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First enantiospecific synthesis of marine sesquiterpene quinol akaol A†‡

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The first enantiospecific synthesis of akaol A, a marine sesquiterpene quinol, has been achieved. Key steps of the synthetic sequence are the oxidative degradation of (−)-sclareol to a dinorlabdane ketoester, mediated by the ozone–lead(IV) acetate system, the diastereoselective α-methylation of a ketoaldehyde, followed by an intramolecular aldol condensation and the further Diels–Alder cycloaddition of a dienol ether.

Merosesquiterpenes are natural products of mixed biosynthetic origin (polyketide-terpenoid) containing a sesquiterpene unit joined to a phenolic or quinone moiety. The most important group of this family of compounds, due to the wide variety of structural types and to their important, potent biological activities, are those bearing a bicyclic terpene (drimane) moiety. Smenodiol (**1**)[1] and siphonodictyal C,[2] which exhibits CDK4/cyclin D1 complex inhibitory activity,[3] are examples of drimenyl phenols. The sphingosine kinase inhibitor (−)-F-12509[4] is a representative drimenyl quinone (Fig. 1).

Another important group of compounds belonging to this family of metabolites is that of marine puupehenones, which possess a tetracyclic structure, including a pyran ring.[5] During the last decade a new type of merosesquiterpene, presenting a tetracyclic structure, including a cyclopentane ring, has been isolated from marine sponges and terrestrial fungi. Examples of this include pelorol (**2**),[6] akaol A (**3**),[2] dasyscyphin B (**4**),[7] C (**5**),[7] D (**6**)[8] and E (**7**).[8] Though the bioactivities of this family of compounds have yet to be examined comprehensively, recent studies have revealed that pelorol (**2**) is an activator of the inositol 5-phosphatase SHIP,[9] whereas dasyscyphin B (**4**) and C (**5**) present potent cytotoxic activities in several human cell lines,[7] and dasyscyphin D (**6**) and E (**7**) exhibit antifungal properties.[8]

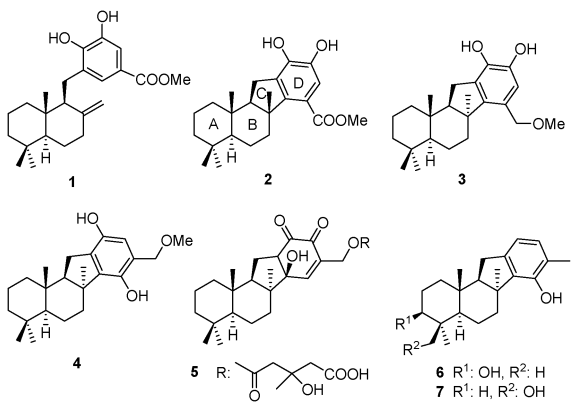

Fig. 1 Some representative merosesquiterpenes.

Many efforts have been made to synthesise drimenyl phenols and puupehenone-related compounds.[10] In most cases, the carbon skeleton of these compounds has been elaborated through a two-synthon strategy, involving the reaction of an aryllithium derived from a suitably protected polyphenol with a bicyclic sesquiterpene (drimane derivative) electrophile. However, little work has been done concerning tetracyclic merosesquiterpenes bearing the cyclopentane C ring, such as compounds **2–7**. Andersen *et al.* recently reported the first synthesis of pelorol (**2**) starting from (+)-sclareolide.[11] These authors utilized the two-synthon strategy to construct the carbon skeleton of the target compound, by condensation of an aryllithium with a drimane hydroxy aldehyde. Andersen's group came up against some difficulties in creating the cyclopentane C ring, *via* intramolecular Friedel–Crafts alkylation, which required a sufficiently activated aromatic moiety.[12] As was to be expected, a tetracyclic precursor with the appropriate configuration on C-8 was achieved in good yield after careful selection of the aromatic substrate and cyclization conditions.

Continuing our research into the synthesis of bioactive merosesquiterpenes, we examined the synthesis of sesquiterpene quinols such as compounds **3–7**, which have not been yet synthesized, probably because the B/C *cis* fused system is unattainable utilizing the strategies previously reported. The results reported by Andersen's group in their synthesis of pelorol (**2**), corroborated by our preliminary studies, revealed that the two-synthon strategy followed by intramolecular Friedel–Crafts alkylation led to the tetracyclic intermediate bearing a C8β methyl group as the major diastereomer. Considering the above arguments, we planned the synthetic strategy shown in Scheme 1 to achieve akaol A (**3**). The cyclopentane C ring of the target compound will be obtained through the intramolecular aldol condensation of a ketoaldehyde. The aromatic D ring of precursor **8** will be

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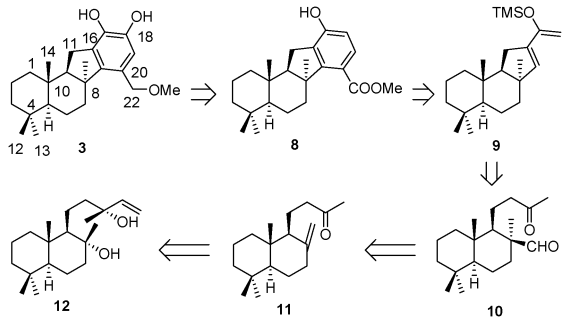
† Electronic supplementary information (ESI) available: Full experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}C NMR. See DOI: 10.1039/c1cc14608d

‡ This work is dedicated to the memory of Professor Rafael Suau.

