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14β-HYDROXY STEROIDS - III.[1]
SYNTHESIS OF DIGOXIGENIN FROM DEOXYCHOLIC ACID

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Abstract: A new synthetic approach to cardenolides is discussed which employs singlet oxygen addition to dienol ethers and an intramolecular Prins reaction.

The cardiac glycosides are widely used drugs because of their positive inotropic effect on the failing heart.[2] Their aglycones (cardenolides, c. f. digoxigenin (13)) are steroids characterized by an α,β-unsaturated γ-lactone substituent at the 17β-position as well as 14β-hydroxy group. Much effort has been expended on the synthesis of naturally occuring cardenolides. In most cases construction of the butenolide side chain has relied on C_{21} steroids as starting materials.[3] Recently, direct transformations of 17-oxo-androstane derivatives to cardenolides were reported.[4,5] Introduction of the 14β-hydroxy group in all recorded syntheses was achieved via a Δ^{14}-olefinic precursor.[3]

We wish to disclose new solutions to both synthetic problems. Our approach is exemplified by a short and efficient synthesis of digoxigenin (13) starting from readily available deoxycholic acid (1).

Treatment of 1 with a slight excess of N,N'-carbonyldiimidazole in tetrahydrofuran (0.25 M concentration of 1, 3 h at 20°C) led to imidazolide 2 [6] which was in situ irradiated in 0.02 M tetrahydrofuran solution with a high pressure mercury lamp (HPK 125) through a water cooled quartz immersion well (Iwasaki method[7]) to give after chromatography on silica gel a 58% overall yield of 3.

Inversion of configuration at C-3 applying Mitsunobu's method[8] to 3 (1.1 equivalents of acetic acid) gave 3β-acetate 4 in 73% yield. Photosensitized oxygenation of 4 in acetone (8 h at 25°C, 1000 W halogen lamp, tetraphenylporphine as sensitizer) followed by hydroperoxide reduction with sodium iodide afforded,

after silica gel chromatography, 18% of unsaturated aldehyde 6 and 61% of allylic alcohol 7, which upon manganese dioxide oxidation in methylene chloride generated 6 in 88% yield.

6 was transformed by reaction with 1.2 equivalents of methoxymethylenetriphenylphosphorane [9] (prepared from the phosphonium chloride with potassium t-butoxide) in ether into the isomeric dienol ethers 5. Since these dienol ethers proved to be very sensitive compounds [10] they were (after centrifugation to remove solid material and evaporation) immediately allowed to react in methylene chloride solution with singlet oxygen (20 min at 25°C, 1000 W halogen lamp, rose bengal as sensitizer). The isomeric cycloaddition products 8 [11] were not isolated. On treatment with triethylamine in methylene chloride (10 min at 20°C) they were smoothly converted into cardenolide 9. The reaction in assumed to proceed by proton abstraction at C-23 and heterolytic opening of the peroxide group to the anion of a hydroxy ester, followed by lactone formation. [11] The overall yield of 9 from 6 was, after chromatographic separation, 57%.

The next task, stereospecific introduction of the 14β-hydroxy group, was accomplished by a very efficient remote oxidation process. [1,12] Photolysis of ketone 10, obtained from 9 by pyridinium chlorochromate oxidation, [13] in methylene chloride (30 min at 15°C, HPK 125, pyrex filter) furnished a mixture of 14 and 15. Secoaldehyde 14 is formed by well-known α-cleavage and hydrogen migration from C-14 to C-12, 15 by Paterno-Büchi reaction of 14. Mild acid (tetrahydrofuran / acetic acid / trifluoroacetic acid / water = 1 : 1.2 : 0.4 : 0.4, 24 h at 15°C) effected rearrangement of 15 to 14 and an intramolecular Prins reaction [1] of 14 to give 11 and 12, which were isolated in 28% and 44% yield. 11 and 12 were identified by comparison with authentic samples. [14] Finally, ester hydrolysis (1.5% methanolic HCl 16 h at 20°C) transformed 11 cleanly into 13, identical with an authentic sample.

