

Absolute Configuration and Synthesis of the Liverwort Sesquiterpene Alcohol Tamariscol

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The relative configuration of the liverwort sesquiterpene alcohol (–)-tamariscol (**1**) has been confirmed by total synthesis and its absolute configuration has been established from the CD spectrum of the hydrindanone degraded from (–)-(**1**).

Tamariscol [(–)-(**1**)] is a sesquiterpene alcohol isolated from the liverwort *Frullania tamarisci*, the structure of which was determined by extensive high resolution NMR techniques.¹ Its stereochemistry however was established only on the basis of ¹H NMR coupling constant, measurements made in the presence of shift reagents, and by comparing its ¹³C NMR spectral data with those of known compounds. Since (–)-(**1**) has a pleasant smell and may have industrial importance,² we became interested both in its absolute configuration, not previously established, as well as its total synthesis in order to confirm its relative stereochemistry. We now report the results

for the relative and absolute configuration of (–)-(**1**) by both its total synthesis and its degradation.

Tamariscol [(–)-(**1**)][†] [α]_D –20.5° (c 3.46 in CHCl₃),[‡] isolated from the liverwort *F. tamarisci* collected in Taiwan, was oxidised by *m*-chloroperbenzoic acid to give a mixture of diastereoisomers (**2**), which was treated with lithium aluminium hydride in dry benzene§ under reflux. The resulting diol (**3**) was cleaved by sodium metaperiodate (MeOH–H₂O) to yield hydrindanone (+)-(**4**), [α]_D +10.1° (c 0.76 in CHCl₃).||

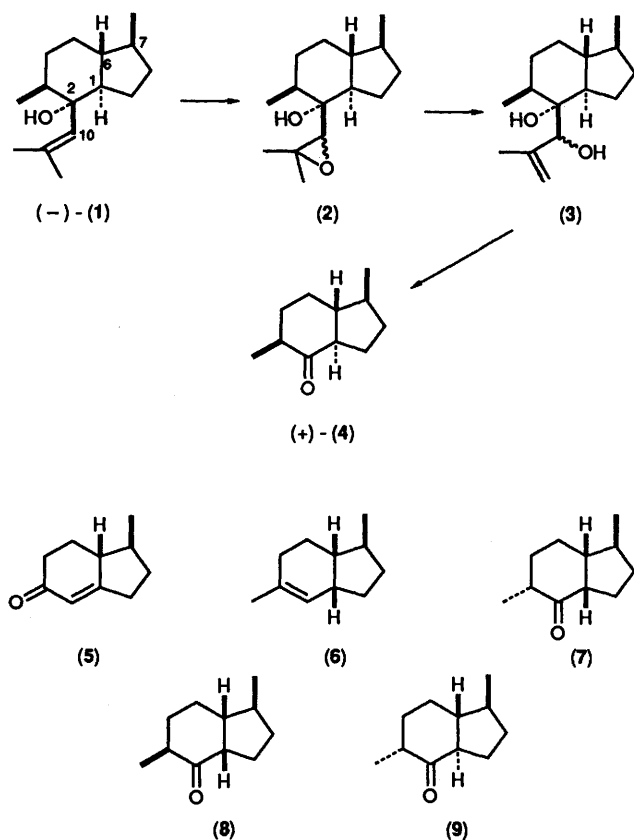
The known enone (±)-(**5**)³ was subjected to a Wittig reaction

[†] (–)-(**1**): [α]_D –20.5° (c 3.46 in CHCl₃); ν_{\max} (film) 3450 cm⁻¹; δ_{H} (CHCl₃) 0.89 (3 H, d, *J* 6.6 Hz), 0.94 (3 H, d, *J* 6.6 Hz), 1.76 (3 H, s), 1.90 (3 H, s), and 5.08 (1 H, s); δ_{H} (C₆D₆) 0.92 (3 H, d, *J* 6.6 Hz), 0.99 (3 H, d, *J* 6.6 Hz), 1.72 (3 H, d, *J* 1.5 Hz), 1.99 (3 H, d, *J* 1.2 Hz), and 5.13 (1 H, m); δ_{C} (CDCl₃) 14.9 (CH₃), 18.8 (CH₃), 19.9 (CH₃), 23.7 (CH₂), 28.1 (CH₃), 30.0 (CH₂), 31.7 (CH₂), 32.8 (CH₂), 39.5 (CH), 45.4 (CH), 49.9 (CH), 58.3 (CH), 79.0 (C), 121.5 (CH), and 136.3 (C); δ_{C} (C₆D₆) 15.3 (CH₃), 19.0 (CH₃), 20.1 (CH₃), 24.2 (CH₂), 28.3 (CH₃), 30.5 (CH₂), 32.3 (CH₂), 33.2 (CH₂), 40.0 (CH), 46.2 (CH), 50.3 (CH), 59.2 (CH), 79.1 (C), 121.9 (CH), and 136.5 (C); *m/z* 222 (*M*⁺), 204, 189, and 165 (base).

[‡] Although the original paper¹ reports the specific rotation [α]_D +19.7° (CHCl₃), both our samples from Taiwan, [α]_D –20.5° (CHCl₃), –22.6° (MeOH), and from France –17.4° (MeOH) show (–). Dr. J. D. Connolly, Glasgow University, is now checking his results. We thank him for pertinent information.

§ The reaction in ether gave complete recovery of starting material. We thank Dr. L. J. Harrison for helpful discussions.

