

## Synthesis and Stereochemistry of Occidenol, a 4,5-Dihydrooxipin-containing Sesquiterpene: a Pericyclic Approach

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The first synthesis of occidenol (**1**), a 4,5-dihydrooxipin-containing sesquiterpene, is reported. The stereochemistry is corrected from that postulated by Tomita and Hirose, by a synthesis starting with natural occidentalol (**4**), the stereochemistry of which was also initially in error. The route (schemes 1 and 2) utilizes a retro-electrocyclic [2+2+2] fragmentation with N<sub>2</sub> expulsion from **9** to produce, quantitatively, the acid sensitive dihydrooxipin system.

**Keywords:** Occidenol, Sesquiterpene, Occidentalol, Retro-electrocyclic, Dihydrooxipin, Diels-Alder.

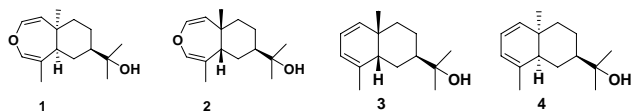
Occidenol (**1**) is a sesquiterpene with a 4,5-dihydrooxipin ring structure. Such a functionality is acid sensitive and is rare among natural products. We report here the first synthesis of occidenol, which was originally isolated from the heartwood of *Thuja occidentalis* L., the Eastern white cedar tree [1a], and later from *T. koraiensis* Nakai [1b]. The compound was also isolated from tobacco, *Nicotinia rustica*, and shown to be a phytoalexin [1c,1d] against tobacco mosaic virus. [2a] The initially proposed structure [1a] was incorrect and led to the name occidiol. The correct structure was determined by Tomita and Hirose [2b]. However, the stereochemistry was postulated as in **2**, which has an axial isopropanol side chain in the conformation that is required by the observed 11 Hz diaxial coupling between H-5 and one H at C-6. At the time of the assignment, occidentalol (**3**), which had also been isolated from *T. occidentalis*, was postulated [3] to have analogous stereochemistry, but has since been corrected to **4**, by biogenetic reasoning and further spectroscopic analysis [4] and verified by several stereospecific syntheses [5]. However, the question of the stereochemistry of occidenol has not been revisited in the literature, but it seems obvious that

the stereochemistry needs to be revised to **1**. We report the first synthesis of this stereoisomer and find that it is identical in all respects with natural occidenol.

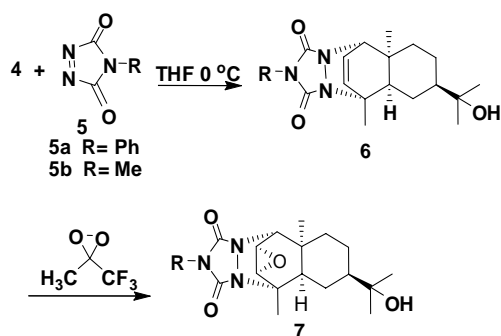
After several abortive attempts to synthesize occidenol via other routes, we decided to use occidentalol as the starting material, since we could duplicate the literature [3] claim of 36% isolated yield from the acetone extract of the heartwood of *T. occidentalis*.

Diels-Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (**5**) with purified occidentalol gave a single adduct (**6a**). Fairly impure occidentalol could be used in practice, since it is the only diene in the terpene fraction [3], and the adduct crystallized easily. The stereochemistry was assigned from a detailed <sup>1</sup>H NMR analysis (*vide infra*) of the next compound in the sequence, the epoxide **7**.

