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Synthesis of 1,3-Aminoalcohols and Spirocyclic Azetidines via Tandem Hydroxymethylation and Aminomethylation Reaction of *β*-Keto Phosphonates with *N*-Nosyl-*O*-(2-bromoethyl)hydroxylamine

Binyu Wu, Hongbing Chen, Min Gao, Xiangnan Gong, and Lin Hu*

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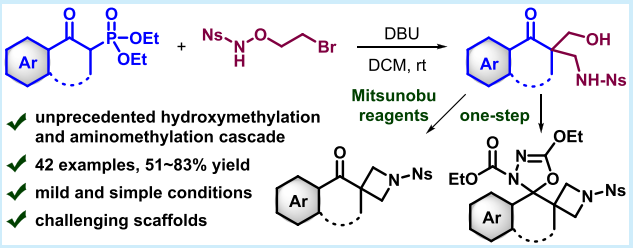
ABSTRACT: An unprecedented tandem *α*-hydroxymethylation and *α*-aminomethylation reaction of aromatic cyclic *β*-keto phosphonates with *N*-nosyl-*O*-(2-bromoethyl)hydroxylamine in the presence of DBU base has been developed, affording a range of 1,3-aminoalcohols in good yields. The resultant products could be flexibly transformed into the spirocyclic and bispirocyclic azetidines via one step of Mitsunobu reaction. Mechanistic study revealed that hydroxylamine in situ generated the formaldehyde and nosylamide, which in turn triggered the sequential Horner–Wadsworth–Emmons, Michael, and aldol reactions.



1,3-Aminoalcohols are a prominent motif widely employed in synthetic and medicinal chemistry.[1] As a subclass of such compounds, *α*-hydroxymethyl-*α*-aminomethyl ketones are exceptionally useful building blocks, because the free OH and NH moieties as well as the carbonyl functional group provide convenient handles for structural derivatizations. For example, the biologically important azetidines, which are found in many natural products and therapeutic agents,[2] may be rapidly assembled from these 1,3-aminoalcohol precursors via an intramolecular cyclization reaction (Scheme 1A). Surprisingly, although their structure looks simple, synthetic methods for such *α*-hydroxymethyl-*α*-aminomethyl carbonyl compounds are rather rare.[3] The only relevant work that involved the condensation of tetralone derivatives with paraformaldehyde and imidazole or triazoles to afford the *α*-hydroxymethyl-*α*-azolylmethyl compounds was reported by Bhandari.[3a] However, the reaction introduced the specific imidazole or triazole groups into the products, thus heavily limiting their further transformation. On the other hand, hydroxylamines characterized by a weak N–O bond within the structure are commonly used reagents in organic synthesis.[4] Conventionally, they were extensively exploited as amination reagent in transition metal-catalyzed C–N bond-forming reactions.[5] In recent years, they have also been exploited as nitrogen-centered radical precursors in photocatalytic C–N bond-forming reactions[6] (Scheme 1B). Conversely, applying hydroxylamine derivatives as novel hydroxymethylation and aminomethylation reagents has not been achieved to date. In this regard, development of an efficient approach toward *α*-hydroxymethyl-*α*-aminomethyl ketones by using hydroxylamine derivatives as novel C–C bond-forming reagents will be highly attractive.

Herein, we report that the simple *N*-nosyl-*O*-(2-bromoethyl)hydroxylamine **2a**, a stable solid, could participate in the unprecedented tandem hydroxymethylation and aminomethylation reactions with aromatic cyclic *β*-keto phosphonates under mild DBU basic conditions, directly affording the *α*-hydroxymethyl-*α*-aminomethyl ketones in good yields at room temperature (Scheme 1C). Moreover, the resultant 1,3-aminoalcohols are versatile synthons, which could be flexibly transformed into two types of spirocyclic- and bispirocyclic azetidine products via one simple Mitsunobu cyclization reaction. Notably, the latter bispirocyclic scaffold bearing two vicinal azetidine and 1,3,4-oxadiazoline rings is synthetically challenging, which is prepared for the first time.

