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

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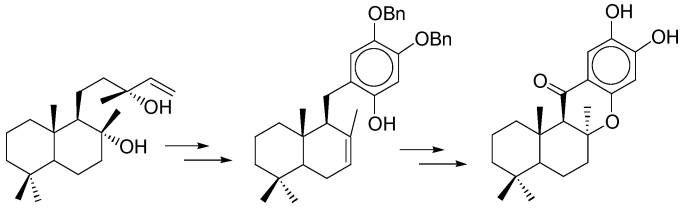
ABSTRACT



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-oxopuupehenol, 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**),[2b] 15-cyanopuupehenol (**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,[6f] antituberculosis,[6h,l] antioxidant,[6i] insecticidal,[6d] and antifungal activities.[6e] More recently some of them have been shown to inhibit angiogenesis[7b] and

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(1) (a) Capon, R. J. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed; Elsevier Science: New York, 1995; Vol. 15, pp 289−326. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75−125.

(2) (a) Navi, B. N.; Perzanovski, H. P.; Ross, R. A.; Erdman, T. R.; Scheuer, P. J.; Finar, J.; Clardy, J. *Pure Appl. Chem.* **1979**, *51*, 1893−1898. (b) Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1993**, *58*, 6565−6569. (c) Urban, S.; Capon, R. J. *J. Nat. Prod.* **1996**, *59*, 900−901. (c) Hua, D. H.; Huang, X.; Chen, Y.; Battina, S. K.; Tamura, M.; Noh, S. K.; Koo, S. I.; Namatame, I.; Tomoda, H.; Perchellet, E. M.; Perchellet, J. P. *J. Org. Chem.* **2004**, *69*, 6065−6078.

(3) Hamann, M. T.; Scheuer, P. J. *Tetrahedron Lett.* **1991**, *32*, 5671−5672.

(4) Nasu, S. S.; Yeung, B. K. S.; Hamann, M. T.; Scheuer, P. J.; Kelly-Borges, M.; Goins, K. *J. Org. Chem.* **1995**, *60*, 7290−7292.

(5) Takao, K.-I.; Sasaki, T.; Kozaki, T.; Yaganisawa, Y.; Tadano, K.-I.; Kawashima, A.; Shinonaga, H. *Org. Lett.* **2001**, *3*, 4291−4294 and references therein.

(6) (a) Kohmoto, S.; McConnell, O. J.; Wright, A.; Koehn, F.; Thompson, W.; Lui, M.; Snader, K. M. *J. Nat. Prod.* **1987**, *50*, 336−341. (b) Sova, V.; Fedoreev, S. A. *Khim. Prir. Soedin.* **1990**, 497−500. (c) Longley, R. E.; McConnel, O. J.; Essich, E.; Harmody, D. *J. Nat. Prod.* **1993**, *56*, 915−920. (d) El Sayed, K. A.; Dunbar, D. C.; Perry, T. L.; Wilkins, S. P. Hamann, M. T.; Greenplate, J. T.; Wideman, M. A. *J. Agric. Food Chem.* **1997**, *45*, 2735−2739. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1998**, 113−158 and references therein. (f) Bourguet-Kondracki, M. L.; Lacombe, F.; Guyot, M. *J. Nat. Prod.* **1999**, *62*, 1304−1305. (g) Popov, A. M.; Stekhova, S. I.; Utkina, N. K.; Rebachuk, N. M. *Pharm. Chem. J.* **1999**, *33*, 71−73. (h) El Sayed, K. A.; Bartyzel, P.; Shen, X.; Perry, T. L. Zjawiony, J. K.; Hamann, M. T. *Tetrahedron* **2000**, *56*, 949−953. (i) Takamatsu, S.; Hodges, T. W.; Rajbhandari, I.; Gerwick, H.; Hamann, M. T.; Nagle, D. G. *J. Nat. Prod.* **2003**, *66*, 605−608. (j) Pina, I. C.; Sanders, M. L.; Crews, P. J. *J. Nat. Prod.* **2003**, *66*, 2−6. (k) Hamann, M. T. *Curr. Pharm. Des.* **2003**, *9*, 879−889. (l) Graus, G. A.; Nguyen, T.; Bae, J.; Hostetter, J. Steadham, E. *Tetrahedron* **2004**, *60*, 4223−4225.

