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PAPER

A highly diastereoselective three-component tandem 1,4-conjugated addition–cyclization reaction to multisubstituted pyrrolidines†

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A highly diastereoselective three-component tandem 1,4-conjugate addition–cyclization reaction of diazoacetophenones with anilines and unsaturated ketoesters was developed. The reaction provides general, easy, and highly efficient access to multisubstituted pyrrolidines in good yield with high diastereoselectivity.

Introduction

Pyrrolidines are important structural motifs present in a myriad natural alkaloids and biologically active substances (Fig. 1).[1] Moreover, they also serve as building blocks and intermediates in the synthesis of natural products and medicinally relevant compounds.[2] Many methods have been developed for the construction of important heterocyclic compounds. However, the reported methods often suffer from poor diastereoselectivity, low efficiency, and less generality when applied to the synthesis of multisubstituted pyrrolidines.[3] The development of efficient methods to access pyrrolidine skeletons from simple, readily available starting materials with high stereoselective control is undoubtedly appealing in organic synthesis.

Multicomponent reactions[4] (MCRs) and cascade reactions[5] have received considerable attention because they enable the formation of several bonds and stereogenic centres in a single synthetic operation without the need for the isolation of intermediates. Transition metal catalyzed diazo decomposition reactions *via* metal carbenoid intermediates have a broad range of application in organic synthesis,[6] including those documented in our recent reports on MCRs.[7,8] Davies and Beckwith classified the metal carbenoids into three major types: acceptor, acceptor–acceptor, and donor–acceptor.[9] The three types of carbenoid intermediates display different reactivity and/or selectivity.[10] Due to the balanced reactivity and selectivity, donor–acceptor carbenoids offer many synthetic advantages over conventional carbenoids, which were demonstrated by a number of transition-metal catalyzed diazo decomposition reactions. In these reactions, good stereoselectivity has been obtained by using donor–acceptor carbenoids.[7c–g,8d,10w,11] However, due to the high reactivity of acceptor carbenoids such as those derived from diazoacetophenones, it has generally proved to be difficult to obtain high stereoselective control in transition metal catalyzed reaction.[11f,12]

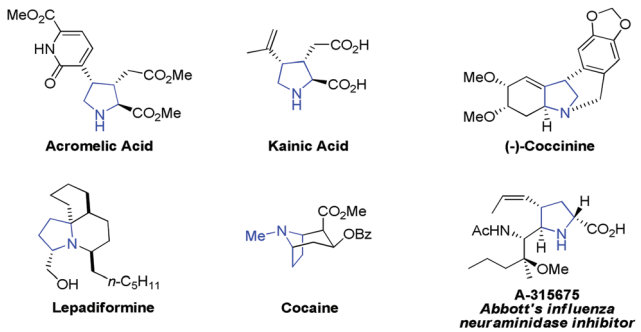

Fig. 1 Natural alkaloids and biologically active substances containing pyrrolidine motifs.

Recently, we reported a donor–acceptor carbenoid-initiated three-component reaction of α-aryl-substituted diazoacetates with anilines and β,γ-unsaturated α-keto esters.[8c] This reaction proceeds *via* 1,4-addition–cyclization to provide four diastereomeric pyrrolidines, which are subjected to sequential one-pot dehydration to afford 2,3-dihydropyrroles in poor diastereoselectivity. Herein, we report that an acceptor carbenoid-initiated three-component reaction of diazoacetophenones with anilines and β,γ-unsaturated α-keto esters *via* 1,4-conjugated addition–cyclization pathway, leading to multisubstituted pyrrolidines in good yields with high diastereoselectivity. This is an interesting example showing that acceptor carbenoids provide higher selectivity control than donor–acceptor carbenoids.

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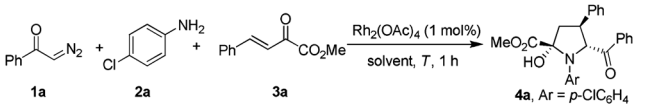
Results and discussion

