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# ABSOLUTE STEREOCHEMISTRY OF THE TRIOL MOIETY OF GYMNOPRENOLS: A REINVESTIGATION

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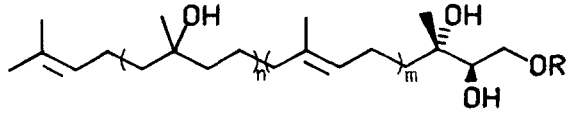
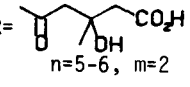
SUMMARY: The absolute configurations of the C-2 and C-3 positions of gymnoprenol A (1), gymnoprenol B (2), and gymnopilin (3) have been revised from 2S,3R to 2R,3S.

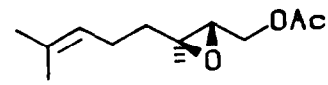
Recently Nozoe et al.[1] reported the determination of the absolute configuration of the triol moiety of gymnoprenols. Their conclusion, based on the asymmetric epoxidation of geraniol and subsequent ring opening, should be reversed. The experimental findings described below support the proposal that the stereochemistry of gymnoprenol A (1), gymnoprenol B (2), and gymnopilin (3) is 2R,3S, rather than 2S,3R.



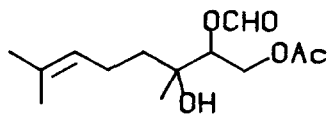

1: R=H, n=5-6, m=2
2: R=H, n=7-9, m=1
3: R= 

n=5-6, m=2

These workers presumed that opening of geranyl acetate-2,3-epoxide (4) with perchloric acid in dimethyl formamide results in inversion at the C-2 position, a conclusion based on the isolation of formate 5. Under the conditions employed, however, formate 5 may be the product of group transfer from the initially formed perchlorate salt 6 (via a cyclic orthoamide).[2]



4



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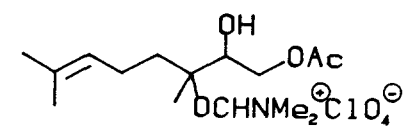
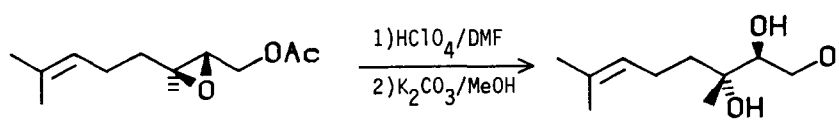
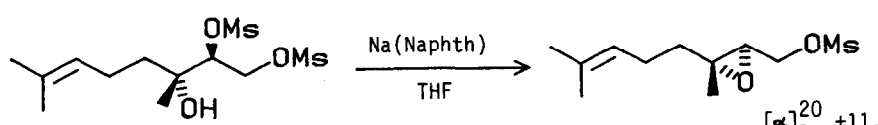


6

Since literature reports relating to epoxide opening under acidic conditions do not provide a clear precedent in such a case,[3] the following experiments were carried out: Treatment of optically active epoxy acetate 4 (143 mg, $[\alpha]_D^{20}$ $-24^{\circ}$,c 1.5 $CHCl_3$)[4] with 0.03 mL of 70% aqueous perchloric acid in 1 mL of dimethyl formamide at room temperature for 8 h provided a crude mixture of esters, which was directly hydrolyzed (potassium carbonate in anhydrous methanol) to give triol 7 (104 mg, 82%).[6] This triol (45 mg) was mesylated (excess methanesulfonyl chloride and triethylamine in dichloromethane at $0^{\circ}$) to give bis-mesylate 8.[7] Treatment of the purified bis-mesylate with 1.2 equivalents of 0.1 M sodium naphthalide in tetrahydrofuran cleanly provided epoxy mesylate 9.[8]



