Notes

Synthesis of Digitoxigenin from 3*β*-[(*tert*-Butyldimethylsilyl)oxy]-17α-iodo-5*β*-androstan-14*β*-ol via 17*β* Stereoselective Free-Radical Introduction of *γ*-Butyrolactone Moiety

Nicoletta Almirante* and Alberto Cerri

Prassis Istituto di Ricerche Sigma-Tau, Via Forlanini 3, 20019 Settimo Milanese (MI), Italy

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Digitalis cardiac glycosides, such as digoxin, digitoxin, and ouabain, are naturally occurring inotropic drugs clinically used for the treatment of congestive heart failure,[1] although their low therapeutic index makes their use not completely safe. The search for less toxic agents prompted a lot of work on natural compounds.[2] Recently, the identification of endogenous digitalis-like factors that may be responsible for essential hypertension[2] has opened a new field in the study of digitalis compounds.

The genins of these molecules (cardenolides), *e.g.*, digitoxigenin **8** (Scheme 1), are steroids with three peculiar structural characteristics, all of them of utmost importance for the pharmacological action: the *cis* C/D ring junction, the 17*β*-butenolide moiety, and the 14*β*-hydroxyl function.

As a part of our work aimed at searching new digitalis-like compounds with a better pharmacological profile, we wish to report an improvement to a known synthetic approach to digitoxigenin.

The synthesis of cardenolides starting from more readily available steroids, *i.e.*, with a *trans*-fused C/D ring system, is still the aim of several research groups, and 17-oxoandrostane derivatives have been widely used as cardenolide precursors.[3] In most of the published syntheses, the 14*β*-hydroxylation step follows the introduction of a 17*β* substituent. Actually, if the 14*β*-hydroxyl group is added before the elaboration of the ketone at the 17 position, due to the *cis* C/D ring junction, only the isomer possessing the thermodynamically more stable 17α residue is obtained, either directly by nucleophilic attack to the 17-keto group or by hydrogenation of the $\Delta^{16(17)}$ or $\Delta^{17(20)}$ double bond.[3]

However, we needed to construct the 17*β*-butenolide moiety starting from steroidal compounds with a *cis* C/D ring junction.

Quite recently, Daniewsi[4] and Wicha[5] reported that 14*β*-hydroxy-17*β*-cyanoandrostane derivatives were good starting materials for the synthesis of digitoxigenin and its 9(11)-dehydro derivative. The introduction of the 17*β*-cyano group was easily and selectively accomplished from a 14*β*-hydroxy-17α-iodo derivative *via* an S_N2-type free-radical reaction with *tert*-butyl isocyanide without the protection of the 14*β*-hydroxy function. This strategy resulted in a new and highly stereospecific method for the 17*β* functionalization of a *cis* C/D ring steroid. However, the four-step process leading to the butenolide ring from the 17*β*-cyano group was troublesome and low yielding (10% yield).

In order to find a more efficient process, we decided to investigate whether the high *β* stereoselectivity shown by the carbon radical generated at the 17 position in the attack to *tert*-butyl isocyanide could be preserved as a peculiarity of the structure, in the reaction with other suitable functionalized reagents. Actually, in the literature, simple cyclopentyl radicals or cyclic radicals from sugars with substituents at the α position are reported to yield preeminently the *trans*-substituted product.[6] Since 2-buten-1,4-olide and its derivatives were reported to be unreactive as radical acceptors by Daniewski,[4] we directed our attention to a similar but handier and more reactive compound, conveniently designed for further synthetic manipulation. We chose maleic anhydride, a most frequently used radical acceptor in free-radical chemistry, which had two important requirements: it allowed us to achieve the desired five-membered ring in the *β* configuration in one step and the intermediate adduct could undergo a polar intramolecular reaction with the already present 14*β*-hydroxyl to discriminate the two carbonyl functions.