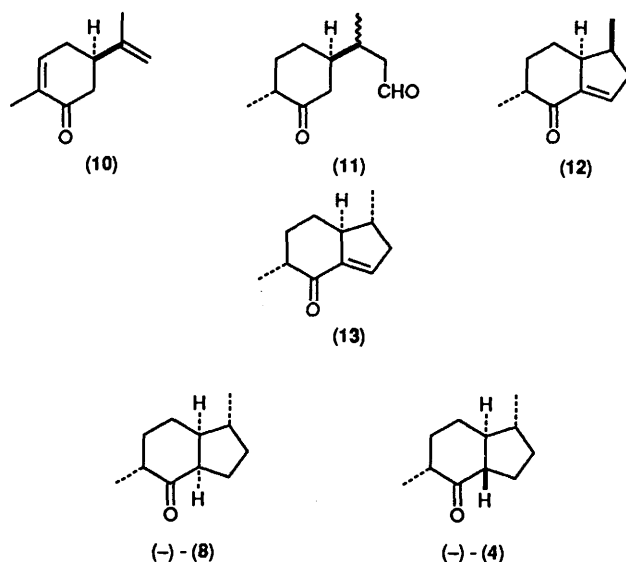
|| (+)-(**4**): [α]_D +10.1° (c 0.76 in CHCl₃); ν_{\max} (film) 1710 cm⁻¹; δ_{H} (C₆D₆) 0.79 (3 H, d, *J* 6.6 Hz), 1.08 (3 H, d, *J* 6.6 Hz), and 2.09 (1 H, m); δ_{C} (C₆D₆) 14.6 (CH₃), 18.1 (CH₃), 21.5 (CH₂), 29.4 (CH₂), 32.0 (CH₂), 37.3 (CH₂), 40.6 (CH), 44.7 (CH), 56.8 (CH), 58.0 (CH), and 209.5 (C); *m/z* 166 (*M*⁺), 137, and 109 (base); [θ]_{294nm} –4.384 (c 0.047 in CHCl₃).



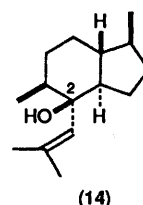
followed by Birch reduction to afford a *cis* hydrindene (\pm)-(6). Hydroboration-oxidation of (\pm)-(6) and PDC oxidation gave a *cis* hydrindanone (\pm)-(7), whose spectral data were identical with those reported previously.³ Since MM2 calculations predicted the stability of the four hydrindanones (4) > (7) > (8) > (9), (\pm)-(7) was subjected to the isomerization conditions ($K_2CO_3/MeOH$). HPLC separation gave mainly (\pm)-(7) and (\pm)-(4) as well as a small amount of (\pm)-(8) and (\pm)-(9). The spectral data of these two hydrindanones (\pm)-(8) and (\pm)-(9) were also identical with those reported previously.³ Thus (\pm)-(4) was the missing *trans* hydrindanone and it was identical with that derived from natural tamariscol, confirming the relative stereochemistry of (-)-(1) except for the C-2 position.

(-)-Carvone (10) was reduced by NaHTe in EtOH to give *trans* dihydrocarvone,⁴ which was reduced ($NaBH_4$) and protected as a THP ether. Ozonolysis (CH_2Cl_2/PPh_3), Wittig reaction [$NaH/(MeO)_2POCH_2CO_2Me$], hydrogenation ($PtO_2/AcOEt$), reduction ($LiAlH_4$), deprotection ($PPTS/MeOH$), and Swern oxidation afforded a keto aldehyde (11), which was treated with $PhCO_2H/Et_3N$ under reflux to give a mixture of enones (12) and (13). Separation of this mixture was carried out by HPLC. Each enone was assigned from the chemical shift of the secondary-methyl group; final confirmation came from hydrogenation ($Pd-C/hexane$) of (13) to yield the optically active *cis*-fused hydrindanone (-)-(8), $[\alpha]_D -58.0^\circ$ (*c* 1.3 in MeOH). Thus (-)-(8) was treated with $K_2CO_3/MeOH$ as before followed by HPLC separation to afford (-)-(4), $[\alpha]_D -14.3^\circ$ (*c* 0.25 in $CHCl_3$), $[\theta]_{294nm} +3638$ ($CHCl_3$).

The CD spectrum of (+)-(4) derived from (-)-(1) showed a (-)-Cotton effect, $[\theta]_{294nm} -4389$ ($CHCl_3$). These results show that the ketone (-)-(4) derived from (-)-carvone is enantiomeric to that derived from (-)-(1), indicating the



absolute configuration as shown in the displayed formula which was predicted from the back octant of (+)-(4). Because of the limited availability of (-)-(4), the racemic ketone (\pm)-(4) was alkylated with 2-methylprop-1-enyl-lithium to afford (\pm)-(1)



and its C-2 isomer (\pm)-(14)* in the ratio of 1:50. Both isomers at the C-2 position were separated by column chromatography over silica gel and by HPLC to afford synthetic (\pm)-(1). The spectral data for (\pm)-(1) were identical with those of the authentic (-)-(1). Since the attack from the axial face (β -side) was severely sterically hindered, even though in the presence of MAD or MAT,⁵ attack from the equatorial face predominated. A Grignard reagent did not give a good result.

These results show that tamariscol [(-)-(1)] has the relative and absolute configuration as depicted in the displayed formula.

* (\pm)-(14): $\nu_{max}(film)$ 3550 cm^{-1} ; $\delta_H(C_6D_6)$ 0.96 (3 H, d, *J* 6.6 Hz), 0.98 (3 H, d, *J* 6.6 Hz), 1.67 (3 H, s), 1.91 (3 H, s), and 4.91 (1 H, s); $\delta_C(C_6D_6)$ 15.7, 18.9, 19.1, 23.5, 28.0, 30.1, 30.6, 31.9, 39.8, 42.1, 46.4, 56.3, 76.5, 130.9, and 132.1; *m/z* 222 (M^+), 191, 177, and 165 (base).

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