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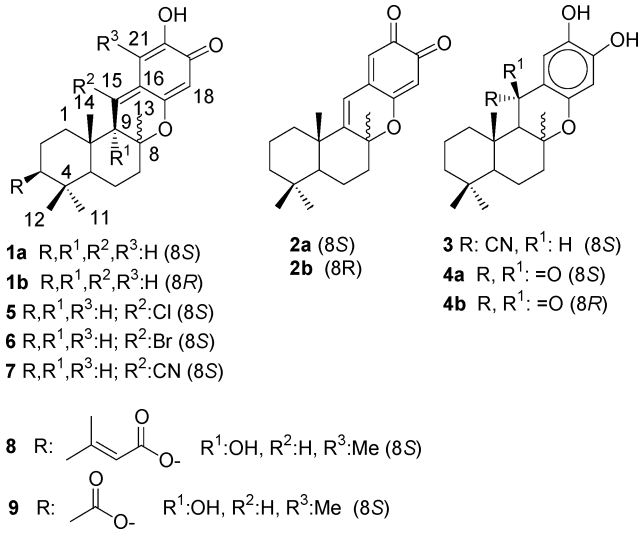


Figure 1. Examples of puupehenone (**1a**)-derived marine sponge metabolites.

lipoxygenase,[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.[5,9−11] The drimane synthon, an 8-oxygenated aldehyde[8b−c,9a] or an 8,9-epoxyaldehyde[5] 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.[9b]

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.[8a] Our further studies of these processes revealed a low degree of stereoselectivity, with the 8-epiderivative found to be the major isomer,[9a] which is quite different from the previously reported results.[8a,10] Electrocyclization of a conjugated tetraenone, similar to **19a,b**, also allowed the present authors to prepare 8-epipuupehedione (**2b**);[9a] the same strategy was followed by Banerjee et al.[9b] The obtention of natural 8-epimers, such as (+)-puupehenone (**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 (+)-puupehenone (**1a**).[8b] An α-oxacyclopropane was the intermediate in our synthesis of (+)-puupehedione (**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.[8c]

Following our research into the synthesis of puupehenone-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-epimer[10] 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 drimenylphenol precursor, itself derived from a condensation between a suitably protected trihydroxyaryllithium with drimenal (**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 PPh_3 in benzene; this finding resulted from our investigation into the synthesis of carbonyl compounds under the Mitsunobu conditions.[15] The drimane precursor is the

(7) (a) Amagata, T.; Whitman, S.; Johnson, T. A.; Stessman, C. C.; Loo, C. P.; Lobkovsky, E.; Clardy, J.; Crews, P.; Holman, T. R. *J. Nat. Prod.* **2003**, *6*, 230−235. (b) Castro, M. E.; Gonzalez-Iriarte, M.; Barrero, A. F.; Salvador-Tormo, N.; Muñoz-Chapuli, R.; Medina, M. A.; Quesada, A. R. *Int. J. Cancer* **2004**, *110*, 31−38.

(8) Synthesis of **1a,b** in racemic form: (a) Trammel, G. L. *Tetrahedron Lett.* **1978**, 1525−1528. Synthesis of **1a** in optically active form: (b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **1997**, *38*, 2325−2328. (c) Quideau, S.; Lebon, M.; Lamidey, A.-M. *Org. Lett.* **2002**, *22*, 3975−3978.

(9) Synthesis of **2a,b** in optically active form: (a) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortés, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181−15208. Synthesis of **2b** in optically active form: (b) Maiti, S.; Sengupta, S.; Giri, C.; Achari, B.; Banerjee, A. K. *Tetrahedron Lett.* **2001**, *42*, 2389−2391. (c) Armstrong, V.; Barrero, A. F.; Alvarez-Manzaneda, E. J.; Cortés, M.; Sepúlveda, B. *J. Nat. Prod.* **2003**, *66*, 1382−1383. (d) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122−11123.

