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A New Approach to the Synthesis of the 17β-Butenolide Fragment of Cardenolides

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Abstract: A new, efficient synthesis of the 17β-butenolide fragment characteristic of cardenolides is effected by [2 + 2]-cycloaddition of dichloroketene to 3β-acetoxypregna-5,20-diene, as a key step.

Keywords: Cyclobutanones; Steroids; Cardenolides

Cardenolides are plant steroids, which occur as glycosides and possess powerful cardiotonic activity. They are considered as "the most ingested drugs in medicine".[1] Since the pioneering studies by Ruzicka[2] and the first synthesis of digitoxigenin[3] in 1962 enormous efforts have been directed toward synthetic cardenolides.[4] Despite the long history of research in the area, the interest in cardenolides continues. Recently reported work on cardenolides concerns the total synthesis,[1a] the biosynthesis,[5] and the search for new, less toxic digitalis-like compounds for therapeutic use with better pharmacological properties.[6] The new methods of introduction of the 17β-butenolide moiety[4] and synthetic approaches to complex cardenolides have also been reported.[7] Besides the 14β-hydroxyl group, the 17β-butenolide moiety is one of the crucial features of cardenolides indispensable for their biological activity. 17-Oxoandrostanes and 21-hydroxy-20-oxopregnanes have been widely used as substrates in the syntheses of cardenolides.[4,8]

This work is a continuation of our interest in steroidal cyclobutanones.[9] Since the transformation of pregnane derivatives into 17β-butenolide steroids requires a two carbon side chain elongation, the reaction of the appropriate olefinic substrate with a reactive ketene appeared to be an attractive approach to the four carbon side-chain moiety characteristic of cardenolides.

The Scheme 1 illustrates the synthetic pathway. The starting olefin **1**, the 3β-acetoxypregna-5,20-diene, was obtained from 3β-acetoxypregn-5-en-20-one following the reported procedure.[10] The regioselective [2 + 2] cycloaddition of **1** and dichloroketene[11a] afforded dichlorocyclobutanone **2** in 58% isolated yield.[11b] This could be effectively reduced with zinc in AcOH to **3** or **4**, depending on the reaction conditions.[12] However, when the crude cycloaddition product was immediately reduced **4** was isolated in 82% yield.[11c] At this stage of the synthesis, the 3β-hydroxyl group had to be protected as a TBDMS-ether in two steps: hydrolysis of **4** (K_2CO_3, MeOH; 98% yield of **5**) followed by the reaction with t-butyldimethylsilyl chloride (imidazole, DMF, 1h, r.t.) gave **6** in 92% yield. The Baeyer-Villiger oxidation of **6** (30% H_2O_2, MeOH-THF, NaOH) resulted in formation of the lactone **7** (87% yield after short column chromatography) as a 1:1 mixture of C-20 epimers.[11d] The dehydrogenation of the lactone **7** was achieved by taking advantage of the phenylselenylation-oxidation procedure.[13] Compound **8** was isolated in 75% yield from the reaction of **7** with LDA and PhSeCl (THF, -70 °C), while oxidation of **8** (30% H_2O_2, THF-AcOH) gave butenolide **9** in 67% yield. The deprotection of the TBDMS-ether afforded the known 3β-hydroxy derivative **10**.[14]

