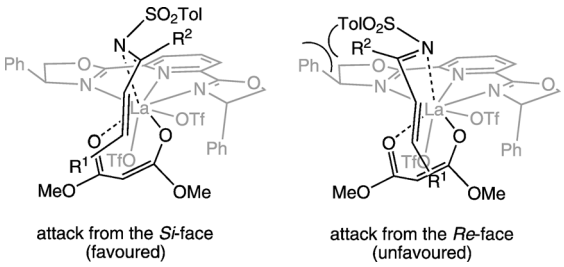
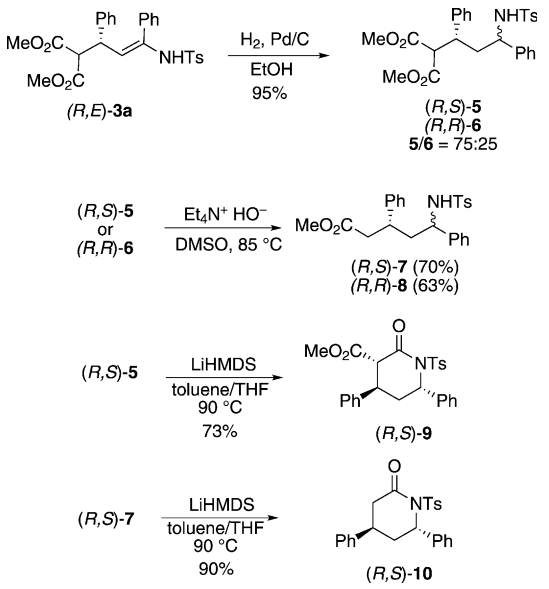


Figure 1. Proposed stereochemical model for the $La(OTf)_3$/PyBOX-1-catalyzed enantioselective conjugate addition of methyl malonate to α,β-unsaturated *N*-sulfonyl imines **2**.

60% yield, respectively. Finally, we carried out the lactamization of compounds **5** and **7** to give the chiral piperidones **9**[21] and **10**, respectively, by basic treatment with lithium hexamethyl disilazide (LiHMDS) in toluene.[22]

Conclusion

In summary, we have reported the first enantioselective conjugate addition of dimethyl malonate to α,β-unsaturated *N*-tosylimines to give the corresponding γ-dehydro-δ-amino diesters bearing a stereogenic center at the allylic position, which is catalyzed by La^{III}/PyBOX complexes. The reaction provides the *E*-enamine as the major diastereomer with



Scheme 3. Synthesis of δ-aminoesters and lactams from **3a**.

good yields and enantioselectivities. The enamino esters are effective synthons for the preparation of optically active δ-aminoesters bearing two stereogenic centers at the β and δ-positions, and for the preparation of optically active lactams.

Experimental Section

General methods: Commercial reagents were used as purchased. Dichloromethane was freshly distilled from CaH_2. Powdered 4 Å MS were stored in the oven at 140 °C and left to reach room temperature in a dissicator prior to use. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin-layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. NMR spectra were recorded in the deuterated solvents as stated, using residual nondeuterated solvent as an internal standard ($CHCl_3$: $\delta = 7.26$ for ^1H and 77.16 ppm for ^{13}C). The carbon type was determined by DEPT experiments. Specific optical rotations were measured using sodium light (D line 589 nm). Mass spectra (ESI) were recorded on a mass spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV. Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector by using chiral stationary columns from Daicel. Retention times are given in min.

General procedure for the enantioselective conjugate addition of methyl malonate to α,β-unsaturated *N*-sulfonylimines 2: Anhydrous $La(OTf)_3$ (7.3 mg, 0.0125 mmol) and PyBOX-1 (4.6 mg, 0.012 mmol) were introduced to a Schlenk tube and it was filled with nitrogen. Dry CH_2Cl_2 (0.4 mL) was added via syringe and the mixture was stirred for 30 min. Powdered 4 Å MS (20 mg) were then added followed by a solution of imine **2** (0.12 mmol) dissolved in dry CH_2Cl_2 (0.4 mL) and dimethyl malonate (35 μL, 0.3 mmol). The mixture was stirred at room temperature for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **3**. In general the minor *Z* diastereomer eluted first from the column followed by the major *E* diastereomer.

Dimethyl 2-[(*R*,*E*)-1,3-diphenyl-3-(tosylamino)allyl]malonate (3a): Chiral HPLC analysis: (Chiralpakl AD-H, hexane/*i*PrOH 80:20, 1 mL min^{-1}): *E* diastereomer, major enantiomer (*R*): $t_r = 13.9$ min, minor enantiomer (*S*): $t_r = 18.3$ min; *Z* diastereomer unresolved: $t_r = 65.3$ min.

