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Enantiospecific Synthesis of (+)-Puupehenone from (-)-Sclareol and Protocatechualdehyde

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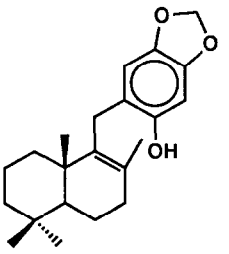
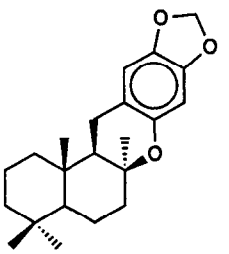
Abstract: *The first enantiospecific synthesis of the antitumor and cholesteryl ester transfer protein (CETP) inhibitor (+)-puupehenone (**19**) from (-)-sclareol (**10**) and protocatechualdehyde (**4**) is described. The key steps of the reaction sequence are the organoselenium-induced cyclization of the mixture of regioisomers **15a-b** to give **16** and **17**, with complete diastereoselectivity, and the simultaneous removal of benzyl and phenylselenyl groups of **16** and **17** by treating with Raney Ni.* © 1997 Elsevier Science Ltd.

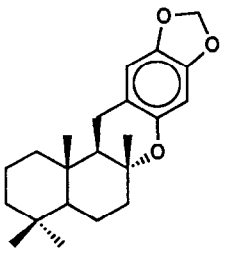
(+)-Puupehenone (**19**) and its derivatives are among the most important marine metabolites because they show a wide variety of biological activity including cytotoxic, antiviral, antifungal and inmunomodulatory properties.[1-3] Moreover, some of them inhibit reproduction of the HIV virus[4] and cholesteryl ester transfer protein (CETP),[5] properties which have heightened the interest in this class of compounds. In spite of their biological significance no appropriate synthesis of **19** has yet been reported. The only described preparation involves electrophilic cyclization of **1**, which was obtained from farnesyl bromide and sesamol, affording diastereomers **2** and **3** (ratio 2.4:1); (+)-puupehenone was isolated after deprotection of **2** and further oxidation.[6]



1



2

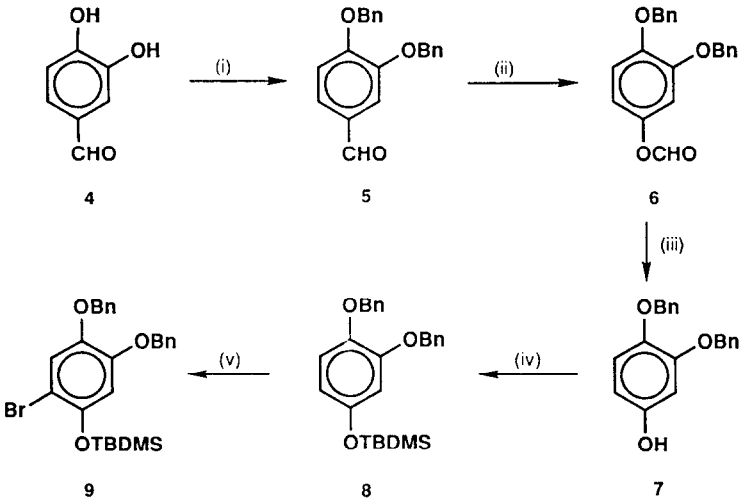


3

When the present authors attempted to repeat the cyclization of **1** and further deprotection under the same reported conditions, very different results were obtained. Compounds **2** and **3** were isolated in the 1:2.4 ratio. Moreover, treatment with PCl_5 to remove the methylendioxy group[6] yielded a complex mixture of products.

In this paper the first enantiospecific synthesis of (+)-puupehenone (**19**) is described (Scheme 2). The first step involves nucleophilic addition of the organolithium derived from **9** to the drimanic acetoxyaldehyde **11**, whose efficient preparation from (-)-sclareol (**10**) has previously been reported by the present authors.[7] The aromatic synthon **9**,[8] which was prepared at high yield from protocatechualdehyde (**4**) (Scheme 1), is highly suitable for the synthetic purpose. Benzyl and *tert*-butyldimethylsilyl groups can be removed at the opportune moment under mild conditions.

