COMMUNICATION

On the synthesis of cardioactive steroid glycosides. On cardioactive steroids. XI[1]

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A stereoselective β-glycosidation of digitoxose and digitoxigenin involving a 1−3 participation of a urethane group is described. The conversion of digitoxin (**10**) to its furyl derivative **11** and the reoxidation of **11** to digitoxin and isodigitoxin (**12**), respectively, in high yield is reported for the first time. This is of fundamental importance for the use of the new glycosidation method in the total synthesis of digitoxin and its analogues.

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On décrit une β-glycosidation stéréosélective de la digitoxose et de la digitoxigénine qui implique une participation 1−3 d'un groupe uréthane. On rapporte pour la première fois la transformation de la digitonine (**10**) en son dérivé furyle (**11**) et la réoxydation de ce dérivé en digitonine et en isodigitonine (**12**) respectivement avec un rendement élevé. Cette réaction est très importante pour l'application de la nouvelle méthode de glycosidation dans la synthèse totale de la digitonine et de ses analogues.

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In previous communications of this series we have disclosed a simple and efficient methodology for the synthesis of cardenolides and bufadienolides and their analogues. As a result of this novel technique, we have succeeded in synthesizing several derivatives which, when tested in the form of glucosides, have shown a high level of inotropic activity and a margin of safety one or two orders of magnitude greater than the precariously narrow margin displayed by the natural digitalis glycosides used in therapy.[2] As our studies progressed it gradually became clear that glucosides invariably have a duration of action too short to be of practical use. Consequently, it became imperative to work out methods for the attachment of the natural glycosidic chain of digitoxin to our synthetic steroids.

A stereoselective β-glycosidation of 2-desoxyhexoses is unknown and specifically in the case of digitoxigenin and digitoxose the ß-glycoside was obtained in a yield of 4.5% in mixture with 5.4% of the corresponding α-glycoside (2). At this point we have noticed a paper by Hanessian *et al.* (3) in which 1,2,3-trideoxy-4,6-di-*O*-*p*-nitrobenzoyl-3-trifluoroacettamido-L-arabino-hex-1-enopyranose yielded on acid catalysis stereospecifically the α-glycoside with daunomicinone. It seemed to us that this process must operate via the intermediate **1** (cf. also ref. 4). We have first attempted with no success to control the glycosidation of digitoxose derivatives by 1−3 participation of a variety of esters. Finally, we decided to try a urethane group which is very similar to an acetamide by its electronic properties. We have prepared by a straightforward process starting from the known compound **2** (5) both anomers of **3** (6). (β-anomer mp 130−131°C; ir ($CHCl_3$): 3475 (NH), 1720 (C=O), 1610 cm^{-1} (aromatic); pmr ($CDCl_3$): δ = 3.87 (s, 3H, aromatic OCH_3), 3.52 (s, 3H, 1-OCH_3), 2.74 (d, J = 5 Hz, N—CH_3), 1.30 (d, J = 6 Hz, 6-CH_3); $[\alpha]_D^{22}$ = +59.18 ($CHCl_3$).)

The β-anomer **3** was hydrolysed with aqueous acetic acid at 110°C for 40 min to the foamy anomeric mixture **4**. Compound **4** was reconverted with high stereoselectivity to the β-anomer **3** with methanol under the conditions described below for a digitoxigenin derivative.

The furyl derivative of digitoxigenin (7) was coupled with 2 mol of **4** and 0.2 mol of *p*-toluenesulfonic acid in CH_2Cl_2−benzene (1:1) for 45 min at room temperature. The anomeric mixture **5** was obtained besides some starting material in a yield of 83% on the basis of starting material consumed. A small amount of the cyclic urethane **8** (mp 146−148°C; ir ($CHCl_3$): 1700 (C=O), 1610 cm^{-1} (aromatic); pmr ($CDCl_3$): δ = 3.88 (s, 3H, aromatic OCH_3), 3.12 (s, 3H, NCH_3), 1.31 (d, J = 6 Hz, 3H, 6-CH_3); $[\alpha]_D^{22}$ = +159.93 ($CHCl_3$)) was also found in this experiment. Compound **8** may be obtained quantitatively from **3** or **4** on prolonged reflux with aqueous acetic acid. Its utilization for a second method of stereospecific β-glycosidation of digitoxose is being studied. For the separation of the anomers **5**, it is necessary to deblock R_1 or both R_1 and R_2.