We first investigated a model reaction of diazoacetophenone (**1a**), *p*-chloroaniline (**2a**), and (3*E*)-2-oxo-4-phenylbut-3-enoic acid methyl ester (**3a**) in CH_2Cl_2 at 40 °C using $Rh_2(OAc)_4$ (1 mol%) as a catalyst. To our delight, the desired three-component tandem 1,4-conjugated addition–cyclization pyrrolidine product **4a** was obtained in 55% yield with high diastereoselectivity (90 : 10) (Table 1, entry 1). This three-component tandem reaction almost produced only one diastereomer out of four possible diastereomers. Encouraged by the preliminary results, we next examined the effect of reaction parameters on product yield and diastereoselectivity, and the results are summarized in Table 1. It was found that the solvent had a significant effect on the product yield (Table 1, entries 1–4). While CH_2Cl_2 gave a reasonable 55% yield, a coordinating solvent, THF, afforded trace amounts of product (Table 1, entry 1 *vs.* entry 4). The effect of reaction temperature on the yield was also investigated. A significant decrease in the product yield was observed at lower reaction temperature (Table 1, entries 5 and 6). Having established the choice of solvent and reaction temperature, we next examined the effect of equivalent ratio of the reactants on the yield and diastereoselectivity. Higher yield and diastereoselectivity were obtained when the reaction was performed with higher equivalent ratio of **1a** : **2a** : **3a** (Table 1, entry 1 *vs.* entries 7 and 8). Thus, we established the following optimized reaction conditions: 1 mol% of $Rh_2(OAc)_4$ as the catalyst, CH_2Cl_2 as the solvent, and the reaction temperature of 40 °C with a substrate ratio of **1a** : **2a** : **3a** = 1.8 : 1.8 : 1. The reaction conditions gave the desired product **4a** in 69% yield with 96 : 4 dr (Table 1, entry 8).

With the optimized reaction conditions in hand, we then explored the generality of the three-component reaction with different substituted anilines, diazoacetophenones, and β,γ-unsaturated α-keto esters. As shown in Table 2, the current reaction was very tolerant to electronic properties of the substrates. Moderate to good yields and high diastereoselectivity were obtained

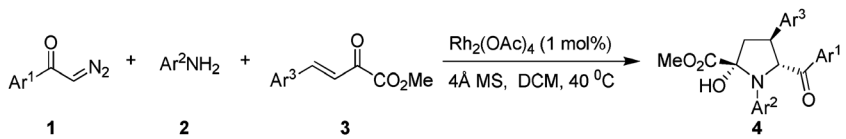
Table 1 Optimization of reaction conditions[a]



Entry	Solvent	*T*/°C	Yield[b] (%)	*syn* : *anti* dr[c]
1	DCM	40	55	90 : 10
2	DCE	40	23	—
3	Toluene	40	10	—
4	THF	40	trace	—
5	DCM	20	26	—
6	DCM	0	19	—
7[d]	DCM	40	60	95 : 5
8[e]	**DCM**	**40**	**69**	**96 : 4**

[a] Unless otherwise noted, the reaction was carried out on a 1.0 mmol scale in a solvent (1 mL) in the presence of $Rh_2(OAc)_4$ (1 mol%) for 1 h, and the ratio of **1a**/**2a**/**3a** was 1.2/1.2/1. [b] Isolated yield after column chromatography purification. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Carried out with **1a** (1.5 mmol), **2a** (1.5 mmol) and **3a** (1.0 mmol). [e] Carried out with **1a** (1.8 mmol), **2a** (1.8 mmol) and **3a** (1.0 mmol).

Table 2 Three-component reaction of diazoacetophenones with anilines and β,γ-unsaturated α-keto esters[a]



Entry	**1** (Ar^1)	**2** (Ar^2)	**3** (Ar^3)	Product	Yield[b](%)	*syn* : *anti* dr[c]
1	**1a** (Ph)	**2a** (*p*-ClPh)	**3a** (Ph)	**4a**	69	96 : 4
2	**1a** (Ph)	**2b** (Ph)	**3a** (Ph)	**4b**	68	90 : 10
3	**1a** (Ph)	**2c** (*p*-FPh)	**3a** (Ph)	**4c**	60	89 : 11
4	**1a** (Ph)	**2d** (*p*-BrPh)	**3a** (Ph)	**4d**	54	94 : 6
5	**1a** (Ph)	**2e** (*m*-BrPh)	**3a** (Ph)	**4e**	73	91 : 9
6	**1a** (Ph)	**2f** (*p*-NO_2Ph)	**3a** (Ph)	**4f**	76	91 : 9
7	**1a** (Ph)	**2g** (*p*-CF_3Ph)	**3a** (Ph)	**4g**	45	91 : 9
8	**1a** (Ph)	**2h** (*p*-MePh)	**3a** (Ph)	**4h**	68	89 : 11
9	**1a** (Ph)	**2b** (Ph)	**3b** (*p*-FPh)	**4i**	80	94 : 6
10	**1a** (Ph)	**2b** (Ph)	**3c** (*p*-ClPh)	**4j**	84	94 : 6
11	**1a** (Ph)	**2b** (Ph)	**3d** (*p*-MeOPh)	**4k**	72	90 : 10
12	**1a** (Ph)	**2b** (Ph)	**3e** (*p*-MePh)	**4l**	76	93 : 7
13	**1a** (Ph)	**2b** (Ph)	**3f** (*m*-BrPh)	**4m**	71	91 : 9
14	**1a** (Ph)	**2b** (Ph)	**3g** (*m*-MePh)	**4n**	66	93 : 7
15	**1a** (Ph)	**2b** (Ph)	**3h** (2-thienyl)	**4o**	67	91 : 9
16	**1b** (*p*-ClPh)	**2b** (Ph)	**3a** (Ph)	**4p**	62	87 : 13
17	**1c** (*p*-BrPh)	**2b** (Ph)	**3a** (Ph)	**4q**	79	93 : 7
18	**1d** (*p*-MeOPh)	**2b** (Ph)	**3a** (Ph)	**4r**	65	94 : 6
19	**1e** (2-furyl)	**2b** (Ph)	**3a** (Ph)	**4s**	84	95 : 5

