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Regio- and stereoselective $C_{10\beta}$–H functionalization of sinomenine: an access to more potent immunomodulating derivatives

Yang-Tong Lou [a], Li-Yan Ma [b], Meng Wang [c], Dongsheng Yin [b], Ting-Ting Zhou [c], Ai-Zhong Chen [b], Zhao Ma [b], Chao Bian [b], Shaozhong Wang [c], Zhen-Yu Yang [a,*], Bing Sun [b,*], Zhu-Jun Yao [a,c,*]

[a] State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China
[b] Shanghai Institute of Biochemistry and Cell Biology, Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences, 219 Yueyang Road, Shanghai 200031, China
[c] State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, School of Chemistry and Chemical Engineering, Nanjing University, 22 Hankou Road, Nanjing, Jiangsu 210093, China

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ABSTRACT

Regio- and stereoselective $C_{10\beta}$–H functionalization of sinomenine, an economically available natural immunomodulating alkaloid, has been studied, developed and successfully applied to the synthesis of new immunosuppressive sinomenine derivatives in a protecting-free fashion. Regioselective oxidation of sinomenine with (diacetoxyiodo)benzene (DIB) in water provided a single stable benzoquinone derivative **4**, and subsequent 1,6-conjugated addition of **4** with alcohols, amines, and thiols afforded a new series of $C_{10\beta}$–H functionalized sinomenine derivatives stereoselectively. Some derivatives with a newly introduced 10β-bezenesulfanyl substituent exhibited much higher TNF-α inhibitory potency than their natural parent sinomenine. This work opens a convenient access to novel sinomenine derivatives with medicinal interests.

1. Introduction

Bioactive natural products have been used as important source of modern drugs for a long history.[1] Sinomenine (SIN, **1**, Fig. 1) is an economically available natural alkaloid from the Chinese medicinal plant *Sinomenium acutum*.[2] It has been used as an immunemodulating and anti-inflammatory ingredient of several traditional medicines for treatment of rheumatoid arthritis (RA) for thousands of years in China and other Asian countries. However, sinomenine alone exhibits unsatisfactory immunomodulating activity in the clinical applications, and its mechanism in treating rheumatoid arthritis remains ambiguous yet.[3,4] Because of the easy availability of sinomenine, development of its derivatives is considered as the most economic way to acquire new chemical entities of pharmaceutical interests. To improve its poor bioactivities, a variety of modifications have been attempted upon the natural skeleton of sinomenine and a considerable number of derivatives have been developed in the past several decades.[5,6] Among these, most are prepared with simple transformations of the naturally

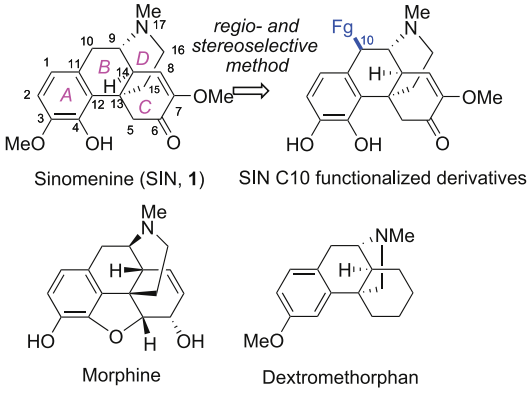

Fig. 1. Structures of sinomenine (**1**), morphine, and dextromethorphan, and the task of this study.

presented functionalities, including acetylation and etherification of phenol functionality,[5a–d] reduction of ketone,[5e–g] oxidative dimerization,[5h–k] and incorporation of small heterocycles into the C-ring.[6] Compared to the large number of sinomenine derivatives, very few successes have been achieved through such chemical

* Corresponding authors. Tel.: +86 21 54925133; fax: +86 21 54925123; e-mail addresses: yangzhenyu@sioc.ac.cn (Z.-Y. Yang), bingsun@sibs.ac.cn (B. Sun), yaoz@sioc.ac.cn, yaoz@mail.sioc.ac.cn (Z.-J. Yao).

