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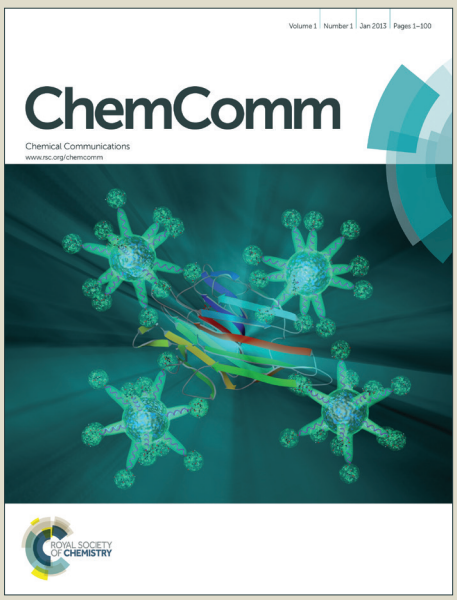

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A short route towards merosesquiterpenes with a benzoxanthene skeleton

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A short synthetic sequence for the preparation of merosesquiterpenes with a benzoxanthene skeleton starting from commercial (-)-sclareol is reported. The D ring of the target compound is obtained through a Diels-Alder cycloaddition, involving the dienoldiether derived from a tricyclic α,β-enone synthesized in two steps from the starting diterpene. Utilizing this, the preparation of (+)-hongoquercin A and the first synthesis of (+)-cyclospongiaquinone-1 were achieved.

Merosesquiterpenes are natural products of mixed biosynthetic origin (polyketide–terpenoid) containing a sesquiterpene unit joined to a phenolic or quinone moiety. The most important metabolites of this family of compounds, with respect to their potent biological activities, are those bearing a bicyclic terpene (drimane) moiety. Among these, two main types of compounds can be distinguished: a) metabolites with a drimanyl (or drimenyl) phenol (or quinone) structure, such as the antitumor *ent*-yahazunol (**1**, Figure 1),[1] and hyatellaquinone (**2**);[2] b) compounds with a benzoxanthene skeleton, such as the antitumour and antimalarial 15-oxopuupehenol (**3**),[3] 8-epipuupehedione (**4**), an angiogenesis inhibitor with potential antileukemic activity,[4] the antitumour cyclospongiaquinone-1 (**5**)[5] and the antibiotic hongoquercin A (**6**)[6] (Figure 1).

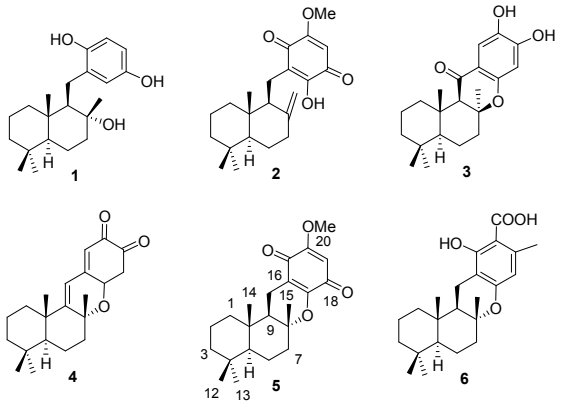
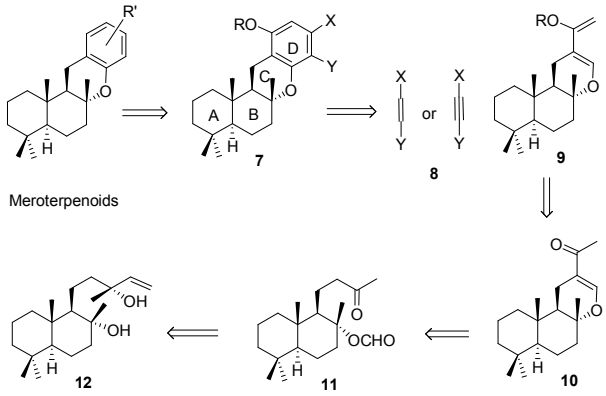


Fig. 1 Merosesquiterpenes with a benzoxanthene skeleton and related metabolites.

