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Gold catalysis-facilitated rapid synthesis of the daphnane/tigliane tricyclic core

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ABSTRACT

A concise approach to synthesize the 5-7-6 tricyclic carbon skeleton of the daphnane/tigliane diterpene natural products has been accomplished *via* a sequential gold-catalyzed furan formation and furan-allene [4+3] cycloaddition. This work provides new avenues for rapid and diverted synthesis of the medicinally important daphnane/tigliane diterpenes and their unnatural analogs.

1. Introduction

The daphnanes and tiglianes, isolated from *thymelaeaceae* and *euphorbiaceae*, are two large groups of structurally diverse diterpene natural products which share a characteristic 5-7-6 tricyclic carbon skeleton.[1] These structurally complex molecules have received a significant amount of attention due to their appealing chemical structures and promising therapeutic potential. They have demonstrated a broad range of biological activities, including anticancer, antiviral, analgesic, and neurotrophic effects.[1b,2] For example, kirkinine[3] (**1**, Fig. 1), isolated from the roots of *synaptolepis kirkii*, is the most potent neurotrophically active natural product reported so far. It effectively promotes neuronal survival against serum deprivation in nanomolar concentrations, which is comparable to the nerve growth factor itself. Phorbol (**2**)[4] is a well-known tumor promotor and protein kinase C activator. On the other hand, phorbol 12-myristate 13-acetate, also a protein kinase C activator, has been advanced into human clinical trials for the treatment of acute myeloid leukaemia. Prostratin (**3**),[5] is a promising therapeutic agent that targets latent HIV reservoirs. Resiniferatoxin (**4**)[6] exhibits an analgesic effect through activation of transient receptor potential vanilloid 1 (TRPV1), which induces desensitization of nociceptive neurons.

The structural complexity and promising therapeutic applications of these daphnane and tigliane diterpenes have identified themselves as attractive synthetic targets. Many synthetic approaches toward the core structures of these natural products have been reported since the early 1980s.[7] These synthetic efforts cultimated in the total syntheses of phorbol and resiniferatoxin by Wender[8] and co-workers, a formal synthesis of phorbol by Cha[9] et al., a total synthesis of crotophorbolone, a derivative of the daphnane/tigliane diterpenes, by the Inoue[10] group, and an impressive 19-step total synthesis of phorbol by the Baran group[11] (Fig. 2). The Wender synthesis features a [5+2] cycloaddition to construct the 6,7-fused bicycle. The Cha synthesis utilized a [4+3] cycloaddition to build the central 7-membered ring and the Inoue group used a radical cyclization to close the 7-membered ring. An allene-alkene Pauson-Khand reaction[12] was employed by the Baran group to set up the 5,7-fused ring system.

Despite all these synthetic efforts, concise and highly efficient synthetic routes toward these complex diterpenes are still valuable and necessary. Herein, we report our efforts in developing a synthetic approach to rapidly construct the 5-7-6 carbotricyclic ring system by using a gold-catalyzed furan formation and furan/allene [4+3] cycloaddition.

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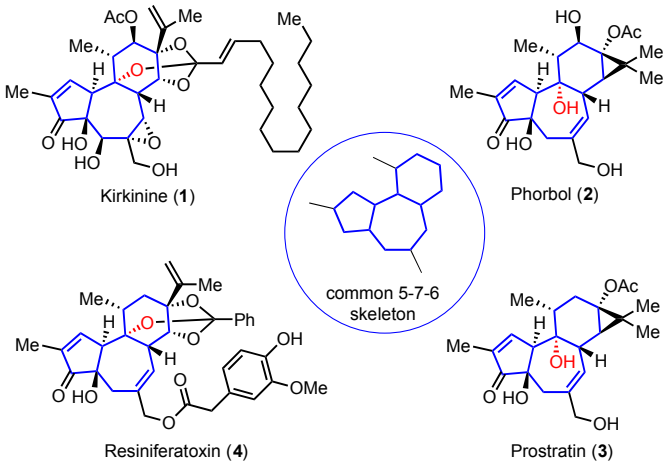

Fig. 1. Representative daphnane/tigliane diterpenes.

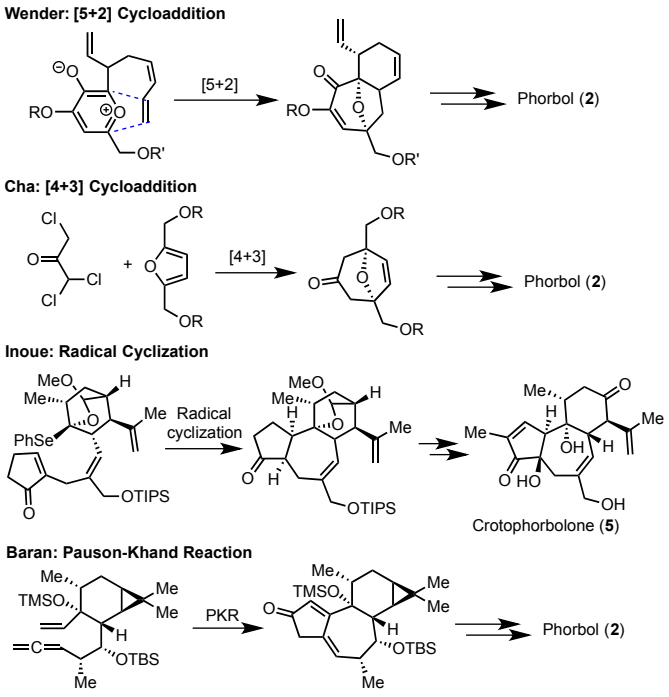

Fig. 2. Selected strategies for daphnane/tigliane synthesis.