[a] The reaction was carried out on a 1.0 mmol scale in the presence of $Rh_2(OAc)_4$ (1 mol%) in CH_2Cl_2 (1 mL) at 40 °C for 1 h, and the ratio of **1**/**2**/**3** was 1.8/1.8/1. [b] Isolated yield after column chromatography purification. [c] Determined by ^{1}H NMR of the crude reaction mixture.

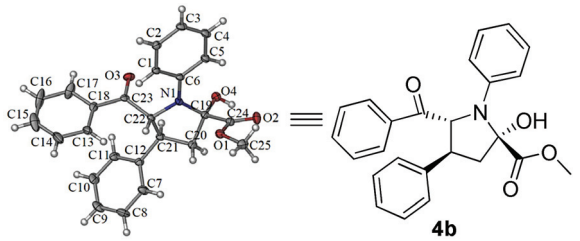
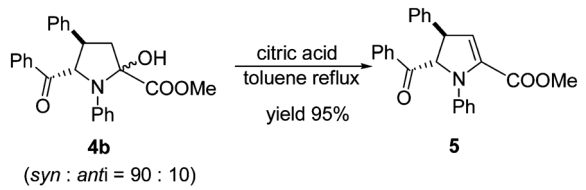
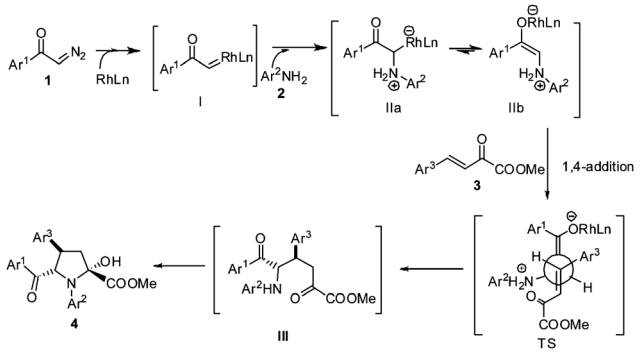


Fig. 2 X-Ray crystal structure of *syn*-**4b**.



Scheme 1 Dehydration of **4b**.



Scheme 2 Proposed reaction mechanism for the formation of **4**.

with substrates bearing either electron-withdrawing or donating groups at either the *para* or *meta*-position on the aryl rings of anilines and β,γ-unsaturated α-keto esters (Table 2, entries 1–15). The substitution of diazo compounds **1** with electron-withdrawing or donating groups at the *para*-position was very well tolerated in the reaction, leading to the multisubstituted pyrrolidine products in good yields with high diastereomeric ratios (Table 2, entries 16–18). Good yield (84%) and high diastereoselectivity (95 : 5 dr) were also observed in the reaction with the diazo compound **1e** bearing a heteroaromatic substituent (Table 2 entry 19).

The relative stereochemistry of the pyrrolidine product was established by single-crystal X-ray analysis of major isomer *syn*-**4b** (Fig. 2).†

In order to determine the relative configuration of the minor diastereomer, a mixture of **4b** (*syn* : *anti* = 90 : 10) was cleanly converted to a single dehydration product **5** (Scheme 1), indicating the minor *anti* isomer is in an opposite relative absolute configuration at the C-2 position.

