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Organocatalytic Mannich Reactions on a Carbapenem Core – Synthesis of Mannich Bases and Bicyclic Diazanonanes

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An efficient diastereoselective synthesis of carbapenem Mannich bases was developed using organocatalysis. This method also provides a route to new highly functionalized diazabicyclo[4.2.1]nonanes of proposed biological significance.

Introduction

The Mannich reaction is one of the most important C–C bond formation reactions used for the construction of nitrogenous molecules in organic syntheses.[1] This reaction is useful for the preparation of synthetically and biologically significant optically enriched β-amino carbonyl compounds.[2] The Mannich reaction has also received continuous attention because the aminocarbonyl products can also undergo transformations to give useful β-peptides and β-lactams, which are present in several biologically active molecules.[3] Despite the immense importance of the direct-type Mannich reaction, it suffers from a number of limitations. The challenge of controlling the roles of the three components in one reaction vessel, i.e., the carbonyl donor, amine, and aldehyde, may lead to competitive side-reactions and consequently lower yields.[4]

Furthermore, only ketones or aldehydes can be used as enolate precursors, as other carbonyl groups such as esters and amides are inert to aminomethylation.[5] These limitations may be partially overcome by using preformed imines and enolates, and through the appropriate use of catalysts and reaction conditions.[6]

Traditionally, small organometallic catalysts were used to mediate asymmetric Mannich reactions.[7] List and co-workers developed the first organocatalytic asymmetric Mannich reaction, which was based on enamine activation of carbonyl compounds, and catalysed by L-proline.[1a,6a,8] The provision of well-defined mechanistic insight was crucial for the widespread recognition of this concept. Since then, several organocatalytic approaches to Mannich-type reactions have been successfully developed.[9] Nevertheless, applications of organocatalytic Mannich reactions for the derivatization of β-lactam scaffolds are rare.[10]

β-Lactam-containing substances, with their characteristic four-membered ring system, represent a highly desirable target for preparative organic chemistry. Firstly, β-lactam antibiotics, especially from the carbapenem class, play an immensely important role in the treatment of serious infections caused by extended-spectrum beta-lactamase (ESBLs) producing organisms.[11] The global challenge of microbial resistance[12] has triggered massive efforts to find new antibacterial agents, even among known classes such as β-lactams.[13] Secondly, the enhanced reactivity of β-lactams renders them useful as chiral building blocks for organic synthesis.[14] Medium-ring heterocycles, commonly encountered structural elements in biologically active natural products, may be prepared by ring expansion of β-lactams with neighbouring nitrogen nucleophiles.[15]

In this paper, we show how an organocatalytic Mannich reaction of a key β-lactam intermediate effectively leads to products that fall within both of the focus areas outlined above. Initially, we explored the substrate scope of the mild organocatalytic asymmetric Mannich reaction to synthesize β-lactam carbapenem intermediates of potential value for the preparation of new antibacterial agents. During this work, we discovered a new intramolecular rearrangement that leads to a class of hitherto unreported diazabicyclononanes with natural-product-like complexity.

Results and Discussion

We recently reported the mild completely stereoselective organocatalytic C–C bond functionalization of the carbapenem intermediate 4-nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-

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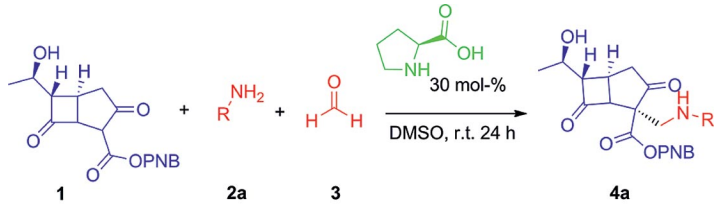
Table 1. Optimization of the catalytic asymmetric three-component Mannich reaction (PNB = *para*-nitrobenzyl).



1 2a 3 4a
R = 4-MeOC$_6$H$_4$ R = 4-MeOC$_6$H$_4$

Entry[a]	Catalyst/additive	Solvent	Yield [%][b]
1	L-proline	DMSO	55
2	L-proline	DMF	23
3	L-proline	MeCN	11
4	D-proline	DMSO	53
5	phenylalanine	DMSO	n.r.
6	pyrrolidine	DMSO	n.r.
7	pyrrolidine/benzoic acid	DMSO	15
8	L-proline/acetic acid	DMSO	50
9	L-proline/formic acid	DMSO	43
10	L-proline/benzoic acid	DMSO	25

[a] Unless otherwise noted, the reaction conditions were: carbapenem **1** (0.287 mmol), formaldehyde **3a** (2.0 equiv.), *p*-anisidine (2.0 equiv.), DMSO, room temp., 24 h. [b] Yield of isolated product.

hydroxyethyl]-3,7-dioxo-1-azabicyclo-[3.2.0]heptane-2-carboxylate (**1**), based on enamine-activated aldol, Mannich, and Michael reactions.[10c] In this paper, we fully explore the substrate scope of the Mannich reaction.

Initially, *p*-anisidine (**2a**) and formaldehyde (**3**) were selected for a model three-component Mannich reaction with 4-nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-hydroxyethyl]-3,7-dioxo-1-azabicyclo-[3.2.0]heptane-2-carboxylate (**1**; carbapenem intermediate), using L-proline as a catalyst in DMSO. As previously established,[10c] the reaction proceeded by enamine catalysis, and the new C–C bond was formed on the carbon α to the carbonyl (ketone), resulting in the formation of Mannich base **4a** in 53% yield (Table 1, entry 1). As reported, this reaction was completely regio- and stereoselective.[10c] In this case, the relative configuration of Mannich product **4a** was confirmed to be (*S*) by 2D NMR spectroscopy.

