Synthesis of *cis*- and *trans*-15,16-Epoxycleroda-13(16),14-dien-3-ones: Incompatibility with the Structure of Cascarillone

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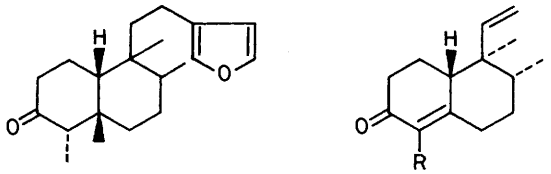
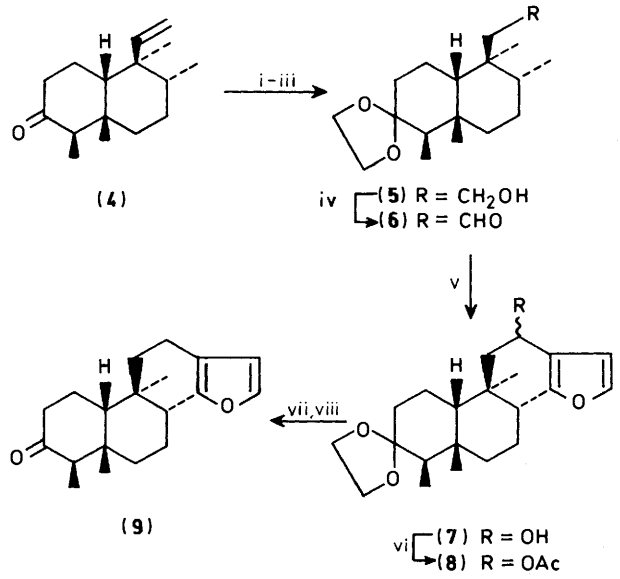
The title *cis*- and *trans*-clerodanes the structures of which correspond to that proposed for cascarillone have been efficiently synthesized from previously reported intermediates; neither proved to be identical with cascarillone.

Cascarillone is a diterpene which was isolated from cascarilla oil and for which the *cis*-clerodane structure (**1**) without stereochemical details was proposed on the basis of a spectroscopic analysis.[1] With the aim of settling the structure of cascarillone including its stereochemistry, we have synthesized both *cis*-(**9**) and *trans*-clerodane (**15**), the structures of which correspond to (**1**). For this purpose, our general method for synthesizing clerodane diterpenoids[2,3] was utilized.



(**1**) (**2**) R = H (**3**) R = Me

The synthesis of the *cis*-clerodane (**9**) started from the *cis*-decalone intermediate (**4**), derivable from either the octalone (**2**) or (**3**).[3] After protection of the oxo group, (**4**) was converted into the aldehyde (**6**) *via* the alcohol (**5**) by a hydroboration-oxidation and oxidation sequence. Introduction of a 3-furyl group into (**6**),[3] followed by deprotection, afforded the target compound (**9**). In its ^{1}H n.m.r. spectrum (**9**) exhibited signals at

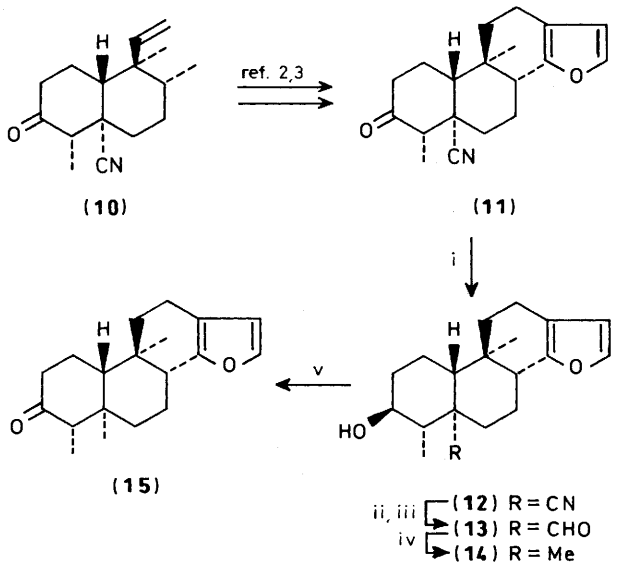


(**4**) (**9**)

Scheme 1. *Reagents and conditions:* i, $HOCH_2CH_2OH$, CSA-C_6H_6; ii, B_2H_6–THF; iii, H_2O_2, NaOH; iv, $(COCl)_2$, Me_2SO–CH_2Cl_2; Et_3N; v, 3-furyl-lithium–THF, −78 °C; vi, Ac_2O–C_5H_5N; vii, Li–liq NH_3; viii, HCl, H_2O–Me_2CO.

δ (60 MHz, CCl_4) 0.80 (s, 3 H), 0.86 (d, 6 H, *J* 7 Hz), 1.08 (s, 3 H), 2.78 (q, 1 H, *J* 7 Hz), 6.10 (m, 1H), 7.07 (m, 1 H), and 7.19 (m, 1 H). These as well as other spectral data (high resolution m.s. and i.r.) were consistent with the expected structure. The reported chemical shifts for four methyl signals were δ(60 MHz, CCl_4) 0.72 (C-20), 0.83 (C-17 and C-18), and 0.91 (C-19).[1] Since a steroidal conformation for (**9**) would be more stable (severe nonbonded interaction between 19-methyl and 11-methylene groups in the non-steroidal form), it is very unlikely that the 18-methyl group of cascarillone has α-axial conformation as implicated in (**1**).[4] The appearance of the 19-methyl signals in cascarillone in a shielded position suggested the possibility of a *trans* ring juncture[5] and the synthesis of *trans* clerodane diterpene (**15**) was undertaken.

The starting point for (**15**) was the *trans*-clerodane derivative (**11**), an intermediate in our synthesis of maingayic acid, which was prepared from (**3**)—(**10**) in eight steps.[2,3] First, the 3-oxo



(**10**) (**11**) (**15**)

Scheme 2. *Reagents and conditions:* i, Li/$C_5H_{11}OH$–NH_3; ii, Bu^i_2AlH–PhMe; iii, AcOH, H_2O–THF; iv, NH_2NH_2·H_2O, KOH–diethylene glycol, 210 °C; v, CrO_3Cl·C_5H_5NH–CH_2Cl_2.

group in (**11**) was converted into a β-equatorial hydroxy group by metal reduction in order to avoid intramolecular interference during the transformation of the angular cyano group. The latter was then transformed into a methyl group *via* an aldehyde group and subsequent Wolff-Kishner reduction. The furyl alcohol (**14**) thus obtained was oxidized to give the final product (**15**), which exhibited signals at δ(100 MHz, $CDCl_3$) 0.75 (s, 3 H), 0.77 (s, 3 H), 0.86 (d, 3 H, *J* 7 Hz), 0.90 (d, 3 H, *J* 6.8 Hz), 6.28 (m, 1 H), 7.23 (m, 1 H), and 7.36 (m, 1 H). Again the spectrum did not accord with that of cascarillone.

Consequently our synthetic results suggest the necessity of reinvestigating the structure of cascarillone.

References

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3 T. Tokoroyama, K. Fujimori, T. Shimizu, Y. Yamagiwa, M. Monden, and H. Iio, *Tetrahedron*, 1988, **44**, 6607.
4 R. McCridle, E. Nakamura, and A. B. Anderson, *J. Chem. Soc., Perkin 1*, 1976, 1590. In this paper the 4-epimer structure corresponding to (**9**) was assigned to a product derived from a natural clerodane diterpene, but it is most probably identical with (**9**) on the basis of the close identity of the ^{1}H n.m.r. spectral data.
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