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Studies toward synthesis of the core skeleton of spiroaspertrione A

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Bioassay-guided isolation of spiroaspertrione A from cultures of *Aspergillus sp*. TJ23 in 2017 demonstrated potent resensitization of oxacillin against methicillin-resistant *Staphylococcus aureus* by lowering the oxacillin minimal inhibitory concentration up to 32-fold. To construct this unique spiro[bicyclo [3.2.2]nonane-2,1′-cyclohexane] system, a protocol for ceric ammonium nitrate-induced intramolecular cross-coupling of silyl enolate is disclosed.

KEYWORDS

studies, synthesis, core skeleton, spiroaspertrione A, natural product

Introduction

The expansion of multidrug-resistant pathogens is a threat to human health that can effectively take us back to the pre-antibiotic era for many infectious diseases (Walsh et al., 2011). Considering its grave roles in hospital and community-acquired infections, methicillin-resistant *Staphylococcus aureus* (MRSA) is a “superbug” with an extreme array of resistance and virulence factors (Gonzales, et al., 2015). Drug-resistance gene mutations of MRSA are exemplified by *mecA*, the disruption of which can produce inducible resistance to *β*-lactam antibiotics because it encodes penicillin-binding protein 2a (Fuda et al., 2005). With the rapid acquisition of resistance restricting therapeutic options for MRSA, many scientists have explored treatment methods combining the use of small molecules to render MRSA sensitive to the effects of conventional *β*-lactam antibiotics (Van Hal et al., 2011; Long et al., 2014; Bush, 2015; Gonzales et al., 2015).

In 2017, Zhang group used a bioassay-guided approach to isolate a novel terpene-polyketide hybrid spiromero-terpenoid from a culture of *Aspergillus sp*. TJ23, spiroaspertrione A **(1)**, which bears a unique spiro[bicyclo[3.2.2]nonane-2,1′-cyclohexane] carbocyclic skeleton (Figure 1) (He et al., 2017). Spiroaspertrione A demonstrated potent resensitization of oxacillin against MRSA by lowering the oxacillin minimal inhibitory concentration (MIC) up to 32-fold from 32 μg/mL to 1 μg/mL (He et al., 2017). This promising bioactivity together with a unique spiro [bicyclo[3.2.2]nonane-2,1-cyclohexane] carbocyclic skeleton renders spiroaspertrione A an interesting and challenging target for total synthesis. To date, no synthesis method for spiroaspertrione A has been reported.

Here, we analyzed and constructed the core skeleton of this spiromeroterpenoid, culminating in a strategy of intramolecular enol oxidative coupling (Figure 2). When

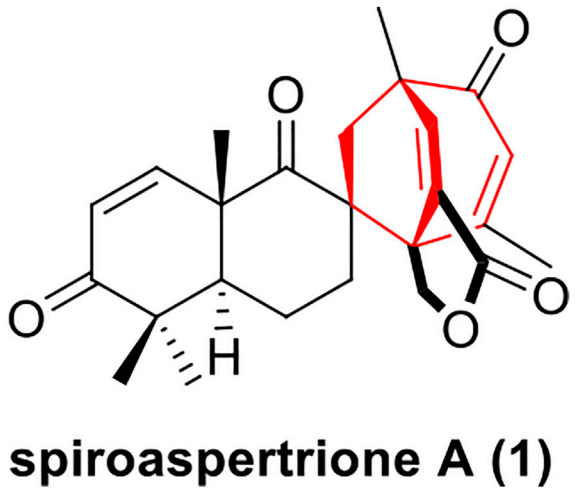


FIGURE 1
Structure of spiroaspertrione A (1).

designing this synthetic strategy for spiroaspertrione A, we noticed that the E lactone ring can be obtained by simple lactonization during later synthesis. Construction of the spiro [bicyclo[3.2.2]nonane] system of the ABCD rings exhibits a high degree of ring tension and rigidity–the most interesting and challenging feature of spiroaspertrione A synthesis. The core skeleton of spiroaspertrione A could be constructed through *Birch* reduction followed by methylation of the naphthene compound 2. This synthetically significant and more tractable spiro-ring system can then be built by an intramolecular enol oxidative coupling (EOC) reaction of precursor 3, which can then be traced back to a 1,4-conjugate addition of western fragment 5 and eastern fragment 4.

