PHOTOCHEMICAL REARRANGEMENTS OF 18-HYDROXYLATED LANOSTEROL DERIVATIVES

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Several lanosterol derivatives with 18-hydroxyl group were subjected to the hypoiodite reaction. A new C-secosteroid was obtained as well as the desired 5-membered 18,20-epoxy compound.

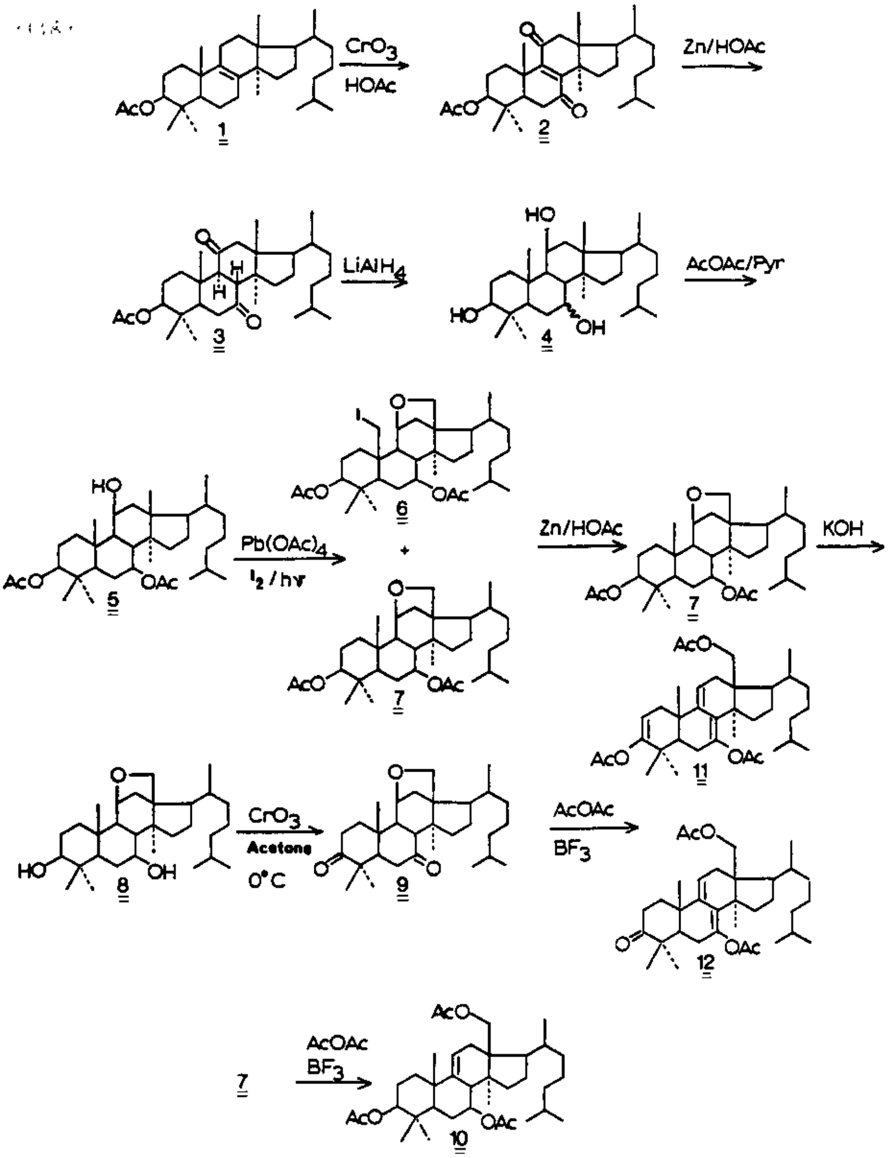
During work on the synthesis of seychellogenin[1,2] and other holothurinogenins, we studied intensely the photochemistry of lanosterol derivatives with the aim of synthesizing 18,20-epoxy compounds.

Therefore the first problem was the synthesis of a 18-hydroxylanostane derivative to be used as a key compound. We achieved this aim by a multiple step synthesis starting from dihydrolanosterol acetate (1), which was oxidized with chromous oxide in acetic acid[3] to yield 3β-acetoxy-lanost-8-en-7,11-dione (2).

