Synthesis of Ptaeroxylin (Desoxykarenin): An Unusual Chromone from the Sneezewood Tree *Ptaeroxylon obliquum*

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Dedicated to Professor Sir Jack Baldwin on the occasion of his 70th birthday

Abstract: The first synthesis of the oxepinochromone ptaeroxylin (also known as desoxykarenin) isolated from the sneezewood tree is described, in which the key steps are a Claisen rearrangement and a ring-closing metathesis to form the seven-membered oxygen heterocyclic ring.

Keywords: natural products, chromones, Claisen rearrangement, ring-closing metathesis reaction

African trees of the *Ptaeroxylon* genus produce timber that is valued for its extreme durability, although once sawn, the dust apparently causes violent sneezing - hence the tree is more commonly known as sneezewood. The constituents of Ptaeroxylon obliquum were investigated independently by two research groups in the 1960s, and resulted in the isolation of a number of novel chromones upon extraction of the heartwood.^{1–3} The first of these, ptaeroxylin, was originally assigned the oxepinochromone structure $\mathbf{1}^{1}$, but upon reisolation by the second research group was reassigned the linear oxepino[3,2g]chromone structure 2 and given the name desoxykare $nin.^2$ Karenin (3) was isolated from the same source,² and the isomeric ptaeroxylinol 4 was subsequently isolated from the tree (Figure 1).³ We now report the first synthesis of a member of this group of natural products.

Our plan was to form the seven-membered oxygen heterocycle by a ring-closing metathesis (RCM) reaction, and therefore the problem reduced to a relatively simple chromone derivative. The key starting material, 5,7-dihydroxy-2-methylchromen-4-one (**5**), is a natural product itself known as noreugenin,⁴ and was readily prepared in modest yield using the Kostanecki–Robinson synthesis



Figure 1

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from 2,4,6-trihydroxyacetophenone.⁵ Selective protection of the nonhydrogen-bonded phenol as its methoxymethyl (MOM) ether **6** was followed by formation of the allyl aryl ether **7**. At this stage it proved more effective to deprotect the MOM-ether under acidic conditions before conducting a Claisen rearrangement to transfer the allyl group to C-6. The rearrangement was conveniently carried out by heating ether **8** in *N*,*N*-dimethylaniline and acetic anhydride in a microwave reactor, and gave a mixture of the acetates **9** and **10**, which, although they could be separated and characterised, were more conveniently hydrolyzed together to give the chromone **11**.⁶ A further selective alkylation of the C-7 hydroxy group gave the



Scheme 1

methallyl ether 12, the substrate for the RCM reaction. The RCM reaction has rapidly gained acceptance as a key tactic in the construction of a wide range of carbo- and heterocyclic ring systems, and has found use in the synthesis of fused medium ring ethers.⁷ In the present case, treatment of the precursor 12 with bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride (Grubbs first-generation catalyst) resulted in formation of the desired seven-membered ring 2 (Scheme 1).⁸ Although one has to exercise caution in comparing spectroscopic data from over 40 years ago, the melting point, ¹H NMR, IR, and UV data quoted for the natural product^{1,2} very closely match those of our synthetic sample, leading us to conclude that they are the same compound (Table 1).⁹ Hence we have completed a short synthesis of one of the sneezewood oxepinochromones, ptaeroxylin (2), thereby confirming its structure.

