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PSEUDOGUAIANOLIDES : A STEREOSELECTIVE APPROACH TO 8(α)-OXYGENATED HELENANOLIDES. X-RAY STRUCTURAL DETERMINATION OF A SYNTHETIC INTERMEDIATE.

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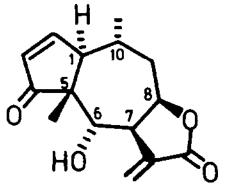
SUMMARY

The synthesis of perhydroazulenic lactone 8, a potential precursor for several helenanolides is described. Its structure is determined by X-ray diffraction of the corresponding alcohol 9.

During the past three years several groups have reported on the synthesis of pseudoguaianolides possessing a β-oriented methyl group at C-10, commonly known as ambrosanolides[1]. Very recently Grieco and coworkers[2] performed the first synthesis of a member (1; helenalin) of the helenanolide subgroup, characterized by the reversed configuration at C-10. In previous communications we have described an efficient entry into both series involving stereocontrol at C-10 and which led inter alia to the synthesis of the hydroazulenone 2[3].

In the present paper we describe a remarkable stereoselective functionalization of the 8-position, a prerequisite condition for synthesizing helenanolides, which all possess an α- or β-oriented oxyfunction (as γ-lactone) at C-8[4]. In a first stage the hydroxyketone 2 was transformed into olefin 3 using the Bamford-Stevens sequence : the p-toluenesulfonhydrazone, obtained from 2 by reaction with p-toluenesulfonhydrazide in ethanol (90°C, 4 h), was treated with methyllithium in ether (25°C, 4 h) yielding 3 (78 %) |ν(neat) 3400, 1650, 1455, 1370 and 1030 cm^{-1}; δ(CDCl$_3$) 0.88 (3H, s), 0.96 (3H, d), 3.75 (1H, d, 4.8 Hz), ~5.76 (2H, m); M$^{+\cdot}$ at m/z 180|.

After conversion of the alcohol 3 into the tert-butyldimethylsilyl ether 4 (75 % yield, tert-butyldimethylsilyl chloride and imidazole), the introduction of a hydroxyl group at C-8 was achieved in the second sequence.



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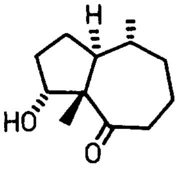

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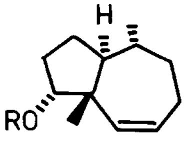

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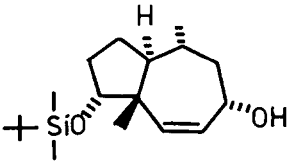
4 R = Si+



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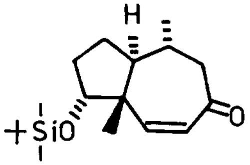

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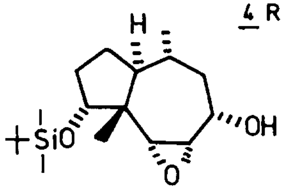

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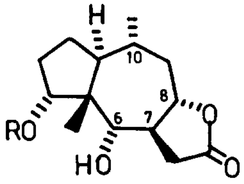


8 R = Si+
9 R = H

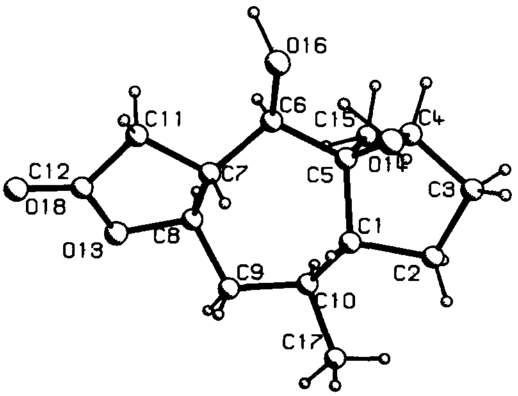
Treatment of 4 with N-bromosuccinimide in carbon tetrachloride afforded the diastereoisomeric allylic bromides which were directly converted into the alcohol 5 (50 % from 4) upon reaction with silver carbonate on celite in acetone containing one equivalent water (0°C, 1 h)^{5}. Although 5 |δ(CDCl$_3$) 0.76 (3H, s), 3.71 (1H, d, 4.5 Hz), 4.5 (1H, dq, 10.8 and 3 x 2.4 Hz), 5.5-6.0 (2H, m)| was found to be stereohomogeneous absolute proof for the indicated α-orientation at C-8 was only obtained at a later stage. Surprisingly when enone 6, obtained from 5 in 74 % yield by manganese dioxide oxidation in acetone (6 h, r.t.), was reduced with diisobutylaluminum hydride in toluene; the same alcohol 5 was obtained exclusively (yield 90 %)^{6}. We have so far found no rationalization for the remarkable stereoselectivity displayed in both reactions.