Recently, we attempted to synthesize the compound **4** from *β*-keto phosphonate **1a** and hydroxylamine **2a** in DMF under the Cs_2CO_3 basic conditions. Accidentally, instead of obtaining the target alkylation product, we isolated the 1,3-aminoalcohol **3a** in 49% yield (Scheme 2). This unexpected result immediately triggered our interest of this reaction, not only because the *α*-hydroxymethyl-*α*-aminomethyl ketones could be generated in such a simple way but also because the intriguing role of the hydroxylamine played in this complicated bond cleavage and formation process.

On the basis of this initial discovery, we decided to optimize the reaction first (Table 1). We found that the base had a

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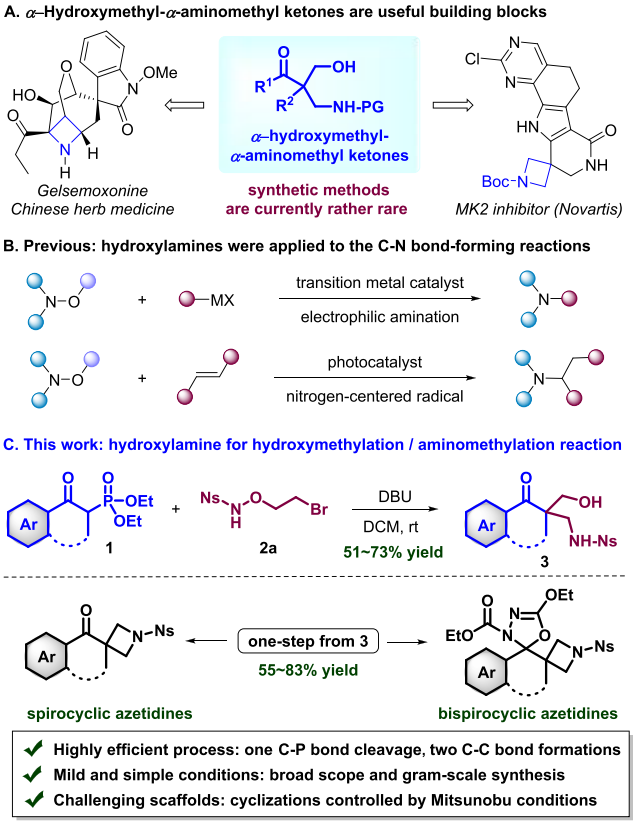
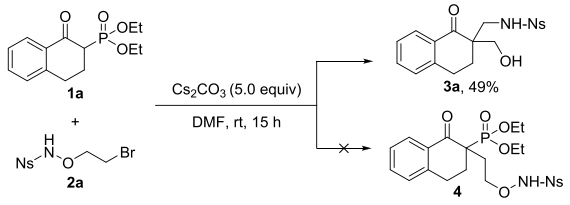
Scheme 1. Background and Our Synthetic Approach

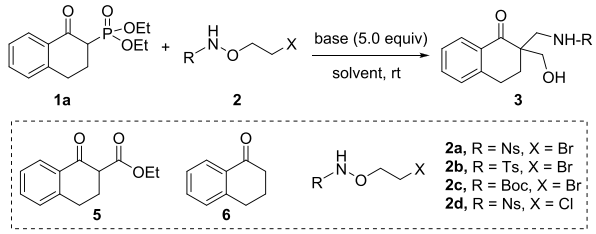


Scheme 2. Initial Discovery



significant impact on the reaction. Weaker base K_2CO_3 provided the product **3a** in 45% yield, while stronger base KOH caused the quick decomposition of the hydroxylamine **2a**. Thus **3a** was obtained in very low yield (Table 1, entries 1−3). Organic base DBU turned out to be the best, which improved the yield to 73% in DCM solvent. Other commonly used organic bases such as TEA and pyridine were ineffective to promote the reaction (Table 1, entries 4−7). We also observed that both the structures of hydroxylamines and nucleophiles affected the reaction drastically (Table 1, entries 8−12). No reaction happened when tosyl- and Boc-protected hydroxylamines **2b** and **2c** were used as substrates, but the *N*-nosyl hydroxylamine **2d** bearing a less reactive chloro group still delivered the product **3a** in 62% yield. In addition, replacing the phosphonate nucleophile with *β*-keto carboxylate **5** and tetralone **6** only afforded a trace amount of product **3**. Next, other reaction parameters such as temperature and the amounts of base were examined, but they could not further improve the yield (Table 1, entries 14−16). Eventually, we determined to conduct the reaction of *β*-keto phosphonate **1** (1.0 equiv) and *N*-nosyl-*O*-(2-bromoethyl)hydroxylamine **2a** (1.5 equiv) in DCM at room temperature by using DBU (5.0 equiv) as base (see the Supporting Information for details).

