Synthesis of (-)-Juvabione and (-)-Epi-Juvabione

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Dois epímeros da (-)-juvabiona foram sintetizados como uma mistura a partir do (-)-perialdeido (**IV**). A etapa chave da síntese foi a cloração alílica regioespecífica na posição 9 do (-)-perilato de metila (**V**) usando hipoclorito de cálcio e gêlo seco. O cloreto alílico formado (**VI**) foi condensado com isovaleraldeido usando zinco. O produto final foi obtido em bom rendimento por oxidação catalítica. A mistura de (-)-juvabiona e (-)epi-juvabiona foi obtida em rendimento global de 43% a partir do (-)-perialdeido (**IV**).

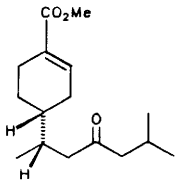
Two epimeric (-)-juvabiones were synthesized as a mixture from (-)-perillaldehyde (**IV**). The Key step was the regiospecific allylic chlorination in the position 9 of methyl(-)-perillate (**V**), using calcium hypochlorite and dry ice. The allylic chloride thus formed (**VI**) was coupled with isovaleraldehyde using acid-washed zinc. The final product was obtained in good yield by successive oxidation (PCC) and homogenous hydrogenation of the alcohol (**VII**). Since the separation of (-)-juvabione and (-)-epi-juvabione has been done before, the present sequence represents an improved alternative route for preparing (-)-juvabione and (-)-epi-juvabione in the overall yield of 43% from (-)-perillaldehyde (**IV**).

Key words: *(-)-Juvabione, (-)-Perillaldehyde.*

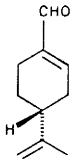
Introduction

(+)-Juvabione (**I**) is a sesquiterpene ester with bisabolane skeleton isolated from Balsam fir (*Abies balsamea* L. Miller) and shows interesting juvenile hormone activity in *Pyrrhocoris apterus*[1].

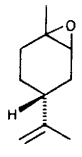
Several non-stereoselective synthesis[2] as well as stereoselective preparation of this molecule are reported in the literature[3]. Earlier work using (+)-perillaldehyde (**II**) as starting material has also been described[4]. This starting natural material is very attractive because it has the desired chiral center in the position 4 of the p-mentadiene skeleton.



(I)
(+)-Juvabione



(II)
(R)-(+)-Perillaldehyde



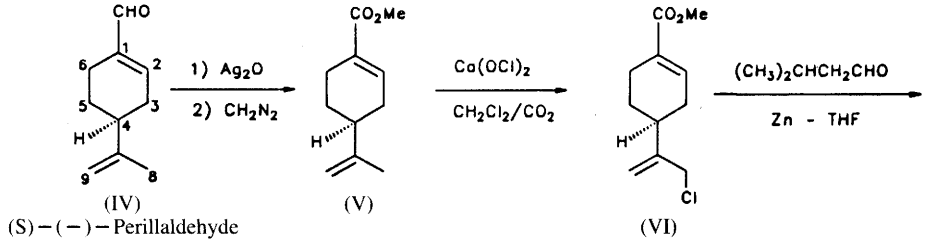
(III)
Limonene Epoxide

Coupling of allylic chloride (**VI**) with isovaleraldehyde, using zinc to promote the C10 + C5 junction in the bisabolane skeleton toward juvabione synthesis, was also reported in the literature[5], however, in this case the starting material was (+)-limonene which had the 1,2 double bond "protected" by epoxidation before the chlorination step, leading to limonene 1,2 epoxide (**III**).

Therefore, it was decided to use (S)-(-)-perillaldehyde(**IV**) as the starting material in the present work and verify if the allylic chlorination works in the desired position 9 of the methyl (-)-perillate (**V**), without chlorination in the position 3 allylic to the conjugated double bond. This reaction was used before in the chlorination of carvone[5] and there was a good indication that it could work well in the present case.

