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Total synthesis of (±)-villosin C and (±)-teuvincenone B†

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Herein, we report the first total synthesis of 17(15 → 16)-*abeo*-abietane diterpenoids (±)-villosin C (**5**) and (±)-teuvincenone B (**4**) in 11 steps. The A/B/C ring system was assembled *via* a modified three-step sequence on gram-scale, while the D ring was constructed by intramolecular iodoetherification. This synthesis relied largely on the rational design of the order for oxidation state escalation (C6/11/14 → C7 → C12 → C17), which was realized through sequential benzylic iodination/Kornblum oxidation, Siegel–Tomkinson C–H oxidation and iodoetherification. In addition, villosin C (**5**) and its epimer (**5a**) were found to have indistinguishable NMR data and the correct configuration for villosin C was elucidated by comparing HPLC trace with a natural sample.

Introduction

Abietanes represent a rich array of naturally occurring diterpenoids isolated from a variety of terrestrial plant sources.[1] Skeleton rearrangements were frequently observed in this family, where 17(15 → 16)-*abeo*-abietane is amongst the most common one, as was found in various natural products (Fig. 1).[2] Villosin C (**5**), characterized by this framework, was first isolated by Ulubelen in 1994 from *Teucrium divaricatum* subsp. *Villosum*.[3] In the past decade, this natural product was reisolated from several other plant sources independently, including *Teucrium polium*,[4] the Chinese medicinal plants *Clerodendrum trichotomum*[5] and *Clerodendrum bungei*,[6] and *Akebia quinata*.[7] Multiple biological activities such as antioxidative,[4] NO production inhibitory[5c] and antitumor activities[5d] were reported for villosin C (**5**), which could partly account for the therapeutic effects of *Clerodendrum trichotomum* (known as "Chou-Wu-Tong") in traditional Chinese medicine. Teuvincenone B was first isolated from the root of *Teucrium polium*[8] and was later found to exhibit antioxidant[4] and antitumor activities.[5d] Nonetheless, these natural products are rather scarce from natural sources, with less than 1 mg kg^{-1} isolated from the corresponding dried plants. Thus, the development of a synthetic strategy allowing the access to teuvincenone B (**4**), villosin C (**5**), and their natural and unnatural analogs would be highly desired. Herein, we present our study on the total synthesis of (±)-villosin C (**5**) and (±)-teuvincenone B (**4**) by a convergent approach.

Structurally, villosin C (**5**) and teuvincenone B (**4**) were characterized by a 6/6/6/5 tetracyclic ring system with an aromatized C ring and a dihydrofuran D ring. The synthetic challenge is mainly embedded in the highly oxidized nature (9 out of 10 carbons of the B/C ring are unsaturated and 5 are directly

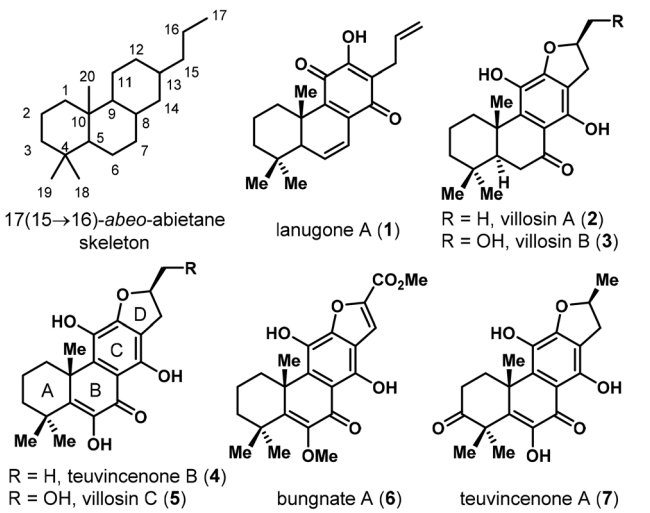

Fig. 1 Representative natural products bearing 17(15 → 16)-*abeo*-abietane skeleton.

