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BIOMIMETIC TRANSFORMATION OF A GUAIANOLIDE TO A PSEUDOGUAIANOLIDE

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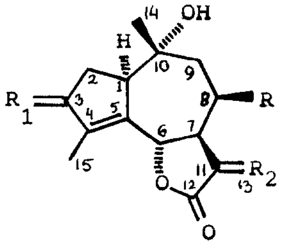
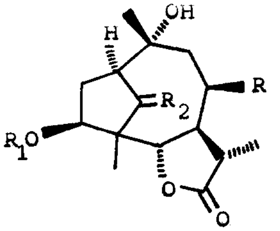
Summary - The long awaited transformation of the guaianolide skeleton to the pseudoguaianolide skeleton (1a ⟶ 6a) has been achieved.

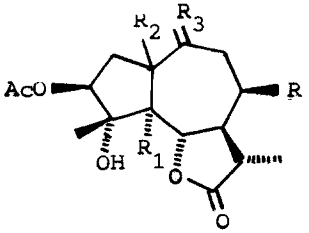
The discovery[1] of pseudoguaianolides - a class of sesquiterpene lactones exhibiting a wide spectrum of biological activities[2], was made long time ago by Herz et al. Almost all the naturally occurring pseudoguaianolides reported so far, are found to be oxygenated at C-4. It has, therefore, been postulated that the pseudoguaianolide skeleton is formed from the guaianolide skeleton bearing a hydroxyl at C-4[3] or an epoxide function at C-4, C-5[4]. Although in vitro formation of the guaianolide skeleton from its biogenetic precursor - the germacranolide, has been reported several times[5], the conversion of the former to the pseudoguaianolide skeleton has not been achieved so far[6]. We present evidence for the transformation of guaianolide 1a to pseudoguaianolide 6a.

It has been described earlier that cyclization of tagitinin C with $SnCl_2$ furnishes cyclotagitinin C 1a[7]. Sodium borohydride reduction of 1a yielded the diol 1c which on treatment with m-chloroperbenzoic acid (MCPBA) at r.t. furnished a mixture of three compounds and two of them were quickly identified as the epoxide 1d (65%) and the ketone 1b (10%). The third compound (15%, m.p. 146°) exhibited an absorption band at $1750 cm^{-1}$ in the IR spectrum suggesting the possibility of structure 2a or the corresponding pseudoguaianolide for it. It was reduced with $NaBH_4$ and subsequent acetylation furnished a diacetate whose $^1H-^1H$ correlated 2D NMR spectrum fully confirmed its structure as 2b[8]. The epoxide 1d was acetylated and the acetate was exposed to $BF_3.Et_2O$ in dry ether to furnish a mixture of four products. The major product (28%) was found to be unstable and mild treatment with an acid or base quantitatively transformed it into a more polar compound (m.p. 152°) whose spectral data established its identity as 4[9]. Thus the parent unstable compound was assigned structure 3a. When the ^1H NMR spectrum of 4 was recorded in the presence of a drop of trichloroacetyl isocynate (TAI), H-3 at δ 4.85 ppm underwent paramagnetic shift to δ 5.4 ppm, confirming that the hydroxyl at C-4 is α, and therefore, convincingly established the stereochemistry of the epoxide 1d. The other three compounds were identified as 1b, 3b and 3c.

Having failed to get any product of the pseudoguaianolide skeleton from the above reaction sequences, it was decided to carry out the rearrangement studies on the epoxide of 5[10]. Treatment of compound 5[11] with MCPBA yielded a mixture of one major (25%) and several minor products. The major product (m.p. 135°) was reduced with $NaBH_4$ and the resulting alcohol was subjected to







1 a R_1=O, R_2=CH_2

b R_1=O, R_2=H, α-Me

c R_1=H, β-OH, R_2=H, α-Me

d R_1=H, β-OH, R_2=H, α-Me, 4,5-α-epoxide

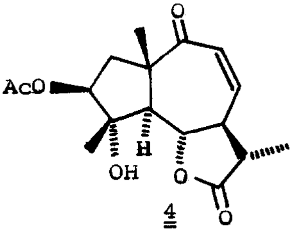
2 a R_1=H, R_2=O

b R_1= Ac, R_2=H,OAc

3 a R_1=H, R_2=β-Me, R_3=O

b R_1=F, R_2=α-H, R_3=OH, β-Me

c R_1=H, R_2=α-F, R_3=OH, β-Me



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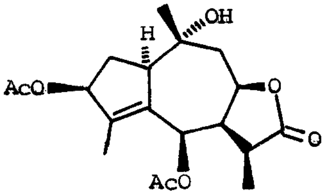
R = OCOCHMe$_2$



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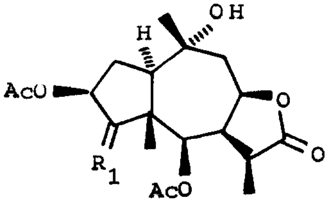

6 a R_1=O

b R_1=H, β-OH

rigorous ^{1}H NMR decoupling experiments which unequivocally proved its structure as **6**b, therefore, structure **6**a was assigned to the parent major compound[12]. Recording the ^{1}H NMR spectrum of **6**b in presence of a drop of TAI shifted the methyl at C-5 to δ 1.45 ppm, implying that it is β-oriented.

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8. Compound **2**a is most likely formed from the β-epoxide, as α-epoxide **1**d on treatment with excess MCPBA for a longer period remains unaffected.
9. ^{1}H NMR of **4** ($CDCl_3$): 1.30d (6.5Hz,H-13), 1.50s (H-15), 1.58s (H-14), 4.66t (10.2Hz,H-6), 4.85dd (1.8, 8.5Hz,H-3), 6.08 (2 protons singlet H-8 & H-9).
10. Most of the naturally occurring pseudoguaianolides contain lactone ring closed towards C-8.
11. **5** was prepared by treating **1**c with NaOMe/MeOH (when the lactone ring closes towards C-8 and epimerization at C-6 takes place) followed by acetylation.
12. ^{1}H NMR of **6**b ($CDCl_3$): 1.1d (7Hz,H-13), 1.18s (H-14), 1.36s (H-15), 3.5dbr (11Hz,H-4), 4.7m (H-8), 4.80m (H-3), 5.25d (4.5Hz, H-6).

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