As shown in Scheme 2, $Rh_2(OAc)_4$-catalyzed decomposition of diazoacetophenones **1** gave corresponding carbenoids **I**. Attack of the lone electron pair of anilines **2** by the carbenoids **I** gave ammonium ylide intermediates **II**. It was proposed that the three-component reaction proceeded through the ammonium ylide intermediates (**II**) trapping process.[8c] To rationalize the resulting stereoselective outcome of the product formation, we propose here that the enolate form **IIb** is more likely to be trapped by the β,γ-unsaturated α-keto esters **3** *via* a 1,4-addition fashion to result in intermediates **III** through a transition state (TS). Products **4** were formed from an intramolecular ring closure of **III** under the reaction conditions.

Conclusion

In summary, we have developed a three-component tandem 1,4-conjugated addition–cyclization reaction of diazoacetophenones with anilines and β,γ-unsaturated α-keto esters. The present reaction performed well over a broad range of substrates to give the desired multisubstituted pyrrolidine products in moderate to high yields (up to 84%) with high diastereoselectivity. Further investigation on its asymmetric variant is in progress in our laboratory.

Experimental section

General

All moisture sensitive reactions were performed under an argon atmosphere in a well-dried reaction flask. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane ($ClCH_2CH_2Cl$) were freshly distilled over calcium hydride, toluene and THF from sodium benzophenone ketyl, respectively, prior to use. All commercially available reagents were directly used as received from vendors, unless otherwise stated. ^1H and ^{13}C NMR spectra were recorded on a Bruker-500 MHz or a Bruker-400 MHz spectrometer. Chemical shifts are reported in ppm relative to the internal standard tetramethylsilane (δ = 0 ppm) for ^1H NMR and deuteriochloroform (δ = 77.00 ppm) for ^{13}C NMR spectroscopy. HRMS spectra were recorded on Bruker micrOTOF-II mass spectrometer.

General procedure for the one-pot three-component tandem reaction of diazoacetophenones with anilines and β,γ-unsaturated α-ketoesters

To a stirred solution of $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol), anilines **2** (1.8 mmol) and β,γ-unsaturated α-ketoesters **3** (1 mmol) in CH_2Cl_2 (2 mL) was added a solution of diazoacetophenones (1.8 mmol) in CH_2Cl_2 (1 mL) over 1 h *via* a syringe pump at 40 °C. After completion of the addition, the reaction mixture was cooled to room temperature. Solvent was removed, and a portion of crude product was subjected to ^1H NMR analysis for determination of the product ratio. The crude product was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether = 1 : 40 to 1 : 10) to give the corresponding three-component products **4**.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-1-(4-chlorophenyl)-2-hydroxy-4-phenylpyrrolidine-2-carboxylate (4a).** ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.79 (d, *J* = 7.8 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.35–7.29 (m, 7 H), 7.06 (d, *J* = 8.9 Hz, 2 H), 6.69 (d, *J* = 8.9 Hz, 2 H), 5.67 (d, *J* = 7.2 Hz, 1 H), 4.60 (s, 1 H), 3.78–3.73 (m, 4 H), 2.83–2.78 (m, 1 H), 2.71–2.66

