Enantiospecific Synthesis of the Antituberculosis Marine Sponge Metabolite (+)-Puupehenone. The Arenol Oxidative Activation Route
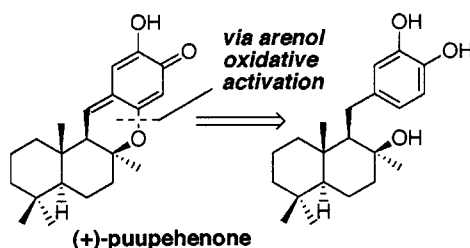
Stéphane Quideau,* Marjolaine Lebon, and Anne-Marie Lamidey

Laboratoire de Chimie des Substances Végétales, Centre de Recherche en Chimie Moléculaire, Université Bordeaux 1, 351 Cours de la Libération, F-33405 Talence Cedex, France

s.quideau@lcsv.u-bordeaux1.fr

ABSTRACT

The total synthesis of the marine sesquiterpene quinone (+)-puupehenone, a promising new antituberculosis agent, was achieved in 10 steps starting from commercially available (+)-sclareolide. The key feature of this synthesis is the construction of the heterocycle via an intramolecular attack of the terpenoid-derived C-8 oxygen function onto an oxidatively activated 1,2-dihydroxyphenyl unit.

(+)-Puupehenone (**1**)[1] belongs to a family of marine sesquiterpene-quinones and quinols that today has more than a hundred members.[2] First isolated by Scheuer and co-workers from a yellow encrusting sponge, which was collected off the island of Lanai and tentatively identified as *Chondrosia chucalla*,[3] this naturally occurring quinone methide has since been found in many sponge specimens such as *Heteronema, Hyrtios,* and *Strongylophora* sp.[4] The special chemical reactivity of the quinone methide moiety of **1**[5] engenders

the formation of numerous other puupehenone-derived metabolites such as puupehedione (**2**),[6] 15-cyanopuupehenol (**3**),[7] 15-oxopuupehenol (**4**),[4c] and the halopuupehenones **5a** and **5b**,[3] as well as dimers such as the most recently discovered dipuupehedione (**6**)[4d] (Figure 1). All of these compounds display a wide range of biological properties as antitumor, antiviral, antimalarial, antibiotic, and immuno-modulatory agents. Most remarkably, (+)-puupehenone (**1**) was recently reported to fully inhibit the growth of *Mycobacterium tuberculosis* at a concentration of 12.5 µg/mL (i.e., MIC = 38 µM).[8] This remarkable antituberculosis activity is perhaps today the most promising biological property of

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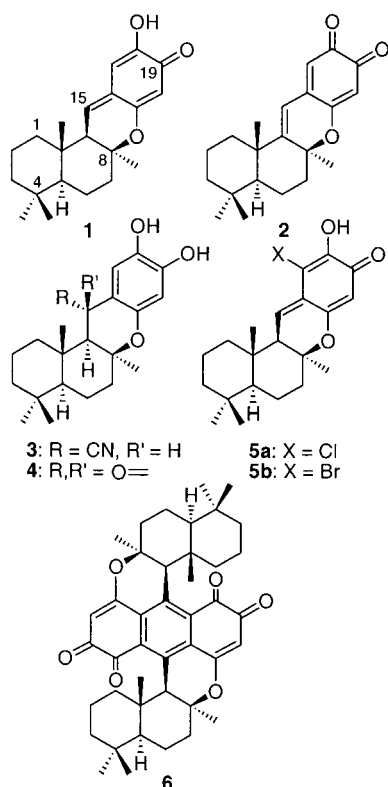
Figure 1. Examples of puupehenone (**1**)-derived marine sponge metabolites.

(+)-**1** in view of the current re-emergence of tuberculosis coinciding with the AIDS epidemic, a dramatic event that has resulted in the development of new multidrug-resistant strains of *M. tuberculosis*.

The sesquiterpene moiety of **1** features a normal drimane skeleton annelated to a shikimate-derived hydroxyquinone unit. Only two total syntheses of **1** have been described. The first one was reported by Trammel[9] in 1978 and started from a phenol-bearing polyene that was subjected to an initial cationic bicyclization to construct the drimane unit. This reaction was followed by an acid-catalyzed electrophilic addition of the phenol to the remaining drimane olefin. An ultimate oxidation furnished racemic **1**. Despite the lack of reproducibility of this synthesis noted by Barrero and co-workers, the electrophilic addition approach to the oxygen heterocycle probably inspired these authors, who reported twenty years later the second synthesis of **1** via an orga-noselenium-induced heterocyclization step.[10] This latter synthesis proceeded in an enantiospecific manner in 15 steps starting from (−)-sclareol [**8**, lab-14-en-8,13-(*S*)-diol], the main constituent of the flowerheads of *Salvia sclarea* L. (clary sage).

