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COMMUNICATION

Divergent Total Syntheses of Five Illudalane Sesquiterpenes and Assignment of the Absolute Configuration

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Concise, divergent total syntheses of five bioactive illudalane sesquiterpenes have been achieved. Our synthesis features an intermolecular [2+2+2] cycloaddition, a lactone-directed aromatic C–H oxygenation to generate a temporary phenolic hydroxyl group which enables a regioselective methylation. Furthermore, the absolute configuration of radulactone was assigned by chemical synthesis.

Illudalane sesquiterpenes are a group of secondary metabolites which have been majorly discovered in ferns and fungi,[1] and recently were also isolated from the Antarctic[2] and sub-Antarctic[3] marine soft corals. Structurally, these sesquiterpenes share a multisubstituted indane core which usually comprises a pentasubstituted phenyl ring, but differ in the oxygenation types. The illudalane skeletons are biosynthetically derived from the protoilludane skeletons probably through specific bond cleavage and aromatization.[4] To date, over a hundred illudalane sesquiterpenes have been identified (Fig. 1), many of them displays interesting biological activities, such as antimicrobial, pesticidal, and anticancer activities.[5] Notably, echinolactone A (**2**) significantly promotes radicle elongation at 100 ppm in lettuce seedling assay, which suggests it might be involved in reproduction process.[5c] Riparol B (**5**)[5d] exhibits potent pesticidal activity against thrips.[5e] Their fascinating structure features and promising applications in the pharmaceutical or agrochemical industry have attracted considerable synthetic interest,[6] and several strategies have been developed for the construction of multisubstituted indane skeletons.

Herein, we report the first asymmetric synthesis of radulactone (**1**)[5b] and concise divergent syntheses of the other four illudalane sesquiterpenes **2**-**5**, featuring a Rh-catalyzed [2+2+2] cycloaddition[7] and a Ru-catalyzed aromatic C–H oxygenation.[8]

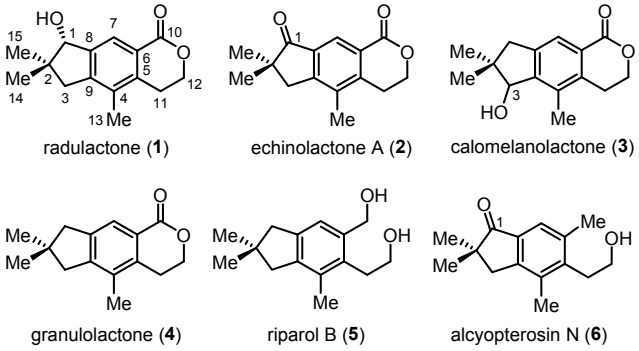

Fig.1 Selected examples of illudalane sesquiterpenes.

At the outset of our synthetic studies, the structural relevance of these sesquiterpenes inspired us that this natural product family could be rapidly accessed from a less functionalized natural precursor granulolactone (**4**)[5e] through a late-stage divergent functionalization strategy.[9] As outlined in Scheme 1, radulactone (**1**), echinolactone A (**2**) and calomelanolactone (**3**)[5a] could be obtained from **4** by specific oxygenation. We anticipated that the key intermediate **4** bearing a pentasubstituted phenyl ring could be accessed from tetrasubstituted benzene derivative **8** by a regioselective methylation. However, due to the low reactivity and poor regioselectivity of the congested tetrasubstituted phenyl ring in **8** towards methylation, a more reactive phenol intermediate **7** was employed. We expected that the temporary introduction of the C7 phenolic hydroxyl group can facilitate the desired methylation by increasing the electron density of the aromatic ring and meanwhile blocking a competing reaction site (C7). We envisioned that C7 hydroxyl group could be introduced by a lactone carbonyl directed aromatic C–H oxygenation in the presence of transition metals. Through this C–H activation manipulation, two competitive sites (C4 and C7) could be differentiated while the extra phenolic hydroxyl group could be easily removed afterwards. Then the tetrasubstituted phenyl

