AN ALTERNATIVE MODEL FOR THE BIOGENESIS OF XANTHANOLIDES

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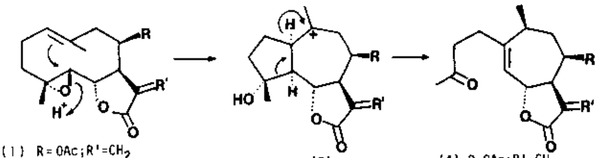
Abstract – Hydroperoxide transposition of 4-hydroperoxyguaianolide (**10**) afforded xanthanolide (**12**). The possible biogenetic implications of this process are discussed.

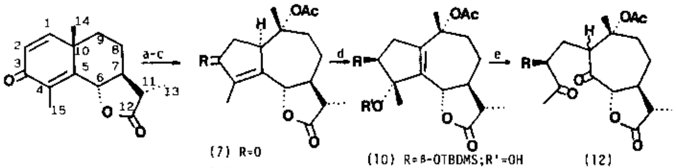
It has been speculated that the xanthanolides, a sizeable group of sesquiterpene lactones[1], may be formed biogenetically by the cyclization of a 4-epoxygermacranolide[2]. Wilton and Doskotch[3] transformed lipiferolide (**1**) to **4** by BF$_3$.Et$_2$O-induced cyclization and, more recently, Parodi and Fischer[4] repeated the same procedure with dihydroparthenolide (**2**), obtaining **5**. However, in both cases, the yields were low (6.5 and 2%, respectively), the major products obtained being guaiane and germacrane derivatives.

This paper offers an alternative biogenetic hypothesis whereby xanthanolides might be biosynthesized via the fragmentation of 4-hydroperoxyguaianolides.



(1) R=OAc;R'=CH$_2$
(2) R=H;R'=(α-Me;β-H)
(3)
(4) R=OAc;R'=CH$_2$
(5) R=H;R'=(α-Me;β-H)

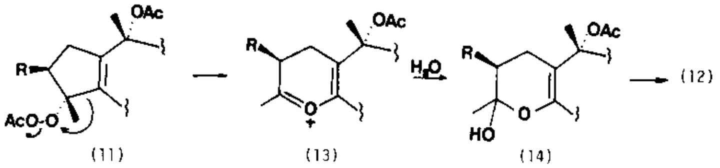
Photolysis of α-santonin (**6**)[5], followed by reduction of the resulting isophotosantonic lactone (**7**), afforded alcohol (**8**) which, after protection and sensitized photo-oxygenation, gave the hydroperoxide (**10**)[4] (12% overall). Treatment of **10** with Ac$_2$O-Py yielded **12** (35%, mixture of isomers at C-1) very probably via



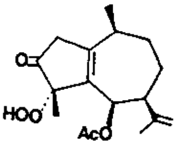
(7) R=O
(8) R=β-OH
(9) R=β-OTBDMS
(10) R=β-OTBDMS;R'=OH
(11) R=β-OTBDMS;R'=OAc
(12)

a) hν
b) NaBH$_4$/MeOH-H$_2$O
c) TBDMSCl/imidazole-DMF
d) O$_2$/hν-methylene blue
e) Ac$_2$O/Py, 12 h, rt

the peroxyacetate **11** (Criegee rearrangement[7]) with preferred migration of the vinylic bond[8].



An enzymatic process similar to that described above might be an alternative biogenetic pathway to the formation of natural xanthanolides from guaianolides via 4-hydroperoxy derivatives. In support of this hypothesis, Hoeneisen and Silva[9] have obtained the hydroperoxide (**15**) from <u>Pleocarpus revolutus</u> while clavukerin A (**16**), clavukerin C (**17**) and clavularin A (**18**) have been isolated from <u>Clavularia koellikeri</u> by Kobayashi <u>et al</u>.[10] and xanthanolide (**19**) was isolated by Bohlmann and co-workers[11] from <u>Ditrichia graveolens</u>. The hydroperoxide cleavage enzyme responsible for



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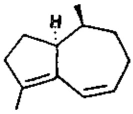

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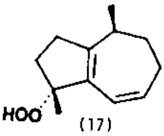

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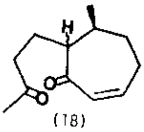

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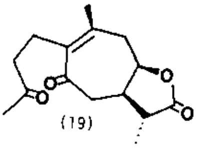

(19)

Table I: ^{1}H-Nmr Data of Compounds **8**, **9**, **10** and **12**

Proton	**8**	**9**	**10**	**12**
H-1	3.77 c	3.68 c	–	2.97 c
H-3	4.56 br s	4.45 br s	4.54 dd (6.9, 7.2)	3.97 dd (8.0, 7.9)
H-6	4.66 d (8.6)	4.61 d (10.7)	4.69 d (10.3)	4.70 d (10.7)
H-13	1.22 d (6.8)	1.16 d (6.9)	1.21 d (6.8)	1.25 d (7.0)
H-14	1.19 s	1.16 s	1.21 s	1.29 s
H-15	1.88 br s	1.77 br s	1.46 s	2.18 s
Other	1.98 s (OAc)	1.94 s (OAc)	2.02 (OAc) 8.21-8.30 (HOO)	2.09 (OAc)

H-nmr taken in $CDCl_3$; δ in ppm (TMS);
J in Hz is given in parentheses;
c=complex, s=singlet, br s=broad singlet,
d=doublet, dd=double doublet

the direct fragmentation of fatty acid hydroperoxide derivatives exists in certain vegetable species[12] and in principle acts in the same way[13] as the transposition described above.

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