Total Synthesis of Stemarene and Betaerene Diterpenoids: Divergent Ring-Formation Strategy and Late-Stage C–H Functionalization

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A unified protecting group-free approach to two stemarene and two betaerene diterpenoids through a bioinspired two-phase strategy has been developed, and three of them were obtained for the first time via chemical synthesis. Starting from a common intermediate, two distinct tetracyclic frameworks containing diastereoisomeric bridged bicycles were constructed by a divergent ring reorganization strategy. Late-stage C–H functionalization through a xanthylation-oxygenation protocol furnished the corresponding oxygenated stereocenters or oxo functionality in high regio- and diastereoselective fashion within a complex hydrocarbon system. The stereochemical puzzles in (−)-2-acetoxybetaer-13(17)-ene and (+)-7-acetoxybetaer-13(17)-ene were first predicted by the comparison of density functional theory (DFT)-nuclear magnetic resonance (NMR) data with the reported data and then unambiguously addressed through the total syntheses of natural products and three diastereomers.

Keywords: total synthesis, late-stage C–H functionalization, divergent synthesis, diterpenoids, structure reassignment

Introduction

Labdane-related diterpenoids (LRDs) are a superfamily of natural products that contain the characteristic trans-decalin core structure (A/B-fused rings) found in the labdane diterpenoids. To date, over 7000 LRDs have been discovered, and many of them display diverse biological activities, such as antiviral, antitumor, antimalaria, and antifungal. Among them, tetracyclic LRDs bearing various bridged bicyclic C/D ring systems constitute most of this natural product family. Interestingly, the tetracyclic frameworks containing pseudoenantiomeric bridged C/D rings (bearing two bridgehead stereocenters of opposite configurations) often occur in pairs in nature, such as stemodane and aphidicolane, phyllocladane and kaurene, as well as stemarane and betaerane (Scheme 1a, the isomeric bridged C/D bicycles are highlighted with colors).

Biosynthetically, these tetracyclic LRDs are derived from the general precursor geranylgeranyl diphosphate (GGPP), mostly through two enzyme-catalyzed cyclization processes and subsequent oxidative metabolism.
Scheme 1 | (a–d) Divergent synthetic strategy for stemarene and betaerene diterpenoids.

In the second cyclization stage, the pimarenyl cation and its three diastereomers at C9 and C13 are involved as important intermediates, which undergo further cyclizations and rearrangements to give rise to the different skeletons of the aforementioned tetracyclic diterpenoids (Scheme 1b). Usually, the stereochemistry of the bridged bicycle is determined by the configuration of the C13 stereocenter of the pimarenyl cation, which is the origin of the pseudoenantiomeric bridged C/D rings.

Due to their complex architectures and diverse biological activities, LRDs have received intense attention from the synthetic community. Many elegant approaches to these diterpenoids have been developed in the past decades, especially for the families of aphidicolane, atisane, and ent-kaurane. Despite these significant advances, a unifying approach to these tetracyclic skeletons, especially those containing the pseudoenantiomeric bridged C/D rings, remains unknown. Furthermore, regio- and stereoselective installation of various oxygenated functional groups constitutes another formidable challenge for the total synthesis of these diterpenoids. Herein, we describe our implementation of such an intriguing two-phase strategy by merging divergent ring-formation strategy with diverse late-stage C–H functionalization for the unified syntheses of two stemarene diterpenoids (1 and 2) and two betaerene diterpenoids (3 and 4) (Scheme 1c). Furthermore, we reassigned the stereochemistry of 3 and 4 through density functional theory (DFT)-nuclear magnetic resonance (NMR) and chemical synthesis.
Experimental Methods

Experimental procedures, characterization of NMR spectra for all synthetic compounds, comparison of the synthetic natural products with isolated samples, X-ray crystallographic data and corresponding CCDC numbers, computational methods and Cartesian coordinates, and copies of NMR spectra are available in the Supporting Information. All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. All chemicals were purchased commercially and used without further purification, unless otherwise stated. The photochemical xanthylation reactions were carried out with a Kessil® Blue PR 160–456 nm 28 W light-emitting diode (LED) Grow Light from the side (2 cm away).