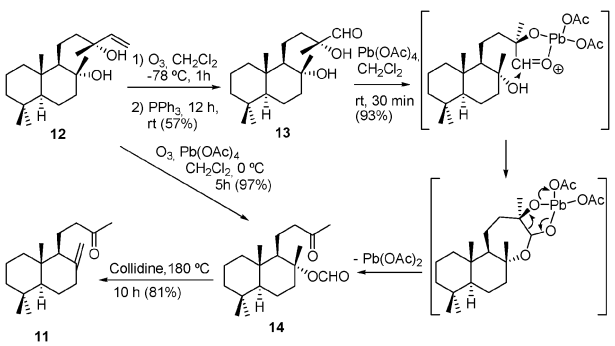


Scheme 1 Retrosynthesis of akaol A (**3**).

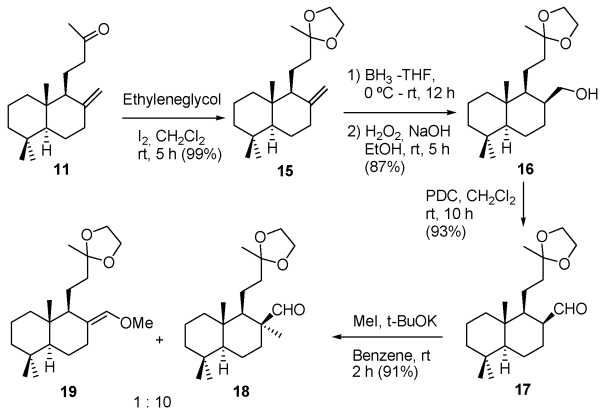
elaborated after the Diels–Alder cycloaddition of silyl dienol ether **9** derived from the α,β-enone resulting from the intramolecular aldol condensation of ketoaldehyde **10**. The C8α methyl group of compound **3** will be introduced after the diastereoselective C-methylation of enol derived from the corresponding suitably protected ketoaldehyde; this will be obtained from ketone **11**, after oxidative hydroboration. Ketone **11** will be prepared from commercial sclareol (**12**).

First, the preparation of ketone **11** was investigated. This compound has been widely utilized as the key intermediate in the synthesis of many natural products and other compounds of interest.[13] However, only a total synthesis of compound **11**, utilizing a long synthetic sequence which involves optical resolution, has been reported.[13c] The most efficient methods for preparing ketone **11** use natural products as starting materials; the most common procedure entails the degradative oxidation of the side chain of a diterpene labdane, which possesses the exocyclic carbon–carbon double bond of the target compound.[13a,d,e] Procedures starting from (−)-sclareol (**12**), a naturally abundant, inexpensive commercial diterpene, have also been reported; these utilize as an intermediate the corresponding 8-acetyloxy ketone prepared by selective acetylation of the 8-hydroxy group and subsequent side chain oxidation, or otherwise the palladium catalyzed allylic rearrangement of sclareol diacetate followed by ozonolysis.[13b] Even though a moderate yield (60%) for the monoacetylation of (−)-sclareol (**12**) has been reported, we encountered serious difficulties in attaining this result.

Scheme 2 shows a more efficient means of preparing ketone **11** from (−)-sclareol (**12**). Treatment of hydroxy aldehyde **13**, obtained in high yield after the ozonolysis of diterpene **12**, with lead(IV) acetate in dichloromethane at room temperature for 30 min gave ketoester **14**[14] in 93% yield. Compound **12** was



Scheme 2 Synthesis of ketone **11**, *via* formate **14**.

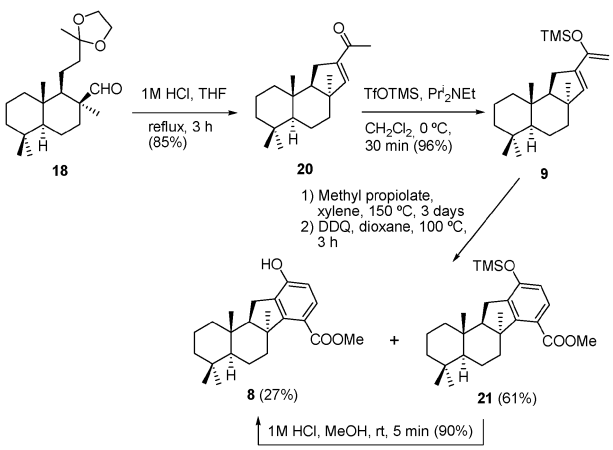


Scheme 3 Synthesis of aldehyde **18**.

