35. On Cardioactive Steroids. XVI. Stereoselective β-Glycosylation of Digitoxose: The Synthesis of Digitoxin[1])

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Two methods for stereoselective β-glycosylation of digitoxose were developed. The first achieved stereocontrol by a 1,3-participation of a *N*-methylurethane group under acid catalysis. The second utilized mercuric-ion catalyzed cleavage of thioglycosides and a 1,3-participation of a *p*-methoxybenzoyl group in a neutral medium. The first highly stereoselective and quite efficient synthesis of digitoxin (**C7**) was achieved by a combination of these methods. The furyl-substituted precursor **IV** of digitoxigenin (*Scheme 1*) was used as aglycone, and the furan group was converted to the unsaturated lactone of digitoxin by our known oxidation procedure (*m*-chloroperbenzoic acid/$NaBH_4$) after the assembly of the carbohydrate portion of the molecule and its deblocking was completed.

Introduction. – In previous communications of this series, we have described a novel and efficient methodology for the synthesis of cardenolides, bufadienolides and their analogues. As a result of this technique, we were able to synthesize up to now some 50 derivatives which were submitted for pharmacological testing in the form of their β-D-glucosides. Several of these derivatives have shown not only a high level of positive inotropic activity, but also 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]).

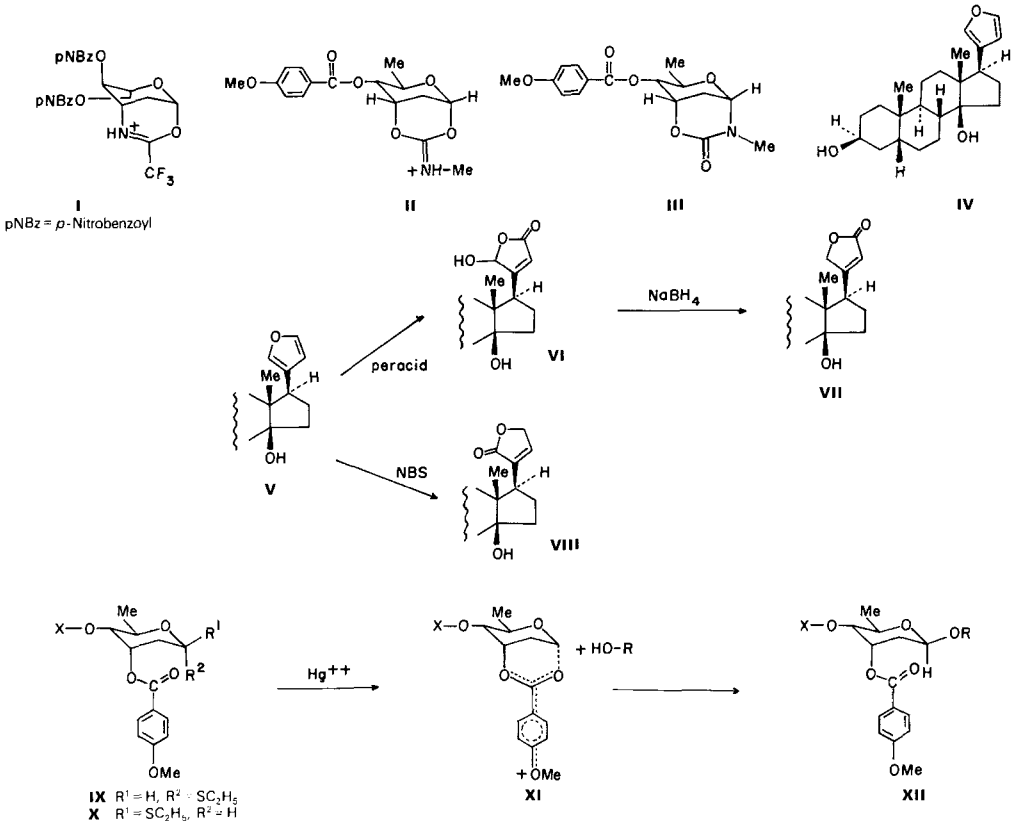
However, as our studies progressed, it became gradually clear, that glucosides invariably have a duration of action too short to be of practical use. Besides duration of action, there are other secondary, but important, therapeutic parameters that have to be considered. The compounds must be water soluble, orally acceptable, and must be unable to cross the blood-brain barrier and thus be free of central effects. Also, in all these respects glucosides cause difficulties. Thus, we came to the conclusion that it would be desirable to attach the natural digitoxin glycosidic chain instead of glucose to our best synthetic steroidal derivatives. However, since digitoxin (**C7**) itself, in spite of its crucial importance[3]) has never been synthesized, it is clear that a fundamental improvement in the stereoselective glycosylation technique for digitoxose (= 2,6-dideoxy-D-*ribo*-hexose) is necessary before this ambition can be realized. We have now succeeded to achieve such an improvement, and in the present paper we wish to demonstrate our new glycosylation

[1]) For communication No. XV, see [1]. Systematic names of all compounds are given in the *Exper. Part.*

[2]) Systematic testing of our compounds is being conducted by Professor *Rafael Mendez* and his collaborators at the *Instituto Nacional de Cardiologia Ignacio Chavez*, Mexico City.

[3]) In the opinion of many cardiologists, *Digitalis* glycosides are irreplaceable drugs. They have been used in medicine, first in the form of crude extracts, later as well defined crystalline materials for 200 years.

