Total Synthesis of (+)-Occidentalol[1]

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A synthesis of (+)-occidentalol (**1**) has been realized in six steps, starting from the readily available enone alcohol **3**.

La synthèse du sesquiterpène (+)-occidentalol (**1**) a été réalisée en six étapes en utilisant un produit de départ très facilement accessible, l'énone alcool **3**.

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The structure of (+)-occidentalol, a sesquiterpene isolated (1) from the wood of Eastern white cedar (*Thuja occidentalis L.*) was first formulated as **2** (2) and later corrected to structure **1** (3).

We wish now to report a total synthesis of (+)-occidentalol which confirmed the proposed structure **1** for this sesquiterpene. A synthesis of (−)-occidentalol has recently appeared in the literature (4) and a synthesis of the naturally occuring (+)-occidentalol together with a chemical correlation have been completed by Heathcock and Amano (5).

The enone alcohol **3** is very readily available in large scale from (+)-dihydrocarvone in three steps (6). This compound (**3**) has served as key intermediate in a synthesis of α-agarofuran (6).

Structurally, compound **3** and (+)-occidentalol (**1**) have the same skeleton and both of which possess the same absolute stereochemistry at C-7 and -10. Thus, a specific reduction of the double bond of **3** to obtain a *cis*-decalone system (**4**), and the use of the remaining carbonyl group for the introduction of the diene chromophore in ring A, seemed to be a very logical approach. Consequently, the enone alcohol **3** appears to be an excellent precursor for (+)-occidentalol and it was therefore selected as starting material.

Catalytic hydrogenation of compound **3** in methanol in the presence of 10% palladium-on-charcoal gave directly the crystalline *cis*-ketol **4** in 65% yield. Treatment of the resulting mother liquor[5] with methanolic sodium hydroxide furnished a further crop of **4**, bringing up the total yield to 83%.

In order to confirm the *cis* juncture of **4**, a reduction of **3** with lithium in liquid ammonia was carried out and a mixture of two compounds was obtained. The minor product was found identical with **4**. Since, it is known that this reduction (7) generally affords the *trans* product, the major product must have the *trans* structure.[6]

The introduction of a double bond between C-1 and -2 was next considered and to realize such a transformation in a specific manner, ketol **4** was first converted into the corresponding hydroxy methylene derivative **5** in essentially quantitative yield. From this intermediate (**5**), we have developed two different routes to obtain the enone **6**.

Treatment of the sodium salt of **5** with bromine gave an unstable mixture of the two epimeric bromo-aldehydes **7** which was therefore directly subjected to dehydrobromination condition ($LiCl–Li_2CO_3$/DMF (8)) and the crystalline enone aldehyde **8** was readily isolated in 65% yield after column chromatography.

Deformylation of **8** to give the crystalline enone **6** was achieved in 80% yield with tris-triphenylphosphinerhodium chloride in boiling dichloromethane (9).

Alternatively, the transformation of bromo-aldehydes **7** to enone **6** can be accomplished by first performing a retro Claisen reaction (**7** → **9**)

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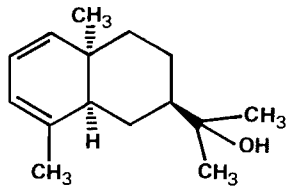
[5]The n.m.r. studies of the mother liquor before and after the basic treatment indicated the presence of C-4 epimers in the hydrogenated mixture. For a more detailed study of a similar reaction, see ref. 5.

[6]A systematic study of the metal ammonia reduction of **3** has been carried out, the result of which will be reported in a separate paper.



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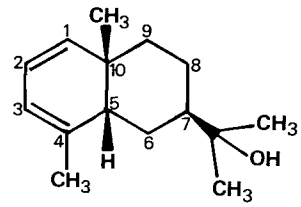

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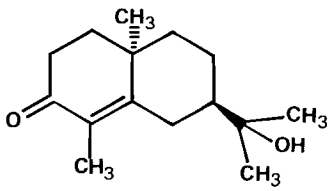

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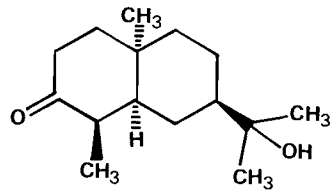