As an efficient synthetic method to directly construct C-C bonds, the oxidative coupling reaction of enol derivatives has been applied in the syntheses of polyketides, alkaloids, and other natural products. (Murarka and Antonchick 2018). Although the first oxidative coupling reaction of enol derivatives dates back to 1935, it did not receive widespread attention from chemists until the 1970s because the efficiency and practicality of this reaction were less than satisfactory (Fujii et al., 1992; Kohno and Narasaka 1995; Ryter and Livinghouse 1998; Ekebergh et al., 2011; Rathke and Lindert 1971; Dessau and Heiba 1974; Xie and Huang 2010; Renaud and Fox 1998). In 2005, Baran group began to conduct in-depth research on the oxidative coupling reaction of enolates and successfully applied their findings to the total synthesis of multiple complex natural products (Baran et al., 2005; Richter et al., 2007; DeMartino et al., 2008). To date, the oxidative coupling reaction of enol derivates remains under constant development and optimization. The EOC reaction can be broadly divided into two categories: direct oxidation, involving the construction of C-C bonds under single-electron oxidants (e.g., ketones, carboxylic acids, esters, and amides) bound to the corresponding enols or enolates; and indirect oxidation, in which single-electron oxidants are converted to the corresponding enol (e.g., silanes and enamines) prior to construction of the C-C bonds (Figure 3). The EOC reaction has been reviewed by Plumet (Csákÿ and Plumet 2001), Baran (Baran 2006), Dong (Yeung Dong 2011), Thomson (Guo et al., 2012), Ma (Nagaraju and Ma 2018), Chen (Chen and Liu 2021), and others.

In recent years, intermolecular and intramolecular EOC reactions have been applied to many natural products as an efficient method of constructing C-C bonds (Figure 4). Baran

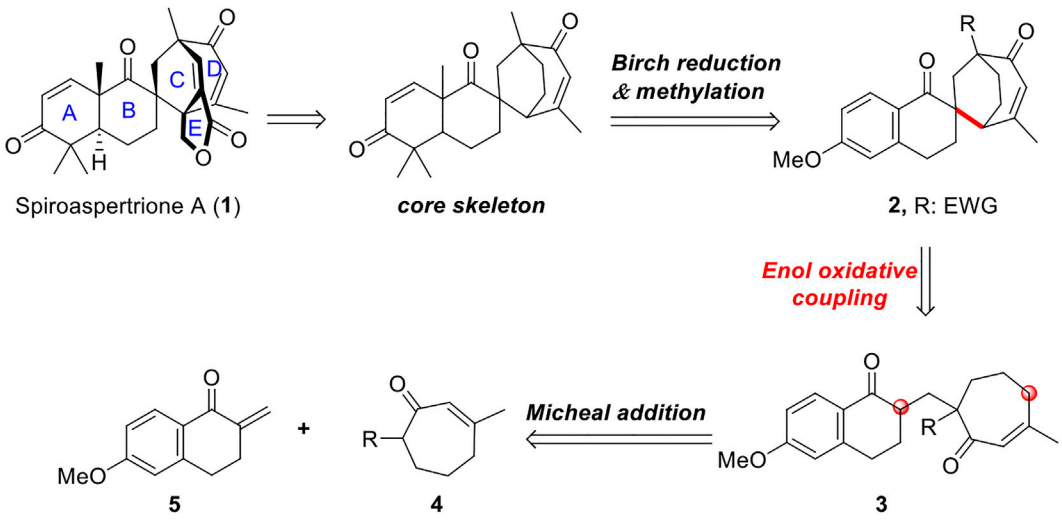


FIGURE 2
Retrosynthetic analysis.

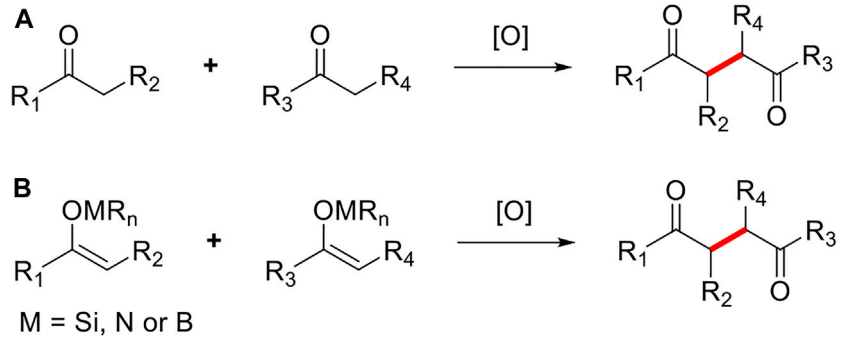


FIGURE 3
Types of enol oxidative coupling reaction.