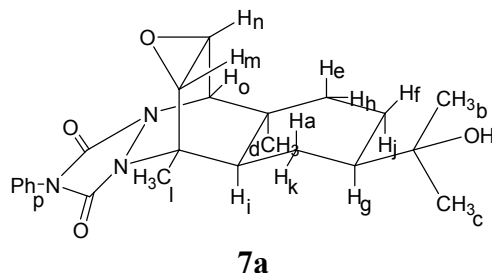
Epoxidation of **6a** proved to be difficult, as expected. Compound **6a** was recovered unchanged after either *m*-chloroperbenzoic acid or peroxytrifluoroacetic acid treatment. The desired epoxide was obtained in variable yield, along with starting material, when subjected to treatment with dimethyldioxirane [6]. However, the epoxide **7a** was the only product detectable by NMR spectroscopy (95% yield) when the more reactive methyl trifluoromethyl dioxirane [7] was used.



**Figure 1:** The revised structure of occidenol (**1**) and the originally proposed structure (**2**). The originally proposed structure of occidentalol **3** and its revised structure **4**.



**Table 1:** NMR spectroscopic data of **7a**. The assignments of letters to the various protons are made in the order of relative chemical shifts.



H <sub>x</sub>	Shift (δ)	Multiplicity	J (Hz)	NOESY corr.
a	1.01	ddd	$J_{g,i,k} = 13, 13, 13$	m, k
b	1.16	s	----	----
c	1.21	s	----	g
d	1.30	s	----	i, o
e	1.35	dd	$J_{h,j} = 13, 6$	n, h
f	1.47	ddd	$J_{g,h,j} = 2.5, 2.5, 13$	j
g	1.56	dddd	$J_{a,j,f,k} = 13, 9, 2.5, 2.5$	c
h	1.69	ddd	$J_{e,j,i} = 13, 5.5, 2.5$	e
i	1.74	dd	$J_{k,a} = 13, 5.5$	l, d, k
j	1.78	dddd	$J_{f,g,e,h} = 13, 9, 6, 2.5$	f
k	1.87	ddd	$J_{a,i,g} = 13, 5, 2.5$	a, i
l	1.92	s	----	i, m
m	3.39	d	$J_n = 4.5$	a, l, n
n	3.65	dd	$J_{n,o} = 3, 4.5$	e, m, o
o	4.19	d	$J_n = 3.0$	n, d
p	7.44	m	----	----

The epoxide **7a**, within TLC and spectroscopic detection limits, was the only stereoisomer formed. A detailed NMR analysis was performed on this compound, with the assignments for the 8 unique hydrogens on the B-ring spin system all being assignable. The data are summarized in Table 1.

The starting point for the assignments (see conformational structure of **7a**) was the proton at C6-H<sub>a</sub>, which appears at the highly shielded position of  $\delta = 1.01$  as a nominal quartet, but which is actually a ddd ( $J = 13, 13, 13$  Hz), due to geminal and two *trans*-diaxial couplings, as verified by the COSY spectrum (the analogous signal in **6a** appeared at  $\delta = 0.61$ ). This assignment allowed unambiguous assignments to C5-H<sub>i</sub> and C7-H<sub>g</sub>. This in turn allowed the assignments of the other signals, with substantial verification by COSY and HMBC spectra. The assignments were dramatically

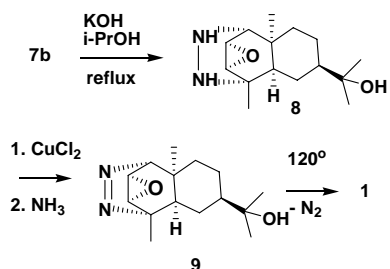
verified by two long range NOESY correlations, one between C3-H<sub>m</sub> and C6-H<sub>a</sub> and one between C2-H<sub>n</sub> and C9-H<sub>e</sub>, the only correlations between protons on the A ring and ones on the B ring. These NOESY correlations assign the unique stereostructure shown. The data support the fact that the B ring is forced into a boat conformation by the rigid structure, which is also suggested by examination of molecular models.

