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[A0010]

Stereoselective Synthesis of New Simplified Digitalis-Like Compounds from (+)-(3aS,7aS)-3a-Hydroxy-7a-Methylperhydroinden-1,5-Dione[1]

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INTRODUCTION

Cardiac glycosides of *Digitalis* species are well known heart-stimulating drugs, clinically used for treatment of congestive heart failure.[2] In the steroidal moiety of the aglycons (cardenolides) the C/D *cis* ring junction, the 14b-OH and the 17b-butenolide could be recognized as three peculiar features for a potent pharmacological action, while the A/B ring junction can vary from *cis* (e.g. **digitoxigenin**) to *trans* (e.g. **uzarigenin**) (**Fig. 1**) without a dramatic loss of activity. As a part of our work aimed at searching new digitalis-like compounds with an improved pharmacological profile, we synthesized compound **9** (**Fig. 1**) in which the C/D part of the molecule was maintained while the A/B part was simplified in a 5b-cyclohexyl substituent.

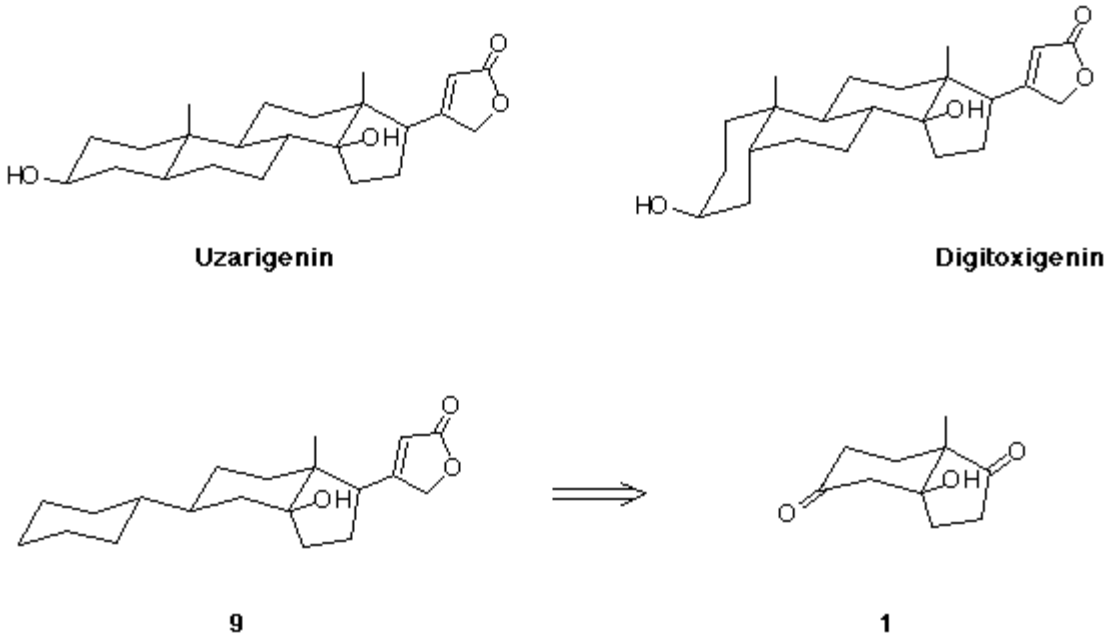
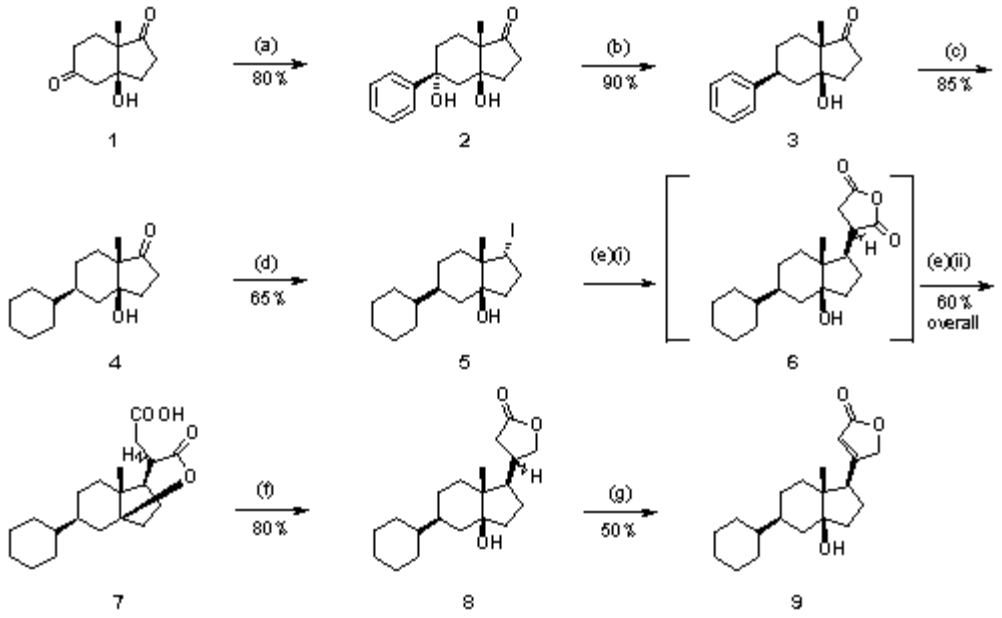


