Pure & Appl. Chem., Vol. 61, No. 3, pp. 353–356, 1989.
Printed in Great Britain.

Guggultetrols: a new class of naturally occurring lipids

Sukh Dev

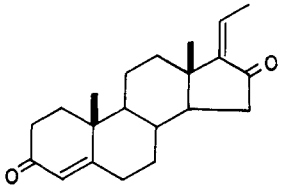
Malti-Chem Research Centre, Nandesari
Vadodara 391340, India

Abstract — The gum-resin from *Commiphora mukul* has yielded a number of long-chain aliphatic 1,2,3,4-tetrols esterified with ferulic acid at the primary hydroxyl function. The tetrols are mainly C_{18} and C_{20} compounds with minor amounts of C_{16}, C_{17}, C_{19}, C_{21} and C_{22} entities. Evidence has been obtained for the occurrence of corresponding mono-olefinic analogues in the exudate. All these tetrols are configurationally homogenous. Configuration has been established as D-*xylo* by unambiguous synthesis of D-*lyxo*-, L-*ribo*- and L-*xylo*-octadecane-1,2,3,4-tetrols and comparison with the naturally occurring C_{18} guggultetrol.

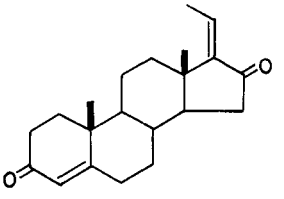
A number of plants belonging to different families have been screened for the presence of such tetrols.

INTRODUCTION

Commiphora mukul (Hook, ex Stocks) Engl. (Syn. *Balsamodendron mukul* Hook, ex Stocks) is a small tree of the family Burseraceae, endemic to the Hindustan peninsula. On incision, the plant exudes a yellowish gum-resin, which rapidly solidifies to an agglomerate of tears or stalactitic pieces. This product, called *guggulu* in Sanskrit, is valued in Ayurveda, the ancient Indian system of medicine, for the treatment of several diseases, especially rheumatoid arthritis and lipid disorders.[1] Work[2-8] aimed at isolation of compounds with hypocholesterolemic and hypolipaemic activity led, not only to the isolation and characterization of the active principles *Z*- and *E*-pregna-4,17(20)-diene-3,16-diones (*Z*- and *E*-guggulsterones; 1, 2)[2], but also to the isolation of a series of long-chain 1,2,3,4-tetrols, a class of compounds not met in nature earlier. The gross structure (3) of these tetrols was established several years ago.[4] In this lecture I propose to discuss the form in which they occur in the exudate, their absolute configuration,[9] the isolation of olefinic tetrols, and the general question of their occurrence in other plant materials.



1



2

$CH_3(CH_2)_nCHOH.CHOH.CHOH.CH_2OH$

n = 13, 15 (major)
n = 14 (minor)
n = 11, 12, 15, 16 (v. minor)

3

GUGGULTETROL ESTERS

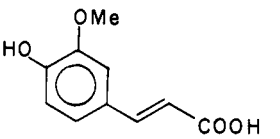
Guggultetrols were isolated[4] from *guggulu* only after saponification of its EtOAc extract. These tetrols, apparently, do not occur free. When EtOAc extract of the gum-resin was partitioned between 90% MeOH aq and hexane, and the material contained in the 90% MeOH aq phase again partitioned between 60% MeOH aq and benzene, the latter carried material, which on test saponification furnished tetrols. Systematic column chromatography of benzene-phase

material, followed by crystallization of appropriate fractions yielded the "tetrol ester" as a crystalline solid (m.p. 84-86°). Its saponification gave the same mixture of tetrols (C_{18}, C_{19}, C_{20}) and ferulic acid (4). That the "tetrol ester" is, in fact, a mixture of homologous compounds was also clear from its electron-impact mass spectrum (M^+ ions at m/z 522, 508 and 494). This mixture is readily separable by HPLC (reverse phase: C_{18} bonded SiO_2, MeOH-H_2O).

From a comparison of the ^{1}H-NMR spectra (Table 1) of the "tetrol ester", its triacetate (m.p. 52-55°), its triformate (m.p. 78-81°), and guggultetrol-18, it is obvious that the primary hydroxyl in 3 is estrified (by ferulic acid) in the tetrol esters.