Solvent screening did not give any improvement in the yields, and DMSO was still the best solvent for this reaction (Table 1, entry 1 vs. entries 2 and 3). D-Proline gave results similar to those with L-proline in terms of yield and diastereoselectivity (Table 1, entries 1 and 4). This result shows that the carbapenem substrate (i.e., **1**) rather than the catalyst controls the stereochemical outcome of the reaction, and therefore the cheaper L-proline was preferred as the organocatalyst for the reaction. Similar results have been reported for the direct aldol and nitroaldol reactions between enantiopure azetidine-2,3-diones (β-lactams) and ketones or nitromethane.[16] It was reported in that paper that the use of either enantiomer of proline or of *N*-methylephedrine as the organocatalyst resulted in an identical level of sterecontrol in these reactions. Neither pyrrolidine − an achiral secondary amine, nor phenylalanine − a primary amine, catalysed the reaction (Table 1, entries 5 and 6).[17]

Brønsted acids were then evaluated as co-catalysts to try to improve the reactivity and yield. Unfortunately, there was no improvement in the yield of the Mannich product (Table 1, entries 7–10). Encouraged by the results obtained under the initial conditions (Table 1, entry 1), the substrate scope of the three-component Mannich reaction was examined using different amines and formaldehyde (Table 2). In general, regardless of the electronic properties of the substituents on the aromatic ring of aniline, the Mannich bases could be obtained in moderate yields and with excellent diastereoselectivities (Table 2, entries 1–4). Notably, even a condensed-ring amine (2-naphthylamine) performed well to give the corresponding product in 52% yield and with a *dr* of >99:1 (Table 2, entry 5). We observed the formation of the aldol addition product as a result of an expected side-reaction, which also occurs under similar conditions,[10c] and this explains the reduced yields.[1a,18]

Table 2. Substrate scope of the catalytic asymmetric three-component Mannich reaction using aromatic amines.[a]

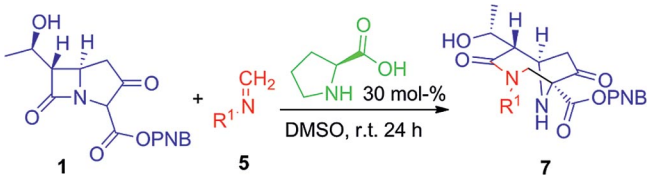
Entry[a]	R	Product	Yield [%][b]	*dr*[c]
1	4-MeOC$_6$H$_4$	**4a**	55	>99:1
2	Ph	**4b**	55	>99:1
3	4-MeC$_6$H$_4$	**4c**	53	>99:1
4	4-BrC$_6$H$_4$	**4d**	55	>99:1
5	2-naphthyl	**4e**	52	>99:1

[a] Unless otherwise noted, the reaction conditions were: carbapenem intermediate **1** (0.287 mmol), formaldehyde **3** (2.0 equiv.), amine derivative (2.0 equiv.), DMSO, room temp., 24 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy.

In contrast to the results with aromatic amines, when benzyl and aliphatic amines were tested in the three-component Mannich reaction with formaldehyde, aldol reaction products were formed almost exclusively. Fortunately, these

amines can form stable imines by treatment with paraformaldehyde and magnesium sulfate in $CHCl_3$ (Table 3). Surprisingly, and to our delight, the two-component Mannich reaction of benzyl imine **5b** with carbapenem intermediate **1** resulted in the formation of diazabicyclo[4.2.1]nonane compound **7b** in one pot. We propose that this reaction occured via Mannich base intermediate **6b**, as may be seen in the plausible catalytic cycle shown in Scheme 1. We attribute this result to a combination of the proximity of the new bond and the nucleophilicity of the amine. No rearranged products were observed for the aromatic amines tested, and we attribute this to the lower pK_a of these groups. The decreased basicity of the NH functionality renders it less nucleophilic, but this can also negate the proximity effect by hydrogen bonding to the ketone.

Table 3. Substrate scope of the catalytic asymmetric two-component Mannich reaction using aliphatic amines.[a]

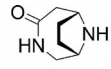


Entry[a]	R^1	Product	Yield [%][b]	*dr*[c]
1	4-$MeOC_7H_6$	**7a**	58	>99:1
2	Bn	**7b**	61	>99:1
3	4-ClC_7H_6	**7c**	54	>99:1
4	4-BrC_7H_6	**7d**	52	>99:1
5	2-picolyl	**7e**	58	>99:1
6	Ph-Et	**7f**	60	>99:1
7	(*S*)-1-Ph-Et	**7g**	57	>99:1
8	*n*Bu	**7h**	46	>99:1

[a] Unless otherwise noted, the reaction conditions were: amine (1.0 mmol), paraformaldehyde (1.0 mmol), $MgSO_4$ (1.0 g), $CHCl_3$, r.t., 7 h, and **1** (0.5 equiv.). [b] Yield of isolated product. [c] Determined by ^1H NMR spectroscopy.

