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CHEMICAL TRANSFORMATION OF AROMATICIN INTO PULCHELLIN—A FORMAL SYNTHESIS OF PULCHELLIDINE

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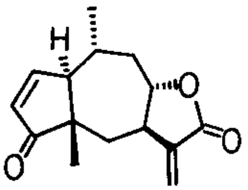
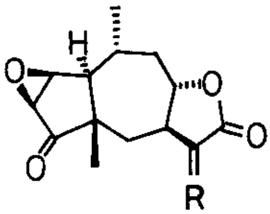
Abstract——A chemical transformation of aromaticin into pulchellin implying the formal synthesis of pulchellidine was achieved. The stereochemistry of the diol isomers of dihydropulchellin was also revealed.

In the course of our studies on plant-derived bioactive sesquiterpenoids, besides eudesmanolides (pulchellins B, C, D, E and F[1]) and guaianolides (gaillardin[2] and neogaillardin[3]), pulchellin,[4,5] neopulchellin[6] and pulchelloid A,[7] B[7] and C[8] as well as pulchellidine,[4,5,9] neopulchellidine,[6] and pulchellon,[10] were isolated as the pseudoguaianolide principles from Gaillardia pulchella (Compositae). Concerning synthesis of pseudoguaianolides other than ambrosanolides,[11] synthesis of only a few helenanolides such as helenalin,[12] aromatin[13] and aromaticin[14] has been reported, because of their interesting structural features and cytotoxic properties.[15] These molecules involve a cyclopentenone moiety in the pseudoguaiane skeleton with only five or six chiral centres. From the point of view of synthesis in the preliminary study on bioactive and highly oxygenated helenanolides having many asymmetries, we now wish to report the transformation of a helenanolide, aromaticin, into pulchellin with additional two chiral centres, which implies the formal synthesis of pulchellin and pulchellidine.

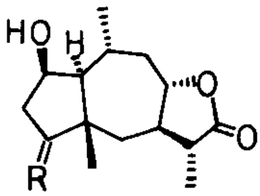
The starting aromaticin was provided by the facile conversion of pulchellin (1) isolated from the cultivar of G. pulchella.[16] 2-Acetylpulchellin[17] separated from 2,4-diacetylpulchellin[4] by silica gel chromatography was submitted to Jones



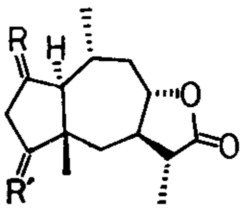
(1)



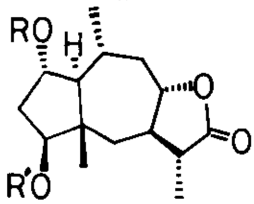
(2) R=CH_2
(3) R<$^{CH_3}_{H}$



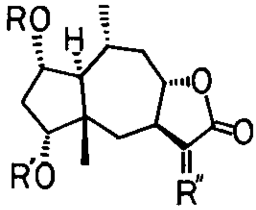
(4) R=O
(5) R<$^{OH}_{H}$



(6) R=O, R'<$^{OH}_{H}$
(13) R=O, R'<$^{OH}_{H}$
(14) R<$^{OH}_{H}$, R'<$^{OH}_{H}$



(7) R=R'=H
(8) R=Ac, R'=H



(9) R=Ac, R'=Bz, R"<$^{Me}_{H}$
(10) R=R'=H, R"<$^{Me}_{H}$
(11) R=R'=H, R"=CH_2
(12) R=Ac, R'=H, R"<$^{Me}_{H}$

oxidation and the intermediate 4-keto-2α-acetate was heated in pyridine, giving a good yield of aromaticin (1).[18] Epoxidation of 1 with alkaline hydrogen peroxide in tetrahydrofuran (THF) and methanol at -25∼-15°C regio- and stereospecifically afforded 2β,3β-epoxyketone (2) [mp 184-187°C, ir ν (KBr) 1760, 1649 (α-methylene-γ-lactone), 1738 cm^{-1} (cyclopentanone)] in almost quantitative yield.

The stereospecific β-site epoxidation of the cyclopentenone ring in tenulin and its related sesquiterpenes was proposed by Toromanoff on the basis of the dynamic stereochemistry of the cyclopentenone, using a torsion angle notation.[19] The configuration of epoxide (2) has now been confirmed by the X-ray analysis of dihydroepoxide (3) described below, as shown in Fig. 1. Crystal data: $C_{15}H_{20}O_4$, MW 264.3, monoclinic, space group, $P2_1$, a = 20.923(1), B = 6.912(3), c = 9.889(1), β = 98.95(5), U = 1415 $Å^3$, z = 4, D_{calc} = 1.243 g cm^{-3}, final R value = 0.054 for 2362 reflections.