Table 1. Optimization of the Reaction Conditions[a]

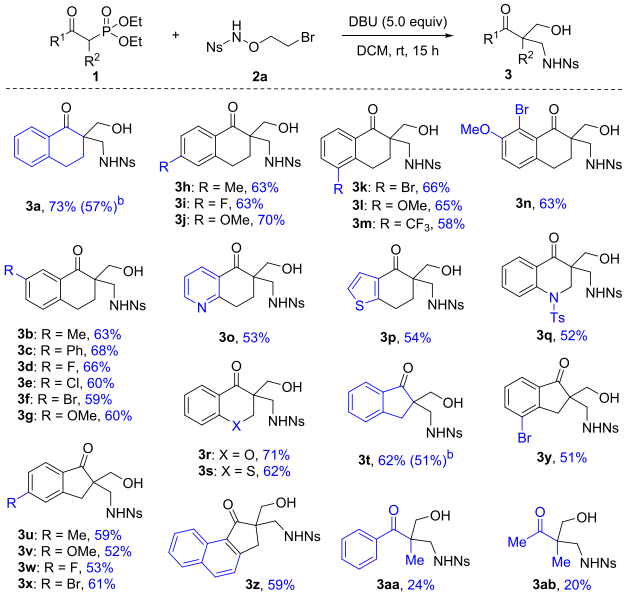


entry	substrates		base	solvent	*t* (h)	yield (%)[b]
1	**1a**	**2a**	Cs_2CO_3	DMF	24	49
2	**1a**	**2a**	K_2CO_3	DMF	24	45
3	**1a**	**2a**	KOH	DMF	24	8
4	**1a**	**2a**	DBU	DMF	15	64
5	**1a**	**2a**	DBU	DCM	15	73
6	**1a**	**2a**	TEA	DCM	48	0[c]
7	**1a**	**2a**	pyridine	DCM	48	0[d]
8	**1a**	**2b**	DBU	DCM	48	0[c]
9	**1a**	**2c**	DBU	DCM	48	0[c]
10	**1a**	**2d**	DBU	DCM	15	62
11	**5**	**2a**	DBU	DCM	48	10
12	**6**	**2a**	DBU	DCM	48	8
13	**1a**	**2a**	DBU (3.0 equiv)	DCM	15	51
14	**1a**	**2a**	DBU (10.0 equiv)	DCM	15	44
15	**1a**	**2a**	DBU	DCM	48	19[e]
16	**1a**	**2a**	DBU	DCM	48	28[f]

[a]Unless otherwise noted: nucleophile (0.10 mmol), **2** (0.15 mmol), and base (0.50 mmol) in indicated solvent at room temperature. [b]Isolated yield. [c]**1a** was recovered, and **2** was partially converted into 1,2-oxazetidine. [d]**1a** and **2a** were recovered. [e]Run at 0 °C. [f]1.0 equiv of **2a** was used.

After establishing the optimal conditions, the scope of the *α*-hydroxymethylation and *α*-aminomethylation reaction was explored. As summarized in Scheme 3, a range of *α*-

Scheme 3. Substrate Scope[a]



[a]Standard conditions: **1** (0.2 mmol), **2a** (0.3 mmol), and DBU (1.0 mmol) in 2.0 mL of DCM at room temperature for 15 h. [b]Yield for 6 mmol of **1** and 9 mmol of **2a**.