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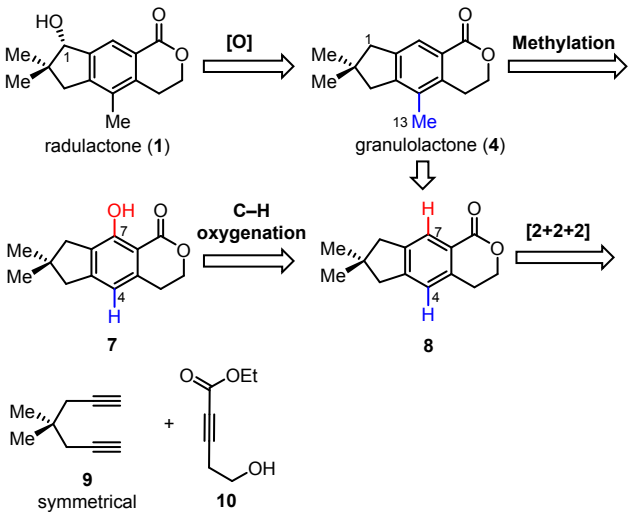
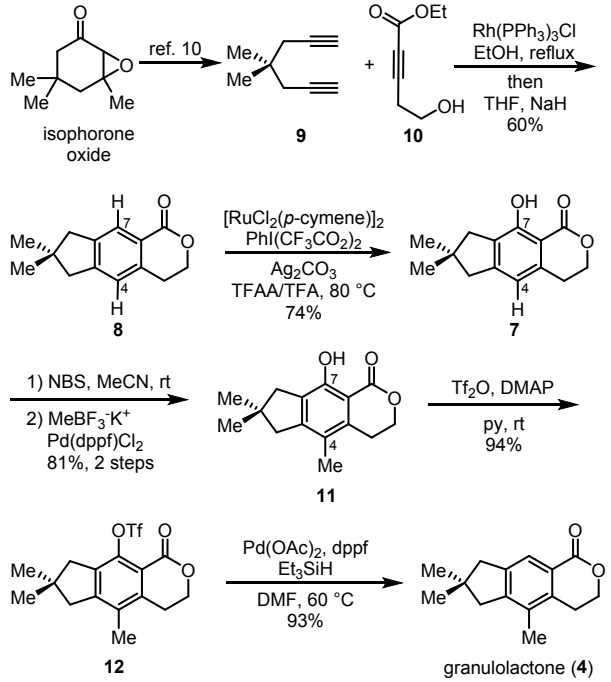


Scheme 1 Retrosynthetic analysis of illudalane sesquiterpenes.

ring could be constructed by a transition metal catalyzed intermolecular [2+2+2] cycloaddition of diyne **9** and ethyl 5-hydroxypent-2-ynoate **10**.

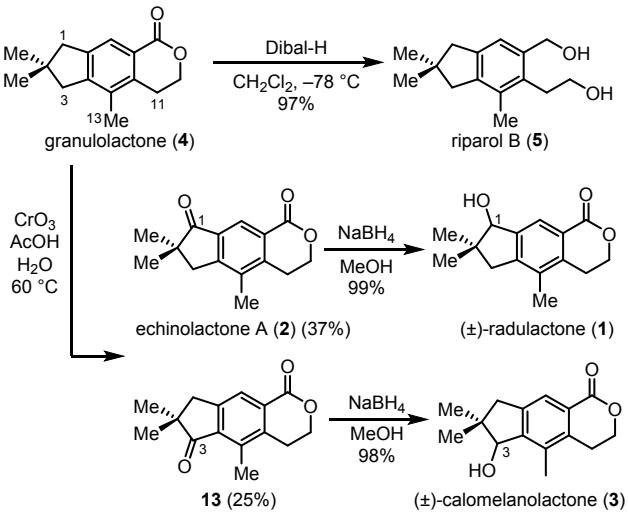
As depicted in Scheme 1, our synthesis commenced with the known diyne **9**,[10] which can be readily prepared in four steps from commercially available isophorone oxide. Rh-catalyzed [2+2+2] cycloaddition of **9** and **10** with Wilkinson's catalyst[11] followed by treatment with NaH afforded indane lactone **8** in 60% yield. Actually, the initial attempts of [2+2+2] cycloaddition between unsymmetrical diyne **S6** and **10** only produced the desired product **4** as a minor product in very low yield (see the Supporting Information (SI)), together with the undesired regioisomer.[12] With **8** in hand, the initial attempts of methylation at C4 through halogenation or borylation[13] were all



