A stereoselective synthesis of digitoxin. On cardioactive steroids. XIII[1]

THOMAS Y. R. TSAI, HAOLUN JIN, AND KAREL WIESNER[2]
Natural Products Research Centre, University of New Brunswick, Fredericton, N. B., Canada E3B 6E2

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The first highly stereoselective synthesis of digitoxin is described. The furyl derivative of digitoxigenin was coupled with one unit of digitoxose using our previously described acid catalyzed method. For the second and third glycosylation a new method involving ethyl thioglycosides and 1,3-participation by a *p*-methoxy benzoate group was developed. As the final step after deprotection of the triglycoside, the 17-furyl group in the steroid aglycone was converted to a butenolide by our oxidative method.

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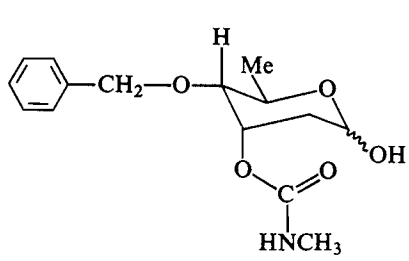
On décrit la première synthèse très stéréosélective de la digitoxine. On a couplé le dérivé furyle de la digitoxigénine avec une unité de digitoxose en faisant appel à la méthode acido-catalysée que nous avons décrite antérieurement. Afin de réaliser les deuxième et troisième glycosylations, on a développé une nouvelle méthode impliquant les thioglycosides d'éthyle et une participation-1,3 d'un groupement *p*-méthoxy benzoate. Dans la dernière étape, qui suit la déprotection du triglycoside, on utilise notre méthode oxydative pour transformer, en buténolide, le groupement furyle en position 17 de l'aglycone stéroidique.
[Traduit par le journal]

Digitoxin (**16**), first in the form of crude Digitalis extracts, later as a pure crystalline glycoside, has been used in medicine for 200 years. Even today, in spite of the deadly toxicity of natural Digitalis glycosides, these compounds belong among the ten most prescribed drugs. Our interest in the total synthesis of digitoxin started when it became desirable to attach the natural digitoxin glycosidic side chain to our totally synthetic relatively nontoxic cardenolide and bufadienolide analogues in order to prolong their duration of action and modify some other of their pharmacologic parameters.

The reaon why digitoxin, in spite of its importance, resisted previous attempts at total synthesis was the nonexistence of a highly stereoselective β-glycosylation method for 2-deoxy sugars in general and digitoxose in particular. We have partly remedied this situation in a previous communication of this series (2) in which we have shown that a 1,3-participation of a urethane group can control the stereochemistry of the acid catalyzed glycosylation of a digitoxose derivative.[3]

The starting material for the present synthesis was the protected glycoside **6** (mp 151–153°C; $[\alpha]_D$ −7.68; ^{1}Hmr ($CDCl_3$) δ: 8.03, 6.98 (d, J = 10 Hz, 2H each, 4 aromatic H), 7.34, 7.23, 6.49 (br s, 1H each, furan), 5.56 (br s, 1H, 3′-H), 4.93 (d, J = 10 Hz, 1H, 1′-H), 4.08 (br s, 1H, 3-H), 3.90 (s, 3H, —OCH_3), 1.35 (d, J = 6 Hz, 3H, 6′-CH_3), 0.92 (s, 3H, 19-CH_3), 0.71 (s, 3H, 18-CH_3)) which we have prepared by the previously described stereoselective method (2) followed by a simple modification of the protecting groups as portrayed in the formulae **1**–**6**.



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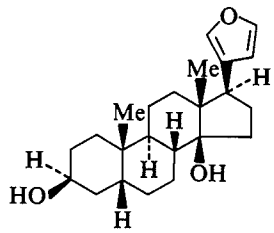

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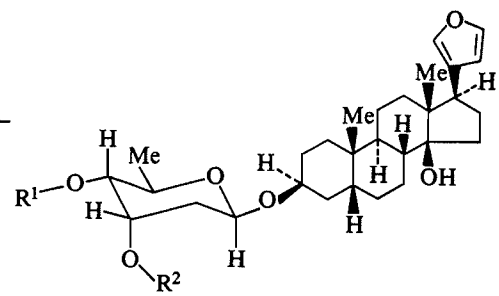
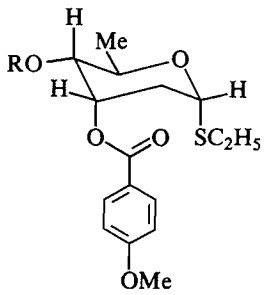