Scheme 1



methodology by describing a stereoselective and quite efficient synthesis of natural digitoxin.

When we started on the digitoxin problem no satisfactory stereoselective method for the glycosylation of 2-deoxy-hexoses in general and digitoxose in particular existed. In an acid-catalyzed glycosylation of digitoxigenin (= 3β,14-dihydroxy-5β,14β-card-20(22)-enolide) and digitoxose, *Zorbach* and his coworkers [2] obtained 4.5% of the β-D-glycoside in mixture with 5.4% of the α-D-anomer. A considerable improvement was achieved by *Boivin et al.* [3] who have raised the yield of this reaction to 35% with a β:α stereoselectivity of 1.4:1. Nevertheless, it was clear that the available glycosylation techniques were quite inadequate for a digitoxin synthesis.

We have started our experimental work by trying to improve the stereoselectivity of the acid-catalyzed β-glycosylation of digitoxose derivatives *via* 1,3-participation by a variety of esters. The results which we obtained were not encouraging, and they were comparable to those described in [3]. At this point, we have noticed a paper by *Hanessian* and coworkers [4] in which 1,2,3-trideoxy-4,6-di-*O*-(*p*-nitrobenzoyl)-3-(trifluoroacetamido)-L-*arabino*-hex-1-enopyranose yielded, on acid catalysis, stereospecifically the α-L-glycoside with daunomycinone. It seemed to us that this must be a genuine case of

1,3-participation and that the process must operate *via* the intermediate **I**[4]) (see also [5]). Thus, it seemed clear that the special electronic properties of the amide group are a prerequisite for an efficient glycosylation *via* bridged intermediates of the type **I**, at least under the acid-catalyzed conditions used by *Hanessian* and ourselves. The only function which has an amidic carbonyl group and at the same time may be attached to the digitoxose skeleton through an O-atom and consequently is easily removable is a urethane group. For this reason, we have decided to study the control of the glycosylation of digitoxose by a 1,3-participation of *N*-methylurethane derivatives. This time we have obtained satisfactory results, and the intermediacy of bridged species like **II** is a reasonable explanation of the stereoselectivity which was achieved.

In the urethane-assisted glycosylations, we have frequently isolated the crystalline, well defined cyclic urethane **III**. This material is, however, unreactive under the conditions of the glycosylation, and we consider it to be a by-product.

There were some additional problems. The removal of a urethane requires either strong alkali or a hydride reduction, both incompatible with the cardenolide system. This was solved by using the furyl precursor **IV** [6] as aglycone in the glycosylation. The finished deprotected digitoxoside was then converted into a cardenolide (**V**→**VI**→**VII**) or isocardenolide (**V**→**VIII**) by *m*-chloroperbenzoic acid and $NaBH_4$ or NBS, respectively [6].

Another, more serious difficulty arose when we realized that we cannot use our acid-catalyzed method for the second and third glycosylation stage. With glycosidic bonds present, both in starting materials and products, degradation prevailed over synthesis, and the higher glycosides were isolated only in traces. It was necessary to perform the glycosylation in a neutral medium, and we decided to use mercury-catalyzed cleavage of ethyl thioglycosides as the coupling reaction.

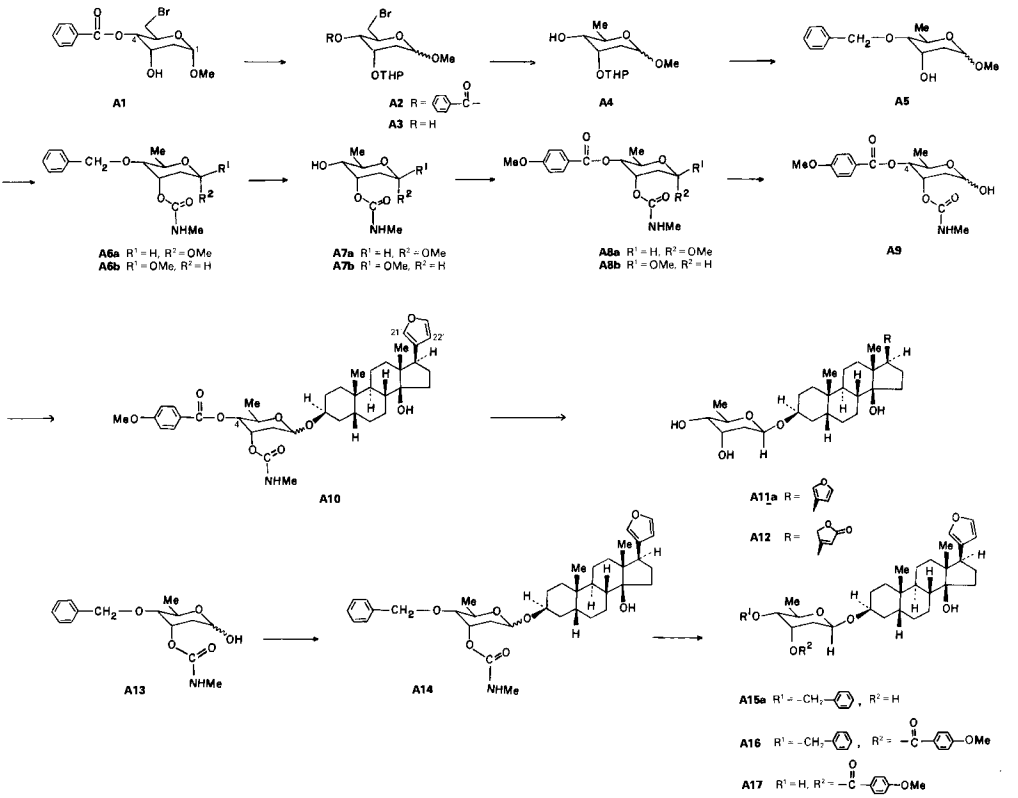
Glycosylation *via* phenyl thioglycosides was first described by *Ferrier* [7], and several subsequent uses of thioglycosides in glycosylation may be found in the literature [8].