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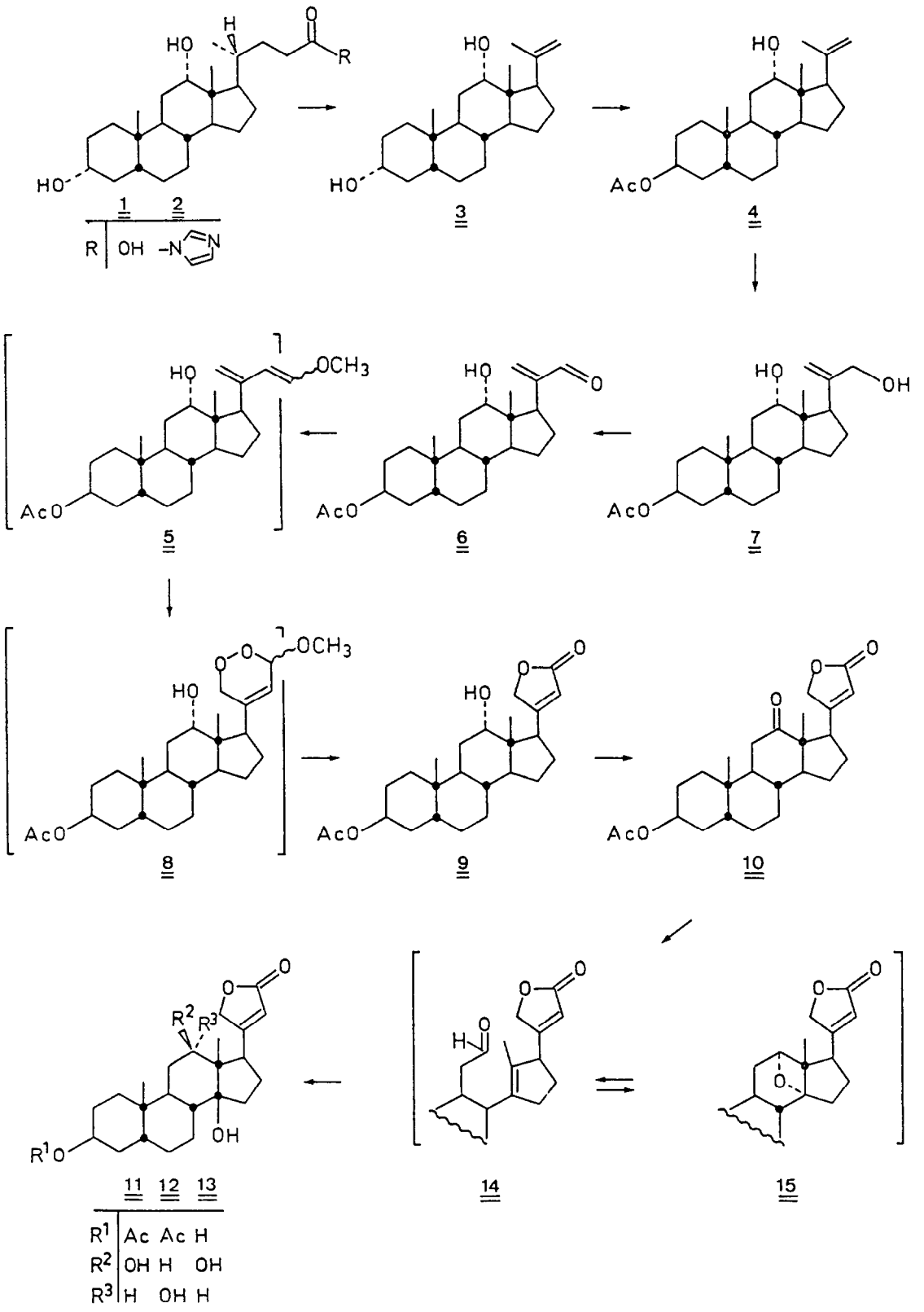
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R1 Ac Ac H
R2 OH H OH
R3 H OH H
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