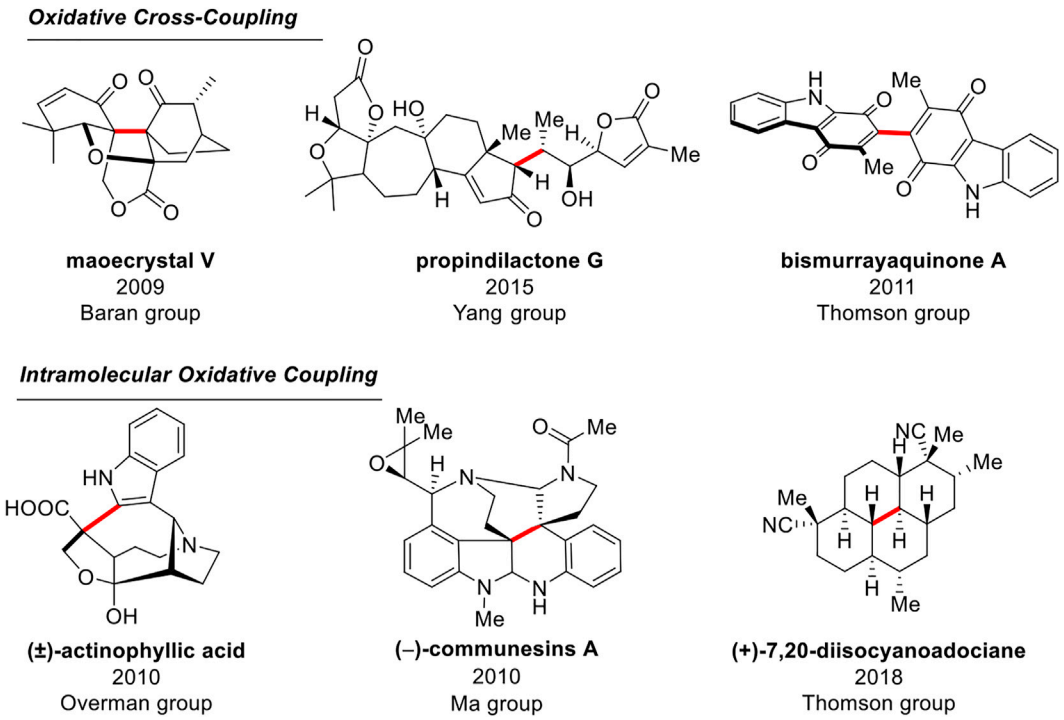


FIGURE 4
Application of EOC reaction in the synthesis of natural products.

group completed the construction of the core skeleton of the natural product *maoecrystal* V using intermolecular EOC reactions (Krawczuk et al., 2009). Furthermore, Yang group (You et al., 2015) used enol silyl ethers substrates to realize the enantioselective synthesis of *propindilactone* G from the Schisandra family by cross-oxidative coupling reaction. Moreover, Thomson groups disclosed a method of *self*-intermolecular EOC reactions applied to the synthesis of dimerized natural product *bis-murrayaquinone* A (Konkol et al., 2011).

Using intramolecular EOC reactions, Overman group (Martin et al., 2008; Martin et al., 2010) made important progress toward the total synthesis of the indole alkaloids (±)-*actinophyllic acid*. From 2010 to 2014, Ma group (Zuo