Results and Discussion

Stemarene and betaerane diterpenoids are biosynthetically originated from syn-pimareneryl cation, which undergoes 1,2-hydride shift (C9 to C8) to generate cation species (I) (Scheme 1b). Two C13 epimers of I then, respectively, undergo cyclization and subsequent rearrangement to form stemaranyl cation (IV) and betaeranyl cation (V), probably through nonclassical cation species II and III. Recently, Hong and Tantillo,16 clarified that direct interconversion of IV and V via concerted cationic rearrangements is energetically possible. However, this proposal remains to be verified either in vivo or in vitro. In the context of chemical synthesis, these two natural product families received much less attention compared with other tetracyclic LRDs.35-40

Our insights into the retro synthetic analysis of stemarane and betaerane diterpenoids 1-4 were greatly influenced by their biosynthesis, which usually involves a cyclization phase and an oxidation phase. We envisioned that diterpenoids 2-4 with higher oxidation levels could arise from the precursors 6 and 7, which contain the tetracyclic frameworks of natural products, through the C-H oxygentions at the C2 and C7 positions (Scheme 1c). In the cyclization phase, we anticipated that the tricyclic diol 5 could serve as an advanced common intermediate for constructing the isomeric tetracyclic frameworks of 6 and 7 through different skeletal reorganization strategies. Diol 5 could be traced back to the inexpensive chiral pool (+)-scclareolide (8).

Although the C2-oxxygenation of (+)-stemar-13-ene (1)41 is a biosynthetically viable process37,42,43 to generate (+)-2-oxostemar-13-ene (2),43 given the high competitiveness of allylic positions (C8 and C17) present in 1 during the C2-H oxygention with chemical oxidants, we postulated that compound 6 would be a more superior substrate for C2-H oxygention than 1. The C2-H oxygentions of a less complicated system scclareolide have been well studied in recent years.45-48 However, a much more complicated system like 6 posed considerable challenges for a site- and diastereoselective C-H oxygention due to the existence of many C-H bonds with a similar chemical environment. The DFT-calculated bond dissociation energy (BDE) of C-H bonds of 6 revealed that the C2-H bond appears to be indistinguishable from other C-H bonds, such as C1-H, C3-H, C6-H, C7-H, C11-H, C12-H, and C14-H, toward radical oxygention (Scheme 1d). However, the C13 carbonyl group would significantly decrease the electron density of the C-H bonds on C/D rings, thus reduce their reactivity toward electrophilic oxidants. In addition, the C4 and the C10 quaternary carbon centers would cause severe steric hindrance to the adjacent C1, C3, and C6 hydrogens, thereby rendering the C2 and C7 positions as the sterically most accessible, electron-rich sites. Further considering strain release in the transition state of oxidation, the equatorial C2-H would be the most reactive site in 6. Therefore, we anticipate a bulky electron-deficient radical oxidant could facilitate a site- and diastereoselective C-H oxygention on 6. Furthermore, we envisaged that such a strategy would also be applicable to the oxygention of ketone 7 for the synthesis of betaerene diterpenoids 349 and 41 (Scheme 1c).