Scheme 1 illustrates the synthetic pathway. The starting iodide **1** was obtained from 3*β*,14*β*-dihydroxy-5*β*-androstan-17one[5] *via* elaboration of the corresponding 17-hydrazono compound to the 17-iodo-16-dehydro derivative and then hydrogenation of the double bond with diimide (55% overall yield) following a reported procedure.[5] The 3*β*-hydroxy group of **1** was protected as the TBDMS ether **2** to prevent reaction with maleic anhydride. The free-radical reaction was performed with tris(trimethylsilyl)silane[7] (TTMSS) and AIBN in toluene at 90 °C with 2 equiv of maleic anhydride, since TTMSS is known to react with it. Following the reaction by TLC, we could spot the formation of an intermediate that slowly evolved to a new more polar pruduct during the reaction. We found that the best workup for the reaction was a basic treatment (DBU/Et_2O)[8] that allowed the complete conversion of the first intermediate to the more polar product and prevented the dehydration of the acid-labile 14*β*-hydroxy function. The structure of the polar product was identified with the 17*β*-functionalized compound **5** (70% yield from the iodide **2**). In principle, lactone **5** could derive from iodide **2** through two different intermediates (Scheme 1): the 14*β*-*O*-maleate derivative **3** or the anhydride **4**. We can affirm that the unisolated intermediate of the reaction is the anhydride **4** because, even if the high stereoselectivity shown by the free-radical reaction might be ascribed to an intramolecular

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(3) Recent leading reference: Kabat, M. *J. Org. Chem.* **1995**, *60*, 1823.

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(5) Daniewski, A. R.; Kabat, M. M.; Masnyk, M.; Wojciechowska, W.; Wicha, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1064.

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(8) Modification of Curran procedure without treatment with iodine: Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.

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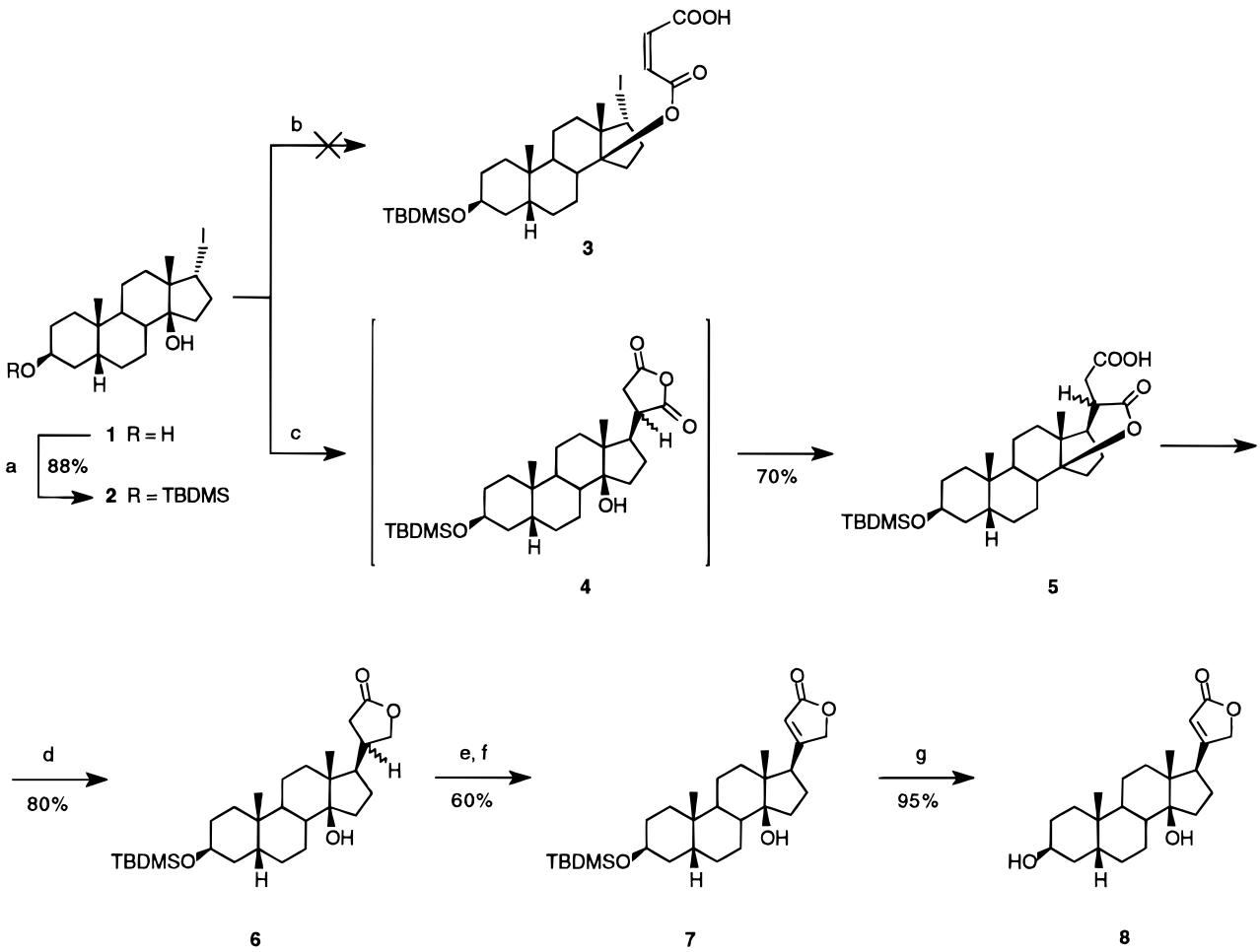
Scheme 1[a]



