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Rapid access to the core skeleton of the [3 + 2]-type dimeric pyrrole–imidazole alkaloids by triplet ketone-mediated C–H functionalization

Lin You, Chuo Chen*

Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9038, USA

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ABSTRACT

The ability of triplet ketones to abstract a hydrogen atom from hydrocarbons is reminiscent of that of the high-spin metal-oxo complexes in C–H oxidation enzymes. In practice, the reactivity of triplet ketones is easier to control and applicable to promoting a wider range of reactions. We demonstrate herein the synthetic utility of triplet ketone-mediated *C*-addition of methanol to cyclopentenone derivatives with an expedient synthesis of the core skeleton of the [3 + 2]-type dimeric pyrrole–imidazole alkaloids. Remarkably, this photochemical C–H functionalization reaction is highly regioselective and can tolerate a good range of functional groups.

1. Introduction

The [3 + 2]-type dimeric pyrrole–imidazole alkaloids such as massadine (**1**) possess a unique molecular skeleton that has fascinated synthetic chemists for decades (Fig. 1).[1] Numerous labs have developed synthetic approaches to construct their cyclopentyl core structure. The Baran lab, the Namba and Tanino labs, and our lab have further accomplished the syntheses of various members of this family of natural products.[2–4] Previously, we followed the Molinski–Romo and Scheuer biosynthetic hypotheses to guide our synthesis of **1**.[4] We report herein an alternative approach to assemble its core skeleton **2** using a triplet ketone-mediated C–H functionalization reaction.

Photoexcited carbonyl (carbon-oxo) compounds are functional equivalent to the metal-oxo complexes in C–H oxidation enzymes as both species can abstract a hydrogen atom from unactivated C–H groups.[5] Whereas the reactivity of metal-oxo complexes is difficult to control, that of triplet ketones can be tuned easily by changing the n/π* energy gap through modifying the ketone substituent groups. This unique feature has inspired us to develop a new photochemical C–H halogenation reaction.[6] We have also demonstrated that CFL-irradiation of cyclopentenone (**3**) with isopropanol (**4**) gave the C–C coupling product **5** directly.[6b] This photochemical C–H functionalization reaction was first reported by Schenck,[7] and its synthetic utility has been explored briefly by Fraser-Reid[8] and Mann.[9] We now show that this photoreaction helps provide a rapid access of **2**.

2. Results/discussion

In our previous synthesis of the dimeric pyrrole–imidazole alkaloids, we used a single-electron oxidation reaction to generate a radical species that undergoes tandem cyclization to produce the core skeleton of **1**.[10] While it has allowed us to examine the Molinski–Romo biosynthetic hypothesis,[11] the lengthy synthesis and low overall yield prompted us to develop a new synthetic approach to support functional studies of this class of natural products.

We envisioned that sequential introduction of the C1- and C15-side-chains to a cyclopentyl ring using triplet ketone-mediated ethereal C–H functionalization to generate **2** would form the basis for a facile synthesis of **1**. Our new synthesis starts from installation of a handle at the C2-position of **3** to enable the construction of the C3–C7 cyclic guanidine group and to control the stereochemistry of the subsequent C–H functionalization reactions.

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* Corresponding author.
E-mail address: Chuo.Chen@UTSouthwestern.edu (C. Chen).

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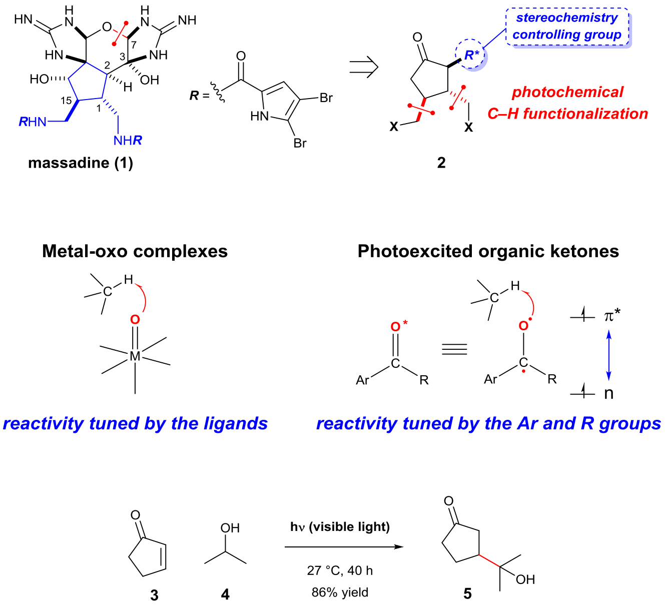
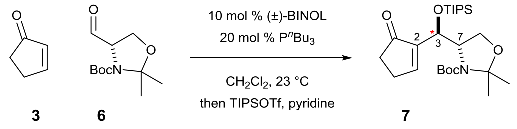


Fig. 1. The core skeleton of massadine (**1**) can be accessed by triplet ketone-catalyzed C–H functionalization of methanol easily. Triplet ketones have diradical characteristics and are functionally equivalent to the high-spin metal-oxo species that are frequently used to catalyze C–H oxidation. In addition to catalyzing C–H oxidation, triplet ketone can also catalyze C–C formation.

