

be of importance for the synthesis of certain natural products, as exemplified by the following communication [17].

REFERENCES

- [1] H. M. R. Hoffmann, *Angew. Chem.* **81**, 597 (1969); *ibid.*, Int. Ed. **8**, 556 (1969).
- [2] T. R. Kelly, *Tetrahedron Letters* **1973**, 437.
- [3] J. A. Berson, R. G. Wall & H. D. Perlmutter, *J. Amer. chem. Soc.* **88**, 187 (1966).
- [4] M. G. Ettlinger & J. E. Hodgkins, *J. Amer. chem. Soc.* **77**, 1831 (1955).
- [5] S. F. Reed, Jr., *J. org. Chemistry* **30**, 3258 (1965).
- [6] R. T. Arnold, O. C. Elmer & R. M. Dodson, *J. Amer. chem. Soc.* **72**, 4359 (1950).
- [7] A. Sh. Sharifkanov & Sh. S. Shkmedova, *Chem. Abstr.* **61**, 13275b (1964).
- [8] T. J. Petcher, *Sandoz Ltd.*, unpublished work.
- [9] R. B. Woodward & R. Hoffmann, *Angew. Chem.* **81**, 797 (1969); *ibid.*, Int. Ed. **8**, 781 (1969).
- [10] H. Strickler, G. Ohloff & E. Kováts, *Helv.* **50**, 759 (1967).
- [11] W. D. Huntsman, P. C. Lang, N. L. Madison & D. A. Uhrick, *J. org. Chemistry* **27**, 1983 (1962).
- [12] M. Furdik & E. Sidova, *Chem. Abstr.* **63**, 13095a (1965).
- [13] H.-P. Weber, *Sandoz Ltd.*, unpublished work.
- [14] K. Taguchi & F. H. Westheimer, *J. org. Chemistry* **36**, 1570 (1971).
- [15] N. M. Yoon & H. C. Brown, *J. Amer. chem. Soc.* **90**, 2927 (1968).
- [16] W. D. Huntsman & R. P. Hall, *J. org. Chemistry* **27**, 1988 (1962).
- [17] W. Oppolzer, *Helv.* **56**, 1812 (1973).

184. The Total Synthesis of (\pm) β -Acorenol¹⁾

Preliminary Communication²⁾

by Wolfgang Oppolzer

Pharmaceutical Chemical Research Laboratories, SANDOZ Ltd., CH-4002 Basle

(4. VI. 73)

Zusammenfassung. Die erste Totalsynthese des Spiro-sesquiterpenes β -Acorenol, ausgehend vom bekannten Cyclohex-1-enylessigsäureäthylester, wird beschrieben. Die Schlüsselstufe **2** \rightarrow **3** + **4** verläuft über eine thermische intramolekulare En-Reaktion.

β -Acorenol, a spirocyclic sesquiterpene, isolated from the wood of *Juniperus rigida* has been shown by chemical and spectroscopic evidence [1] to have structure **8**³⁾. This communication describes the first total synthesis of racemic β -acorenol **8** and β -acoradiene **9** [1], the key step of which utilizes recent observations on the stereocontrolled synthesis of five-membered ring systems [4]⁴⁾.

The known ethyl cyclohex-1-ene-1-acetate **1** [5] was alkylated [6] with 1-bromo-3-butene to give the oily diene **2**⁵⁾ (b.p. 91–92°/0.3 Torr; IR.: 1730 cm⁻¹). The latter cyclized in toluene (19% solution in a sealed ampoule) at 280° with 3 days⁷⁾ to a 1:1 mixture (65% yield) of the esters **3**⁵⁾ and **4**⁵⁾, which were separated by

¹⁾ Presented in part at the International Symposium: «Neue Methoden der Organischen Synthese», Basle, Switzerland, May 11, 1973.

²⁾ The content of this communication will appear as part of a full paper in this journal.

³⁾ For isolation and structure of the closely related alaskenes see [2].

