First Enantiospecific Synthesis of the Antitumor Marine Sponge Metabolite (−)-15-Oxopuupehenol from (−)-Sclareol


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ABSTRACT

A new route toward puupehenone-related bioactive metabolites from (−)-sclareol, based on the palladium(II)-mediated diastereoselective cyclization of a drimenylphenol, is described. Utilizing this, the first enantiospecific synthesis of the antitumor and antimalarial (−)-15-cyanopuupehenone, together with improved syntheses of (+)–puupehenone, (+)–puupehedione, and (−)–15-cyanopuupehenone, were accomplished.

An important group of biologically active natural products, many of marine origin,1 is based on a sesquiterpene unit joined to a phenolic moiety. The series includes puupehenone (1a),2 puupehedione (2a),1,2b 15-cyanopuupehenone (3),3 15-oxopuupehenol (4a),4 the halopuupehenones 5 and 6,2a,2c and 15-cyanopuupehenone (7).2b More recently, two puupehenone-related compounds, UPA0043 (8) and UPA0044 (9), have been reported.5

All of these compounds display a wide range of important biological properties, including antitumor,6a–c–g–j antiviral,6e antimalarial,4 antibiotic,6d–e antituberculosis,6b–c antioxidant,6a insecticidal,6d and antifungal activities.6e More recently some of them have been shown to inhibit angiogenesis7b and


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lipoxigenase,7a further heightening the interest in this class of compounds.

The unique structural features and biological activities of these compounds have prompted chemists to study their synthesis.5,8–11 Most current approaches to this type of compounds are based on a strategy involving the initial formation of a suitably functionalized bicyclic terpenoid unit, with the pyrane ring being generated late in the sequence. Two strategies have been devised to elaborate the carbon skeleton of these compounds. The first involves the reaction of an aryllithium derived from a suitably protected phenolic unit with an acyclic (farnesane derivative) or bicyclic (drimane derivative) electrophile.5,9 The drimane synthon, an 8-oxygenated aldehyde8b–c,9a or an 8,9-epoxyaldehyde8 or an unsaturated aldehyde,10,11 possesses the correct chirality for three of the four stereogenic centers, i.e., C-5, C-9, and C-10, presented by these compounds. The alternative strategy to create the carbon skeleton lies in the reaction of a nor-drimane anion with a protected polyhydroxybenzaldehyde; this procedure was utilized by Banerjee et al. to prepare 2a,b, which lack the chirality on C-9.3b

The construction of the C pyrane ring constitutes the second phase in the complete synthetic sequence. The stereoselectivity of this process determines the C-8 stereochemistry, affording the natural (C8α-Me) compounds or their epimers. Different methodologies have been utilized to elaborate the pyrane ring. Electrophilic acid cyclization of a drimenyl phenol, similar to compounds 20a,b, was first utilized by Trammel.8b Our further studies of these processes revealed a low degree of stereoselectivity, with the 8-epiderivative found to be the major isomer,9b which is quite different from the previously reported results.8a,b Electrocyclization of a conjugated tetraene, similar to 19a,b, also allowed the present authors to prepare 8-epipuupehedione (2b);9c the same strategy was followed by Banerjee et al.5b The obtention of natural 8-epimers, such as (+)-pupuhenone (1a) and related compounds, starting from drimenyl phenols, was accomplished by the β-attack of the phenol hydroxyl group on an α-seleno- or α-oxacyclopropane generated from the carbon–carbon double bond; an α-selenocyclopropane was utilized in our synthesis of (+)-pupuhenone (1a).5b An α-oxacyclopropane was the intermediate in our synthesis of (−)-pupuhephedione (2a),9a this latter strategy also being utilized by Tadano et al. in synthesizing 8 and 9.5 More recently, Quideau et al. synthesized 1a, starting from an 8-hydroxydrimane with a suitable configuration on C-8, by attack onto an oxidatively activated 1,2-dihydroxyphenyl unit.5c