Scheme 2 Total synthesis of granulolactone (**4**).

fruitless, presumably for reasons of high steric hindrance. To enhance the reactivity of the phenyl ring and control the regioselectivity of the methylation, a hydroxyl group was introduced to C7 through lactone carbonyl group directed oxygenation. By using Hong's Ru (II) catalysis methodology,[8i] phenol **7** was obtained in 74% yield. Subsequent two-step methylation involving C4 bromination and Suzuki coupling smoothly provided compound **11** in 81% overall yield. Finally, the extra phenolic hydroxyl group was removed by palladium catalyzed hydrogenation of its triflate derivative to deliver granulolactone (**4**) in 6 overall steps.

Starting from the key intermediate granulolactone (**4**), four illudalane sesquiterpenes were synthesized through simple reduction or C–H oxygenation and reduction sequence. Specifically, Dibal-H reduction of the lactone afforded riparol B (**5**), a potent pesticide against thrips, in 97% yield. Treatment of **4** with CrO_3 in acetic acid afforded echinolactone A (**2**) in 37% yield together with its constitutional isomer **13**. Notably, no oxygenation products at benzylic C11 or C13 positions were observed, probably due to the less electron density of those C–H bonds. Reduction of the former ketone with $NaBH_4$ delivered racemic radulactone (**1**) in 99% yield while the reduction of the later one produced calomelanolactone (**3**) in 98% yield. At this stage, we have achieved concise total syntheses of five illudalane sesquiterpenes.



Scheme 3 Divergent total syntheses of riparol B, echinolactone A, (±)-radulactone, and (±)-calomelanolactone.

Although the optical rotation of radulactone was reported by Anke and coworkers, its absolute configuration is still unknown to date. An asymmetric synthesis of a natural product can serve as a reliable way for the determination of its absolute stereochemistry.[14] After a brief screening of reductants and catalysts (see SI), we found that, reduction of the ketone group with (*S*)-Corey-Bakshi-Shibata (CBS) catalyst[15] and BH_3•SMe_2 afforded (+)-radulactone (**1**) in 38% yield and 87.2% *ee*.[16] The low yield was probably for reasons of high steric hindrance around the ketone group and overreduction of lactone group.[17] The optical rotation matched well with that of naturally