Divergent ring-formation for the syntheses of stemarane and betaerane diterpenoids

Our synthetic endeavors began with the Diels-Alder cycloaddition of isoprene and the known bicyclic enone 9, which could be prepared on a large scale from (+)-scclareolide by Li group’s12 method in five steps, to deliver the spirotricyclic enone 10 in 70% yield (Scheme 2a). Dihydroxylation with K2O2SO4 and N-methylmorpholine-N-oxide (NMO) furnished the common diol intermediate 5 as a single diastereomer whose stereochemistry was confirmed by X-ray crystallographic analysis of its C12-acetate derivative (5a) (see inset image in Scheme 2). Selective mesylation of the C12 secondary alcohol and subsequent semipinacol rearrangement triggered by potassium tert-butoxide (t-BuOK) afforded diketone 12 as a pair of epimers of undetermined configuration at C12 in a 1:1 ratio in 70% overall yield. Further treatment of 12 with p-toluenesulfonic acid (p-TSA) (1.0 equiv) in refluxing toluene for 3 h furnished the tetracyclic enone 13 in 55% yield together with an inseparable mixture of skeletally rearranged products. Then, 13 was hydrogenated with Adam’s catalyst and H2 to give ketone 6 in 80% yield.

As depicted in Scheme 2b, ketone 7 was synthesized in three steps from 5. Cleavage of diol 5 with silica-supported NaIO4 generated unstable tricarbonyl intermediate, which was quickly treated with 1M HCl without further purification to afford enone 14 in 58% yield through an intramolecular aldol condensation. Notably, the basic conditions only led to the decomposition.
of the labile intermediate. After the saturation of the enone double bond in 14 with Adam’s catalyst and H2, the second aldol condensation was promoted by p-TSA to furnish the tetracyclic enone 15 in 56% yield. The facial-selective hydrogenation of enone 15 with Pd/C and H2 furnished the key intermediate 7 in 95% yield. At this stage, 6 and 7 were in hand as the entries into the oxidation phase toward stemarane and betaerane diterpenoids.

Total synthesis of stemarane diterpenoids

Nucleophilic addition of the ketone group of 6 with MeLi delivered (+)-18-deoxystemarin (16) in 90% yield as a single diastereomer and subsequent dehydration with Amberlyst® 15 afforded (+)-stemar-13-ene (1) in a quantitative yield (15.4% overall yield from 9) (Scheme 3a). As mentioned above, Hong and Tantillo predicted that stemaranyl cation (IV) and betaeranyl cation (V) could be interconverted through concerted triple shift rearrangements. Interestingly, although the tertiary cation species (IV) is probably involved in the dehydration of the tertiary alcohol 16, no betaene-type products resulting from the cationic ring rearrangement (Scheme 1b) were observed in our reaction. The spectroscopic data for the synthetic sample (1) were fully consistent with those reported.

Starting from tetracyclic ketone 6, our synthesis of (+)-2-oxostemar-13-ene (2) entered into the oxidation phase (Scheme 3). Initial attempts to install the C2 oxo functionality using White group’s54,55 Fe-catalyzed oxidation protocol led to complex product mixtures. Electrochemical oxidation developed by Baran et al.17 could convert 6 to diketone 17 in 24% isolated yield, however, accompanied by a small amount of uncharacterized byproducts (Scheme 3b). In consideration of the formidable challenge to differentiate the reactivity of C2 and C14 keto groups of 17 in the following conversions toward 2, Alexanian xanthylation-oxygenation protocol56,57 was employed to attach the oxygenated functional groups.

First, we examined the direct conversion of 13-stemarene (1) to 2 through this protocol. However, by treatment of 1 with xanthylamide 18, C17-xanthylated product 19 was obtained in 36% isolated yield accompanied by a complex mixture of other xanthylation products (Scheme 3b). We then examined the xanthylation of alcohol 16, which led to complex product mixtures and failed to produce the desired product in a meaningful yield. These failures were presumably due to the ineffective or weak electronic control in these two substrates. Interestingly, when enone 13 was exposed to the xanthylation conditions, C2-xanthylated product 20 was obtained in 36% isolated yield (77% yield based on the recovery of starting material). This excellent site selectivity could be attributed to the extended electronic effect over the tetracyclic backbone through the enone functionality. Unfortunately, further elaboration of 20 to 2 failed.