Following our research into the synthesis of pupuhenone-related compounds based on homochiral synthons obtained from natural sources, we are interested in developing a new route to this type of compounds utilizing alternative synthons and cyclizing reagents. We focused on 15-oxopuupehenol (4a), an antitumor and antimalarial metabolite, which has not been synthesized hitherto. The 15-oxopuupehenol derivative previously reported, the configuration of which on C-8 was assigned on the basis of the absence of NOE effect, was actually the non-natural 8-epimer10 as is shown in the present paper. Our planned synthesis of 4a is based on the benzylic oxidation of a tetracyclic advanced intermediate, which will result from a diastereoselective cyclization of a dimenylphenol precursor, itself derived from a condensation between a suitably protected trihydroxyaryllithium with driminal (15).12

The drimane synthon 15 is easily prepared by the oxidation of (−)-drimenol (14).13,14 Scheme 1 shows a new and efficient synthesis of 15 from (−)-sclareol (10), the key step being regioselective dehydration of diol 13, by treatment with DEAD and PhP3 in benzene; this finding resulted from our investigation into the synthesis of carbonyl compounds under the Mitsunobu conditions.15 The drimane precursor is the


iodoester 11, which was obtained in a three-step sequence from 10 in 75% overall yield. The treatment of 11 with t-BuOK in DMSO–H₂O gave alcohol 12, which leads to diol 13 by oxidative hydroboration. Subsequently, 13 was dehydrated to 14 and then converted into 15.

The efficiency of strategies for synthesizing these types of compounds depends strongly upon the careful choice of protective groups bearing the aromatic synthons. Trammel utilized sesamol (16b) to achieve the first approach to puupehenone (1a); Plomet et al. also made use of the methylene group to protect the 1,2-dihydroxy fragment in preparing the methylenedioxy derivatives of 15-oxopuupehenol, which could not be deprotected. In view of the difficulty in deprotecting the methylenedioxy group, which our previous studies also revealed, we proposed the use of the more easily removable benzyl groups. With respect to the protection of the 4-hydroxy group, the tert-butylidimethylsilyl group, first utilized in our synthesis of 1a, was found to be a very suitable protective group. However, our recent investigations have revealed that the carbamyl group is a more effective one. Besides being cheap, its use does not require anhydrous conditions, most importantly, it is removed under basic condensation conditions. Therefore, we prepared the new synthons 18a from the 3,4-bis(benzyl-

Scheme 1

\[
\begin{align*}
10 & \quad \text{CHO} \quad \text{PCC} \\
11 & \quad \text{CH}_2\text{Cl}_2, \text{r.t.}, 1 \text{h} (71\%) \\
12 & \quad \text{H}_2\text{O}, \text{pyr}, \text{reflux, 24h (99/92%)}
\end{align*}
\]

\[
\begin{align*}
13 & \quad \text{DEAD, PPh_3} \\
14 & \quad \text{benzene, r.t., 1h (92%)} \\
15 & \quad \text{CHO} \quad \text{PH_3} \\
16 & \quad \text{NaOH, H}_2\text{O, EtOH, H}_2\text{O, r.t., 12h (94%)} \\
17 & \quad \text{NBS, CCl_4, Br}
\end{align*}
\]

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Scheme 2

\[
\begin{align*}
16a & \quad \text{R: Bn} \\
16b & \quad \text{R, R': -CH_2-} \\
17a & \quad \text{R: Bn} \\
17b & \quad \text{R, R': -CH_2-} \\
18a & \quad \text{R: Bn} \\
18b & \quad \text{R, R': -CH_2-}
\end{align*}
\]

\[
\begin{align*}
\text{CICO}_{2} & \quad \text{OH} \\
\text{Br} & \quad \text{OR}
\end{align*}
\]

oxy)phenol 16a in a two-step sequence in 83% overall yield (Scheme 2). Compound 16a was obtained from 3,4-dihydroxybenzaldehyde in a three-step sequence in 84% overall yield. The sesamol derivative 18b was also prepared to complete the acid cyclization study.

