

REVIEW

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The present and future synthetic strategies of structural modifications of sinomenine

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Sinomenine is a tetracyclic alkaloid that is extracted from the traditional Chinese medicine *sinomenium acutum*. It has been reported to possess low cytotoxicity and a variety of biological activities, such as anti-tumor, anti-inflammatory and anti-arthritic effects. However, the relatively short biological half-life of sinomenine hinders its extensive clinical application. Hence, extensive research on its structural modifications has been carried out in recent decades. The reaction sites can be classified into four categories based on functional groups—aromatic ring (A-ring), benzylic position (B-ring), enone (C-ring) and trialkylamine (D-ring). This review summarizes the representative examples of each modification to date and discusses the synthetic difficulties, especially the chemoselectivity and stereoselectivity of reactions. The future prospects of synthesis of sinomenine derivatives from sinomenine-like derivatives and by some novel late-stage functionalizations, which can be potentially applicable to sinomenine, of structurally similar derivatives are also discussed.

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1. Introduction

Sinomenine **1** is an alkaloid and is a biologically active component extracted from the root of an herbal plant *sinomenium*

acutum. Traditionally, *sinomenium acutum* has been used for treating arthritis patients in China.¹ Recent studies showed that its primary ingredient, sinomenine **1**, was responsible for the anti-arthritic effect.^{2–4} Sinomenine has also exhibited a wide spectrum of biological activities, such as anti-tumor, anti-arrhythmic, immunosuppressive, anti-hypertensive, and anti-inflammatory effects.^{1,5,6} In particular, sinomenine was used as a combinational therapy with methotrexate to treat rheumatoid arthritis effectively.⁷ Despite the promising biological properties of sinomenine, some potential adverse clinical

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Paolo Coghi

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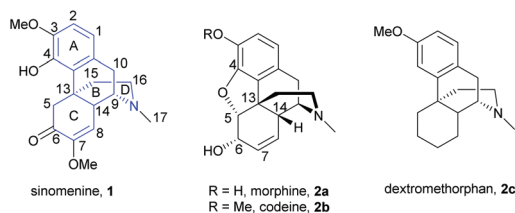


Fig. 1 Structures of sinomenine **1**, morphine **2a**, codeine **2b** and dextromethorphan **2c**.

cal effects and relatively short biological half-life of sinomenine were reported.^{8,9} Structural modification thus became a hot topic for optimizing the properties of sinomenine.

Sinomenine is a morphine-type compound consisting of a tetracyclic framework (Fig. 1). Structurally, it is similar to codeine except for having an oxa-bridge between C4 and C5, opposite stereochemistry of the D-ring and different substituents at C6 and C7 positions. Other natural products like dextromethorphan **2c** also possess a similar tetracyclic framework without having the oxa-bridge that is found in morphine **2a** and codeine **2b**. Sinomenine is composed of three labile functional groups—tetrasubstituted aromatic ring, α,β -unsaturated ketone and trialkylamine. Therefore, four major reaction sites are identified as aromatic ring (A-ring), benzylic position (B-ring), enone (C-ring) and amine (D-ring). The multifunctional groups of sinomenine also give rise to difficulties in the chemoselectivity of reactions upon modifications. In some cases, one single step generated several products that pure compounds were inseparable¹⁰ or one useful synthetic intermediate was obtained in a low yield.¹¹ In view of these, developing high selectivity synthetic protocols is of the utmost importance for advanced research in the future drug design of sinomenine.

The pharmacological effects, mechanisms and clinical applications of sinomenine and its derivatives have been summarized in numerous reviews.^{1,5,6,12} Although some reviews briefly summarized the synthesis of some important deriva-

tives, the systematic analysis of selectivity and reactivity issues in synthetic protocols was not made.^{12–14} Thus, we would like to reveal some representative examples of each modification and discuss the synthetic issues found in the synthesis. To provide new insight into the development of novel sinomenine derivatives, synthetic strategies of sinomenine derivatives from functionalizations of other naturally or commercially available sinomenine-like derivatives are also reviewed.

2. Modifications of the aromatic ring (A-ring)

Among different chemically active functional groups of sinomenine **1**, the tetrasubstituted aromatic ring of sinomenine is the most considerable site for modifications due to its broad scope of chemical reactivity and less sterically hindered environment.

2.1 Electrophilic aromatic substitution

Electrophilic aromatic substitution is a typical reaction for benzene. The A-ring of sinomenine **1** is highly prone to electrophilic attack due to the high electron density and extra stabilization of cationic intermediates by electron-rich substituents. Electrophilic aromatic substitution of the A-ring of **1** and its derivatives has been reported with high regioselectivity at the C1 position by halogenation, nitration and Friedel–Crafts alkylation.

Halogenation of **1** with *N*-halosuccinimide (NXS, X = Cl, Br or I) resulted in aryl halides **3a–c** with moderate to high yields (55–85%, Scheme 1).^{15,16} In the absence of the enone moiety, the iodination of C-ring non-functionalized derivatives also provided iodide **4** with a comparable yield (84%).¹⁷ Halogenations using NXS also worked well in other substrates with 1,2- and 1,4-reduced enone of the C-ring.¹⁶ Only mono-halogenated products were observed when using NXS as the halogenating reagent. Similarly, bromination of **1** with bromine in dichloromethane only generated mono-halogen-



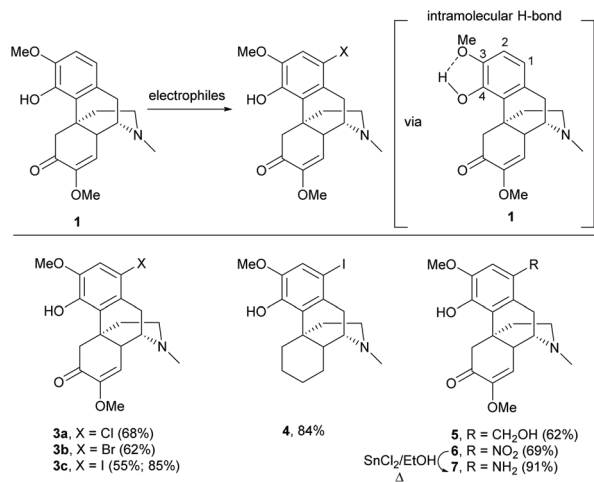
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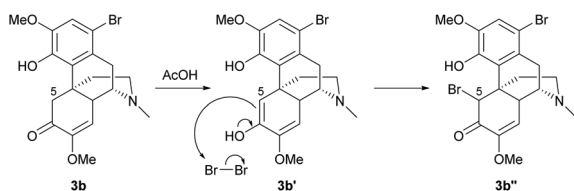


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Liang Liu received his Ph.D. in Medicine from Guangzhou University of Traditional Chinese Medicine in 1990. He is currently the President of Macau University of Science and Technology and Director of State Key Laboratory of Quality Research in Chinese Medicine. His research in the integrative approach of Western and traditional Chinese medicine has been recognized by many awards and honorary titles.



Scheme 1 Electrophilic aromatic substitutions of sinomenine **1**.



Scheme 2 Proposed reaction mechanism of α-bromination of **3b**.

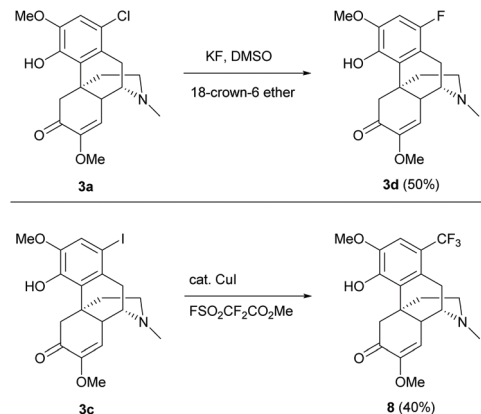
nated derivatives. However, the reaction of **1** with bromine in acetonitrile afforded intermediate **3b''** with dibromide at C1 and C5 positions, and subsequently basic treatment caused ring closure between the C4-hydroxy group and C5-bromide to afford morphine derivatives.¹⁸ The α-bromination of ketone at C5 involves the formation of enol (Scheme 2). A more polar solvent stabilizes the formation of enol and consequently facilitates the α-bromination. Hence, bromination using a rela-



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research focuses on the relationship between autophagy and multi-drug-resistant, apoptosis-resistant anti-tumor effects via SERCA inhibition and AMPK activation.

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Scheme 3 Fluorine-halogen exchange of **3a** and nucleophilic trifluoromethylation of **3c**.

tively more polar solvent, MeCN (dielectric constant of MeCN vs. CH₂Cl₂ = 37.5 vs. 8.93), occurs at both C1 and C5.

Other 1-substituted electron-withdrawing groups were synthesized from halides **3a/3c** but not directly from **1** (Scheme 3).¹⁹ Fluoride **3d** was generated by fluorine-halogen exchange using potassium fluoride as the fluorinating reagent. Similarly, nucleophilic trifluoromethylation of iodide **3c** afforded 1-trifluoromethyl derivative **8** (Scheme 3).

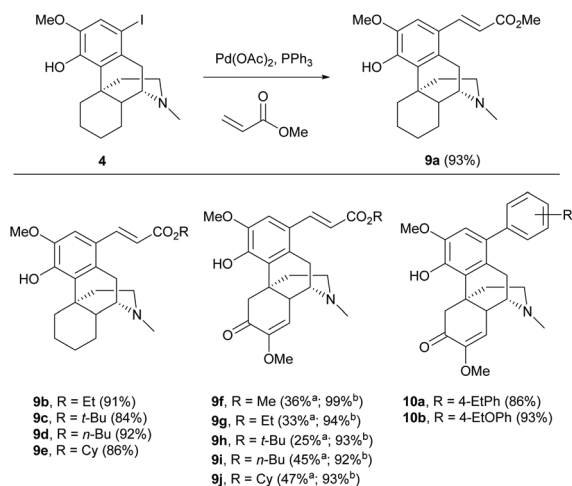
The Friedel-Crafts type reaction with formaldehyde and nitration with sodium nitrite generated 1-hydroxymethyl derivative **5** and 1-nitro derivative **6** respectively (Scheme 1), which were important synthetic intermediates for further functionalization, such as alkylation and acylation.^{20–22} Furthermore, the reduction of the nitro group with SnCl₂/EtOH under reflux conditions was performed selectively to yield amine **7** without over-reduction in the C-ring. Otherwise, typical reduction conditions using a palladium catalyst and hydrogen afforded the 1,4-reduced product as mentioned in Scheme 25.

