Stereospecific Synthesis of (−)-Agarospirol and (−)-β-Vetivone

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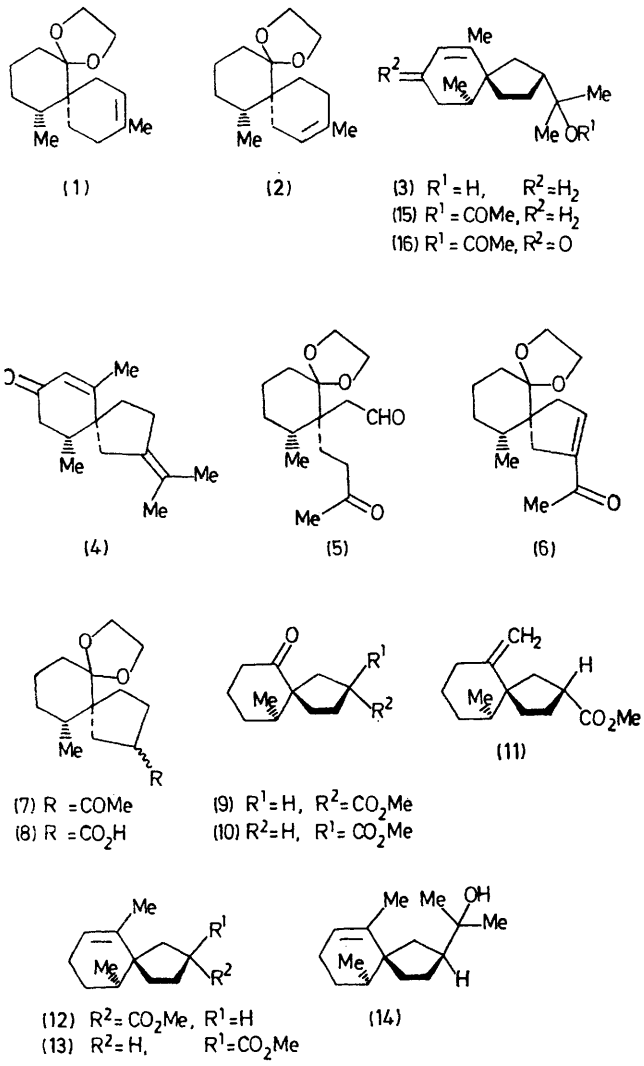
Summary The acetal (**1**) was converted into (−)-agarospirol (**3**) and subsequently into (−)-β-vetivone, thus establishing the absolute stereochemistry of (**3**).

THE utility of acetals (**1**) and (**2**) in the stereospecific synthesis of spiro[4,5]decane sesquiterpenes has been exemplified previously by the synthesis of (−)-α-acorenol and (+)-β-acorenol.[1] We now report the synthesis of (−)-agarospirol (**3**) and (−)-β-vetivone (**4**) from (**1**). (−)-Agarospirol (**3**) was the first recognised[2] member of the spirovetivane[3] family of sesquiterpenes. In recent years there has been a considerable effort directed towards the synthesis[4] of racemic spirovetivane sesquiterpenes, including (±)-agarospirol.[5]

Ozonolysis of (**1**) followed by reductive cleavage (Me_2S) of the intermediate ozonide afforded the keto-aldehyde (**5**) which was cyclised (5% KOH; 80 °C) to the αβ-unsaturated ketone (**6**), $[\alpha]_D^{25}$ − 56·8° (*c* 4·0, $CHCl_3$); ν_{max} 1665 and 1625 cm^{-1}. The alternative mode of intramolecular cyclisation could be eliminated by spectral analysis of (**6**). Hydrogenation (Pd, C) produced the mixture of ketones (**7**) which were converted (Br_2, NaOH) into the corresponding acids (**8**). Esterification (CH_2N_2) followed by acidolytic cleavage (3N HCl, dimethoxyethane) of the acetal grouping gave the keto-esters (**9**), $[\alpha]_D^{25}$ − 27·8° (*c* 8·2, $CHCl_3$) and (**10**), $[\alpha]_D^{25}$ −11·5° (*c* 8·0, $CHCl_3$) which were separable by alumina chromatography. Stereochemical assignment of (**9**) and (**10**) could be derived from equilibration studies (KOMe) which afforded (**9**) : (**10**) in the ratio 7 : 3. Consideration of interactions in these keto-esters favoured the epimer (**9**).