While this work was in progress, a report appeared by Liao and White [8] on the thermal fragmentation, with nitrogen extrusion, of exo- and endo-6,7-diaza-3-oxotricyclo[3.2.2.0<sup>2,4</sup>]non-6-ene. The exo isomer rearranged to 4,5-dihydrooxipin below room temperature, whereas the endo isomer was stable to *ca.* 150°C and produced only cyclohex-2-enone above that temperature. Presumably, the model exo isomer rearranges via orbital symmetry control and the endo one via diradical fragmentation. This seemingly valid model compound predicted that our compound **9**, potentially derivable from **7a**, had the wrong stereochemistry (epoxide endo to the bicyclo carbon bridge). However, we decided to investigate this system further, in spite of this ominous precedent.

With the epoxide **7a** in hand, we attempted to remove the urazole ring, either reductively or hydrolytically. Surprisingly, the compound was inert, even to such forcing conditions as either refluxing with NaOH in ethylene glycol or refluxing with excess LAH in THF. The starting material was recovered unchanged; even the epoxide group withstood the reaction conditions.

To solve the hydrolysis problem, we made the methyl derivative, **7b**, which proceeded without incident by replacing the phenyl urazole with its methyl analog, 4-methyl-1,2,4-triazoline-3,5-dione and repeating the sequence. Fortunately, **7b** proved to be much less recalcitrant, and was hydrolyzed with KOH in refluxing isopropyl alcohol under N<sub>2</sub> to the hydrazine derivative **8**, which was somewhat unstable and was, in practice, oxidized to the azene **9** by adding CuCl<sub>2</sub> to the hydrolysis mixture. It was expected that cleavage of the azene via a [2+2+2] cycloreversion with extrusion of N<sub>2</sub> would be fairly trivial by simply heating. It was found from the GC/MS of **9** that it decomposed quantitatively to occidenol, doubtlessly in the inlet of the GC, giving a MS that was identical to that of natural occidenol (**1**).

After some experimentation, we found that we could effect the thermal fragmentation by heating the azene **9** in MeCN in a sealed tube at 135°C. This process gave only occidenol (**1**), with no other detectable compounds. The more rigid bicyclo structure of occidenol evidently precludes C-O fragmentation of the epoxide and forces C-C fragmentation instead. This experience verifies the



Scheme 2: Basic hydrolysis of 7 and synthesis of occidenol (1).

danger of relying too heavily on the use of model compounds. The successful synthesis verifies the stereochemistry of occidenol postulated in structure 1.

## Experimental

**Extraction and isolation of occidentalol (4):** A generous supply of the heartwood from the Eastern white cedar, *Thuja occidentalis* L., was supplied as wood chips by Bob Nadeau of the Sovebec Furniture Company in Canada. A sample (306.0 g) of the wood was extracted in a continuous extractor with acetone for 36 h. After removal of the solvent under reduced pressure, the dark brown viscous residue was poured into 500 mL diethyl ether. The ether solution was stirred for 2 h, filtered through celite, and then extracted with 3 aliquots of 10% aqueous KOH solution to remove all the phenolic and other acidic material. After washing with water, the solution was dried over anhydrous MgSO<sub>4</sub>, and then evaporated to yield an oily material (5.72 g, 1.9%). This was fractionally distilled through a vacuum-jacketed 6 in Vigreux column at 1.0 mm pressure. The fraction collected between 148-149°C contained 1.8 g. This material proved to be 71% occidentalol, determined by GC/MS, which was used in the subsequent step without any further purification.

**Preparation of the Diels-Alder adduct 6a:** To a solution of occidentalol (1.1 g, of 71% purity, 5.0 mmol) in 30 mL of dry THF was added dropwise at 0°C a solution of 4-phenyl-1,2,4-triazoline-3,5-dione (0.875g, 5.0 mmol) in 30 mL of dry THF. The resulting mixture was stirred for 10 h at room temperature, and the solvent was removed by rotary evaporation. The crude mixture was chromatographed on silica gel by eluting with a 30:70 mixture of diethyl ether and ethyl acetate to yield 6a (1.38 g, 70%) as a white powder.

MP: 188-189°C.

