Total synthesis of conosilane A via a site-selective C–H functionalization strategy†

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The first total synthesis of conosilane A, a densely oxygenated nonisoprenoid sesquiterpene, has been achieved through stereo-selective intramolecular radical cyclization and double utilization of site-selective C–H functionalization as key steps, thus simplifying the synthetic endeavors in natural product synthesis.

Members of the genus Conocybe are a rich source of biologically active natural products. In the past ten years, a series of novel tremulane-type sesquiterpenes from the culture of mushroom C. siliginea have been reported by Liu and co-workers. Among these, conosilane A, a novel highly oxygenated nonisoprenoid sesquiterpene with an unprecedented carbon skeleton, was isolated from the cultures of the basidiomycete Conocybe siliginea in 2012. The plausible biogenetic pathway for the synthesis of conosilane A was that nature uses its two phases (cyclase and oxidase phase) to synthesize the natural product (Scheme 1), and its structure was elucidated by extensive spectroscopic methods and further confirmed by single crystal X-ray diffraction analysis. Structurally, conosilane A consists of bicyclo[3.3.0] frameworks bearing three continuous stereocenters including a quaternary one, and it is comprised of a unique cyclopentenone fused with both a cyclohexenone unit and a tetrahydrofuran moiety.

Due to our long-term interest in the total syntheses of sesquiterpenes with a novel skeleton, the impressive structural complexity together with potential bioactivities has rendered conosilane A as an attractive target for our synthetic endeavor. Herein, we reported the first total synthesis of conosilane A in a stereocntrol manner.

C–H functionalization, especially, the C–H oxidation has been gaining tremendous interest in organic syntheses since it can dramatically increase synthetic efficiency in terms of step, atom and redox economy when incorporated into retrosynthetic analyses of complex natural products. Logically, conosilane A (1) (Scheme 1) was envisioned to ultimately arise from a late-stage C–H (C1–H and C12–H) oxidation of 2 or 3 to install the 1, 4-dienone unit and the bicyclo[3.3.0] framework, respectively. 3 could be achieved from 4 by a 5-exo-trig radical cyclization reaction to obtain a unique cyclopentenone core with the C-8 quaternary stereocenter and subsequential functional group interconversion. Finally, the essential precursor α,β-unsaturated ester 4 could be regioselectively...
prepared from known aldehyde 5 and ketone 6 followed by the Horner–Wadsworth–Emmons reaction.

Our synthetic study commenced with the coupling reaction of the known compound aldehyde 5 and ketone 6 (Scheme 2). Inspired by the work of Kraus, the predominant kinetic enolate prepared from 6 and lithium diisopropyl amide (LDA) reacted with 5 to afford the desired hydroxyl ketone 7, presumably via the kinetic deprotonation of the non-oxygenated methylene of the tetrahydrofuran ring and subsequential nucleophilic addition using the Zimmerman–Traxler principle. As an anticipated process, was accessed by a sequential regioselective aldol reaction and TBS-protection in 62% yield over two steps (anti/syn = 2.8/1).

Subsequently, the condensation of anti-8 with ethyl (diethoxyphosphoryl)acetate via a Horner–Wadsworth–Emmons reaction generated the chromatographically inseparable a,b-unsaturated ester 4 in 82% combined yields with (Z)-configuration of C8–C10 double bond as the major isomer. Notably, compound 4 was light and base-sensitive since the ratio of aromatization by-product 9 increased when the reaction was conducted at higher temperature such as 0 °C or room temperature.

Having developed an approach capable of efficiently yielding 4 with all carbon atoms for natural conosilane A, we next focused on the key cyclization reaction to furnish the essential cyclopentenone skeleton. Initially, we attempted the [Ni(cod)2]-mediated cyclization under typical reaction conditions and improved conditions developed by the Ma group. We could recover only the starting materials under both conditions. While ester 4 was treated with the Pd-catalyzed reductive Heck reaction, a complex mixture was formed under variant conditions.

Fortunately, ester 10 bearing a quaternary stereocenter was obtained in 91% yield via the classic radical cyclization. Ester 3, the precursor of the natural product conosilane A, was obtained through two simple reactions in 83% yield.

To complete the synthesis of conosilane A, a bold strategy involving late-stage C–H functionalization/cyclization was explored. To our disappointment, no desired product was detected under various conditions for substrate 2 or 3, including DDQ, PCC, PDC, CrO3, DMDO (prepared or in situ) and peroxide combined with metals (Scheme 2).

Due to the negative results for substrate ester 3 and acid 2, we modified our synthetic route wherein the C–H hydroxylation occurred before the key radical cyclization reaction (Scheme 2). As for ester 4, we have to deal with the site-selectivity in the presence of four allylic oxidizable positions. To our delight, we could successfully obtain the desired hemiacetal 13 with high selectivity under the SeO2 conditions. The good selectivity in allylic C–H hydroxylation might is due to the steric hindrance and the electronic effect. Ester 15 was formed when acetal 14 was subjected to the previously optimized conditions for the key radical cyclization in 89% yield. Subsequently, a two step protocol, the removal of TBS protection of 15 and oxidation of the resulting allylic alcohol with Dess–Martin periodinane, generated 16 in 77% yield. Upon treatment of 16 with methane-sulfonic acid at low temperature, the lactonization proceeded.
smoothly generating lactone 11 in 80% yield which consisted of the essential tetra-cyclic framework of conosilane A.

To accomplish the synthesis of conosilane A, conditions for a late-stage and site-selective C–H oxidation was screened (Table 1). Lactone 11 was recovered in most of the conditions (entries 1–3) or converted to the desired product in a low yield (entries 4 and 5). To our delight, when lactone 11 (entry 6). However, the reaction mixture was totally decomposed under harsher conditions (entries 7 and 8).


4. It should be noted that compound was recovered in most of the conditions (c) J. M. Smith, J. Felding and P. S. Baran, ACS Cent. Sci., 2017, 3, 47.


9. The stereochemistry of the major diastereomer was elucidated by nuclear Overhauser effect (NOE) studies of compound 15, in which the correlation was found between C6–H and C7–H. More information of the NOE study is in the ESI.

Conflicts of interest
There are no conflicts to declare.

Notes and references


