The First Biomimetic Conversion of a Germacrolide-4-epoxide into a Xanthanolide

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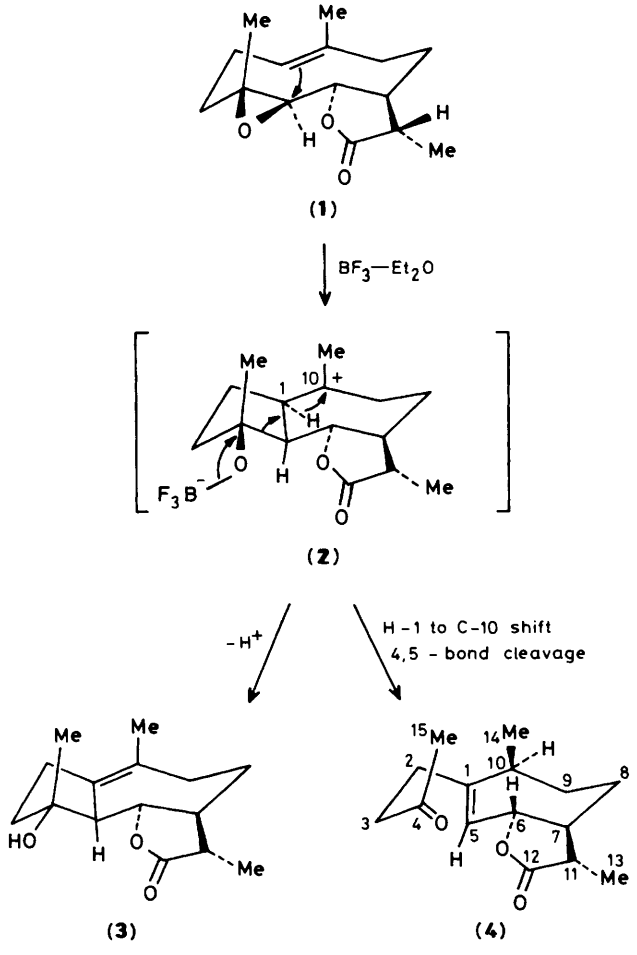
Boron trifluoride catalysed cyclization of the germacrolide-4-epoxide dihydroparthenolide (**1**) provided two known guaianolides and the xanthanolide (**4**), the latter transformation representing the first biomimetic conversion of a germacrolide into a xanthanolide.

Biogenetic hypothesis proposes that germacrolides and their epoxide derivatives represent the precursors for other skeletal types of sesquiterpene lactones.[1—4] For instance, Lewis acid-catalysed reactions of germacra-1(10),4,5-dienes as well as their 1(10)-epoxide derivatives give *trans*-decalin-type eudesmanolides. Alternatively, guaianolides result from germacrolide-4-epoxide cyclizations.[1—4] For instance, Scheme 1 outlines the BF_3-initiated Markovnikov-type transannular cyclization of dihydroparthenolide (**1**). From its chair-like transition state, conformation (**1**), the *cis*-fused guaianolide cation (**2**) is generated which by loss of a proton from C-1 forms the guaianolide (**3**). Alternatively, shift of the C-1α hydrogen to C-10 in cation (**2**) could initiate a fragmentation of the C-4–C-5 bond, as indicated by the arrows, to form the xanthanolide (**4**).[1,2] Although this biogenetic route toward xanthanolides has been proposed,[1,4] a biogenetic-type *in vitro* conversion of a germacrolide into a xanthanolide (secoguaianolide)[1] has not been previously reported.



Scheme 1. Boron trifluoride-initiated transannular cyclization of dihydroparthenolide (**1**).

