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Total Synthesis

Divergent Total Synthesis of Euphoranginol C, Euphoranginone D, *ent*-Trachyloban-3β-ol, *ent*-Trachyloban-3-one, Excoecarin E, and *ent*-16α-Hydroxy-atisane-3-one

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Abstract: *A divergent synthetic approach to biogenetically related diterpenoids such as ent-kauranes, ent-trachylobanes, ent-beyerane, and ent-atisane has been developed. The unified synthetic route involves the De Mayo reaction to rapidly generate the bicyclo[3.2.1]-octane moiety of ent-kaurane. The key reactions also include bioinspired nucleophilic cyclopropanation generating the [3.2.1.0^{2,7}]-tricyclic core of ent-trachylobane and regioselective cyclopropane fragmentation furnishing ent-beyerane and ent-atisane through the nucleophilic attack and protonation of the cyclopropane ring. This strategy enables the asymmetric total syntheses of six diterpenoids from the commercially available geraniol.*

Tetracyclic diterpenoids constitute a large family of plant terpenoids, and they mainly refer to the biogenetically related carbon skeletons derived from *ent*-copalyl diphosphate (*ent*-CPP). *ent*-Kauranes are the most common type of tetracyclic diterpenoids, which also include *ent*-beyerane, *ent*-atiserane, *ent*-trachylobane, and *ent*-grayanane (Figure 1).[1,2] Structurally, each family has a characteristic bicyclo[3.2.1]-, bicyclo-[2.2.2]-, or tricyclo[3.2.1.0^{2,7}]-octane framework containing several consecutive stereocenters. These natural diterpenoids have been found to exhibit many promising biological activities, including antitumor, antiviral, and antifungal activities.

Not surprisingly, the intriguing architectures of these diterpenoids as well as their potential biological activities have attracted considerable attention from the synthetic community, culminating in many elegant synthetic approaches to these target molecules (see the Supporting Information).[3–7] Despite the significant advances, interconversions of the bicyclooctane subunit of these diterpenoids with satisfactory selectivity and yield are highly sought after.[4d,s] In the course of our ongoing investigations on the biological activities of these molecules,[8] we sought to develop a divergent protocol for the synthesis of these biogenetically related diterpenoids. Herein, the asymmetric syntheses of euphoranginol C (**1**), euphoranginone D (**2**), *ent*-trachyloban-3β-ol (**3**), *ent*-trachyloban-3-one (**4**), excoecarin E (**5**) and *ent*-16α-hydroxy-atisane-3-one (**6**) are reported.

Our retrosynthetic analysis is depicted in Scheme 1. The bicyclo[3.2.1]- and bicyclo[2.2.2]-octane subunits of *ent*-beyerane (**5**) and *ent*-atisane (**6**) could be accessed through the regioselective cyclopropane fragmentation of **7**.[9] While the synthesis of *ent*-kaurane (**1**) would require an intramolecular ether formation,[4f] we postulated that *ent*-trachylobane **7** could be realized through nucleophilic cyclopropanation.[10] Accordingly, dione **8** could serve as the common

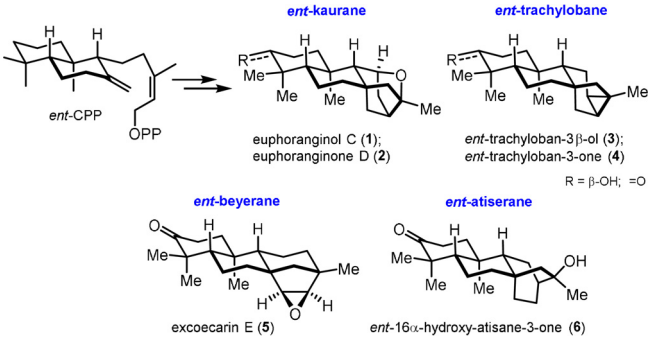
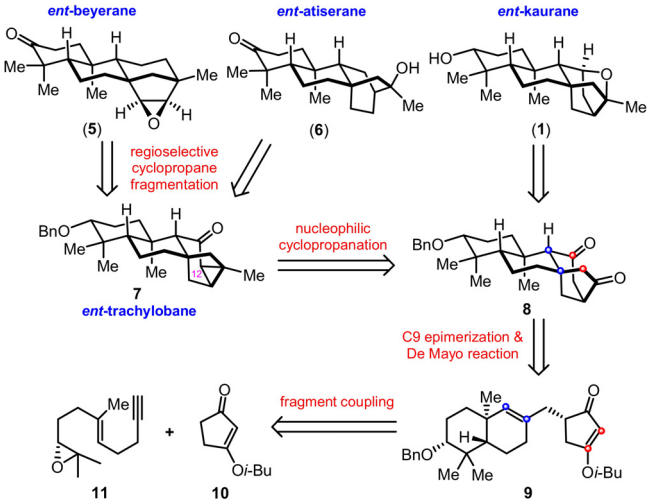


Figure 1. Structures of biogenetically related tetracyclic diterpenoids.



