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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-ene synthesized in two steps from the starting diterpene. Utilizing this, the preparation of (+)-hongoquercin A and the first synthesis of (+)-cyclosporinaguanine-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 drimyl (or drimenyl) phenol (or quinone) structure, such as the antitumor ent-yahazunol (1, Figure 1), and hyatelquinone (2); b) compounds with a benzoxanthene skeleton, such as the antitumour and antimalarial 15-oxopuupehenol (3), 8-epipuupehedione (4), an angiogenesis inhibitor with potential antileukemic activity, the antitumour cyclosporinaguanine (5) and the antibiotic hongoquercin A (6) (Figure 1).

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 famesylphenols and a two synthon strategy, involving in most cases the reaction of a drimane electrophile with a nucleophilic phenol derivative, usually an aryllithium compound. A two synthon strategy, utilizing the terpenyl radical precursor “borono-sclareolide”, was recently reported by Baran’s group. 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 C15 dienol ether derived from sclareol oxide and hongoquercin A (6) has been synthesized utilizing an unusual cationic [2+2] cycloaddition.

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 their 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 pyran 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 an immediate precursor of the target merosesquiterpenes.

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

† Electronic Supplementary Information (ESI) available: Full experimental procedures, spectroscopic data and copies of 1H and 13CNMR. 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 at 0 °C for 5 h afforded the formate 11 in almost quantitative yield. Tricyclic α,β-ene 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(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 merosesquiterpene skeleton. The treatment of (-)-sclareol (130) with a benzoxanthene skeleton, such as compounds 13a-b, as mixture of two stereoisomers in a 1.2:1 ratio. The β disposition 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 sulphone 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).

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

100 Scheme 3 Synthesis of aryl drimane 15.

101 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. CrO3 in Ac2O/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 regiosomer 21. The cine-substitution product 21 was avoided by utilizing the azide group as the leaving group.100 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) ([α]25° = +87.9; c 3.5, CHCl3) was similar to that reported for the natural product ([α]25° = +94.6; c 0.06, CHCl3); the spectroscopic properties were identical to those previously described.100 These results corroborate the absolute stereochemistry of this natural quinone.

Scheme 5 Synthesis of hongoquercin A (6).
when compound 17 was refluxed with paraformaldehyde, MgCl$_2$ and Et$_3$N 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$_3$K in the presence of catalytic Pd(OAc)$_2$, $^{6c}$ methylation and simultaneous de-$O$-acetylation took place affording the desired compound 6. The optical rotation of synthetic (+)-hongoquerin A (6) ([α]$^2_D$: +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. $^{6a, 6c, 6c}$

In summary, a short synthetic sequence for the preparation of merosqiuterpenes 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 (+)-hongoquerin A (6) and the first synthesis of (+)-cyclospongiaquione-1 (5) were achieved utilizing this procedure.

The authors thank the Spanish Ministry of Science and Innovation (Project CTQ2009-09932) and the Regional Government of Andalucia (Projects P07-FQM-03101 and P11-CTS-7651, and assistance for the FQM-348 group) for financial support. A. Fernández thank the Spanish Ministry of Science and Innovation for the predoctoral grant provided.

Notes and references

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