Table 1. Tetrol ester and derivatives: ^{1}H-NMR data

No.	Compound	δ (ppm)	
		CHOR(m,3H)	CH_2OR(t,2H)
1	Guggultetrol ester	3.30-4.10	4.30
2	Guggultetrol ester triacetate	5.00-5.40	4.30
3	Guggultetrol ester triformate	5.10-5.60	4.33
4	Guggultetrol	3.20-3.60	



4

ABSOLUTE STEREOCHEMISTRY

To define the structure of the tetrol esters uniquely, the absolute configuration at the three chiral centres must be elucidated. There are four possible configurations for each antipodal series (D or L): *arabino-*, *lyxo-*, *ribo-*, and *xylo-*. *arabino*-Configuration was ruled out, as guggultetrol-20 with m.p. 85-87°[10] is clearly different from the known[11] synthetic L-*arabino*-1,2,3,4-tetrahydroxyeicosane (or its enantiomer) with the reported m.p. 116-119°. To differentiate between the remaining possibilities, the most unequivocal approach appeared to be through synthesis.[12]

An analysis of the structures of the target molecules revealed that compound 5 can serve as a versatile intermediate for the synthesis of all the three tetrols. This strategy is depicted in Fig. 1. According to an empirical rule of Kishi,[13] osmylation of *cis*-olefin 5 (preferred conformation) would result in formation of *ribo*-tetrol (6) as a predominant product. On the other hand, *trans*-hydroxylation of 5 would furnish the other two tetrols. However, it was realised that it would be still necessary to carry out unambigous synthesis of tetrols 9 and 10 (or their antipodes), as it is difficult to predict which of the *trans*-hydroxylation pathways shown in Fig. 1 will be favoured. Despite this ambiquity, this synthetic strategy was exploited as it offered an easy access to these compounds, which appeared worthy of biological evaluation.

Olefin 5 was synthesised from 2,3-*O*-isopropylideneglyceraldehyde by its reaction with ylid from pentadecyltriphenylphosphonium bromide. Osmylation of 5 was effected with OsO_4 (catalytic) and sodium chlorate and the crude *cis*-hydroxylation product hydrolyzed to furnish, after chromatography, only one crystalline tetrol, which was expected to be L-*ribo*-octadecane-1,2,3,4-tetrol (6). This was then confirmed by a straight-forward synthesis from D-ribose. *trans*-Hydroxylation of 5 was carried out with performic acid. The product, after saponification gave a material, which on fractional crystallization yielded two compounds: m.p. 81-83° (∿30%) and m.p. 138-140° (∿15%). The major product was found to be identical, except for its sign of optical rotation, with guggultetrol-18. By an unambigous synthesis, discussed below, the main compound was characterized as L-*xylo*-octa-decane-1,2,3,4-tetrol (10), whence the compound with m.p. 138-140° should be the D-*lyxo* isomer (9). That this indeed was so was established by its synthesis from D-arabinose.

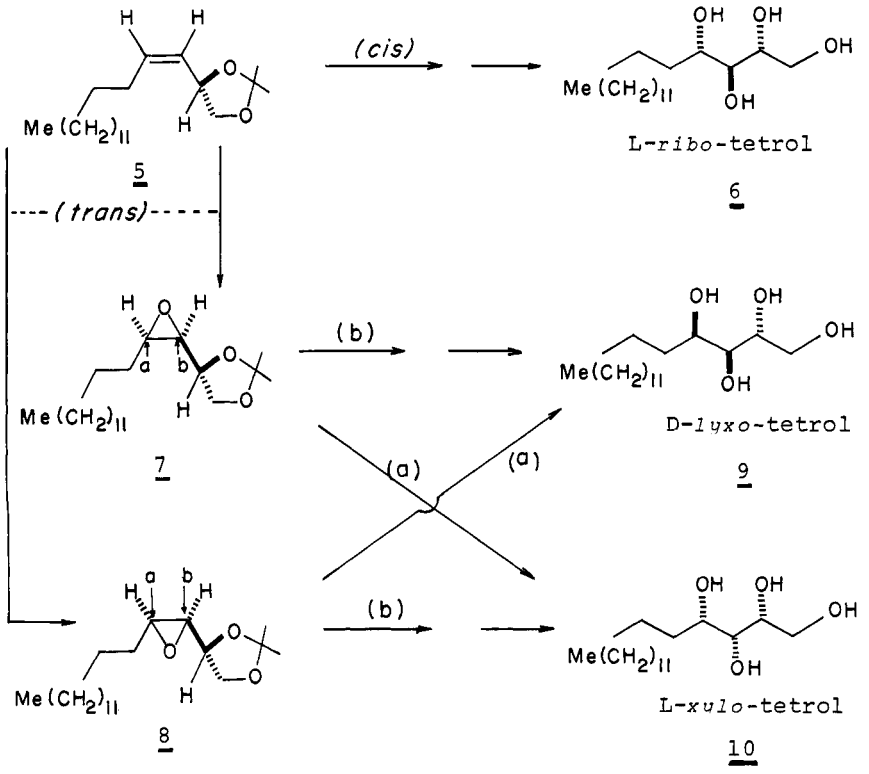
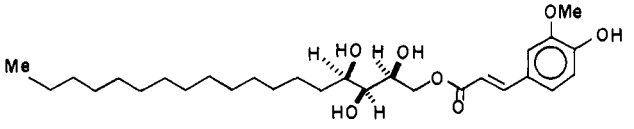