Interestingly, the electrophilic aromatic substitution of **1** is highly regioselective at the C1-position. The intramolecular H-bond between C3-methoxy and C4-hydroxy was proposed to increase the mesomeric and inductive effects of the C4-hydroxy group toward the *para*-position (C1) (Scheme 1).²³ Meanwhile, the intramolecular H-bond diminished both effects of the C3-methoxy group toward the *ortho*-position (C2). The steric strains for substitutions at C1- and C2-positions are similar. Therefore, the regioselectivity of **1** was governed by the electronic factor.

2.2 C(sp²)-C(sp²) coupling reaction

The C(sp²) functionalization of the A-ring of **1** can be achieved by palladium-catalyzed C(sp²)-C(sp²) coupling reaction *via* the key intermediates aryl halides derived from halogenation as mentioned in section 2.1.

Catalytic cross-coupling reactions of aryl iodide **4** with various acrylates and Pd(OAc)₂ by the Heck reaction generated cinnamate derivatives **9a–c** with high yields (84–93%,



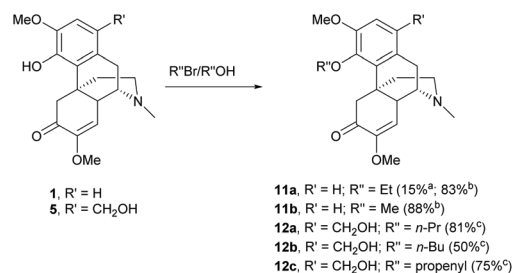
Scheme 4 Cross-coupling reactions of aryl halides with aryl and alkenyl coupling partners catalyzed by palladium. ^a Reactions were performed without a microreactor. ^b Reactions were performed with a microreactor.

Scheme 4).¹⁷ Using a microreactor for the Heck reaction provided the same products **9f–j** with higher yields by 46–68% in a short reaction time (20 min).²⁴ Generally, palladium-catalyzed cross-coupling reactions afforded (*E*)-isomers of adducts as the major products because the *syn*-β-hydride elimination of the reaction occurred *via* the less steric congestion to afford the thermodynamically favourable (*E*)-olefin. Milder reaction conditions using Suzuki coupling with aryl boronates also produced the corresponding aryl–aryl coupling products **10a–b** with comparable yields (86–93%, Scheme 4).²⁵ Further extension of the substrate scope of coupled products is potentially performed by using the Heck reaction in conjunction with CO insertion.

2.3 O-Alkylations and esterifications

Sinomenine possesses the C4-hydroxy group which is prone to further chemical modifications and is one of the major nucleophilic sites of sinomenine. To date, the *O*-alkylations and esterifications have been reported leading to ether and ester derivatives respectively.

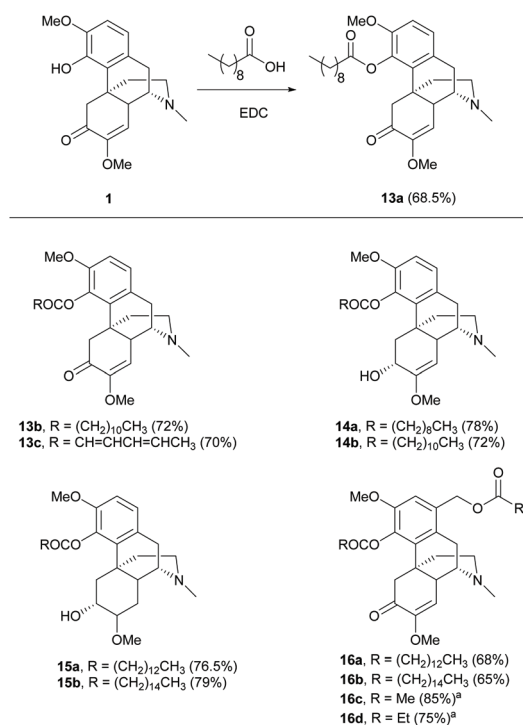
Alkylations of the labile C4-hydroxy group proceeded either *via* S_N2 reactions with alkyl halides²¹ or the Mitsunobu reaction with alcohols.²⁶ Alkylation of **1** with ethyl bromide using K₂CO₃ as the base resulted in a low yield of **11a** (15%, Scheme 5) because of the formation of a *N*-alkylated product (81% yield).²⁶ Generally, *N*-alkylation is more favorable than *O*-alkylation. When Cs₂CO₃ was used as a base, the yield of **11a** was improved up to 83% (Scheme 5).²¹ High yield and chemoselective alkylation of the C4-hydroxy group was also observed in derivative **11b** probably due to the cesium effect. The cesium effect resulted in a weak coordination of the cesium cation with the phenolic anion. The phenolic anion became more nucleophilic and the *O*-alkylation was predominant over *N*-alkylation.²⁷ Moreover, the cesium cation was proposed to



Scheme 5 The 4-*O*-alkylations of sinomenine derivatives. ^a K₂CO₃ was used as the base. ^b Cs₂CO₃ was used as the base. ^c Reactions were performed under Mitsunobu reaction conditions.

coordinate with trialkylamine to form a quaternary ammonium compound.²⁸ The lone pair of N atom was no longer available for the alkylation. Alternatively, the alkylation of the C4-hydroxy group by the Mitsunobu reaction provided chemo-selective alkylated products **12a–c** in high yields (50–81%, Scheme 5).²⁶

Esterification of the C4-hydroxy group of **1** afforded ester derivatives **13a–c** with saturated and unsaturated alkyl chains in similar yields (~70%, Scheme 6).^{29,30} Moreover, the phenolic hydroxy group at the C4 position reacted chemoselectively over the secondary hydroxy group at the C6-position, resulting in esters **14–15** due to the higher acidity of the C4-hydroxy group.³⁰ Notably, the primary alcohol at the C1-position of derivative **5** was also susceptible to esterification, resulting in di-esters **16a–b**.²⁹ Incorporation of the PEG moiety at the



Scheme 6 The 4-*O*-acylations of sinomenine derivatives. ^a Reactions were performed with acid anhydrides.

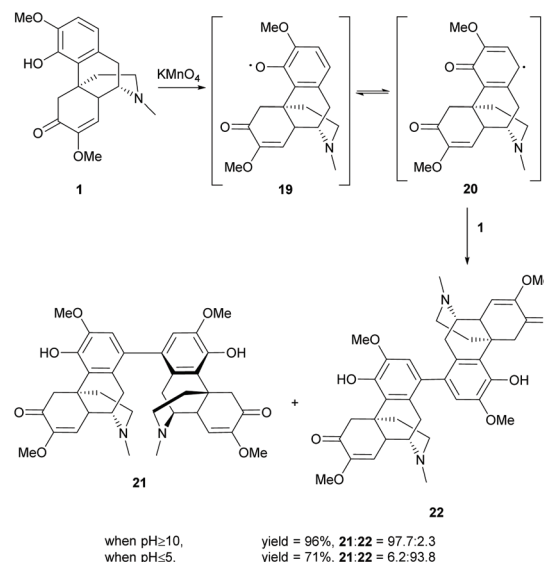
C4-substituent by esterification with EDC was also reported.³¹ Despite using EDC as the coupling reagent, the acylation of **5** with acid anhydrides generated di-esters **16c–d** with higher yields (75–85%, Scheme 6).²¹ However, the installation of longer alkyl chains by acid anhydrides is not as good as the methodology using EDC with carboxylic acids due to expensive or commercially unavailable acid anhydrides with long alkyl chains and the poor atom economy of the reaction.

Derivative **17** with terminal alkyne was obtained using KOH as the base in an exceptionally high yield (96%, Scheme 7). The tolerance of sinomenine derivative **17** towards 1,3-dipolar cycloadditions was reported.³² The 1,3-dipole was not prepared from sinomenine due to the incompatibility of the C6-carbonyl group towards its formation. Therefore, the alkyne component was incorporated into the C4-position of **1** by an S_N2 reaction with 3-chloropropyne (Scheme 7). The subsequent cycloaddition of **17** worked well with both electron-rich and electron-deficient 1,3-dipoles derived from the corresponding aromatic aldehydes, to afford cycloadducts **18a–e** with moderate to high yields (76–91%, Scheme 7). Under similar reaction conditions, 1,3-dipolar cycloaddition of C1-cinnamate derivative **9f** (Scheme 4) with 1,3-dipoles resulted in similar yields (81–93%).²⁴ The cycloaddition of the enone of the C-ring was not observed probably due to the steric effect of the α -substituent.

2.4 Dimerizations

Synthesis of dimers of sinomenine was reported by using oxidative coupling reactions and the 4-*O*-alkylation/esterification conditions as mentioned in section 2.3. Dimers generated by 4-*O*-alkylation/esterification used dibromoalkanes, diacyl chlorides or diols as linkers. The full substrate scope can be referred to the literature.³³

Another strategy for coupling of **1** at the C1-position by oxidation with KMnO₄ synthesized stereoisomers **21** and **22** stereoselectively at different pH values (Scheme 8).³⁴ The oxidation of **1** under basic conditions (pH ≥ 10) provided **21** as the major stereoisomer (**21:22** = 97.7:2.3) while that under acidic conditions (pH ≤ 5) provided **22** as the major stereoisomer (**21:22** = 6.2:93.8). The total yield of both stereoi-



Scheme 8 Dimerization of **1** by oxidative coupling.

somers diminished at low pH probably due to the strong oxidative effect of KMnO₄ under acidic conditions.

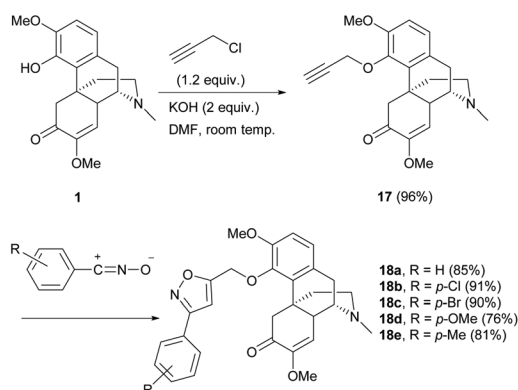
The reaction was proposed to undergo a radical oxidative aromatic coupling *via* aryl radical **20**, similar to the synthesis of BINOL.³⁵ The stereoselectivity was probably controlled by the reaction rate of radical formation. Under acidic conditions, the stronger oxidizing power of KMnO₄ allows the fast formation of radicals, leading to kinetically stable product **22** with less steric hindrance. While the alkaline conditions diminished the oxidizing power of KMnO₄, the slower formation of radicals allowed the re-organization of the conformations of radicals **20** and **1**. Finally, thermodynamically stable product **21** was formed probably due to the extra stability arising from intermolecular π - π stacking of the A-ring.

