Acid-induced Rearrangements of the Melampolide Schkuhriolide. An Alternative Approach to the Oplopane Skeleton

Guillermo Delgado* and Salvador Guzmán

Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitaria, Coyoacán 04510, México, D.F.

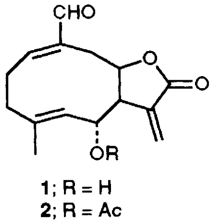
The acid catalysed transformation of the melampolide schkuhriolide **1** provided a mixture of epimers and the oplopanolide **5** *via* sequential rearrangements.

The transannular cyclization of germacrolides or their synthetic equivalents, which create σ-bonds regio- and stereospecifically,[1,2] may be considered as a classical methodology for the preparation of eudesmanolides, guaianolides[3,4] and xanthanolides,[5,6] among others. However, knowledge of the possible transannular cyclizations of the geometric isomers of germacrolides, namely, melampolides, heliangolides, and *cis,cis*-1(10),4-germacradienolides appears to be limited to a few studies,[7,8] and accumulated results do not permit any generalization. Described herein are the products of the acid-catalysed reaction of the natural melampolide schkuhriolide **1**,[9] which involves sequential rearrangements and represents a novel alternative approach to the bicyclo-[4.3.0]nonane ring system.

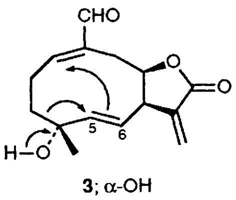
Treatment of an acetone solution of **1** or its acetyl derivative **2** with perchloric acid at room temperature for 15 min gave a mixture of three isolated products which included the epimers **3** and **4** and the oplopanolide **5**.

The *trans* nature of the C-5–C-6 double bonds and the antiperiplanar orientation of 6-H and 7-H of the tertiary alcohols **3** (84%) and **4** (7%) were evident by the observed couplings ($J_{5,6}$ 16 and $J_{6,7}$ 9 Hz) in the ^{1}H NMR spectra. The sequence from C-3 through C-7 clockwise was identified by ^{1}H and ^{13}C NMR and found to correspond to the starting material **1**.[9] Compounds **3** and **4** showed essentially the same ^{1}H and ^{13}C NMR features but showing the chemical shifts of 5-H and 6-H in reverse order ($\delta_{5\text{-H}}$ in **3**: 5.63; 5.18 in **4** and $\delta_{6\text{-H}}$ in **3**: 5.15; 5.60 in **4**). This difference established the epimeric relationship of **3** and **4** at C-4, since the magnetic anisotropy effect of the polar substituent β-oriented in **4** causes a downfield shift to 6-H, which is *syn* to the hetero-atom.

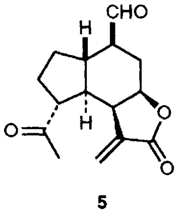
Compound **5** (5%) is also isomeric with **1**. IR and ^{13}C NMR data† of **5** supported the presence of three carbonyls: an aldehyde, γ-lactone carbonyl and a ketone. The lack of double bonds additional to the α-methylene group indicates the presence of the bicyclic system **5** whose structure was



1; R = H
2; R = Ac



3; α-OH
4; β-OH



5

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† *Selected spectral data* for **5**: IR ν/cm^{-1} (CHCl$_3$) 1765, 1726 and 1705; ^{13}C NMR (CDCl$_3$) 202.2 (d, *C*HO), 209.3 (s, Me*C*O) and 170.0 (s, lactonic *C*O).

confirmed by X-ray analysis.‡ The oplopanolide **5** may be derived by a transannular Michael reaction followed by a pinacol rearrangement as indicated in structure **3**.

The epimers **3** and **4** displayed marked differences in their behaviour toward $HClO_4$. At room temperature (for 15 min) **3** gave the mixture **3**–**5** in a similar ratio with respect to the reaction of **1** and **2**, whereas **4** remained practically unaffected. In addition, the ratio **3** : **5** of the acid induced reaction of **1**, **2** or **3** decreased significantly with time (from 20 : 1 in 15 min to 2 : 1 in 2 h). These experiments indicate that **3** is an intermediate in the formation of **5**.

The conversion of **1** into **5** represents an alternative entry to the oplopanoid-type natural products.[10]

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‡ *Crystal data* for oplopanolide **5**: $C_{15}H_{18}O_4$, monoclinic, space group P_12_1, $a = 8.5445(4)$, $b = 7.6576(4)$, $c = 10.7214(5)$ Å, $\alpha = 90(0)$, $\beta = 109.231(3)$, $\gamma = 90(0)°$, and $D_c = 1.3132$ g cm^{-3} for $Z = 2$, $\mu = 0.88$ cm^{-1}. The intensity data were measured on a Nicolet R3m diffractometer, λ = Mo-Kα, ω scans; a crystal measuring approximately 0.38 × 0.70 × 0.80 mm, $U = 662.36$ Å^3(0.48) was used for data collections; 50 kV, 20 mA, $2\theta/\theta$ scan mode, $3 < 2\theta < 105°$. A total of 1271 reflections were measured, of which 1228 were considered to be observed, $F_o > 3\sigma(F_o)$, $R = 0.364$, $R_w = 0.430$, $(\Delta/\sigma)_{avg} = 0.07$, $s = 1.384$, $U = 0.05$ Å^2, $k = 0.14254$, final $G = 0.001$. The application of direct methods techniques yielded the positions for all non-hydrogen atoms. Block-matrix least squares refinement with H-atom parameters fixed converged to indicated indexes. SHELXTL (G. M. Sheldrick, SHELXTL, University of Göttingen, Germany, 1983) was used for all calculations. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.