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SYNTHESIS OF 2,6-DIMETHYL-6-(8-METHYL-4-METHYLENE-7-NONENYL)-2-CYCLOHEXEN-1-YLMETHANOLS. A COMMENT ON THE STRUCTURE OF MAGYDAR-2,10(20),13-TRIEN-17-OL, THE DITERPENE OF *MAGYDARIS PANACIFOLIA*

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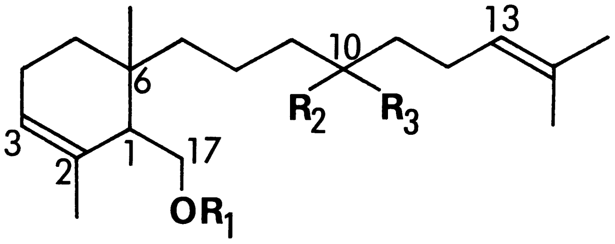
α-Santonin was stereoselectively converted to a pair of diastereomers of 2,6-dimethyl-6-(8-methyl-4-methylene-7-nonenyl)-2-cyclohexen-1-ylmethanols (Ia and Ib). Both spectral data of Ia and Ib were found to be different from those reported for magydar-2,10(20),13-trien-17-ol isolated from *Magydaris panacifolia* (Vahl) Lange. This indicates that the structure of the natural diterpene must be revised.

Magydar-2,10(20),13-trien-17-ol (I), its acetate (II), and magydar-2,13-diene-10,17-diol (III) have been isolated from *Magydaris panacifolia* (Vahl) Lange (Umbelliferae) and structurally elucidated by J. de Pascual Teresa *et al.*[1] However, the stereochemistry of these diterpenes with a novel carbon skeleton has been left undetermined.

In this communication we wish to report a stereoselective transformation of α-santonin to a pair of diastereomers of 2,6-dimethyl-6-(8-methyl-4-methylene-7-nonenyl)-2-cyclohexen-1-ylmethanols (Ia and Ib), *i.e.*, the two possible stereoisomers for the structure of magydar-2,10(20),13-trien-17-ol (I) or its enantiomer.

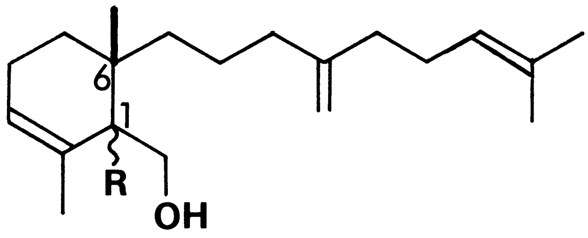
Hydroxylation of 5βH-eudesmanolide (1a)[2],[3] ((i) LiN(*i*-Pr)$_2$, (ii) MoO$_5$.pyridine.HMPT)[4] gave a hydroxy lactone (2a) (75% yield; mp 131 - 132.5 °C; 3430 and 1755 cm^{-1}; δ 1.42 (s, C11-CH$_3$) and δ 4.73 (dd, J = 10.5 and 4.5 Hz, C6-H)).[5] Reduction of 2a with LiAlH$_4$ in THF under reflux afforded a triol (3a) (75% yield; mp 129 - 129.5 °C; 3300 cm^{-1}; δ 3.37 and 3.45 (ABq, J = 10.5 Hz, -CH$_2$OH)). Oxidative cleavage of 3a with NaIO$_4$ in aqueous THF gave an oily hydroxy ketone (4a) (98% yield; 3550 and 1710 cm^{-1}; δ 2.18 (s, -COCH$_3$)). The Beckmann rearrangement of 4a ((i) *O*-mesitylenesulfonylhydroxylamine, (ii) basic alumina)[6] gave an amide (5a) (oil; 50%