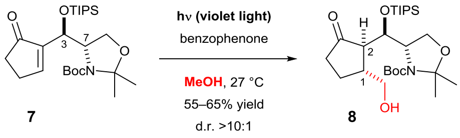
Specifically, we used a Morita–Baylis–Hillman reaction[12] of **3** and Garner's aldehyde (**6**) to produce enone **7** following in situ protection of the newly generated hydroxyl group (Fig. 2). A combination of a substoichiometric amount of tri-*n*-butylphosphine and racemic 1,1′-bi-2-naphthol (*rac*-BINOL)[13] promoted this reaction efficiently giving **7** in 73% yield. Using either (*R*)- or (*S*)-BINOL did not provide improved diastereoselectivity. Performing this reaction in toluene, *N*,*N*-dimethylformamide (DMF), or tetrahydrofuran (THF) instead of methylene chloride resulted in reduced diastereoselectivity and/or yield. However, 1,4-diazabicyclo[2.2.2]octane (DABCO) also promoted this reaction effectively.

With **7** in hand, we searched for conditions suitable for *C*-addition of methanol[8,9,14] to the enone group to introduce the C1-side-chain. In contrast to our previous reaction of **3** and **4** (Fig. 1), no reaction occurred when irradiating **7** in methanol directly with light generated from a CFL lamp (Fig. 3). Whereas addition of benzophenone alone did not facilitate the reaction, together with switching to using 16 broadband UV–visible lamps (360–750 nm, λ_{max} 575 nm) led to the formation of **8** in 25% yield. Irradiation with violet light (375–465 nm, λ_{max} 419 nm) provided improved conversion. Specifically, irradiation of a 1:1 mixture of **7** and benzophenone in methanol with violet light at room temperature gave the desired product **8** in 55–65% yield together with des-acetonide-**8** in about 10% yield. In contrast, irradiation with UV light (300–420 nm, λ_{max} 350 nm; or 250–375 nm, λ_{max} 300 nm) gave a faster reaction rate but a lower yield of **8** due to decomposition. Among all other C–H abstracting ketones examined, only acetophenone was effective under these reaction conditions, providing **8** in 15% yield after 96 h of reaction time. It is noteworthy that the chiral C2-side-chain provided a good stereochemical control (d.r. >10:1) of the formation of the C1-and C2-stereocenters.



Solvent	d.r.	yield
THF	3:1	52%
toluene	3:2	70%
DMF	5:1	73%
CH$_2$Cl$_2$	4:1	91%

Fig. 2. Introduction of a chiral handle at the C2-position allows for the construction of the C3–C7 cyclic guanidine group and controlled formation of the C1- and C2-stereogenic centers in the subsequent photoreactions.



diaryl ketone	light source	time	yield
none	1 × CFL	64 h	no reaction
benzophenone	1 × CFL	64 h	no reaction
benzophenone	16 × RPR-5750 Å	64 h	25%
benzophenone	16 × RPR-4190 Å	64 h	63%
benzophenone	16 × RPR-3500 Å	12 h	31%
benzophenone	16 × RPR-3000 Å	6 h	decomposition
acetone	16 × RPR-4190 Å	64 h	no reaction
acetophenone	16 × RPR-4190 Å	96 h	15%
fluorenone	16 × RPR-4190 Å	96 h	no reaction
xanthone	16 × RPR-4190 Å	96 h	trace amount
anthraquinone	16 × RPR-4190 Å	96 h	trace amount

Fig. 3. The C3- and C7-stereogenic centers of **7** control the selective installation of the C1- and C2-stereocenters in the photochemical C–H functionalization reaction.

After installation of the C1-side-chain, we introduced an enone group to the C14–C15 position of **8** to enable the installation of the C15-side-chain. We first protected the hydroxyl group of **8** as a trimethylsilyl (TMS) ether and then treated the reaction mixture with lithium bis(trimethylsilyl)amide (LiHMDS) to give a lithium enolate that was directly reacted with *N*-*tert*-butylbenzenesulfinimidoyl chloride to give enone **9** in 65% yield (Fig. 4). Unreacted alcohol **8** was also recovered in 25% yield. Whereas attempts to react the lithium enolate with phenylselenyl chloride followed by oxidation with hydrogen peroxide failed to produce **9**, protection of the hydroxyl group of **8** as a *tert*-butyldimethylsilyl (TBS) ether provided a more stable substrate that could be oxidized by the phenylselenyl chloride/hydrogen peroxide method. However, after TBS-deprotection, the overall yield of **9** for this four-step procedure is only 24%.

To install the C15-side-chain by photochemical ethereal C–H functionalization, we irradiated **9** and benzophenone in methanol with violet light and obtained a 46% yield of **10** together with a 24% yield of its C15-diastereomer (Fig. 5). The stereoselectivity of this photoreaction could be improved by increasing the size of the C1 side-chain. For example, reaction of the TBS-protected **9** gave a 3.5:1 mixture of the diastereomeric products. The diastereoselectivity could be further improved to 4.7:1 by triisopropylsilyl (TIPS) protection. However, the overall yield of **10** remains comparable due to the additional protection and deprotection steps. Additionally, longer reaction time is needed for the more hindered

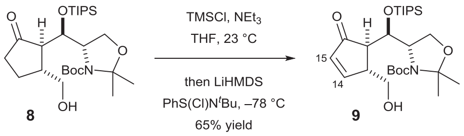


Fig. 4. Introduction of the C14–C15-enone group by sulfinimidoyl chloride-mediated oxidation set the stage for the second photochemical C–H functionalization.