(m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.63, 172.71, 141.97, 139.77, 134.74, 134.07, 129.11, 128.97, 128.70, 128.62, 127.78, 127.57, 124.96, 116.29, 91.88, 73.03, 53.40, 49.80, 47.58; HRMS (ESI) calcd for $C_{25}H_{22}ClNNaO_4$ $[M + Na]^+$ = 458.1130, found 458.1185.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxyl-1,4-diphenylpyrrolidine-2-carboxylate (4b).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.83 (d, J = 7.5 Hz, 2 H), 7.54(t, J = 7.4 Hz, 1 H), 7.35–7.29 (m, 7 H), 7.39–7.28 (m, 7 H), 7.17–7.12 (m, 2 H), 6.81–6.76 (m, 3H), 5.76 (d, J = 7.1 Hz, 1 H), 4.74 (s, 1 H), 3.80–3.74 (m, 4 H), 2.86–2.80 (m, 1 H), 2.75–2.70 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.07, 172.94, 143.24, 140.16, 134.86, 133.90, 129.17, 128.91, 128.77, 128.65, 128.50, 127.66, 127.59, 119.93, 114.99, 91.84, 72.90, 53.23, 49.92, 47.48; HRMS (ESI) calcd for $C_{25}H_{23}ClNNaO_4$ $[M + Na]^+$ = 424.1519, found 424.1528.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-1-(4-fluorophenyl)-2-hydroxy-4-phenylpyrrolidine-2-carboxylate (4c).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.81(d, J = 7.9 Hz, 2 H), 7.52 (t, J = 7.3 Hz, 1 H), 7.34–7.28 (m, 7 H), 6.84–6.69 (m, 4 H), 5.63 (d, J = 7.6 Hz, 1 H), 4.67 (s, 1 H), 3.80–3.69 (m, 4 H), 2.85–2.79 (m, 1 H), 2.70–2.65 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.86, 172.85, 139.86, 139.69, 134.85, 133.95, 128.94, 128.79, 128.65, 128.53, 127.83, 127.72, 127.57, 116.59, 116.52, 115.84, 115.62, 92.10, 73.50, 53.29, 49.72, 47.57; HRMS (ESI) calcd for $C_{25}H_{22}FNNaO_4$ $[M + Na]^+$ = 442.1425, found 442.1507.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-1-(4-bromophenyl)-2-hydroxy-4-phenylpyrrolidine-2-carboxylate (4d).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.79 (d, J = 7.5 Hz, 2 H), 7.52(t, J = 7.4 Hz, 1 H), 7.35–7.27 (m, 7 H), 7.20 (d, J = 9.0 Hz, 2 H), 6.64 (d, J = 9.0 Hz, 2 H), 5.67 (d, J = 7.3 Hz, 2 H), 4.59 (s, 1 H), 3.75–3.74 (m, 4 H), 2.80–2.77 (m, 4 H), 2.70–2.69 (m, 4 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.56, 172.66, 142.44, 139.77, 134.74, 134.08, 131.99, 128.97, 128.84, 128.70, 128.61, 127.79, 127.57, 116.72, 112.32, 91.86, 72.97, 53.40, 49.80, 47.57; HRMS (ESI) calcd for $C_{25}H_{22}BrNNaO_4$ $[M + Na]^+$ = 502.0624 found 502.0616.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-1-(3-bromophenyl)-2-hydroxy-4-phenylpyrrolidine-2-carboxylate (4e).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.78 (d, J = 7.5 Hz, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.35–7.28 (m, 8 H), 6.96 (t, J = 8.3 Hz, 1 H), 6.90 (d, J = 7.2 Hz, 2 H), 6.67 (d, J = 7.5 Hz, 2 H), 5. 67 (d, J = 7.2 Hz, 2 H), 4.64 (s, 1 H), 3.77–3.72 (m, 4 H), 2.82–2.78 (m, 1 H), 2.71–2.66 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.52, 172.57, 144.64, 139.86, 134.81, 130.45, 129.00, 128.73, 128.70, 128.64, 127.81, 127.58, 123.15, 122.99, 118.02, 113.68, 91.86, 72.87, 53.44, 49.83, 47.54; HRMS (ESI) calcd for $C_{25}H_{22}BrNNaO_4$ $[M + Na]^+$ = 502.0624 found 502.0636.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxyl-1-(4-nitrophenyl)-4-phenylpyrrolidine-2-carboxylate (4f).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.01 (d, J = 7.3 Hz, 2 H), 7.73 (d, J = 7.3 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 2 H), 7.36–7.30 (m, 7 H), 6.71 (d, J = 5.1 Hz, 2H), 5.77(d, J = 7.6 Hz, 2 H), 4.57 (s, 1 H), 3.82–3.75 (m, 4 H), 2.86–2.81 (m, 4 H), 2.74–2.69 (m, 4H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 199.09, 172.15, 148.79, 140.25, 139.12, 134.46, 129.12, 128.88, 128.64, 128.08, 127.57, 125.67, 114.10, 91.77, 72.68, 53.75, 49.60, 47.67, 29.68; HRMS (ESI) calcd for $C_{25}H_{22}N_2NaO_6$ $[M + Na]^+$ = 469.1370 found 469.1398.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxy-4-phenyl-1-(4-(trifluoromethyl)phenyl)pyrrolidine-2-carboxylate (4g).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.79 (d, J = 7.8 Hz, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.36–7.32 (m, 9 H), 6.76 (d, J = 8.0 Hz, 1 H), 5.75 (d, J = 7.1 Hz, 1 H), 4.63 (s, 1 H), 3.76–3.73 (m, 4 H), 2.85–2.79 (m, 1 H), 2.74–2.68 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.14, 172.50, 146.01, 139.71, 134.68, 134.23, 129.03, 128.92, 128.78, 128.62, 127.88, 127.73, 127,57, 126.51, 126.48, 114.46, 91.79, 72.65, 53.47, 49.82, 47.58; HRMS (ESI) calcd for $C_{26}H_{22}F_3NNaO_4$ $[M + Na]^+$ = 492.1393 found 492.1422.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxyl-4-phenyl-1-*p*-tolylpyrrolidine-2-carboxylate (4h).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.81 (d, J = 7.6 Hz, 2 H), 7.52 (t, J = 7.4 Hz, 1 H), 7.35–7.27 (m, 7 H), 6.91 (d, J = 8.3 Hz, 2 H), 6.68 (d, J = 8.6 Hz, 2 H), 5.71 (d, J = 7.1 Hz, 2 H), 4.70 (s, 1 H), 3.74–3.70 (m, 4 H), 2.83–2.77 (m, 1 H), 2.72–2.67 (m, 1 H), 2.17 (s, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.38, 172.96, 140.81, 140.3836, 134.89, 133.86, 129.74, 129.20, 128.90, 128.65, 128.63, 127.85, 127.59, 115.14, 91.87, 73.09, 53.19, 49.97, 47.45, 20.35; HRMS (ESI) calcd for $C_{26}H_{25}NNaO_4$ $[M + Na]^+$ = 438.1676 found 438.1709.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-4-(4-fluorophenyl)-2-hydroxy-1-phenylpyrrolidine-2-carboxylate (4i).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.89 (d, J = 8.0 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.43–7.40 (m, 2 H), 7.36–7.32 (m, 2 H), 7.17 (t, J = 7.8 Hz, 2 H), 7.06 (t, J = 8.5 Hz, 2 H), 6.85–6.80 (m, 3 H), 5.71 (d, J = 7.4 Hz, 1 H), 4.77 (s, 1 H), 3.83–3.79 (m, 4 H), 2.84–2.79 (m, 1 H), 2.76–2.72 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.81, 172.94, 143.14, 134.78, 134.02, 129.20, 129.15, 128.73, 128.60, 120.08, 115.88, 115.67, 115.00, 91.75, 73.00, 53.30, 49.88, 46.72; HRMS (ESI) calcd for $C_{25}H_{22}FNNaO_4$ $[M + Na]^+$ = 442.1425 found 442.1406.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-4-(4-chlorophenyl)-2-hydroxy-1-phenylpyrrolidine-2-carboxylate (4j).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.87 (d, J = 7.6 Hz, 2 H), δ7.55 (t, J = 7.5 Hz, 1 H), 7.39–7.35 (m, 2 H), 7.31–7.27 (m, 3 H), 7.12 (t, J = 7.8 Hz, 2 H), 6.80–6.75 (m, 3 H), 5.66–5.64 (d, J = 7.1 Hz, 1 H), 4.72 (s, 1 H), 3.76–3.71 (m, 4 H), 2.77–2.67 (m, 2 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.74, 172.87, 143.07, 138.79, 134.67, 134.09, 133.45, 129.22, 129.06, 128.95, 128.77, 128.62, 120.13, 115.03, 91.73, 72.86, 60.35, 53.31, 49.79, 46.73; HRMS (ESI) calcd for $C_{25}H_{22}ClNNaO_4$ $[M + Na]^+$ = 458.1130 found 458.1142.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxy-4-(4-methoxyphenyl)-1-phenylpyrrolidine-2-carboxylate (4k).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.87 (d, J = 7.6 Hz, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.36 (d, J = 7.1 Hz, 2 H), 7.28–7.23 (m, 2 H), 7.12 (d, J = 7.3 Hz, 2 H), 6.85 (d, J = 8.6 Hz, 2 H), 6.77–6.73 (m, 2 H), 5.67 (d, J = 7.1 Hz, 1 H), 4.65 (s, 1 H), 3.80 (s, 3 H), 3.74–3.69 (m, 4 H), 2.79–2.73 (m, 1 H), 2.69–2.64 (m, 1H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.24, 173.03, 159.05, 143.30,