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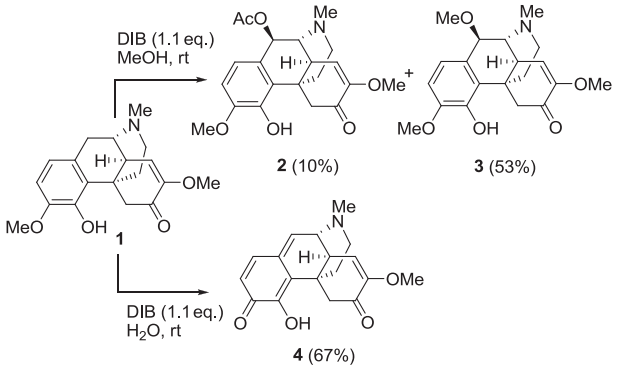
modifications. So far, no sinomenine derivative has been developed into the clinical applications yet. For lack of efficient methods, some potentially available modification positions, including the CH_2 at the C10 position, have not been investigated. However, recent advances in the C–H functionalization make such modifications of bioactive natural products more and more possible. Such powerful methodologies are believed to be fascinating tools in future drug discovery, aiming for new diverse chemical entities.[7] In this article, we want to report our recently developed methodology for the regio- and stereoselective C_{10}–H functionalization of natural sinomenine, as well as its application to the discovery of new immunosuppressive agents based on the natural template of sinomenine.

2. Results and discussion

The properties of the CH_2 moiety of sinomenine C10 position are closely related with the A-ring. As shown in Fig. 1, the A-ring of sinomenine is electron-rich and characterized with a phenol functionality, which is susceptible to undergo some oxidative transformations or aromatic electrophilic additions. Though very few oxidative transformations of sinomenine have been attempted, oxidation of sinomenine with $KMnO_4$ has been recently reported, providing reasonable yield of sinomenine dimers via an oxidative free-radical homo-coupling of its A-ring.[5i] To achieve the above mentioned CH_2 functionalization, undoubtedly, a proper chemo- and regioselective oxidation is essentially needed, avoiding various competitive oxidations of the phenol ring. In addition, the stereoselectivity should also be considered if a new C–O, C–N, or C–S bond was introduced after proper reactions. To continue our efforts to discover more potent immunomodulating small-molecule compounds,[6] we recently explored this challenging C–H functionalization using natural sinomenine as the substrate without any protecting groups.

Previous studies on morphine, a pain-relieving opium alkaloid with similar plain structure (Fig. 1), reported that treatment with CrO_3/H_2SO_4, $(NH_4)_2Ce(NO_3)_6$, $CrO_3/NaIO_4/H_2SO_4$ could provided low-yield of C_{10}–H oxidation products (alcohol or ketone).[8] Furthermore, reaction of dextromethorphan hydrogen bromide (Fig. 1), an antitussive (cough suppressant) drug, with $FeCl_3/O_2$ in methanol under UV irradiation also resulted in the production of three oxidized compounds at its benzylic position.[9] Examinations of these known conditions on sinomenine also provided multiple products, including the corresponding C_{10}-alcohol (methyl ether if using methanol as solvent), ketone, and phenol oxidation products in relatively poor yields and selectivity. It was rather difficult to improve the ratio and yields of these products by tuning the amount of oxidants and modifying reaction conditions.

