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 immunomodulatory properties.1-3 Moreover, some of them inhibit reproduction of the HIV virus4 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

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 PCl₅ to remove the methylendioxy group6 yielded a complex mixture of products.

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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.

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-butyldimethylsilyl ether and elimination of the acetoxy group, favoured by its benzyl location, affording the endiennone 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 16a 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.
(i) Ref. 7. (ii) $t$-BuLi, $\text{Et}_2\text{O}, -78^\circ\text{C}, 88\%$. (iii) $\text{Cl}_2\text{SO}, \text{Py}, \text{rt}, 1\text{h}, 94\%$. (iv) TBAF, THF, rt, 15 min, 81\%.
(v) $\text{NaBHa}, \text{EtOH}, \text{rt}, 20\text{min}, 91\%$. (vi) NPSP, $\text{SnCl}_4$, $\text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 2\text{h}, 91\%$. (vii) Raney Ni, THF, rt, 20h, 75\%.
(viii) PDC, $\text{CH}_2\text{Cl}_2$, rt, 3h, 70\%.
References and notes:


7. Representative physical data are given below:

9 1H RMN (CDCl₃, 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)+. 1H RMN (CDCl₃, 400 MHz) : signals assignable 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 assignable to 14b : δ 7.51-7.31 (m, 10H), 7.15 (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, 3H).

16, 17 1H RMN (CDCl₃, 500 MHz) signals assignable 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-buty methyl ether of the mixture of selenylderivatives allows purification to the isomer 16 : MS(Cl) : m/e 667 (M+H)+. 1H RMN (CDCl₃, 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), 13C RMN (CDCl₃, 125 MHz) : δ 39.9 (C1), 18.6 (C2 or C6), 41.8 (C3), 33.0 (C4), 50.3 (C5), 22.4 (C6 or C2), 46.9 (C7), 79.4 (C8), 56.3 (C9), 38.9 (C10), 33.4 (C11), 22.3 (C12), 27.1 (C13), 14.8 (C14), 25.5 (C15), 114.8 (C16), 142.8 (C17), 103.9 (C18), 148.7 (C19 or C20), 149.6(C20 or C19), 116.9 (C21).

18 1H RMN (CD₃COCD₃, 300 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). 13C RMN (CD₃COCD₃, 100 MHz) : δ 40.6 (C1), 18.9 (C2 or C6), 41.3 (C3), 33.7 (C4), 50.3 (C5), 19.1 (C6 or C2), 42.6 (C7), 75.3 (C8), 55.8 (C9), 39.0 (C10), 34.0 (C11), 22.2 (C12), 27.3 (C13), 14.7 (C14), 22.6 (C15), 113.6 (C16), 139.4 (C17), 104.7 (C18), 144.5 (C19 or C20), 148.4 (C20 or C19), 115.2 (C21).


(Received in UK 23 December 1996; revised 10 February 1997; accepted 14 February 1997)