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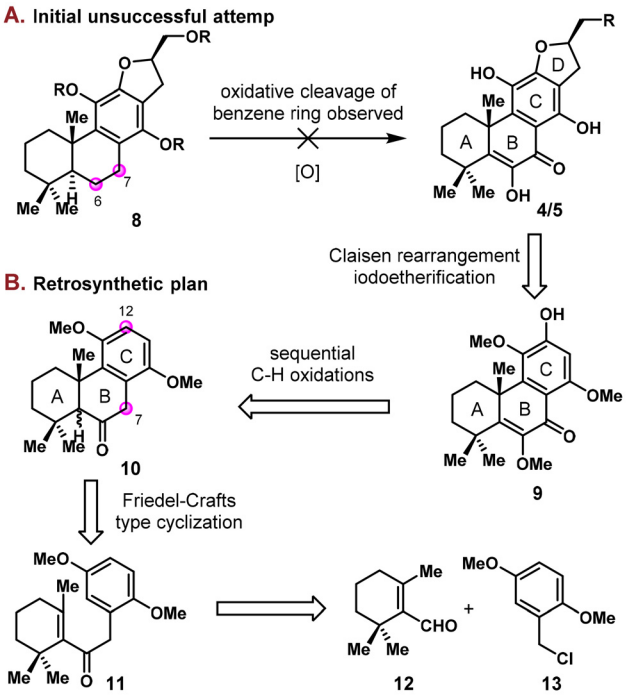
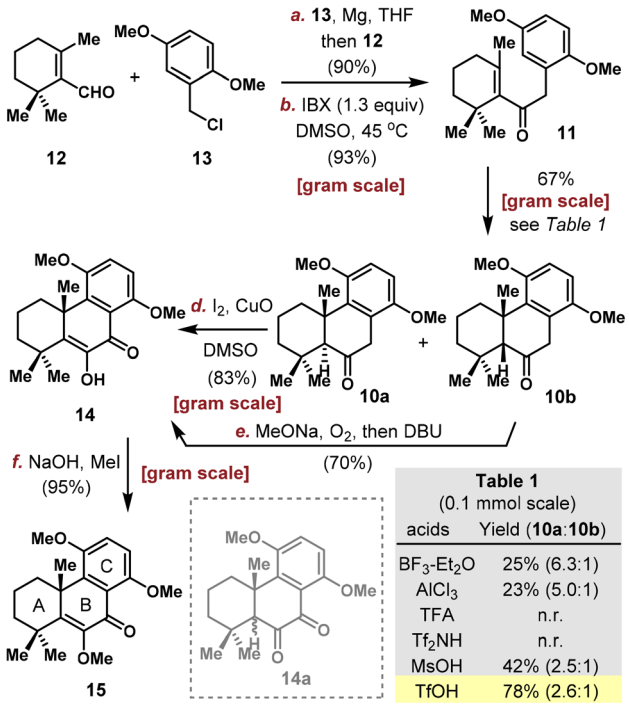
attached to oxygen) and that the C ring is a fully substituted benzene moiety. Although there is a plethora of synthetic studies on C ring aromatized abietane diterpenoids,[9] seldom has targeted those with high oxidation states and fully substituted benzene in this family,[10] and the total synthesis of villosin C (**5**) and teuvincenone B (**4**) are yet to be reported. In an initial synthetic study, one of us (Mao) obtained an elaborated intermediate (**8**) with fully established carbon skeleton and ring system. Unfortunately, the late stage oxidation of the C6/C7 sites proved unsuccessful (Scheme 1A). Instead, oxidative cleavage of the strong electron rich benzene ring was observed. These results prompted us to sketch a new retrosynthetic design, where the α-hydroxy enone moiety in the B ring was constructed prior to installation of the C12 oxidation state (Scheme 1B). Thus, the D ring of **4**/**5** was envisaged to be built *via* a Claisen rearrangement/iodoetherification sequence from phenol **9**. The C12 and C7 oxidation states could be introduced *via* sequential C–H oxidations from ketone **10**, which was then disconnected to commercially available β-cyclocitral **12** and a known benzyl chloride **13**.