Major E *diastereomer*: Oil; $[\alpha]_D^{20} = -76.0$ ($c = 1.0$ in $CHCl_3$, e.r. = 93:7); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.57$ (d, $J_{H,H} = 8.4$ Hz, 2H), 7.35–7.18 (m, 6H), 7.16 (d, $J_{H,H} = 8.4$ Hz, 2H), 6.96 (dd, $J_{H,H} = 8.1$, 2.4 Hz, 2H), 6.90 (dd, $J_{H,H} = 8.1$, 1.5 Hz, 2H), 6.05 (s, 1H), 5.95 (d, $J_{H,H} = 10.8$ Hz, 2H), 4.00 (t, $J_{H,H} = 10.5$ Hz, 1H), 3.77 (d, $J_{H,H} = 10.5$ Hz, 1H), 3.67 (s, 3H), 3.40 (s, 3H), 2.41 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.0$ (C), 167.7 (C), 143.7 (C), 141.2 (C), 136.4 (C), 135.8 (C), 135.3 (CH), 129.6 (CH), 129.1 (CH), 128.70 (CH), 128.69 (CH), 128.6 (CH), 127.7 (CH), 127.0 (CH), 117.2 (CH), 58.1 (CH), 52.6 (CH_3), 52.4 (CH_3), 44.1 (CH), 21.7 ppm (CH_3).

Minor Z *diastereomer*: Oil; $[\alpha]_D^{20} = -23.4$ ($c = 0.95$ in $CHCl_3$, e.r. = n.d.); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$ (s, 1H), 7.50 (d, $J_{H,H} = 8.1$ Hz, 2H), 7.36–7.32 (m, 2H), 7.22–7.05 (m, 8H), 6.70–6.69 (m, 2H), 5.45 (dd, $J_{H,H} = 10.8$, 0.3 Hz, 2H), 3.89 (t, $J_{H,H} = 10.5$ Hz, 1H), 3.74 (d, $J_{H,H} = 10.2$ Hz, 1H), 3.63 (s, 3H), 3.37 (s, 3H), 2.30 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.7$ (C), 167.7 (C), 143.4 (C), 138.8 (C), 137.8 (C), 137.3 (C), 136.5 (C), 129.7 (CH), 128.8 (CH), 128.6 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.4 (CH), 123.0 (CH), 57.8 (CH), 53.3 (CH_3), 52.8 (CH_3), 43.3 (CH), 21.6 ppm (CH_3); HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{27}NNaO_6S$: 516.1451 [M^++Na]; found: 516.1453.

Hydrogenation of compound (*R*,*E*)-3a: A solution of (*R*,*E*)-**3a** (140 mg, 0.29 mmol, e.r. = 93:7) in MeOH (12 mL) was stirred under a hydrogen atmosphere (balloon) in the presence of 5% Pd/C (4 mg) for 4 h. Then, the reaction mixture was filtered through a short pad of silica gel eluting with EtOAc. The solvent was removed under reduced pressure to give 134 mg (95%) of compound as an approximately 25:75 mixture of two diastereomers, which were separated after column chromatography on silica gel eluting with hexane/EtOAc (90:10 to 60:40). Order of elution: compound **6** (minor diastereomer) first, compound **5** (major diastereomer) second. Chiral HPLC analysis (Chiralpak IC, hexane/*i*PrOH 80:20, 1 mL min^{-1}): major diastereomer **5**, major enantiomer (1*R*,3*S*): $t_r =$ 55.6 min, minor enantiomer (1*S*,3*R*): $t_r = 63.6$ min; minor diastereomer **6**, major enantiomer (1*R*,3*R*): $t_r = 39.7$ min, minor enantiomer (1*S*,3*S*)-**5**: $t_r =$ 46.6 min.

*Major diastereomer (1*R,*3*S*)-**5**: Oil; $[\alpha]_D^{20} = -3.4$ ($c = 1.0$ in $CHCl_3$, e.r. = 93:7); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (d, $J_{H,H} = 8.4$ Hz, 2H), 7.30–7.27 (m, 3H), 7.24–7.17 (m, 3H), 7.08 (d, $J_{H,H} = 8.4$ Hz, 2H), 3.00–6.97 (m, 2H), 6.84–6.81 (m, 2H), 4.61 (d, $J_{H,H} = 6.0$ Hz, 1H), 3.77–3.70 (m, 1H), 3.72 (s, 3H), 3.59 (d, $J_{H,H} = 10.5$ Hz, 1H), 3.32 (s, 3H), 2.91 (td, $J_{H,H} = 11.2$ Hz, 1H), 2.45–2.26 (m, 2H), 2.37 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 168.5$ (C), 167.9 (C), 143.2 (C), 138.9 (C), 138.7 (C), 137.0 (C), 129.5 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.6 (CH), 127.3 (CH), 127.2 (CH), 58.4 (CH), 56.4 (CH), 52.7 (CH_3), 52.3 (CH_3), 42.3 (CH), 39.7 (CH_2), 21.6 ppm (CH_3).

