

Cascarillone: Revised Structure and Total Synthesis

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The structural revision and a full stereochemical assignment for cascarillone are advanced; the proposed structure has been confirmed by a total synthesis.

In the preceding communication¹ we have shown, on the basis of our synthetic work, that the proposed structure (1) for cascarillone,² a constituent of cascarilla oil, needs to be re-examined. Since we had cascarilla oil to hand, we were able to isolate cascarillone and carry out a spectral analysis of it: this has led to a revision of its structure. The new structure (2) for cascarillone has been confirmed by a total synthesis.

Cascarillone, $[\alpha]_D = -9.22^\circ$ ($c = 0.77$, MeOH), $C_{20}H_{30}O_7$ (high resolution m.s.), obtained in 0.16% yield from cascarilla oil by repeated silica gel chromatography, showed a good conformity with reported data² [i.r. and 1H n.m.r. (60 MHz)]. The 400 MHz 1H n.m.r. spectrum in C_6D_6 exhibited well-resolved signals which were assigned by the 1H - 1H COSY technique. The result as well as ^{13}C n.m.r. data (100 MHz, assisted by 1H - ^{13}C COSY) are reproduced in the Table. The clerodane formulation of cascarillone was supported by the presence of two secondary and two tertiary methyl groups as evidenced by 1H n.m.r. spectral results. The ^{13}C n.m.r. chemical shifts of C-19 and C-20 were diagnostic for a *trans* ring junction.³

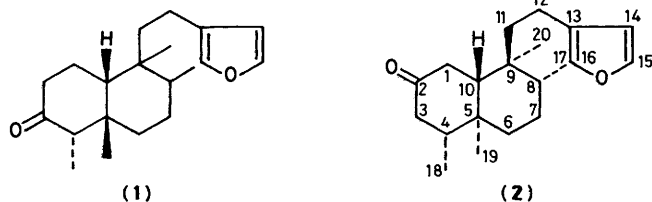
A remarkable finding was the presence of four proton signals due to two methylene groups α to a carbonyl group; this indicated the location of the carbonyl group at the 2 instead of the 3-position. This finding agreed with the observation of long-range coupling between the C-1 and C-3 equatorial protons seen from the 1H - 1H COSY spectrum. The 1,3-diaxial relationship between the 19- and 20-methyl groups was supported by the presence of n.o.e. between their proton resonances and by the observation of long-range couplings between the 19-methyl protons and the 6-axial H, and between the 20-methyl protons and the 10-axial H. The equatorial disposition of the C-18 methyl group was substantiated by a large value for the coupling constant (14.3 Hz) between the 3-axial H and 4-H. The appearance of n.o.e. between the 17- and 20-methyl protons

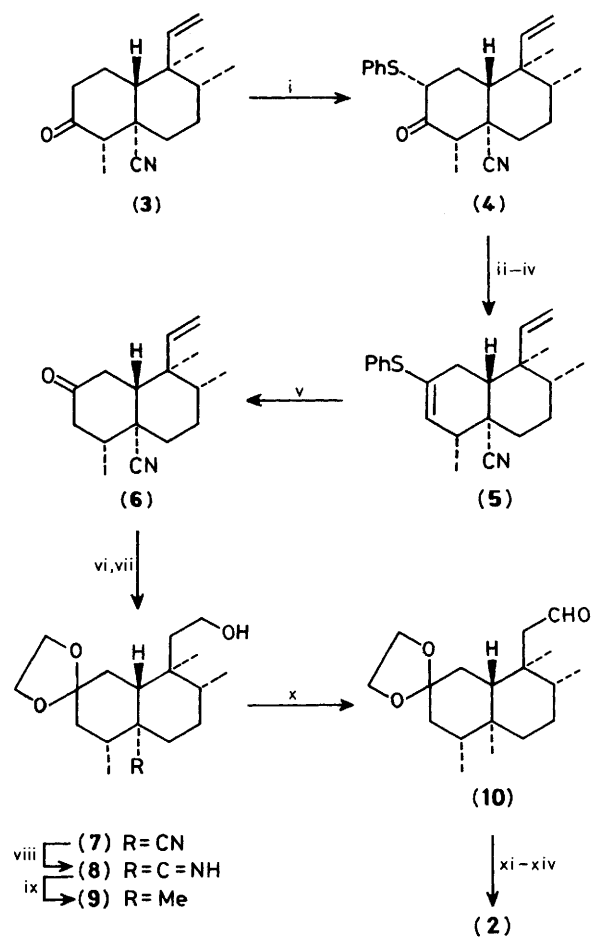
Table. 1H and ^{13}C N.m.r. spectra of cascarillone