The central double bond could now be reduced with zinc in acetic acid, to achieve the trans B/C connected ring system in compound 3[4]. Reduction of the two keto groups in positions 7 and 11 with lithiumaluminumhydride in tetrahydrofuran led to the expected 3β,7β,11β-trihydroxylanostane (4) and the corresponding 7α-hydroxyl compound. Under mild conditions the sterically hindered 11β-hydroxyl group does not react during acetylation. After this step, the resulting mixture of the 7α- and 7β-acetates had been separated by fractional recrystallization from methanol/methylenechloride.

The pure 3β,7β-diacetoxylanostan-11β-ol (5) yielded in the hypoiodite reaction[5] a mixture of two 11β,18-ethers 6 and 7. Separation of this mixture is not necessary as 3β,7β-diacetoxy-19-iodo-11β,18-expoxylanostane (6) could easily be converted into 3β,7β-diacetoxy-11β,18-epoxylanostane (7) by treatment with zinc and acetic acid.

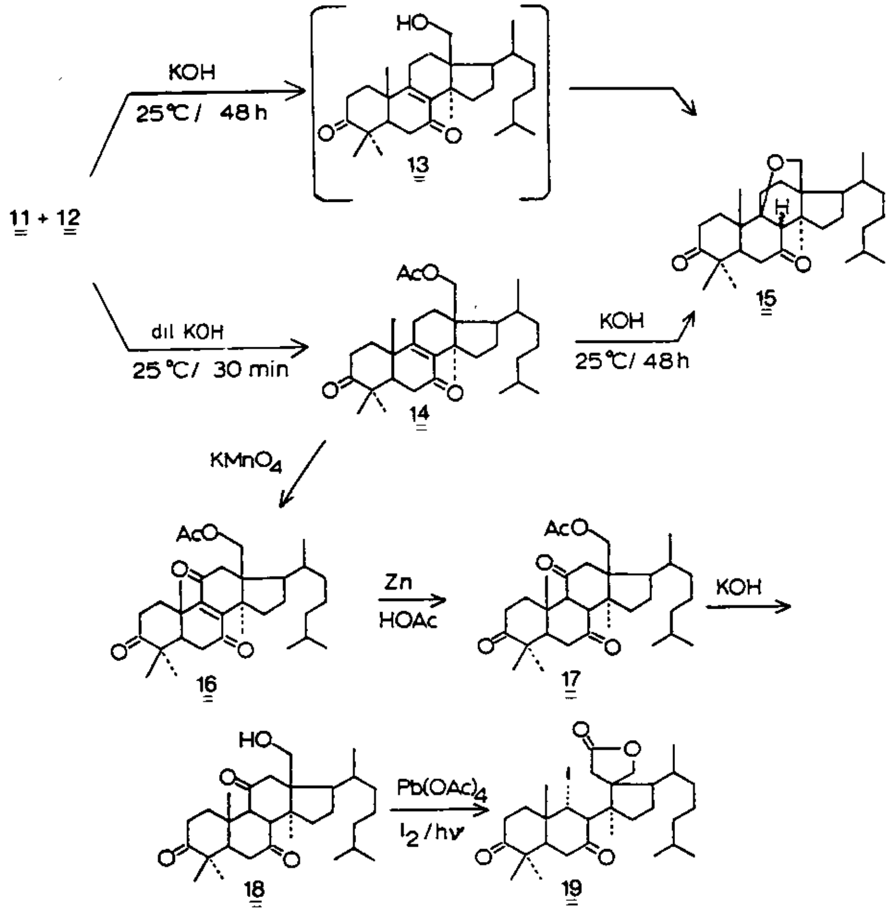
SCHEME I



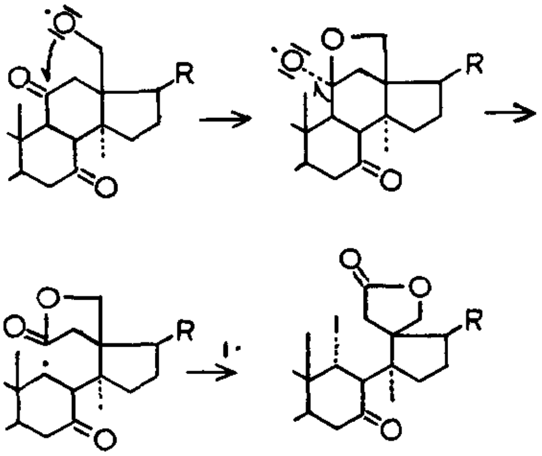
After saponification in methanolic potassium hydroxide solution, we obtained the 3β,7β-dihydroxyl compound 8, and by Jones-reaction, the corresponding diketone 9 resulted. Cleavage of the cyclic ether was easily achieved by treatment with borontrifluoride in acetic acid anhydride[6]. By this 7 yielded 3β,7β,18-triacetoxylanost-9(11)-ene (10); under the same conditions 9 gave a mixture of the enol acetates 11 and 12[7].

The further procedure required hydrolysis of compounds 11 and 12, respectively. Rather surprisingly, treatment with methanolic potassium hydroxide did not yield the 18-hydroxyl compound expected, but the 9,18-epoxylanostane-3,7-dione (15). Under the applied alkaline conditions compound 13 underwent self-cyclization and could not be isolated. By reducing the reaction time, 18-acetoxylanost-8-ene-3,7-dione 14 could be isolated, which again formed 15 under prolonged reaction time.