*Minor diastereomer (1*R,*3*R*)-**6**: Oil; $[\alpha]_D^{20} = -2.0$ ($c = 0.6$ in $CHCl_3$, e.r. = 93:7); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (d, $J_{H,H} = 8.4$ Hz, 2H), 7.25–7.21 (m, 3H), 7.15–7.08 (m, 5H), 6.94–6.87 (m, 4H), 5.45 (d, $J_{H,H} = 6.6$ Hz, 1H), 4.08–4.01 (m, 1H), 3.77 (s, 3H), 3.59 (d, $J_{H,H} = 10.2$ Hz, 1H), 3.42 (td, $J_{H,H} = 10.2$, 3.0 Hz, 1H), 3.41 (s, 3H), 2.38 (s, 3H), 2.08–1.92 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 169.3$ (C), 168.0 (C), 143.0 (C), 142.0 (C), 139.5 (C), 137.8 (C), 129.5 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 57.7 (CH), 56.1 (CH), 53.0 (CH_3), 52.5 (CH_3), 43.4 (CH_2), 43.3 (CH), 21.6 ppm (CH_3); HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{29}NNaO_6S$: 516.1608 [M^++Na]; found: 518.1613.

Decarboxylation of compound (*R*,*S*)-5: A 25% solution of tetraethylammonium hydroxyde in MeOH (157 μL, 0.23 mmol) was added to a solution of compound **5** (95.4 mg, 0.19 mmol, e.r. = 91:9) in dimethylsulfoxide (5.2 mL) under nitrogen, and the reaction flask was introduced in a bath at 80 °C. Additional tetraethylammonium hydroxyde was added after 6 (157 μL, 0.23 mmol) and 24 h (53 μL, 0.08 mmol). After a total reaction time of 24 h, the reaction mixture was diluted with EtOAc (60 mL), washed with water (3×4 mL), brine (4 mL), and dried over $MgSO_4$. Purification by column chromatography eluting with hexane/EtOAc gave 9 mg (10%) of lactam **9** (see below), followed by 58.0 mg (70%) of compound **7**. Chiral HPLC analysis (Chiralpak IC hexane-*i*PrOH 80:20, 1 mL min^{-1}): major enantiomer: $t_r = 26.5$ min, minor enantiomer: $t_r =$ 29.1 min. Oil; $[\alpha]_D^{20} = -9.1$ ($c = 1.0$ in $CHCl_3$, e.r. = 91:9); ^1H NMR

(300 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J_{H,H} = 8.4$ Hz, 2H), 7.35–7.25 (m, 3H), 7.21–7.12 (m, 3H), 7.08 (d, $J_{H,H} = 8.4$ Hz, 2H), 7.05–6.97 (m, 2H), 6.91–6.82 (m, 2H), 5.09 (d, $J_{H,H} = 6.6$ Hz; NH), 3.88 (ddd, $J_{H,H} = 10.5$, 6.6, 5.4 Hz), 3.52 (s, 3H), 2.73 (m. 1H), 2.52 (m, 2H), 2.37 (s, 3H), 2.35–2.12 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.2$ (C), 143.0 (C), 142.2 (C), 139.6 (C), 137.2 (C), 129.4 (CH), 128.76 (CH), 128.75 (CH), 128.0 (CH), 127.8 (CH), 127.2 (CH), 127.1 (CH), 127.0 (CH), 56.4 (CH), 51.5 (CH_3), 42.2 (CH_2), 41.7 (CH_2), 38.7 (CH), 21.6 ppm (CH_3); HRMS (ESI): *m/z*: calcd for $C_{25}H_{27}NNaO_4S$: 460.1553 [M^++Na]; found: 460.1560.

Lactamization of compound (*R*,*S*)-5: A solution of compound **5** (27.7 mg, 0.056 mmol) in toluene (1.2 mL) under nitrogen was treated with 1 M LiHMDS in THF (112 μL, 0.112 mmol). The mixture was stirred at 90 °C for 18 h. Then, the reaction was quenched with 1 M HCl (1 mL), diluted with water (4 mL), extracted with dichloromethane (3×30 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give 19 mg (73%) of compound **9**: Oil; $[\alpha]_D^{20} = +2.1$ ($c = 0.8$ in $CHCl_3$, e.r. = 91:9); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.56$ (d, $J_{H,H} = 8.4$ Hz, 2H), 7.40–7.20 (m, 8H), 7.14 (d, $J_{H,H} = 8.4$ Hz, 2H), 7.10–6.98 (m, 2H), 5.90 (dd, $J_{H,H} = 5.1$, 2.4 Hz), 3.72 (d, $J_{H,H} = 12.0$ Hz, 1H), 3.58 (s, 3H), 3.50 (td, $J_{H,H} = 12.0$, 3.0 Hz, 1H), 2.59 (td, $J_{H,H} = 13.5$, 5.4 Hz, 1H), 2.40 (s, 3H), 2.21 ppm (dt, $J_{H,H} = 13.8$, 2.7 Hz), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 169.2$ (C), 166.8 (C), 144.3 (C), 140.0 (C), 139.5 (C), 135.9 (C), 129.8 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 126.8 (CH), 59.9 (CH), 58.3 (CH), 52.6 (CH_3), 37.8 (CH_2), 37.4 (CH), 21.6 ppm (CH_3); HRMS (ESI): *m/z*: calcd for $C_{26}H_{26}NO_5S$: 464.1526 [M^++H]; found: 464.1529.

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