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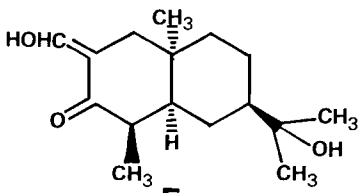

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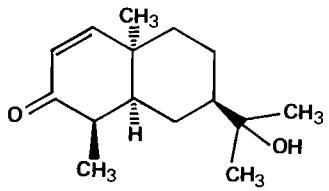

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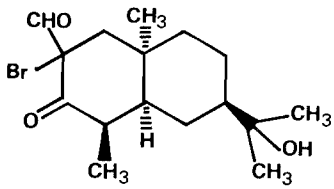

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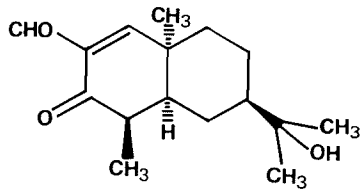

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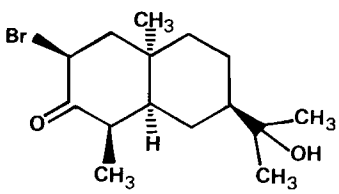

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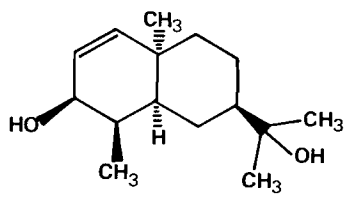

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followed by dehydrobromination (**9** → **6**). This procedure (10) has the advantage of avoiding the use of the expensive rhodium complex.

In fact, we have carried out the bromination and the deformylation reaction in a single operation without the isolation of the unstable isomer **7**. Treatment of the hydroxymethylene **5** with bromine in the presence of an excess barium

hydroxide in ethanol gave directly the bromoketone **9**. Barium hydroxide served to generate the enolate salt of **5** necessary for bromination (→**7**) and to mediate *in situ* the retro Claisen reaction (**7** → **9**) (11).

Dehydrobromination of **9** proceeded smoothly to give the desired enone **6**. This sequence of reaction afforded **6** in 74% overall yield from **5**.

The enone **6** was then reduced in high yield with lithium aluminum hydride in ether to give the allylic alcohol **10**. The crude allylic alcohol dissolved in benzene containing *p*-toluenesulfonic acid at room temperature gave the alcohol **1** which was found to be completely identical with authentic (+)-occidentalol.

Experimental

Melting points are not corrected. The U.V. spectra (λ_{max}) were measured on a Cary model 14 spectrophotometer and i.r. spectra (ν_{max}) were recorded on a Perkin–Elmer spectrophotometer, model 257. The n.m.r. spectra (τ values) were taken on a Varian A60 spectrometer with tetramethylsilane as an internal standard. Anhydrous magnesium sulfate was used as the drying agent in working up reaction. Fisher Florisil 100–200 mesh was used for preparing all column chromatograms. Low boiling petroleum ether (b.p. 30–60 °C) was used.

(+)-Dihydrocarvone was prepared by the method of Malhotra *et al.* (12). The method of Hortmann *et al.* (13) was found superior to the one of Howe and McQuillin (14) to prepare (+)-5-α-hydroxy-4,7α*H*-eudesm-11-en-3-one which is the precursor of **3** (6).

cis-Ketol **4**

Enone alcohol **3** (9.45 g, 40 mmol) was hydrogenated in freshly distilled methanol (500 ml) with 10% palladium-on-charcoal (1 g) for 24 h. The catalyst was removed by filtration on Celite and the filtrate was evaporated to dryness to give a white solid (9.54 g). Crystallization from hexane afforded pure *cis*-ketol **4** (6.19 g, 65% yield).

The mother liquor (3.35 g) was dissolved in methanol (100 ml) and treated with 50% aqueous sodium hydroxide (10 ml) for 3 h at room temperature. After removal of the methanol and addition of water, the reaction mixture was extracted twice with ether. The combined extract was washed with brine, dried, and evaporated. Column chromatography yielded an additional quantity of the ketol **4** (1.72 g). Total yield 83%. The analytical sample was prepared by crystallization with petroleum ether, m.p. 87–88 °C; i.r. ν_{max} 3600, 3460, and 1710 cm^{-1}; n.m.r.: τ ($CDCl_3$) 8.69 (3H, s, CH_3), 8.83 (6H, s, *i*-propylol CH_3), and 9.02 (3H, d, $J = 6.5$ Hz, CH_3).

