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REVISED STRUCTURE OF METHYL SCIADOPATE

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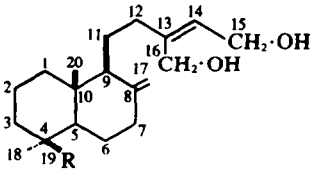
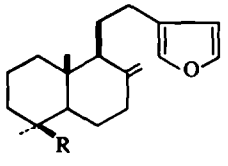
Abstract—In the diterpene ester methyl sciadopate the substituted butenediol side chain is shown to be *trans* and not *cis* as was previously supposed.

The diterpene ester methyl sciadopate was isolated[1] from the heartwood of *Sciadopitys verticillata* Sieb. and Zucc. Its structure was determined as (1) by degradation[2] and conversion[3] to the furanoid acid (3), lambertianic acid, subsequently isolated from natural sources.[4] Because of the relative ease of formation of the furan ring from an intermediate aldehydo-alcohol, and also because methyl sciadopate may be oxidised to a dicarboxylic acid which can be converted to the cyclic anhydride (5), the 13,14 double bond was ascribed the *cis* geometry shown in 1 rather than the alternative *trans* structure (6). In a footnote Henrick and Jefferies[5] suggested that the formation of a dicarboxylic acid rather than a lactone on oxidation of methyl sciadopate was more indicative of the *trans* structure. We show here that methyl sciadopate is indeed the *trans* compound (6) and not 1.

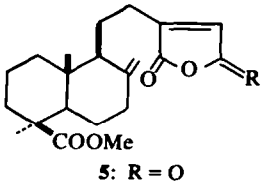
The diterpene lactone pinusolide (8) was isolated from the resins of two *Pinus* species[6] and its structure proved by synthesis from lambertianic acid (3). Recently it has been obtained also from the resin of *Calocedrus decurrens*.[7] Reduction of this lactone should give a product with the *cis* arrangement of the hydroxy-methylene groups and the product triol (2) should be identical with the triol obtained by reduction of methyl sciadopate. In fact two different triols are obtained. Moreover in some reductions of pinusolide using old and hence somewhat deactivated LAH the main product was a dihydroxy-ester closely resembling methyl sciadopate in IR, GLC, and SiO_2 TLC characteristics but capable of separation from it (after acetylation of both) by $AgNO_3/SiO_2$ TLC. This ester, in contrast to methyl sciadopate, did not give a dicarboxylic acid on oxidation with Jones's reagent



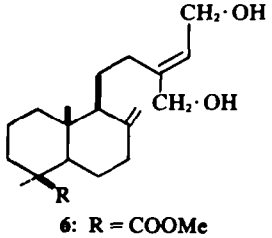
1: R = COOMe
2: R = CH_2·OH



3: R = COOH
4: R = COOMe



5: R = O
8: R = H_2



6: R = COOMe
7: R = CH_2·OH

but a mixture in which the main component was methyl lambertianate (resulting from cyclization and dehydration of an aldehydo-alcohol), together with the lactone pinusolide and a third unidentified component.

Confirmation that the difference between both the pair of triols and the pair of dihydroxy-esters lies in the geometry of the 13,14 double bond is provided by their 220 MHz NMR spectra, the relevant portion of which for the esters is shown in Fig 1. The full spectral data appear in Table 1. For solubility reasons the triols were examined in dimethylsulfoxide. The assignment of the 7 Hz coupling was verified by double resonance experiments. However the splitting of about 2 Hz in the C16 methylene resonance of the pinusolide-derived compounds and in the C15 resonance of methyl sciadopate and its derived triol had no complement in the rest of the spectrum. This suggested that it was the splitting between the central components of a close AB pattern resulting from restricted rotation of the methylene groups concerned. Variable temperature studies were therefore carried out with the dihydroxy-esters on the methylene resonances between 4·0 and 4·2δ, and the typical temperature dependence of an AB pattern arising from restricted rotation was found (Fig 2). This implies that rotation is more restricted for the C16 methylene group of the *cis* compounds and for the C15 methylene group of the *trans*, and examination of space-filling Courtauld models supported this.

Methyl sciadopate then is the *trans* compound

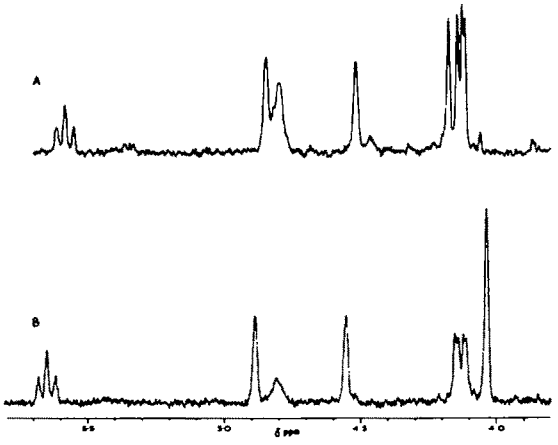


Fig 1. Part of 220 MHz n.m.r. spectrum of (A) the ester (1) and (B) methyl sciadopate (6) (after OH proton exchange with D_2O).