Results and discussion

Our synthesis commenced from the assembly of aldehyde **12** and benzyl chloride **13** through a similar three-step sequence previously utilized in other abietane natural product and analog synthesis (Scheme 2).[11] In these studies, stoichiometric Li/naphthalene was used unexceptionally to activate benzyl chloride, which is problematic for scale-up. Here, the union of



Scheme 1 (A) Initial unsuccessful attempt and (B) Retrosynthetic plan.



Scheme 2 Synthesis of tricyclic α-methoxy enone **15**.

12 and **13** through Grignard addition afforded 90% yield on multigram-scale. After oxidation with IBX, enone **11** was obtained in 93% yield. Friedel–Crafts cyclization of a similar type was previously reported for either enone[11] or unconjugated alkene substrates[12] under Lewis and Brønsted acid conditions. In our case, condition screening on 0.1 mmol scale revealed that $AlCl_3$ and $BF_3{\cdot}Et_2O$ delivered cyclized products **10a** and **10b** in poor yields while TFA and Tf_2NH proved ineffective (Table S1, see the ESI† for more details). The optimum result was obtained with 3 equivalents of TfOH in DCE at 0 °C on 0.1 mmol scale, furnishing **10a** and **10b** in 78% combined yield with 2.6/1 dr as determined by crude ^{1}H NMR, and the efficiency could be well maintained on gram-scale (67% isolated yield).[13]

Both diastereoisomers could be used in the subsequent synthesis, however, under different conditions. Jones oxidation and O_2 under basic conditions are two common methods reported in literature for converting ketone to the corresponding α-diketone or α-hydroxy enone moiety in abietane natural product synthesis.[14,11c,12a] In our attempt to oxidize ketone **10a**, while the Jones oxidation was messy, base/O_2 provided variable 30–70% yields depending on reaction scale. After optimization, a one-pot benzylic iodination/Kornblum oxidation using CuO and I_2 in DMSO was found to deliver α-hydroxy enone **14** efficiently in 83% yield on gram-scale.[15] Surprisingly, application of this condition to the other diastereomer **10b** gave a messy reaction. Interestingly, this diastereomer was found to be easily oxidized by air, even when placed on bench without any reagent. MeONa/O_2 was then used to achieve the desired oxidation in high conversion, however,

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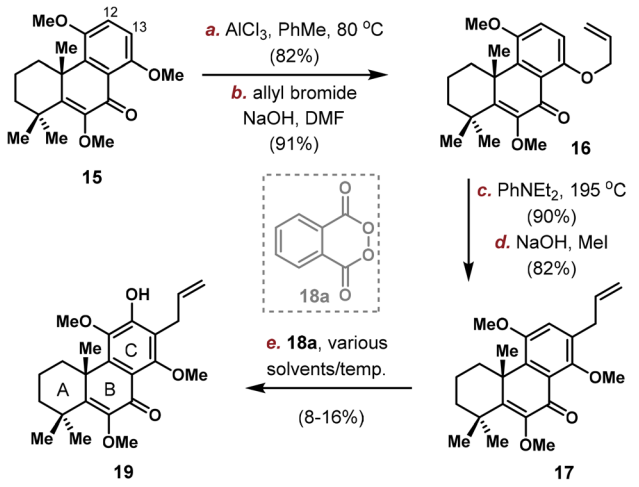
affording a mixture of α-hydroxy enone **14** and α-diketone **14a**. After treating the mixture with DBU, **14** could be obtained in 70% overall yield from **10b**. Protection of the free enol with NaOH/MeI afforded the tricyclic α-methoxy enone **15** in 95% yield.