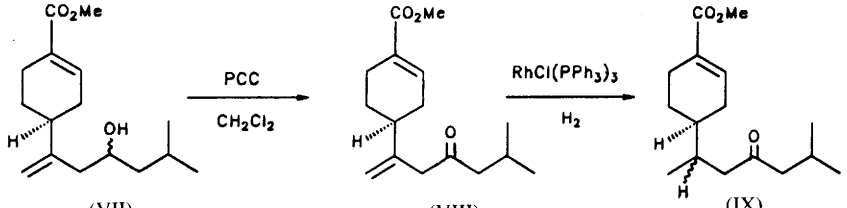
Results and Discussion

The overall synthetic scheme followed is shown in Figure 1. (S)-(-)-perillaldehyde (**IV**) was oxidized[6], in 95% yield, to (-)-perillic acid which was esterified to methyl (-)-perillate (**V**) in 88% yield[7]. The allylic chloride **VI** was formed in 70.4% yield by treatment of V with a solution of calcium hypochlorite and dry ice using CH_2Cl_2 as solvent[8]. This chloride (VI) was coupled with isovaleraldehyde using zinc in THF, giving a mixture of two epimeric alcohols (**VII**) in 78,6% yield[9]. The ketone (**VIII**) was formed in high yield (96%) by treatment of the mixture of alcohols (**VII**) with PCC, using sodium acetate as buffer[10]. Finally reduction of



(IV) (S)-(-)-Perillaldehyde (V) (VI)

Figure 1.



(VII) (VIII) (IX) (-)-Juvabione and (-)-Epi-Juvabione

VIII was done by homogeneous hydrogenation using Wilkinson catalyst[11], giving a mixture of (-)-juvabione and (-)-epi-juvabione (**IX**) in a overall yield of 43% from (-)-perillaldehyde (**IV**). Reduction of **VII** was also tried with the same catalyst but the mixture of alcohols formed presented no selectivity at position[7].

Conclusion

(-)-juvabione and (-)-epi-juvabione (**IX**) were synthesized as a mixture from (-)-perillaldehyde (**IV**) in 43% overall yield. The sequence of reactions has an allylic chlorination of methyl (-)-perillate (**V**) as a key step in the synthesis.

This approach represents a new improved route to (-)-juvabione and (-)-epijuvabione (**IX**), starting from (-)-perillaldehyde (**IV**), because less steps and high yields are involved. It is also a formal total synthesis of these two sesquiterpenes because the isolation of the final epimers has been already done[12]. Although (-)-perillaldehyde is an article of commerce[13], it (+)-isomer is apparently unavailable commercially. However one short and convenient preparation in high yield was recently reported[14], being both enantiomers of perillaldehyde now easily available.

Starting from (+)-perillaldehyde (**II**) and following the same scheme it is also possible to prepare (+)-juvabione and (+)-epi-juvabione. The present process thus represents an easy scheme for obtention of the four possible epimers of Juvabione.

Experimental

(-)-Perillic acid[6] - To a solution of (-)-perillaldehyde (**IV**) (15.0g; 99.75 mmol) and silver nitrate (35.62g; 209.5 mmol) in 200 ml of ethanol and 170 ml of water was added, over a period of 15 min, a solution of sodium hydroxide (16.35 g; 408.82 mmol) in 150 ml of water.

The reaction mixture was stirred for a total of 2 hours and then filtered. The filtrate was concentrated under reduced pressure, diluted with water washed with ether, acidified with dilute hydrochloric acid, and extracted with ether. The combined ether extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue afforded 16.95 g of (-)-Perillic acid in 95.0% yield: M.p. (131 - 132) °C; IR 330-2500, 1685 cm^{-1}; ^{1}HNMR (90MHz, $CDCl_3$) δ 11.50 (1,s, OH), 7.20 (1H, m, H-2), 4.75 (2H, m, H-9), 1.78 (3H, s, H-10). ^{13}C NMR (75 MHz, $CDCl_3$); δ 173.06 (s, C-7); 148.65 (s, C-8), 141.83 (d, C-2), 129. 75 (s, C-1). 109.35 (t, C-9), 40.15 (d, C-4), 31.36 (t, C-3), 27.08 (t, C-5), 24.28 (t, C-6), 20.74 (q, C-10).