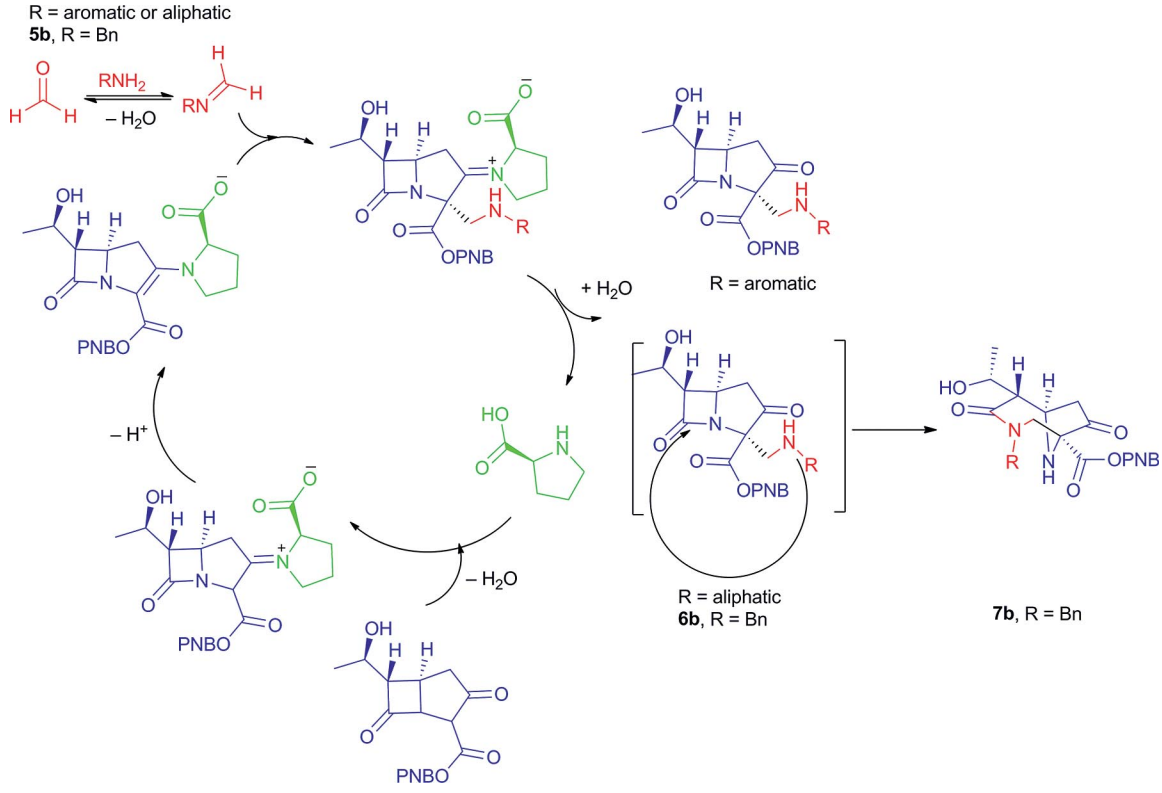
To establish whether the reaction proceeds by intramolecular rearrangement of intermediate **6b**, we then used *N*-methyl benzylamine as an amine component in the Mannich reaction (Scheme 2). In this case, only the anticipated Mannich base (i.e., **8a**) was obtained in acceptable yield (42%) and with excellent diastereoselectivity (>99%), which gives further support for postulated intermediate **6b**. This reaction also demonstrated the successful use of secondary amines in the organocatalytic two-component Mannich reaction. The secondary amine *N*-methyl aniline was also tested in the organocatalytic three-component reaction (Scheme 2), and it gave a good yield (51%) of tertiary Mannich base **8b**.

The diazabicyclo[4.2.1]nonane ring system in **7** represents an interesting molecular skeleton.

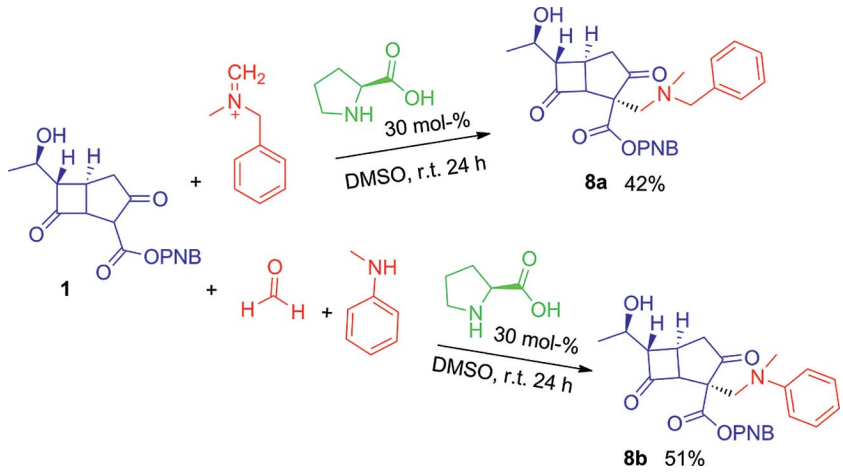


7

The bicyclic diazabicyclo[4.2.1]nonane core has been reported in patents and papers relating to compounds with various biological effects, e.g., as histamine H3 inverse agonists and antagonists, dual orexin receptor antagonists, and opioid receptor agonists.[19] To the best of our knowledge,



Scheme 1. Catalytic cycle of the proline-catalysed Mannich reaction of carbapenem core **1**.



Scheme 2. Organocatalytic Mannich reaction.

only one paper discussing the organocatalytic asymmetric synthesis of an all-carbon bicyclononane ring system has been published, which makes both the synthetic route and the highly functionalized diazabicyclo scaffold novel.[20]

Excited by the rather unexpected and efficient formation of highly functionalized analogues of this valuable molecular scaffold, we explored this reaction further, and the results are given in Table 3.