Scheme 1. Retrosynthetic analysis of tetracyclic diterpenoids.

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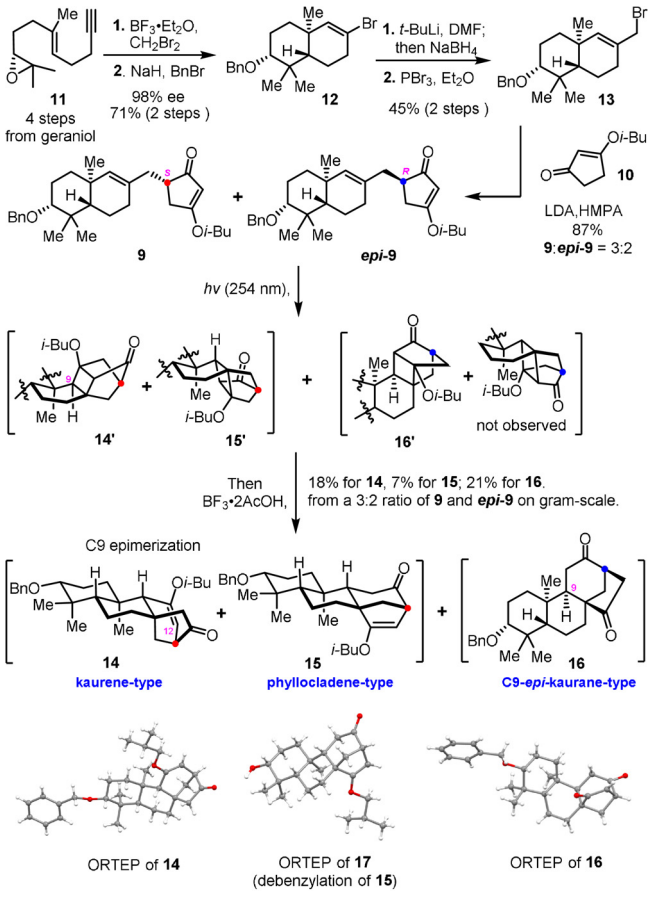
precursor. To construct the bicyclo[3.2.1]-octane moiety of **8**, a cascade reaction of diene **9** was developed, which involved C9 epimerization followed by De Mayo reaction.[11] Diene **9** could be readily obtained from the coupling of synthons **10** and **11**.

The synthesis commenced with the preparation of diene **9**. As outlined in Scheme 2, $BF_3{\cdot}Et_2O$-induced biomimetic cationic cyclization of polyenoid **11** (prepared from geraniol in four steps, Supporting Information) gave a known halogenated decalin, which has been elegantly exploited by Rodríguez and Yang.[12] Benzyl protection of the newly formed secondary alcohol group in decalin, followed by formylation and reduction, afforded an allylic alcohol, which was further converted to allylic bromide **13** using PBr_3. Finally, treatment of **13** with the enolate of **10** generated coupling product **9**.

With **9** in hand, we attempted to conduct the De Mayo reaction (Scheme 2). Gratifyingly, irradiation of **9** with 254 nm light triggered a smooth [2+2] photocycloaddition, and the anticipated dione **8** could be isolated using HCl (aq), along with enol ether **14** bearing a potential C12 nucleophile. Since **14** played a key role in the latter nucleophilic cyclopropanation, we next screened different acids to improve the yield of **14**. Eventually, we found that $BF_3{\cdot}2\,AcOH$[13] gave *ent*-kaurene-type **14** and *ent*-phyllocladene-type[2e] **15** in a one pot reaction, and the structures were unambiguously confirmed by X-ray analysis.[14] It is noteworthy that the treatment of intermediate **14′** with $BF_3{\cdot}2\,AcOH$ resulted in its C9 epimerization via an oxonium intermediate. In parallel, the De Mayo reaction was attempted on substrate *epi*-**9**, affording C9-*epi*-kaurane-type **16** as the single isomer. To understand the reason for the moderate regioselectivity with substrate **9**, we performed density functional theory (DFT) calculations.[15] DFT calculations demonstrated that intermediate **INT1** with kaurane-type skeleton is favored both kinetically and thermodynamically compared to the phyllocladane-type skeleton. (Figure 2)

Once the common precursor **14** was obtained, we proceeded for the synthesis of the biogenetically related polycyclic diterpenoids (Scheme 3 A). Hydrolysis of vinyl ether **14** with 3 N HCl (aq) afforded the desired dione **8** in 95 % yield, which then underwent regioselective methenylation in the presence of phosphine salts to produce **18**. Unfortunately, reduction of **18** with L-selectride or DIBAL-H predominantly produced an undesired diastereomer. Thus, a radical reduction approach was adopted and the desired diastereomer **19** was obtained using sodium in isobutanol.[16] Treatment of **19** with PTSA generated **20**. Subsequent removal of the benzyl group afforded euphorangiol C (**1**), which furnished euphoranginone D (**2**) upon further oxidation.