Many attempts have been made to synthesize this type of compound. In this respect, the most frequently utilized strategies are based on the biomimetic cyclization of farnesylphenols[7] and a two synthon strategy, involving in most cases the reaction of a drimane electrophile with a nucleophilic phenol derivative, usually an aryllithium compound.[3b, 6c, 8] A two synthon strategy, utilizing the terpenyl radical precursor "borono-sclareolide", was recently reported by Baran's group.[6e] Alternative strategies have recently been developed for synthesizing some of the above compounds. Thus, 8-epipuupehedione (**4**) has been prepared, via a Diels-Alder cycloaddition of a C_{19} dienol ether derived from sclareol oxide [4b] and hongoquercin A (**6**) has been synthesized utilizing an unusual cationic [2+2] cycloaddition.[6d]

The wide range of potent activities presented by the above meroterpenoids makes it desirable to develop processes which would allow us to access this type of natural compounds and derivatives rapidly and economically, in order to explore their therapeutic potential. Accordingly, we planned a short synthesis of merosesquiterpenes with the benzoxanthene skeleton from commercial (-)-sclareol (**12**)(Scheme 1). The pyrane C ring of the target compound, which possesses compound **10**, will be obtained after an intramolecular Claisen condensation of keto ester **11**, which is obtained in one step from diterpene **12**, in almost quantitative yield. The aromatic D ring of the final compounds is elaborated via the Diels- Alder cycloaddition of dienol diether **9** with the suitable dienophile **8**. The benzoxanthene derivative **7**, obtained after aromatization of the corresponding cycloadduct, is a immediate precursor of the target merosesquiterpenes.



Scheme 1 Retrosynthesis of merosesquiterpenes with a benzoxanthene skeleton.

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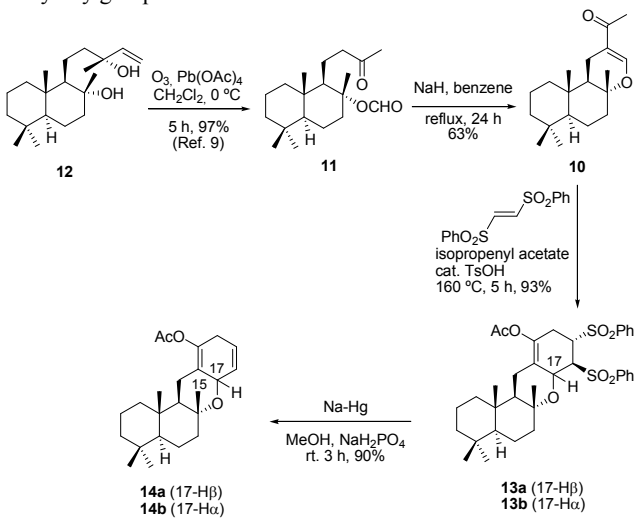
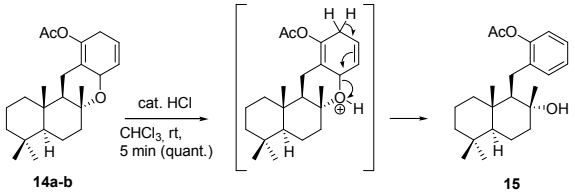
† Electronic Supplementary Information (ESI) available: Full experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}CNMR. See http://dx.doi.org/10.1039/b000000x/

Scheme 2 shows the construction of the tetracyclic merosesquiterpene skeleton. The treatment of (-)-sclareol (**12**) with the ozone-lead(IV) acetate system[9] at 0 ºC for 5 h afforded the formate **11** in almost quantitative yield. Tricyclic α,β-enone **10** was obtained when the ketoester **11** was refluxed with NaH in benzene for 24 h. The treatment of ketone **10** with *E*-1,2-bis(phenylsulphonyl)ethylene and isopropenyl acetate, in the presence of cat. TsOH, at 160 ºC for 5 h produced the tetracyclic bis sulphone **13a-b**, as mixture of two stereoisomers in a 1.2:1 ratio. Reduction of the latter with Na-Hg afforded the unstable diene **14a-b** as an unresolvable mixture of epimers (1.2:1 ratio). The β dispositon of proton H-17 in the major stereoisomer **14a** was established on the basis of the NOE effect observed between Me-15 (singlet at 1.35 ppm) and H-17 (triplet at 4.81 ppm). These results reveal that bis sulfone **13a-b** also consists of a mixture of 17-epimers, with the 19-phenylsulphonyl group placed away from the acetyloxy group.



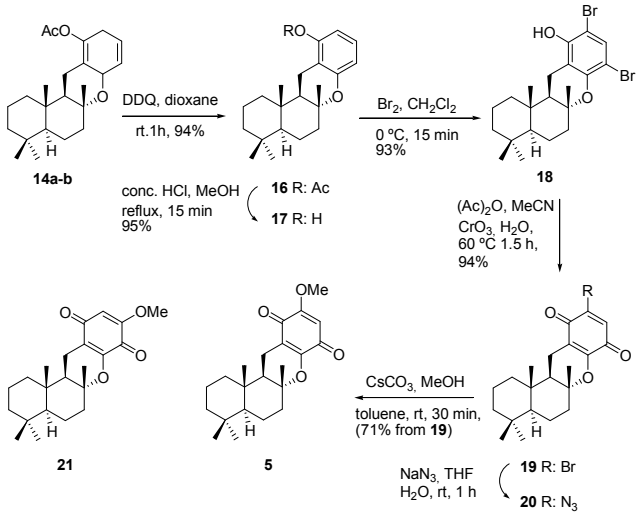
Scheme 2 Construction of the tetracyclic merosesquiterpene skeleton.