For faster screening of the bioactivity of both stereoisomers, other oxidants, such as MnO₂ and FeCl₃/H₂O₂, afforded both stereoisomers in a ratio of approximately 1:1. More examples of dimers with a modified C-ring of **1** were found in the literature.³⁶

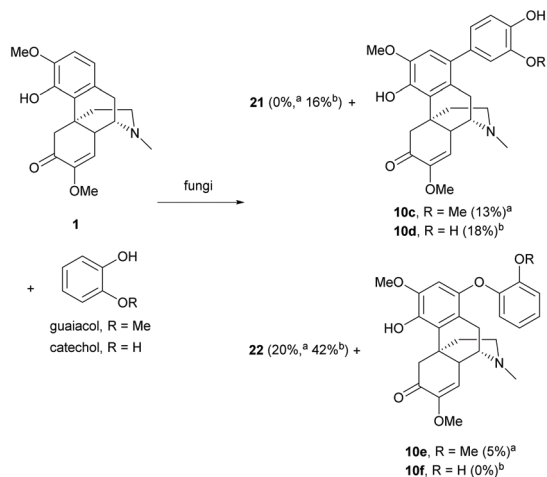
Other than the chemical methods, dimerization of **1** can also be achieved by biotransformation.^{37,38} Biotransformation of **1** with *Antrodia semisupina* generated dimer **22** in a low yield (20%).³⁸ The reaction was capable of coupling on multiple substrates. The biotransformation of **1** with guaiacol generated dimer **22** (20%) together with C–C coupled derivative **10c** (13%) and C–O coupled derivative **10e** (5%, Scheme 9).

However, no cross-coupled product was obtained when the reaction of **1** and catechol was performed with the same fungus *Antrodia semisupina*.³⁷ Another screened fungus *Coriolus unicolor* catalyzed the reaction to synthesize both dimers **21** and **22** (58% combined yield) and C–C coupled derivative **10d** (18%) as a minor product (Scheme 9).

As proposed by the authors, the biotransformation proceeded *via* a mechanism similar to the oxidative radical



Scheme 7 The 4-*O*-alkylations of **1** and the subsequent 1,3-dipolar cycloaddition of alkyne derivative **17**.



Scheme 9 Dimerization and cross-coupling of **1** by biotransformation. ^a Reaction was performed with *Antridiella semisupina*. ^b Reaction was performed *Coriolus unicolor*.

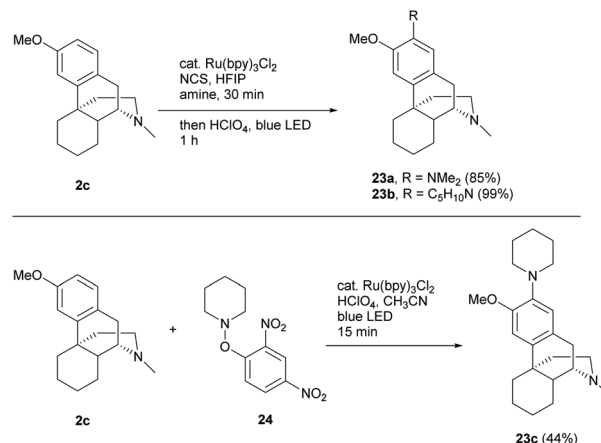
pathway as depicted in Scheme 8. The oxidation of **1** and guaiacol/catechol generated oxygen radicals at hydroxy groups, which were delocalized to form carbon radicals for subsequent homo- and cross-couplings. The proposed mechanism was verified by acetylation of the 4-hydroxy group of **1**.³⁸ Once the 4-hydroxy group was protected, no coupled product was observed. In general, the homo-coupling of **1** was predominant over cross-coupling probably due to the formation of a more stable radical derived from **1**.

2.5 Future prospects of synthesis of A-ring modified sinomenine derivatives from late-stage functionalizations of other derivatives with similar core structures

Sinomenine and the related structures possessed an absolute configuration of the D-ring opposite to that of codeine derivatives and this was confirmed by X-ray crystallography of the cyclization product of 1,4-reduced derivative **61** (Scheme 25).³⁹ Despite the direct modification of sinomenine **1**, dextromethorphan **2c** or other structurally similar derivatives became an alternative option of the starting material due to the similarity of the tetracyclic framework and low cost. For example, **2c** was shown to be a neuroprotective and anti-inflammatory agent, similar to **1**.⁴⁰ Moreover, the novel functionalizations of **2c** and other similar derivatives may be possibly applicable to sinomenine, especially C-ring non-functionalized derivative **58** (Scheme 24).

Recent developments of novel chemical reactions showed their compatibility towards complex biomolecules by using dextromethorphan as one of the examples. Ruffoni *et al.* showed the regioselective radical amination of arenes with aliphatic amines by photocatalysis.⁴¹ The amination of dextromethorphan **2c** with 24 different aliphatic amines afforded 2-aminated products with >50% yields in most cases of which two representative examples are shown in Scheme 10.

The reaction showed high tolerance to the hydroxy group, halide, ester and alkene. This may allow the reaction to be

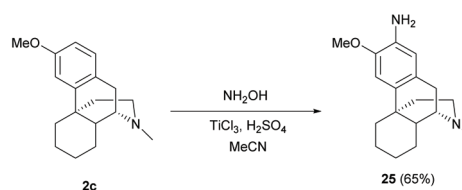


Scheme 10 Regioselective amination of **2c** by alkyl amines.

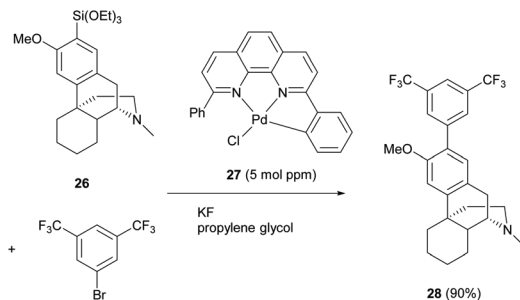
applied in the late-stage modifications of sinomenine and its derivatives with a protecting-group-free strategy. Notably, radical amination of **2c** with *O*-aryl hydroxylamine **24** afforded **23c** with a diminished yield (44%) but a faster conversion within 15 min (Scheme 10).⁴²

The direct C–H amination of arenes with hydroxylamine mediated by titanium(III) chloride was reported to be applicable in complex natural products including sinomenine-like derivative **2c** to provide a shorter synthetic step than typical amination steps (nitration and subsequent nitro reduction).⁴³ The reaction of **2c** with hydroxylamine proceeded *via* the formation of the aminyl radical ($\cdot\text{NH}_2$), which was derived from TiCl_3 -mediated N–O bond cleavage, to afford aniline **25** in one step (65%, Scheme 11). Notably, labile functional groups such as hydroxy and enone have to be protected prior to utilizing this protocol.

Similar to the reaction mechanism of the $\text{C}(\text{sp}^2)\text{--}\text{C}(\text{sp}^2)$ coupling reaction as described in section 2.2, Ichii *et al.* demonstrated the Hiyama cross-coupling of aryl bromides with aryl(trialkoxysilanes) at a ppm level loading of Pd catalyst **27**.⁴⁴ Only one example of the cross-coupling reaction of silylated dextromethorphan **26** was demonstrated in a high yield (90%, Scheme 12). Notably, the synthesis of silylated **26** involved the use of *n*-BuLi which was incompatible with the enone of the C-ring of **1**. However, using C-ring non-functionalized derivative **58** or switching the role of **1** from a silylating reagent to a bromide reagent will be feasible for the reaction.



Scheme 11 The TiCl_3 -mediated C–H amination of arene **2c** with hydroxylamine.

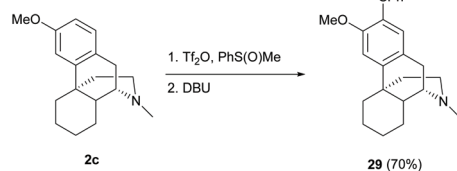


Scheme 12 Hiyama cross-coupling of dextromethorphan derivative **26** with aryl bromide.

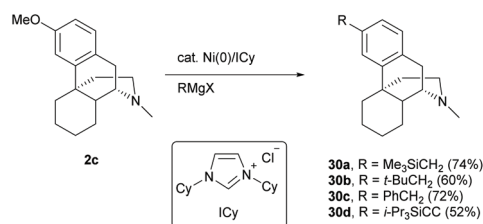
The synthesis of unsymmetrical diaryl sulfide **29** by direct $C(sp^2)$ -H thioarylation using phenyl methyl sulfoxide activated by triflic anhydride resulted in a high yield (70%, Scheme 13).⁴⁵ The reactions demonstrated a high functional group tolerance, such as aldehyde and enone, which showed its suitability in the late-stage modification of sinomenine derivatives.

Direct modification of the C3-methoxy group of **2c** with Grignard reagents by nickel catalysis underwent C-O cleavage and subsequent C-C bond formation to afford derivatives **30a-d** in moderate to high yields (52–74%, Scheme 14).^{46,47} Similarly, C-ring non-functionalized derivative **58** will work well for the reaction preventing **1** from the 1,2-addition with Grignard reagents.

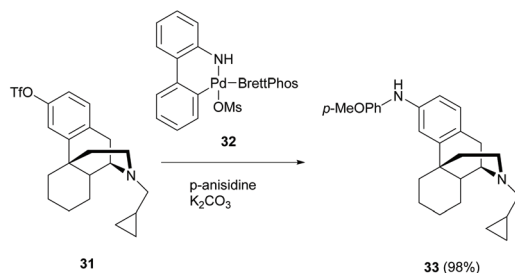
The amination of the aryl ring of aryl triflate **31**, an enantiomeric derivative of **2c**, was also reported by Pd-catalyzed cross-coupling of aryl triflate with aromatic amine. A nearly quantitative yield of coupled product **33** was isolated (98%, Scheme 15).⁴⁸ The opposite enantiomer of **31** also underwent the reaction analogously to yield the corresponding enantiomer of **33** in 89% yield. However, another Pd-catalyzed amin-



Scheme 13 The $C(sp^2)$ -H thioarylation of **2c** with sulfoxide.



