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A NEW NON-HEAD-TO-TAIL MONOTERPENE FROM ARTEMESIA TRIDENTATA. (2R, 3R)-1,2-EPOXY-2,5-DIMETHYL-3-VINYL-4-HEXENE. (OXIDO SANTOLINA TRIENE).

Thomas A. Noble and W. W. Epstein*
Department of Chemistry, University of Utah, Salt Lake City, Utah 84112

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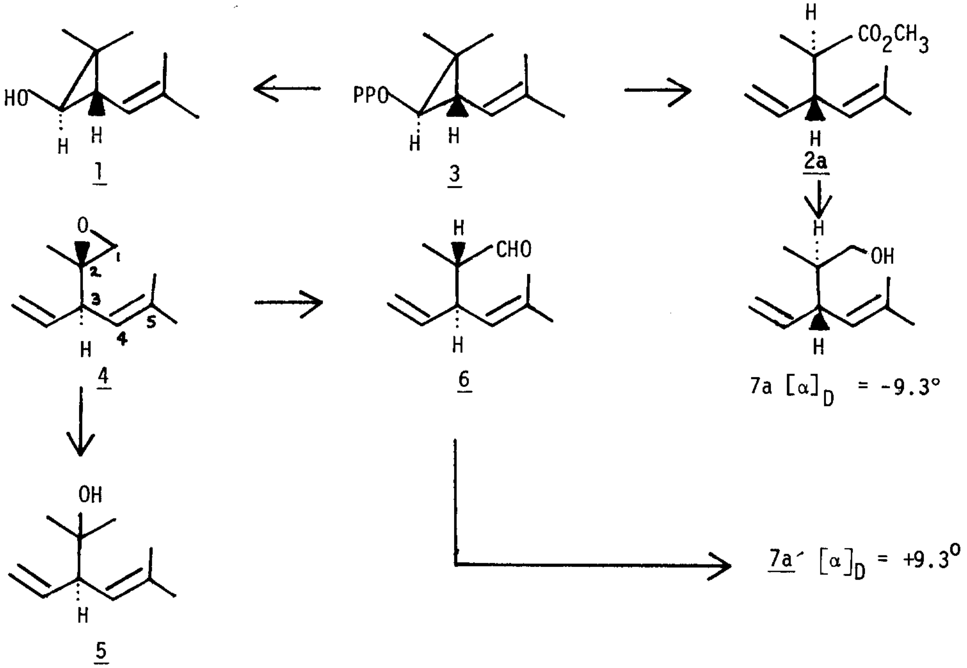
Biosynthesis of non-head-to-tail monoterpenes as a model for biosynthesis of the biologically important triterpene squalene continues to be of interest.[1,2,3] The occurrence and in particular the absolute stereochemistry of two new recently reported monoterpenes, 1[4] and 2a,[5] isolated from sagebrushes Artemesia ludoviciana and A. tridentata respectively lent support to the hypothesis that (1R, 3R) chrysanthemyl pryophosphate 3, a C_{10} analogue of pre-squalene pyrophosphate, is the biogenetic precursor to the non-head-to-tail monoterpenes with chrysanthemyl and santolinyl skeletons (e.g. 1 & 2a). We wish to report the isolation and structure including total stereochemistry of 4 from A. tridentata which bears directly on this hypothesis.



Essential oils, isolated by pentane extraction of leaves and stems of A. tridentata collected near Lehi, Utah,[6] were fractionated by vacuum distillation and analyzed by gas chromatography/mass spectroscopy. A previously unreported compound with mass ion m/e = 152, $C_{10}H_{16}O$,[7] was separated by preparative glc from the fraction which had b.p. 65-70° at 18-19 mm Hg.[8]

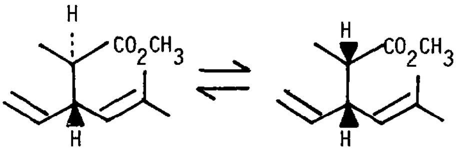
The colorless oil was optically active, $[\alpha]_D = -37.2^{\circ}$ (.80, $CHCl_3$) and possessed the following spectral properties: IR (neat 1630, 1450, 1380, 1065, 1000, 915, 860, 806 cm^{-1}, NMR ($CDCl_3$) δ 1.3 (s) 3H, 1.65 (s) 3H, 1.75 (s) 3H, 2.57 (ABd) 2H, 3.0 (m) 1H, 5.0 (m) 3H, 5.72 (m) 1H, Mass, m/e (rel inten %), 152 (1.3), 137 (10.6), 95 (100), 79 (31.5), 67 (53.7), 55 (39.8), 41 (63.3).