Anal. Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.26; H, 10.96.

Hydroxy Methylene Derivative **5**

To sodium hydride (4 g, 50% suspension), which was previously washed with dry benzene to remove the oil, was added ketol **4** (2 g, 8.4 mmol), ethyl formate (50 ml), and anhydrous ether (400 ml). The mixture was refluxed for 5 h. After cooling, water was cautiously added and the aqueous phase was washed with ether, acidified to p*H* 5 with dilute hydrochloric acid and extracted with ether. The organic phase was washed with brine, dried, and evaporated to dryness to give crude **5** (2.24 g); i.r.: ν_{max} ($CHCl_3$) 3600, 3450, 1710, 1650, and 1580 cm^{-1}; n.m.r.: τ ($CDCl_3$) 1.52 and 2.08 (1H, s, hydroxymethylene hydrogen), 8.85 (6H, s, *i*-propylol CH_3) 8.85 (3H, d, $J = 7$ Hz, CH_3), and 9.00 (3H, s, CH_3).

Bromo-aldehydes **7**

Compound **5** (2.24 g, 8.4 mmol) dissolved in chloroform (100 ml) was mixed with an aqueous solution of sodium hydroxide (0.25 *N*, 33.6 ml). To the above mixture was added dropwise a solution of bromine in chloroform (1%, 44.8 ml) with stirring. After 45 min at room temperature, water was added and the phases were separated. The organic layer was washed with water, dried, and evaporated *in vacuo* at room temperature to give the crude bromo-aldehydes **7** (2.7 g) as an oil; i.r.: ν_{max} ($CHCl_3$) 3600, 3460, 1730, and 1710 cm^{-1}; n.m.r.: ($CDCl_3$) 0.33 and 0.67 (1H, 2s, (intensity ratio 4:1), aldehydic H). This unstable material was used immediately for the next step.

Enone Aldehyde **8**

The crude bromo-aldehydes **7** (2.7 g, 7.08 mmol) dissolved in dimethyl formamide (300 ml) containing lithium chloride (2.42 g, 55 mmol) and lithium carbonate (484 mg, 6.5 mmol) was heated at 125 °C (oil bath temperature) under nitrogen for 2.5 h. After cooling, water was added and the mixture was extracted with ether. The organic phase was washed with brine, dried, and evaporated to dryness. The resulting product was purified by column chromatography. Elution with ether–benzene (4:1) gave crystalline **8** (1.44 g, 65% yield from ketol **4**). The analytical sample was prepared by crystallization with ether–petroleum ether, m.p. 101.5 °C; $\alpha_{578}^{CHCl_3}$ −247°; i.r.: ν_{max}($CHCl_3$) 3600, 3500, 1730, 1705 and 1685 cm^{-1}; n.m.r.: τ ($CDCl_3$) 0.07 (1H, s, aldehydic H), 2.64 (1H, d, $J = 2$ Hz, olefinic H), 8.67 (3H, s, CH_3), 8.88 (3H, d, $J = 6$ Hz, CH_3), and 8.95 (6H, s, *i*-propylol CH_3); u.v.: λ_{max} (EtOH) 237 nm (ε 8100).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.54, H, 8.91.

Bromo-ketone **9**

To a stirred mixture of the hydroxymethylene derivative **5** (266 mg, 1 mmol) and barium hydroxide (946 mg, 3 mmol) in ethanol (95%, 8 ml) was slowly added a solution of bromine (160 mg) in ethanol (5 ml). After 45 min at room temperature, water was added and the resulting mixture was extracted with ether. The organic phase was washed with dilute hydrochloric acid, brine, dried, and evaporated to dryness. The crude product (315 mg, 100% yield) was suitable for the next step. The analytical sample was purified by column chromatography (eluant: benzene–ether (7:3)) and crystallized from etherpetroleum ether, m.p. 88.5 °C (dec.), $\alpha_{578}^{CHCl_3}$ +206°; i.r.: ν_{max} ($CHCl_3$) 3590, 3440, and 1727 cm^{-1}; n.m.r.: τ ($CDCl_3$) 5.05 (1H, oct, $J = 1$, 6.5 and 12 Hz, H_2), 8.36 (3H, s, CH_3), 8.86 (6H, s, *i*-propylol CH_3), and 8.93 (3H, d, $J = 6.5$ Hz, CH_3).