All the diazabicyclo[4.2.1]nonanes were obtained in good yields and with excellent diastereoselectivities, regardless of the electronic nature of the aryl ring of the benzylamines (Table 3, entries 1–4). Similary, if a heteroaromatic imine such as that obtained from picolylamine was used, the corresponding Mannich base was obtained with excellent diastereoselectivity and with no effect on the yield (Table 3, entry 5). The imines of aliphatic amines such as phenylethylamine and *n*-butylamine also reacted with **1** to give the corresponding diazabicyclo[4.2.1]nonanes with excellent diastereoselectivities and with no significant change in yield (Table 3, entries 6–8).

The structures of diazabicyclo[4.2.1]nonane products **7a**–**7h** were confirmed by 2D NMR measurements, and a single-crystal X-ray structure of **7b** was obtained (Figure 1).

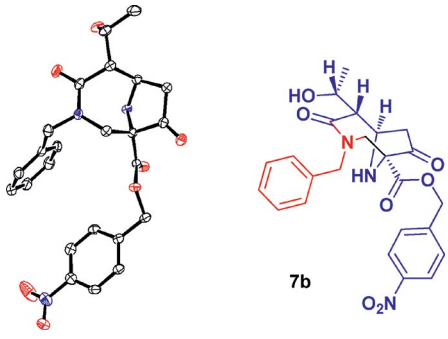


Figure 1. Single-crystal X-ray structure of **7b**. Displacement ellipsoids are scaled to the 50% probability level.

In summary, the two-component organocatalytic Mannich reaction provides a unique method for the construction of highly functionalized, natural-product like diazabicyclo[4.2.1]nonanes. These compounds appears to represent a privileged molecular scaffold for the preparation of biologically active compounds.

NMR correlations observed in the spectra of the products revealed some interesting features. The spectra of compound **4b** (HMBC: H-18–C-9, purple arrow; and NOE: H-18–H-4, green arrow) clearly confirmed the presence of the β-lactam ring and the relative stereoselectivity at C-8 in the structure (Figure 2). The NMR spectrum of compound **7b** (HMBC: H-17–C-2 and H-18–C-2) verified the formation of the bicyclic ring, which is consistent with the crystal data (Figure 1). We observed an upfield shift for the ketone (C=O) signal of compounds **4a**–**4e** in their ^{13}C NMR spectra (compared to compound **1**). This may be attributed to intramolecular hydrogen bonding between the oxygen of the carbonyl group and the amine group attached to the aromatic ring. When *N*-methylaniline was used as a substrate, resulting in Mannich base product **8a**, no upfield shift was observed for the carbonyl signal, which indicates the importance of the postulated hydrogen bonding (Scheme 2).

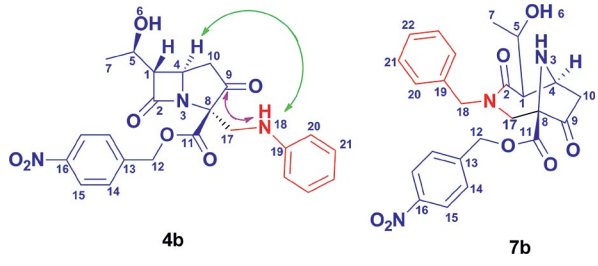


Figure 2. β-Lactam Mannich base **4b** and bicyclo[4.2.1]nonane **7b**.

Conclusions

In summary, we have demonstrated that it is possible to alter the reactivity patterns of a β-lactam substrate in its organocatalytic Mannich reaction with formaldehyde and

anilines/aliphatic amines. Carbapenem intermediate **1** reacts with formaldehyde and anilines to produce β-lactam Mannich bases, while reaction with aliphatic or benzylic amines results in the formation of diazabicyclo[4.2.1]nonane product(s) in one pot. Highly distereoselective diazabicyclo[4.2.1]nonane formation was observed in all reactions of aliphatic amines, and this led to highly functionalized analogues of compounds with postulated biological significance. The reported organocatalytic functionalization of carbapenem intermediate **1** may be used to access new β-lactams, as well as new highly functionalized diazabicyclo[4.2.1]nonanes Both of these compound classes are highly valuable as starting points for the synthesis of compounds with biologically important features.

Experimental

General Methods: Reagents and solvents were purchased from Aldrich, Merck, and Fluka. All solvents were dried using standard procedures. Thin layer chromatography (TLC) was carried out using Merck Kieselgel 60 F254. Crude compounds were purified by column chromatography using silica gel (60–200 mesh unless otherwise stated). NMR spectra were recorded with Bruker AVANCE III 400 or 600 MHz instruments at room temperature. Chemical shifts are expressed in ppm downfield from tetramethylsilane, which was used as an internal standard, and coupling constants are reported in Hz. Optical rotations were recorded with a Perkin–Elmer Polarimeter (model 341). High-resolution mass spectrometric data were obtained using a Bruker micrOTOF-Q II instrument operating at ambient temperatures, with a sample concentration of approximately 1 ppm.

Representative Procedure for the Mannich Reaction of Aromatic Amines with Carbapenem: A substituted aniline (2 equiv.) was added to a stirred solution of formaldehyde (36% aqueous solution; 0.574 mmol) in DMSO (3 mL) at ambient temperature. After 4 h, carbapenem intermediate **1** (0.1 g, 0.287 mmol) and a catalytic amount of L-proline (30 mol-%) were added. The reaction mixture was stirred at room temperature for 20 h and monitored by TLC. The reaction mixture was then quenched by the addition of PBS (phosphate-buffered saline) buffer (0.01 M; 1 mL) and water (3 mL). The aqueous phase was extracted with EtOAc (3×). The combined organic extracts were dried with anhydrous $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure, and the crude product mixture was purified by silica gel column chromatography.