Scheme 1

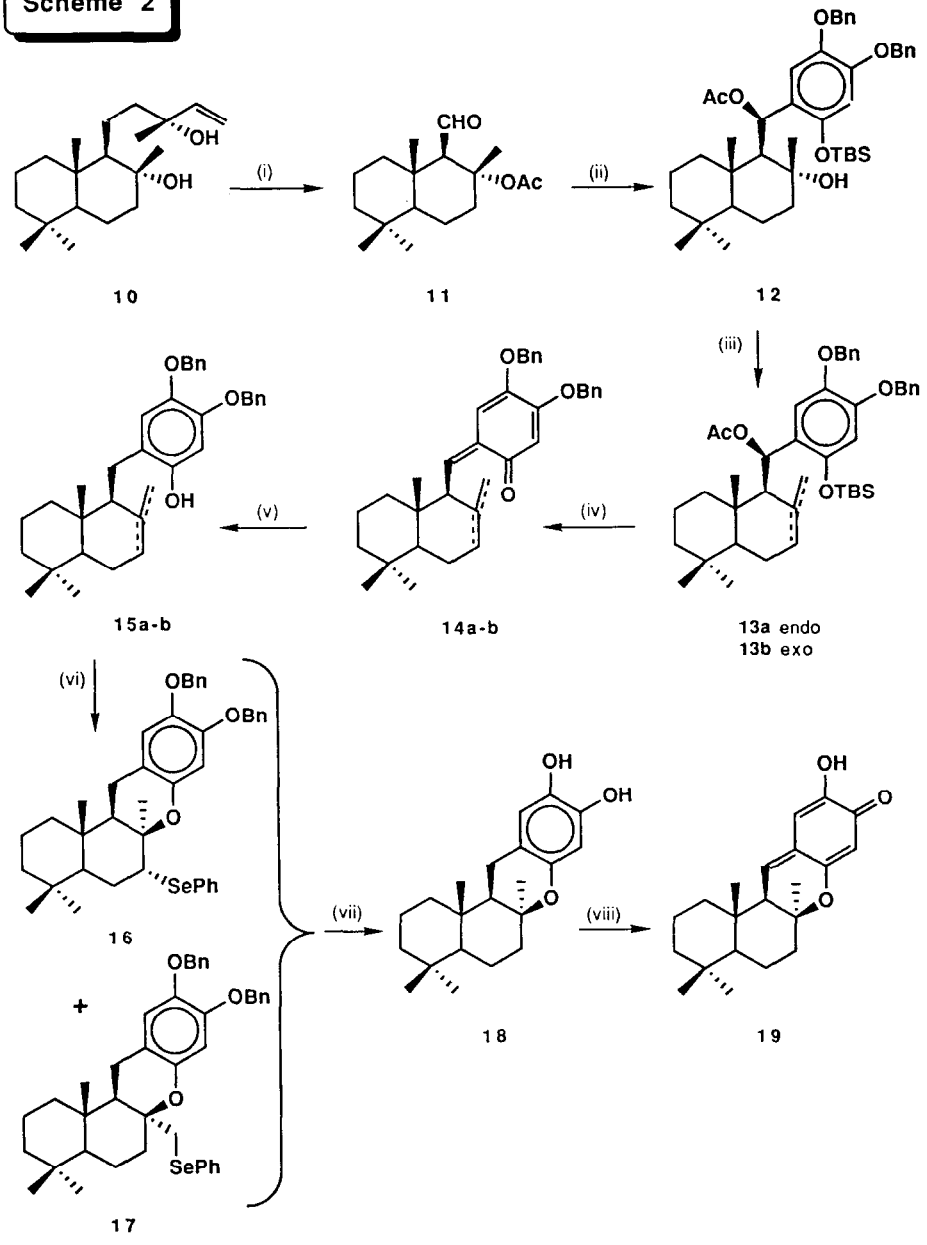


(i) BnBr, K_2CO_3, acetone, reflux, 15h, 92%. (ii) MCPBA, CH_2Cl_2, rt, 12h, 95%. (iii) 6N NaOH-MeOH, rt, 5min, 96%. (iv) TBDMSCl, imidazole, DMF, rt, 15h, 92%. (v) NBS, CCl_4, Silicagel, 97%.

Condensation of **11** with the aryllithium derived from **9** yielded with complete diastereoselectivity the acetoxy alcohol **12**, which after dehydration gave a mixture of regioisomers **13a-b** (ratio 2:1), which could not be resolved. The treatment with tetra-*n*-butylammonium fluoride (TBAF) allowed the simultaneous deprotection of *tert*-butyldimethylsiliyl ether and elimination of the acetoxy group, favoured by its benzyl location, affording the en-dienones **14a-b**,[8] which were reduced to the phenolic derivatives **15a-b**. Electrophilic cyclization of **15a-b** under different reaction conditions revealed a low diastereoselectivity, similar to that of **1**. However, complete diastereoselectivity was achieved by organoselenium-induced cyclization.[9] The treatment of **15a-b** with *N*-phenylselenophthalimide (NPSP) and $SnCl_4$ yielded a mixture of the selenyl derivatives **16**[8] and **17**.[8] Treatment with Raney Ni allowed the simultaneous deprotection of the benzyl ethers and removal of the phenylselenyl group, yielding puupehenol (**18**)[8] as the only product, which underwent easy oxidation in the presence of PDC to (+)-puupehenone (**19**), whose optical rotation and spectroscopic properties were identical to those of an authentic sample.

Acknowledgments: We thank Dr. P. Scheuer and Dr. C. Mau of Department of Chemistry of the University of Hawaii for an authentic sample of (+)-puupehenone.

Scheme 2



(i) Ref. 7. (ii) **9**, *t*-BuLi, Et_2O, -78°C, 88%. (iii) Cl_2SO, Py, rt, 1h, 94%. (iv) TBAF, THF, rt, 15 min, 81%. (v) $NaBH_4$, EtOH, rt, 20 min, 91%. (vi) NPSP, $SnCl_4$, CH_2Cl_2, -78°C, 2h, 91%. (vii) Raney Ni, THF, rt, 20h, 75%. (viii) PDC, CH_2Cl_2, rt, 3h, 70%.