However, while *Ferrier* [7] in his studies always observed glycosylation with inversion of configuration, our aim was to trigger, by the mercury-catalyzed cleavage of the thioglycoside bond, the formation of a bridged species of the type **I** and **II** and thereby to achieve a selective β-glycosylation. To our surprise under these conditions, practically complete stereospecificity in the second and third glycosylation stage was achieved with the use of 3-*O*-(*p*-methoxybenzoyl) derivatives. Since both α- and β-D-thioglycosides (**IX** and **X**) gave the β-D-glycoside **XII** in identical yields, we believe that the reaction must proceed *via* the bridged species **XI**. Much less easy to understand is the circumstance that this method shows only a modest stereoselectivity when applied to the first glycosylation stage. Thus, we have decided to construct digitoxin by using our urethane method for the first and the thioglycoside-methoxybenzoate method for the subsequent stages of the synthesis.

Discussion. –*Monodigitoxosides.* The first digitoxose derivative which we decided to synthesize in order to try the urethane method was the anomeric mixture **A9**. We supposed that a bulky substituent at C(4) would help to keep the urethane group axial

[4]) In order to help the reader to find his way through the large number of structural formulae these are divided as follows. *Roman numerals: Formulae* accompanying the *Introduction. Series* **A**: synthesis of monodigitoxosides. *Series* **B**: synthesis of bisdigitoxosides. *Series* **C**: synthesis of trisdigitoxosides.

Scheme 2. *Synthesis of Monodigitoxosides*



and thus facilitate the participation. Compound **A9** was prepared very simply according to *Scheme 2*[5]). The starting bromo compound **A1** was readily obtained from methyl α-D-glucoside [9]. Protection of the OH-group of **A1** with dihydropyran caused also anomerization at C(1) to yield the mixture **A2** (^{1}H-NMR: 3.41 and 3.48 ppm (2*s*, 2 CH_3O)). Alkaline saponification of **A2** gave **A3** and the Br-atom was removed by $LiAlH_4$ (→**A4**). By the action of $LiAlH_4$, **A4** was also directly obtained from **A2**, but in large-scale preparations, a considerable saving of hydride could be achieved by the two-step process. The anomeric mixture **A4** was benzylated, and acid treatment on workup gave the benzyl derivative **A5** which had lost the THP protecting group. The anomeric mixture **A5** was treated with methyl isocyanate to give **A6a**/**A6b** which were separated without difficulty. The synthesis was then carried on with both pure anomers separately. Hydrogenolysis of **A6a** and **A6b** gave the alcohols **A7a** and **A7b**, respectively, which were reacted with *p*-methoxybenzoyl chloride in pyridine (→**A8a** and **A8b**, resp.). Final treatment of **A8a**, **A8b** or **A8a**/**A8b** with aqueous AcOH at 110°C yielded the desired anomeric mixture **A9**.

The furyl-steroid precursor **IV** [6], compound **A9**, and a small amount of *p*-toluenesulfonic acid (TsOH) in benzene/CH_2Cl_2 were stirred for 2.5 h to give 47.5% of the

[5]) For the full characterization and spectra of all compounds, see *Exper. Part.*

anomeric mixture **A10** which at this stage was difficult to separate, 34.7% of unreacted **IV**, and some of the already mentioned cyclic urethane **III**. Reduction of **A10** with $LiAlH_4$ gave finally 78.9% of the β-D-anomer **A11a** (^{1}H-NMR: 4.91 (*dd*, J = 3,10, H_{ax}–C(1)) and 11.2% of the easily separable α-D-anomer **A11b** (^{1}H-NMR: 5.03 (*d*, J = 4, H_{eq}–C(1)). The β-D-anomer **A11a** was found to be identical with the same material obtained by partial hydrolysis from the naturally derived furyldigitoxin (= furyl-substituted precursor of digitoxin) **C6** *(vide infra)*. Oxidation of the furyl derivative **A11a** with *m*-chloroperbenzoic acid followed by reduction with $NaBH_4$ (*cf.* [6]) gave the known [2] digitoxigenin β-digitoxoside (**A12**) in a yield of 71.4%. All the data of this material agreed with the literature, and the compound was found to be identical with an authentic specimen prepared from digitoxin.