Scheme 14 Nickel-catalyzed cross-couplings of **2c** with Grignard reagents.



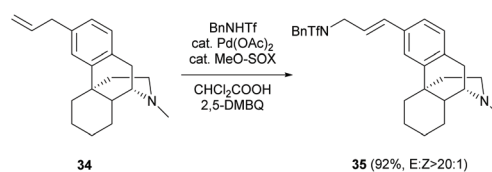
Scheme 15 Buchwald-Hartwig amination of aryl triflate **31** with *p*-anisidine.

ation of triflate derivatives with amines was reported with low yields (<20%) probably due to improper choice of ligands.⁴⁹

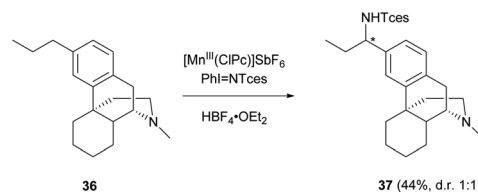
A novel synthetic protocol for allylic $C(sp^3)$ -H amination was developed. One example of Pd catalysis of $C(sp^3)$ -N fragment coupling reaction of olefin **34** derived from **2c** was reported to give **35** in a high yield (91%) and *E*-selectivity (Scheme 16).⁵⁰ The reaction is well-tolerant to tertiary amine (D-ring) by protonation with dichloroacetic acid.

Other than $C(sp^2)$ -H functionalization at the A-ring, $C(sp^3)$ -H amination at the benzylic position of 3-alkyl substituted **36** by manganese catalysis was reported in a moderate yield (44%, Scheme 17).⁵¹ The amination occurred chemoselectively at the remote benzylic position but not the benzylic position at C-10 resulting from the electron-deficiency induced by the protonation of 3° amine with $HBFe_4$. Changing the catalyst from manganese to rhodium provided amination at 3° amine to furnish hydrazine as the major product.⁵²

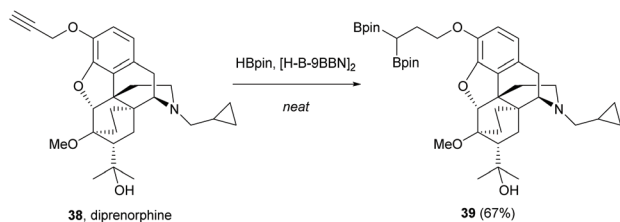
Alkyne, an electron-rich functional group, has demonstrated one of its reactivities towards 1,3-dipolar cycloaddition in the modifications of sinomenine (Scheme 7). Recently, diprenorphine **38** with similar core structures to sinomenine possessed terminal alkyne which underwent double hydroboration.⁵³ Unlike the typical hydroboration using transition



Scheme 16 The $C(sp^3)$ -N fragment coupling reaction of olefin **34** with BnNHTf.



Scheme 17 The $C(sp^3)$ -H amination of **36** by manganese catalysis.



Scheme 18 Borane-catalyzed alkyne double hydroboration of diprenorphine **38**.

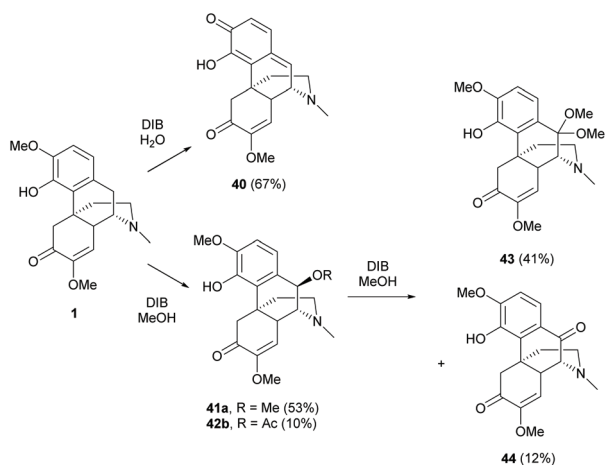
metals, the double hydroboration of diprenorphine was catalyzed by 9-borabicyclo[3.3.1]nonane (H-B-9BBN) to afford *gem*-diboryl product **39** (67%, Scheme 18).

3. Modifications of the B-ring

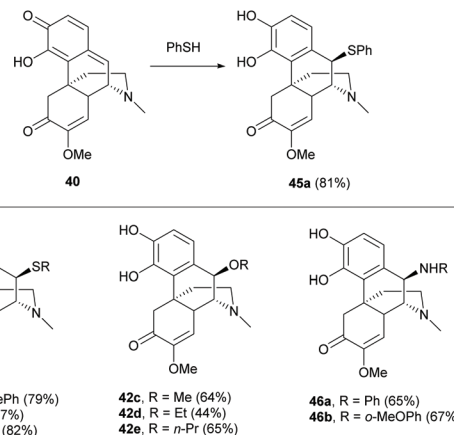
3.1 The modifications of the benzylic position of sinomenine (B-ring)

The B-ring of sinomenine is one of the most difficult positions for chemical modifications due to the steric effects of A-, C- and D-rings.

One strategy is to functionalize the benzylic position by oxidizing the A-ring of **1** into a quinone methide **40** with $\text{PhI}(\text{OAc})_2$ (DIB).^{54,55} The products obtained were solvent-dependent (Scheme 19). The oxidative dearomatization in H_2O provided quinone methide **40** while that in methanol generated re-aromatized products **41a** and **41b**. The formation of **41a** and **41b** was postulated to result from 1,6-conjugated addition of **40** prepared *in situ* from **1**, with methanol from solvent or acetate from DIB. The results showed that activated **40** was highly susceptible to the attack of nucleophiles, even as weak as acetate. Similar nucleophilic addition was also observed when **41a** was oxidized with DIB in methanol. After the first oxidation of **41a**, 1,2-addition of oxidized product **44** proceeded with methanol to afford **43** as the major product (Scheme 19).



Scheme 19 Oxidation of **1** by DIB in different solvents.



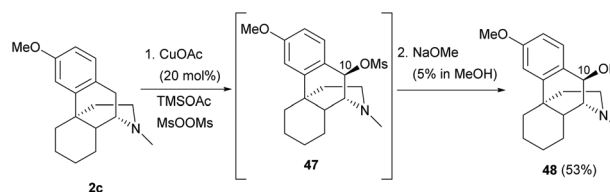
Scheme 20 The 1,6-conjugated addition of **40** with thiols, alcohols and amines.

After the formation of quinone methide **40**, the subsequent conjugated addition with thiophenol occurred selectively to afford adduct **45a** with a good yield (81%, Scheme 20). Aliphatic and electron-rich aromatic thiols also worked well in the reaction ($\geq 79\%$ yields). Moreover, the reaction proceeded with hard nucleophiles, alcohols and amines, to afford **42** and **46** respectively, but with lower yields (44–67%, Scheme 20) compared with soft nucleophiles (thiols). Generally, the chemoselectivity of the quinone (A-ring) over the enone in the C-ring resulted from the formation of a more energetically feasible product by rearomatization of the A-ring upon the addition. Surprisingly, the conjugated addition occurred stereospecifically at the *Si*-face of **40** due to the sterically hindered D-ring.

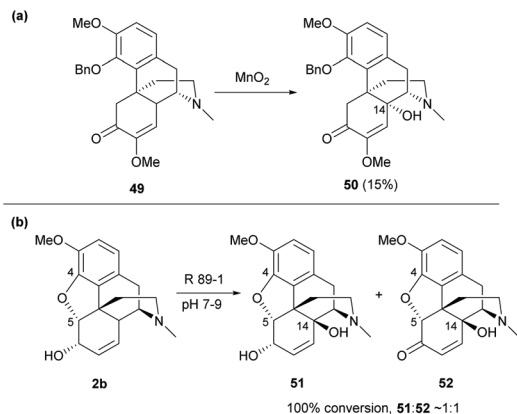
3.2 Future approaches of functionalizations of ring B of sinomenine

As described in section 3.1, the present synthetic strategy on the benzylic position of ring B is limited to quinone methide **40** and its 1,6-conjugated adducts. Future prospects of modifications of ring B are possible to be developed by modifying the synthetic protocols of sinomenine-like derivatives.

The C10-H oxygenation of sinomenine-like derivative **2c** generated mesylate **47** *via* proton coupled electron transfer between the mesyloxyl radical and **2c** (Scheme 21).⁵⁶ Subsequent $\text{S}_{\text{N}}1$ reaction of mesylate with acetate and hydro-



Scheme 21 The C10-H oxidation of **2c** with bis(methanesulfonyl) peroxide.



Scheme 22 (a) The chemical oxidation of 4-O-benzyl protected derivative **49** by MnO_2 ; (b) the oxidation of codeine **2b** by the biocatalyst *Rhizobium radiobacter* R89-1.

lysis provided C10-hydroxy derivative **48** (53%). A minor over-oxidation product with C10-carbonyl was also observed (10%).

Despite the functionalization at the C10-benzylic position of sinomenine, oxidation of 4-O-benzyl protected derivative **49** with MnO_2 yielded the C14-hydroxy derivative **50** (15%, Scheme 22a).⁵⁷ Notably, the protection of the C4-hydroxy group is the key to C14 oxidation. Otherwise, the dimerization of sinomenine occurred as shown in Scheme 8.

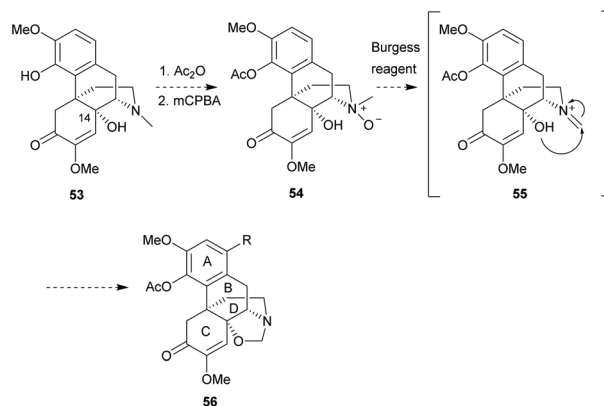
Other than the chemical method for C14 oxidation, it is also possible to synthesize the C14-hydroxy derivatives from codeine by using a biocatalyst. The biotransformation of **2b** with the biocatalyst *Rhizobium radiobacter* R89-1 afforded C14-hydroxy derivatives **51–52** in nearly 1:1 (Scheme 22b).⁵⁶ The tetracyclic framework of sinomenine can be obtained by C4,5-ether cleavage of codeine derivatives which will be further discussed in section 4.2.