Methyl (-)-Perillate (V)[7]: (-)-perillic acid (10.05 g; 60.45 mmol) was dissolved in 150 ml of ethyl ether, and 0.28 M solution. of diazomethane in ether (258 ml) was slowly added at 0°C. The mixture was stirred for an addictional hour at 0°C and the ether removed under reduced pressure. The residue was distilled under vacuum (b.p. = (70-72)°C; 0.18 mmHg) to give 9.58 g (88% yield) of methyl (-)-perillate (**V**): IR (film) 3080, 2970, 2860, 1720 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 7,05 (1H, m, H-2), 4.77 (1H, d, J=1,5 Hz, H-9a), 4.80 (1H, d, J=1,5 Hz, H=9b), 3.75 (3H, s, -OCH_3), 1.8(3H, s, H-10); ^{13}CNMR (75 MHz,, $CDCl_3$): δ 167.82 (s,C-7), 148.78 (s, C-8), 139.16 (d, C-2), 129.92 (s, C-1), 109.20 (t, C-9), 51.50 (q,-OCH_3), 40.06 (d, C-4), 31.08 (t, C-3), 27.05 (t, C-5), 24.57(t, C-6), 20.71 (q, C-10); MS (M^+) (m/z) 180.

Methyl(-)-10-chloroperillate[8] *(VI)* - To a suspension of 6.89g of "65%" calcium hypochlorite in 34 ml of water was added 8,46 g (47 mmol) of methyl (-)-perillate (**V**) in 140 ml of dichloromethane. Approximately 36g of dry ice was added in small portion to this mixture with stirring over a period of 2 hours. At the end of this period the reaction mixture was filtered to remove insoluble salts. The organic layer was separated dried (Na_2SO_4), and concentrated under reduced pressure. Distillation of the residue afforded 7.04g (70.40%) of **VI** as a yellow liquid: b.p. (115-116°)C (0.18 mmHg); IR(FILM) 760 cm^{-1}; ^{1}H NMR (90MHz, $CDCl_3$) 7.06 (1H, m, H-2), 5.23 (1H, s, H-9), 5.03 (1H, s, H-9), 4.13 (2H, s, H-10), 3.75 (3H, s, -OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 167.58 (s, C-7), 148.54 (s, C-8), 138.47 (d, C-2), 129.95 (s, C-1), 113.84 (t, C-9), 51.53 (q, -OCH_3), 47.55 (t, C-10), 35.55 (d, C-4), 31.44 (t, C-3), 27.14 (t, C-5), 25.40 (t, C-6); MS (M+) (m/z) 214.

(-)-Dehydrojuvabiol(VII)[9] - a mixture of 5.01 g (23.33 mmol) of methyl (-)-10-chloro-perillate (**VI**), 3g (34.88 mmol) of isovaleraldehyde, 5.81 g of acid-washed zinc[15], and 31 ml of THF was refluxed under a nitrogen atmosphere for 8 hours. The reaction mixture was cooled to room temperature and filtrated. The filtrate was diluted with water and extracted with ether. After washing with dilute HCl, saturated

$NaHCO_3$, and saturated brine, the ether layer was dried ($Na2SO_4$) and concentrated under reduced pressure. Distillation of the residue yielded 4.88 g (78.60%) of (**VII**), as a yellow liquid: b.p. (141-143)°C (0.18 mmHg); IR (FILM) 3500 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 7.02 (1H, m, H-2), 4.92 (2H, s, H-9), 3.80 (1H, m , H-11), 3.70 (3H, s, -OCH_3), 0.92 (6H, d, J=7.5 Hz, H-14, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.71 (s, C-7), 150.32 and 149.98 (s, C-8), 138.94 and 138.85 (d, C-2), 129.98 and 129.85 (s, C-1), 111.15 and 110.97 (t, C-9), 67.24 and 67.20 (d, C-11), 51.53 (q, -OCH_3), 46.41 (t, C-10), 44.01 and 43.89 (t, C-12), 38.46 and 38.40 (d, C-4), 31.91 and 31.35 (t, C-3), 27.52 and 27.32 (t, C-5), 24.68 (d, C-13), 24.52 (t, C-6), 23.41 (q, C-14), 22.2 (q, C-15); MS (M^+) m/z 266.