Since the IR spectrum lacks absorption due to hydroxyl or carbonyl groups, an ether linkage is required. The AB system at δ 2.57 is indicative of a terminal epoxide $\text{R-}\underset{|}{\text{C}}\overset{\text{O}}{\text{—}}\text{CH}_2$, and the three hydrogen singlet at δ 1.3 consistent with a methyl group attached to the epoxy function. The data also suggest the presence of vinyl ($-CH=CH_2$) and isobutenyl ($-CH=C(CH_3)_2$) groups, leaving only the methine (CH) at δ 3.0 which must be bonded to the above three groups suggesting 4 as the gross structure.

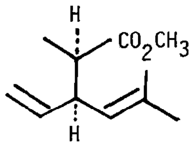
Structure 4 was confirmed by chemical means utilizing two degradative pathways. $LiAlH_4$ reduction of 4 yielded the known compound, santolina alcohol 5, identical in spectra (NMR, IR) and glc retention time to an authentic sample. Secondly, treatment of 4, with $BF_3 \cdot Et_2O$ in pentane at -70° yielded aldehyde 6 which was reduced with $LiAlH_4$ to alcohol 7 identical (except in specific rotation) to 7 produced by $LiAlH_4$ reduction of ester 2a.

These sequences were also used to determine the absolute stereochemistry at the two chiral centers. Compound 5 produced by $LiAlH_4$ reduction of 4 possessed an optical rotation $[\alpha]_D = -18.5^{\circ}$ (.96, ethanol) equal but opposite in sign to (3S)-2 isolated from Ormenis multicaulis,[9] establishing a (3R) absolute stereochemistry for 4.[10]

Elucidation of the absolute configuration of C_2 of 4 was approached by experiments which related the C_2 and C_3 centers of esters 2a and 2b to the C_2 and C_3 centers of 4 via the common alcohol derivative, 7 and by examination of the stereochemistry of the epoxide to aldehyde rearrangement 4 → 6.



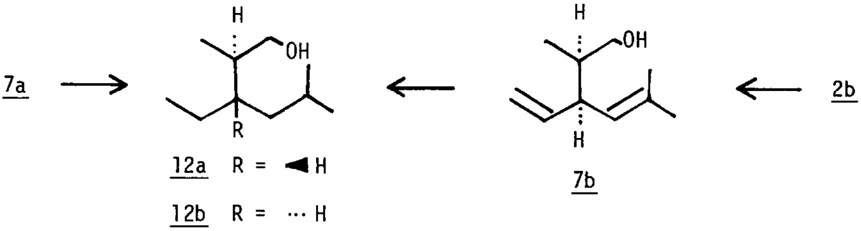
2a



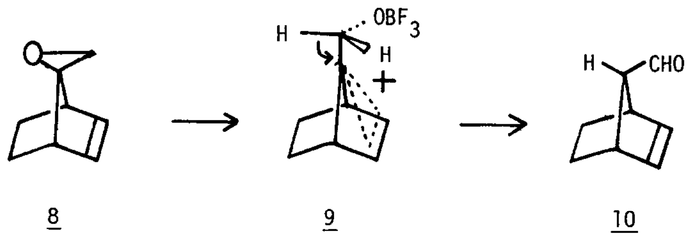
2b

From essential oils of Lehi and Price A. tridentata was isolated 2b, a diastereomer of 2a, nearly identical in IR and NMR spectra but easily separable by preparative glc. (Both diastereomers have now been synthesized as racemic pairs).[11] The absolute configuration of this naturally occurring diastereomer was established as follows. Pure (2R, 3S)-2 was allowed to equilibrate in refluxing sodium methoxide/methanol solution giving a mixture of (2S, 3S)-2 and starting material. The (2S, 3S) ester isolated from the reaction mixture by preparative glc was found to have IR and NMR spectra and glc retention time identical to 2b, with equal but opposite sign of rotation establishing 2b to be the (2R, 3R) enantiomer.