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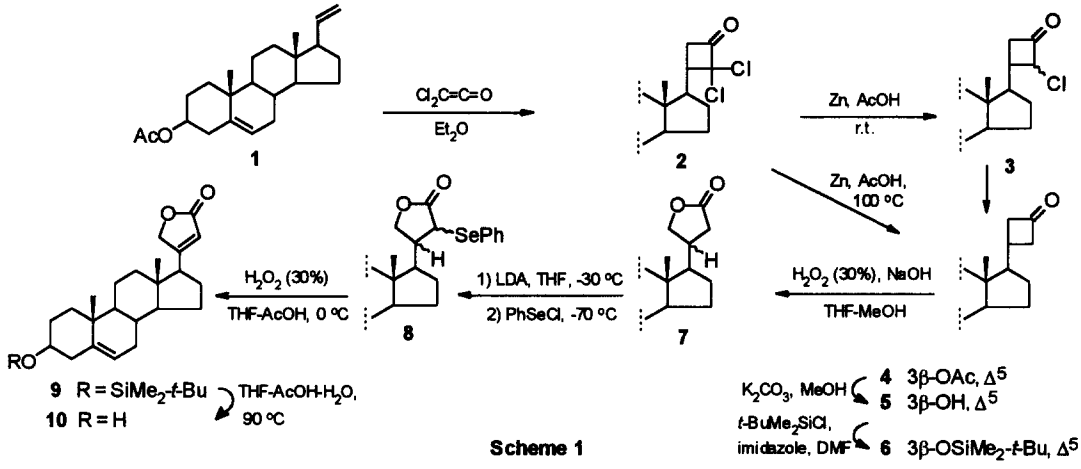
This method of constructing the butenolide fragment of cardenolides is relatively simple and efficient (the total yield of the five step synthesis of **9** from the readily available **1** is 32 %). The transformation of 14α-card-20(22)-enolide to the Δ^{14} olefin and 14β-hydroxy derivatives has been reported.[15]



Scheme 1

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11. (a) $Cl_2C=C=O$ was generated *in situ* from Cl_3COCl and Zn in Et_2O, under sonification conditions; (b) purification of the crude reaction product on SiO_2 column is usually accompanied by the slow decomposition of the dichlorcyclobutanones (ref. 9b); (c) Δ^5-double bond was unreactive toward dichloroketene; (d) the ratio was estimated from the integration of the low field signals at δ: 4.47, 4.37, 3.93 and 3.83 in the ^1H NMR spectrum.
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16. **2**: IR ($CHCl_3$): ν = 1805, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.38 (br d, J = 4.9 Hz, 1H, 6-H), 4.60 (m, 1H, 3α-H), 3.22 - 3.03 (m, 2H, CH_2CO), 2.03 (s, 3H, CH_3CO_2), 1.03 and 1.02 (s, 3H, 19H,), 0.78 and 0.72 (s, 3H, 18-H). **4**: m.p. 130-132°C (MeOH),); IR: ν = 1775, 1725 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.38 (br d, J = 5.1 Hz, 1H, 6-H), 4.60 (m, 1H, 3α-H), 3.14 - 3.00 (m, 2H, CH_2CO), 2.87 - 2.70 (m, 2H, CH_2CO), 2.03 (s, 3H, CH_3CO_2), 1.03 (s, 3H, 19-H), 0.70 (s, 3H, 18-H). **7**: m.p. 201-205 °C; IR ($CHCl_3$): ν = 1775 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.33 (bd, J=5.2 Hz, 1H, 6-H), 4.47 (dd, J_1 = 8.24 Hz, J_2 = 8.52 Hz, 1H, CH_2O, isomer A) and 4.37 (dd, J_1 = 8.24 Hz, J_2 = 7.97 Hz, 1H, CH_2O, isomer A), 3.93 (dd, J_1 = 9.07 Hz, J_2 = 9.34 Hz, 1H, CH_2O, isomer B) and 3.83 (dd, J_1 = 9.07 Hz, J_2 = 9.61 Hz, 1H, CH_2O, isomer B), 3.48 (m, 1H, 3α-H), 2.65-2.48 (m, 2H, CH_2CO), 1.00 (s, 3H, 19-H), 0.89 [9H, s, $C(CH_3)_3$], 0.70 and 0.69 (s, 3H, 18-H), 0.06 [s, 6H, $Si(CH_3)_2$]. **9**: mp: 183-185 °C (heptane), $[\alpha]_D$ = - 40° (c = 0.25, $CHCl_3$); IR ($CHCl_3$): ν = 1785, 1750, 1630 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.85 (d, J = 1.6 Hz, 1H, 22-H), 5.32 (bd, J = 5.2 Hz, 1H, 6-H), 4.83 and 4.69 (ABX, J = 17.6 Hz and 1.6 Hz, 2H, CH_2O), 3.48 (m, 1H, 3α-H), 1.00 (s, 3H, 19-H), 0.89 [s, 9H, $C(CH_3)_3$], 0.64 (s, 3H, 18-H), 0.06 [s, 6H, $Si(CH_3)_2$].