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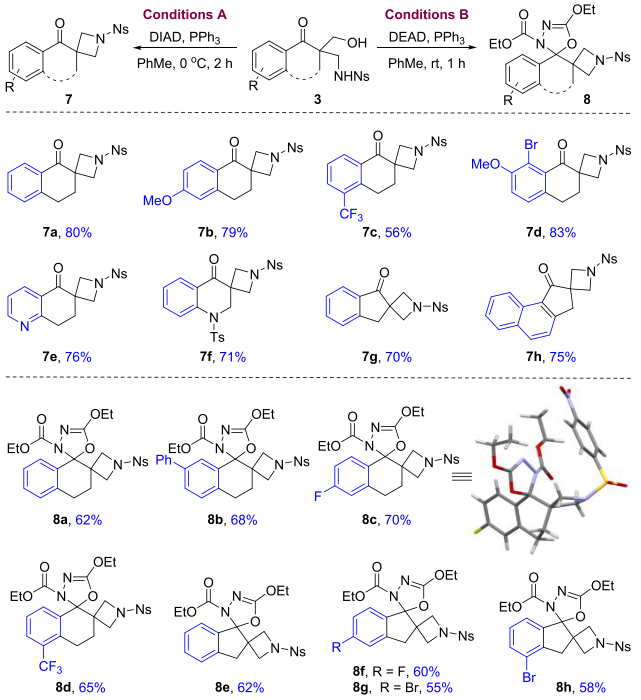
hydroxymethyl-α-aminomethyl ketones could be prepared in good yields under standard conditions. Tetralone phosphonate substrates bearing various 7-alkyl, -aryl, and -halo substituents on the phenyl ring were well tolerated, affording the products in 59−68% yields (Scheme 3, **3b−g**). Substrates bearing different 5- and 6-substitutents on the phenyl ring had a slightly influence on the yield (Scheme 3, **3h−n**). Hetero-aromatic substrates such as pyridine- and thiophene-fused cyclic ketones also reacted with hydroxylamine **2a** well and provided products **3o−p** in around 53% yield. In addition, indanone phosphonate substrates, regardless of the position and the electronic nature of the substituents on the phenyl ring, also produced the corresponding products in 51−62% yields (Scheme 3, **3t−z**). Moreover, other substrates such as benzoyl, acetyl, 2-oxocyclopentyl, and 2-oxocyclohexyl phosphonates were also tried. However, the reactions for these substrates were complex. Only the benzoyl and acetyl phosphonates afforded the target 1,3-aminoalcohol products in 24% and 20% yield, respectively.(Scheme 3, **3aa,ab**). Finally, we attempted the scalable synthesis under the standard conditions. The reactions of **1a** and **1t** still performed well at the 6 mmol scale, which furnished 1.3 g of **3a** and 1.15 g of **3t** in 57% and 51% yield, respectively.

As mentioned above, azetidines are a class of important heterocyles exhibiting a wide range of interesting biological and pharmacological properties such as *anti*-influenza virus A and *anti*-HIV activities.[2] Due to the strained nature, efficient construction of such a small ring structure remains a challenging task.[7] Especially, the synthetic approaches for spirocyclic azetidines are currently limited.[8] Considering the pendant *N*-nosyl and hydroxyl functional groups that provide convenient handles for the Mitsunobu reaction,[9] we envisioned that the above α-hydroxymethyl-α-aminomethyl ketone products could be used for the rapid assembly of the spirocyclic azetidines via one-step cyclization. Accordingly, we subjected **3a** to the Ph_3P and diisopropyl azodicarboxylate mixture. To our delight, the reaction smoothly furnished the spirocyclic azetidine **7a** in 80% yield at 0 °C (Scheme 4, conditions A). This protocol was also efficient for the construction of other spirocyclic azetidines in good yields (Scheme 4, **7b−h**). For example, pyridine- and piperidinone-containing and indanone-fused azetidines were prepared in 56−83% yields. Impressively, by simply changing the Mitsunobu reagent to diethyl azodicarboxylate and by conducting the reaction at room temperature (Scheme 4, conditions B), a series of structurally complex azetidine−1,3,4-oxadiazoline bispiocycles could be alternatively obtained in good yields (Scheme 4, **8a−h**). To our knowledge, such challenging structure bearing two congested vicinal spirocycles, which was confirmed by the single crystal X-ray analysis of compound **8c**, has not been prepared previously.