134.94, 133.89, 132.18, 129.20, 128.90, 128.69, 128.67, 119.94, 115.01, 114.30, 91.81, 73.20, 55.31, 53.27, 50.08, 46.84; HRMS (ESI) calcd for $C_{26}H_{25}NNaO_5$ $[M + Na]^+$ = 454.1625 found 454.1667.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxy-1-phenyl-4-*p*-tolylpyrrolidine-2-carboxylate (4l).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.84 (d, J = 7.9 Hz, 2 H), 7.54 (t, J = 7.4 Hz, 1 H), 7.36–7.33 (m, 2 H), 7.22–7.21 (m, 2 H), 7.14–7.10 (m, 4 H), 6.78–6.74 (m, 3 H), 5.69 (d, J = 7.1 Hz, 2 H), 4.67 (S, 1 H), 3.74–3.70 (m, 4 H), 2.80–2.75 (m, 1 H), 2.68–2.66 (m, 1 H), 2.35 (S, 3 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.27, 172.98, 143.24, 137.33, 137.14, 134.83, 133.89, 129.57, 129.17, 128.67, 128.64, 127.44, 119.89, 114.95, 91.80, 73.04, 53.25, 50.03, 47.11, 21.04; HRMS (ESI) calcd for $C_{26}H_{25}NNaO_4$ $[M + Na]^+$ = 438.1676 found 438.1696.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-4-(3-bromophenyl)-2-hydroxy-1-phenylpyrrolidine-2-carboxylate (4m).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.87 (d, J = 7.5 Hz, 2 H), 7.56–7.51 (m, 1 H), 7.24–7.23 (m, 1 H), 7.20–7.18 (m, 1 H), 7.13 (t, J = 8.0 Hz, 2 H), 6.79–6.75 (m, 3 H), 5.67 (d, J = 6.85 Hz, 1 H), 4.68 (s, 1 H), 3.74 (s, 1 H), 3.72–3.71 (m, 1 H), 2.78–2.69 (m, 2 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.61, 172.84, 143.07, 142.61, 134.70, 134.09, 130,82, 130.55, 130.42, 129.21, 128.77, 128.63, 128.51, 126.42, 122.93, 120.16, 115.08, 91.70, 72.69, 53.31, 49.59, 46.89; HRMS (ESI) calcd for $C_{25}H_{22}BrNNaO_4$ $[M + Na]^+$ = 502.0624 found 501.0628.