Quantities of **15** was produced through the implementation of the above-mentioned sequence on gram-scale and the stage is now setting for the introduction of C12/C13 substituents. Electronic analysis pointed C13 position as the more electron rich site, which was confirmed by exclusive electrophilic bromination at C13.[16] Thus, we planned to first install an allyl group on C13 and then an oxygen atom at C12. Selective removal of 1 methyl group out of 3 was realized using $AlCl_3$ in PhMe (Scheme 3). Allylation provided **16** in 91% yield, with the location of allyl group confirmed by NOESY spectrum analysis. Claisen rearrangement took place efficiently to position the allyl group on C13, and **17** was obtained after methyl protection. Unfortunately, the subsequent C(12)–H oxidation proved problematic. While electrophilic bromination/iodination were unsuccessful, radical based arene C–H oxidation developed by Siegel using **18a** yielded the desired phenol **19** in very low productivity (8–16% yield under various solvents/temperatures), probably due to steric hindrance and incompatibility with the terminal alkene group.[17]

In an optimized protocol, we tried to switch the order of C(12)–H oxidation and C13 allylation (Scheme 4, upper left). Direct oxidation of **15** with **18a** provided a mixture of C12–OH (**9**) and C13–OH products in 1 : 1.6 ratio. After optimization (Table S2†), cyclopropane malonyl peroxide **18c** in TFE delivered the desired phenol **9** in 37% isolated yield along with the C13–OH isomer in 1 : 1.2 ratio.[18,19] Subsequent allylation and Claisen rearrangement proceeded smoothly to provide phenol **19** in 79% yield.



Scheme 3 Synthesis of the fully substituted C ring intermediate **19**.

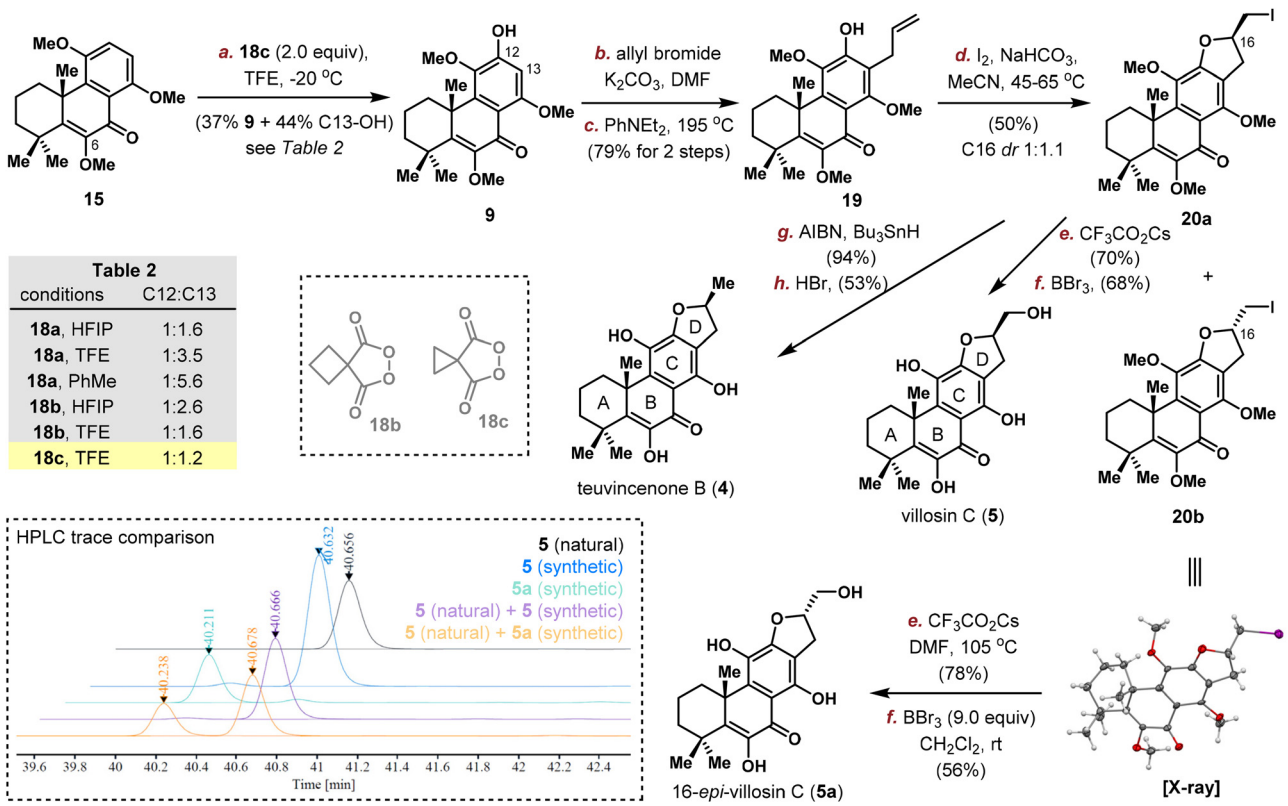


Table 2

conditions	C12:C13
18a, HFIP	1:1.6
18a, TFE	1:3.5
18a, PhMe	1:5.6
18b, HFIP	1:2.6
18b, TFE	1:1.6
18c, TFE	1:1.2