The monodigitoxoside derivatives described above were unsuitable to serve as substrates for the second-stage coupling. It turned out that the urethane-containing monodigitoxosides were unreactive in this reaction due to poor solubility. Consequently, it became necessary to replace the urethane group before the next coupling reaction was attempted. Since we intended to extend the glycosidic chain by coupling with 3-*O*-(*p*-methoxybenzoyl)-substituted thioglycosides, we decided to replace the urethane in the starting material also with a 3-*O*-(*p*-methoxybenzoyl) group. To this end, it was of course necessary to prepare a new monodigitoxoside derivative in which the urethane could be selectively removed in the presence of the blocking group in the C(4) position. We have, therefore, decided to perform the first glycosylation with **A13**. This material was easily prepared by heating a mixture of the anomers **A6a** and **A6b** with aqueous AcOH. The acid-catalyzed glycosylation of **IV** and **A13** was carried out exactly as before, and the unresolvable anomeric mixture **A14** was obtained in a yield of 47.6% besides 40.6% of the unreacted furyl-steroid **IV**. Compound **A14** was reduced with $LiAlH_4$ and the desired β-D-glycoside **A15a** easily separated in a yield of 67.7% from 22.4% of the α-D-glycoside **A15b**. The stereoselectivity ratio was thus in this case only 3:1[6]). The β-D-glycoside **A15a** was then acylated with *p*-methoxybenzoyl chloride and pyridine, and the resulting derivative **A16** was subjected to a hydrogenolytic removal (Pd/C, EtOH) of the benzyl group to give the β-D-glycoside **A17**, which is suitable for the attachment of the second digitoxose unit.

It was necessary to conduct the hydrogenolysis of **A16** with only small quantities of Pd/C for short periods of time to avoid a hydrogenation of the furan ring. Thus, some starting material was always isolated, together with the product. However, after a few recyclings, the crystalline (m.p. 151–153°) **A17** was obtained in a good yield.

Bisdigitoxosides. The thioglycosides **B5a** and **B5b** *(Scheme 3)* were selected as suitable reagents for the attachment of the second digitoxose unit. They were readily prepared starting with the anomeric mixture **A5** *(Scheme 2)*. Treatment of **A5** with *p*-methoxybenzoyl chloride and pyridine and chromatographic separation of the products yielded the two anomers **B1a** and **B1b**. In order to reduce the number of necessary characterizations, the oily minor anomer **B1b** was reconverted to the starting material, and the

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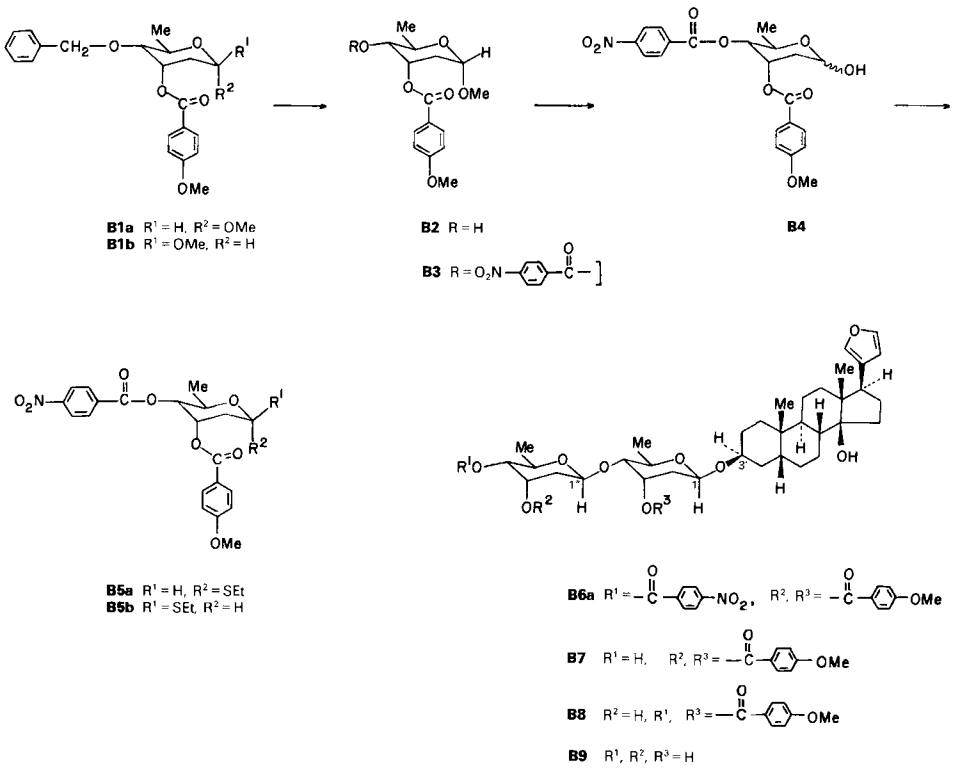
[6]) Since the preparation of both materials **A10** and **A14** was repeated many times with consistent results, it seems necessary to conclude that the size of the equatorial C(4)-substituent plays the expected role in determining the stereoselectivity ratio. Consequently, the next logical step would be to try an analogue of compound **A13** with a heavily substituted benzyl group in the first glycosylation. We have, however, decided to leave further development work for the future and to be satisfied with the intermediate **A14** for the present synthesis.

Scheme 3. *Synthesis of Bisdigitoxosides*



synthesis was carried on only with the major crystalline anomer **B1a**. This material was subjected to hydrogenolysis, and the product **B2** was *p*-nitrobenzoylated to **B3**. Finally, hydrolysis with aqueous AcOH yielded the anomeric mixture **B4**.

The synthesis of thioglycosides by *Lewis*-acid catalysis was previously described by *Lemieux* [10]. In the present case, we obtained the best results by stirring **B4** with ethanethiol and TsOH in CH_2Cl_2. The thioglycosides **B5a** and **B5b** were easily separable crystalline solids and were obtained in a ratio 1.2:1 in an overall yield (from **B3**) of 91.3% [^{1}H-NMR (**B5b**): 5.11 (*dd*, $J = 4{,}10$, H_{ax}–C(1)); ^{1}H-NMR (**B5a**): 5.40 (*d*, $J = 6$, H_{eq}–C(1))].