To our delight, just as expected, treatment of 6 with xanthylamide 18 in PhCF3 using blue LED irradiation delivered inseparable C2 and C7 xanthenes 21 and 22 in

Scheme 2 | (a and b) Syntheses of advanced intermediates 6 and 7 through divergent ring-formation strategy.
a 3:1 ratio as single diastereomers (69% combined yield) accompanied by dixanthylation product 23 (23% yield) (Scheme 3c). The xanthylation exclusively occurred at the equatorial positions of C2 and C7 to generate thermodynamically stable products. Notably, this is the first direct C–H functionalization at the C7 position being observed in a similar framework except for enzymatic transformations. The xanthates were then smoothly converted to the corresponding alcohols 24 and 25 stereospecifically through a radical oxygenation and subsequent reduction in a one-flask manner.\(^{56}\) The structure of 25 was confirmed by X-ray crystallographic analysis. These results revealed that the xanthylation occurred at the sterically most accessible, electron-rich methylene sites (C2 and C7). The overall yield of C2–H oxygenation (32%) is remarkable since the substrate contains nine methylene sites and three tertiary C–H bonds. Moreover, the byproducts could be used to prepare otherwise inaccessible analogs with different levels of oxidation. Finally, three-step routine transformations furnished (+)-2-oxostemar-13-ene (2) in 82% yield from 24 (4.5% overall yield from 9), thus completing the first synthesis of this stemarene diterpene.

**Total syntheses and reassignment of the stereochemistry of betaerene diterpenoids 3 and 4**

With the success of the two-phase synthesis strategy for the stemarene diterpoid, we next examined its feasibility for betaerene diterpenoids. Since the isolation chemists did not define the configurations of the C8 stereocenters of 3 and 4, before setting out, we reassigned the stereochemistry of 3 (2S,5S,8S,9S,10S,15S) and 4 (2S,5S,8S,9S,10S,15S) as shown in Scheme 1c by the comparison of DFT-NMR data of four possible diastereoisomers 4 and 4a–4c with the reported data (see Supporting Information for details). Besides, the reported (7R) configuration of the C7 stereocenter of 4 was corrected as (7S). Because their skeletons belong to the betaerene class defined by Oikawa et al.,\(^ {8}\) we also renamed 3 as (+)-2-acetoxybetaer-13(17)-ene and 4 as

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**Scheme 3** | (a–c) Total syntheses of (+)-stemar-13-ene (1) and (+)-2-oxostemar-13-ene (2).
Encouraged by the success of C–H functionalization in both the C2 and C7 positions of stemarane scaffold, we envisioned that betaerane diterpenoids 3 and 4 could also be accessed from tetracyclic ketone 7 through a similar protocol. However, we wondered whether the significant conformation change from C–D rings from 6 to 7 would lead to any adverse effects on the site selectivity and diastereoselectivity of C–H functionalization. As shown in Scheme 4a, upon treatment with xanthylamide 18 in PhCF3 under blue LED irradiation, 7 was smoothly converted to the C2 xanthate 27 in 52% yield and the C7 xanthate 28 in 18% yield as single diastereomers. Interestingly, the conformational change from 6 to 7 did not lead to a significant difference in the site selectivity (C2∶C7 = 3∶1) and diastereoselectivity (complete equatorial substitution) but suppressed the formation of the dixanthate byproduct. Then 27 and 28 were transformed into the corresponding secondary alcohols 29 and 30 by the method mentioned above. To our great delight, the current artificial C–H functionalization strategy realized the site selectivity of the late-stage C–H oxygenation in the biosynthesis of 3 and 4. It is noteworthy that enzymatic hydroxylation occurred predominantly at the axial C7–H in Renata’s oxidation of tetracyclic diterpenoid frameworks, and extra oxidation–reduction manipulations were required to invert the configuration of the C7 stereocenter to generate the equatorial alcohol.27

Scheme 4 | (a–d) Total syntheses of betaerane diterpenoids (3) and (4) and three diastereoisomers (4a–4c).