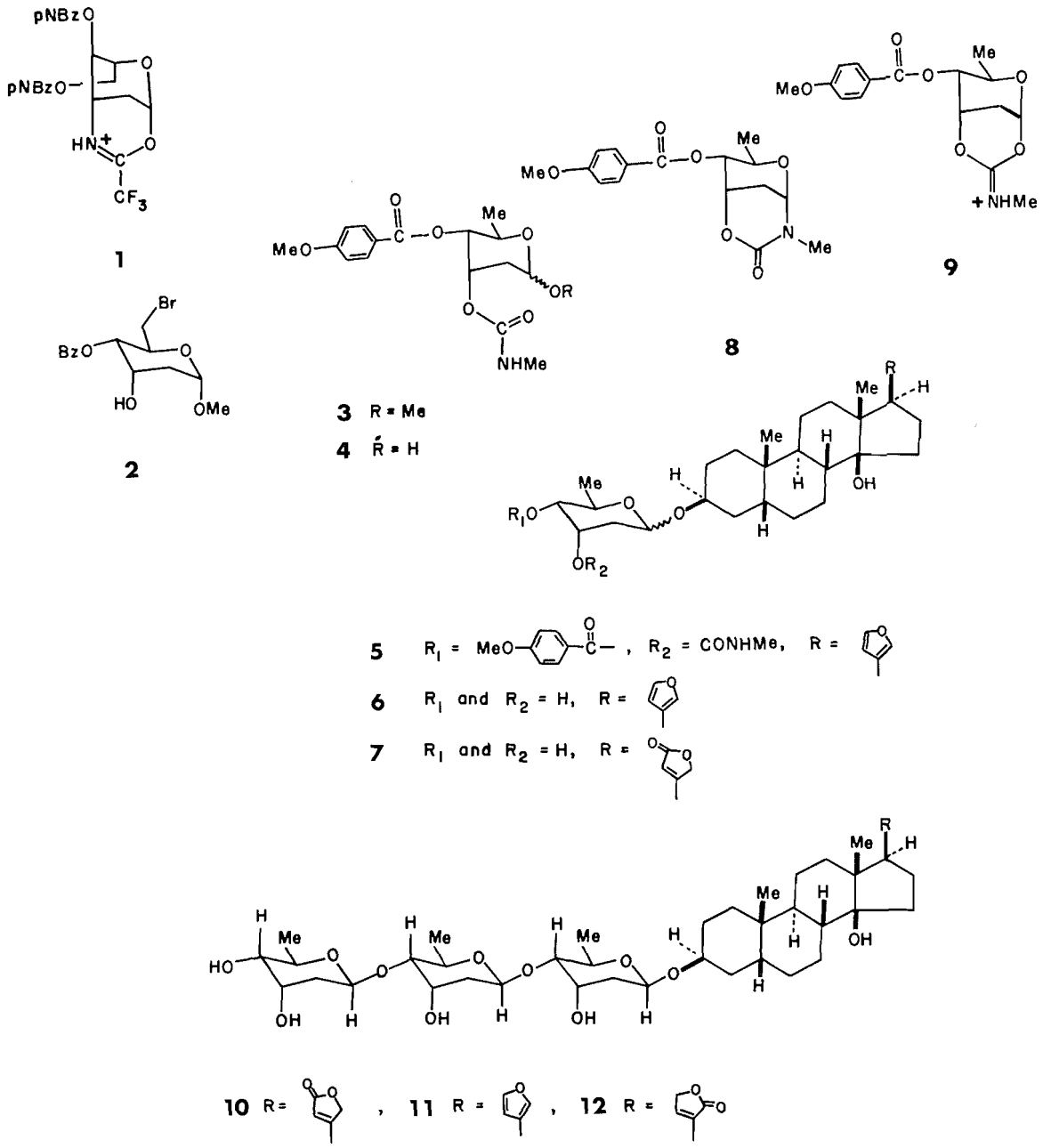
The anomeric mixture **5** was reduced with $LiAlH_4$ and the anomers **6** were easily separated by chromatography on silicic acid.The ratio β:α was found to be 7:1. (The α-anomer mp 173−175°C; pmr ($CDCl_3$): δ = 7.34 (br. s, 1H, 23-H), 7.24 (br. s, 1H, 21-H), 6.50 (br. s, 1H, 22-H), 5.03 (d, J = 4 Hz, 1H, 1′-H), 3.16 (m, 1H, 5′-H), 0.95 (s, 3H, 19-CH_3), 0.72 (s, 3H, 18-CH_3); $[\alpha]_D^{22}$ = +73.79 ($CHCl_3$). The major β-anomer mp 189−191°C; pmr ($CDCl_3$): δ = 7.34 (br. s, 1H, 23-H), 7.24 (br. s, 1H, 21-H), 6.49 (br. s, 1H, 22-H), 4.91 (d, J = 10 Hz, 1H, 1′-H), 3.35 (m, 1H, 5′-H), 0.92 (s, 3H, 19-CH_3), 0.72 (s, 3H, 18-CH_3); $[\alpha]_D^{22}$ = −10.51 ($CHCl_3$).)