I R_1 = H R_2, R_3 = CH_2

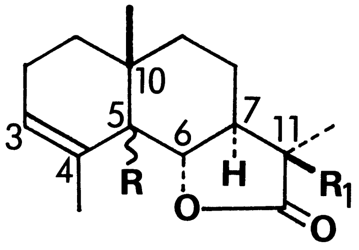
II R_1 = $COCH_3$ R_2, R_3 = CH_2

III R_1 = H R_2 = OH, R_3 = CH_3



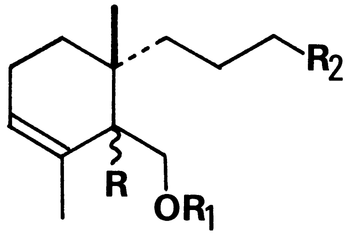
Ia R = β-H

Ib R = α-H



1a, 1b R_1 = H

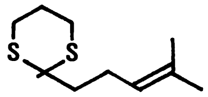
2a, 2b R_1 = OH

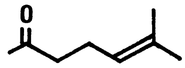


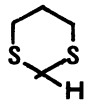
7a, 7b R_1 = H R_2 = OH

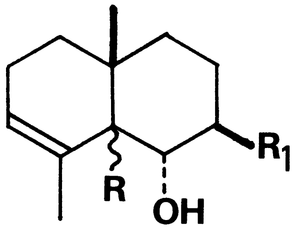
8a, 8b R_1 = H R_2 = I

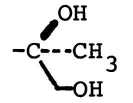
9a, 9b R_1 = THP R_2 = I

11a, 11b R_1 = THP R_2 = 

12a, 12b R_1 = H R_2 = 

13b R_1 = THP R_2 = 



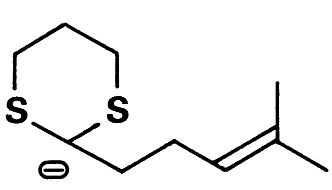
3a, 3b R_1 = 

$-\overset{\mathrm{OH}}{\underset{\backslash\mathrm{OH}}{\mathrm{C}}}\cdots\mathrm{CH_3}$

4a, 4b R_1 = $COCH_3$

5a, 5b R_1 = $NHCOCH_3$

6a, 6b R_1 = $NHCH_2CH_3$



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1a – 9a, 11a, 12a: R = β-H

1b – 9b, 11b – 13b: R = α-H

yield; 1645 and 1545 cm^{-1}; δ 2.02 (s, $-NHCOC\underline{H}_3$)), which was then reduced with $LiAlH_4$ to afford a hydroxy amine (6a) (oil; 80% yield; 3400 cm^{-1}; δ 1.12 (t, *J* = 7 Hz, $-NHCH_2C\underline{H}_3$) and δ 2.69 (q, *J* = 7 Hz, $-NHC\underline{H}_2CH_3$); *m/z* 223, M^+). Oxidative cleavage of 6a with $NaIO_4$ in aqueous THF gave an unstable dialdehyde, which was reduced, without isolation, with $NaBH_4$ at 0 °C to an oily diol (7a) (3350 cm^{-1}; δ 2.27 (br. s, OH) and δ 3.65 (m, $-C\underline{H}_2OH$)).

Completion of the side chain transformation was brought as follows. The diol (7a) was partially tosylated with 1 molar equivalent of *p*-TsCl in pyridine at 5 °C. The resulting reaction mixture was then treated with NaI in acetone under reflux to give a monoiodide (8a) (oil; 18% overall yield from 6a; δ 0.86 (s, $C10-CH_3$), δ 3.19 (t, *J* = 6.5 Hz, $-CH_2-I$), and δ 3.72 (d, *J* = 3.5 Hz, $-C\underline{H}_2OH$))7) as the major product. Tetrahydropyranylation of 8a with dihydropyran in the presence of *p*-TsOH gave 9a in quantitative yield. Treatment of 9a with the carbanion (10) generated from 2-(4-methyl-3-pentenyl)-1,3-dithiane8) with *n*-butyllithium gave 11a (oil; 52% yield),9) which on hydrolysis with copper(II) chloride-copper(II) oxide in acetone10) afforded an oily hydroxy ketone (12a) (40% yield; 3470 and 1710 cm^{-1}; *m/z* 274, $[M - H_2O]^+$). Finally, 12a was methylenated with Ph_3PCH_2 to give Ia (oil; *ca.* 30% yield; 3450 and 885 cm^{-1}; *m/z* 290, M^+),11) whose ^1H NMR spectral data were obviously different from those reported for I (Table).