Wittig reaction ($Ph_3P{=}CH_2$) with (**9**) gave the expected product (**11**), $[\alpha]_D^{24}$ − 29·8° (*c* 4·8, $CHCl_3$), which smoothly rearranged (toluene-*p*-sulphonic acid, benzene, reflux) to the endocyclic olefin (**12**), $[\alpha]_D^{20}$ − 18·6° (*C* 7·3, $CHCl_3$). Comparison of the n.m.r. data of (**11**) and (**12**) eliminated the possibility of undesired migration of the spiro-centre adjacent to the developing carbonium ion during the acid treatment. Analogous treatment of (**10**) gave the same products (**11**) and (**12**) owing to epimerisation during the Wittig reaction, for which there is analogy.[6] Thus, the aforementioned separation of (**9**) and (**10**) could be dispensed with for this particular series of reactions. Equilibration studies (KOMe) failed to epimerise (**12**) to any significant extent (<5%). Comparison of steric interactions in (**12**) and (**13**) indicate the former to be more stable, in accord with the results of Yamada.[7] Treatment of (**12**) with MeLi afforded (−)-agarospirol (**3**), $[\alpha]_D^{25}$ − 10° (*c* 6·4, $CHCl_3$), (lit.,[3] −5·9°); δ (CCl_4) 0·91 (>CHMe, d, *J* 7 Hz), 1·16 (>CMe_2 s), 1·65 [=C(Me)−], and 5·18 (HC=, br). Reversal of assignment of the epimeric esters (**12**) and (**13**) would have produced the tertiary alcohol (**14**), enantiomeric with (−)-hinesol, $[\alpha]_D$ − 48°. The physical data of synthetic (−)-(**3**) agreed closely with natural (−)-agarospirol; however in our opinion the natural material was slightly contaminated. Epoxidation of (−)-(**3**) (*m*-chloroperbenzoic acid, $CHCl_3$) gave epoxyagarospirol, m.p. 106—108 °C; $[\alpha]_D^{26}$ + 38·4° (*c* 1·1, $CHCl_3$), (lit.,[3] m.p. 109—110°, $[\alpha]_D^{21}$ + 44·8°). Acetylation of (−)-(**3**) (NaOAc, Ac_2O) gave (**15**), $[\alpha]_D^{19}$ + 1·22° (*c* 9·3, $CHCl_3$), (lit.,[3] $[\alpha]_D$ + 11·3); δ (CCl_4) 0·94 (>CHMe, d, *J* 7 Hz), 1·46 and 1·48 (>CMe_2, 2s), 1·96 ($MeCO_2$, s), and 5·24 (=C(H)−). The complex n.m.r. signal in the *C*-methyl region quoted for the acetate of natural (−)-agarospirol is due to contamination and therefore inadmissible as stereochemical evidence.

Following the route delineated by Marshall,[8] the synthetic (−)-agarospirol acetate (**15**) was oxidised (Na_2CrO_4, $HOAc,Ac_2O$) to the αβ-unsaturated ketone (**16**), $[\alpha]_D^{25}$ + 14·3 (*c* 5·2, $CHCl_3$), and then treated with BF_3,Et_2O, followed by chromatography ($AgNO_3$, alumina), to give



(−)-β-vetivone (**4**), $[\alpha]_D^{26}$ − 23·6° (*c* 1·0, $CHCl_3$), (lit.,[9] $[\alpha]_D$ − 24°). The identity of synthetic and natural β-vetivone was established by g.l.c., and i.r., u.v., n.m.r., and mass spectral comparison and by conversion into the same 2,4-dinitrophenylhydrazone derivative, m.p. 182—184 °C.

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