Esters 2a and 2b were reduced with $LiAlH_4$ to alcohols 7a, $[\alpha]_D$ = -9.3° ($CHCl_3$, .70) and 7b, $[\alpha]_D$ = -10.6° ($CHCl_3$, .70) (mixtures of these diastereomeric alcohols showed almost no tendency to separate on Carbowax 20M or OV glc columns). Since epoxide 4 has the (3R) configuration, it can lead only to the (3R) alcohols 7b (2R, 3R) or 7a′ (2S, 3R) the enantiomer of the known 7a. $BF_3\cdot$ etherate catalyzed rearrangement of 4 to 6 followed by $LiAlH_4$ reduction gave a product with $[\alpha]_D$ = +5.3° which is calculated to be a mixture 80% 7a′ ($[\alpha]_D$ = +9.3°) and 20% 7b ($[\alpha]_D$ = -10.6°).



These data demonstrate that the sequence 4 → 6 is stereoselective. To discover the absolute configuration of C_2 of 4 it is then necessary to determine whether the rearrangement 4 → 6 proceeded primarily with inversion or retention of configuration at C_2. Bly and Bly[12] reported that the homoallylic norbornenyl epoxide 8 was rearranged in $BF_3\cdot Et_2O$/benzene to aldehyde 10 with complete retention of configuration explained by the π-electrons assisting in carbon/oxygen heterolysis with a "backside push" yielding intermediate ion 9. Non-classically stabilized 9 allows C_7-C_8 bond rotation followed by hydride migration from the "anti-side" to give retention of configuration.



Since compound 4 is doubly homoallylic, and if the π systems analogous to 10 participate in the reaction 4 → 6 causing overall retention of configuration, then prior reduction of the double bonds should decrease or reverse the stereoselectivity of the reaction.

In order to test this hypothesis compound 4 was catalytically hydrogenated (Pt) to 11, rearranged to the aldehyde, and reduced with LiAlH$_4$ to 12 $[\alpha]_D = +7.8^0$ (CHCl$_3$, .81) calculated to be a 51/49 mixture of (2S, 3R) -12a′, $[\alpha]_D = -10.8^0$ (CHCl$_3$, .79), and (2R, 3R) -12b, $[\alpha]_D = +27.7^0$ (CHCl$_3$, .52). Optically active standards 12a and 12b were prepared by catalytic reduction of 7a and 7b respectively.

It can thus be seen that participation of the double bonds is required for the stereoselectivity of the step 4 → 6 and therefore we concluded that this rearrangement proceeds mainly with retention of configuration. Since the product alcohol 7 was found to have predominantly the (2S) configuration, 4 must have the (2R) absolute configuration (while configuration is retained, the designation changes due to a change in the priorities of the substituents). Further evidence supporting this conclusion is offered at the end of the following article.

The R absolute stereochemistry at C$_3$ is contrary to that expected if (1R, 3R)-chrysanthemyl pyrophosphate 3 is the biogenetic precursor to the santolinyl skeleton. If a chrysanthemyl pyrophosphate is precursor to non-head-to-tail monoterpenes, it must occur in both (3R), and (3S) forms. The isolation of optically pure (1R, 3R) chrysanthemol, 1, from *A. ludoviciana* suggests that it should be the *cis* diastereomer (1R, 3S).

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References and Footnotes

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5. J. Shaw, W. W. Epstein, and T. Noble, *J. Chem. Soc.*, *Chem. Commun.*, 15, 590 (1975).
6. A voucher specimen is available at the University of Utah Herbarium.
7. Satisfactory chemical analysis was obtained for all new compounds.
8. Compound 4 was found to be unstable towards acids and hot metal surfaces, i.e., steam distillation in metal containers, glc in unsilanized metal tubing and high glc collector or injection port temperatures caused decomposition and/or rearrangement to 6.
9. C. D. Poulter, R. J. Goodfellow and W. W. Epstein, *Tetrahedron Lett.* 71 (1972).
10. *Artemesiatridentata* collected near Price, Utah and processed identically to the Lehi sage consistantly produced 4 as a mixture of diastereomers barely detectable by analytical glc (in a ratio of about 2:1) and not found to be separable by preparative glc. LiAlH$_4$ reduction of this mixture produced 5 (>95% glc yield) with an optical rotation $[\alpha]_D = -3.8^0$; (ethanol, .70) corresponding to a mixture which is 60% (3R).
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