In both of these syntheses, the heterocyclic oxygen is delivered from a 1,2,4-trihydroxyphenyl unit. This strategy is common to all reported syntheses of puupehenone-related metabolites and analogues (Scheme 1).[10,11] Whether or not such an approach has some biogenetic relevance, we decided to proceed in a different and reverse way by exploiting the
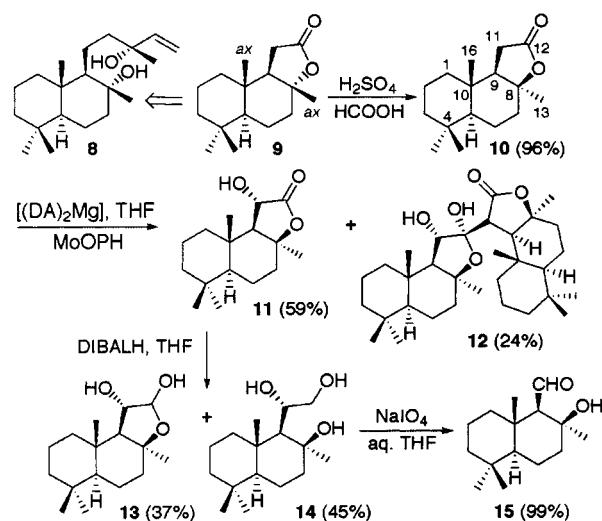
Scheme 1
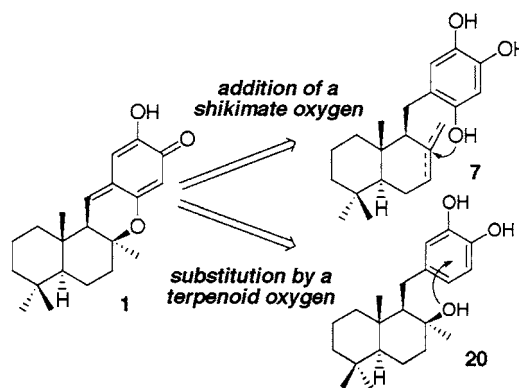
presence of an oxygen function at C-8 of (+)-sclareolide (**9**). This drimane unit precursor already possesses the correct chirality for three of the four (+)-puupehenone (**1**) stereo-genic centers, i.e., C-5, C-9, and C-10. It can be purchased from commercial sources or conveniently prepared from labdane (−)-**8**.[12] In our synthesis scenario, the nucleophilic character of the terpenoid 8-oxygen will serve to mediate the desired heterocyclization by attacking an oxidatively activated 1,2-dihydroxyphenyl moiety (Scheme 1).

The first task to surmount in our synthesis plan is inversion of the configuration at C-8. Indeed, the 8-oxygen is α-oriented in terrestrial plant-derived (+)-**9**, whereas it is β-oriented in marine metabolite (+)-**1**. The prerequisite epimerization was achieved in the first step of our synthesis via simple acid treatment (Scheme 2). The ease of this

Scheme 2

inversion of configuration at C-8 is attributed to the release of the 1,3-diaxial interaction between the 13- and 16-methyl groups in (+)-**9** (Scheme 2).

The γ-lactone unit of the resulting levorotatory isosclar-eolide **10** was then α-hydroxylated using Vedejs' MoO5·