The coupling of the monodigitoxoside derivative **A17** *(Scheme 2)* and of the α-D-thioglycoside **B5a** was performed in CH_2Cl_2 in the presence of $HgCl_2$, $CdCO_3$, and a drop of dimethylformamide at room temperature. After two days of vigorous stirring, workup yielded 58.6% of the β-D-derivative **B6a**, 2.3% of the stereoisomer **B6b** with an α-glycosidic linkage between the two digitoxose units, and 27.3% of unreacted **A17**. The assignment of the configuration at the anomeric C-atoms of **B6a** and **B6b** was easily derived from their ^{1}H-NMR spectra (see *Exper. Part.*). This assignment was rigorously corroborated by a correlation of **B6a** with the crystalline compound **B9** prepared from digitoxin *(vide infra)*. When the β-D-thioglycoside **B5b** was used in the coupling reaction with **A17**, the result was qualitatively and quantitatively the same.

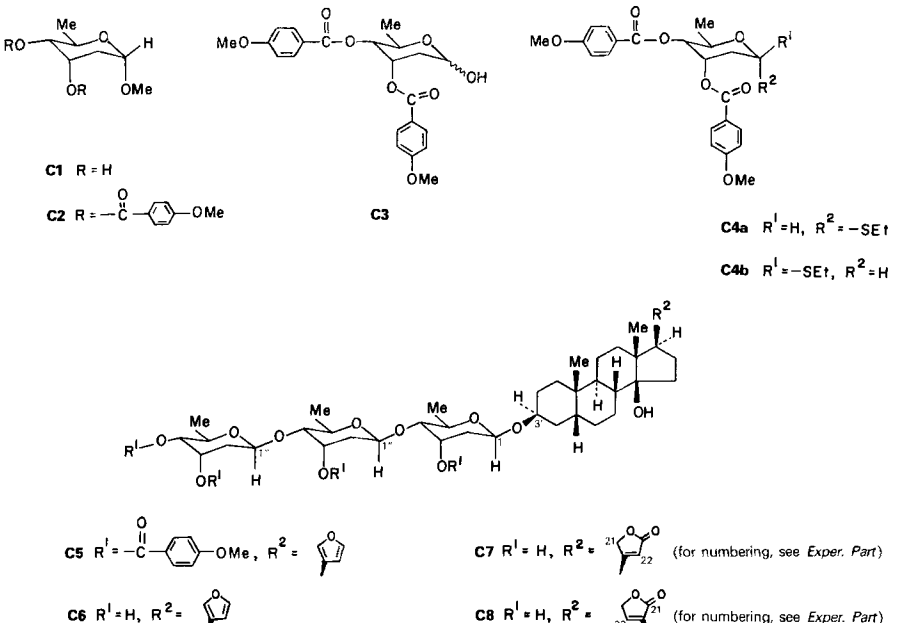
It was next necessary to remove selectively the *p*-nitrobenzoyl group from the glycoside **B6a** to prepare it for the final coupling reaction. The compound was stirred with saturated NH_3/EtOH at room temperature for 30 minutes yielding **B7** and **B8** in a ratio 3.5:1 and an overall yield of 89%. When the ammonolysis was repeated with the minor product **B8**, the two compounds (**B7** and **B8**) were again obtained in the same yield and the same ratio. Thus, **B7** and **B8** are in equilibrium under the conditions of the ammonolysis, and this equilibrium is reached by a base-catalyzed acyl migration on the terminal digitoxose unit.

The analysis of the ^{1}H-NMR spectra of both compounds **B7** and **B8** has first of all shown that they contain only β-glycosidic linkages and that an (*a priori* improbable) base-catalyzed anomerization has not occurred. In the major product **B7**, the equatorial H-atoms (H–C(3) and H–C(3″)) of both digitoxose units give rise to signals shifted downfield (δ 5.45 and 5.65 ppm) which indicates the presence of *p*-methoxybenzoyl groups at these positions. Conversely, the signals for the axial H–C(4) and H–C(4″) overlap at δ 3.47 ppm. This indicates clearly that there must be a free OH-group at C(4″) of the second digitoxose unit and that the major compound **B7** is the product of simple ammonolysis of the *p*-nitrobenzoyl group without acyl migration.

In order to characterize the oily product **B6a** of the second coupling reaction as a crystalline compound, it was reduced with $LiAlH_4$ to the beautifully crystalline (m.p. 185–187 °C) glycoside **B9** in 85% yield. It proved to be identical with the corresponding material obtained by partial hydrolysis of naturally derived furyldigitoxin **C6** (*Scheme 4*). The partial hydrolysis of **C6** to **B9** is described in the *Exper. Part.*

Trisdigitoxosides. The stage was now set for the third and final coupling reaction. After the completion of this process, it is no longer necessary to differentiate between the

Scheme 4. *Tridigitoxosides*



individual OH-groups of the three digitoxose units, and consequently the thioglycosides **C4a** and **C4b** were selected as the most convenient and easily accessible reagents for this step. Another reason for this selection was the fact that the expected product **C5** of the final coupling was a beautifully crystalline compound, which we had previously prepared and fully characterized starting from digitoxin.