Table ^1H NMR spectral data ($CDCl_3$, δ values)

	$C6-CH_3$	$C=C-CH_3$	$C\underline{H}_2OH$	$C=CH_2$	$C\underline{H}=C(CH_3)_2$	C3-H
I	0.71(s)	1.53(s, 6H) 1.63(s, 3H)	3.65 (ABdq)	4.76(s) 4.62(s)	5.03(m)	5.03(m)
Ia	0.85(s)	1.62(s) 1.70(s) 1.74(s)	3.73(m)	4.72(s)	5.16(m)	5.62(m)
Ib	0.99(s)	1.60(s) 1.69(s) 1.74(d, *J*= 1.5 Hz)	3.73(m)	4.70(s)	5.11(m)	5.61(m)

5αH-Eudesmanolide (1b)3) was converted to an alcohol (8b)7) (12% overall yield; δ 1.00 (s, $C10-CH_3$), δ 3.13 (t, *J* = 7 Hz, $-CH_2-I$), and δ 3.72 (d, *J* = 3 Hz, $-C\underline{H}_2OH$)) by the same procedure described above.12) 8b was then transformed to a tetrahydropyranyl ether (9b), which was then treated with 2-lithio-1,3-dithiane at 0 °C to give 13b (oil; 34% yield from 8b). The carbanion generated from 13b with *n*-butyllithium was treated with 4-methyl-3-pentenyl iodide8) to give 11b (oil; 60% yield).9) Hydrolysis of 11b with copper(II) chloride-copper(II) oxide in acetone10) gave a hydroxy ketone (12b) (oil; 40% yield; 3450 and 1710 cm^{-1}). Methylenation of 12b with Ph_3PCH_2 afforded Ib (oil; *ca.* 25% yield; 3400 and 890 cm^{-1}; *m/z* 290, M^+).11) The ^1H NMR spectral data of Ib were clearly different from those reported for I (Table).

We therefore suggest that the structure of the natural diterpenes (I, II, and III) should be revised.

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References

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2) Numbering of the eudesmane skeleton is used for all the compounds derived from eudesmanolides (1a and 1b) except for Ia and Ib.
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11) Ia and Ib were isolated by preparative TLC (SiO_2, hexane-ether (2:1), R_f(Ia) = 0.66 and R_f(Ib) = 0.5). GLC (20% Carbowax 20M, 3 mm×2 m, 195 °C, N_2 (1.2 Kg/cm^2)): t_R(Ia) = 9.0 min and t_R(Ib) = 9.2 min. Both Ia and Ib were contaminated with a more volatile component (<10%, t_R = 4.5 min). MS: Ia, *m/z* 290(7%, M^+), 272(8, $[M-H_2O]^+$), 135(23), 123(20), 122(23), 121(38), 110(24), 109(63), 107(54), 95(37), 93(46), 81(46), 79(20), and 69(100); Ib, *m/z* 290(5, M^+), 272(12, $[M-H_2O]^+$), 149(26), 135(27), 122(52), 121(48), 119(27), 109(46), 107(94), 95(48), 93(54), 91(23), 81(57), 79(23), and 69(100).
12) Spectral data of 2b - 7b are shown below. 2b,5) mp 185 - 186.5 °C, 3470 and 1755 cm^{-1}, δ 1.44 (s, C11-CH_3) and δ 4.37 (dd, *J* = 12 and 9 Hz, C6-H); 3b, oil, 3350 cm^{-1}, δ 3.37 and 3.53 (ABq, *J* = 12 Hz, -$C\underline{H}_2OH$); 4b, mp 66 - 67 °C, 3420 and 1708 cm^{-1}, δ 2.18 (s, -$COCH_3$); 5b, mp 125 - 127 °C, 1655 and 1545 cm^{-1}, δ 2.01 (s, -$NHCOC\underline{H}_3$), *m/z* 237, M^+; 6b, mp 64 - 65 °C, 3400 cm^{-1}, δ 1.07 (t, *J* = 7 Hz, -$NHCH_2C\underline{H}_3$) and δ 2.3 - 2.9 (m, C7-H and -$NHC\underline{H}_2CH_3$), *m/z* 223, M^+; 7b, oil, 3340 cm^{-1}, δ 3.5 - 3.8 (m, -$C\underline{H}_2OH$).

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