Diene **14a-b** is a suitable intermediate to achieve the synthesis of merosesquiterpenes with a benzoxanthene skeleton and related compounds. The treatment of this with cat. HCl in chloroform causes pyrane ring opening, leading to the aryl drimane **15**, which is a suitable precursor of merosesquiterpenes such as *ent*-yahazunol (**1**)(Scheme 3).



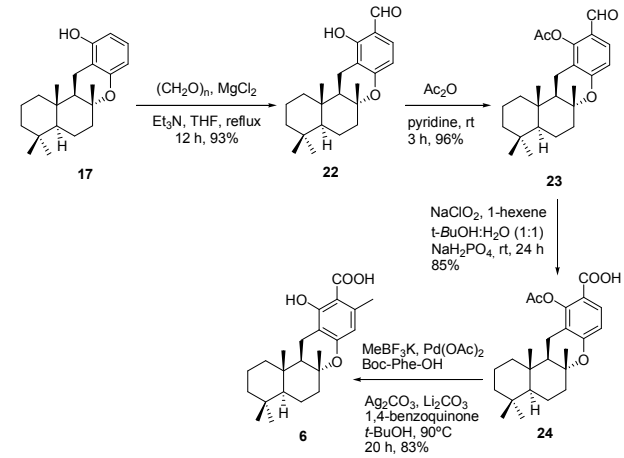
Scheme 3 Synthesis of aryl drimane **15**.

Next, the transformation of diene **14a-b** into merosesquiterpenes with a benzoxanthene skeleton, such as compounds **5** and **6** was undertaken. Scheme 4 shows the synthesis of cyclospongiaquinone-1 (**5**). The treatment of diene **14a-b** with DDQ in 1,4-dioxane at room temperature gave the aromatic acetate **16**, which was subsequently hydrolyzed to phenol **17**. This was then transformed into dibromide **18** (83 % from **14a-b**). Oxidation of the latter with aq. CrO_3 in Ac_2O/MeCN gave the quinone **19** in high yield. Methoxylation of bromoquinone **19** using MeONa in MeOH took place in high yield, but disappointingly afforded a 1 : 1 mixture of the desired compound **5** and its regioisomer **21**. The *cine*-substitution product **21** was avoided by utilizing the azide group as the leaving group.[10] The treatment of bromoquinone **19** with sodium azide gave azidoquinone **20**, which without further isolation, was cleanly converted into the desired cyclospongiaquinone-1 (**5**) after treatment with cesium carbonate in MeOH/toluene. The above described sequence constitutes the first synthesis of metabolite **5**. The optical rotation of synthetic cyclospongiaquinone-1 (**5**) ($[\alpha]^{25}_D$: +87.9; c 3.5, $CHCl_3$) was similar to that reported for the natural product ($[\alpha]^{25}_D$: +94.6; c 0.06, $CHCl_3$); the spectroscopic properties were identical to those previously described.[5b] These results corroborate the absolute stereochemistry of this natural quinone.



Scheme 4 Synthesis of cyclospongiaquinone-1 (**5**).

Phenol **17** was also transformed into the merosesquiterpene hongoquercin A (**6**) (Scheme 5). The aldehyde **22** was obtained



Scheme 5 Synthesis of hongoquercin A (**6**).

when compound **17** was refluxed with paraformaldehyde, $MgCl_2$ and Et_3N in THF for 12 h. Acetylation of the hydroxyl group and oxidation with $NaClO_2$, yielded the acetoxy acid **24**. When this was treated with $MeBF_3K$ in the presence of catalytic $Pd(OAc)_2$,[6e] methylation and simultaneous de-*O*-acetylation took place affording the desired compound **6.** The optical rotation of synthetic (+)-hongoquercin A (**6**) ($[\alpha]^{25}_D$: +139.1; c 0.56, MeOH) was similar to those previously reported by Roll, for the natural product,[6a] and Mori, for the compound **6** synthesized starting from (-)-sclareol (**12**).[6c] Synthetic **6** exhibited identical spectral properties to those previously reported. [6a, 6c, 6e]

In summary, a short synthetic sequence for the preparation of merosesquiterpenes with a benzoxanthene skeleton starting from (-)-sclareol (**12**) has been developed. The key steps of the sequence are the intramolecular Claisen condensation of ketoester **11** providing the tricyclic α,β-enone **10**, whose dienoldiether was utilized for the elaboration of the D ring of the target compounds through a Diels-Alder cycloaddition. The preparation of (+)-hongoquercin A (**6**) and the first synthesis of (+)-cyclospongiaquinone-1 (**5**) were achieved utilizing this procedure.

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