Recently, some authors⁵⁸ discovered that a novel fused-ring between B- and D-rings was constructed by the Burgess reagent⁵⁹ ($\text{Et}_3\text{NSO}_2\text{NCO}_2\text{Me}$) in a one-pot sequence from a sinomenine-like derivative, oxymorphone. Based on the protocol, C14-hydroxy sinomenine derivative **53** was proposed to form intermediate **54** with C4-acetylation and N-oxide formation (Scheme 23). Notably, the N-oxidation of sinomenine has been reported in the literature (Scheme 43a).⁶⁰ Iminium **55** was postulated to be obtained by demethylation of N-oxide using the Burgess reagent, and then trapped by 14-hydroxy to form a novel oxazolidone ring in **56**. Future strategies could involve the functionalization between C14- and N-positions to increase the structural complexity of sinomenine.

4. Modifications of the C-ring

4.1 The modifications of enone of sinomenine (C-ring)

The C-ring of sinomenine possesses the major functional group, enone, which is reactive towards nucleophilic attack, amination, reduction, etc.

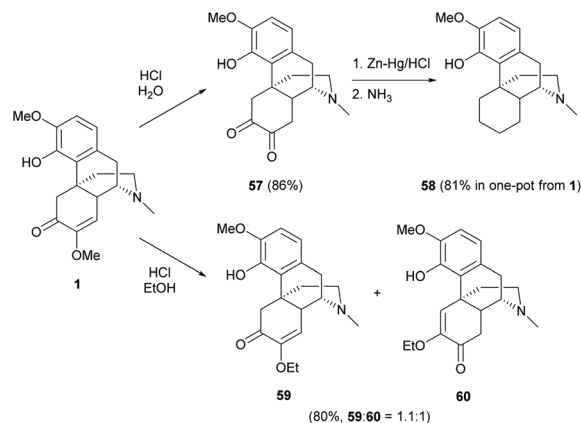


Scheme 23 Proposed synthetic plan for forming a new fused-ring between rings B and D.

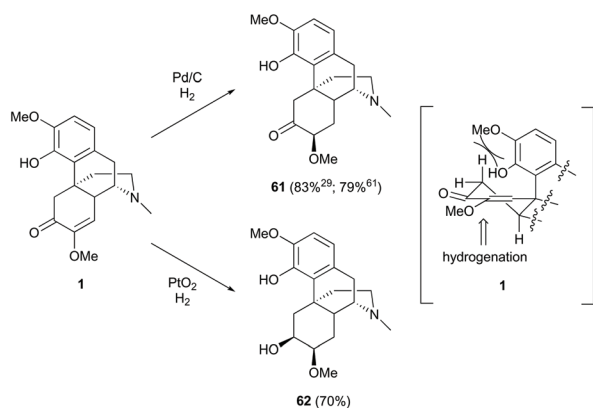
Interestingly, simple acidic treatment of sinomenine **1** yielded several different products. The enol ether of **1** was hydrolyzed to a diketone **57** by using HCl in H_2O (86% yield, Scheme 24).⁶¹ Further reduction of the C-ring yielded **58** in one-pot from **1** with a high yield (81%) via the Clemmensen reduction of the *in situ* generated diketone **57** from hydrolysis (Scheme 24).¹⁷ A small amount of two incomplete reduction products was also reported with either one ketone or one hydroxy group left in the C-ring, but the actual structural configurations were not determined.

When treating **1** with HCl in ethanol, the transformation provided the displacement of OMe with the OEt group and/or rearrangement of enone **59** into **60** in a ratio of nearly 1:1 (Scheme 24).⁶¹ Various chain lengths of saturated and unsaturated alcohols also worked smoothly as reported in the literature.⁶²

Hydrogenation of enone **1** was performed chemoselectively and stereoselectively with different catalysts (Scheme 25). Treatment of enone **1** with Pd/C as the catalyst generated 1,4-reduction product **61** in high yields (83%;²⁹ 79%⁶¹), while that with PtO_2 afforded over-reduction product **62** in a comparable



Scheme 24 Hydrolysis and/or hydrogenation of the C-ring of sinomenine **1**.

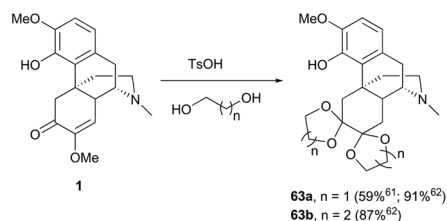
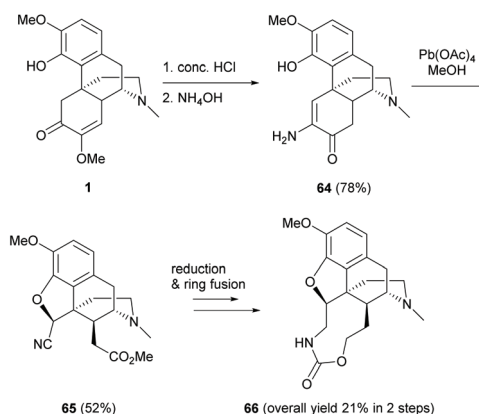
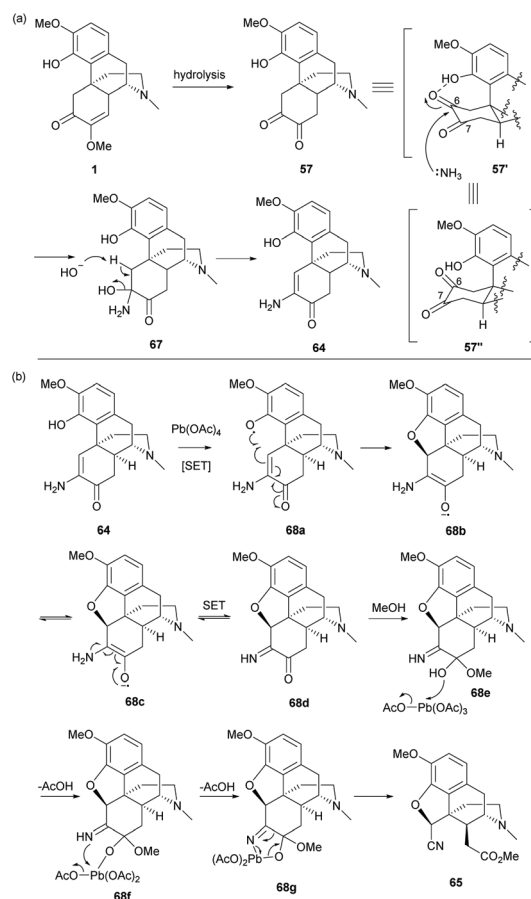
Scheme 25 Catalytic reduction of **1** with hydrogen.

yield (70%).⁶¹ Under hydrogenation conditions, Pt catalyst reacted with the carbonyl group faster than Pd catalyst.⁶³ Therefore, reduction of **1** with PtO_2 afforded **62** *via* the reduction of the C6-carbonyl group followed by C7,8-alkene. As shown in the half-chair conformation of **1**, the sterically hindered A-ring prevents the catalyst from approaching the top side; thus, the hydrogenation occurs at the less hindered bottom side, resulting in stereoselective products **61** and **62** (Scheme 25).

To avoid unnecessary side reactions like nucleophilic addition in the modifications of other reaction sites, protection of enone with ethylene glycol under acidic conditions yielded vicinal diacetal **63a** in a moderate yield (59%, Scheme 26).⁶¹ Inconsistently, higher yields of diketals **63a–b** (87–91%) were reported probably due to the driving force from removing water by the Dean-Stark technique.⁶²

Alternatively, hydrolysis of **1** in the presence of HCl and ammonium hydroxide produced keto-enamine **64** with a high yield (78%, Scheme 27).¹¹ The regioselectivity of the nucleophilic attack of NH_3 on the C6-carbonyl group of **57** was probably facilitated by the intramolecular H-bond of phenol in **57'** (Scheme 28a). Treating **64** with lead tetraacetate caused oxidative cleavage of the C-ring and intramolecular ring-closure between the C4-hydroxy group and C5 position respectively to afford nitrile ester **65** as a single diastereomer (Scheme 27).

As depicted in the proposed mechanism in Scheme 28b, the ring closure of **64** proceeded *via* a radical oxidation with $\text{Pb}(\text{OAc})_4$, resulting in keto-imine **68d**. The stereochemistry of

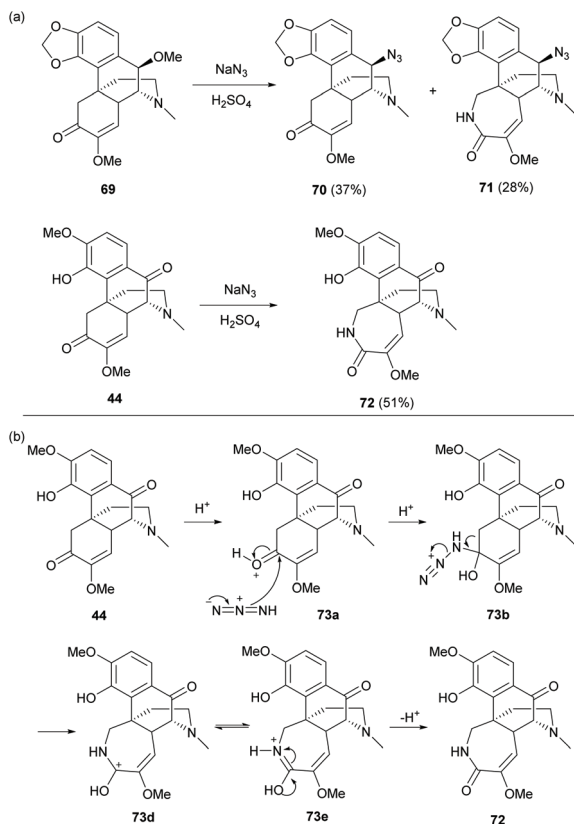
Scheme 26 Protection of **1** with glycols under acidic conditions.Scheme 27 Hydrolysis and subsequent ring distortion of sinomenine **1**.