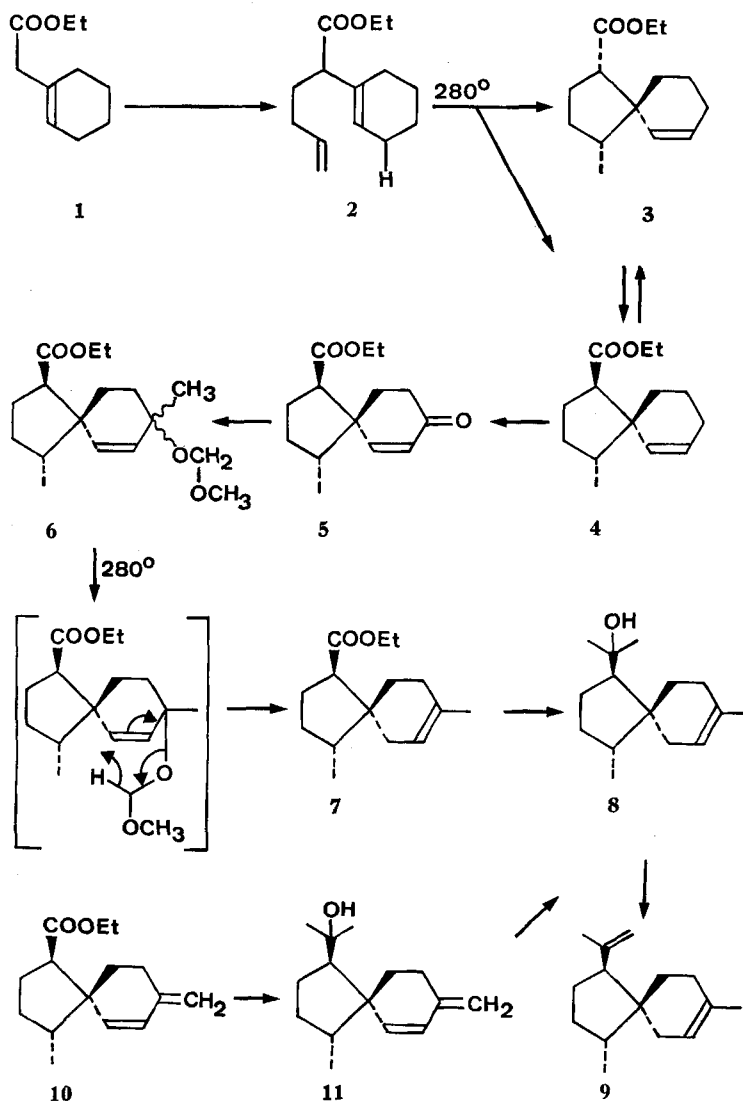
⁴⁾ For previous approaches to acorane-type compounds see [3] [8].

⁵⁾ The IR- and NMR-spectra were in agreement with the assigned structure.

⁶⁾ Satisfactory elemental analytical data were obtained for this substance.

⁷⁾ 1-(5-methyl-4-hexenyl)-cyclohexene is reported not to cyclize at temperatures up to 500° [7].

chromatography on silica gel. The esters **3** and **4** could be cleanly interconverted upon exposure to 1N ethanolic sodium ethoxide at 70° to give a 3:2-equilibrium mixture. In the NMR.-spectrum (CDCl_3) the CHCH_3 -doublet of the more polar ester **3** appears at $\delta = 0.89$ ppm and is shifted to $\delta = 0.96$ ppm on hydrogenation of the olefinic double bond, thus indicating the *cis*-relationship of the double bond and the methyl group. The methylene quartets due to $\text{COOCH}_2\text{CH}_3$ occur at $\delta = 4.07$ ppm in the ester **3** and at $\delta = 4.10$ ppm in the ester **4**⁸⁾.



⁸⁾ This assignment is based on the assumption that the olefinic double bond exerts a weak shielding effect upon the *cis*-carboxy group in the ester **3**. In fact, on hydrogenation of the double bond the corresponding CH_2 -quartet shifts to $\delta = 4.11$ ppm.