[a] Reagents and conditions: (a) TBDMSCl, imidazole, DMF, rt, 20 h; (b) maleic anhydride, $PhCH_3$, 90 °C, 4 h; (c) (i) maleic anhydride, TTMSS, AIBN, $PhCH_3$, 90 °C, 1.5 h; (ii) DBU, Et_2O, rt, 20 h; (d) (i) $NaBH_4$, MeOH, THF, reflux, 1.5 h; (ii) HCl (aq), Et_2O, rt, 20 h; (e) (i) LDA, THF, −30 to 0 °C; (ii) PhSeCl, −70 °C, 3 h; (f) AcOH, H_2O_2, THF, −10 °C to rt, 1.5 h; (g) 0.2 N H_2SO_4(aq), MeOH, reflux, 1 h.

addition, as in the case of derivative **3**, an ester adduct between 14β-OH and maleic anhydride was never observed. In fact, the two reactants were recovered unchanged after prolonged heating in the absence of the radical initiator (besides, it is known that a 14β-ester derivative is not easily prepared).[9]

The isolation of lactone **5** confirmed both of our hypotheses: an advanced precursor of the butanolide ring could be selectively introduced at position 17β in one step, and the 14β-OH allowed the discrimination between the two carbonyl functions of the intermediate anhydride. Further, the presence of the lactone in compound **5** was a confirmation of the β-stereoselective pathway of the radical reaction.

Compound **5** could be easily transformed into the cardanolide derivative **6** by a chemoselective reduction of the lactone ring with $NaBH_4$−MeOH in refluxing THF.[10] After a careful workup, compound **6** was isolated in 80% yield as a diastereoisomeric mixture. Lactone **6** was transformed into the unsaturated lactone **7** (60% yield) through the oxidation of the corresponding α-(phenylselenyl) derivative, following a general method.[11] Subsequent acid removal of the silyl group gave digitoxigenin **8**, in 95% yield, whose analytical and spectral data were in full agreement with those of an authentic sample.

In conclusion, this reaction sequence provides an efficient method for the stereoselective introduction of a γ-butyrolactone moiety at the 17β-position of 14β-hydroxy steroids through an advanced precursor such as **5**, which offers the advantage of presenting differently manageable functionalities in the desired lactone skeleton that permit an easy and efficient transformation into the desired butenolide ring.

Experimental Section

Melting points were determined by the capillary method on an electrothermal apparatus and are uncorrected. NMR spectra were recorded at 300.13 MHz (^{1}H NMR) or at 75.48 MHz (^{13}C NMR) in $CDCl_3$ solution with Me_4Si as the internal standard; J values are in Hz. Mass spectral data were obtained with an electron-impact ionization technique at 70 eV using the direct exposure probe (DEP). Flash chromatography was carried out on silica gel (70−230 mesh). After workup, organic solvents were dried over anhydrous Na_2SO_4 and then filtered, and the solvent was evaporated under reduced pressure on a rotary evaporator.

(9) Acetylation of the 14β-hydroxy group was accomplished with acetic anhydride in pyridine in the presence of DMAP after 6 days at room temperature; see: Lindig, C.; Repke, K. R. H. *J. Prakt. Chem.* **1987**, *329*(5), 841.

(10) Soai, K.; Oyamada, H. *Synthesis* **1984**, 605.