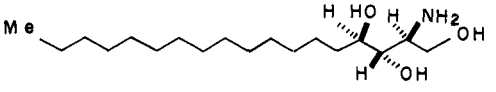
Fig. 1. Synthesis of guggultetrols

Synthesis of L-*xylo*-octadecane-1,2,3,4-tetrol (10) was carried out from D-xylose. D-xylose diethyldithioacetal on exposure to acetone in presence of catalytic amount of $FeCl_3$ furnished the known 2,3:4,5-di-*o*-isopropylidene-D-xylose. This was converted into the corresponding aldehyde by dethioketalization with $HgCl_2$ and $CdCO_3$ in CH_3CN aq. Wittig condensation of the aldehyde with ylid from tridecyltriphenylphosphonium bromide furnished an olefin, which on hydrogenation, followed by aq acid hydrolysis gave the required L-*xylo*-tetrol (10). Tetrols 6 and 9 were also synthesised likewise.

The work described so far leads to absolute stereostructure 11 for guggultetrol-18 ferulate. Based on comparison of IR and PMR spectra of guggultetrol-18 and guggultetrol-20 and their derived acetonides, it is concluded that both of these tetrols have the same configuration at the chiral centres. As a matter of fact, since the plot of log of GLC retention time *vs* chain length (of the derived acetonides) gives a straight line, it is inferred that in all likelihood other lower and higher homologous tetrols occurring in *guggulu* have D-*xylo* configuration.



11

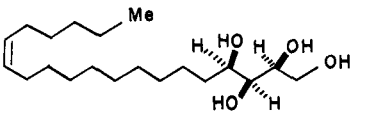


12

Guggultetrols are reminiscent of the biologically important phytosphingosines (C_{18} and C_{20}), widely distributed in the plant sphingolipids and certain animal tissues. These compounds, however, have a well-defined D-*ribo* configuration (e.g. 12).

UNSATURATED GUGGULTETROLS (ref. 14)

Examination of mother liquors from the crystallization of tetrol esters indicated the presence of unsaturated analogues. By a combination of acetonide formation, $AgNO_3$-SiO_2-gel column chromatography, and preparative GLC, C_{18} and C_{20} unsaturated analogues have been separated from the saponified material. From spectral data (PMR of acetonide) it is clear that the tetrol moiety has the same D-*xylo* configuration. From reductive ozonolysis of the C_{20} compound (bisacetonide) it became clear that the ethylenic linkage is at C_{14}-C_{15}, and from its IR spectrum it is concluded that the olefinic linkage in *cis*-configurated, leading to structure 13 for the C_{20} olefinic tetrol.



13

DISTRIBUTION (ref. 15)

A detection procedure was developed and used to screen 56 plants belonging to 22 families, for occurrence of guggultetrols. Only three of these, namely *Achras sapota* (Sapotaceae), *Plumeria acutifolia* (Apocynaceae), and *Syzygium cuminii* (Myrtaceae), gave positive response.

REFERENCES AND NOTES

1. See e.g.: (a) Wealth of India (Raw Materials), Vol. II, p. 313, Council of Scientific Industrial Research, New Delhi, 1950; (b) V.V.S. Sastry, Bull. Indian Inst. Hist. Medicine, 6, 102 (1976).
2. V.D. Patil, U.R. Nayak and Sukh Dev, Tetrahedron, 28, 2341 (1972).
3. V.D. Patil, U.R. Nayak and Sukh Dev, Tetrahedron, 29, 341 (1973).
4. V.D. Patil, U.R. Nayak and Sukh Dev, Tetrahedron, 29, 1595 (1973).
5. R.S. Prasad and Sukh Dev, Tetrahedron, 32, 1437 (1976).
6. A.G. Bajaj and Sukh Dev, Tetrahedron, 38, 2949 (1982).
7. S. Nityanand and N.K. Kapoor, Indian J. Exptl. Biol., 9, 376 (1971).
8. S. Nityanand and N.K. Kapoor, Indian J. Exptl. Biol., 11,395 (1973).
9. Since submission of abstract, full details of this work have been published: Vijay Kumar and Sukh Dev, Tetrahedron, 43, 5933 (1987).
10. All natural and synthetic tetrols examined by us melt at the indicated temp to a transluscent mass, which becomes a clear liquid only at a much higher temperature, a behaviour typical of liquid crystals.
11. R. Gigg and C.D. Warren, J. Chem. Soc.(C), 1879 (1966).
12. Also see: A. Kjaer, D. Kjaer and T. Skrydstrup, Tetrahedron 42, 1439 (1986).
13. J.K. Cha, W.J. Christ and Y. Kishi, Tetrahedron,40, 2247 (1984).
14. Unpublished results by Haridas Kochat and C.C. Shah
15. Unpublished results by P.V. Purohit