Synthesis and Absolute Configuration of the Terpenes (—)-Campherenone, (+)-Epicampherenone, (—)-β-Santalene, and (+)-Epi-β-santalene

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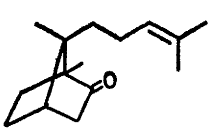
Summary Biosynthetic considerations prompted synthetic studies which have resulted in reassignment of absolute configuration to (—)-campherenone and have established the absolute configuration of (+)-epicampherenone, (—)-β-santalene, and (+)-epi-β-santalene.

We have put forward an alternative biosynthetic route to certain structurally-related mono- and sesqui-terpenes[1] and have suggested that a biosynthetic relationship should exist between appropriate enantiomers of campherenone (**1**), campherenol (**2**), β-santalene (**3**), and α-santalene (**4**). The co-occurrence[2] of (—)-campherenone, (—)-campherenol, β-santalene, and (+)-α-santalene in *Cinnamomum camphora*-Siebold (Lauraceae) supports this suggestion. However, an apparent anomaly exists in this group of sesquiterpenes since (—)-campherenone (**5**) and (—)-campherenol (**6**) have been assigned absolute configurations which preclude a biosynthetic relationship with (+)-α-santalene (**4**). In addition, (+)-α-santalene, (—)-β-santalene, and (+)-epi-β-santalene (**7**) also co-occur in *Santalum album* and it is reasonable to presume that these compounds are biosynthetically related to each other. Since the absolute configuration of (+)-α-santalene (**4**) is known[3] we decided to obtain independent evidence for the absolute configuration of (—)-campherenone, (—)-β-santalene, and (+)-epi-β-santalene.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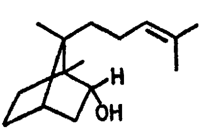
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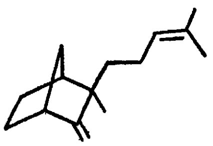
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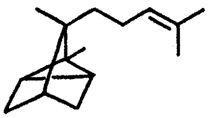
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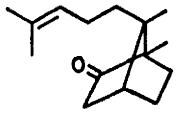
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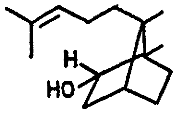
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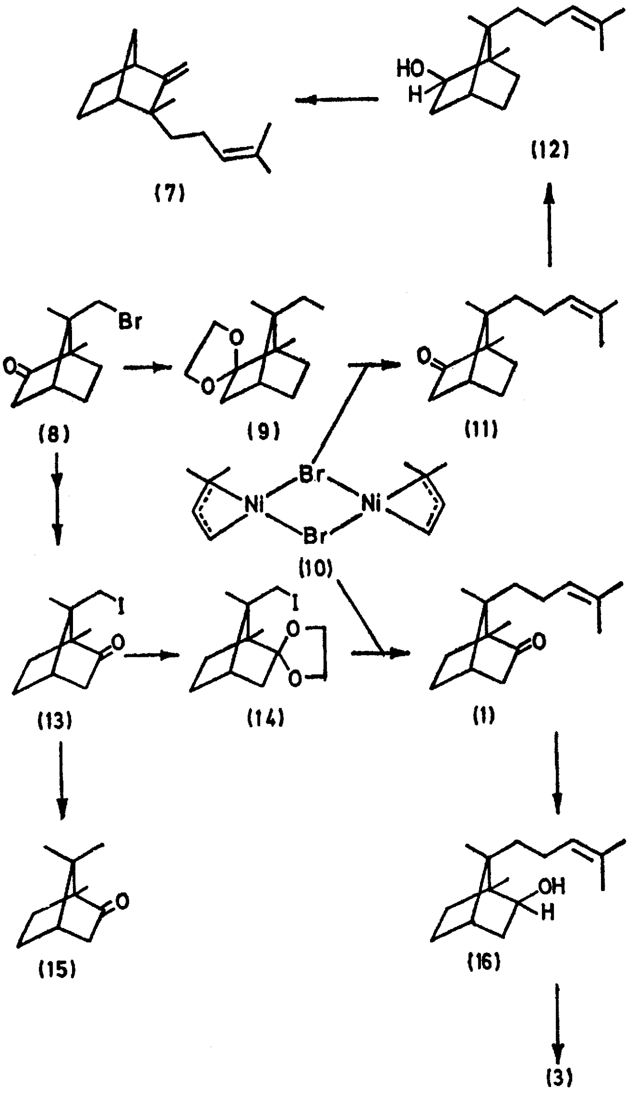