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References and Notes

- (1) Dean, F. M.; Taylor, D. A. H. J. Chem. Soc. C 1966, 114.
- (2) McCabe, P. H.; McCrindle, R.; Murray, R. D. H. J. Chem. Soc. C 1967, 145.
- (3) Dean, F. M.; Parton, B.; Somvichien, N.; Taylor, D. A. H. *Tetrahedron Lett.* **1967**, 3459.
- (4) Brown, R. T.; Blackstock, W. P.; Chapple, C. L. J. Chem. Soc., Perkin Trans. 1 1975, 1776.
- (5) Rehder, K. S.; Kepler, J. A. Synth. Commun. 1996, 26, 4005.
- (6) Synthesis of 6-Allyl-5,7-dihydroxy-2-methyl-4Hchromen-4-one (11) 5-Allyloxy-7-hydroxy-2-methyl-4H-chromen-4-one (8, 0.15 g, 0.65 mmol) was heated in N,N-dimethylaniline (1.5 mL) and Ac₂O (1.5 mL) at 200 °C for 1.5 h in a microwave reactor (300 W). The mixture was poured into HCl (6 M, 40 mL) and then extracted with EtOAc $(3 \times 30 \text{ mL})$. Chromatography (CH₂Cl₂-EtOAc, 95:5) gave a mixture of 6-allyl-5-hydroxy-2-methyl-4-oxo-4H-chromen-7-yl acetate (9, 0.06 g, 34%) and 6-allyl-2-methyl-4-oxo-4Hchromene-5,7-yl diacetate (10, 0.12 g, 58%). To the above mixture (0.13 g) was added a solution of K₂CO₃ (0.15 g) in MeOH (2.5 mL). The solution was heated under reflux for 30 min. The solvent was removed in vacuo and H₂O (10 mL) was added. The solution was then acidified with HCl (6 M) and the resulting solid filtered to give the title compound **11** as a colourless solid (0.09 g, 87%); mp 232–234 °C. HRMS: *m/z* calcd for C₁₃H₁₃O₄: 233.0808; found [MH⁺]: 233.0811. IR (CHCl₃): $v_{max} = 3007$, 1657, 1634, 1587, 1456, 1152 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 13.08 (1 H, s, OH), 10.78 (1 H, s, OH), 6.40 (1 H, s, H-8), 6.15 (1 H, s, H-3), 5.91-5.81 (1 H, m, =CH), 4.96-4.90 (2 H, m, =CH₂), 3.25 (2 H, d, J = 6.0 Hz, CH₂), 2.33 (3 H, s, Me). ¹³C NMR (100 MHz; CDCl₃): $\delta = 183.3$ (C), 167.9 (C), 162.3 (C), 159.1 (C), 156.2 (C), 136.1 (CH), 115.1 (CH₂), 109.3 (C), 108.3 (CH), 103.6 (C), 93.4 (CH), 26.4 (CH₂), 20.3 (Me).

- (7) (a) Stefinovic, M.; Snieckus, V. J. Org. Chem. 1998, 63, 2808. (b) Chattopadhyay, S. K.; Dey, R.; Biswas, S. Synthesis 2005, 403. (c) Rotzoll, S.; Görls, H.; Langer, P. Synthesis 2008, 45.
- (8) Synthesis of 5-Hydroxy-6,9-dihydro-2,8-dimethyl-4H-oxepino[3,2-g]chromen-4-one (Ptaeroxylin, 2)
 A solution of 6-allyl-5-hydroxy-2-methyl-7-[(2-methyl-prop-2-en-1-yl)oxy]-4H-chromen-4-one (12, 0.035 g, 0.135 mmol) in CH₂Cl₂ (65 mL, 0.002M) was treated with a single portion (0.021 g, 20 mol%) of
 bis(tricyclohexylphosphine)benzylidene ruthenium(IV)
 dichloride. The solution was heated under reflux for 18 h. The solvent was removed in vacuo and the brown residue filtered through a short pad of Celite using cyclohexane–EtOAc (9:1) as eluent. The solvent was then removed and the residue purified by chromatography (cyclohexane–EtOAc, 9:1) to give the title compound 2 as a colourless solid (0.020g, 64%); for analytical data, see ref. 9.

(9) **Table 1** Comparison of Data for Natural and Synthetic Ptaeroxylin

	Natural product (ref. ¹)	Natural product (ref. ²)	Synthetic sample
Мр	135–138 °C	133–135 °C	126–128 °C
¹ H NMR	CDCl ₃	CDCl ₃	CDCl ₃
ОН			13.02 (1 H, s)
H-11		6.51 (1 H, s)	6.56 (1 H, s)
H-3		6.01 (1 H, s)	6.06 (1 H, s)
H-7	5.6 (1 H, t)	5.67 (1 H, t, <i>J</i> = 6 Hz)	5.73-5.70 (1 H, br t, <i>J</i> = 4.4 Hz)
H-9	4.4 (2 H, s)	4.53 (2 H, s)	4.53 (2 H, s)
H-6	3.4 (2 H, m)	3.48 (2 H, d, <i>J</i> = 6 Hz)	3.60 (2 H, d, <i>J</i> = 4.4 Hz)
2-Me		2.34 (3 H, s)	2.37 (3 H, s)
8-Me	1.54 (3 H, s)	1.60 (3 H, s)	1.62 (3 H, s)
IR	Nujol (cm ⁻¹)	CHCl ₃ (cm ⁻¹)	$\mathrm{CHCl}_3(\mathrm{cm}^{-1})$
		ca. 2970	3011
	1650	1656	1655
	1610	1627	1626
	1590	1595	1592
UV	EtOH (nm)	EtOH (nm)	MeCN (nm)
	206 (log ε 4.20)	209 (log ε 4.23)	
	230 (log ε 4.17)	232 (log ε 4.27)	232 (log ε 4.2)
		241 (log ε 4.22)	
	255 (log ε 4.15)	255 (log ε 4.24)	254 (log ε 4.1)
		284 (log ε 3.68)	
	320 (log ε 2.60)	321 (log ε 3.59)	322 (log ε 3.5)

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