3 R^1 = Bzl, R^2 = $CONHCH_3$
4 R^1 = Bzl, R^2 = H, mp = 166.5–168°C; $[\alpha]_D$ = +6.22
5 R^1 = Bzl, R^2 = —CO—C$_6$H$_4$—OMe
6 R^1 = H, R^2 = —CO—C$_6$H$_4$—OMe

3 → **4** $LiAlH_4$/THF reflux; **4** → **5** *p*-methoxybenzoyl chloride/pyridine; **5** → **6** Pd/C, H_2

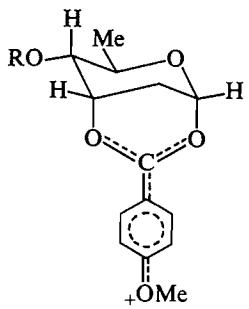
[1]For Part XII, see ref. 1.
[2]Author to whom correspondence should be addressed.
[3]In ref. 2 we have neglected to quote the preparation of digitoxigenin β-digitoxoside in a yield of 35%, β/α stereoselectivity 1.4:1 (cf. ref. 3). We thank the authors for drawing our attention to their paper.

It soon became clear that it is not possible to continue the synthesis by the same method. With glycosidic bonds present, both in starting material and product, cleavage predominated over glycosylation and the higher glycosides were obtained only in traces. In order to deal with the second and third stage of the synthesis, we have prepared by simple acid catalyzed glycosylation (anhydrous CH_2Cl_2 *p*-toluenesulfonic acid) the ethyl α-thioglycosides **7** and **8** and the corresponding β-glycosides (4(*a*)).[4] Treatment of **6** in CH_2Cl_2 at 20°C for 40 h with 4 mol of the α-thioglycoside **7**, 4 mol of $HgCl_2$, and



7 R = O_2N—C(=O)—, mp = 94–95°C; $[\alpha]_D$ = +214.12

8 R = MeO—C(=O)—, mp = 104–105°C; $[\alpha]_D$ = +266.51



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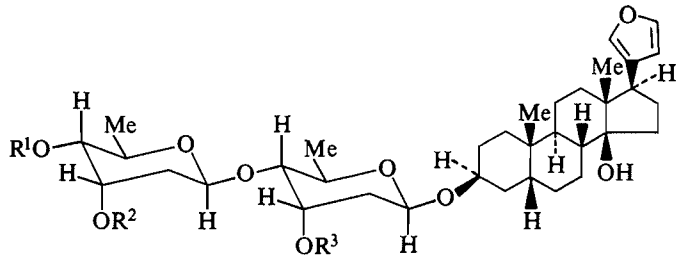
an excess of $CdCO_3$ yielded the oily product **10** besides starting material. Compound **10** was obtained in a yield of 60% on the basis of starting material not recovered (^{1}Hmr ($CDCl_3$) δ: 8.19, 8.03, 7.96, 6.99 (m, 12H in all, 12 aromatic H), 7.34, 7.22, 6.48 (br s, 1H each, furan), 5.76, 5.68 (br s, 1H each, 3′- and 3″-H), 5.06 (d, J = 10 Hz, 1H, 1″-H), 4.86 (m, $W_{1/2}$ = 20 Hz, 2H, 1′- and 4″-H), 4.05 (br s, 1H, 3-H), 3.92, 3.90 (s, 3H each, OCH_3 × 2), 3.52 (dd, J = 4, 10 Hz, 1H, 4′-H), 1.35, 1.16 (d, J = 6 Hz, 3H each, 6′- and 6″-CH_3), 0.91 (s, 3H, 19-CH_3), 0.70 (s, 3H, 18-CH_3)). A trace of a product containing an α-glycosidic linkage was found in some runs and separated. The use of the corresponding β-thioglycoside gave the identical result. For this reason the more easily available α-glycosides **7** and **8** were employed throughout the synthesis. We believe that the species **9** plays a part in the glycosylation reaction. In none of the systems tried have we observed a displacement of the thioglycosidic bond without participation and with inversion of configuration as described by Ferrier *et al.* (5). Ammonolysis of **10** in methanol yielded 90% of an equilibrium mixture of **11** and **12** in a ratio 3.5:1. Compound