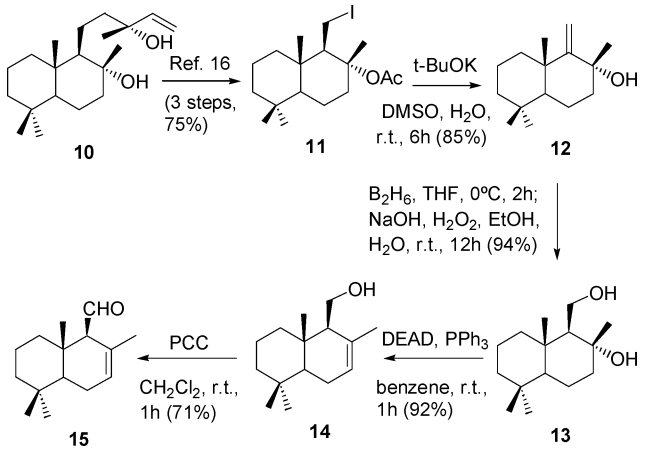
(10) Synthesis in optically active form of the methylenedioxyderivative of **4b**: Arjona, O.; Garranzo, M.; Maluego, J.; Maroto, E.; Plumet, J.; Sáez, B. *Tetrahedron Lett.* **1997**, *38*, 7249−7252.

(11) Synthesis in racemic form of monoterpene analogues of **1** and **2**: Barrero, A. F.; Alvarez-Manzaneda, E. J.; Herrador, M. M.; Valdivia, M. V.; Chahboun, R. *Tetrahedron Lett.* **1998**, *39*, 2425−2428.

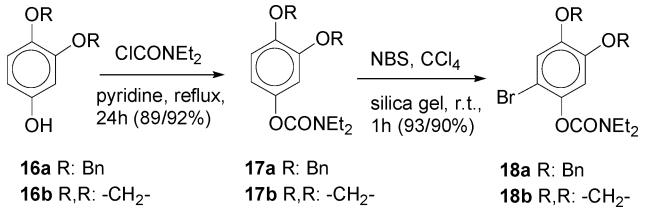
(12) Scher, J. M.; Speakman, J.-B.; Zapp, J.; Becker, H. *Phytochemistry* **2004**, *65*, 2583−2588.

(13) Isolated from the bark of *D. winteri*. See: Appel, H. H.; Brooks, J. W.; Overton, K. H. *J. Chem. Soc.* **1959**, 3322−3332.

Scheme 1



Scheme 2



16a R: Bn
16b R,R: -CH_2-

17a R: Bn
17b R,R: -CH_2-

18a R: Bn
18b R,R: -CH_2-

iodoester **11**, which was obtained in a three-step sequence from **10** in 75% overall yield.[16] The treatment of **11** with *t*-BuOK in DMSO−H_2O gave alcohol **12**,[17] which leads to diol **13**[14c] 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 synthon. Trammel utilized sesamol (**16b**) to achieve the first approach to puupehenone (**1a**);[8a] Plumet et al. also made use of the methylene group to protect the 1,2-dihydroxy fragment in preparing the methylenedioxyderivatives of 15-oxopuupehenol, which could not be deprotected.[10] In view of the difficulty in deprotecting the methylenedioxy group, which our previous studies also revealed,[9a] we proposed the use of the more easily removable benzyl groups.[8b,9a] With respect to the protection of the 4-hydroxy group, the *tert*-butyldimethylsilyl group, first utilized in our synthesis of **1a**,[8b,9a] 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 synthon **18a** from the 3,4-bis(benzyloxy)phenol **16a**[8b,18] 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.[8b,18] 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**.[19] Cyclization of **20a,b** under different acid conditions gave **21a,b**,[20] with the C8β-Me configuration being the main epimer. After trying new cyclization reagents as an alternative to selenium derivatives,[8b] 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 $PdCl_2$ and catalytic $Pd(OAc)_2$ in MeOH−H_2O (99:1). Thus, **20a** was transformed in high yield into **22**, which after catalytic hydrogenation gave puupehenol (**23**).[8b] The configuration on C-8 can be unequivocally established by analyzing the benzylic protons pattern in the ^{1}HNMR spectra of the corresponding 8-epimers.[21] 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 (s, 7.40 ppm). The spectroscopic properties of **4a** were identical to those reported in the literature.[4] (+)-Puupehenone (**1a**) and (+)-puupehedione (**2a**) were obtained in good yield by oxidation of **23** with the appropriate reagent. The treatment of puupehenol (**23**) with Ag_2O in aqueous THF afforded **1a**; **2a** resulted after refluxing the diphenol **23** with DDQ in dioxane. The latter transformation represents a considerable

(14) −-Drimenol (**14**) can be obtained in optically pure form from *trans,trans*-farnesol. Resolution of racemic **14** was achieved via chromatographic separation of the diasteromeric camphonates. See ref 11 and (a) Jordine, C.; Bick, S.; Möller, U.; Welzel, P.; Daucher, B.; Maas, C. *Tetrahedron* **1994**, *50*, 139−160. (−)-Drimenol (**14**) can also be obtained from (−)-sclareol through drimenyl acetate in a five-step synthesis with 42% overall yield. See: (b) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Altarejos, J.; Salido, S.; Ramos, J. M. *Tetrahedron Lett.* **1994**, *35*, 2945−2948. (c) Barrero, A. F.; Manzaneda, E. A.; Altarejos, J.; Salido, S.; Ramos, J. M.; Simmonds, M. J. S.; Blaney, W. M. *Tetrahedron* **1995**, *51*, 7435−7450.

