# Stereoselective Synthesis of (—)-Acorenone and (—)-Acorenone B; the Absolute Configuration of Natural (—)-Acorenone

By Mario Pesaro* and Jean-Pierre Bachmann
(*Givaudan Research Company Ltd.*, 8600 *Dübendorf, Switzerland*)

*Summary* The spiroenone (**7**), stereoselectively prepared from (+)-*p*-menth-1-ene (**3**) in four steps, was converted by two different reaction sequences into the natural sesquiterpenes (—)-acorenone (**1**) and (—)-acorenone B (**2**), respectively, thus establishing the absolute configuration of (**1**).

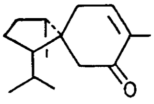
Much attention has been directed recently towards the development of new syntheses of the acoranes, a group of sesquiterpenes with a spiro[4.5]decane skeleton. We describe here a new route to (—)-acorenone[1](**1**) and to (—)-acorenone B[2,3] (**2**), two members of the acorane family.

Ozonolysis of (+)-*p*-menth-1-ene[4] (**3**) ($[\alpha]_D^{22}$ + 109°, *c* 1·1, $CHCl_3$) in methanol, followed by reductive cleavage, gave a ketoaldehyde, which was cyclised[5] (piperidine, AcOH, $CHCl_3$ reflux) to the $\alpha\beta$-unsaturated aldehyde (**4**) (60% overall yield). The C=C double bond of (**4**) was hydrogenated (Pd–$CaCO_3$, $K_2CO_3$, MeOH, $H_2O$), as expected, on the side of the cyclopentane ring opposite to the isopropyl group; after spontaneous epimerization, the *trans,trans*-cyclopentane derivative (**5**) was obtained 95% pure †(80% yield). The structure of (**5**) was confirmed by its identity with the hydrogenation product ($PtO_2$, AcOEt) of *trans,-trans*-photocitral[6] (**6**).

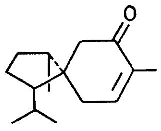
Robinson annelation of the aldehyde (**5**) with methyl vinyl ketone (MVK) was expected to be stereoselective, since electrophilic attack of MVK on the enolate anion of (**5**) should occur from the less hindered, upper face of the molecule. In fact, the spirocyclic enone (**7**) was obtained (KOH, dioxan, 70 °C, 10 min) in *ca.* 20% yield‡ [calculated on 50% recovery of (**5**)] with a purity of > 92%;† the structure of (**7**) was secured by comparison of its i.r. and $^1H$ n.m.r. spectra with those of the racemic compound.[3b] Reaction of (**7**) with MeLi provided the epimeric alcohols (**8**) in quantitative yield.

Owing to the shielding effect of the isopropyl and methyl groups on C-6 and to the directing influence of the allylic hydroxy-function,[7] the hydroboration of (**8**) should be regioselective and afford a mixture of 1,2-diols. However these were not detected in the reaction product of (**8**) with excess of borane ($BH_3$–tetrahydrofuran, 20 °C, 3 h; $H_2O_2$, NaOH); a mixture of the monoalcohols (**9**) was obtained instead.§ This was oxidized (Jones) to the C-8 epimeric cyclohexanones (**10**) (ratio 75:25), separable by layer chromatography [50% yield from (**8**)].

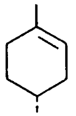
Introduction of the missing double bond was effected in 65% yield by bromination of the ketones (**10**) ($Br_2$, $CH_2Cl_2$, 0 °C) and dehydrobromination ($Li_2CO_3$, boiling dimethylformamide, 2 h) to give (—)-acorenone (**1**) ($[\alpha]_D^{22}$ — 29°, *c* 0·4, $CHCl_3$), identical by spectral and g.l.c.† comparison with natural (—)-acorenone ($[\alpha]_D^{22}$ — 34·9°, *c* 0·55, $CHCl_3$).



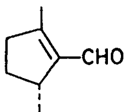
(1)



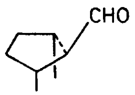
(2)

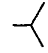


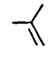
(3)

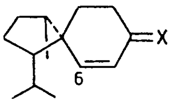


(4)

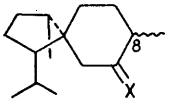


(5) R = 

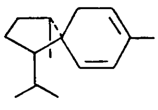
(6) R = 



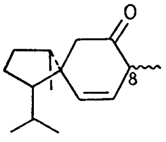
(7) X = O
(8) X = Me,OH
(11) X = $CH_2$



(9) X = H,OH
(10) X = O

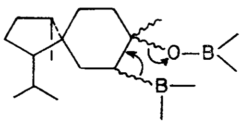


(12)



(13)

Acorenone B could also be synthesized from the spiroenone (**7**) as follows. While treatment of the alcohols (**8**) at room temperature with a saturated solution of toluene-*p*-sulphonic acid (TsOH) in benzene (35 min) led chiefly to



(a)

---

† As determined on a 45 m Ucon 50 HB glass capillary g.l.c. column.

