



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

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Abstract: A new, efficient synthesis of the 17 β -butenolide fragment characteristic of cardenolides is effected by [2 + 2]-cycloaddition of dichloroketene to 3 β -acetoxypregna-5,20-diene, as a key step.
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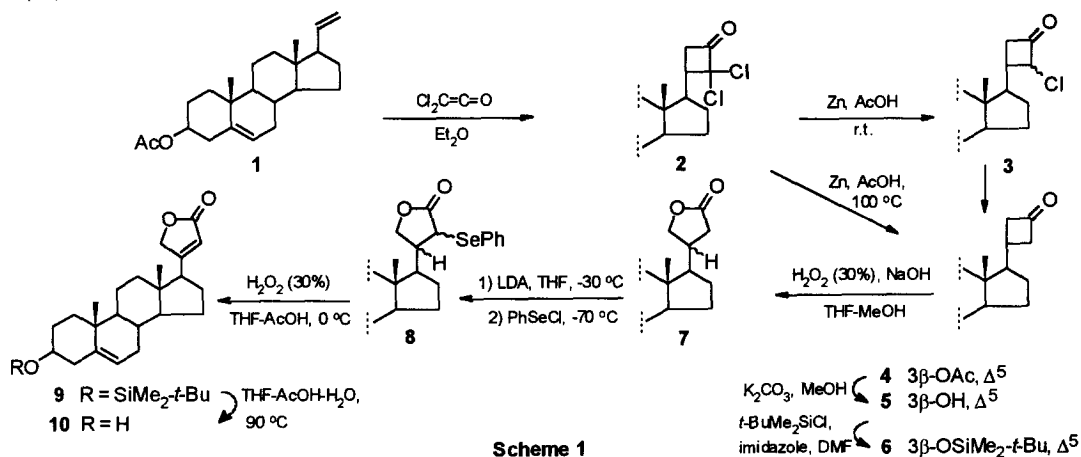
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Cardenolides are plant steroids, which occur as glycosides and possess powerful cardiotonic activity. They are considered as "the most ingested drugs in medicine".¹ Since the pioneering studies by Ruzicka² and the first synthesis of digitoxigenin³ 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 17 β -butenolide moiety⁴ and synthetic approaches to complex cardenolides have also been reported.⁷ Besides the 14 β -hydroxyl group, the 17 β -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 17 β -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 3 β -acetoxypregna-5,20-diene, was obtained from 3 β -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 3 β -hydroxyl group had to be protected as a TBDMS-ether in two steps: hydrolysis of **4** (K₂CO₃, 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% H₂O₂, 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% H₂O₂, THF-AcOH) gave butenolide **9** in 67% yield. The deprotection of the TBDMS-ether afforded the known 3 β -hydroxy derivative **10**.¹⁴

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 14 α -card-20(22)-enolide to the Δ^{14} olefin and 14 β -hydroxy derivatives has been reported.¹⁵



References and notes

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- (a) $\text{Cl}_2\text{C}=\text{C}=\text{O}$ 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 dichlorocyclobutanones (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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- 2**: IR (CHCl_3): $\nu = 1805, 1725 \text{ cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3): $\delta = 5.38$ (br d, $J = 4.9 \text{ Hz}$, 1H, 6-H), 4.60 (m, 1H, 3 α -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 $^\circ\text{C}$ (MeOH); IR (CHCl_3): $\nu = 1775, 1725 \text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 5.38$ (br d, $J = 5.1 \text{ Hz}$, 1H, 6-H), 4.60 (m, 1H, 3 α -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 $^\circ\text{C}$; IR (CHCl_3): $\nu = 1775 \text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 5.33$ (bd, $J = 5.2 \text{ Hz}$, 1H, 6-H), 4.47 (dd, $J_1 = 8.24 \text{ Hz}$, $J_2 = 8.52 \text{ Hz}$, 1H, CH_2O , isomer A) and 4.37 (dd, $J_1 = 8.24 \text{ Hz}$, $J_2 = 7.97 \text{ Hz}$, 1H, CH_2O , isomer A), 3.93 (dd, $J_1 = 9.07 \text{ Hz}$, $J_2 = 9.34 \text{ Hz}$, 1H, CH_2O , isomer B) and 3.83 (dd, $J_1 = 9.07 \text{ Hz}$, $J_2 = 9.61 \text{ Hz}$, 1H, CH_2O , isomer B), 3.48 (m, 1H, 3 α -H), 2.65-2.48 (m, 2H, CH_2CO), 1.00 (s, 3H, 19-H), 0.89 [9H, s, $\text{C}(\text{CH}_3)_3$], 0.70 and 0.69 (s, 3H, 18-H), 0.06 [s, 6H, $\text{Si}(\text{CH}_3)_2$]. **9**: mp: 183-185 $^\circ\text{C}$ (heptane), $[\alpha]_D^{25} = -40^\circ$ (c = 0.25, CHCl_3); IR (CHCl_3): $\nu = 1785, 1750, 1630 \text{ cm}^{-1}$; ^1H NMR (CDCl_3): $\delta = 5.85$ (d, $J = 1.6 \text{ Hz}$, 1H, 22-H), 5.32 (bd, $J = 5.2 \text{ Hz}$, 1H, 6-H), 4.83 and 4.69 (ABX, $J = 17.6 \text{ Hz}$ and 1.6 Hz, 2H, CH_2O), 3.48 (m, 1H, 3 α -H), 1.00 (s, 3H, 19-H), 0.89 [s, 9H, $\text{C}(\text{CH}_3)_3$], 0.64 (s, 3H, 18-H), 0.06 [s, 6H, $\text{Si}(\text{CH}_3)_2$].