10 R^1 = O_2N—C(=O)—, R^2 = R^3 = MeO—C(=O)—

11 R^1 = H, R^2 = R^3 = MeO—C(=O)—

12 R^2 = H, R^1 = R^3 = MeO—C(=O)—

13 R^1 = R^2 = R^3 = H

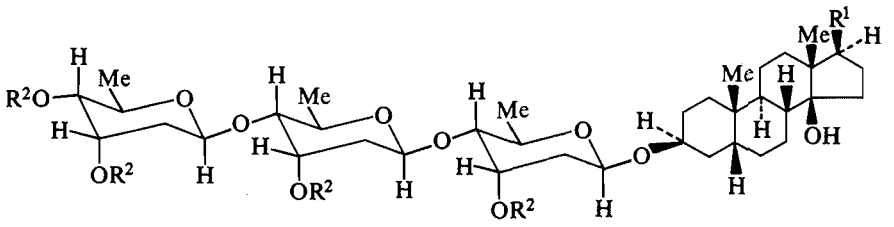
12 could be reequilibrated to yield the same product in the identical ratio. Both products **11** and **12** remained oily. (**11**: ^{1}Hmr ($CDCl_3$) δ: 8.03, 6.98 (m, 4H each, aromatic H), 5.64, 5.45 (br s, 1H each, 3′- and 3″-H), 4.88 (m, $W_{1/2}$ = 20 Hz, 2H, 1′- and 1″-H), 4.03 (br s, 1H, 3-H), 3.90, 3.89 (s, 3H each, OCH_3 × 2), 3.47 (m, 2H, 4′- and 4″-H); **12**: ^{1}Hmr ($CDCl_3$) δ: 8.02, 6.96 (m, 4H each, aromatic H), 5.63 (br s, 1H, 3′-H), 5.00, 4.85 (d, J = 10 Hz, 1H each, 1′- and 1″-H), 4.68 (dd, J = 4, 10 Hz, 1H, 4″-H), 4.29 (br s, 1H, 3″-H), 3.89, 3.87 (s, 3H each, OCH_3 × 2), 3.47 (dd, J = 4, 10 Hz, 1H, 4′-H).) Reduction of compound **11** with $LiAlH_4$ yielded **13** ($[\alpha]_D$ +4.15; mp 185–187°C; ^{1}Hmr ($CDCl_3$) δ: 7.33, 7.23, 6.49 (br s, 1H each, furan), 4.91 (m, $W_{1/2}$ = 20 Hz, 2H, 1′- and 1″-H), 4.27, 4.15, 4.05 (br s, 1H each, 3-, 3′-, and 3″-H), 3.28 (m, $W_{1/2}$ = 20 Hz, 2H, 4′- and 4″-H), 1.29, 1.23 (d, J = 6 Hz, 3H each, 6′- and 6″-CH_3), 0.91 (s, 3H, 19-CH_3), 0.69 (s, 3H, 18-CH_3)) identical with a product obtained by partial hydrolysis (two-phase system *p*-toluenesulfonic acid in H_2O/CH_2Cl_2) of the naturally derived compound **15** (2).

Coupling of the protected glycoside **11** with the thioglycoside **8** under identical conditions as in the step **6** → **10** yielded 58% of the protected glycoside **14** identical with the same derivative obtained by treatment of naturally derived **15** (2) with *p*-methoxybenzoylchloride and pyridine ($[\alpha]_D$ +112.92; mp 159–161°C; ^{1}Hmr ($CDCl_3$) **20** δ: 8.05, 7.98, 7.80, 6.98, 6.81 (m, 16H in all, aromatic H), 7.33, 7.22, 6.48 (br s, 1H each, furan), 5.67, 5.59 (br s, 2H and 1H, 3′-, 3″-, and 3‴-H), 4.96, 4.82 (d, J = 10 Hz, and m, $W_{1/2}$ = 20 Hz, 4H in all, 1′-, 1″-, 1‴-, and 4‴-H), 3.90, 3.89, 3.81 (s, 12H in all, OCH_3 × 4), 3.41 (m, 2H, 4′- and 4″-H), 1.26, 1.21, 1.14 (d, J = 6 Hz, 3H each, 6′-, 6″-, and 6‴-CH_3), 0.90 (s, 3H, 19-CH_3), 0.70 (s, 3H, 18-CH_3)). No product containing an α-glycosidic linkage was found. Finally, $LiAlH_4$ reduction of **14** gave 87% of compound **15**, identical by mixture mp and all spectral and chromatographic criteria with the same material described in our previous communication (2). The oxidative conversion of the furyl derivative **15** to either digitoxin (**16**) or isodigitoxin (**17**)[5] can be found in the same publication (2).

It remains to be mentioned that (for reasons which we shall discuss in a full publication) the thioglycoside method is only mildly stereoselective when used in the first step of the syn-

[4]For the preparation of ethyl thioglycosides by glycosylation with a Lewis acid, see ref. 4 (*b*).

[5]We have now found that **17** (mp 149–150°C) contains ether of crystallization. After vigorous drying at elevated temperature *in vacuo*, **17** melts at 214–216°C.



14 $R^2 = MeO$—  —CO—, $R^1 =$ 

15 $R^2 = H$, $R^1 =$ 

16 $R^2 = H$, $R^1 =$ 

17 $R^2 = H$, $R^1 =$ 

thesis and consequently we have preferred to prepare compound **6** by our acid catalyzed method (2).

Acknowledgements

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