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8. Representative physical data are given below:
   9 ^{1}H RMN ($CDCl_3$, 300 MHz) δ 7.41-7.31 (m, 10H), 7.08 (s, 1H), 6.44 (s, 1H), 5.09 (s. 2H), 5.03 (s, 2H), 0.99 (s, 9H), 0.09 (s, 6H).
   14a-b MS(CI): m/e 509 $(M+H)^+$.^{1}H RMN ($CDCl_3$, 400 MHz) : signals asignable to **14a** : δ 7.51-7.31 (m, 10H), 7.22 (d, J= 10.8 Hz, 1H), 6.01 (s, 1H), 5.82 (s, 1H), 5.09 (d, J= 12.2 Hz, 1H), 5.06 (s, 2H), 5.02 (d, J= 12.2 Hz, 1H), 4.74 (s, 1H), 4.37 (s, 1H), 2.69 (d, J= 10.8 Hz, 1H), 2.47 (dt, J= 13.5 y 2.1 Hz, 1H), 2.09 (m, 2H), 1.70 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H); signals asignable to **14b** : δ 7.51-7.31 (m, 10H), 7.05 (d, J= 12.2 Hz, 1H), 6.17 (s, 1H), 5.84 (s, 1H), 5.57 (sa, 1H), 5.15 (d, J= 12.6 Hz, 1H), 5.07 (s, 2H), 5.02 (d, J= 12.6 Hz, 1H), 2.86 (d, J= 12.9 Hz, 1H), 2.01 (m, 2H), 1.42 (s, 3H), 0.92 (s, 3H), 0.89 (s, 6H).
   16, 17 ^{1}H RMN ($CDCl_3$, 500 MHz) signals asignable to **17** δ 7.60-7.25 (m, 15H), 6.58 (s, 1H), 6.37 (s, 1H), 5.04-5.02 (s, 4H), 3.10 (d, J=12.2 Hz, 1H), 3.05 (d, J= 12.2 Hz, 1H), 2.62 (dd, J= 17.8 , 8.7 Hz, 1H), 2.54 (d, J= 17.8 Hz, 1H), 0.88 (s, 3H), 0.79 (s, 3H), 0.69 (s, 3H).
   The recrystallization in *t*-butyl methyl ether of the mixture of selenylderivatives allows purification to the isomer **16** : MS(CI): m/e 667 $(M+H)^+$.^{1}H RMN ($CDCl_3$, 500 MHz) : δ 7.60 (m, 2H), 7.40-7.25 (m, 13H), 6.61 (s, 1H), 6.35 (s, 1H), 5.02 (s, 2H), 5.01 (s, 2H), 3.79 (t, J= 2.9 Hz, 1H), 2.77 (dd, J= 17.0, 7.7 Hz, 1H), 2.60 (d, J= 17.0 Hz, 1H), 2.23 (m, 1H), 1.84 (m, 2H), 1.33 (s, 3H), 0.82 (s, 3H), 0.76 (s, 3H), 0.69 (s, 3H). ^{13}C RMN ($CDCl_3$, 125 MHz) : δ 39.9 (C_1), 18.6 (C_2 or C_6), 41.8 (C_3), 33.0 (C_4), 50.3 (C_5), 22.4 (C_6 or C_2), 46.9 (C_7), 79.4 (C_8), 56.3 (C_9), 38.9 (C_{10}), 33.4 (C_{11}), 22.3 (C_{12}), 27.1 (C_{13}), 14.8 (C_{14}), 25.5 (C_{15}), 114.8 (C_{16}), 142.8 (C_{17}), 103.9 (C_{18}), 148.7 (C_{19} or C_{20}), 149.6(C_{20} or C_{19}), 116.9 (C_{21}).
   18 ^{1}H RMN (CD_3COCD_3, 400 MHz) : δ 6.39 (s, 1H), 6.09 (s, 1H), 2.65 (dd, J= 17.5, 8.03 Hz, 1H), 2.48 (d, J= 17.5 Hz, 1H), 1.32 (s, 3H), 0.99 (s, 3H), 0.76 (s, 3H), 0.59 (s, 3H). ^{13}C RMN (CD_3COCD_3, 100 MHz) : δ 40.6 (C_1), 18.9 (C_2 or C_6), 41.3 (C_3), 33.7 (C_4), 50.3 (C_5), 19.1 (C_6 or C_2), 42.6 (C_7), 75.3 (C_8), 55.8 (C_9), 39.0 (C_{10}), 34.0 (C_{11}), 22.2 (C_{12}), 27.3 (C_{13}), 14.7 (C_{14}), 22.6 (C_{15}), 113.6 (C_{16}), 139.4 (C_{17}), 104.7 (C_{18}), 144.5 (C_{19} or C_{20}), 148.4 (C_{20} or C_{19}), 115.2 (C_{21}).
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