IR (thin film): 3300, 3050, 2950, 1725, 1700, 1580, 1450, 1300 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 0.59 (ddd, *J* = 13.0, 13.0, 13.0 Hz, 1H), 1.12 (s, 3H), 1.16 (s, 3H), 1.28 (s, 3H), 1.22 (dd, *J* = 13, 6.6 Hz, 1H), 1.37 (ddd, *J* = 13, 7.0, 2.5 Hz, 1H), 1.53 (ddd, *J* = 13, 9, 2.5 Hz, 1H), 1.54 (ddd, *J* = 13, 5.5, 2.5 Hz, 1H), 1.61 (dd, *J* = 13, 5.5 Hz, 1H),

1.74 (ddd, *J* = 12.5, 5.5, 2.5 Hz, 1H), 1.75 (ddd, *J* = 12.5, 5.0, 2.5, 1H), 1.91 (s, 3H), 4.19 (d, *J* = 3.0 Hz, 1H), 6.18 (d, *J* = 4.5, 1H), 6.44 (dd, *J* = 3.0, 4.5 Hz, 1H), 7.43-7.45 (m, 5H).

<sup>13</sup>C NMR: (125 MHz, CDCl<sub>3</sub>): 18.8 (CH<sub>3</sub>), 19.2 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 26.3 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>), 28.7 (CH<sub>3</sub>), 37.2 (CH), 40.8 (C), 41.2 (CH), 49.9 (CH), 58.6 (CH), 63.9 (C), 73.1 (C), 128.0 (CH), 128.0 (CH), 128.9 (CH), 130.3 (CH), 131.5 (CH), 132.6 (C), 133.3 (CH), 133.5 (CH), 153.7 (C), 154.5 (C).

Anal. Calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>O<sub>3</sub>: C, 69.85; H, 7.39; N, 10.62. Found C, 69.70; H, 7.22; N, 10.65.

**Preparation of compound 7a:** Compound 6a (237.7 mg, 0.60 mmol dissolved in 20 mL of CH<sub>3</sub>CN) was added to an aq. Na<sub>2</sub>EDTA solution (3 mL, 4 × 10<sup>-4</sup> M). The resulting solution was cooled to 0°C, followed by addition of trifluoroacetone (2 mL). After 5-10 min of stirring, a mixture of NaHCO<sub>3</sub> (0.5 g, 6.0 mmol) and oxone (2.5 g, 6.0 mmol) was added at once. The mixture was stirred for 24 h at room temp. The solution was added to 20 mL of water and extracted with 2 × 15 mL of CH<sub>2</sub>Cl<sub>2</sub> and worked up as usual to yield 7a (242 mg, 0.59 mmol, 98%), this was crystallized from EtOH.

MP: 185-186°C.

IR (thin film): 3300, 3050, 2950, 1725, 1700, 1600, 1540, 1450, 1300, 1150 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 1.01 (ddd, *J* = 13.0, 13.0, 13.0 Hz, 1H), 1.16 (s, 3H), 1.21 (s, 3H), 1.30 (s, 3H), 1.35 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.47 (ddd, *J* = 13.0, 7.0, 2.5 Hz, 1H), 1.56 (ddd, *J* = 13.0, 9.2, 5.0 Hz, 1H), 1.69 (ddd, *J* = 13.0, 5.5, 2.5 Hz, 1H), 1.74 (dd, *J* = 13, 5.5 Hz, 1H), 1.78 (ddd, *J* = 12.5, 5.5, 22.5 Hz, 1H), 1.87 (ddd, *J* = 12.5, 5.0, 2.5 Hz, 1H), 1.92 (s, 3H), 3.39 (d, *J* = 4.5, 1H), 3.65 (dd, *J* = 3.0, 4.5 Hz, 1H), 4.19 (d, *J* = 3.0 Hz, 1H), 7.43-7.45 (m, 5H).