Figure 1

CHEMISTRY

In **Scheme 1** the synthetic approach for the synthesis of **9**, starting from the known (+)-(3aS,7aS)-3a-hydroxy-7a-methylperhydroinden-1,5-dione **1**[3] is reported.



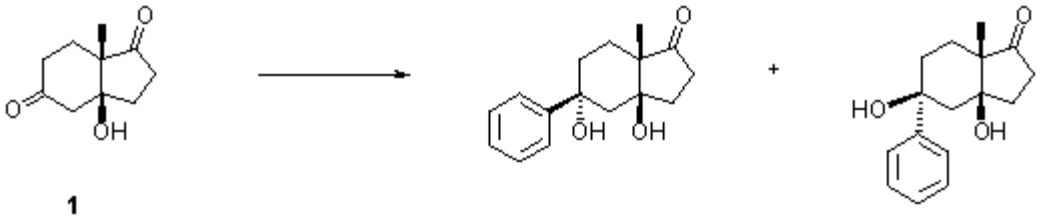
Scheme 1. Reagents and condition: (a) $CeCl_3$, PhLi, THF, -78deg.C ; (b) Raney-Ni, EtOH, reflux ; (c) H_2, Rh/Al_2O_3, 48 psi, MeOH ; (d) (i) NH_2NH_2, TEA, EtOH, reflux ; (ii) I_2, TEA, THF; (iii) NH_2NH_2, O_2, AcOH, EtOH (96 deg.), reflux ; (e) (i) Maleic anhydride, TTMSS, AIBN, $PhCH_3$, 90deg.C ; (ii) DBU, Et_2O then NaH_2PO_4/ HCl 3N (pH 3.5), Et_2O ; (f) $NaBH_4$, MeOH, THF, reflux then HCl, pH 1.4 ; (g) (i) LDA, THF, -20deg.C / 0deg.C then, PhSeCl - 78deg.C / rt ; (ii) H_2O_2, AcOH, THF.

The first problem was to find a reagent and/or reaction conditions permitting a regio- and stereoselective nucleophilic attack of the 5-keto function.

A reaction with an organometallic reagent could do the trick, owing to the higher reactivity of 5- vs. 1-keto group and the easier approach from the b-face compared to the more hindered a-face (**Fig. 1**).

Disappointingly the reaction with PhLi gave an almost 1:1 mixture of 5a and 5b-phenyl derivatives in only 40% yield, probably due to enolization of the ketone.

To overcome the problem we repeated the arylation on the $CeCl_3$/C=O complex[4]: this time the yield was 73% and the ratio between the 5b-phenyl **2** and the corresponding 5a-phenyl was 4.6:1 (**Scheme 2**).



Scheme 2.

The two diastereoisomers were easily separated by flash chromathography and the benzylic 5a-hydroxy group of **2** was eliminated by hydrogenolysis with Raney-Nickel with complete retention of configuration.

The desired cyclohexyl derivative **4** was obtained by hydrogenation with Rh/Al_2O_3 as a catalyst.

At this point, a b-substituent in position 1 had to be introduced.

First we transformed, with a known, stereospecific reaction sequence, the 1-keto derivative **4** into the 1a-iodo compound **5**; then applied a stereospecific free-radical reaction with maleic anhydride, recently published by us,[5] to obtain the advanced precursor **7** of the 1b-butenolide target compound, probably through the anhydride **6**. Chemoselective reduction of the ester function of **7** led to the butanolide derivative **8** which was transformed into the final compound **9** in 7% overall yield.

CONCLUSIONS

The simplified cardenolide **9**, with a perhydroindene skeleton, was obtained from the known, enantiopure compound **1** with a simple and versatile reaction sequence. The key steps were the introduction of a cyclohexyl substituent at 5b-position and of the butenolide moiety at 1b-position. The transformations were achieved through few stereo- and regioselective reactions. The free-radical introduction of an advanced precursor of the butenolide ring, performed by us on a 14b-androstane derivative,[5] could thus be successfully exported to a more flexible nucleus.

REFERENCES and NOTES

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