Scheme 28 Proposed reaction mechanisms of (a) the formation of enamine; (b) ring closure and subsequent ring cleavage.

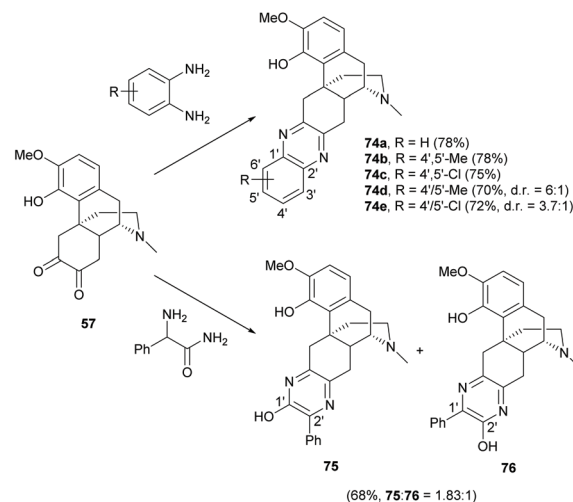
C5 is in the (*S*)-configuration due to the ring closure at the less hindered β -face. The consequent oxidative cleavage of **68d** generated **65** as a single diastereomer without altering the stereochemistry at C14. Further modification of **65** to **66** was performed by reduction with LiAlH_4 followed by ring fusion with triphosgene (Scheme 27).

Based on the synthesis of C10-substituted product **42c** as mentioned in section 3.1, treatment of diol-protected **69** under Schmidt reaction conditions ($\text{NaN}_3/\text{H}_2\text{SO}_4$) proceeded *via* substitution at the C10-position and/or ring expansion to afford compounds **70** and **71** respectively (Scheme 29a).¹¹ Both C-10 substituted derivatives **70** and **71** were obtained with retention of stereochemistry. The azide approached from the less hindered upper face of secondary carbocation which was formed and stabilized by delocalization of the A-ring. Similar ring-expansion product **72** was also observed (51% yield) when **44** was treated under Schmidt reaction conditions (Scheme 29a). The proposed mechanism of the ring-expansion reaction under Schmidt conditions is exemplified by **44** (Scheme 29b). Under acidic conditions, azide attacks the activated and less hindered C6-carbonyl group, leading to intermediate **73b**. The azide easily extrudes nitrogen gas in many reactions such as the Staudinger ligation. The formation of nitrogen gas as the leaving group becomes the driving force for generating intermediate **73e** by a Baeyer–Villiger-like reaction. Finally, derivative **72** was obtained.

A series of sinomenine-pyrazine derivatives were prepared from the condensation of diketone **57**, which was derived from the HCl hydrolysis of sinomenine **1**, with diamines (Scheme 30).¹⁰ Condensation reactions of **57** with symmetrical diamines provided **74a–c** as single products in high yields



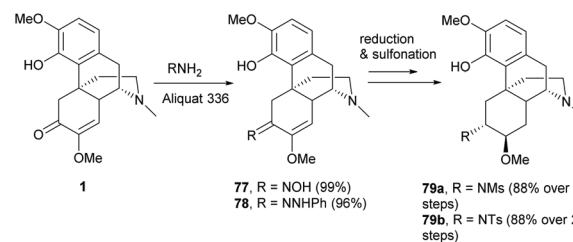
Scheme 29 (a) Substitution and/or ring expansion of **69** and **44** under Schmidt reaction conditions; (b) proposed reaction mechanism of ring expansion of **44** under Schmidt reaction conditions.



Scheme 30 Synthesis of sinomenine-pyrazine derivatives by condensation reactions of diketone **57** with diamines.

($\geq 75\%$). The reactions with unsymmetrical diamines also afforded **74d–e** in high yields (70–72%) but poor regioselectivity (ranging from 3.7:1 to 6:1). Unfortunately, the regioisomers of **74d** and **74e** were inseparable and it was difficult to determine their structures due to the spectral similarity. One solution was to synthesize separable regioisomers by increasing the polarity difference of regioisomers by switching either the 1' or 2'-position with a more polar hydroxy group.⁶⁴ Therefore, condensation of **57** with phenylglycinamide generated two separable regioisomers **75** and **76** in a high combined yield (68%), where **75** was the major regioisomer (Scheme 30). The phenolic hydroxy groups of **75** and **76** at 1' and 2'-positions were further diversified by triflylation and Suzuki couplings with various boronic acids for biological evaluation. Over 30 examples of condensation products were synthesized, including imidazole-fused derivatives.^{10,61,64–66}

Similarly, C6-ketone of **1** was also reactive towards the condensation reaction without any pre-treatment. The reaction proceeded smoothly with hydroxylamine and phenyl hydrazine respectively to afford **77** and **78** in nearly quantitative yields (Scheme 31).^{36,67} Condensations of **1** with other aromatic amines and hydrazines produced imine and hydrazone derivatives with yields of $\geq 81\%$.⁶² Further transformation of oxime **77** yielded sul-



Scheme 31 Condensation reactions of **1** with hydroxylamine and phenyl hydrazine and further transformation of **77** to **79** by reduction and sulfonation.

fonamides **79a–b** by the stereoselective reductions of imine and enol ether with Pd/C and subsequent reactions of amines with sulfonyl chlorides (Scheme 31).³⁶ Alternatively, tosylated oxime was also obtained by direct tosylation of **77** with TsCl.⁶²

Despite the 1,4-reduction of enone **1** as depicted in Scheme 25, 1,2-reduction of enone proceeded stereoselectively with LiAlH₄ to afford alcohol derivatives **81a–d** with high yields (88–95%) and in the (*S*)-configuration at the C6-position (Scheme 32a).⁶⁸ Reductions of other 1- or 4-substituted derivatives were also reported with high yields and in the (*S*)-configuration.^{16,68} The C6-hydroxy group with the (*R*)-configuration was prepared by using another reducing reagent, NaBH₄, in a lower yield even in large excess (19 equiv., Scheme 32a).⁶⁹ The different stereochemical outcomes between LiAlH₄ and NaBH₄ were probably due to different intermediates formed prior to reduction (Scheme 32b). The reaction of **1** with LiAlH₄ first generated lithiated intermediate **84**. The hydride was then proposed to approach C6-carbonyl from the less sterically hindered side of **84**. In contrast, the reaction of **1** with NaBH₄ generated a boron complex **85** by alcoholysis.⁷⁰ The hydride was delivered to C6-carbonyl from C4-borohydride of **85**, resulting in a different stereochemical outcome.

Treatment of the C6-hydroxy group of **82** with DAST (Et₂NSF₃) underwent an S_N2-like mechanism to provide C6-fluorinated derivative **83** with inversion of stereochemistry.

4.2 Future prospects of synthesizing sinomenine derivatives from other naturally and commercially available products (C-ring)

Apart from direct modification of sinomenine, other morphine derivatives with the C4,5-ether bridge, such as codeine, would

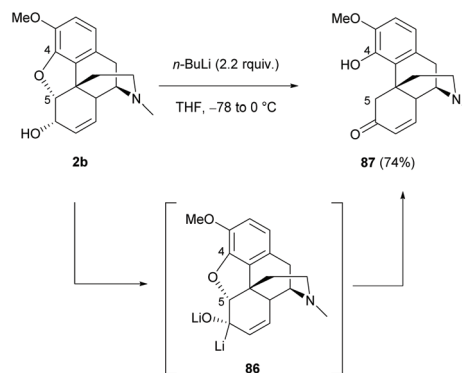
be a readily available source for synthesizing opposite enantiomers of sinomenine by breaking the C4,5-ether bridge.

The ring-opening of **2b** with excess *n*-BuLi resulted in sinomenine-like tetracyclic derivative **87** in a high yield (74%, Scheme 33).⁷¹ The reaction was proposed to proceed *via* an E1cB (Elimination Unimolecular conjugate Base) mechanistic pathway with the formation of dilithiated intermediate **86**.

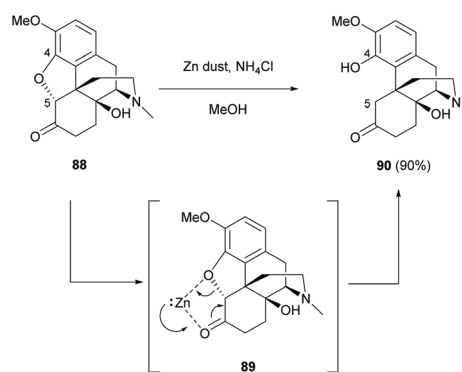
The breaking of the oxa-bridge of thebaine derivative **88** with zinc under acidic conditions also yielded sinomenine derivative **90** (90%, Scheme 34).⁷² The reductive cleavage of C4,5-ether bridge was postulated to proceed *via* zinc-activated complex **89**.

Alternatively, the cleavage of the C4,5-ether bridge of the morphine derivative naloxone was reported by a modified Wolff–Kishner reduction (Scheme 35).⁷³ The reaction proceeded *via* a one-pot, two-step synthesis. The C6-carbonyl of **91** was first converted to *N*-*tert*-butyldimethylsilylhydrazone derivative **92** with 1,2-bis(*tert*-butyldimethylsilyl)hydrazine. Subsequent modified Wolff–Kishner reduction at room temperature generated the desired tetracyclic sinomenine derivative **93** (81%).