Anal. Calcd. for $C_{15}H_{25}BrO_2$: C, 56.78; H, 7.94; Br, 25.19. Found: C, 56.92; H; 7.91; Br, 25.15.

Enone 6

(a) From Enone Aldehyde 8

The enone aldehyde **8** (83 mg, 0.3 mmol) and tris-triphenylphosphinerhodium chloride (335 mg, 0.36 mmol) in dichloromethane (12 ml) were kept at reflux for 16 h under nitrogen and 14 h at room temperature. The solvent was removed *in vacuo* and the residue was triturated with ethanol. After evaporation of the ethanolic extract the crude product was purified by chromatography. Elution with benzene–ether (7:3) gave crystalline **8** (66 mg, 83% yield). The analytical sample was prepared by crystallization from hexane, m.p. 84 °C, i.r.: ν_{max} ($CHCl_3$) 3600, 3450, 1675, and 1640 cm^{-1}; n.m.r.: τ (CCl_4) 3.65 (1H, quad, $J = 2$ and 10 Hz, H_1), 4.23 (1H, d, $J = 10$ Hz, H_2), 8.79 (3H, s, CH_3), 8.99 (6H, s, *i*-propylol CH_3), and 9.01 (3H, d, $J = 6.5$ Hz, CH_3); u.v.: λ_{max} (EtOH) 230 nm (ε 7950).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.23. Found: C, 76.22; H, 10.08.

(b) From Bromo-ketone 9

The bromo-ketone **9** (3.1 g, 10 mmol) dissolved in dimethylformamide (150 ml) containing lithium bromide (3.1 g, 35 mmol) and lithium carbonate (2.6 g, 35 mmol) was heated at 130 °C (bath temperature) for 24 h. Water was added to the cooled reaction mixture which was then extracted with ether. The organic phase was washed with brine, dried, and evaporated to dryness (2.2 g). A portion of this crude material (812 mg) was purified by column chromatography with silica gel. Elution with benzene–ether (4:1) gave a pure sample (639 mg) which was identical to enone **6** obtained by the above procedure. The overall yield from the hydroxymethylene derivative **5** was 75%.

(+)-Occidentalol (1)

The enone **6** (371 mg, 1.7 mmol) dissolved in ether (25 ml) was slowly added to a suspension of lithium aluminum hydride (123 mg) in ether (25 ml) cooled in an ice bath. After 1 h at room temperature, the excess hydride was destroyed by addition of brine. The organic phase was separated, dried, and evaporated to dryness to give the crude allylic alcohol **10** (374 mg, 100% yield); i.r.: ν_{max} ($CHCl_3$) 3600, 3470, and 3450 cm^{-1}; n.m.r.: τ ($CDCl_3$) 4.17 (1H, quad, $J = 4$ and 10 Hz, H_2), 4.52 (1H, d with additional splitting, $J = 10$ Hz, H_1), 6.05 (H, t, $J = 4$ Hz), 8.86 (6H, s, *i*-propylol CH_3), 8.88 (3H, d, $J = 6$ Hz, CH_3), and 9.02 (3H, s, CH_3).

The above crude product dissolved in benzene (60 ml) was treated with *p*-toluenesulfonic acid (58 mg) for 3 h at room temperature. Water was added and the benzene layer was separated. The aqueous phase was extracted with ether and the combined organic solution was dried and evaporated to dryness. The crude product (345 mg) was purified by column chromatography. Elution with benzene gave (+)-occidentalol (214 mg, 62% yield from **6**). The allylic alcohol **10** (98 mg, 26%) was recovered from further elution with benzene–ether (1:1).

The (+)-occidentalol was further purified by sublimation and crystallization (petroleum ether), m.p. 95 °C; $\alpha_{578}^{CHCl_3}$ +369° (lit. (*2b*) m.p. 94–96.5 and 97.5–98 °C; $\alpha_{D}^{CHCl_3}$ +363.2°). The i.r. and n.m.r. spectra were identical with those of an authentic sample of (+)-occidentalol. Also, a mixed m.p. showed no depression.

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