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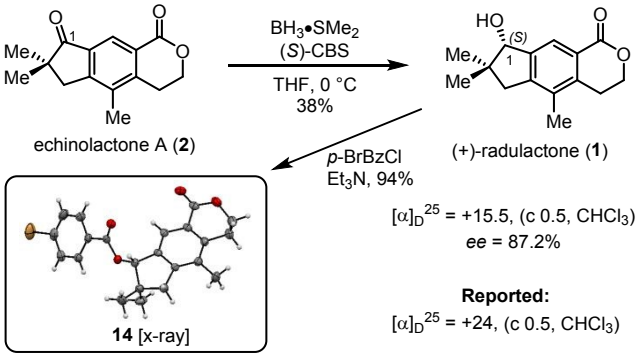
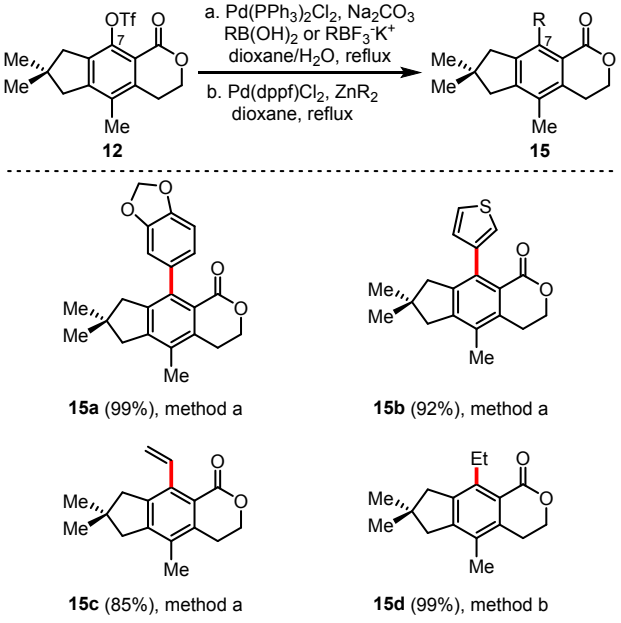
occurring radulactone. Furthermore, the single crystal x-ray crystallography of its *p*-bromobenzoate derivative **14** unambiguously defined the absolute configuration of **1** as (*1S*) (Scheme 4). At this point, we have achieved the first asymmetric total synthesis of radulactone (**1**) in 8 overall steps.



Scheme 4 Asymmetric synthesis of (+)-radulactone and assignment of absolute configuration.

Finally, to further demonstrate the synthetic value of the temporary phenol intermediate **11** which was prepared through the aromatic C–H bond activation, four illudalane analogues were prepared (Scheme 5). By palladium catalyzed Suzuki coupling (method a) or Negishi coupling (method b) over its triflate derivative **12**, the analogues bearing benzodioxole (**15a**), thiophene (**15b**), vinyl (**15c**) and ethyl (**15d**) groups at C7 position were obtained in high yields. Overall, we not only developed an efficient way to make illudalane analogues, but also provided a useful strategy for the synthesis of challenging hexasubstituted phenyl ring.[18]



Scheme 5 Synthesis of illudalane analogues through a late-stage functionalization.

In summary, we have developed a divergent strategy for the syntheses of five illudalane sesquiterpenes in 6 to 8 steps from known diyne **9**, and four of them [radulactone (**1**), echinolactone A (**2**), granulolactone (**4**) and riparol B (**5**)] were obtained by chemical synthesis in laboratory for the first time. The key transformations include a Rh-catalyzed [2+2+2] cycloaddition to generate a tetrasubstituted phenyl ring, a Ru-catalyzed aromatic C–H bond oxygenation to form reactive phenol intermediate and late-stage divergent oxygenations. The well-orchestrated transition metal catalysis secured the high efficiency of the synthesis. Moreover, the absolute configuration of naturally occurring (+)-radulactone (**1**) was assigned as (*1S*) on the basis of our total synthesis. The success of the C–H activation strategy also enables efficient syntheses of four illudalane analogues which bear a synthetically challenging hexasubstituted phenyl ring. The reported strategy and technologies are clearly applicable for the syntheses of other illudalane sesquiterpenes and their derivatives.

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Conflicts of interest

There are no conflicts to declare.

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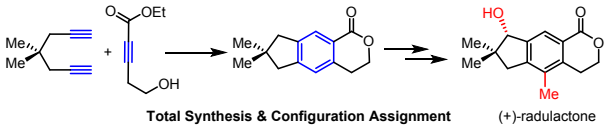

Total Synthesis & Configuration Assignment (+)-radulactone

Transition metal catalyzed [2+2+2] cycloaddition and aromatic C–H oxygenation enables concise, divergent total syntheses of five bioactive illudalane sesquiterpenes.

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