<sup>13</sup>C NMR: (500 MHz, CDCl<sub>3</sub>): 18.8 (CH<sub>3</sub>), 20.1 (CH<sub>3</sub>), 23.7 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 26.3 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>), 28.8 (CH<sub>3</sub>), 37.2 (CH), 40.8 (C), 41.2 (CH), 42.1 (CH), 49.9 (CH), 58.6 (CH), 63.9 (C), 73.1 (C), 130.4 (CH), 130.4 (CH), 130.4 (CH), 131.5 (CH), 131.5 (CH), 132.6 (C), 153.7 (C), 154.5 (C).

Anal. Calcd for C<sub>27</sub>H<sub>29</sub>N<sub>3</sub>O<sub>4</sub>: C, 67.13; H, 7.10; N, 10.21. Found C, 67.00; H = 6.82; N, 10.31.

**Preparation of Diels-Alder adduct 6b:** To a solution of occidentalol (0.610 g of 71% purity, 1.97 mmol) in 20 mL of dry CH<sub>2</sub>Cl<sub>2</sub>, a solution of 4-methyl-1,2,4-triazoline-3,5-dione was added dropwise at 0°C. The resulting mixture was stirred for 10 h at room temp. The solvent was removed in a rotary evaporator. The crude mixture was chromatographed on silica gel with a 30:70 mixture of diethyl ether and ethyl acetate to yield 6b (0.55 g, 84%) as a yellow powder, mp 145-148°C, spectra similar to those of 6a.

**Preparation of compound 7b:** Compound **7b** was prepared analogously to compound **7a**. To a solution of compound **6b** (292.7 mg, 0.869 mmol) dissolved in 30 mL of acetonitrile was added an aqueous Na<sub>2</sub>EDTA solution (4 mL, 4 x 10<sup>-4</sup> M). The resulting solution was cooled to 0°C, followed by addition of trifluoroacetone (3 mL). Usual workup as mentioned for **7a** gave the essentially pure product **7b**, as judged by <sup>1</sup>H NMR.

**Preparation of compound 9:** A 50-mL round bottomed, two necked flask, equipped with a reflux condenser, gas inlet and outlet tubes, and magnetic spinbar was charged with 500 mg (8.91 mmol) of KOH and 0.3497 g (1.00 mmol) of urazole (**7b**) in 20 mL of isopropyl alcohol. The reaction was refluxed under N<sub>2</sub> for 24 h. The solution was cooled and then 3 g of ice was added, followed by conc. HCl to acidify the solution to pH 1-2. The solution was subsequently adjusted to pH 5-6 with 5 M NH<sub>4</sub>OH, and then, with gentle stirring, a 3 M aq. solution of CuCl<sub>2</sub>·2H<sub>2</sub>O was added, dropwise. The solution turned brown. The pH was readjusted to pH 5-6, and after 15 min the solution was extracted with 3 X 30 mL of CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with 2 X 20 mL of water, then dried over

anhydrous MgSO<sub>4</sub>, and concentrated in a rotary evaporator.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): 0.93 (s, 3H), 1.16 (s, 3H), 1.20 (s, 3H), 0.9-1.8 (m, 8H), 1.98 (s, 3H), 3.19 (d, *J* = 3.5 Hz, 1H), 3.48 (dd, *J* = 3.5, 2.5 Hz, 1H), 5.14 (d, *J* = 2.5 Hz, 1H).

**Occidenol (1):** A solution of the diazo compound **9** (61 mg, 0.23 mmol) in 5 mL of acetonitrile was heated to 135°C in a sealed tube for 4 h. After cooling, the mixture was poured into 10 mL of ice water and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 X 10 mL). The combined organic extracts were washed with brine and dried over MgSO<sub>4</sub>. Rotary evaporation of the filtrate gave the essentially pure product **1** (47 mg, 90%).

**Supplementary data:** <sup>1</sup>H and <sup>13</sup>C NMR spectra for compounds **4**, **6a**, **7a**, **6b**, **7b**, **9**, and **1** are contained in the supplementary data, as well as IR and MS data for occidenol (**1**).

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