The intramolecular nucleophilic cyclopropanation attack by C12 was next investigated in connection with the synthesis of trachylobane-type diterpenoids (Scheme 3 A). Wittig methenylation of **14** furnished terminal alkene **21** in 90 % yield. To our delight, despite the concurrent hydrolysis of the vinyl ether, treatment of **21** with stoichiometric amount of 1 N HCl (aq) afforded the desired cyclopropenone **7** along with **18** in a nearly 1:1 ratio. The structure of **7** was unambiguously determined through X-ray analysis.[14] Better yield was obtained later by using 0.6 equivalents 1 N HCl (aq) after stirring for 5 h. This procedure may serve as an example of nucleophilic displacement in the formation of cyclopropanes. Moving forward, reduction of the highly sterically hindered C11 ketone was achieved under drastic Wolff–Kishner conditions by stirring at 210 °C for 50 h. Using the same procedure described above, pentacyclic trachylobanes *ent*-



Scheme 2. Investigation of the De Mayo reaction. BnBr = benzyl bromide, DMF = N, N-dimethylformamide, HMPA = hexmethylphosphoramide, LDA = lithium diisopropylamide, DCM = dichloromethane.

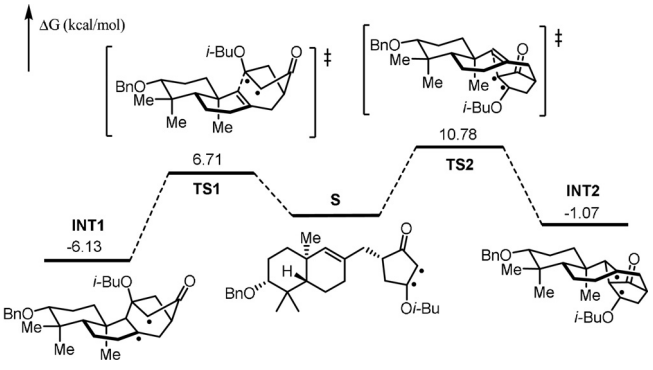
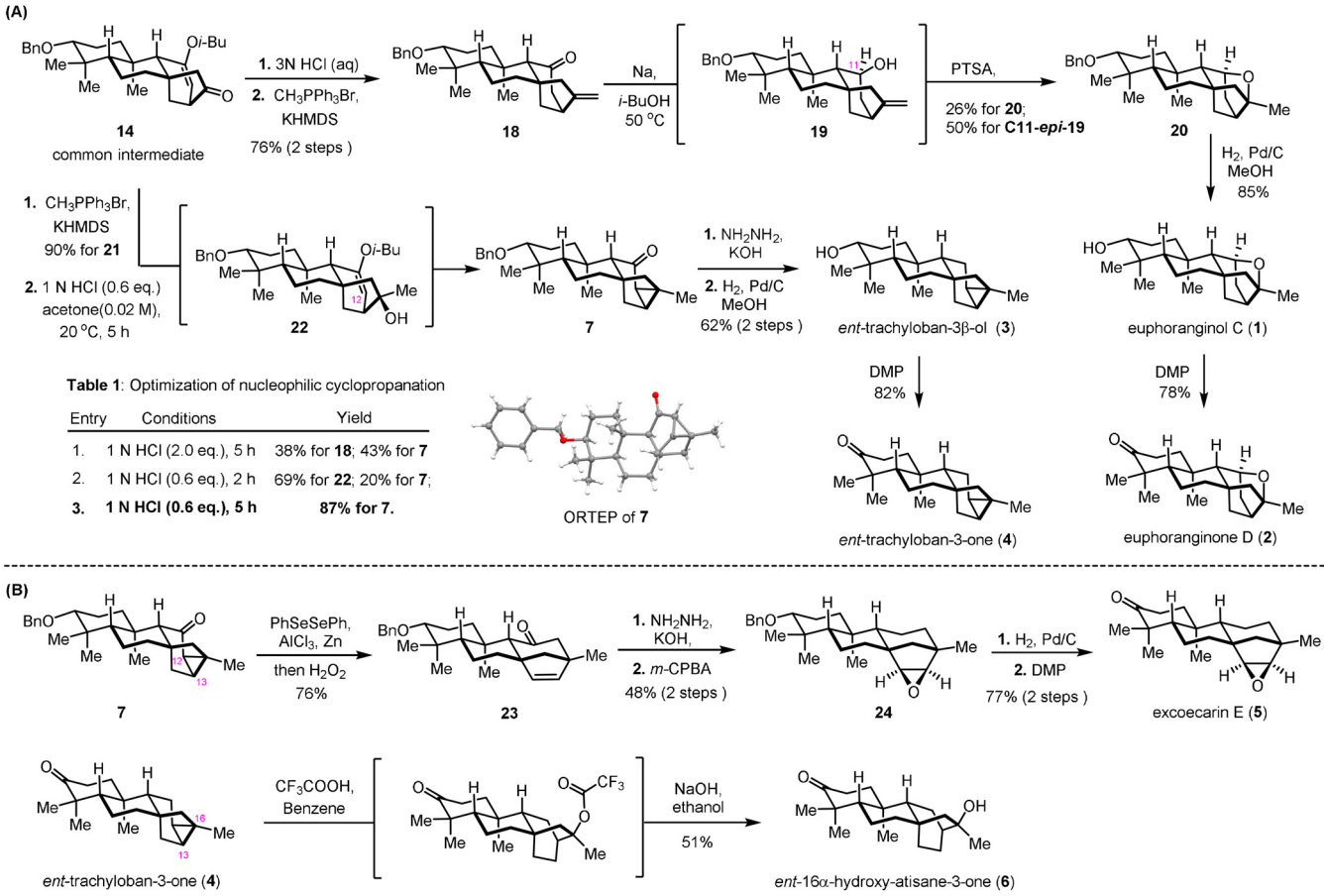