(15) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron Lett.* **2000**, *41*, 1959−1962.

(16) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; González Díaz, C. *Synlett* **2000**, 1561−1564.

(17) (a) Wada, K.; Tanak, S.; Marumo, S. *Agric. Biol. Chem.* **1983**, *47*, 1075−1078. (b) Shishido, K.; Omodani, T.; Shibuya, M. *J. Chem. Soc., Perkin Trans 1* **1991**, 2285−2287. (c) Dominguez, G.; Hueso-Rodriguez, J. A.; De la Torre, M. C.; Rodriguez, B. *Tetrahedron Lett.* **1991**, *32*, 4765−4768.

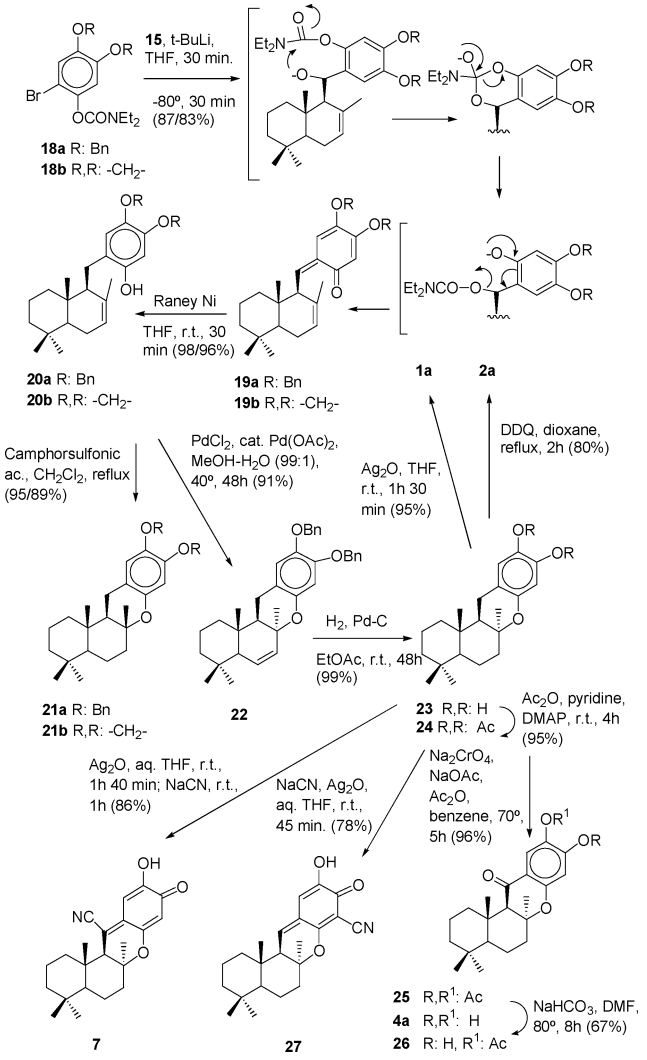
(18) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R. *Tetrahedron* **1998**, *54*, 5635−5650.

(19) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chaboun, R.; Meneses, R. *Synlett* **1999**, 1663−1666.

(20) Compound **21b** was also obtained after cyclization with camphosulfonic 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.

Scheme 3



improvement with respect to the synthesis of (+)-puupehedione (**2a**) from (−)-sclareol (**10**), previously reported by our group;[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_2O in aqueous THF surprisingly afforded in good yield a cyano derivative that was identified as 18-cyanopuupehenone (**27**), in accordance with the ^{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 ^{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**[2b] was obtained in one-pot reaction from **23**, by treating it successively with Ag_2O 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 ($[\alpha]_D$, ^{1}H and ^{13}C NMR, IR, EIMS and HRMS) of all new compounds, and copies of ^{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.

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