Our previous synthetic studies[4] provided racemic forms of the title compounds and therefore alternative synthetic routes from (+)-camphor were developed. The ethylene acetal of (+)-9-bromocamphor (**8**)[5] was converted into (−)-9-iodocamphor ethylene acetal (**9**) by heating with NaI in Me_2SO under reflux. Subsequent treatment of (**9**) with the π-allylnickel complex[6] (**10**) derived from 1-bromo-3-methylbut-2-ene, followed by hydrolysis, provided (+)-epicampherenone (**11**),† $[\alpha]_D$ +84·4° (*c* 4·88, $CHCl_3$) in 45% yield. Reduction of (**11**) with $LiAlH(OMe)_3$ gave (+)-isoepicampherenol (12),† $[\alpha]_D^{30}$ +7·0° (*c* 5·10, $CHCl_3$) which, on heating with toluene-*p*-sulphonyl chloride in pyridine,[4a] was converted in 80% yield into (+)-epi-β-santalene (**7**),† $[\alpha]_D^{29}$ +26·9° (*c* 2·6, $CHCl_3$). [A sample of natural epi-β-santalene isolated from sandalwood oil had $[\alpha]_D^{22}$ +23·3° (*c* 4·12, $CHCl_3$)].

Treatment of the ethylene acetal (**14**) of (−)-8-iodocamphor (**13**)[7] with the π-allylnickel complex (**10**), followed by hydrolysis, gave (−)-campherenone (**1**)† {$[\alpha]^{30}$ −36° (*c* 10·06, $CHCl_3$); $[\alpha]_D^{27}$ −27° (*c* 10·03, MeOH); $[\Delta\epsilon]_{295}^{MeOH}$ −0·95°, $[\Delta\epsilon]_{210}^{MeOH}$ +0·36; $[\theta]_{295}^{MeOH}$ −3120; $[\theta]_{210}^{MeOH}$ +1195} in *ca.* 80% yield. The c.d. data quoted above differ from those previously reported[2] for the natural compound {$[\alpha]_D$ −33° (*c* 10·00, $CHCl_3$); $[\theta]_{298}^{MeOH}$ +600} and, at present, we have no explanation for this discrepancy. Reduction of (**1**) with $LiAlH(OMe)_3$ afforded (+)-isocampherenol (**16**),† $[\alpha]_D^{32}$ +25° (*c* 2·6, $CHCl_3$), lit.[2] $[\alpha]_D$ +15·3° (*c* 2·6, $CHCl_3$), which, on heating with toluene-*p*-sulphonyl chloride in pyridine,[4] was converted (in 70% yield) into (**3**),† $[\alpha]_D^{28}$ −112° (*c* 5·01, $CHCl_3$). The specific rotation of a sample of natural β-santalene isolated from sandalwood oil was $[\alpha]_D^{28}$ −102° (*c* 5·01, $CHCl_3$).

These absolute configurational assignments support the postulated biosynthetic relationship between (−)-campherenone, (−)-campherenol, (−)-β-santalene,‡ and (+)-α-santalene in *Cinnamomum camphora* and between (+)-α-santalene, (−)-β-santalene, and (+)-epi-β-santalene in *Santalum album*. The biosynthesis of α- and β-santalene could involve dehydration of a precursor such as isocampherenol while epi-β-santalene (and presumably β-santalene) could arise from cleavage of the cyclopropane ring in α-santalene.

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† Spectral (n.m.r., i.r.) and g.l.c. characteristics identical to those previously recorded for the racemic compound, *cf.* ref. 4a.

‡ We have assumed that the β-santalene which occurs in *Cinnamomum camphora* is laevorotatory.

[1] An account of these suggestions was given at the CIC–ACS Conference, Toronto 1970; see also T. Money, *Progr. Org. Chem.*, 1973, **8**, 29; *J.C.S. Perkin I*, in the press.

[2] H. Hikino, N. Suzuki, and T. Takemoto, *Chem. and Pharm. Bull.* (*Japan*), 1971, **19**, 87, and references therein.

[3] E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, 1957, **79**, 5773; G. Ourisson, *Chem. and Ind.*, 1953, 918.

[4] G. L. Hodgson, D. F. MacSweeney, and T. Money, (a) *Chem. Comm.*, 1971, 766; (b) *Tetrahedron Letters*, 1972, 3683.

[5] Derived from commercially available (+)-3-bromocamphor: *cf.* E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, 1957, **79**, 5773.

[6] E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, 1967, **89**, 2755; *cf.* K. Sato, S. Inoue, S. Ota, and Y. Fujita, *J. Org. Chem.*, 1972, **37**, 462.

[7] Derived from (+)-9-bromocamphor by a combination of known reaction sequences (E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, 1959, **81**, 6305; O. R. Rodig and R. J. Sysko, *J. Org. Chem.*, 1971, **36**, 2324; A. M. T. Finch and W. R. Vaughan, *J. Amer. Chem. Soc.*, 1969, **91**, 1416.) The configurational homogeneity of (**13**) was confirmed by hydrogenolysis (Pd–C–H_2; 40 lb in^{-2}) to (−)-camphor (**15**), $[\alpha]_D^{32}$ −44·8° (*c* 1·82, EtOH) [lit.[8] $[\alpha]_D^{16}$ −43·6° (EtOH)].

[8] ‘Handbook of Chemistry and Physics,’ 49th edn., ed. R. C. Weast, The Chemical Rubber Co., Cleveland, Ohio, 1968–1969.