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SYNTHESIS OF STROPHANTHIDIN

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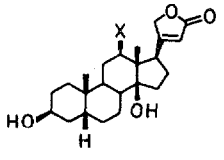
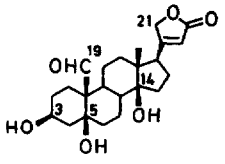
Abstract: A 16-step synthesis of strophanthidin (3) from a commercially available steroid 4 is described. Salient features of this approach are the selective reduction of the dienone system in 7 to give 8 and a one-pot introduction of 5ß- and 14ß-hydroxyls by addition of HOBr (14 → 15). The stereo- and regioselectivity of the HOBr addition to the 5,6-double bond is controlled by 19-formyloxy group.

Steroidal cardiotonic glycosides are indispensable drugs for treatment of heart insufficiency. Aglycones of the most common compounds possessing this unique activity are digitoxigenin (1), digoxigenin (2) and strophanthidin (3).[1] Although 1 has been synthesized more than a dozen of times,[2] to date there is only one synthesis of 3 described in the literature[3,4] which represents a 24-step sequence. Here we wish to report on a considerable shorter synthesis of 3 based on our methodology[5] of the stereo- and regiocontrol of electrophilic additions by neighboring groups.



1, X = H
2, X = OH



3

Retrosynthetic analysis suggested 5,16-pregnadien-3ß-yl-20-one acetate (4) as the starting material. Comparison of the latter with the structure of strophanthidin (3) indicates four strategic steps: hydroxylation in positions 5ß and 14ß, oxidation of the angular methyl (C-19) into CHO-group, and oxygenation of C-21 followed by construction of the unsaturated lactone ring. For the functionalization of C-14 we intended to use chemistry[6] in which the 5,6-double bond of 4 would interfere so that a protection of this part of the molecule was required. Fortunately, the methodology known[7,8] for oxidation of C-19 could also serve as a masking technique for the 5,6-double bond. Thus, it was obvious that the

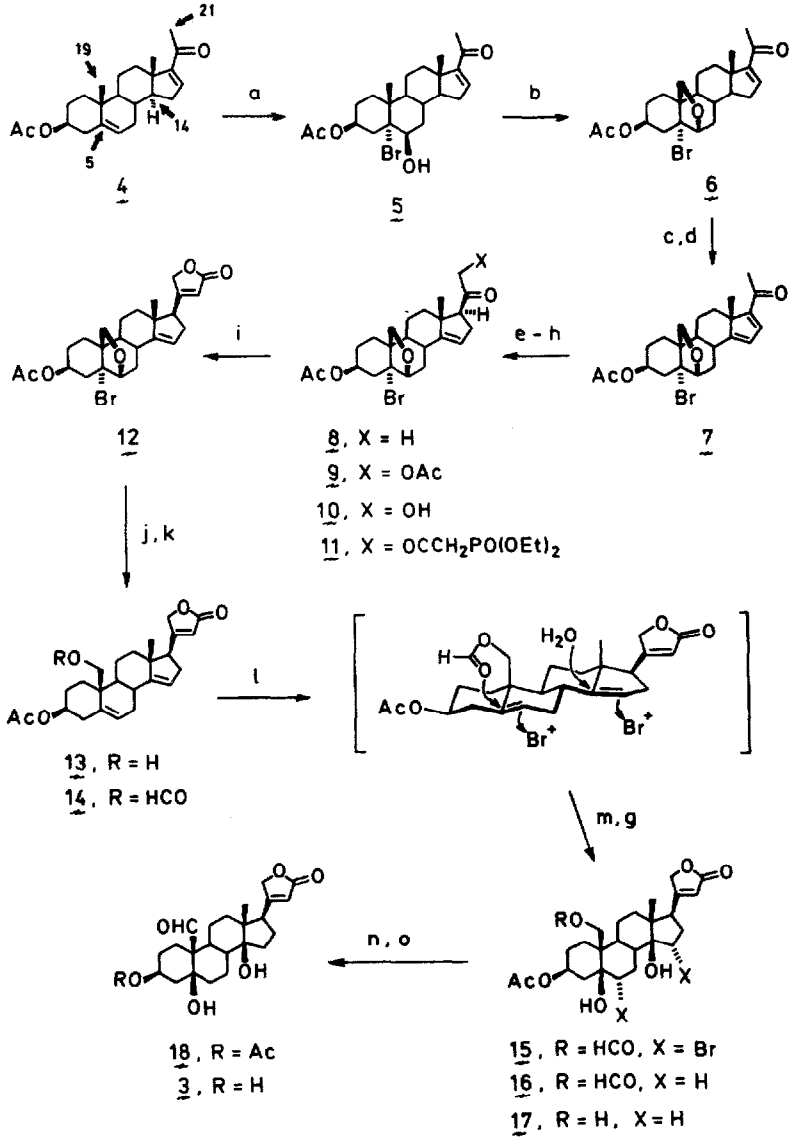
C-19 functionalization should be done in an early stage of the synthesis. A number of methods are available for the construction of the lactone ring[9] and some of them appeared mild enough to tolerate functional groups in our intermediates. Finally, a method for the stereo- and regiocontrolled 5β-hydroxylation has been recently developed in our laboratory[5] and had the promise of bringing the major short-cut of our synthesis. After some experimentation with timing of the particular steps and compromising the yields, the synthesis was carried out as follows.