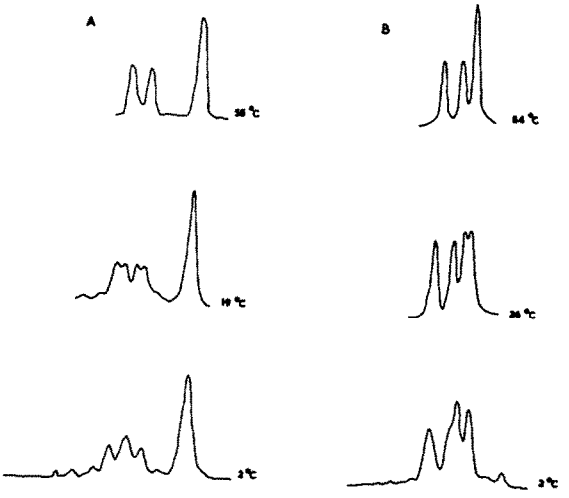


Fig. 2. Temperature dependence of the C15 and C16 methylene protons for (A) methyl sciadopate (6) and (B) the ester (1).

Table 1. NMR data for the dihydroxy-esters and corresponding triols

	Ester (1) in $CDCl_3$ δ	Me Sciadopate (6) in $CDCl_3$ δ		Triol (2) in DMSO-d_6 δ	Triol (7) in DMSO-d_6 δ
C14 H	5·58	5·65	C14 H	5·45	5·23
C17 H_a	4·52	4·55	C17 H_a	4·55	4·54
H_b	4·85	4·89	H_b	4·80	4·79
C15 H_2	4·16	4·13*	C15 H_2	3·90	3·97*
C16 H_2	4·12*	4·04	C16 H_2	3·81*	3·91
C18 H_3	1·18	1·18	C18 H_3	0·86	0·86
C20 H_3	0·51	0·50	C20 H_3	0·56	0·58
Ester Me	3·60	3·60	C19 H_a	3·48 (d)	3·48 (d)
			H_b	3·07 (d)	3·08 (d)
			OH	4·19	4·19
				4·50	4·49
				4·71	4·56
J_{14-15}	7Hz	7 Hz	J_{14-15}	7 Hz	7 Hz

*Mean chemical shift of methylene group. The spectra were recorded on a Varian HR220 spectrometer as 0·15 M solutions with TMS as internal reference, before and after exchange with 1 drop of D_2O. This removed the complication of coupling from the OH protons but caused no other changes.

(6) and its conversion to furanoid and similar compounds must be due to the ready ring closure of *cis* derivatives' leading to rapid displacement of the *cis-trans* equilibrium under isomerising conditions.

EXPERIMENTAL

Rotations are in $CHCl_3$ unless stated. M.ps are in capillary and are uncorrected.

LAH reduction of pinusolide. Pinusolide (300 mg) in ether (20 ml) was treated with an excess of LAH and stirred at r.t. for 2·5 hr. After dropwise addition of Na_2SO_4 aq and drying over Na_2SO_4 the ether solution was filtered off and evaporated. Labd-8(17), Z13-dien-15,16,19-triol (2) was obtained by crystallization from ether, aqueous MeOH, and acetonitrile, from each of which it had m.p. 135–137°. $[\alpha]_D$ + 23° (*c*, 0·9 in EtOH). Raldugin *et al.*[6] report m.p. 92–93°, $[\alpha]_D$ + 25°, and the compound is presumably polymorphic. (Found: C, 74·46; H, 10·61. Calc. for $C_{20}H_{34}O_3$: C, 74·48; H, 10·62%).

In several earlier experiments in which old stock of LAH was used little triol was produced under the above conditions but a mixture with a main component of the same R_f as methyl sciadopate on SiO_2 TLC. Isolated by column chromatography on silica gel, 1 was obtained as an oil, $[\alpha]_D$ + 54° (*c*, 2·9). (Methyl sciadopate remeasured had $[\alpha]_D$ + 28°, *c*, 2·5). After acetylation these two esters were clearly separated by $AgNO_3/SiO_2$ TLC, developing with benzene (R_f s 0·49 and 0·6 respectively) and neither was found to be contaminated with the other.

Oxidation of methyl labda - 8(17),Z13 - dien - 15,16 - diol - 19 - oate. The ester 1 (30 mg) in acetone (1 ml) was treated with a slight excess of 8N CrO_3/H_2SO_4. After standing for 2 min at r.t. water was added and the product isolated with ether. GLC (on OV-1) showed it to consist of a mixture of methyl lambertianate with lesser amounts of pinusolide and a third component of slightly higher R_f. The IR spectrum was almost superimposable on that of methyl lambertianate with the addition of a band at 1762 cm^{-1} (lactone).

LAH reduction of methyl sciadopate via the bistetrahydropyranyl ether. Methyl sciadopate (350 mg) was dissolved in benzene (30 ml) and part of the solvent boiled off to remove water. To the cooled soln were added dihydropyran (0·5 ml) and a few small crystals of *p*-toluenesulphonic acid. After 15 min formation of the bis-THP derivative was complete (TLC), and 5 drops of pyridine were added and the benzene removed *in vacuo*. The residue, dissolved in dry ether, was stirred with an excess of LAH for 3 hr at r.t. After the usual work-up the ether solution was evaporated and the residual oil dissolved in MeOH (15 ml) and treated with dilute HCl (15 drops, 3N). After 1 hr water and a little $NaHCO_3$ were added. The product separated as an oil which solidified on standing. Crystallised twice from di-isopropyl ether and then from acetonitrile this yielded 7 m.p. 106–108°, depressed to 97–102° on admixture with the triol described above. $[\alpha]_D$ − 1° (*c*, 1·3 in EtOH). (Found: C, 74·66; H, 10·69. $C_{20}H_{34}O_3$ requires: C, 74·48; H, 10·62%). The same triol was obtained by direct reduction of methyl sciadopate but in lower yield, after longer reaction time, and only after chromatography.

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