Finally, let us consider the coupling of 15 and 18a,b, and further cyclization (Scheme 3). The treatment of aryllithium derived from 18a,b with drimenal (15) in THF at –80 °C gave the enone 19a,b, which resulted in condensation with simultaneous carbamate elimination. Reduction of 19a,b with Raney Ni gave phenol 20a,b. Cyclization of 20a,b under different acid conditions gave 21a,b with the C8β-Me configuration being the main epimer. After trying new cyclization reagents as an alternative to selenium derivatives, we found that palladium(II) can induce cyclization with complete diastereoselectivity, providing the desired C8α-Me epimer; the most satisfactory results were obtained by treating with PdCl₂ and catalytic Pd(OAc)₂ in MeOH–H₂O (99:1). Thus, 20a was transformed in high yield into 22, which after catalytic hydrogenation gave puupehenol (23). The configuration on C-8 can be unequivocally established by analyzing the benzylic protons pattern in the 1H NMR spectra of the corresponding 8-epimers. Thus, in the spectrum of 21a these protons appear as a doublet (J = 8.2 Hz) at 2.52 ppm, whereas for 23 they give rise to a doublet (J = 17.5 Hz) at 2.48 and a double doublet (J = 17.5, 8.0 Hz) at 2.65 ppm.

Puupehenol (23) was the starting material for the preparation of (−)-15-oxopuupehenol (4a) and the other puupehenone-related metabolites. The benzylic oxidation of diacetate 24 led to 25, which after hydrolysis under mild conditions produced 4a, together with a small quantity of monoacetate 26; the remaining acetoxyl group was located on C-20 on the basis of the nOe observed with H-21 (7.40 ppm). The spectroscopic properties of 4a were identical to those reported in the literature and (−)-Puupehenone (1a) and (+)-pupehedione (2a) were obtained in good yield by oxidation of 23 with the appropriate reagent. The treatment of puupehenol (23) with Ag₂O in aqueous THF afforded 1a; 2a resulted after refluxing the diphenol 23 with DDQ in dioxane. The latter transformation represents a considerable


(20) Compound 21b was also obtained after cyclization with camphorsulfonic acid, under the conditions reported by Plumet et al. (see refs 9a and 10 and Supporting Information).

(21) See ref 9a for methylenedioxypuupehenol and its 8-epimer.
improvement with respect to the synthesis of (+)-puupehedione (2a) from (−)-sclareol (10), previously reported by our group;\textsuperscript{9a} that process, based on the dehydration of a 9-hydroxyderivative, takes place in low yield because of rearrangement side reactions (Scheme 3).

The direct transformation of puupehenol (23) into (+)-15-cyanopuupehenone (7) was finally undertaken. The treatment of 23 with NaCN and Ag\textsubscript{2}O in aqueous THF surprisingly afforded in good yield a cyano derivative that was identified as 18-cyanopuupehenone (27), in accordance with the \textsuperscript{1}H NMR spectrum, which shows two olefinic protons at 6.54 (d, J = 7.1 Hz) and 5.95 (s), assignable to H-15 and H-21, respectively, on the basis of NOE experiments. The cyano group appears in the \textsuperscript{13}C NMR at 108.6 ppm. This regioisomer of the natural compound probably results from the 1,6-conjugate addition to the corresponding o-quinone. Compound 7\textsuperscript{2b} was obtained in one-pot reaction from 23, by treating it successively with Ag\textsubscript{2}O in aqueous THF and NaCN; this sequence involves the first enantiospecific synthesis of (+)-15-cyanopuupehenone (7) from (−)-sclareol (10).

In summary, a new route to puupehenone-related compounds from (−)-sclareol (10) and 3,4-dihydroxybenzaldehyde has been developed. Utilizing this, the first enantiospecific synthesis of (−)-15-oxopuupehenol (4a) (19 steps, 14% overall yield) and improved syntheses of (+)-puupehenone (1a), (+)-puupehedione (2a), and (+)-15-cyanopuupehenone (7) were achieved.

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Supporting Information Available: Experimental procedures and spectroscopic characterization ([\(\alpha\)]\textsubscript{D}, \textsuperscript{1}H and \textsuperscript{13}C NMR, IR, EIMS and HRMS) of all new compounds, and copies of \textsuperscript{1}H NMR spectra for compounds 18a, 19a, 20a, 21a, 21b, 22, 23, and 25. This material is available free of charge via the Internet at http://pubs.acs.org.