Stereospecific Synthesis of (—)-α-Acorenol and (+)-β-Acorenol

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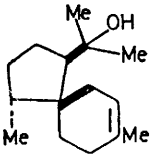
Summary Acetals (**9**) and (**10**) were synthesised from (+)-(3*R*)-methylcyclohexanone and the utility of these intermediates in sesquiterpene synthesis is illustrated by their conversion into α-acorenol (**1**) and β-acorenol (**3**).

SESQUITERPENES having spiro[5,4,0]decane structures have been invoked[1] as intermediates in the biosynthesis of the cedrane and tricyclovetivane classes of sesquiterpenes. In order to test these proposals *in vivo* and *in vitro* it was decided to develop a stereospecific route to α-acorenol (**1**)[2] and β-acorenol[3] (**3**) which was capable of extension into the enantiomeric series. The acid-catalysed transformation of α-acorenol (**1**) into (—)-α-cedrene (**2**) has already been accomplished[2,5] and proves the stereochemistry of the former.



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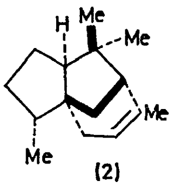

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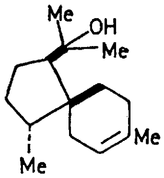
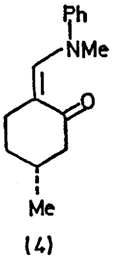


(3)

(+)-(3*R*)-Methylcyclohexanone was protected at C-6 by formylation† and subsequent formation of the *N*-methylanilino-derivative (**4**), m.p. 33°; $[\alpha]_D$ −80° (*c* 2·0, $CHCl_3$); λ_{max} (EtOH) 247 nm (ε 21,800). Cyanoethylation using Triton B in Bu^tOH followed by basic hydrolysis then esterification gave the keto-diester (**5**), $[\alpha]_D$ −22° (*c* 2·0, $CHCl_3$) in 22% yield from (+)-(3*R*)-methylcyclohexanone. Dieckmann cyclisation of (**5**) using sodium sand in refluxing benzene gave the β-keto-ester (**6**), λ_{max} (EtOH) 255 nm (ε 5200), λ_{max} ($EtOH–OH^-$) 285 nm (ε 8800), which was demethoxycarbonylated by LiI,H_2O in refluxing dimethylformamide to the diketone (**7**), $[\alpha]_D$ − 25° (*c* 2·0, $CHCl_3$). A selective Wittig reaction using molar equivalents of (**7**) and $Ph_3P{=}CH_2$ in Bu^tOH afforded the ketone (**8**), $[\alpha]_D$ −22° (*c* 2·0, $CHCl_3$) in 55% yield from (**5**). Reaction of (**8**) with ethylene glycol in refluxing benzene using toluene-*p*-sulphonic acid as catalyst gave a mixture (3:2) of acetals in 97% yield. Chromatography on $AgNO_3$–alumina gave the major component (**9**), $[\alpha]_D$ −48·6° (*c* 2·5, $CHCl_3$); $[\Delta\epsilon]_{210}$ (MeOH) −1·63; δ (CCl_4) 0·99 (>CH·CH_3 d, *J* 7 Hz) and (**10**), m.p. 49—50°; $[\alpha]_D$ −13·5° (*c* 2·0, $CHCl_3$); $[\Delta\epsilon]_{210}$ (MeOH) +1·00; δ (CCl_4) 0·95 (>CH·CH_3, d, *J* 7 Hz). Consideration of both the c.d. and n.m.r. data for the diastereoisomers (**9**) and (**10**) suggested the assignment given. The stereochemistry at the spiro-centre was subsequently verified by transformation of (**9**) into α-acorenol (**1**) and (—)-α-cedrene (**2**).



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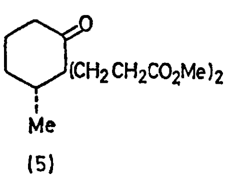

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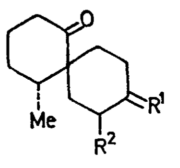

(6) $R^1 = O; R^2 = CO_2Me$
(7) $R^1 = O; R^2 = H$
(8) $R^1 = CH_2; R^2 = H$

Deacetalisation of (**9**) with toluene-*p*-sulphonic acid in refluxing acetone gave the parent ketone (**11**), δ (CCl_4) 0·90 (=CH·CH_3, d, *J* 9 Hz) without migration of the endocyclic