The known [11] methyl α-digitoxoside (**C1**) was a convenient starting material. Treatment of this compound with *p*-methoxybenzoyl chloride and pyridine gave the derivative **C2** which was hydrolyzed with dilute AcOH to the anomeric mixture **C3**. Finally, the anomeric thioglycosides **C4a** and **C4b** were prepared in exactly the same manner as their analogues **B5a** and **B5b**.

The partially protected glycoside derivative **B7** *(Scheme 3)* was coupled with the thioglycoside **C4a** under precisely the same conditions as used for the second glycosylation **A17** + **B5a**. Chromatographic separation yielded 57.8% of the expected derivative **C5** besides 25% of recovered **B7**. The glycosylation seems to be completely stereospecific since in many runs no product with an α-glycosidic linkage was found. Compound **C5** crystallized (m.p. 159–161 °C) and was found to be identical with the same material prepared by treatment of the naturally derived furyldigitoxin **C6** with *p*-methoxybenzoyl chloride and pyridine. Deblocking of the four *p*-methoxybenzoyl groups in **C5** was accomplished smoothly by reduction with $LiAlH_4$ at room temperature in THF. The product **C6** (yield 86.2%) to which we gave the generic name furyldigitoxin (= furyl-substituted precursor of digitoxin) melted at 240–241 °C and was identical with a sample of the same compound obtained by reduction of natural digitoxin with diisobutyl aluminium hydride.

The synthetic compound **C5** was finally converted to digitoxin (**C7**) by treatment with *m*-chloroperbenzoic acid followed by reduction of the intermediate lactal with $NaBH_4$ [6]. After chromatographic purification, the product **C7** was obtained in a yield of 74.6% and melted at 236–237 °C. It was identical in all respects with an authentic sample of digitoxin. Alternatively, oxidation of **C6** with NBS [6] followed by chromatography and crystallization gave 64.9% of isodigitoxin **C8**.

Conclusion. The stereoselectivity of the second and third glycosylation step requires comment. We believe that 1,3-participation *via* species of the type **XI** *(Scheme 1)* is only partially responsible for the results obtained. When we applied the same thioglycosylation method (with the thioglycosides **B5a** and **B5b**) to the first step of the digitoxin synthesis, we observed only a moderately stereoselective outcome ($\beta:\alpha = 1.5:1$). It is, therefore, probable that hindrance by the axial *p*-methoxybenzoyl groups present in the derivatives **A17** and **B7** contributes strongly to the practically complete stereospecificity which we have observed in the glycosylation of these compounds. We hope to clarify this situation by further studies. Work is also in progress on a convergent digitoxin synthesis, which will be more useful for a practical preparation of digitoxin analogues.

We acknowledge financial support by the *Natural Sciences and Engineering Research Council*, Ottawa, Canada, *The New Brunswick Heart Foundation* and *Advance Biofactures Corporation*, New York.

Experimental Part

General. See [1], except for 220-MHz-^{1}H-NMR spectra which were recorded on a *Varian XL200* NMR spectrometer by *Larry Calhoun* at the Department of Chemistry, University of New Brunswick.

*Methyl 4-O-Benzoyl-6-bromo-2,6-dideoxy-3-O-(tetrahydro-2*H*-2-pyranyl)-α- and β-*D*-ribo-hexopyranoside* (**A2**). A soln. of **A1** [9] (34.4 g) in dry CH_2Cl_2 (200 ml) was stirred with 2*H*-3,4-dihydropyran (22.8 ml) and pyridinium *p*-toluenesulfonate (2.6 g) for 9 h at r.t. The mixture was diluted with more CH_2Cl_2, washed with $NaHCO_3$ (5%), H_2O, and brine, and evaporated *in vacuo* to give 42 g of crude **A2**, which was used for the next step without further purification. IR ($CHCl_3$): no OH; 1705 (C=O). ^{1}H-NMR ($CDCl_3$): 1.29–2.00 (*m*, 2H–C(3'), 2H–C(4'), 2H–C(5')); 2.15 (*m*, 2H–C(2)); 3.41, 3.48 (*s*, CH_3O (α,β)); 7.50, 8.07 (*m*, 5 arom. H). MS: 428 ($C_{19}H_{25}BrO_6^+$).

*Methyl 6-Bromo-2,6-dideoxy-3-O-(tetrahydro-2*H*-2-pyranyl)-α- and β-*D*-ribo-hexopyranoside* (**A3**). A soln. of **A2** (42 g) in MeOH (160 ml) was stirred with aq. KOH (10%, 40 ml) for 25 min at r.t., diluted with CH_2Cl_2, washed with H_2O and brine, dried over anh. $MgSO_4$, and evaporated *in vacuo*. The product **A3** (31 g) was used in the next step without purification. IR ($CHCl_3$): no C=O; 3520, 3350 (OH). ^{1}H-NMR ($CDCl_3$): 1.30–2.30 (*m*, 2H–C(3'), 2H–C(4'), 2H–C(5'), 2H–C(2)); 3.37, 3.40 (*s*, CH_3O (α,β)); 4.50–4.80 (*m*, H–C(1), H–C(2')). MS: 324 ($C_{12}H_{21}BrO_5^+$).