Representative Procedure for the Preparation of Imines: A literature procedure was followed.[21]

Representative Procedure for the Mannich Reaction of Imines with Carbapenems: L-Proline (30 mol-%) and the respective imine (2 equiv.) were added to a solution of carbapenem intermediate **1** (562 mg, 1.62 mmol) in DMSO (15 mL). The solution was stirred at room temperature for >20 h and monitored by TLC. The reaction mixture was then quenched by the addition of PBS buffer (0.01 M; 10 mL) and water (15 mL). The aqueous phase was extracted with EtOAc (3×). The combined organic extracts were dried with anhydrous $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure, and the crude product mixture was purified by silica gel column chromatography.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3,7-dioxo-2-[(phenylamino)methyl]-1-azabicyclo[3.2.0]heptane-2-carboxylate (4b): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (403 mg, 55%) as a semisolid. $[a]_D^{20}$ = –30.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.64 Hz, 2 H), 7.70 (s, 1 H), 7.51 (d, *J* = 8.60 Hz, 2 H), 7.45 (d, *J* = 7.88 Hz, 2 H), 7.30 (t, *J* = 7.82 Hz, 2 H), 7.12 (t, *J* = 7.38 Hz, 1 H), 6.14 (s, 1 H), 6.04 (s, 1 H), 5.29 (d, *J* = 9.72 Hz, 2 H), 4.60 (m, 1 H), 4.17 (m, 1 H), 3.06 (m, 1 H), 3.04 (m, 1 H), 2.66 (dd, *J* = 15.84, 9.52 Hz, 1 H), 1.37 (d, *J* = 6.16 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.33, 165.58, 162.15, 148.06, 142.21, 137.22, 130.88, 129.21, 128.69, 125.10, 124.09, 120.23, 115.72, 66.93, 66.02, 64.82, 55.78, 40.24, 21.62 ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{23}N_3O_7$ $[M + H]^+$ 454.1608; found 454.2985.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(4-methoxyphenylamino)methyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (4a): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (431 mg, 55%) as a semisolid. $[a]_D^{20}$ = –50.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 8.72 Hz, 2 H), 7.66 (d, *J* = 8.72 Hz, 2 H), 7.40 (d, *J* = 9.00 Hz, 2 H), 6.83 (d, *J* = 9.00 Hz, 2 H), 5.83 (d, *J* = 9.96 Hz, 2 H), 5.31 (s, 2 H), 5.03 (d, *J* = 4.40 Hz, 2 H), 4.53–4.49 (m, 1 H), 3.97 (q, *J* = 5.44 Hz, 1 H), 3.69 (s, 3 H), 3.11 (dd, *J* = 5.30, 2.38 Hz, 1 H), 2.77–2.69 (m, 2 H), 1.10 (d, *J* = 6.32 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.57, 166.04, 161.87, 155.25, 147.11, 143.23, 131.91, 131.55, 128.53, 123.51, 120.77, 113.75, 113.56, 65.40, 63.47, 62.74, 55.08, 53.45, 40.11, 21.61 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}N_3O_8$ $[M + H]^+$ 484.1714; found 484.1712.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-3,7-dioxo-2-[(*p*-tolylamino)methyl]-1-azabicyclo[3.2.0]heptane-2-carboxylate (4c): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.4) to give the product (400 mg, 53%) as a brown solid. $[a]_D^{20}$ = +5.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (d, *J* = 7.64 Hz, 2 H), 7.51 (d, *J* = 7.72 Hz, 2 H), 7.33 (d, *J* = 7.28 Hz, 2 H), 7.08 (d, *J* = 7.08 Hz, 2 H), 6.11 (s, 1 H), 6.04 (s, 1 H), 5.28 (q, *J* = 7.32 Hz, 2 H), 4.59 (s, 1 H), 4.15 (s, 1 H), 3.02 (m, 2 H), 2.65 (dd, *J* = 15.15, 9.83 Hz, 1 H), 2.28 (s, 3 H), 1.34 (d, *J* = 4.96 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.23, 165.55, 162.02, 147.87, 142.16, 134.65, 130.34, 129.34, 128.54, 123.92, 120.24, 115.55, 66.71, 65.88, 64.59, 42.66, 21.47, 20.87 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}N_3O_7$ $[M + H]^+$ 468.1765; found 468.1770.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-2-[(4-Bromophenylamino)methyl]-6-[(*R*)-1-hydroxyethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (4d): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (473 mg, 55%) as a semisolid. $[a]_D^{20}$ = –70.0 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.52 Hz, 2 H), 7.78 (s, 1 H), 7.52 (d, *J* = 8.52 Hz, 2 H), 7.41–7.35 (m, 4 H), 6.17 (s, 1 H), 6.06 (s, 1 H), 5.29 (q, *J* = 13.2 Hz, 2 H), 4.61–4.59 (m, 1 H), 4.20–4.16 (m, 1 H), 3.06 (dd, *J* = 19.26, 11.34 Hz, 1 H), 2.68–2.64 (m, 2 H), 1.37 (d, *J* = 6.12 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.26, 165.47, 162.17, 148.09, 142.16, 136.36, 132.20, 130.78, 128.67, 124.12, 121.74, 117.72, 115.84, 66.98, 64.79, 55.64, 40.41, 21.69 ppm. HRMS (ESI$^-$): calcd. for $C_{23}H_{22}BrN_3O_7$ $[M - H]^-$ 530.0557; found 530.0612.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-[(naphthalen-1-ylamino)methyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (4e): The crude product was purified by column chromatog-