In fact, only a few isolated examples of cyclizations of dialkyl azodicarboxylate reagents with reactive α-ketoesters or α-diketones to form the 1,3,4-oxadiazolines have been reported,[10] but the above double spirocyclization process of unactivated carbonyl compounds was unprecedented. To elucidate how the azetidine-1,3,4-oxadiazoline bicycles were efficiently installed under such mild Mitsunobu conditions, we examined the reaction of the tetralone **6** under the conditions B. However, no reaction occurred at all. Instead, treatment of spirocyclic azetidine **7a** under the same conditions smoothly generated the bispirocyclic compound **8a** in 75% yield. These results suggested that the azetidine-1,3,4-oxadiazoline product

Scheme 4. Synthesis of Spirocyclic Azetidines[a]

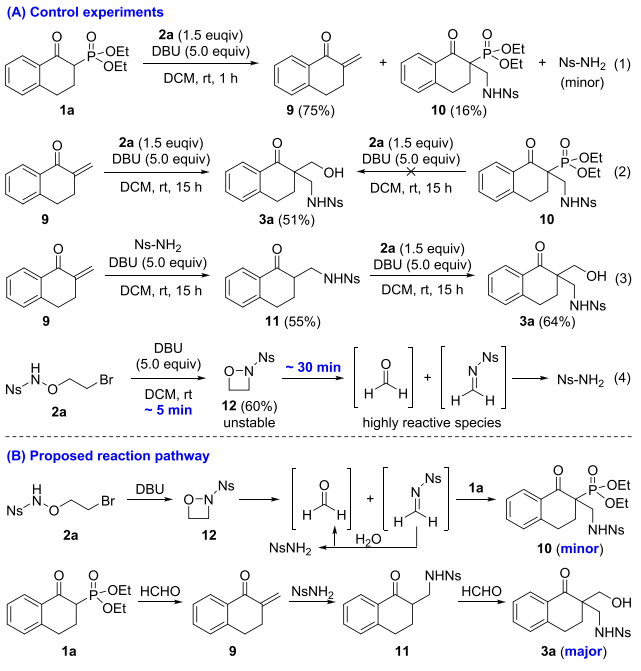


[a]Conditions A: **3** (0.2 mmol), DIAD (0.3 mmol), and PPh_3 (0.3 mmol) in toluene at 0 °C. Conditions B: **3** (0.2 mmol), DEAD (0.48 mmol), and PPh_3 (0.48 mmol) in toluene at room temperature.

should be formed via a sequential intramolecular Mitsunobu reaction and an unusual intermolecular [4 + 1] annulation[11] process (see the Supporting Information for details).

Finally, to gain insight of the α-hydroxymethylation and α-aminomethylation reaction, we carried out the following control experiments (Scheme 5A). We found that several intermediates were formed at the early stage of the reaction of

Scheme 5. Mechanistic Investigations



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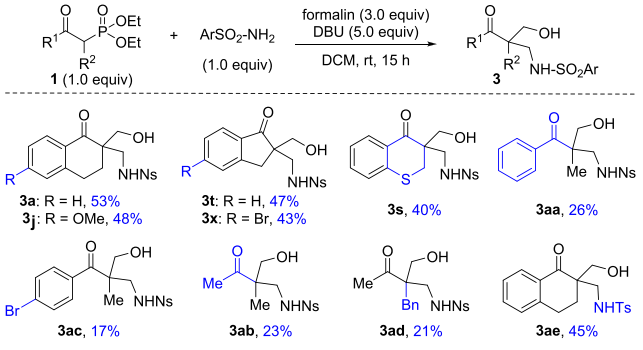
phosphonate **1a** and hydroxylamine **2a**. After quenching the reaction at 1 h, we isolated enone **9** in 75% yield along with α-aminomethyl phosphonate **10** and nosylamide as two minor products (eq 1). To validate if compounds **9** and **10** were the real intermediates of final product **3a**, we resubmitted them to the standard reaction conditions. Interestingly, enone **9** was eventually converted into **3a** in 51% yield, while compound **10** was gradually decomposed to complex mixture (eq 2). This result indicated that enone **9** should be the intermediate of product **3a**. Thus, we speculated that this enone intermediate might undergo the Michael addition reaction with nosylamide. Indeed, treatment of **9** with nosylamide afforded α-aminomethyl tetralone **11** in 55% yield in the presence of DBU base. Moreover, we also found that compound **11** could react with **2a** to produce the final product **3a** (eq 3). To further understand the role of hydroxylamine **2a** in the whole process, we just submitted **2a** to the DBU basic condition. Notably, a four-membered 1,2-oxazetidine[12] intermediate **12** was rapidly formed within 5 min of the reaction. However, this strained compound could be decomposed to 4-nitrobenzenesulfonamide under DBU basic conditions. Therefore, we deduced that the highly reactive formaldehyde and formaldimine intermediates might be involved in this fragmentation process (eq 4).