The conversion of the alcohol 5 into lactone 9 enabled unambiguously its structural determination by a X-ray diffraction study of the latter product. Fast oxidation of 5 (m-chloroperbenzoic acid in methylene chloride, 90 min, 70 %) yielded the epoxide 7 |ν(KBr) 3300, 1470, 1250, 1100, 1080, 835 and 770 cm^{-1}; δ(CDCl$_3$) 0.75 (3H, s), 0.95 (9H, s), 0.93 (3H, d), 3.09 (2H, AB quartet, $\Delta\nu_{AB}$ = 12.3 Hz, J = 4.8 Hz), 3.83 (1H, d, 6 Hz), 4.09 (1H, m)|, which was treated with dilithioacetate[7] (15 eq) in dimethoxyethane (55°C, 48 h); work-up (careful acidification to pH 4) yielded lactone 8 |ν(KBr) 3500, 1750, 1110, 985 cm^{-1}, δ($CDCl_3$) 0.78 (3H, s), 0.79 (9H, s), 0.88 (3H, d, 6.5 Hz), 3.88 (1H, m), 4.21 (1H, m), 4.51 (1H, d, 6.5 Hz)| next to unreacted epoxide 7. Hydrolysis of the silylether 8 yielded finally the dihydroxy lactone 9 |m.p. 127°-128°C; ν(KBr) 3400, 1785, 1230, 1220, 1110, 990 and 970 cm^{-1}; $(M-H_2O)^{+\cdot}$ at m/z 236; δ($CDCl_3$) 0.89 (3H, s), 1.01 (3H, d, 6.6 Hz), 3.54 (1H, d, 10 Hz), 4.10 (1H, m), 4.14 (1H, d, 5 Hz)|.

Table : Atomic coordinates (x 10^4) of 9

Atom*	x	y	z
C1	6479 (4)	5351 (3)	7757 (6)
C2	5807 (6)	5579 (4)	8863 (6)
C3	5743 (7)	6624 (4)	8923 (8)
C4	6424 (5)	6987 (4)	7920 (6)
C5	7416 (5)	6210 (3)	7936 (5)
C6	7974 (5)	6340 (3)	6667 (5)
C7	7550 (5)	5599 (3)	4512 (5)
C8	8213 (5)	4678 (3)	6099 (6)
C9	7393 (5)	4048 (3)	6640 (6)
C10	7155 (5)	4392 (3)	8028 (6)
C11	8038 (6)	5762 (4)	4146 (6)
C12	8294 (5)	4823 (4)	3695 (6)
O13	8398 (4)	4221 (2)	4817 (4)
O14	5330 (3)	7142 (2)	6356 (4)
C15	8683 (6)	6221 (4)	9575 (7)
O16	7595 (4)	7215 (2)	5919 (5)
C17	6273 (7)	3670 (4)	8360 (8)
O18	8439 (4)	4584 (3)	2549 (5)

* The numbers refer to those marked on the stereoview



The structure of the lactone 9 has been determined by X-ray diffraction; the crystals are monoclinic $P2_1/a$, a = 10.666(3), b = 14.593(5), c = 9.423(5)Å, β =

116.10(3)°, V = 1317.1(1.0)Å^3, *Mr* = 254.33, *Z* = 4, D_x = 1.28 g cm^{-3}. 1950 reflections were measured on a Syntex P2 diffractometer, radiation Mo*K*α (λ = 0.7107 Å). The structure was resolved by MULTAN 78[8], refined by SHELX 76[9] to a final *R* = 0.046 for 1365 observed reflections. The atomic coordinates of the carbon and oxygen atoms are given in the table[10]. The cyclopentane has a C-5 envelope conformation and the γ-lactone a C-7 envelope conformation; the cycloheptane is a chair with a pseudo-mirror plane passing through C-9 and the midpoint of the 5,6 bond[10].

Lactone 8 is a potential precursor for helenanolides possessing the α-stereochemistry at C-8 of which several representatives are found in nature[4]. Further work in this area is in progress.

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10. List of other atomic parameters and structure factors will be supplied on request by M. Van Meerssche.

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