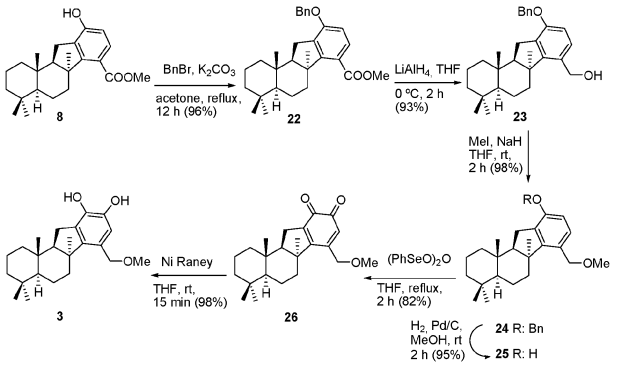
directly converted into formate **14** in almost quantitative yield, after treatment with the ozone–lead(IV) acetate system, previously reported by our group;[15] the scope and limitations of this reaction, which can be utilized in a multigram scale, are currently under study. Ketoester **14** underwent the regioselective elimination of formic acid to give the exocyclic ketone **11**, in high yield, by heating with collidine.

Scheme 3 shows the transformation of ketone **11** into aldehyde **18**, bearing the characteristic C8α methyl group of the target compound. After protecting the ketone group as ethylene ketal, the oxidative hydroboration of the exocyclic carbon–carbon double bond proceeded with complete diastereoselectivity, affording alcohol **16**, which was easily converted into aldehyde **17**. However, the α-methylation of the latter involved some difficulties, because of the strong tendency of this aldehyde to undergo O-alkylation, probably due to steric factors. This forced us to assay the methylation of aldehyde **17** under different reaction conditions. The use of a strong base, such as NaH, in a polar aprotic solvent, such as DMF, considerably favoured the O-methylation (**18/19**, 4 : 6). The highest proportion of C-methylation product was attained utilizing *t*-BuOK in benzene.

After the above-described procedures, we addressed the construction of the cyclopentane C and aromatic D ring of akaol A. Scheme 4 shows the synthesis of intermediate **8**, bearing the tetracyclic skeleton of the final sesquiterpene quinol. The ketal aldehyde **18** after treatment with 1 M HCl in THF under reflux



Scheme 4 Synthesis of the sesquiterpene quinol precursor **8**.



Scheme 5 Synthesis of akaol A (**3**).

for 3 h underwent simultaneous ketone deprotection and intramolecular aldol condensation, affording the tricyclic α,β-enone **20**. Treatment of this with TfOTMS and Pri_2NEt gave silyl dienol ether **9**, which after refluxing with methyl propiolate in xylene and further oxidation with DDQ in dioxane under reflux afforded the tetracyclic compound **21** together with the phenol **8**. The silyl ether **21** was transformed into hydroxy ester **8** after treatment with 1 M HCl in MeOH.

Finally, functionalization of the aromatic D ring was tackled. Scheme 5 shows the transformation of compound **8** into akaol A (**3**). First, the elaboration of the catechol unit was attempted; the treatment of compound **8** with Fremy's salt or benzeneseleninic anhydride gave the unaltered starting material. This result can be attributed to the deactivation of the aromatic ring by the ester group. In order to avoid this inconvenience, the latter was reduced to the hydroxymethyl group. The phenol **25**, resulting from the deprotection of benzyl ether **24**, was then easily converted into *o*-quinone **26**, which was finally transformed into akaol A (**3**) by reaction with Raney nickel. The optical rotation of synthetic akaol A (**3**) ($[\alpha]_D^{25}$: −13.7; *c* 8.0, MeOH) was similar to that reported for the natural product ($[\alpha]_D^{25}$: −12; *c* 0.15, MeOH); the spectroscopic properties were identical to those previously described.[2]

In summary, the first synthesis of (−)-akaol A (**3**) has been achieved starting from (−)-sclareol (**12**). The synthetic sequence includes a new oxidative degradation of the latter, induced by the ozone–lead(IV) acetate system, which affords ketoester **14** in high yield. The suitable configuration on C-8 was attained after the diastereoselective α-methylation of aldehyde **17**. The cyclopentane C ring of the target compound was obtained after intramolecular aldol condensation and the aromatic D ring was constructed through a Diels–Alder cycloaddition involving silyl dienol ether **9**.

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