raphy (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (392 mg, 48%) as a brownish oil. $[\alpha]_D^{20}$ = –45.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.72 Hz, 2 H), 7.51 (d, *J* = 8.68 Hz, 2 H), 5.33 (d, *J* = 3.48 Hz, 2 H), 4.37 (m, 1 H), 4.21 (m, 1 H), 4.04 (d, *J* = 8.72 Hz, 1 H), 3.69 (m, 1 H), 3.31 (t, *J* = 8.16 Hz, 2 H), 2.73 (dd, *J* = 18.6, 8.10 Hz, 1 H) 2.50 (t, *J* = 5.20 Hz, 1 H), 2.28 (d, *J* = 18.65 Hz, 1 H), 1.45–1.25 (m, 4 H), 1.23 (d, *J* = 6.48 Hz, 3 H), 0.86 (t, *J* = 7.26 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.05, 174.03, 167.13, 148.11, 141.83, 128.65, 124.08, 70.57, 66.89, 66.76, 58.28, 51.19, 49.36, 47.67, 43.65, 29.63, 21.02, 20.16, 13.85 ppm. HRMS (ESI$^+$): calcd. for $C_{27}H_{25}N_3O_7$ [M + H]$^+$ 504.1765; found 504.1792.

4-Nitrobenzyl (1*R*)-3-Benzyl-5-[(*R*)-1-hydroxyethyl]-4,8-dioxo-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7b): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.4) to give the product (491 mg, 61%) as a white solid. $[\alpha]_D^{20}$ = –30.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 8.60 Hz, 2 H), 7.45 (d, *J* = 8.52 Hz, 2 H), 7.25–7.34 (m, 5 H), 5.17 (q, *J* = 13.6 Hz, 2 H), 4.92 (d, *J* = 14.6 Hz, 1 H), 4.51–4.45 (m, 1 H), 4.32–4.28 (m, 2 H), 4.06 (d, *J* = 15.68 Hz, 1 H), 3.64 (d, *J* = 15.64 Hz, 1 H), 2.76 (dd, *J* = 18.61, 8.00 Hz, 1 H), 2.57 (q, *J* = 5.24, 3.72 Hz, 1 H) 2.34 (d, *J* = 18.61 Hz, 1 H), 1.29 (d, *J* = 6.60 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.64, 174.72, 166.65, 141.76, 136.34, 128.79, 128.67, 128.42, 127.88, 124.00, 70.24, 66.70, 66.68, 57.62, 51.94, 49.95, 47.50, 43.98, 20.79 ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{27}N_3O_8$ [M + H]$^+$ 498.1870; found 498.1878.

4-Nitrobenzyl (1*R*)-5-[(*R*)-1-Hydroxyethyl]-3-(4-methoxybenzyl)-4,8-dioxo-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7a): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (438 mg, 58%) as a yellow crystalline solid. $[\alpha]_D^{20}$ = –20.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 8.68 Hz, 2 H), 7.42 (d, *J* = 8.68 Hz, 2 H), 7.16 (d, *J* = 8.64 Hz, 2 H), 6.80 (d, *J* = 8.60 Hz, 2 H), 5.14 (q, *J* = 6.68 Hz, 2 H), 4.84 (d, *J* = 14.44 Hz, 1 H), 4.43 (dd, *J* = 6.58, 3.46 Hz, 1 H), 4.24 (q, *J* = 7.34, 6.14 Hz, 1 H), 4.18 (d, *J* = 14.44 Hz, 1 H), 4.02 (d, *J* = 15.72 Hz, 1 H), 3.78 (s, 3 H) 3.58 (d, *J* = 15.64 Hz, 1 H), 2.73 (dd, *J* = 18.57, 7.96 Hz, 1 H), 2.73 (q, *J* = 18.57, 7.96 Hz, 1 H), 2.34 (s, 1 H), 2.29 (d, *J* = 18.49 Hz, 1 H), 1.24 (d, *J* = 6.64 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.55, 174.59, 166.62, 159.22, 141.74, 130.02, 128.30, 128.23, 123.88, 114.04, 70.13, 66.51, 57.49, 55.24, 51.16, 49.66, 47.39, 43.89, 20.66 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}N_3O_7$ [M + H]$^+$ 468.1765; found 468.1772.

4-Nitrobenzyl (1*R*)-3-(4-Chlorobenzyl)-5-[(*R*)-1-hydroxyethyl]-4,8-dioxo-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7c): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.38) to give the product (430 mg, 53%) as a white crystalline solid. $[\alpha]_D^{20}$ = –25.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.40 Hz, 2 H), 7.32 (d, *J* = 8.40 Hz, 2 H), 7.18 (d, *J* = 6.08 Hz, 2 H), 7.14 (s, 2 H), 5.07 (q, *J* = 3.44 Hz, 2 H), 4.84 (d, *J* = 14.69 Hz, 2 H), 4.38 (m, 1 H), 4.21 (t, *J* = 12.76 Hz, 1 H), 4.12 (d, *J* = 14.72 Hz, 1 H), 3.96 (d, *J* = 15.65 Hz, 1 H), 3.53 (d, *J* = 15.65 Hz, 1 H) 2.67 (dd, *J* = 18.67, 7.90 Hz, 1 H), 2.46 (s, 1 H), 2.24 (d, *J* = 18.65 Hz, 1 H), 1.19 (d, *J* = 6.44 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.51, 174.72, 166.41, 141.50, 134.76, 133.67, 130.09, 128.79, 123.95, 70.18, 66.74, 66.71, 57.41, 51.28, 49.82, 47.44, 43.89, 20.66 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{24}ClN_3O_7$ [M + H]$^+$ 502.1375; found 502.1384.