Scheme 4 Modified synthesis of **19** and total synthesis of (±)-villosin C (**5**), (±)-teuvincenone B (**4**), and (±)-16-*epi*-villosin C (**5a**).

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Next, the D ring was constructed through iodoetherification uneventfully to give **20a** and **20b** in 50% combined yield with almost no selectivity at the newly generated stereocenter (1 : 1.1 dr at C16). The two diastereomers were isolated by flash column chromatography and the structure of the undesired isomer **20b** was confirmed by X-ray crystallographic analysis unambiguously. Thus, the conversion of the primary iodide in **20a** to alcohol was achieved using CF_3CO_2Cs in DMF at elevated temperature. After global deprotection with BBr_3, (±)-villosin C (**5**) was obtained in 68% yield. In addition, iodide **20a** was reduced with AIBN/Bu_3SnH and globally deprotected with HBr in HOAc to afford (±)-teuvincenone B (**4**) in 50% yield over two steps. The spectroscopic data for **5** and **4** are all in good agreement with those reported from the isolation literature.

The same two-step sequence (hydroxylation, global deprotection) was also applied to **20b** to deliver 16-*epi*-villosin C (**5a**) in 44% yield (Scheme 4). Surprisingly, the ^{1}H and ^{13}C NMR spectra of synthetic **5a** and **5** were almost identical, and could not distinguish with the reported data in the isolation literature (C11–OH represented the only large difference: 5.12, 4.98 and 4.99 ppm for natural **5**, synthetic **5** and **5a** respectively, see the ESI† for detailed comparison).[5b] Although the C10/C16 relative stereochemistry of some 17(15 → 16)-*abeo*-abietane diterpenoids was elucidated by X-ray crystallographic analysis to be *cis* as drawn in **5**, it is still uncertain in the case of villosin C. Therefore, we requested a sample of natural villosin C from Yang, and the HPLC trace of which was compared to that of synthetic **5** and **5a**, confirming that the true structure of villosin C (**5**) was indeed as originally proposed (Scheme 4, left bottom).[5c] While the C16 stereochemistry in some 17(15 → 16)-*abeo*-abietane diterpenoids was proposed by comparing the chemical shifts and coupling constant values in NMR around C15–C17 to known ones, our work suggests that NMR data might not be sufficient to make a definite conclusion, at least in the category of 17(15 → 16)-*abeo*-abietane natural products.

Conclusions

In summary, total synthesis of 17(15 → 16)-*abeo*-abietane diterpenoids (±)-villosin C (**5**) and (±)-teuvincenone B (**4**) was accomplished for the first time employing a convergent approach. The synthesis features (i) five-step gram-scale assembly of A/B/C ring system with oxidation state of B ring fully positioned through one-pot benzylic iodination/Kornblum oxidation, (ii) Siegel–Tomkinson C–H oxidation and Claisen rearrangement to install all substituents required on C ring, and (iii) iodoetherification to construct D ring. The successful implementation of this route also relied largely on the rational design of the order for oxidation state escalation (C6/11/14 → C7 → C12 → C17). In addition, our finding that villosin C (**5**) and 16-*epi*-villosin C (**5a**) showed indistinguishable NMR spectroscopy called for more prudence during structural characterization of the 17(15 → 16)-*abeo*-abietane family.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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19 Further screening revealed that with Ts protecting group on C6–OH, 1.3 : 1 ratio of **9** to C13–OH isomer could be obtained. However, the overall yield was lower (23% for **9**, see the ESI† for details).

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