Gold catalysis has started to play an important role in facilitating total syntheses of complex bioactive natural products.[13] The gold-catalyzed furan/allene [4+3] cycloaddition, developed by the groups of Mascareñas[14] and Toste,[15] is a very efficient synthetic method for highly functionalized 7-membered ring construction. However, its application in complex natural product synthesis has been very rare.[16] Meanwhile, a number of gold-catalyzed furan formation reactions[17] were reported to access highly substituted furan moieties. Inspired by these works, we envisoned a gold-catalyzed tandem furan formation followed by furan/allene [4+3] cycloaddition as an efficient approach for the synthesis of the daphanane/tigliane 5-7-6 core skeleton (Fig. 3, **6** → **10**). This tandem process would start from relatively simple enyne alcohol **6**, which could be readily assembled by a Sonogashira cross coupling. The gold catalyst would selectively activate the alkyne to trigger a 5-*exo*-*dig* cyclization of the hydroxyl group on the alkyne and

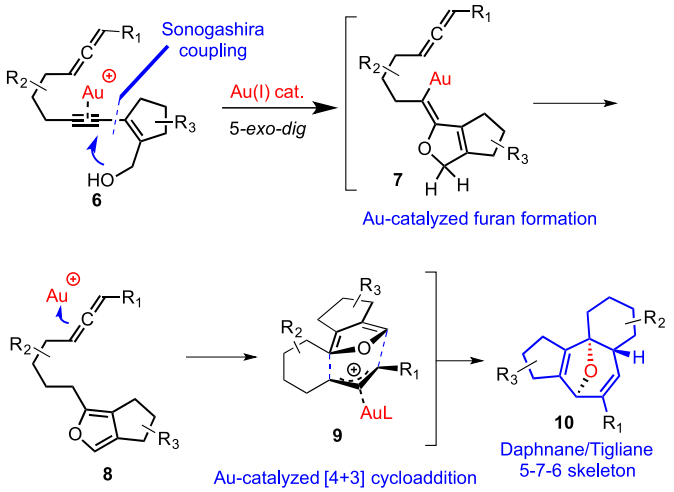

Fig. 3. Proposed synthesis of the daphnane/tigliane 5-7-6 tricyclic ring system via tandem gold catalysis.

generate hydrofuran **7**, which would then isomerize to furan **8**. The gold catalyst would then activate the allene to generate an allylic cation-gold complex for the [4+3] cycloaddition to provide product **10**, which could then be advanced to the daphnane/tigliane diterpenes. This tandem process faces several challenges: (i) How to preferentially activate the alkyne in presence of the allene? (ii) How to avoid other competing cycloisomerization reactions before the furan formation and [4+3] cycloaddition? (iii) Will the reaction provide the desired stereochemistry? Despite these potential problems, such a tandem process would significantly improve synthetic efficiency by converting relatively simple and readily available starting material such as **6** to complex polycyclic intermediate such as **10**, which resembles the core skeleton of the daphnane/tigliane diterpene natural products.

2. Result and discussion

We designed substrates **6a**-**6c** with varying substituents on the allene moiety as our model substrates. Their syntheses are summarized in Scheme 1. Fragment **13** is a known compound[18] which can be synthesized on gram scale in 66% yield through a Vilsmeier-Haack reaction of cyclopentanone **11** followed by a sodium borohydride reduction of the resulting aldehyde **12**. Allenes **17a-17c** were synthesized utilizing the Ma's protocol for allene synthesis[19] followed by propargylation. Sonogashira cross coupling united **13** and **17** successfully and gave the desired coupling products from 52% to 86% yield. In these Sonogashira couplings, the freeze-pump-thaw[20] technique is crucial for high yields; otherwise, a significant amount of alkyne dimerization leads to a dramatic drop of the reaction yield.

We next investigated the feasibility of the gold-catalyzed tandem cyclization and cycloaddition process under various reaction conditions on substrate **6a** (Table 1). Initially, the commonly used gold catalyst systems reported for the [4+3] cycloadditions were tested. To our disappointment, conditions such as PPh_3AuNTf_2 (entries 1 and 4), $^tBuXPhosAuCl/AgSbF_6$ (entry 2), and IPrAuCl/$AgSbF_6$ (entry 3) only gave very complex mixtures, indicating that these highly reactive catalyst systems may be promoting unwanted cycloisomerization pathways instead of the first furan formation step. The combination of $PPh_3AuCl/AgOTf$ in THF was able to produce furan product **8a** in good yield (65%–72%), but it failed to promote the second [4+3] cycloaddition step (entry 6). Interestingly, the furan formation reaction became unproductive by simply