(2*S,4*S**,5*R**)-Methyl-5-benzoyl-2-hydroxy-1-phenyl-4-*m*-tolylpyrrolidine-2-carboxylate (4n).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.81 (d, J = 7.4 Hz, 2 H), 7.53 (t, J = 7.4 Hz, 1 H), 7.35–7.32 (m, 2 H), 7.22–7.19 (m, 1 H), 7.12–7.09 (m, 5 H), 6.79–6.74 (m, 3 H), 6.71 (d, J = 7.2 Hz, 1 H), 4.67 (s, 1 H), 3.74 (s, 3 H), 3.73–3.68 (m, 1 H), 2.82–2.77 (m, 1 H), 2.70–2.66 (m, 1 H), 2.31 (s, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.22, 172.97, 143.30, 140.05, 138.59, 134.97, 133.84, 129.16, 128.78, 128.67, 128.59, 128.39, 128.32, 124.59, 119.93, 115.02, 91.87, 72.97, 53.22, 49.88, 47.46, 21.35; HRMS (ESI) calcd for $C_{26}H_{25}NNaO_4$ $[M + Na]^+$ = 438.1676 found 438.1657.

(2*S,4*R**,5*R**)-Methyl-5-benzoyl-2-hydroxyl-1-phenyl-4-(thiophen-2-yl)pyrrolidine-2-carboxylate (4o).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.93 (d, J = 7.8 Hz, 2 H), δ7.55 (t, J = 7.5 Hz, 1 H), 7.40–7.36 (m, 2 H), 7.23 (d, J = 5.0 Hz, 1 H), 7.10(t, J = 8.0 Hz, 2 H), 6.91–6.87 (m, 2 H), 6.78–6.74 (m, 3 H), 5.63 (d, J = 7.6 Hz, 1 H), 4.57 (s, 1 H), 4.16–4.11 (m, 1 H), 3.71 (s, 3 H), 2.83–2.79 (m, 1 H), 2.74–2.70 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.42, 172.86, 143.20, 142.57, 135.93, 133.89, 129.12, 128.63, 128.61, 128.45, 127.00, 125.85, 124.47, 120.13, 115.01, 91.59, 73.17, 53.28, 50.18, 42.87; HRMS (ESI) calcd for $C_{23}H_{21}NNaO_4S$ $[M + Na]^+$ = 430.1083 found 430.1114.

