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A ONE STEP TRANSFORMATION OF 4α,5β-EPOXYGERMACRANOLIDE INTO PSEUDOGUAIANOLIDE*

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Abstract - Adsorption of the germacranolide 4α,5β-epoxyinunolide (1) on bentonitic earth provided the guaianolide inuviscolide (2) and 4α,5α-epoxy-10α,14H-inuviscolide (3) as well as the *pseudoguaianolide 8-epiconfertin (4). This one step transformation re*presents the first biomimetic conversion of a germacranolide into a pseudoguaianolide, substantiating previously proposed biogenetic pathways.

Although a number of Lewis acid-catalyzed cyclizations of 4,5-epoxygermacranolides to guaianolides has been described in literature[1,2] and more recently the transformation of an 4,5-epoxyguaianolide to a pseudoguaianolide has been achieved,[3] no biomimetic transformation of a germacranolide into the third biogenetic stage, the pseudoguaianolide, has been reported to date.

In our case a chloroform solution of the germacranolide 1[4,5] isolated from Stevia tephrophylla Blake,[6] was treated with bentonitic earth, since it has been described that this particular earth promotes the regioselective and stereospecific opening of epoxides.[7] From the reaction mixture the known guaianolides inuviscolide (2)[8] (yield 1.8%) and 4α,5α-epoxy-10α,14H-inuviscolide (3),[4] (yield 1%) together with the pseudoguaianolide 8-epiconfertine (**4**) (yield 4.1%) were isolated.[9] The guaianolides 2 and 3 were identified by comparison of their physical and spectral features with those described in literature.[4,8]

The new lactone 8-epiconfertine (4), mp 144-146°C, exhibited ir absorptions ($CHCl_3$) for α,β-unsaturated γ-lactone (1761, 1660 cm^{-1}) and cyclopentanone (1738 cm^{-1}). From its ^1H nmr spectrum (90 MHz, $CDCl_3$) the existence of a pseudoguaiane skeleton was evident since a doublet (δ 1.18, J=7.5 Hz) and a singlet (δ 1.10) assigned to Me-14 and Me-15, were observed. Furthermore, the typical low field doublets for H-13 (δ 6.18, J=3.5 Hz) and H-13' (δ 5.53, J=3.2 Hz) together with a ddd *signal* (δ 4.28, J=12, 8 and 3.5 Hz) confirmed the presence of a 8(12)-lactone ring and allowed to assume that the stereochemistry at C-8 was not changed during the reaction, thereof the lactone ring in 4 should be trans fused like in the compound **1**.

The formation of the known *compounds* 2 *and* 3, *together with product* **4** in the bentonite catalyzed re-

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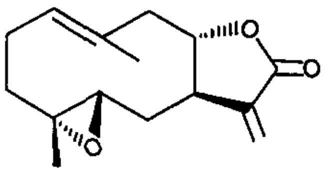
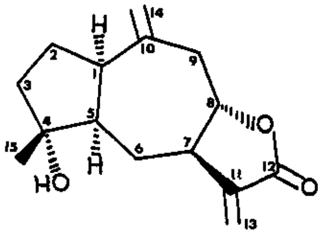
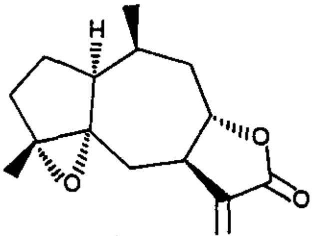


1



2



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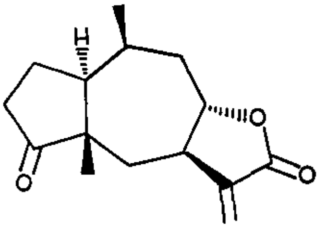


4

arrangement of 1, allowed us to propose the relative stereochemistry of the new ambrosanolide as shown in 4. This was confirmed by an X-ray crystallographic analysis of the new product. Absolute configuration of 4 is shown in Figure 1, if it is assumed the H_{7_α} enantiomorph.

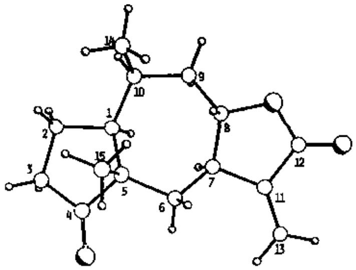
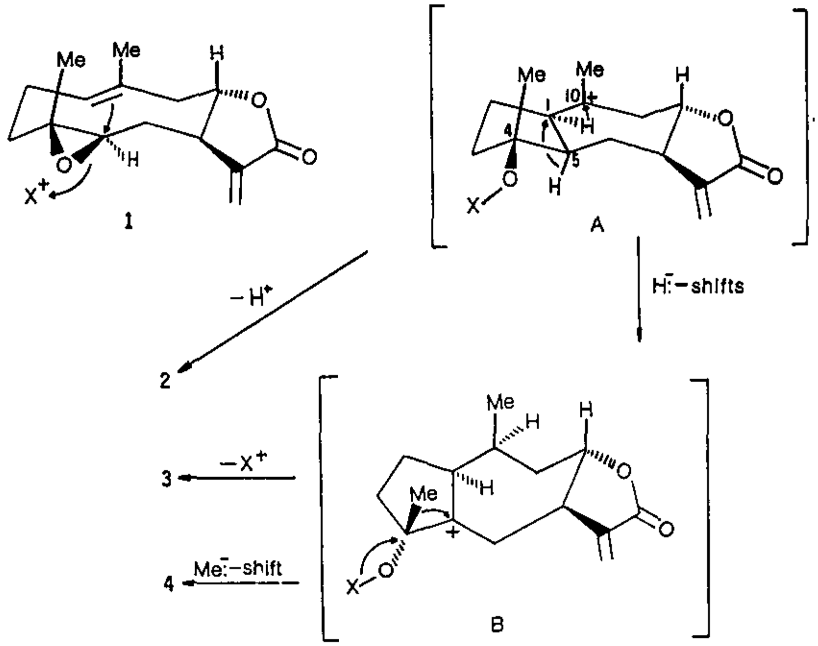