By allylic oxidation [8] the isomer **4** was converted in 64% yield to the unsaturated ketone **5**⁹⁾ (UV.(MeOH) λ_{\max} : 230 nm ($\log \epsilon = 4.05$), 317 nm ($\log \epsilon = 1.48$)). Reaction of the ketone **5** with 1.0 mol of methyllithium in ether at -70° and subsequent treatment of the reaction mixture with an excess of chlorodimethyl ether in ether/hexamethylphosphoramide 1:1 for 1 h. at 25° ⁹⁾ afforded the acetal **6**⁵⁾ as a mixture of epimers. The crude acetal **6** on thermolysis in heptane at 270° (sealed ampoule) within two h. underwent a retro-ene-reaction¹⁰⁾ to give in 30% yield the ester **7**⁵⁾¹¹⁾. This compound was also obtained from the isomer **3**, using the same reaction sequence, followed by epimerization of the reaction mixture with sodium ethylate. Finally, exposure of the ester **7** to an excess of methyllithium in ether at 25° for 40 min, followed by aqueous work-up, led quantitatively to (\pm) β -acorenol **8**, with IR.-(KBr) and NMR.-(CCl₄) spectra identical to those of the natural β -acorenol. Further evidence for the assigned structure was provided by dehydration [1] of the synthetic β -acorenol **8** to (\pm) β -acoradiene **9**, identified by comparison of its IR.-(KBr) and NMR.-(CCl₄) spectra with those of natural β -acoradiene.

An alternative, more efficient synthesis of β -acorenol **8** from the crude acetal **6** involved thermolysis of the latter at 195° for 16 h. This gave in 84% yield a 3:1 mixture of the diene **10**⁵⁾ (UV.(MeOH) λ_{\max} 223 nm ($\log \epsilon \sim 4.3$)) and the monoene **7**. Treatment of this mixture with methyllithium at 25° , followed by reduction of the diene **11**⁵⁾, using excess sodium in ammonia/ethanol [10], gave (\pm) β -acorenol **8** in 60% overall yield from the acetal **6**.

IR.- and NMR.-spectra of various spiro-sesquiterpenes, provided by Professors *B. Tomita* and *N. H. Anderson*, are gratefully acknowledged.

REFERENCES

- [1] *B. Tomita, T. Isono & Y. Hirose, Tetrahedron Letters 1970, 1371.*
- [2] *N. H. Andersen & D. D. Syrdal, Tetrahedron Letters 1972, 899.*
- [3] *E. J. Corey, N. N. Girotra & C. T. Mathew, J. Amer. chem. Soc. 91, 1557 (1969); T. G. Crandall & R. G. Lawton, ibid. 91, 2127 (1969); J. A. Marshall & S. F. Brady, Tetrahedron Letters 1969, 1387; J. M. Conia, J. P. Drouet & J. Gore, Tetrahedron 27, 2481 (1971); P. Naegeli & R. Kaiser, Tetrahedron Letters 1972, 2013.*
- [4] *W. Oppolzer, Helv. 56, 1807 (1973).*
- [5] *J. W. Cook & A. Dansi, J. chem. Soc. 1935, 500.*
- [6] *M. W. Rathke & D. Sullivan, Tetrahedron Letters 1972, 4249.*
- [7] *W. D. Huntsman, P. C. Lang, N. L. Madison & D. A. Uhrick, J. org. Chemistry 27, 1983 (1962).*
- [8] *J. A. Marshall & P. C. Johnson, J. org. Chemistry 35, 192 (1970).*
- [9] *F. Mutterer, J. M. Morgen, J. M. Biedermann, J. P. Fleury & F. Weiss, Tetrahedron 26, 477 (1970).*
- [10] *A. J. Birch & H. Smith, Quarterly Reviews 12, 17 (1958).*

⁹⁾ This reaction has to be performed under rigorous exclusion of moisture and removal of the excess of chlorodimethylether by distillation before aqueous work-up.

¹⁰⁾ The thermal retro-ene-reactions of various allyl acetals have been described by *Fleury et al.* [9]. The specific use of the methoxymethylene group has been studied independently by *Q. Branca*, ETH, Zurich (private communication by Prof. *D. Arigoni*).

¹¹⁾ Satisfactory high-resolution mass-spectra were obtained, using a CEC-21-110 B spectrometer.