(11) Urones, J. G.; Basabe, P.; Marcos, I. S.; Díez Martín, D.; Sexmero, M. J.; Peral, M. H.; Broughton, H. B. *Tetrahedron* **1992**, *48*, 10389.

Yields refer to homogeneous products (TLC). Elemental analyses were performed by Redox, Cologno Monzese, Italy.

3β-[(*tert*-Butyldimethylsilyl)oxy]-17α-iodo-5β-androstan-14β-ol (2). A solution of compound **1**[5] (737 mg, 1.6 mmol), TBDMSCl (583 mg, 3.9 mmol), and imidazole (526 mg, 7.7 mmol) in DMF (10 mL) was stirred at room temperature overnight. The solution was then diluted with water, extracted with Et_2O, and dried. After evaporation, the crude product was purified by flash chromatography (*n*-hexane/EtOAc 90:10) to afford **2** (825 mg, 88%) as a white solid: ^{1}H NMR δ 0.025 (s, 6H), 0.89 (s, 9H), 0.940 (s, 3H), 0.946 (s, 3H), 2.04 (m, 1H), 2.19 (m, 1H), 2.44 (m, 1H), 4.04 (m, 1H), 4.44 (t, J = 9.0, 1H); MS m/z (rel intensity) 532 (M^+, 1), 475 (23), 255 (100). An analytical sample was obtained by crystallization from EtOH/water: mp 177−179 °C. Anal. Calcd for $C_{25}H_{45}IO_2Si$: C, 56.38; H, 8.52; I, 23.83. Found: C, 56.46; H, 8.61; I, 23.66.

(20*RS*)-3β-[(*tert*-Butyldimethylsilyl)oxy]-14β-hydroxy-5β,24-norcholane-21,23-dioic Acid 14,21-Lactone (5). To a solution of iodo derivative **2** (600 mg, 1.12 mmol) and maleic anhydride (222 mg, 2.26 mmol) in toluene (10 mL) heated at 90 °C under a nitrogen atmosphere was added a solution of TTMSS (0.72 mL, 2.38 mmol) and AIBN (19 mg, 0.12 mmol) in toluene (4 mL) dropwise over 1 h. After an additional 0.5 h at 90 °C, the reaction was cooled to 0 °C and a mixture of DBU (0.34 mL, 2.24 mmol) in Et_2O (6 mL) was added dropwise. After being stirred at room temperature overnight, the mixture was poured into 5% aqueous NaH_2PO_4 (30 mL) previously brought to pH 3 with 3 N HCl; additional 3 N HCl was added during the quenching to keep the pH in the range of 3.2−3.5. The mixture was extracted with EtOAc and the organic phase dried and evaporated. The residue was purified by flash chromatography (*n*-hexane/acetone/$CHCl_3$ 60:20:20) to yield **5** (390 mg, 70%) as a white solid, 1:1 diastereoisomeric mixture. The product was essentially pure by TLC and ^{1}H NMR analysis and was used for the next step without further purification: ^{1}H NMR of the 1:1 diastereoisomeric mixture δ 0.024 (s, 12H), 0.89 (s, 18H), 0.97 (s, 3H), 0.98 (s, 3H), 1.01 (s, 3H), 1.13 (s, 3H), 2.42 (dd, J = 16, 7, 1H), 2.58 (dd, J = 13, 9, 1H), 2.90−3.20 (m, 3H), 3.36 (m, 1H), 4.05 (m, 2H); ^{13}C NMR δ 175.5, 175.2, 174.8 174.3, 95.8 and 95.2 (C-14), 44.6 and 45.0 (C-13), 15.7 and 14.5 (C-18); MS m/z (rel intensity) 489 (M^+ − 15, 1), 447 (77), 371 (100). An analytical sample, unchanged in diastereoisomeric ratio, was obtained by crystallization from $CHCl_3$/*n*-hexane. Anal. Calcd for $C_{29}H_{48}O_5Si$: C, 69.00; H, 9.58. Found: C, 68.81; H, 9.61.