Dienone **4** was first converted to the diaxial bromohydrin **5**[10,11] which on a radical reaction with lead tetraacetate[7] afforded the cyclic bromoether **6** in an 83% yield. Having thus simultaneously functionalized the angular methyl and protected the 5,6-double bond we could now introduce the 14,15-double bond through radical allylic bromination[6] of **6** followed by dehydrobromination (**6** ⟶ **7**). Next step, i.e. selective reduction of the dienone system in **7** at the central double bond, turned out to be a difficult problem. After numerous unsuccessful attempts using known methods[3,12] we found that **7** can be transformed to **8** by palladium-catalyzed hydrosilylation which, under specific conditions,[13] produced the desired enone **8** in a 68% yield. The following oxygenation of C-21 was carried out by a modified method developed for the construction of the corticoid side-chain[14] which employs the reaction of lead tetraacetate with the kinetic enol-ether generated *in situ* from the methyl ketone by $MeOH/BF_3$. Resulting acetoxy derivative **9** was selectively saponified with $KHCO_3$ at the primary position and the product **10** was esterified by diethylphosphonoacetic acid to give ester **11** which on reaction with t-BuOK readily cyclized to the lactone **12** (81%).

The bromoether moiety in **12** was then reduced with zinc in boiling acetic acid to furnish unsaturated alcohol **13** that was converted to formate **14** (86%). The formate group was introduced in order to control the regio- and stereochemistry of the next step, i.e. addition of hypobromous acid to the 5,6-double bond. As expected,[5] employment of 2 equivalents of HOBr (generated *in situ* from NBA) resulted in the simultaneous hydroxylation in positions 5β and 14β as the crucial step. One equivalent of the reagent reacted with 14,15-double bond in consonance with Markovnikov rule.[6] The required regiochemistry of the addition of the second equivalent of HOBr was successfully ensured by $6(O)^{\pi,n}$-exo-Trig participation[5] of the formate group so that we have obtained a product with diequatorial arrangement 5β-OH and 6α-Br rather than the diaxial one (compare with the addition in the absence of a neighboring group **4** ⟶ **5**). The double bromohydrin **15** resulting from this one-pot reaction was unstable and was immediately transformed to diol **16** by radical reduction with 2 equivalents of tri-n-butyltin hydride in a 58 % overall yield.

Subsequent selective hydrolysis of the formate group with $KHCO_3$ produced strophanthidol 3-acetate **17**, which on Jones oxidation furnished strophanthidin acetate **18**[15] whose saponification to strophanthidin **3** has been described earlier.[16]

In conclusion, this 16-step sequence shows that strophanthidin (**3**) can be synthesized from a common, commercially available steroid (**4**) in a shorter way than previously reported by the Japanese authors[3] in their 24-step approach. These results have also demonstrated how



Scheme: (a) $CH_3CONHBr$, $HClO_4$, Et_2O, H_2O, r.t.; (b) $(AcO)_4Pb$, I_2, $CaCO_3$, C_6H_6, reflux; (c) NBS, AIBN, CCl_4, reflux; (d) LiI, Li_2CO_3, DMF, 100°C; (e) Ph_2SiH_2, $(dppe)_2Pd$, $ZnCl_2$, $CHCl_3$; (f) $(AcO)_4Pb$, MeOH, $BF_3.Et_2O$, r.t; (g) $KHCO_3$, C_6H_6, MeOH, H_2O; (h) $(EtO)_2P(O)CH_2CO_2H$, DCC, DMAP, Et_2O, C_5H_5N, r.t.; (i) t-BuOK, THF, r.t.; (j) Zn, AcOH, MeOH, 80°C; (k) 85% HCO_2H, 70°C; (l) 2 equiv. $CH_3CONHBr$, $HClO_4$, H_2O, dioxane, r.t.; (m) 2 equiv. Bu_3SnH, AIBN, C_6H_6, reflux; (n) CrO_3, Me_2CO, H_2O, H_2SO_4, 0°C; (o) Et_3N (ref. 16).

the methodology we have developed for controlling electrophilic additions to cyclohexene systems[5] can be applied to the construction of a relatively complex natural product. We currently explore further possible improvements of our synthesis.

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