SCHEME II



A further attempt was made starting with compound 14. Oxidation with potassium permanganate in acetone yielded 18-acetoxylanost-8-ene-3,7,11-trione (16), the double bond of which was again reduced with zinc and acetic acid to give 18-acetoxylanostane-3,7,11-trione (17). 17 then could be hydrolyzed to 18-hydroxylanostane-3,7,11-trione (18). Hypoiodite reaction of 18 now did not yield the expected 18,20-ether, but a C-seco-steroid (19). The explanation could be a sequence of radical reactions as described as follows:



The third approach started again from 3β,7β,18-triacetoxylanost-9(11)-ene (10). Considering that neither an oxygen function nor a double bond should exist at C-11, compound 10 was hydrogenated. Attempts to hydrogenate with platinum in acetic acid and several other hydrogenating reagents did not lead to reasonable results. Hydrogenation, however, was achieved with palladium on activated charcoal as catalyst in methanol and using the 3β,7β,18-trihydroxy compound instead of the triacetate. Reacetylation yielded 3β,7β,18-triacetoxylanostane (20), m.p. 131-132°C.

Another problem at this stage was the stereochemistry at C-9 of 20. The answer could be given by ORD and CD spectra. For this comparison 18-acetoxylanostane-3β-ol-7-one (25) was prepared from 20 by hydrolysis of the acetoxyl groups at C-3 and C-7, oxidation to the 3,7-diketo compound and partial reduction of the 3-keto group to yield 25.

Comparison of the obtained compound 25 with 5α-cholestan-7-one[8] (31) with respect to their ORD- and CD-curves showed that both of them possess the same Cotton effect; the ring connection B/C must therefore be the natural one.