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Finally, Wittig olefination and subsequent acetylation furnished (-)-2-acetoxybetaer-13(17)-ene (3) in 92% yield (4.8% overall yield from 9) and (+)-7-acetoxybetaer-13(17)-ene (4) in 90% yield (1.3% overall yield from 9), respectively. Gratifyingly, the synthetic samples of 3 and 4 exhibited spectroscopic properties identical to those reported for the corresponding natural products.56,51 The structure of 4 was further confirmed by X-ray crystallographic analysis.

To fully confirm the revised structure of 4, we also synthesized the other three diastereoisomers of 4 from tetracyclic enone 15. We envisioned that combining fine-tuning of the conformation56 of B ring with different chemical technologies would ensure the stereoselective introduction of the C8–H and C7–OH, thereby achieving stereochemical diversity of the C7 and C8 stereocenters. Specifically, 15 was first converted to dienol acetate 31, which then underwent hydroxylation at C7 from less-hindered β-face by treatment with m-chloroperbenzoic acid (m-CPBA) to furnish axial alcohol 32 in 51% yield over two steps (Scheme 4b). Hydrogenation of C8–C14 double bond with Adam’s catalyst and H2 afforded ketone 33 in 80% yield as a single diastereomer, which was smoothly transformed to 4a through acetylation and Wittig olefination in 90% yield. The stereochemistry of 4a was unambiguously confirmed by X-ray crystallographic analysis.

When enone 15 was treated with ethylene glycol and p-TSA, the ketal bearing an isomerized double bond (34) was formed in 92% yield. A hydroboration–oxidation guided hydration process over 34 generated a pair of inseparable alcohols with a cis-relationship of the C8–H and C7–OH (dr = 1:1), which then underwent Wittig olefination to afford separable alcohols 35 and 36 in 74% overall yield. Finally, acetylation of alcohol 35 furnished isomer 4b (Scheme 4c). On the other side, a two-step oxidation–reduction manipulation successfully inverted the C7-configuration of 36, affording alcohol 37 in 42% overall yield. The moderate yield was attributed to the overoxidation of 37 under the oxidation conditions. Subsequent acetylation completed the synthesis of 4c in 93% yield (Scheme 4d). The stereochemistry of 4c was also confirmed by X-ray crystallographic analysis.

Not surprisingly, none of the spectroscopic data of these isomers (4a–4c) were consistent with the reported data of 4. Based on the mutual support of DFT-NMR calculation results and chemical syntheses of both the natural product and its three diastereoisomers, the structure of 4 has been determined without dispute.

**Conclusions**

We have developed a unified protecting-group-free approach to four LRDs through a bioinspired two-phase strategy. Starting from a common tricyclic diol intermediate, two distinct tetracyclic frameworks containing diastereoisomeric bridged bicycles were constructed by divergent ring reorganization strategy. Late-stage C–H functionalization through a radical xanthylation–oxygenation process on the well-designed tetracyclic ketone substrates has been achieved in regio- and diastereoselective fashion among 15 kinds of C–H bonds. This artificial C–H oxygenation strategy mimicked the natural site selectivity of oxygenation at the C2 and C7 positions in the biosynthesis of these diterpenes. The total syntheses of (+)-2-oxostemar-13-ene (2), (+)-2-acetoxybetaer-13(17)-ene (3), and (+)-7-acetoxybetaer-13(17)-ene (4) have been achieved for the first time in 9–11 steps from the known enone 9 in 4.5%, 4.8%, and 1.5% overall yields, respectively. Furthermore, the stereochemistry of the latter two betaene diterpenoids was reassigned first by DFT-NMR studies and further confirmed through total syntheses of natural products and three diastereomers.

**Supporting Information**

Supporting Information is available and includes experimental procedures, characterization data, NMR spectra for all products, and Cartesian coordinates of all the DFT-optimized structures.

**Conflict of Interest**

There is no conflict of interest to report.

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