We have reinvestigated our previous BF_3-initiated cyclization studies of dihydroparthenolide (**1**)[5] with a focus on the minor reaction products. Treatment of a solution of (**1**) with freshly distilled BF_3–Et_2O at ambient temperature for two hours provided a crude semi-crystalline product. Column chromatography over SiO_2 by gradient elution (CH_2Cl_2 to acetone) yielded the guaianolide (**3**)[5] and minor amounts of its C-10–C-14-double bond isomer, compressanolide.[6] Further purification of the early chromatographic fractions by preparative t.l.c. (SiO_2, CH_2Cl_2:Et_2O, 10:1) provided in 2% yield the gummy, pure xanthanolide (**4**) which we named 2-desoxy-11β,13-dihydro-6-epiparthemollin.

Xanthanolide (**4**), $C_{15}H_{22}O_3$, had strong absorption bands in the carbonyl region of the i.r. spectrum [$\nu_{max.}$ at 1715 (ketone) and 1779 cm^{-1} (γ-lactone)]. The chemical ionization mass spectrum exhibited a base peak at *m/z* 251 $(M + 1)^+$ and the electron impact spectrum showed major peaks at *m/z* 232 $(M^+ - H_2O)$, 208 $(M^+ - C_2H_2O)$, and 192 $(M^+ - C_3H_6O)$, the latter two fragments further supporting a ketone moiety as shown in (**4**). The ^1H n.m.r. spectrum obtained at 200 MHz in $CDCl_3$ by two dimensional homonuclear shift correlations (COSY)[7] allowed the following assignments: δ 1.09 (d, *J* 7 Hz, C-10–Me), 1.20 (d, *J* 7 Hz, C-11–Me), 2.19 (s, C-4–Me), 5.6 (br. s, *J* 7 Hz, olefinic H-5), 4.8 (br. d, *J* 7 Hz, H-6). Eleven further proton absorptions appeared as complex multiplets near δ 2.6 (2 × H-3), 2.3 (H-11 and 2 × H-2), 1.9 (2 × H-9), and 1.6 (H-7 and 2 × H-8). Irradiation of the C-10–Me signal at δ 1.09 resulted in a positive nuclear Overhauser effect of the lactonic β-proton at C-6, confirming the specificity of the H-1α to C-10 shift, that is, β-orientation of the methyl group at C-10 in (**4**). The ^{13}C n.m.r. data of xanthanolide (**4**) were obtained at 50.32 MHz in $CDCl_3$ by application of the DEPT method[8] and fully support the proposed structure (**4**).†

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References

1 N. H. Fischer, E. J. Olivier, and H. D. Fischer, in: 'Progress in the Chemistry of Organic Natural Products,' vol. 38, eds. W. Herz, H. Grisebach, and G. W. Kirby, Springer-Verlag, Wien, New York. 1979, p. 47.
2 T. A. Geissman, *Recent. Adv. Phytochem.*, 1973, **6**, 65.
3 N. H. Fischer, *Rev. Latinoamer. Quim.*, 1978, **9**, 41.
4 W. Herz, *Isr. J. Chem.*, 1977, **16**, 32.
5 N. H. Fischer, Y-F. Wu-Shih, G. Chiari, F. Fronczek, and S. F. Watkins, *J. Natl. Prod.*, 1981, **44**, 104.
6 M. Ogura, G. A. Cordell, and N. R. Farnsworth, *Phytochemistry*, 1978, **17**, 957.
7 K. Nagayama, A. Kumar, K. Wüthrich, and R. R. Ernst, *J. Magn. Reson.*, 1980, **40**, 321.
8 D. M. Doddrell, D. T. Pegg, and M. R. Bendall, *J. Magn. Reson.*, 1982, **48**, 323.

† δ_C 145.7 (s, C-1), 33.2 (t, C-2), 41.7 (t, C-3), 207.7 (s, C-4), 123.8 (d, C-5), 81.0 (d, C-6), 51.0 (d, C-7), 31.4 (t, C-8), 25.3 (t, C-9), 37.4 (d, C-10), 42.3 (d, C-11), 178.7 (s, C-12), 12.4 (q, C-13), 15.8 (q, C-14), 29.9 (q, C-15).