(-)-Dehydrojuvabione (VIII): pyridinium chlorochromate[10] (814 mg, 3.77 mmol) and sodium acetate (68 mg) were suspended in 20 ml anhydrous CH_2Cl_2 and (-)- dehydrojuvabiol (**VII**) (660 mg; 2.48 mmol) in 10 ml of CH_2Cl_2 was added in one portion to the magnetically stirred solution. After 3 hours, 50 ml of dry ether was added and the filtered reaction mixture was concentrated under reduced pressure. The residue was passed through a short path column of Florisil. The combined organic solution was concentrated under reduced pressure affording 0.6g (96%) of (-)-dehidrojuvabione (**VIII**): IR (FILM) 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 6.94 (1H, m, H-2), 4.96 (1H, s, H-9), 4.87 (1H, s, H-9), 3.67 (3H, s, -OCH_3), 3.11 (2H, s, H-10), 2.31 (2H, d, J=7.75Hz, H-12), 2..14 (3H, m, H-3, H-13), 2.0-1.8 (3H, m, H-6, H-4), 1.46-1.30 (2H, m, H-5), 0.88 (6H, d, J=7.0Hz, H-14 and H-15); ^{13}C NMR (75MHz, $CDCl_3$) δ 208.60 (s, C-11), 167.67 (s, C-7), 146.23(s, C-8), 138.67 (d, C-2), 129.88 (s, C-1), 113.16 (t, C-9), 51.52 (q, -OCH_3), 50.92 (t, C-10), 49.98 (t, C-12), 38.55 (d, C-4), 31.24 (t, C-3), 27.08 (t, C-5), 24.43 (t and d, C-6 and C-13), 22.50 (q, C-14, C-15); MS (M^+) m/z 264.

(-)-Juvabione and (-)-epi-juvabione (IX)[11]: A two-necked flask fitted with a magnetic stirrer bar was charged with 25 ml of dried and deoxigenated benzene and 72.2 mg (0.0806 mmol) of ($RhCl(PPh_3)_3$). One neck was closed and the other was attached with a hydrogen source. The catalyst was first hydrogenated by a cycle of evacuation and refilling of the flask with H_2. This cycle was carried out three times on the stirred mixture to produce a homogenous solution. Using a syringe, 320 mg (1.21 mmol) of (-)-dehidrojuvabione (**VIII**) was introduced and the stirred solution was hydrogenated until GLC indicated complete disappearance of starting material (1-2 hours). The reaction mixture was poured onto a column of Florisil and the product eluted with $CHCl_3$: Hexane (1:1). After concentration it gave 314 mg (97.5%) of (-)-juvabione and (-)-epi-juvabione (**IX**): IR (FILM) 2970, 2860, 1720, 1650, 1270, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (1H, m, H-2), 3.68 (3H,s, -OCH_3), 2.5-1.85 (8H, H-3, H-6, H-10, H-12), 1.85-1.0 (5H, H-4, H-5, H-8, H-13), 0.86 (3H, d, J=7 Hz, H-14), 0.85 (3H, d, J=7 Hz, H-15), 0.82 (3H, d, J=7 Hz, H-9). ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.57 (s, C-11), 167.77 (s, C-7), 139.27 and 139.21 (d, C-2), 130.11 (s, C-1), 54.42 and 52.37 (t, C-12), 51.44 (s,-OCH_3), 47.86 and 47.72 (t, C-10), 37.66 and 37.62 (d, C-4), 32.83 and 32.58 (d, C-8), 29.64 and 28.45 (t, C-3), 26.,05 and 24.87 (t, C-5), 24.78 and 24.67 (t, C-6), 24.49 (d, C-13), 22.56 and 22.49 (q, C-14, C-15(, 16.46 and 16.36 (q, C-9); MS (M^+) m/z 266.

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