Figure 2. Computed free-energy profile of the De Mayo reaction of **9** at the B3LYP method with 6-31G(d) basis set.



Scheme 3. Divergent synthesis of euphoranginol C (**1**), euphoranginone D (**2**), *ent*-trachyloban-3β-ol (**3**), *ent*-trachyloban-3-one (**4**), excoecarin E (**5**) and *ent*-16α-hydroxy-atisane-3-one (**6**). KHMDS = Potassium bis(trimethylsilyl)amide, PTSA = *p*-toluenesulfonic acid, DMP = Dess–Martin periodinane, DCM = dichloromethane, *m*-CPBA = chloroperbenzoic acid.

trachylobane-3β-ol (**3**) and *ent*-trachylobane-3-one (**4**) were also successfully obtained.

To access *ent*-beyerane and *ent*-atisane, we explored the regioselective cyclopropane fragmentation of trachylobane (Scheme 3 B). Compound **7** was first subjected to the nucleophilic attack of electron-deficient cyclopropane.[17] Initial attempts of using halides did not give the desired products. However, the more nucleophilic selenide anion appeared rather promising.[17c] Upon treatment with H_2O_2, the formed C13 substituted selenide was oxidized to **23**. C11 ketone of **23** was converted to methylene by the Wolff–Kishner reaction. The C13-C14 alkene double bond was then epoxidized by *m*-CPBA, and finally, debenzylation and DMP oxidation produced excoecarin E (**5**).

We next focused our attention on the C13-C16 bond cleavage to furnish *ent*-atisane via protonation of the cyclopropane ring.[18] Transformations of natural molecules **3** and **4** were examined. Screening a range of protonic acids suggested that although the decomposition of **3** was unavoidable, the expected C13-C16 bond cleaved product of **4**, namely, natural *ent*-16α-hydroxy-atisane-3-one (**6**), could be isolated smoothly (after hydrolysis of the trifluoroacetate intermediate) by adding trifluoroacetic acid. Spectroscopic data (^{1}H NMR and ^{13}C NMR) collected for the six synthetic diterpenoids were consistent with those reported previously.

In summary, we have developed a divergent route that enables the total synthesis of some biogenetically related polycyclic diterpenoids, namely, *ent*-kauranes, *ent*-trachylobanes, *ent*-beyerane, and *ent*-atisane. De Mayo reaction was employed to generate the pivotal bicyclo[3.2.1] moiety of *ent*-kaurane. Conversion to *ent*-trachylobane from *ent*-kaurane was achieved through bioinspired nucleophilic cyclopropanation. Regioselective cyclopropane fragmentations of *ent*-trachylobane, furnishing *ent*-beyerane and *ent*-atisane, were achieved through the nucleophilic attack and protonation of the cyclopropane ring. Analog synthesis and evaluation of biological activities are being undertaken and will be reported in due course.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis · cyclization · natural products · terpenoids · total synthesis

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contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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