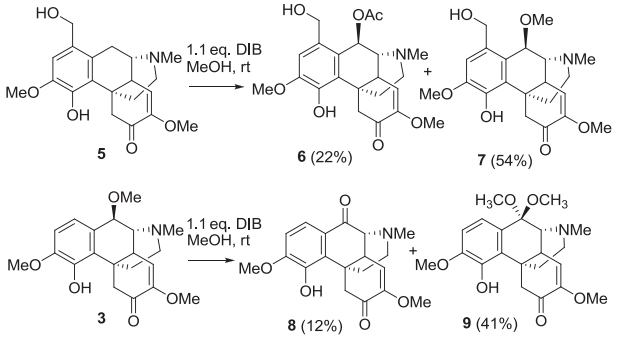
Although the initial results are immature and unsatisfactory, we believe that the mechanisms involved in these reactions are consistent with our goal. To achieve better chemoselectivity and higher chemical yield, a broad number of commercially available oxidants were examined by direct oxidation of sinomenine as the screening platform. To our delight, the corresponding reactions with hyperiodine reagents were found to give much simpler distribution of products. Among them, (diacetoxyiodo)benzene (DIB) was extremely effective. Direct oxidation of **1** with DIB in methanol provided two products, 10β-acetoxyl (**2**, 10%) and 10β-methoxyl derivatives (**3**, 53%) (Scheme 1). More interestingly, the solvent was also found to be critical in the control of the products. In a parallel reaction in water, DIB oxidation of sinomenine afforded a single benzoquinone product **4** in 67% isolated yield. These encouraging results prompted us to further study the selective oxidative transformation of sinomenine to novel C_{10}–H functionalized derivatives of medicinal interests.



Scheme 1. Oxidation of sinomenine with DIB in MeOH or H_2O.

Compound **2** is a white solid with a $[\alpha]_D^{25}$ −73.5 (*c* 1.4, $CHCl_3$). Its HRMS (ESI) exhibits an ion peak at *m*/*z* 388.1755 $[M+H]^+$, indicating a molecular formula $C_{21}H_{25}NO_6$. Compared to sinomenine [$C_{19}H_{23}NO_4$], an additional mass of $C_2H_2O_2$ was introduced by the oxidation. Further comparison of the ^1H NMRs indicates that the integration of H10 of **2** and **3** is changed to a single proton at δ 6.03. Comprehensive analyses of its ^1H NMR, ^{13}C NMR, ^1H–^1H COSY, and HMQC show that an AcO group ($C_2H_3O_2$, δ 2.10 in the ^1H NMR, and δ 21.5, 170.2 in the ^{13}C NMR, see Supplementary data for the details) was introduced. The structure of **2** is thus deduced as 10-acetoxyl sinomenine. The relative stereochemistry of the newly introduced C10-acetoxyl was determined by NOESY experiments. The spatial correlation between H10 and N17–CH_3 was observed, indicating the stereochemistry of C10 in **2** was 9,10-*trans*. Compound **3** is a yellow solid with an $[\alpha]_D^{25}$ −38.8 (*c* 1.4, $CHCl_3$). It is assigned as the C10β-methoxyl derivative of sinomenine. Oxidation product **4** is a bright yellow solid with a much larger rotation ($[\alpha]_D^{25}$ +563.3 (*c* 0.78, $CHCl_3$)). Its HRMS (ESI) peak at *m*/*z* 314.1399 suggests a molecular formula $C_{18}H_{19}N_1O_4$. A mass unit of CH_4 was removed from the skeleton of sinomenine during the oxidation. ^1H NMR and ^{13}C NMR of **4** reveal that the previous methoxyl group at C-3 position of sinomenine disappears. Instead, a carbonyl group is shown there (δc 181.1). Furthermore, the proton of H10 gave a doublet (δ 6.56, d, *J*=5.6 Hz) in the ^1H NMR of **4**. This significant change of chemical shift suggested that a double bond might exist between the C11 and the C10 of this compound. Based on the above spectral evidences and general knowledge on the oxidative transformations of phenol derivatives,[10] product **4** was reasoned as a new benzoquinone derivative as shown in Scheme 1. The structure of **4** was finally confirmed by further ^1H–^1H COSY, HMQC, and HMBC NMR experiments (see Supplementary data for the details).

1-Hydroxylmethyl sinomenine (**5**), a known derivative with C1 hydroxymethyl substituent,[11] was also examined under the same conditions (Scheme 2). Similar to the previous oxidations, 1-hydroxyl-10β-acetoxyl sinomenine (**6**) and 1-hydroxyl-10β-



Scheme 2. Oxidations of **5** and **3** with DIB in MeOH.