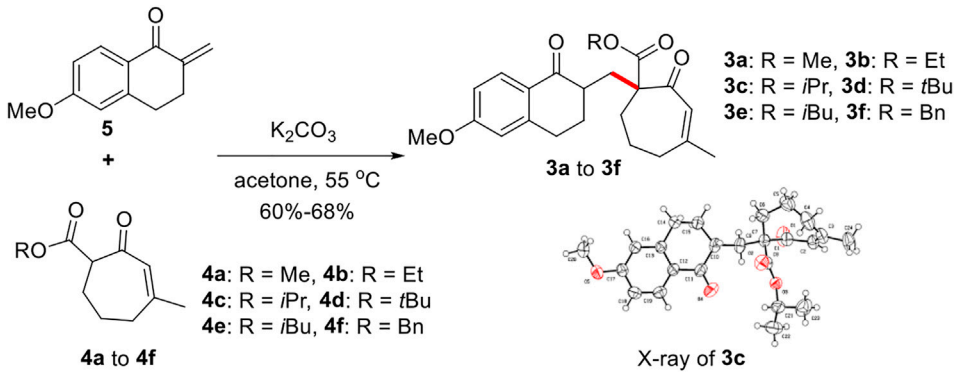
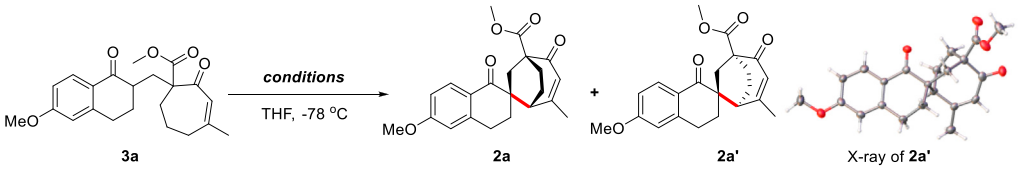
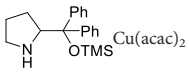


FIGURE 5
Synthesis of precursor 3.

TABLE 1 Optimization of the reaction conditions[a].

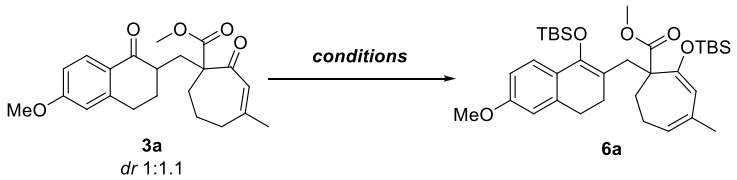


Entry	Conditions	Yield (2a+2a′)
1	LHMDS, $CuCl_2$	<5%, 60% (brsm)[b]
2	LHMDS, $FeCl_3$	<5%, 53% (brsm)[b]
3	LDA, $CuCl_2$	complex mixture
4	KHMDS, $CuCl_2$	9%
5	NaHMDS, $CuCl_2$	11%
6[c]	NaHMDS, $CuCl_2$, O_2	--
7[d]	NaHMDS, $CuCl_2$, air	--
8	NaHMDS, $Cu(acac)_2$	8%
9	NaHMDS, $FeCl_3$	9%
10	NaHMDS, I_2	--
11[e]		--

[a]Reactions were carried out with 3a (30 mg, 0.081 mmol), metal base (0.243 mmol), and single-electricity oxidant (0.162 mmol) in THF (2.0 ml) under N_2.
[b]Brsm = based on the recovered starting material.
[c]Reactions were carried out with $CuCl_2$ (20% mmol) under O_2.
[d]Reactions were carried out with $CuCl_2$ (20% mmol) under air.
[e]Reactions were carried out with 10 mol% catalyst and $Cu(acac)_2$ (20 mol%).

et al., 2010; Zuo and Ma 2011; Zi et al., 2012; Wei et al., 2013; Teng et al., 2014) realized the efficient construction of the core skeleton of indole alkaloids and synthesized several indole alkaloids such as (+)-*communesins* A. In 2018, Thomson group (Guo et al., 2012; Jones et al., 2014; Robinson and Thomson, 2018) reported the strategy of *intra*-EOC reaction using enol *di*-silyl ether to realize the formal synthesis of natural products (+)-7,20-*diisocyanoadociane* and other derived products.

TABLE 2 Optimization of silyl bis-enol etherification conditions[a].