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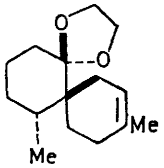
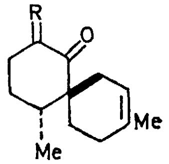
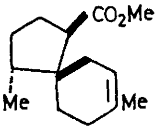
† The regiospecificity of formylation was checked by oxidation to (+)-β-methyladipic acid, m.p. 85°; $[\alpha]_D$ +9·4°. All new compounds gave satisfactory elemental analyses and spectral data.

double bond which would effectively destroy the chirality at the spiro-centre. Oximation of (**11**) with trityl-lithium–pentyl nitrite in dimethoxyethane gave the α-oximino-ketone (**12**) (65%), m.p. 127—128°, $[\alpha]_D$ $-102°$ (*c* 2·5, $CHCl_3$); λ_{max} (EtOH) 235 nm (ε 8960), λ_{max} ($EtOH–OH^-$) 292 nm (ε 13,890) which was treated with chloramine to give the α-diazo-ketone (**13**), ν_{max} 2100 and 1630 cm^{-1}; λ_{max} (EtOH) 295 nm. Photolysis‡ of the crude α-diazo-ketone (**13**) in a solution of $NaHCO_3$ in aqueous tetrahydrofuran followed by esterification of the acidic product afforded the ester (**14**), $[\alpha]_D$ $-104°$ (*c* 4·5, $CHCl_3$); δ (CCl_4) 0·88 ($>CH·CH_3$, d, *J* 7 Hz) and 3·48 (OMe, s), in 55% yield from (**12**). Attempted epimerisation of (**14**) with $KOBu^t$ was unsuccessful and indicates a *trans*-relationship of the *C*-methyl group and the methoxycarbonyl function in the cyclopentane unit. This stereochemical assignment is in agreement with the earlier studies by Corey[4] and Lawton,[5] indeed, the latter synthesised (**14**) and (**18**) as a mixture of racemates. Treatment of (**14**) with MeLi produced (−)-α-acorenol (**1**), $[\alpha]_D$ $-16·5°$ (*c* 1·6, $CHCl_3$) in 95% yield. The synthetic and natural material were identical spectroscopically but the optical rotation differed (lit.,[2] $[\alpha]_D$ $-36·1°$). The integrity of the synthetic material was confirmed by formic acid cyclisation to (−)-α-cedrene, $[\alpha]_D$ $-86°$ (*c* 1·2, $CHCl_3$) (lit., $[\alpha]_D$ $-91°$) in 96% yield.

The above synthetic route, starting from acetal (**10**), produced the intermediates (**15**), (**16**), (**17**), and (**18**). Comparison of the n.m.r. data of (**14**) and (**18**) [δ (CCl_4) 0·84 ($>CH·CH_3$ d, *J* 7 Hz) and 3·57 (O*Me*, s)] indicates greater shielding of the *O*-methyl group by the double bond in (**14**) thus corroborating the earlier assignment of the stereochemistry at the spiro-centre. Reaction of (**18**) with MeLi gave (+)-β-acorenol (**3**), $[\alpha]_D$ +2·7° (*c* 1·7, $CHCl_3$), (lit.,[3] $[\alpha]_D$ ± 0°) identical spectroscopically with the natural product. Formic acid treatment of (+)-β-acorenol (**3**) gave a complex mixture of hydrocarbons which contained < 5% α-cedrene (**2**).


(9)


(11) R = H_2
(12) R = NOH
(13) R = N_2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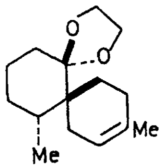
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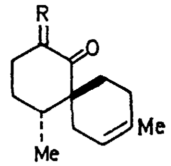
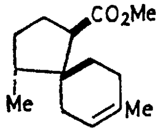

(15) R = H_2
(16) R = NOH
(17) R = N_2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‡ 450 W low-pressure Hanovia lamp (water cooled, quartz filter).

[1] W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev.*, 1967, **21**, 331; N. H. Anderson and D. D. Syrdal, *Tetrahedron Letters*, 1970, 2277; D. F. MacSweeney, R. Ramage, and A. Sattar, *ibid.*, p. 557; N. H. Anderson and M. S. Falcone, *Chem. and Ind.*, 1971, 62.
[2] B. Tomita and Y. Hirose, *Tetrahedron Letters*, 1970, 143.
[3] B. Tomita, T. Isono, and Y. Hirose, *Tetrahedron Letters*, 1970, 1371.
[4] E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Amer. Chem. Soc.*, 1969, **91**, 1557.
[5] T. G. Crandall and R. G. Lawton, *J. Amer. Chem. Soc.*, 1969, **91**, 2127.