Fig. 1 Stereoscopic view of 8-epiconfertine

Crystals of 8-epiconfertine are orthorhombic, $P_{2_12_12_1}$, a=7.149 (3), b=7.751 (3), c=24.247 (8) Å; V= 1343.65 (0.84)$\mathrm{\AA}^3$, Z=4, F(000)=536, μ=0.79 cm^{-1}, ρ_{calc}=1.23 g cm^{-1}. Intensity data were collected on a Nicolet R3m four circle diffractometer operated in the ω scan mode using Mo monochromatic radiation. 954 reflections collected up to $2\theta<45$ (λ=0.7107) yielded 767 observed independent reflections with $F>3\sigma(F)$. The structure was solved by direct methods and refined by a matrix cascade procedure[10] with anisotropic temperature factors U=0.06 $\mathrm{\AA}^2$ for H-atoms to converge until a final R of 0.0477 ($R\omega$=0.0450) using a weighting scheme $\omega={}^1/\sigma^2 2\ (Fo) + G\ (Fo)^2$ with G=0.001. The final difference map had no peaks greater than ± 0.15 $e\mathrm{\AA}^{-3}$.

The stereochemistry of the cyclization products 2-4 is the expected one if we assume that the most stable conformation of the precursor 1 is similar to the conformation of laurenobiolide in which both methyl groups are above the plane of the cyclodecadiene and the double bonds have a crossed orientation.[11] As outlined in Scheme 1, Lewis-acid initiated cyclization of this chair like conformation of 1 produces the cis-fused cationic intermediate A, which upon loss of a proton from the C-10 methyl group provides inuviscolide (2). Alternatively, two consecutive hydride shifts indi-



Scheme 1

cated by arrows (C-1αH to C-10αH; $C_5\alpha H$ to C-1αH), lead to cation B, which by loss of X^+ forms the epoxyguaianolide 3. Another route involves C-4 to C-5 methyl shift, as indicated by the arrows, to give the pseudoguaianolide 4. The bentonitic earth appears to mimic the enzymatic process by fulfilling a two-fold function in this highly specific cyclization rearrangement reactions. Firstly, the cavities of the bentonitic earth enforce conformational rigidity during the chemical transformations. Secondly, stabilization of the cationic center of the intermediates A and B by active sites on the surface of the bentonite increases their life span, thus allowing the necessary hydride and methyl shifts to occur.[12] This unexpected and long searched transformations of 4,5-epoxygermacranolide into pseudoguaianolide lends strong support for the previously presented biogenetic proposal that germacranolides represent the biogenetic precursors for guaianolides and pseudoguaianolides.[1,12,13]

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6. Isolation of **1**. Ground dried aerial parts of *Stevia tephrophylla* (914 g) collected in Cerro Sepultura, Chiapas, México (specimen deposited in National Herbarium, AOH 176) were extracted with hexane, CH_2Cl_2 and MeOH affording 35, 22.4 and 18 g of residues, respectively. The combined hexane and CH_2Cl_2 extracts crystallized spontaneously yielding, after recrystallization from hexane, 7.75 g of **1**, mp 130-131°C.[4,5]

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9. Cyclization of **1**. 2 g of bentonitic earth ("Tonsil", chemical composition (%): SiO_2 (72.5), Al_2O_3 (13.0), Fe_2O_3 (5.0), Mg O (1.5), CaO (0.8), moisture (8.5), pH acid), was added to a soln of 1 (1.12 g) in $CHCl_3$ (5 ml). The mixture was left to stand for 15 min at room temp. The earth was filtered off and washed with Me_2CO. The crude oil was chromatographed on a silica gel column (Merck G, 3 cm diameter x 13 cm height, EtOAc-hexane 1:3). Fractions of 100 ml were collected. Fraction 3 afforded 20 mg of 3[4] as a yellow oil. Fractions 5-7 gave after crystallization (EtOAc-hexane) 82 mg of 8-epiconfertine (**4**). mp 144-146°C; ms 70 eV, m/z: 248 $[M]^+$ ($C_{15}H_{20}O_3$, 51.6), 233 $[M-Me]^+$, 230 $[M-H_2O]^+$, 215 $[M-Me-H_2O]^+$, 204 $[M-CO_2]^+$, 189 $[M-Me-CO_2]^+$, 55 (86), 53 (74), 41 (100). 36 mg of inuviscolide (2)[8] was isolated from fractions 12-16. Several other compounds were present in the reaction mixture, but because of their unstability they could not be isolated.

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