(2*S,4*S**,5*R**)-Methyl-5-(4-chlorobenzoyl)-2-hydroxy-1,4-diphenylpyrrolidine-2-carboxylate (4p).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.82 (d, J = 8.6 Hz, 2 H), 7.35–7.29 (m, 7 H), 7.11 (t, J = 8.5 Hz, 2 H), 6.78 (t, J = 7.4 Hz, 1 H), 6.62–6.61 (m, 1 H), 5.55 (d, J = 8.1 Hz, 1 H), 4.57 (s, 1 H), 3.83–3.79 (m, 1 H), 3.71 (s, 1 H), 2.83–2.79 (m, 1 H), 2.68–2.64 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 199.54, 173.20, 143.34, 140.36, 139.33, 133.14, 130.15, 129.24, 129.01, 128.95, 127.85, 127.61, 120.25, 114.99, 91.97, 73.57, 53.39, 49.54, 47.55, 29.68; HRMS (ESI) calcd for $C_{25}H_{22}ClNNaO_4$ $[M + Na]^+$ = 458.1130 found 458.1167.

(2*S,4*S**,5*R**)-Methyl-5-(4-bromobenzoyl)-2-hydroxy-1,4-diphenylpyrrolidine-2-carboxylate (4q).** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.76 (d, J = 8.6 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.34–7.28 (m, 5 H), 7.13 (t, J = 7.4 Hz, 2 H), 6.80 (t, J = 7.4 Hz, 1 H), 6.75 (d, J = 8.0 Hz, 2 H), 5.56 (d, J = 8.1 Hz, 1 H), 4.61 (s, 1 H), 3.83–3.73 (m, 1 H), 3.73 (s, 1 H), 2.86–2.80 (m, 1 H), 2.71–2.66 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 199.69, 173.18, 143.36, 133.54, 131.90, 131.81, 130.18, 130.08, 129.20, 129.14, 128.97, 128.86, 127.83, 127.58, 120.24, 117.01, 114.98, 91.99, 73.58, 53.33, 49.46, 47.52; HRMS (ESI) calcd for $C_{25}H_{22}BrNNaO_4$ $[M + Na]^+$ = 502.0624 found 502.0639.

(2*S,4*S**,5*R**)-Methyl-2-hydroxy-5-(4-methoxybenzoyl)-1,4-diphenylpyrrolidine-2-carboxylate (4r).** ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm) 7.80 (d, J = 8.8 Hz, 2 H), 7.34–7.29 (m, 4 H), 7.34–7.28 (m, 5 H), 7.11 (t, J = 7.8 Hz, 2 H), 6.82–6.74 (m, 5 H), 5.72 (d, J = 6.6 Hz, 1 H), 4.86 (s, 1 H), 3.83 (s, 1 H), 3.75 (s, 1 H), 3.72–3.68 (m, 1 H), 2.81–2.76 (m, 1 H), 2.73–2.69 (m, 1 H), ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 199.52,172.82, 164.21, 143.23, 140.66, 131.12, 129.13, 128.91, 127.84, 127.57, 119.80, 114.96, 113.88, 91.75, 72.59, 55.43, 53.17, 50.11, 47.52; HRMS (ESI) calcd for $C_{26}H_{25}NNaO_5$ $[M + Na]^+$ = 454.1625 found 454.1660.

(2*S,4*S**,5*R**)-Methyl-5-(furan-2-carbonyl)-2-hydroxy-1,4-diphenylpyrrolidine-2-carboxylate (4s).** ^{1}H NMR (CDCl3, 500 MHz) δ (ppm) 7.54 (d, J = 3.5 Hz, 1 H), 7.50 (s, 1 H), 7.35–7.28 (m, 5 H), 7.13 (t, J = 8.0 Hz, 2 H), 6.79 (t, J = 7.4 Hz, 3 H), 6.43 (d, J = 2.5 Hz, 1 H), 5.23 (d, J = 8.5 Hz, 1 H), 4.57 (s, 1 H), 3.92–3.86 (m, 1 H), 3.67 (s, 1 H), 2.80–2.75 (m, 1 H), 2.64–2.60 (m, 1 H), ^{13}C-NMR (CDCl3, 100 MHz) δ (ppm) 189.10, 173.47, 150.21, 147.36, 143.59, 138.83, 129.21, 128.78, 127.75, 127.63, 127.56, 120.17, 114.90, 112.38, 92.07, 73.64, 53.40, 49.10, 47.82; HRMS (ESI) calcd for $C_{23}H_{21}NNaO_5$ $[M + Na]^+$ = 414.1312 found 414.1355.

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