*Methyl 2,6-Dideoxy-3-O-(tetrahydro-2*H*-2-pyranyl)-α- and β-*D*-ribo-hexopyranoside* (**A4**). Crude **A3** (31 g) was reduced in refluxing THF (250 ml) with $LiAlH_4$ (4 g) for 2 h. The excess reagent was destroyed with wet Et_2O, and the cooled mixture was filtered through a sintered glass funnel. The residue was washed with MeOH/$CHCl_3$ 1:10 and the filtrate evaporated *in vacuo* to yield 19.5 g of **A4**, which was used for the next reaction without purification. IR ($CHCl_3$): 3400 (OH). ^{1}H-NMR ($CDCl_3$): 1.28 (*d*, J = 6, 3H–C(6)); 3.32, 3.35 (*s*, CH_3O (α,β)); 4.63 (br. *s*, $W_{1/2}$ = 10, H–C(1), H–C(2')). MS: 246 ($C_{12}H_{22}O_5^+$).

*Methyl 4-O-Benzyl-2,6-dideoxy-α- and β-*D*-ribo-hexopyranoside* (**A5**). Crude **A4** (19.5 g) in dry dioxane (225 ml) was heated under reflux with NaH (80% suspension in oil, 7.1 g), benzyl bromide (11.4 ml), and a catalytic amount of 18-crown-6 (100 mg) for 1 h. The cooled suspension was filtered and the filtrate evaporated *in vacuo* to a small volume diluted with HCl/MeOH (1%, 120 ml), and stirred at r.t. for 15 min. The mixture was diluted with CH_2Cl_2, washed with H_2O, $NaHCO_3$ (5%), and brine, dried over anh. $MgSO_4$, and evaporated *in vacuo*. The crude product was chromatographed on silica gel to yield 15 g (59.52% overall yield after 5 steps) of **A5**, consisting of α- and β-D-anomers which could not be separated at this stage. IR ($CHCl_3$): 3520 (OH). ^{1}H-NMR ($CDCl_3$): 1.31 (*d*, J = 6, 3H–C(6)); 1.62, 1.82, 2.16 (*m*, 2H–C(2)); 3.10 (*dd*, J = 10, 4, H–C(4)); 3.35, 3.47 (*s*, CH_3O (α,β)); 3.84, 4.04 (*m*, $W_{1/2}$ = 18, H–C(5)); 4.21 (br. *s*, $W_{1/2}$ = 12, H–C(3)); 4.50–4.77 (*m*, PhCH_2, H–C(1)); 7.36 (*s*, 5 arom. H). MS: 220 ($C_{14}H_{20}O_4^+ - CH_3OH$).

*Methyl 4-O-Benzyl-2,6-dideoxy-3-O-(*N*-methylcarbamoyl)-α- and β-*D*-ribo-hexopyranosides* (**A6a** *and* **A6b** resp.). A soln. of **A5** (8.5 g) in dry benzene (170 ml) was stirred with Et_3N (67 ml) and methyl isocyanate (15 ml) for 30 h at 40°C. Evaporation *in vacuo* and chromatography of the crude products on silica gel with acetone/CH_2Cl_2 1:20 yielded 5.852 g (56%) of **A6a**, $[\alpha]_D^{22}$ = +202.89° (*c*, = 1.10, $CHCl_3$), and 4.462 g (42.8%) of **A6b**, $[\alpha]_D^{22}$ = +75.47° (*c* = 1.40, $CHCl_3$). Both products remained oily. Data for **A6a**: IR ($CHCl_3$): 3465 (NH); 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 1.21 (*d*, J = 6, 3H–C(6)); 1.87, 2.08 (*m*, 2H–C(2)); 2,69 (*d*, J = 5, CH_3N); 3.09 (*dd*, J = 4, 10, H–C(4)); 3.22 (*s*, CH_3O); 4.03 (*m*, $W_{1/2}$ = 20, H–C(5)); 4.35, 4.67 (*d*, J = 12, PhCH_2); 4.58 (*d*, J = 4, H–C(1)); 5.22 (br. *s*, $W_{1/2}$ = 18, NH); 5.35 (br. *s*, $W_{1/2}$ = 9, H–C(3)); 7.25 (*s*, 5 arom. H). MS: 277 ($C_{16}H_{23}NO_5^+ - CH_3OH$).

Data for **A6b**: IR ($CHCl_3$): 3455 (NH); 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 1.26 (*d*, J = 6, 3H–C(6)); 1.69 2.12 (*m*, 2H–C(2)); 2.72 (*d*, J = 5, CH_3N); 3.11 (*dd*, J = 4, 10, H–C(4)); 3.44 (*s*, CH_3O); 3.81 (*m*, $W_{1/2}$ = 20, H–C(5)); 4.37, 4,70 (*d*, J = 11, PhCH_2); 4.61 (*d*, J = 10, H–C(1)); 4.89 (br. *s*, $W_{1/2}$ = 16, NH); 5.48 (br. *s*, $W_{1/2}$ = 9, H–C(3)); 7.29 (*s*, 5 arom. H). MS: 277 ($C_{16}H_{23}NO_5^+ - CH_3OH$). MS(HR): 277.1316 ($M^+ - CH_3OH$, calc. 277.1314).

*Methyl 2,6-Dideoxy-3-O-(*N*-methylcarbamoyl)-α-*D*-ribo-hexopyranoside* (**A7a**). Compound **A6a** (7.255 g) was debenzylated in EtOH (200 ml) with Pd/C (10%, 2.2 g) and H_2 for 12 h. The mixture was filtered through *Celite* followed by evaporation of the filtrate *in vacuo* to yield 5.1 g of **A7a**, which was used for the next step without purification. IR ($CHCl_3$): 3465 (NH, OH), 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 1.28 (*d*, J = 6, 2H–C(6)); 2.77 (*d*, J = 5, CH_3N); 3.37 (*s*, CH_3O); 4.67 (br. *s*, $W_{1/2}$ = 8, H–C(1)); 5.02 (br. *s*, $W_{1/2}$ = 9, H–C(3)); 5.48 (br. *s*, NH). MS: 219 ($C_9H_{17}NO_5^+$).