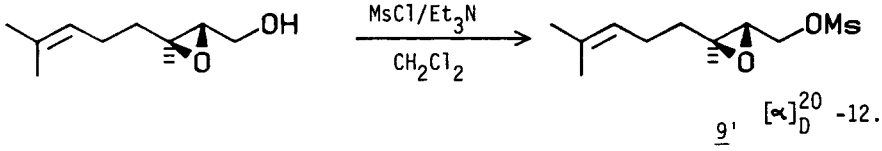

4 7




8 9

$[\alpha]_D^{20}$ +11.9

Epoxy mesylate 9 so obtained had a rotation of +11.9° ($[\alpha]_D^{20}$, c 2.0 $CHCl_3$), whereas mesylate 9', obtained by direct mesylation of the starting epoxy alcohol used to prepare acetate 4, was of opposite rotation ($[\alpha]_D^{20}$ -12.7°, c 2.3 $CHCl_3$).[9]




9' $[\alpha]_D^{20}$ -12.7

Thus, in the process of opening and reclosing of the epoxide ring, inversion occurs at both C-2 and C-3. Since only C-2 inversion occurs in the mildly basic ring-closing reaction, inversion at C-3 must take place at the time of ring opening. Acid-catalyzed opening of epoxy acetate 4 proceeds in a manner consistent with earlier findings on related trisubstituted epoxides:[3a] Tertiary C-3 opening occurs to give the 2S,3R configuration. Since Nozoe's work nicely correlates triol 7 with the natural gymnoprenyl system and shows that the two are of opposite configuration, the absolute stereochemistry of the C-2 and C-3 positions of gymnoprenol A (1), gymnoprenol B (2), and gymnopilin (3) should be designated 2R,3S.

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[2] H. Meerwein, W. Florian, N. Schoen, G. Stopp, Liebigs Ann. Chem., 1961, 641, 1.

[3] acyclic systems:
(a) K. Nakanishi, D. A. Schooley, M. Koreeda, J. Dillon, J. Chem. Soc. Chem. Commun., 1971, 1235.

(b) C. H. Behrens and K. B. Sharpless, Aldrichimica Acta,1983, 16, 4.
(c) C. H. Behrens, Ph.D. Thesis, Massachusetts Institute of Technology, 1984.
(d) D. J. Morgans, K. B. Sharpless and S. G. Traynor, J. Am. Chem. Soc., 1981, 103, 462.
carbocyclic systems:
(e) J. G. Buchanan and H. Z. Sable, in Selective Organic Transformations, B. S. Thyagarajan, Ed. (Wiley: New York, 1972), pp. 1-95.

[4] Prepared by acetylation (acetic anhydride, triethylamine, 4-(N,N-dimethyl amino)-pyridine, dichloromethane) of (-)-geraniol-2,3-epoxide.[5]

[5] T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 1980, 102, 5974.

[6] 250 MHz $^1H$ nmr: ($\delta$ TMS, $CDCl_3$ + $D_2O$) 1.25 3H s, 1.45 1H ddd J=5 11 13, 1.55-1.7 1H obscured, 1.63 3H s, 1.70 3H s, 1.9-2.2 2H m, 2.7 1H m, 4.5 1H t J=5, 4.8 2H d J=5, 5.12 1H broad t J=7.

[7] 250 MHz $^1H$ nmr: ($\delta$ TMS, $CDCl_3$) 1.32 3H s, 1.4-1.7 2H obscured, 1.65 3H s, 1.71 3H s, 2.0-2.3 2H m, 3.10 3H s, 3.18 3H s, 4.42 1H dd J=9 12, 4.61 1H dd J=3 12, 4.80 1H dd J=3 9, 5.12 1H broad t J=7.

[8] 250 MHz $^1H$ nmr: ($\delta$ TMS, $CDCl_3$) 1.35 3H s, 1.4-1.8 2H obscured, 1.62 3H s, 1.70 3H s, 2.10 1H q J=8, 3.10 3H s, 3.05-3.15 1H obscured, 4.25 1H dd J=8 12, 4.45 1H dd J=4 12, 5.08 1H broad t J=7. Sodium naphthalide was chosen as a mild non-nucleophilic base. Traces of linalool in the crude product mixture were observed using thin layer chromatography.

[9] The 250 MHz $^1H$ nmr spectra of 9 and 9' were superimposable.

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