Since aluminium amalgum (Al-Hg) reduction of 2 furnished a complex mixture of unseparable products, dihydroepoxyketone (3) [mp 171-172°C, ir ν (KBr) 1756 (γ-lactone), 1741 cm^{-1} (epoxyketone)] was then prepared by sodium borohydride (NBH) reduction and subsequent Jones oxidation. Careful treatment of 3 with Al-Hg

(0°C, 3.5 h, aqueous THF) gave unstable 4-keto-2β-ol (4) in a reasonable yield. In the 400 MHz ^{1}H-nmr spectrum ($CDCl_3$/TMS), coupling constants for H-2α/H-1α (J = 4.0 Hz), H-2α/H-3α (J = 4.0 Hz) and H-2α/H-3β (J = 1.4 Hz) indicated that the hydroxy group at C-2 must be in the β-configuration. The stereospecific NBH reduction of 4 afforded quantitatively 2β,4β-diol (5) [mp 171-172°C, ir ν (KBr) 3450, 3400 (hydroxyl groups), 1747 cm^{-1} (γ-lactone)]. The regiospecific oxidation with pyridinium dichromate (PDC) and subsequent NBH reduction of diol (5) afforded 2α,4β-diol (7) together with the starting 2β,4β-diol (5) in the approximate ratio of 3:1. After the separation of the required diol (7) from 5 by silica gel chromatography, 7 was acetylated as usual producing 2α-acetoxy-4β-ol (8) [mp 160-162°C] together with 2α-hydroxy-4β-acetate and 2α,4β-diacetate in the approximate ratio of 2:2:1. Monoacetate (8) was submitted to epimerization of the hydroxy group at C-4 using diethyl azodicarboxylate, benzoic acid and triphenyl phosphine (THF, r.t., 4.5 h) yielding 2α-acetyl-4α-benzoate (9) [mp 174-175°C, ir ν (KBr) 1709 (benzoate), 1736 (acetate), 1769 cm^{-1} (γ-lactone)] in a reasonable yield. In the ^{1}H-nmr spectrum of 9, the proton at C-4 (δ = 5.0 ppm, d, J = 6 Hz) showed the characteristic splitting pattern of the methine for pulchellin, neopulchellin and their various derivatives bearing the 4α-acyl group.[4,5,6,7,8] Alkaline hydrolysis of 9 readily provided the required 2α,4α-diol, i.e. dihydropulchellin (10) [mp 143-144.5°C].[4] Finally, sequential treatment of 10 by phenylselenylation (excess LDA, $(PhSe)_2$/HMPA), followed by oxidative elimination of the 11β-phenyselenyl intermediate with hydrogen peroxide afforded a 40% yield of pulchellin (11).[4] Furthermore, in order to confirm the configuration of the hydroxyl groups in the synthetic intermediate 2β,4β-diol (5), four possible diol stereoisomers other than 10 were prepared in the following manners. NBH reduction of 2-keto-4α-ol (13), which is made available by the regioselective PDC oxidation of dihydropulchellin[4] yielded 2α,4α-diol (10) and 2β,4α-diol (14) at a ratio of 8:5. On the other hand, 2-acetyldihydropulchellin (12) [mp 161.5-162.5°C] was prepared by the usual acetylation of 10 together with diacetyldihydropulchellin[4] at the ratio of 7:3. Jones oxidation of 12 and subsequent NBH reduction readily yielded 2α-acetoxy-4β-ol (8), which was further converted by hydrolysis (20% KOH/dioxane) to 2α,4β-diol (7). The regiospecific PDC oxidation of 7 (r.t., 12 h) and subsequent NBH reduction of 2-keto-4β-ol (6) gave 2α,4β- (7) and 2β,4β-diol (5) in the same way as mentioned above.

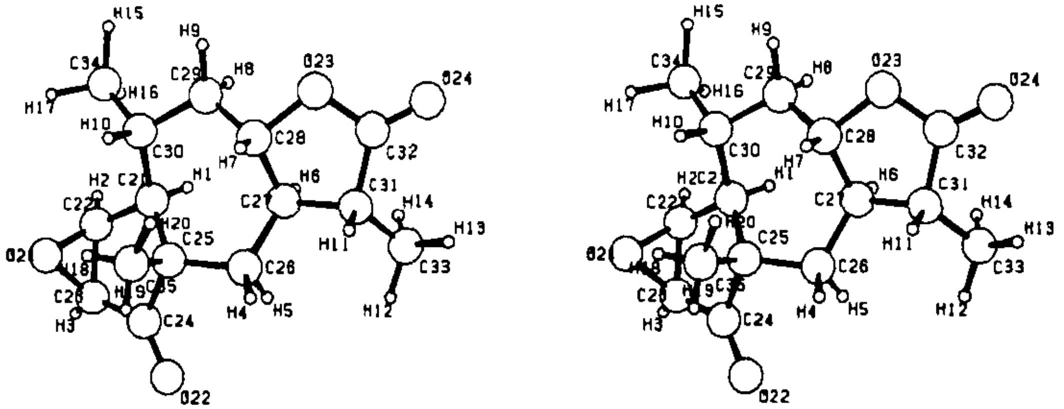


Fig. 1. Stereoview of 2β,3β-epoxy-11βH-dihydropulchellin (3) (B molecule)

Spectroscopic properties of the three diols thus obtained, i.e., 5, 7 and 10 were all in accord with those of the corresponding isomers described above. The transformation of aromaticin into pulchellin has now been accomplished. This means the formal synthesis not only of 11, but also of pulchellidine,[4,9] which is derived stereospecifically by the Michael addition of piperidine to 11.[10] The similar conversion of aromatin into neopulchellin or neopulchellidine is under investigation.

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