The major β-anomer **6** was oxidized as described previously (7, 8) and yielded the known β-digitoxoside **7** (2). We believe that the intermediate responsable for the steric control observed is not the urethane **8** but the charged species **9**.

In order to find out if the methodology described is of potential use for the synthesis of digitoxin and its analogues it was necessary to ascertain whether the lactone, furan, isolactone interconversions (cf. 7, 8) are possible on the level of the

[1]For Part X, see ref. 1.

[2]All the pharmacology of our compounds was performed and will gradually be reported by Professor Rafael Mendez, Departamento de Farmacologia, Instituto Nacional de Cardiologia, Juan Badiano #1, Mexico 22, D. F., Mexico and his collaborators.



triglycosides. We have now finally succeeded in carrying out the conversion of digitoxin (**10**) to the furan derivative **11** and the oxidation of this material back to digitoxin (**10**) and to the isolactone **12** (cf. 7, 8).

Compund **11** was obtained from digitoxin (**10**) in a yield of 86%. (mp 240–241°C; pmr ($CDCl_3$): δ: = 7.34, 7.23, 6.49 (br. s, 1H each, furan), 4.91 (m, $W_{1/2}$ = 20 Hz, 3H, 3 anomeric H, 1.31 (d, J = 6 Hz, 3H, 1 glycosidic-CH_3), 1.25 (d, J = 6 Hz, 6H, 2 glycosidic-CH_3), 0.92 (s, 3H, 19-CH_3), 0.72 (s, 3H, 18-CH_3); $[\alpha]_D^{22}$ = +12.05.) Oxidation of **11** with peracid followed by reduction with $NaBH_4$ (8) gave digitoxin (**10**) in a yield of 75%.

The conversion of **11** to isodigitoxin (**12**) was performed as described (8) and the product was obtained in a yield of 65% after chromatography on silicic acid (mp 149–150°C; ir ($CHCl_3$); 3590, 3500 (OH), 1740 cm^{-1} (C=O); pmr ($CDCl_3$): δ = 7.30 (br. s, 1H, H-22), 4.91 (m, $W_{1/2}$ = 20 Hz, 3H, 3 anomeric H), 4.81 (d, J = 2 Hz, 2H, H-23), 1.31 (d, J = 6 Hz, 3H, 1 glycosidic-CH_3), 1.25 (d, J = 6 Hz, 6H, 2 glycosidic-CH_3), 0.92 (s, 3H, 19-CH_3), 0.82 (s, 3H, 18-CH_3); $[\alpha]_D^{22}$ = +8.68 ($CHCl_3$).)

Thus a synthesis of **11** will represent not only a total synthesis of digitoxin but also a synthesis of the pharmacologically very interesting isodigitoxin (**12**) (1). Our attention has been drawn by a referee to a report in which participation in the glycosidation by a urethane group in the 2-position of a glucose derivative has been previously reported (9).

Acknowledgements

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1. A. SEN, F. J. JÄGGI, T. Y. R. TSAI, and K. WIESNER. Chem. Commun. 1214 (1982).

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2. W. W. ZORBACH, N. HENDERSON, and S. SAEKI. J. Org. Chem. **29**, 2016 (1964).
3. F. ARCAMONE, A. BARGIOTTI, G. CASSINELLI, S. REDAELLI, S. HANESSIAN, A. DI MARCO, A. M. CASASZA, T. DASDIA, A. NECCO, P. REGGIANI, and R. SUPINO. J. Med. Chem. **19**, 733 (1976).
4. P. J. L. DANIELS, A. K. MALLAMS, and J. J. WRIGHT. Chem. Commun. 675 (1973).
5. S. HANESSIAN and N. R. PLESSAS. J. Org. Chem. **34**, 1045 (1969).
6. HAOLUN JIN. Ph.D. Thesis, University of New Brunswick. In preparation.
7. J. M. FERLAND, Y. LEFEBVRE, R. DEGHENGHI, and K. WIESNER. Tetrahedron Lett. **30**, 3617 (1966).
8. T. Y. R. TSAI, A. MINTA, and K. WIESNER. Heterocycles, **12**, 1397 (1979).
9. R. ELY and C. SCHUERCH. Carbohydr. Res. **27**, 63 (1973).

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