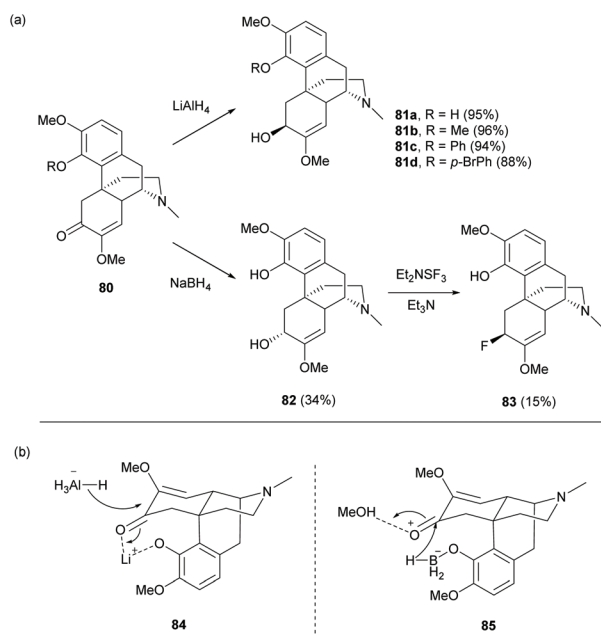
As illustrated by the above examples, breaking the C4,5-ether bridge of morphine derivatives provides a future prospect



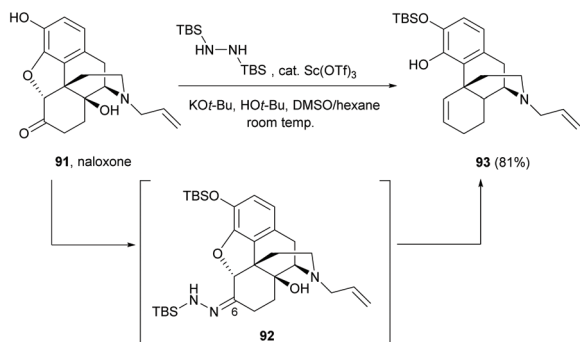
Scheme 33 Ring-opening of the 4,5-ether bridge of **2b** by *n*-BuLi.



Scheme 34 Reductive ring-opening of thebaine derivative **88** with Zn dust under acidic conditions.



Scheme 32 (a) 1,2-Reduction of enone **80** and fluorination of alcohol **82**; (b) proposed intermediates for different stereoselectivity between LiAlH₄ and NaBH₄.



Scheme 35 Ring-opening of naloxone **91** by Wolff-Kishner reduction.

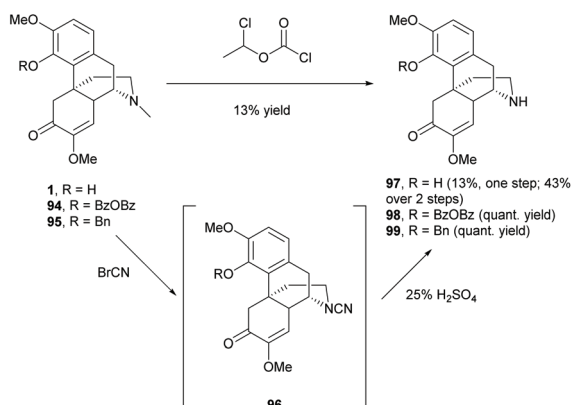
for diverse C-ring derivatization of the enantiomeric isomer of sinomenine, which is naturally unavailable.

5. Modifications of the D-ring

5.1 The modifications of trialkylamine of sinomenine (D-ring)

The D-ring of sinomenine comprises electron-rich trialkylamine which is a very reactive nucleophile. As mentioned in section 2.3, the nucleophilic amine competed with other nucleophiles in the substitution reactions. Efforts have been made on modifications of the D-ring by deactivating the reactivity of amine and switching the *N*-methyl substituent to various biologically active moieties.

In order to replace the *N*-methyl substituent with other functionalities, several demethylation methods were reported to synthesize precursors **97–99** for further alkylation.^{74–77} *N*-Demethylation of 4-*O*-unprotected **1** was performed directly in one step using 1-chloroethyl chloroformate (Scheme 36). However, demethylated product **97** was obtained albeit in low yield (13%). In contrast, 4-*O*-protected **94–95** underwent demethylations smoothly in quantitative yields (Scheme 36).^{75–77} An additional step of 4-*O*-deprotection was required after the functionalization of amine groups of **98–99**. The 4-*O*-BzOBz group of **98** was removed by using trifluoroacetic acid (TFA), while the 4-*O*-benzyl group of **99** was removed by Pd/C in



Scheme 36 *N*-Demethylations of **1**, **94** and **95**.

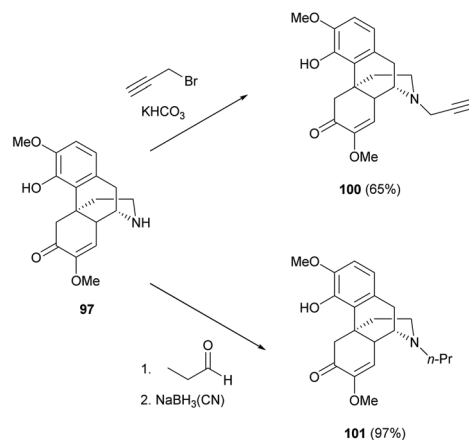
ethanol with cyclohexane (1–10 equiv.). Notably, the debenzylation of **99** under similar reductive conditions as shown in Scheme 25 did not cause 1,4-reduction of enone in the absence of hydrogen.

Alternatively, **97** was also obtained from a 2-step synthesis with an improved yield (43%) compared with the one-step demethylation of **1** (13%, Scheme 36). The *N*-methyl substituent of **1** was first converted to cyanamide **96**, and then subjected to hydrolysis using sulfuric acid without further purification to afford **97** with a yield up to 43%. Finally, the obtained dialkylamines **97–99** were available for further functionalizations like alkylation, protection, *etc.*

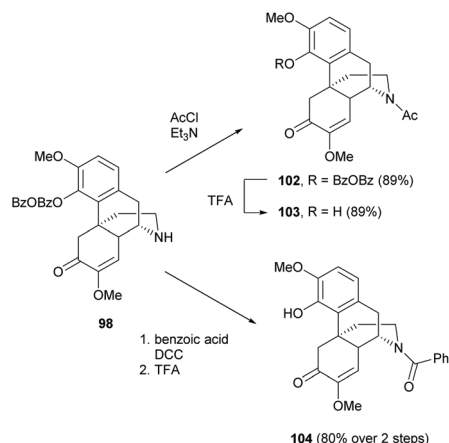
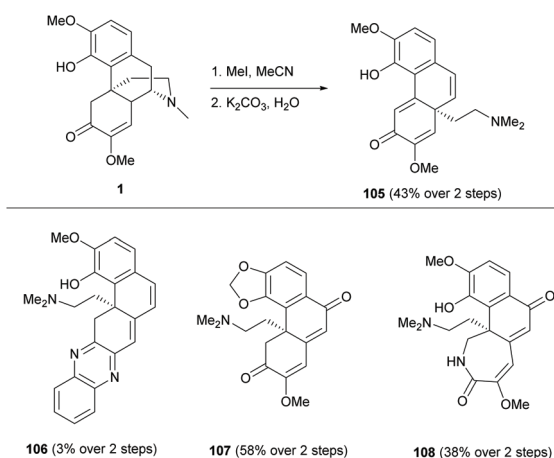
After *N*-demethylation, the *N*-alkylation of dialkylamine **97** was reported to proceed by either an S_N2 reaction with alkyl halide or a reductive amination with aldehyde (Scheme 37).^{74,75} Generally, the latter method provided higher yields by avoiding side reactions, such as 4-*O*-alkylation or *N*-dialkylation. More examples of *N*-alkylations of **97–99** were reported in the literature.⁷⁵ Further transformation of **100** to triazole derivatives by 1,3-dipolar cycloaddition with azides was found to be similar to those shown in Scheme 7.⁷⁴

Similar to the reaction conditions of 4-*O*-acylation as mentioned in section 2.3, *N*-acylation proceeded *via* either a substitution reaction with acyl chlorides or a DCC coupling reaction with carboxylic acids (Scheme 38).⁷⁷ Both strategies generated *N*-acylated derivatives **102** and **104** with high yields (89% and 80% respectively) and the 4-*O*-BzOBz groups were selectively removed by treatment with TFA. Sulfonation of dialkylamine **98** was also reported by replacing acyl chloride with sulfonyl chloride.⁷⁶ Detailed substrate scopes of *N*-acylation and *N*-sulfonation were found in the literature.^{76,77}

A few examples of complex ring distortions of the D-ring of sinomenine **1** were proposed.¹¹ One distinguished example was the D-ring opening of sinomenine derivatives by Hofmann-type elimination (Scheme 39) while the others, such as ring rearrangements and contractions, were reported albeit in low yields (≤11%). Sequential additions of iodomethane and potassium carbonate to sinomenine derivatives cleaved



Scheme 37 *N*-Alkylations of dialkylamine **97**.

Scheme 38 N-Acylations of **98** and its subsequent 4-O-deprotection.

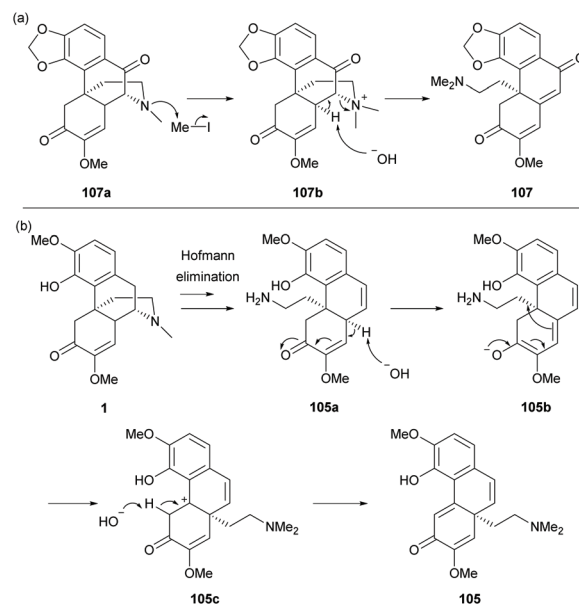
Scheme 39 D-Ring distortions of sinomenine derivatives.

the C–N bond, leading to ring-opened derivatives **105** and **107–108** in moderate yields (38–58%) except for **106** (3%). Only **1** gave alkyl-shifted product **105**.

The mechanism of the cleavage of the C–N bond by Hofmann elimination is exemplified in the formation of derivative **107** (Scheme 40a).