4-Nitrobenzyl (1*R*)-3-(4-Bromobenzyl)-5-[(*R*)-1-hydroxyethyl]-4,8-dioxo-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7d): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.4) to give the product (468 mg, 53%) as a brown crystalline solid. $[\alpha]_D^{20}$ = –10.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.64 Hz, 2 H), 7.42 (d, *J* = 11.10, 8.50 Hz, 4 H), 7.13 (d, *J* = 8.28 Hz, 2 H), 5.14 (d, *J* = 3.24 Hz, 2 H), 4.91 (d, *J* = 14.72 Hz, 1 H), 4.44 (dd, *J* = 6.54, 3.38 Hz, 1 H), 4.27 (q, *J* = 7.44, 6.04 Hz, 1 H), 4.16 (d, *J* = 14.73 Hz, 1 H), 4.01 (d, *J* = 15.68 Hz, 1 H), 3.59 (d, *J* = 15.64 Hz, 1 H), 2.73 (dd, *J* = 18.65, 8.04 Hz, 1 H) 2.53 (q, *J* = 5.44, 3.48 Hz, 1 H), 2.30 (d, *J* = 18.69 Hz, 1 H), 1.25 (d, *J* = 6.56 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.92, 175.09, 166.75, 148.31, 141.85, 135.61, 132.08, 130.76, 128.71, 124.28, 122.09, 70.51, 67.06, 57.73, 51.63, 50.14, 47.75, 44.23, 20.99 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{24}BrN_3O_7$ [M + H]$^+$ 546.0870; found 546.0854.

4-Nitrobenzyl (1*R*)-5-[(*R*)-1-Hydroxyethyl]-4,8-dioxo-3-(pyridin-2-ylmethyl)-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7e): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.3) to give the product (440 mg, 58%) as a white crystalline solid. $[\alpha]_D^{20}$ = –10.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 4.44 Hz, 1 H), 8.15 (d, *J* = 8.68 Hz, 2 H), 7.63 (m, 1 H), 7.42 (d, *J* = 8.64 Hz, 2 H), 7.21 (d, *J* = 7.84 Hz, 1 H), 7.10 (t, *J* = 6.90, 5.34 Hz, 1 H) 5.43 (d, *J* = 16.20 Hz, 1 H), 5.16 (s, 2 H), 4.40 (dd, *J* = 6.62, 2.70 Hz, 1 H), 4.31–4.21 (m, 2 H), 4.12 (d, *J* = 16.21 Hz, 1 H), 3.74 (d, *J* = 15.61 Hz, 1 H), 3.68 (d, *J* = 7.00 Hz, 1 H), 2.88 (dd, *J* = 18.19, 7.38 Hz, 1 H), 2.51 (q, *J* = 5.76, 2.64 Hz, 1 H), 2.31 (d, *J* = 18.17 Hz, 1 H), 1.21 (d, *J* = 6.88 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.93, 174.67, 168.04, 155.82, 148.72, 142.28, 137.19, 128.35, 123.79, 122.56, 122.23 70.27, 66.47, 66.24, 57.04, 53.74, 52.16, 46.91, 44.64, 20.03 ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{24}N_4O_7$ [M + H]$^+$ 469.1717; found 469.1756.

4-Nitrobenzyl (1*R*)-5-[(*R*)-1-Hydroxyethyl]-4,8-dioxo-3-phenethyl-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7f): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.3) to give the product (452 mg, 58%) as a white crystalline solid. $[\alpha]_D^{20}$ = –20.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.64 Hz, 1 H), 7.77 (d, *J* = 8.56 Hz, 2 H), 7.23 (d, *J* = 6.76 Hz, 2 H), 7.18 (m, 1 H), 7.11 (d, *J* = 7.01 Hz, 2 H), 5.29 (s, 2 H), 4.33 (dd, *J* = 6.48, 4.16 Hz, 1 H), 4.19 (q, *J* = 7.48, 6.00 Hz, 1 H), 3.96 (d, *J* = 15.52 Hz, 1 H), 3.69–3.57 (m, 2 H), 3.53–3.45 (m, 1 H), 2.82–2.72 (m, 1 H), 2.71–2.63 (m, 2 H), 2.45 (q, *J* = 5.16, 4.48 Hz, 1 H), 2.26 (d, *J* = 18.61 Hz, 1 H), 1.19 (d, *J* = 6.56 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.02, 174.06, 167.13, 148.11, 141.75, 138.47, 128.67, 126.72, 124.09, 66.92, 66.57, 58.19, 51.64, 51.44, 47.66, 43.71, 33.96, 20.93 ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{27}N_3O_7$ [M + H]$^+$ 482.1921; found 482.1891.