Carbon number	^{13}C N.m.r. (100 MHz, C_6D_6)	1H N.m.r. (400 MHz, C_6D_6)
1	39.01 (t)	α 1.97 (1 H, dd, J 14.7, 14.0 Hz) β 2.29 (1 H, ddd, J 14.7, 3.5, 2.0 Hz)
2	208.55 (s)	
3	46.30 (t)	α 1.86 (1 H, dd, J 14.3, 14.3 Hz) β 2.10 (1 H, ddd, J 14.3, 4.3, 2.0 Hz) 1.18 (1 H, m)
4	45.58 (d)	
5	39.25 (s)	
6	38.79 (t)	α 1.47 (1 H, ddd, J 13.2, 3.2, 3.2 Hz) β 0.72 (1 H, ddd, J 13.2, 13.2, 4.6 Hz) γ 1.20 (1 H, m) δ 1.25 (1 H, m) 1.27 (1 H, m)
7	27.35 (t)	
8	36.81 (d)	
9	36.58 (s)	
10	49.17 (d)	1.28 (1 H, dd, J 14.0, 3.5 Hz)
11	38.69 (t)	1.38 (2 H, m)
12	18.22 (t)	2.12 (2 H, m)
13	125.46 (s)	
14	111.23 (d)	6.23 (1 H, m)
15	143.05 (d)	7.32 (1 H, m)
16	138.93 (d)	7.19 (1 H, m)
17	16.14 (q)	0.70 (3 H, d, J 6.4 Hz)
18	14.74 (q)	0.57 (3 H, d, J 6.8 Hz)
19	12.32 (q)	0.61 (3 H, s)
20	17.38 (q)	0.52 (3 H, s)

suggested an equatorial conformation for the 17-methyl group. Thus, the revised structure (2), with full configurational details, is proposed for cascarillone. The appearance of a positive c.d. curve ($\Delta\epsilon_{286} = +0.242$) indicated that, on the basis of the octant rule, cascarillone has the same absolute configuration as neoclerodane,⁴ the carbonyl group possessing an environment similar to that of the 3-oxosteroid.

The newly proposed structure (2) for cascarillone has been confirmed synthetically. The starting point was our crucial intermediate (3) for the synthesis of *trans*-clerodane.^{5,6} The 1,2-carbonyl transposition followed by the conversion of the angular cyano group into a methyl group and side-chain manipulation should lead to the formation of the desired product (2). Trost's method⁷ was adopted for transfer of the 3-oxo group to the 2-position.





Scheme. Reagents and conditions: i, LDA-THF; (PhS)₂-HMPA, -78 °C → room temp. (80%); ii, NaBH₄-EtOH, THF; iii, MsCl-C₅H₅N; iv, Bu^tOK-THF, 0 °C (ii-iv, 72%); v, TiCl₄-AcOH; water (56%); vi, HOCH₂CH₂OH, CSA-C₆H₆ (99%); vii, Me₂CHCMe₂BH₂-THF; H₂O₂-NaOH (82%); viii, Bu^tAlH-Et₂O, 0 °C (97%); ix, NH₂NH₂·H₂O, K₂CO₃-triethylene glycol, 130 to 250 °C, 3 h (55%); x, CrO₃Cl·C₅H₅NH-CH₂Cl₂ (72%); xi, 3-furyl-lithium-Et₂O, -78 °C; xii, Ac₂O, C₅H₅N-CH₂Cl₂ (xi-xii, 76%); xiii, Li-liq. NH₃ (74%); xiv, 2M HCl-Me₂CO (92%).

Sulphenylation of (3) at -78 °C gave an axial product, which isomerized to more stable equatorial phenylthio ketone (4) on warming to room temperature. Compound (4) was converted into the vinyl sulphide (5), which was hydrolysed under Mukaiyama conditions⁸ to give the 2-ketone (6). After protection of the oxo group, the vinyl side chain was transformed to a hydroxyethyl group. The angular cyano group of the alcohol (7) thus obtained was converted into a methyl group by reduction with di-isobutylaluminium hydride (DIBAL) and subsequent reduction using the Wolff-Kishner procedure; the alcohol (9) was derived *via* the imine (8). The 3-furyl group was introduced into the aldehyde (10), derived from (9), by an established sequence of reactions.⁶ Removal of the protecting group afforded the final product, which proved to be identical with natural cascarillone on the basis of spectroscopic comparison (i.e. and ¹H and ¹³C n.m.r.).

In conclusion the structure of cascarillone is now represented by the formula (2).

Acknowledgements

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