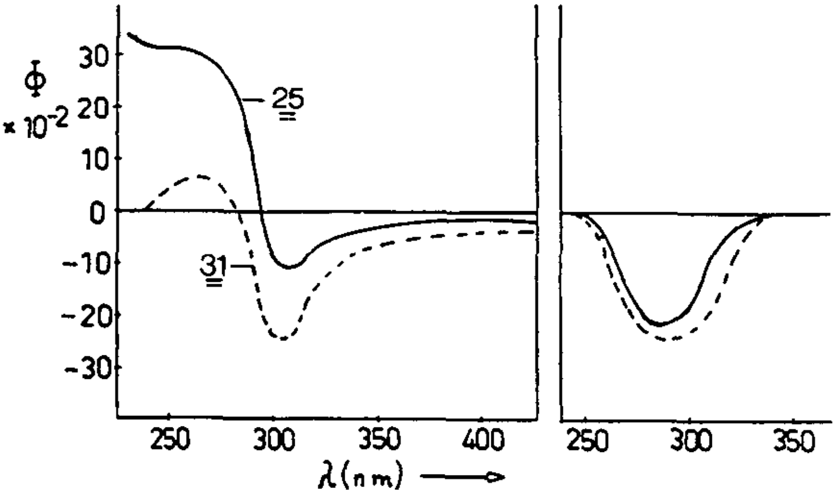
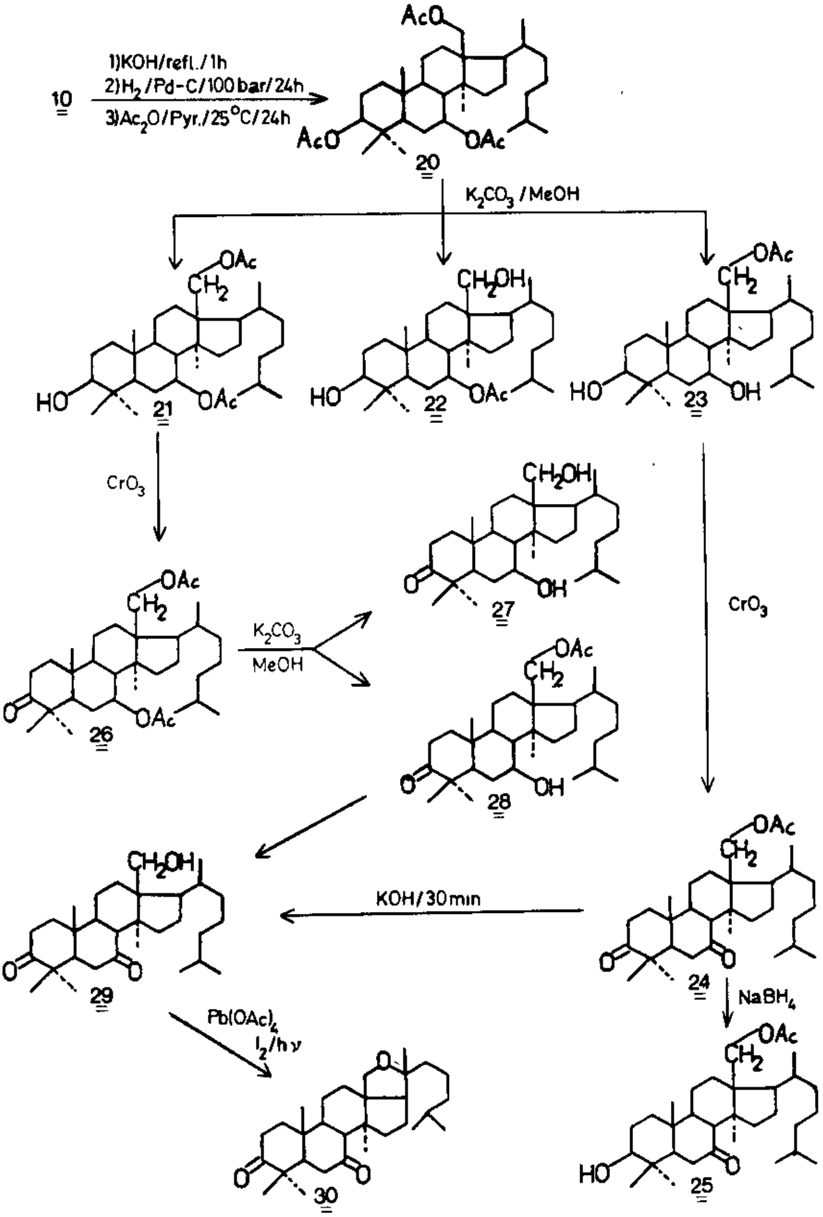


Fig.: CD- and ORD-curves of compounds 25 and 31.

Compound 20 now was converted into 18-hydroxyl-3,7-dione (29) in a four step synthesis.

In this reaction procedure,we made use of the different hydrolysis rates of the 3β,7β and 18-acetoxyl groups. The most reactive one is the 3β-acetoxyl group followed by position 7. The 18-acetate is by far the most stable one. Irradiation of compound (29) was made under the conditions of a hypoiodite reaction. The course of this reaction could be seen by thin layer chromatography. As to be expected, a number of by-products appeared besides the main product, 18,20-epoxylanostane-3,7-dione (30). It could be isolated by chromatography on silica gel. After recrystallization the melting point was 189-191°C, yield: 44%.

SCHEME III



All structures unambiguously resulted from IR, ^{13}C-NMR, ^{1}H-NMR and mass spectra.

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