pyridine·HMPA (MoOPH)-based protocol[13] to furnish **11** in good yield as the sole diastereoisomer. Of particular note is the intriguing inefficiency of LDA in promoting initial deprotonation. The success of this apparently trivial transformation relied on the use of magnesium bis(diisopropylamide) [(DA)$_2$Mg],[14] whose divalent cation advantageously expressed its chelating properties to facilitate access of the nitrogen base to the most labile α-proton. In addition to the formation of the desired acyloin **11** and the recovery of some unreacted (−)-**10** (7.5%), the MoOPH-mediated hydroxylation reaction gave rise to crystalline side-product **12**,[15] resulting from the competitive nucleophilic addition of the enolate intermediate onto α-hydroxylactone **11**. This aldol type side-reaction was also observed in Vedejs' earlier work.[13b] An X-ray crystal structure of **12** established its stereochemistry, which is consistent with the expectation that both MoOPH and the drimane carbonyl should preferentially approach the enolate from its least hindered face.[13b] The synthesis of the sesquiterpenoid unit of **1** continued with a hydride reduction of the lactone ring of **11** into a mixture of lactol **13** and the desired triol **14** in a modest but unoptimized yield of 45%. Surprisingly, reduction using LiAlH$_4$ (LAH) only gave lactol **13** and attempts to further reduce it into **14** with either DIBALH or LAH were to no avail. The triol **14** was then subjected to a nearly quantitative oxidative cleavage of its 1,2-diol moiety into β-hydroxy aldehyde **15** (Scheme 2).

The shikimate unit was elaborated from catechol **16** through bromination and benzylation to give bromide **18**. Coupling of this bromide with aldehyde **15** was achieved via a standard halogen−metal exchange protocol. A subsequent hydrogenolysis under standard conditions allowed removal of both benzyl protective groups, and the benzylic C-15 hydroxy group that was unveiled at the previous coupling reaction (Scheme 3), to afford catechol **20** in good yield. This remarkable deprotection−deoxygenation step[16] set the stage for the key oxidative activation of the catechol

unit toward intramolecular attack by the drimane 8-oxygen. This activation relied on the use of [bis(trifluoroacetoxy)-iodo]benzene (BTI) in CH$_2$Cl$_2$ at −25 °C. Such λ^3-iodane reagents[17] constitute today a convenient alternative to the use of toxic heavy metal-based reagents for activating arenols (i.e., any hydroxylated arene rings) toward oxidative nucleophilic substitution reactions.[18]

The hypervalent iodine(III)-mediated transformation of **20** led to a 3:1 diastereomeric mixture (unassigned) of spirocycle **21** as the only heterocyclic system produced despite the presence of two phenolic hydroxyl groups in starting **20**. The mechanistic consensus about such a phenolic activation process implies passage through an arenoxenium ion intermediate or a transient equivalent thereof.[18a,g] The C-16, C-17, and C-21 centers are positioned either para or ortho to one of the phenolic hydroxy groups in **20** and hence are all available for nucleophilic attack. It thus appears that the drimane unit exhibits an electron-releasing effect sufficient to impose the heterocyclization regiochemistry in favor of an exclusive 5-exo-trig spiroannulation process. Rearrangement of spirocycle **21** into the targeted fused heterocyclic system was achieved by exploiting the acidity of its enol function (Scheme 3). An anionic rearrangement was thus performed by gently heating **21** in anhydrous dioxane in the presence of KH and 18-crown-6. This reaction did not stop at the expected catecholic benzopyran (not shown), and we were very pleased to observe that it had been oxidized in situ to furnish (+)-**1** in 27% yield (unoptimized) over the last two one-pot transformations. This completed the syn-
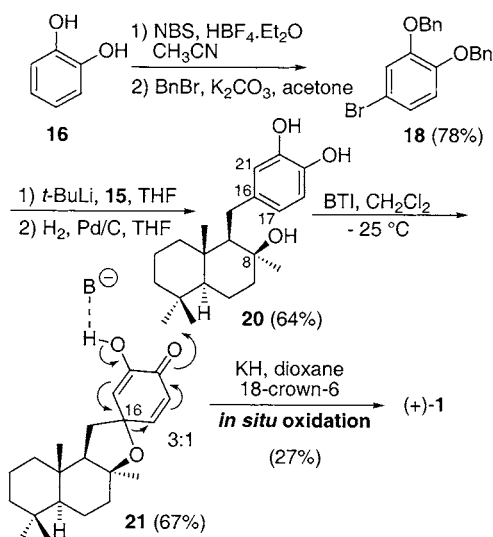
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Scheme 3

thesis of (+)-**1** in only 10 steps. The identity of synthesized (+)-puupehenone (**1**) was confirmed by comparison of ^{1}H NMR data with those of an authentic sample and by comparison of ^{13}C NMR data and optical rotation with published data.

Supporting Information Available: Detailed descriptions of experimental procedures, ^{1}H and ^{13}C NMR spectra of compounds **10**−**15**, **17**−**21**, and (+)-**1**, and an ORTEP diagram of the X-ray structure of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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