‡ The optimization of this step is under study.

§ Presumably, the intermediate 1,2-borane borate (**a**) undergoes elimination followed by rehydroboration. *Cf. e.g.* the hydroboration of *trans*-verbenol (Y. Chretien-Bessière, *Bull. Soc. chim. France*, 1964, 2182).

the exocyclic diene (**11**), the main reaction product of (**8**) with a saturated solution of TsOH in $CH_2Cl_2$ was the desired homocyclic diene (**12**). By epoxidation ($MeCO_3H$, $CH_2Cl_2$, 20 °C, 4 h) the more highly substituted double bond of this diene was attacked preferentially, as expected (*cf.* ref. 8). The resulting unsaturated epoxide is very unstable and rearranged[9] in the presence of traces of TsOH to a 1 : 1 mixture of the C-8 epimeric ketones (**13**) [50—60% overall yield, by single-vessel sequential addition of TsOH and of $MeCO_3H$ to a $CH_2Cl_2$ solution of (**8**)]. The ketones (**13**) were easily isomerized (TsOH, toluene, reflux; 65% yield) to (−)-acorenone B (**2**) ($[\alpha]_D^{22}$ − 16·7°, *c* 0·3, $CHCl_3$) having identical spectra and g.l.c. behaviour† as natural acorenone B ($[\alpha]_D^{22}$ − 17·3, *c* 0·45, $CHCl_3$).

The conversion of (+)-*p*-menth-1-ene (**3**) into (−)-acorenone establishes the hitherto unknown absolute configuration of natural acorenone, as shown in (**1**).¶

We thank Professor W. Oppolzer for the spectra of the racemic enone (**7**), Dr. M. Rohr, Givaudan, for a sample of natural (−)-acorenone, isolated from sweet flag oil,[1] and Professor D. Arigoni for a sample of authentic (−)-acorenone B originating from Professor L. Zalkow.

(*Received, 9th November* 1977; *Com.* 1166.)

¶ *Added in proof:* An alternative synthesis of (−)-acorenone has been reported after submission of this communication (*cf.* G. L. Lange, W. J. Orrom, and D. J. Wallace, *Tetrahedron Letters*, 1977, 4479).

[1] J. Vrkoč, V. Herout, and F. Šorm, *Coll. Czech. Chem. Comm.*, 1961, **26**, 3183.

[2] R. J. McClure, K. S. Schorno, J. A. Bertrand, and L. H. Zalkow, *Chem. Comm.*, 1968, **1135**; R. J. McClure jr., Dissertation, Georgia Inst. Technol., U.S.A., 1968; (*Chem. Abs.*, 1970, **72**, 133 005p)

[3] For previous syntheses of these acoranes *cf.* (a) H. Wolf and M. Kolleck, *Tetrahedron Letters*, 1975, 451; H. Wolf, M. Kolleck and W. Rascher, *Chem. Ber.*, 1976, **109**, 2805; W. Rascher and H. Wolf, *Tetrahedron*, 1977, **33**, 575; (b) W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Letters*, 1975, 3411; *Helv. Chim. Acta*, in the press; (c) B. M. Trost, K. Hiroi, and N. Holy, *J. Amer. Chem. Soc.*, 1975, **97**, 5873; J. F. Ruppert, M. A. Avery, and J. D. White, *J.C.S. Chem. Comm.*, 1976, 978; P. Naegeli, unpublished results.

[4] W. F. Newhall, *J. Org. Chem.*, 1958, **23**, 1274.

[5] J. Wolinsky M. R. Slabaugh, and T. Gibson, *J. Org. Chem.*, 1964, **29**, 3740.

[6] R. Kaiser and D. Lamparsky, *Helv. Chim. Acta*, 1976, **59**, 1797.

[7] H. C. Brown and R. M. Gallivan jr., *J. Amer. Chem. Soc.*, 1968, **90**, 2906.

[8] G. Eletti-Bianchi, F. Centini, and L. Re, *J. Org. Chem.*, 1976, **41**, 1648.

[9] P. de Mayo, 'Molecular Rearrangements,' Interscience, New York, vol. 2, 1964, p. 1035.