On the basis of the above experiments, we proposed a plausible pathway for the above tandem hydroxymethylation and aminomethylation reactions (Scheme 5B). Initially, hydroxylamine **2a** was quickly cyclized to 1,2-oxazetidine **12**, followed by decomposition to the formaldehyde and *N*-nosyl formaldimine in the presence of DBU base. Immediately, the highly reactive formaldehyde intermediate was captured by phosphonate **1** to form the enone **9** via Horner–Wadsworth–Emmons reaction.[13] Meanwhile, the formaldimine intermediate could also be partially captured by phosphonate **1**, thus giving the Mannich adduct **10** as a side product.[14] However, the *N*-nosyl formaldimine reagent was readily decomposed to nosylamide for the subsequent Michael addition reaction.[15] Finally, the intermediate **11** would take place the aldol reaction with in situ generated formaldehyde to form the product **3a**.

The above mechanistic study implied that hydroxylamine **2a** might be replaced by the simple nosylamide and formaldehyde such as formalin for the tandem process. Indeed, the multicomponent reaction of aromatic cyclic β-keto phosphonates (1.0 equiv), formalin (3.0 equiv), and nosylamide (1.0 equiv) could occur in the presence of DBU (5.0 equiv). However, the reaction gave lower yields of **3**, and benzoyl and acetyl substrates provided the products in even poor yields (Scheme 6). Meanwhile, tosylamide was also suitable for the reaction, but $BocNH_2$ and $BnNH_2$ failed to produce the target products. Overall, these results indicated that **2a** was not essential for the tandem process, which could be replaced by the simpler and readily available formalin and nosylamide reagents in practical synthesis.

Scheme 6. Tandem Reaction Scope with Sulfonamides



In conclusion, we have developed an unprecedented tandem hydroxymethylation and aminomethylation reaction of aromatic cyclic β-keto phosphonates with *N*-nosyl-*O*-(2-bromoethyl)hydroxylamine in the presence of DBU base, affording a range of α-hydroxymethyl-α-aminomethyl ketones in good yields. Mechanistic study revealed that hydroxylamine played a unique role in the whole process, which in situ generated the highly reactive formaldehyde and formaldimine reagents and in turn triggered the sequential Horner–Wadsworth–Emmons, Michael addition, and aldol addition reactions. Remarkably, the generated 1,3-aminoalcohols could be flexibly converted into the biologically important spirocyclic azetidines and azetidine-1,3,4-oxadiazoline bispirocycles via one simple Mitsunobu cyclization reaction. In particular, the latter products contain a challenging and novel vicinal bispirocyclic framework, wherein the 1,3,4-oxadiazoline ring was assembled via an unusual [4 + 1] annulation of dialkyl azodicarboxylate with carbonyl group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01091.

Experimental details, characterization data, NMR, and X-ray crystallographic data (PDF)

Accession Codes

CCDC 2074010 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Lin Hu − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China;* orcid.org/0000-0002-8600-965X; Email: lhu@cqu.edu.cn

Authors

Binyu Wu − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Hongbing Chen − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Min Gao − *Chongqing Key Laboratory of Natural Product Synthesis and Drug Research, School of Pharmaceutical Sciences, Chongqing University, Chongqing 401331, P. R. China*

Xiangnan Gong − *Analytical and Testing Center, Chongqing University, Chongqing 401331, China*

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Notes

The authors declare no competing financial interest.

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