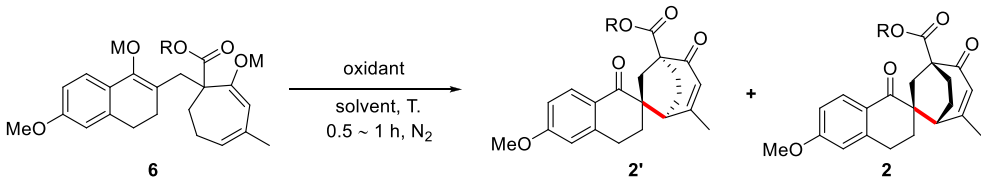
3a
dr 1:1.1

6a

Entry	Conditions	Yield %	
		Bis-silyl	Mono-silyl
1	LDA, TBSOTf, THF	complex mixture	
2	LHMDS, TBSOTf, THF	21	75
3[b]	LHMDS, HMPA, TBSCl, THF	24	74
4	KHMDS, TBSOTf, THF	35	60
5	NaHMDS, TBSOTf, THF	58	30
6[c]	Et_3N, TBSOTf, DCM	0	90

[a]Reactions were carried out with 3a (30 mg, 0.081 mmol), base (0.243 mmol), and TBSOTf (0.162 mmol) in THF (2.0 ml) at -78°C under N_2.
[b]Reactions were carried out with 3a (30 mg, 0.081 mmol), LHMDS (0.243 mmol), TBSCl (0.162 mmol) and HMPA (0.162 mmol) in THF (2.0 ml) at -78°C under N_2.
[c]Reactions were carried out with 3a (30 mg, 0.081 mmol), Et_3N (0.243 mmol), TBSOTf (0.162 mmol) in DCM (2.0 ml) at room temperature under N_2.

TABLE 3 Optimization of intramolecular EOC reaction conditions[a].



6

2'

undesired

2

desired

Entry	R	M	Oxidant	Solvent	T (°C)	dr[b]	Yield[c]
1	Me	TBS	CAN	CH_3CN/THF	0	8.7:1	77%
2	Et	TBS	CAN	CH_3CN/THF	0	8:1	74%
3	***i*Pr**	**TBS**	**CAN**	**CH_3CN/THF**	**0**	**4.9:1**	**69%**
4	*t*Bu	TBS	CAN	CH_3CN/THF	0	12:1	68%
5	*i*Bu	TBS	CAN	CH_3CN/THF	0	6.4:1	62%
6	*i*Pr	TES	CAN	CH_3CN/THF	0	5.8:1	64%
7	*i*Pr	TIPS	CAN	CH_3CN/THF	0	6.8:1	64%
8	*i*Pr	TBS	$CuCl_2$	CH_3CN/THF	−78 to rt	--	21% (50%)[d]
9	*i*Pr	TBS	$Cu(acac)_2$	CH_3CN/THF	−78 to rt	--	--
10	*i*Pr	TBS	$FeCl_3$	CH_3CN/THF	−78 to rt	--	23% (54%)[d]
11	*i*Pr	TBS	AgF, PhBr	CH_3CN	Rt	--	no reaction
12	*i*Pr	TBS	PhI(OH)OTs	DCM	−78	12:1	61%

[a]Reactions were carried out with 6 (0.08 mmol), CAN (0.24 mmol), and $NaHCO_3$ (0.48 mmol) in CH_3CN/THF (0.1 M, 4:1) at 0°C under N_2.
[b]Determined ratio of 2′ and 2 by ^1H NMR.
[c]Isolated yields of 2 and 2′ after purification by column chromatography.
[d]Isolated yields of 3 after purification by column chromatography.

Materials and methods

Unless otherwise noted, all reactions were carried out under N_2 atmosphere. All reagents were from commercial sources and used as received without further purification. All solvents were dried by standard techniques and distilled prior to use. Column chromatography was performed on silica gel (200–300 meshes) using petrol etherand ethyl acetate as eluent. NMR spectra were recorded on a Bruker Avance operating at for ^{1}H NMR at 500 MHz, ^{13}C NMR at 126 MHz and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard and $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as solvent. All high-resolution mass spectra (HRMS) were obtained by Thermo Scientific's UltiMate 3,000 Series liquid system and Thermo Scientific Q-Exactive combined quadrupole Orbitrap mass spectrometer.