4-Nitrobenzyl (1*R*)-5-[(*R*)-1-Hydroxyethyl]-4,8-dioxo-3-(1-phenylethyl)-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7g): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.35) to give the product (444 mg, 57%) as a white crystalline solid. $[\alpha]_D^{20}$ = +15.0 (*c* = 0.1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.24 Hz, 2 H), 7.39 (d, *J* = 8.16 Hz, 2 H), 7.33 (m, 5 H), 6.12 (d, *J* = 6.67 Hz, 1 H), 4.93 (m, 2 H), 4.46 (m, *J* = 3.48 Hz, 1 H), 4.26 (t, *J* = 13.01 Hz, 1 H), 3.87 (d, *J* = 15.85 Hz, 1 H), 3.40 (d, *J* = 15.88 Hz, 1 H), 2.71 (dd, *J* = 18.37, 7.60 Hz, 1 H), 2.45 (s, 1 H), 2.29 (d, *J* = 18.45 Hz, 1 H), 1.48 (d, *J* = 6.84 Hz, 3 H), 1.24 (d, *J* = 6.32 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.20, 174.56, 166.37, 142.16, 139.88, 128.43, 127.99, 124.16, 70.34, 66.66, 66.53, 57.45, 51.42, 47.44, 45.62, 45.07, 20.71, 16.70 ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{27}N_3O_7$ [M + H]$^+$ 482.1921; found 482.1815.

4-Nitrobenzyl (1*R*)-3-Butyl-5-[(*R*)-1-hydroxyethyl]-4,8-dioxo-3,9-diazabicyclo[4.2.1]nonane-1-carboxylate (7h): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (337 mg, 48%) as a brownish oil. $[\alpha]_D^{20}$ = +37.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.72 Hz, 2 H), 7.51 (d, J = 8.68 Hz, 2 H), 5.33 (d, J = 3.48 Hz, 2 H), 4.37 (m, 1 H), 4.21 (m, 1 H), 4.04 (d, J = 8.72 Hz, 1 H), 3.69 (m, 1 H), 3.31 (t, J = 8.16 Hz, 2 H), 2.73 (dd, J = 18.6, 8.10 Hz, 1 H) 2.50 (t, J = 5.20 Hz, 1 H), 2.28 (d, J = 18.65 Hz, 1 H), 1.45–1.25 (m, 4 H), 1.23 (d, J = 6.48 Hz, 3 H), 0.86 (t, J = 7.26 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.05, 174.03, 167.13, 148.11, 141.83, 128.65, 124.08, 70.57, 66.89, 66.76, 58.28, 51.19, 49.36, 47.67, 43.65, 29.63, 21.02, 20.16, 13.85 ppm. HRMS (ESI$^+$): calcd. for $C_{21}H_{28}N_3O_7$ [M + H]$^+$ 434.1927; found 434.1450.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-2-{[Benzyl(methyl)amino]methyl}-6-[(*R*)-1-hydroxyethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (8a): The crude product was purified by column chromatography (EtOAc/hexane, 80:20; R_f = 0.4) to give the product (42%) as a semisolid. $[\alpha]_D^{20}$ = +65.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.45 (d, J = 8.25 Hz, 2 H), 7.66 (d, J = 54 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H), 6.83 (m, 3 H), 5.83 (d, J = 9.96 Hz, 2 H), 5.31 (s, 2 H), 5.03 (d, J = 4.40 Hz, 2 H), 4.53–4.49 (m, 1 H), 3.97 (q, J = 16.24, 5.44 Hz, 1 H), 3.69 (s, 3 H), 3.11 (dd, J = 5.30, 2.38 Hz, 1 H), 2.77–2.69 (m, 2 H), 1.10 (d, J = 6.37 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.57, 168.04, 161.87, 155.25, 142.11, 143.23, 131.91, 133.55, 128.53, 123.51, 118.77, 113.75, 112.56, 64.40, 63.47, 63.74, 55.08, 53.45, 40.21, 21.61 ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{27}N_3O_7$ [M + H]$^+$ 482.1921; found 482.1881.

4-Nitrobenzyl (2*S*,5*R*,6*S*)-6-[(*R*)-1-Hydroxyethyl]-2-{[methyl(phenyl)amino]methyl}-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (8b): The crude product was purified by column chromatography (EtOAc/hexane, 70:30; R_f = 0.4) to give the product (51%) as a semisolid. $[\alpha]_D^{20}$ = +65.0 (c = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.72 Hz, 2 H), 7.48 (d, J = 8.56 Hz, 2 H), 7.20 (m, 3 H), 6.93 (d, J = 8.24 Hz, 2 H), 5.29 (s, 2 H), 5.08 (d, J = 12.28 Hz, 1 H), 4.93 (d, J = 14.16 Hz, 1 H), 4.70 (q, J = 6.88 Hz, 1 H), 4.61 (d, J = 12.25 Hz, 1 H), 4.27 (dd, J = 8.02, 4.18 Hz, 1 H), 4.10 (d, J = 14.16 Hz, 1 H), 3.73 (q, J = 7.01 Hz, 1 H), 3.01 (dd, J = 18.99, 8.18 Hz, 1 H), 2.78 (d, J = 4.12 Hz, 1 H), 2.57 (d, J = 19.01 Hz, 1 H), 2.35 (s, 3 H), 1.59 (d, J = 6.96 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.83, 173.67, 166.90, 142.67, 137.35, 128.24, 123.91, 72.80, 71.41, 71.11, 66.29, 55.75, 53.78, 47.47, 41.35, 21.09, 16.96 ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{25}N_3O_7$ [M + H]$^+$ 468.1765; found 468.1783.

Supporting Information (see footnote on the first page of this article): General methods, representative procedure for the Mannich reaction of aromatic amines with carbapenem; representative procedure for the preparation of imines; representative procedure for the Mannich reaction of imines with carbapenems; copies of NMR spectra of products; copies of HRMS spectra of products.

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