(20*RS*)-14β-Hydroxy-3β-[(*tert*-butyldimethylsilyl)oxy]-5β-cardanolide (6). To a solution of acid **5** (250 mg, 0.49 mmol) in THF (5 mL) was added $NaBH_4$ (129 mg, 3.4 mmol), and the mixture was refluxed while MeOH (1.1 mL) was slowly added dropwise over 1 h. During the reduction a vigorous gas evolution took place. After being refluxed for an additional 0.5 h, the mixture was cooled and dropped into 5% aqueous NaH_2PO_4 (10 mL) previously brought to pH 3 with 3 N HCl; additional 3 N HCl was added during the quenching to keep the pH in the range of 3.2−3.5. After addition of Et_2O, the mixture was acidified to pH 1.4 with 3 N HCl and stirred overnight. Then EtOAc was added and the mixture extracted. After evaporation, the residue was purified by flash chromatography (CH_2Cl_2/EtOAc 95:5) to yield **6** (192 mg, 80%) as a white solid, 1:1 diastereoisomeric mixture: ^{1}H NMR δ 0.022 (s, 12H), 0.89 (s, 18H), 0.93 (s, 6H), 0.95 (s, 3H), 0.97 (s, 3H), 2.18 (dd, J = 17, 10, 1H), 2.38 (dd, J = 18, 10, 1H), 2.57 (dd, J = 18, 10, 1H), 2.70 (dd, J = 17, 10, 1H), 2.88 (m , 2H), 3.88 (t, J = 9, 1H), 4.05 (m, 3H), 4.42 (t, J = 8, 1H), 4.51 (t, J = 9, 1H); MS m/z (rel intensity) 475 (M^+ − 15, 2), 433 (100). Anal. Calcd for $C_{29}H_{50}O_4Si$: C, 70.97; H, 10.27. Found: C, 70.61; H, 10.39.

Digitoxigenin 3-*tert*-Butyldimethylsilyl Ether (7). To a solution of lactone **6** (152 mg, 0.31 mmol) in dry THF (3 mL) cooled to −30 °C, under a nitrogen atmosphere, was slowly added a 2 M commercial solution of LDA in THF/heptane/ethylbenzene (0.93 mL, 1.86 mmol). The temperature was slowly raised to 0 °C during 1 h. The solution was then cooled to −70 °C, and a solution of PhSeCl (370 mg, 1.92 mmol) in THF (3 mL) was slowly added. The mixture was stirred for 3 h and then poured into 5% aqueous NaH_2PO_4 (10 mL) previously brought to pH 3 with 3 N HCl; additional 3 N HCl was added during the quenching to keep the pH in the range of 3.2−3.5. The mixture was extracted with EtOAc, the organic phase dried, and the solvent evaporated. The residue was dissolved in THF (5 mL), and AcOH (0.1 mL) was added. The resulting solution was cooled to −10 °C, and 30% H_2O_2 (0.34 mL, 3 mmol) was slowly added. After 0.5 h, the yellow solution was brought to room temperature and stirred for 1 h. The resulting pale yellow solution was quenched with aqueous $NaHCO_3$ and the mixture extracted with EtOAc. The residue was purified by flash chromatography (CH_2Cl_2/EtOAc 95:5) to yield **7** (90 mg, 60%) as a white solid. An analytical sample was obtained by crystallization from $CHCl_3$/*n*-hexane: mp 228−232 °C; ^{1}H NMR δ 0.023 (s, 6H), 0.98 (s, 9H), 0.88 (s, 3H), 0.93 (s, 3H), 2.14 (m, 2H), 2.80 (m, 1H), 4.05 (m, 1H), 4.81 (d, J = 18, 1H), 5.01 (d, J = 18, 1H), 5.90 (m, 1H); MS m/z (rel intensity) 473 (M^+ − 15, 2), 431 (100). Anal. Calcd for $C_{29}H_{48}O_4Si$: C, 71.27; H, 9.90. Found: C, 70.88; H, 9.90.

Digitoxigenin (8). A mixture of silyl ether **7** (60 mg, 0.12 mmol), MeOH (2 mL), and 0.2 N H_2SO_4 (0.27 mL) was refluxed for 1 h. After cooling, the solution was poured into 5% aqueous NaH_2PO_4 and extracted with EtOAc. The residue was purified by flash chromatography (*n*-hexane/EtOAc 70:30), yielding **8** (44 mg, 95%) as a white solid, pure by TLC and ^{1}H NMR: mp 240−245 °C (from EtOAc; identical to melting points of a commercial sample, Fluka, and of a mixed sample).

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