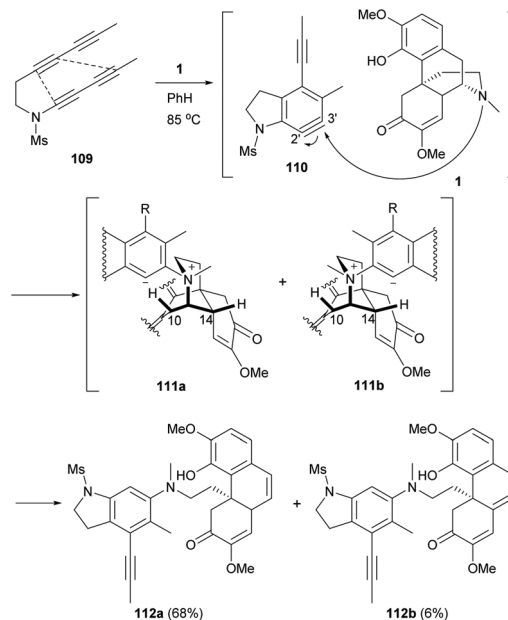
The methylation of trialkylamine provided quaternary ammonium derivative **107b** which became a labile leaving group for the subsequent C–N bond cleavage by deprotonation at the C14-position. For the reaction of sinomenine, derivative **105a** was formed, similar to **107b**, but the deprotonation occurred at less hindered C10-H (Scheme 40b). Under basic conditions, the γ -proton of enone **105a** was deprotonated, followed by a rearrangement reaction to generate carbocation **105c**. The alkyl shift product **105** was obtained by the deprotonation of the C5-proton. The rearrangement reaction was not observed in other substrates probably due to the absence of C14- γ -H of enone.

Based on the C–N bond cleavage, a cascade reaction involving hexadehydro-Diels–Alder (HDDA) and Hofmann-type



Scheme 40 Proposed reaction mechanisms of (a) Hofmann elimination; (b) Hofmann elimination and rearrangement reactions.

elimination was developed.⁷⁸ Under thermal conditions, aryne **110** was *in situ* generated from tetrayne **109** and then trapped by **1** regioselectively at the 3'-position owing to a strong electronic effect of the N-Ms group directing at the *meta*-position (Scheme 41).⁷⁹ The subsequent Hofmann-type elimination of intermediates **111a** and **111b** afforded derivatives **112a** and **112b** (74% combined yield) by trapping the protons at C10 and C14 respectively. The formation of **112b** was less favourable

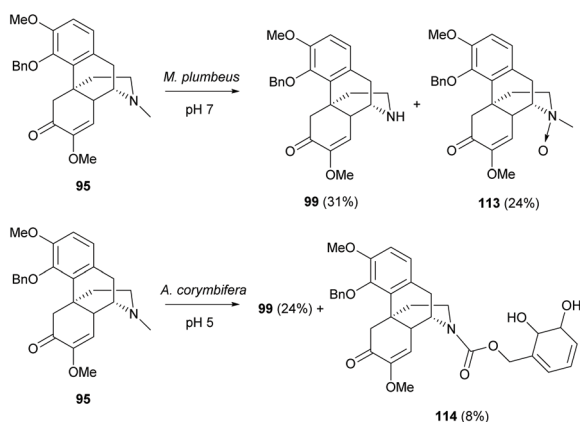
Scheme 41 The two-stage HDDA cascade reaction of **1** with tetrayne **109**.

probably due to the 1,3-allylic strain of the bulky phenyl group of **111b**.

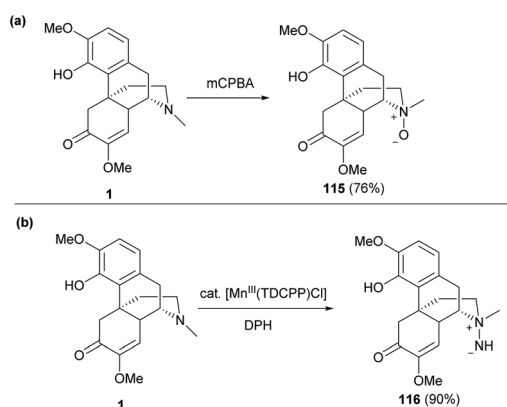
In addition, the biotransformation of 4-*O*-protected derivatives at the D-ring was reported using two screened microorganisms, *Mucor plumbeus* and *Absidia corymbifera* (Scheme 42).⁸⁰ The reaction of **95** with *M. plumbeus* afforded *N*-demethylated derivative **99** (31%) and *N*-oxide derivative **113** (24%). Both derivatives were the metabolites which resulted from a detoxifying action of microorganisms. They have been identified in the herbal plant *Sinomenium acutum*⁸¹ and the metabolites in rats.⁸²

Similarly, the reaction of **95** with *A. corymbifera* also provided *N*-demethylated derivative **99** (24%) as the major product (Scheme 42). A minor dihydroxylated derivative **114** (8%) was obtained. Further experiments suggested only one oxygen atom of **114** originating from oxygen by using ¹⁸O₂ labelling. This illustrated that the mechanistic pathway possibly proceeds *via* the formation of an epoxide followed by its ring-opening by hydrolysis.

Direct *N*-functionalization of **1** was also reported by either *N*-oxidation or *N*-amination (Scheme 43).⁶⁰ The typical *N*-oxidation of **1** with mCPBA proceeded smoothly to afford *N*-oxide **115** in a high yield (76%, Scheme 43a).



Scheme 42 The biotransformations of 4-*O*-protected derivatives **95** and **114** by microorganisms.



Scheme 43 (a) *N*-Oxidation of **1** with mCPBA; (b) *N*-amination of **1** with hydroxylamine catalyzed by Mn(III).

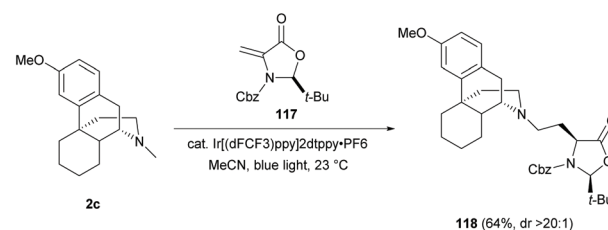
Another novel strategy was the *N*-amination of sinomenine with *O*-(2,4-dinitrophenyl) hydroxylamine (DPH) catalyzed by [Mn(TDCPP)Cl] (Scheme 43b). The reaction was first initiated by the formation of active species, Mn=NH, which was trapped by the trialkylamine of **1** by nucleophilic addition to afford unprotected aminimide **116** (90%).

5.2 Future approaches of functionalizations of ring D of sinomenine

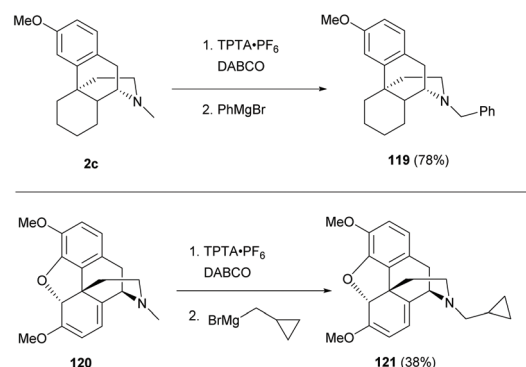
As mentioned in section 5.1, modifications of the D-ring mainly focused on a stepwise manner—*N*-demethylation and subsequent *N*-substitution. A few examples of direct functionalization of the *N*-methyl group of sinomenine have been shown to be an effective method for D-ring diversification. In view of these, late-stage functionalizations in sinomenine-like derivatives become a fast track for diversifying the D-ring of sinomenine without *N*-demethylation.

Direct C–H functionalization of the *N*-methyl substituent of **2c** with dehydroalanine **117** (Dha) was reported to yield amine-Dha adduct **118** *via* the formation of the α -amino radical (64%, Scheme 44).⁸³ The novel *N*-methyl functionalization with unnatural amino acids and peptides would be useful for increasing the complexity of sinomenine derivatives and exploring the corresponding biological activities.

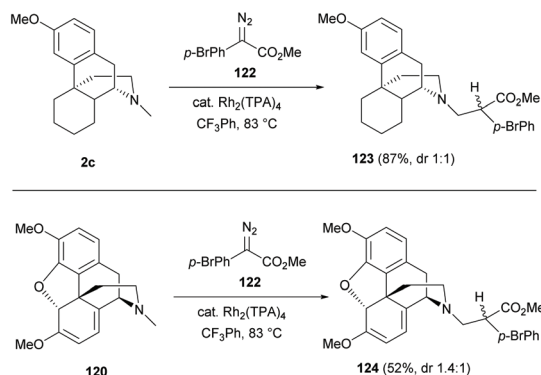
Similarly, another direct *N*-methyl functionalization was reported to proceed with the *in situ* generated α -amino radical by radical hydrogen atom abstraction with the DABCO radical cation (Scheme 45).⁸⁴ The subsequent addition of Grignard



Scheme 44 Amine conjugated addition of **2c** to dehydroalanine **117** by photoredox C–H functionalization.



Scheme 45 *N*-Methyl C–H functionalization of trialkylamines **2c** and **120** *via* hydrogen atom abstraction.



Scheme 46 Dirhodium(II)-catalyzed intermolecular C17-H insertion of sinomenine-like derivatives **2c** and **120** with diazo **122**.

reagents provided sinomenine-like derivatives **119** and **121** in low to high yields (78% and 38% respectively).

Late-stage C–H functionalizations of *N*-methyl sinomenine-like derivatives **2c** and **120** via intermolecular rhodium-carbenoid insertion were reported with high regioselectivities toward the *N*-methyl C–H bond due to sterically demanding carbenoid (Scheme 46).⁸⁵ The donor/acceptor carbenoid derived from diazo **122** inserted selectively to the *N*-methyl of **2c** and **120** to generate derivatives **123–124** (87% and 52% respectively).

6. Conclusions

This review summarizes the chemical modifications of sinomenine by demonstrating selected examples from each type of chemical reaction, in order to show the applicability of organic reactions in this particular chemical structure and analyze the synthetic issues that have been found. Besides chemical modifications, only a few examples of biotransformations have been reported to date. The full substrate scope of each type of reaction was not shown but could be found in detail in the literature. Based on the structure of sinomenine, the reaction sites are generally categorized into substituted aromatic ring (A-ring), benzylic position (B-ring), enone (C-ring) and trialkylamine (D-ring).

Sinomenine benefits from its sterically hindered polycyclic structure. The stereoselectivity of the reactions was not a major concern in the synthesis because the formations of stereoisomers were mostly controlled by steric factors.

Further modifications of sinomenine may consider the latest novel reactions that have been applied in structurally similar natural products and their semi-synthetic products. The enantiomeric isomers of sinomenine derivatives were easily obtained by C4,5-ether cleavage of morphine derivatives. Furthermore, the C3-methoxy group and C2-position of sinomenine have rarely been modified to date. Extensive studies on those positions will help in a deeper understanding of the structure–activity relationships of sinomenine.

Conflicts of interest

There are no conflicts to declare.

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