According to our retrosynthetic analysis, we chose known compound 5 (Li et al., 2019) and 4 self-prepared from 3-methylcyclohept-2-en-1-one as substrates to form the important precursor 3. Following screening of various conditions, we obtained compound 3 as a minor product with a yield of 30% under NaH and MeOH, and compound 5's *O*-1,4-addition byproduct as the major product. Subsequent screening of several Lewis acids, such as BF_3·OEt and $TiCl_4$, yielded substrate 5's *O*-DA reaction byproduct as the major product. To our delight, conducting the reaction in acetone at 55°C in the presence of K_2CO_3(2 eq) afforded the desired 1,4-addition product 3 with 60%–68% yield (Figure 5).

With precursor 3a in hand, we intended to construct the desired C-C bond by single-electron oxidation under conditions including a metal base (Table 1). In the presence of LHMDS and cupric chloride ($CuCl_2$) or ferric chloride ($FeCl_3$), we obtained a very small amount of the EOC product 2a and 2a′, although the recovery yield was 60% (Table 1, entries 1 and 2). We assumed that LHMDS conditions were not conducive to the formation of stable enolates, thus, screened various metal bases. When using LDA as the base, the reaction only provided a complex mixture and trace amount of product with the oxidant $CuCl_2$ (Table 1, entry 3). The substrate was completely consumed under conditions including KHMDS or NaHMDS (Table 1, entries 4 and 5). Although we tried numerous oxidative conditions, the yield of oxidative coupling products was not significantly improved (Table 1, entries 6 to 11).

Results and discussion

According to the unsatisfactory experimental results described above, we assumed that substrate 3a may form more stable metal complexes with Cu(II) or Fe(III) ions under the alkaline system, thereby inhibiting the process of oxidative coupling. Therefore, we envisaged the replacement of this stable complex by enol silyl ether (Table 2). We chose compound 3a as a substrate to first optimize the silyl bis-enol etherification condition. The desired silyl bis-enol ether product 6a was obtained with 21% yield in THF (2.0 ml) at -78°C under N_2 in the presence of LHMDS (0.243 mmol) and TBSOTf (0.162 mmol) (Table 2, entry 2). As previously mentioned, it was not conducive to obtain silyl enol ethers and could be broken down using LDA as the base (Table 2, entry 1). Encouraged by this result, we surveyed other bases including NaHMDS, KHMDS and Et_3N, and found that NaHMDS generated the best yield (58%) while Et_3N only generated monosilyl product (Table 2, entries 3–6).

With the enol bis-silyl ether 6a in hand, we intended to optimize the intramolecular enol oxidative coupling reaction (Table 3). Conducting the reaction in CH_3CN/THF at 0°C in the presence of CAN (0.24 mmol) and $NaHCO_3$ (0.48 mmol) exclusively afforded the coupling products in 77% isolated yield after 0.5 h (Table 3, entry 1). However, the main product 4a′ identified by X-ray analyses was an undesired stereoisomer. We intended to optimize the diastereomeric ratio (*dr*) by changing the ester group of 6 (Table 3, entries 2–5) and found that the isopropyl *dr* of ester substrate (3c) reached 4.9:1. We also explored the effect of different silicon groups (Table 3, entries 6–7). Unfortunately, changing the silicon groups did not decisively progress the EOC reaction. Finally, we evaluated different oxidants to optimize the *dr* of products (Table 3, entries 8–12). Cu(II) chloride and Fe(III) chloride produced the coupling products with 21% and 23% yields, but even more of the desilylation product 3 (Table 3, entries 8 and 10). Other metal oxidants, including $Cu(acac)_2$ and AgF, provided a complex mixture of product and raw product 6c (Table 3, entries 9 and 11), and the result of Koser's reagent (PhI(OH)OTs) was also unsatisfactory (Table 3, entry 12).

Conclusion

In conclusion, we developed an efficient method of constructing the spiro[bicyclo[3.2.2]nonane] system by intramolecular enol oxidative coupling reaction. Although the diastereomeric ratio of products is embarrassing, the high yield of this remote oxidative coupling reaction to build rigid spiro[bicyclo[3.2.2]nonane] structures is encouraging. Our findings once again confirm the practicality of enol oxidative coupling reactions in natural products and provide a new strategy for the synthesis of spiroaspertrione A. Further study for the total synthesis of spiroaspertrione A is underway in our laboratory.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ Supplementary Material.

Author contributions

AM and ZS designed the project and wrote the manuscript. ZS, SL, JZ, XZ, JP, and JZ performed the experiments. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2022.1022533/full#supplementary-material

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