*Methyl 2,6-Dideoxy-3-O-(*N*-methylcarbamoyl)-β-*D*-ribo-hexopyranoside* (**A7b**). Compound **A6b** (5.3 g) was debenzylated in EtOH (170 ml) with Pd/C (10%, 1.5 g) under H_2 for 9 h. Workup exactly as above yielded 3.6 g of **A7b**, which was used in the next step without purification. IR ($CHCl_3$): 3470 (NH, OH); 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 1.33 (*d*, J = 6, 3H–C(6)); 2.80 (*d*, J = 5, CH_3N); 3.47 (*s*, CH_3O); 4.60 (*dd*, J = 3, 10, H–C(1)); 5.16 (br. *s*, $W_{1/2}$ = 12, H–C(3), NH). MS: 219 ($C_9H_{17}NO_5^+$).

Methyl 2,6-Dideoxy-4-O-(p-methoxybenzoyl)-3-O-(N-methylcarbamoyl)-α-D-ribo-hexopyranoside (**A8a**). Crude **A7a** (5.1 g) was treated with *p*-methoxybenzoyl chloride (7.5 g) in pyridine (80 ml) for 30 h at r.t. Pyridine was removed by distillation at reduced pressure, and the residue was dissolved in CH_2Cl_2, washed with citric acid (5%), H_2O and $NaHCO_3$ (5%), dried over anh. $MgSO_4$, and evaporated *in vacuo*. The crude product was chromatographed on silica gel to yield 6.9 g (83%, after 2 steps) of oily **A8a**, $[\alpha]_D^{22} = +168.43°$ ($c = 1.20$, $CHCl_3$). IR ($CHCl_3$): 3470 (NH); 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 2.15 (*m*, $W_{1/2} = 12$, 2H–C(2)); 3.41 (*s*, CH_3O–C(1)); 3.86 (*s*, arom. CH_3O); 4.35 (*m*, $W_{1/2} = 22$, H–C(5)); 4.77 (br. *s*, $W_{1/2} = 8$, H–C(1)); 4.93 (*dd*, $J = 4, 10$, H–C(4)); 5.15 (br. *s*, $W_{1/2} = 14$, NH); 5.36 (br. *s*, $W_{1/2} = 10$, H–C(3)); 6.93, 7.98 (*d*, $J = 9$, 4 arom. H). MS: 353 ($C_{17}H_{23}NO_7^+$). MS(HR): 353.1476 (M^+, calc. 353.1474).

Methyl 2,6-Dideoxy-4-O-(p-methoxybenzoyl)-3-O-(N-methylcarbamoyl)-β-D-ribo-hexopyranoside (**A8b**). Crude **A7b** (3.6 g) was treated with *p*-methoxybenzoyl chloride (5.4 g) in pyridine at r.t. for 24 h. The mixture was worked up as above to yield 5.36 g (86.94% after 2 steps) of **A8b**, which was crystallized from Et_2O/hexane, m.p. 130–131°, $[\alpha]_D^{22} = +59.18°$ ($c = 0.98$, $CHCl_3$). IR ($CHCl_3$): 3475 (NH); 1720 (C=O). ^{1}H-NMR ($CDCl_3$): 1.92, 2.19 (*m*, 2H–C(2)); 3.53 (*s*, CH_3O–C(1)); 3.87 (*s*, arom. CH_3O); 4.09 (*m*, $W_{1/2} = 20$, H–C(5)); 4.76 (*d*, $J = 10$, H–C(1)); 4.87 (*dd*, $J = 4, 10$, H–C(4)); 4.93 (br. *s*, NH); 5.47 (br. *s*, $W_{1/2} = 9$, H–C(3)); 6.93, 7.96 (*d*, $J = 9$, 4 arom. H). MS: 353 ($C_{17}H_{23}NO_7^+$). MS(HR): 353.1491 (M^+, calc. 353.1474). Anal. calc. for $C_{17}H_{23}NO_7$ (353.36): C 57.78, H 6.56, N 3.96; found: C 57.70, H 6.61, N 4.00.

2,6-Dideoxy-4-O-(p-methoxybenzoyl)-3-O-(N-methylcarbamoyl)-α- and β-D-ribo-hexose (**A9**). A mixture of **A8a**/**A8b** (1.4 g), AcOH (4 ml), and H_2O (12 ml) was heated to 110° for 40 min, poured into Et_2O/sat. aq. $NaHCO_3$ in an ice bath, and the aq. layer was extracted with more Et_2O. The Et_2O extracts were washed with brine, dried over anh. $MgSO_4$, and evaporated. The crude product was separated by chromatography on silica gel to yield 0.59 g of **A9** and 0.76 g of **A8a**/**A8b**. After recycling **A8a**/**A8b** 3 times, a total amount of 0.95 g (70.68%) of foamy **A9** was obtained. IR ($CHCl_3$): 3580, 3460 (NH, OH); 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 1.27 (*m*, $W_{1/2} = 12$, 3H–C(6)); 2.73 (*m*, $W_{1/2} = 12$, CH_3N); 3.87 (*s*, CH_3O); 5.46 (*m*, $W_{1/2} = 12$, H–C(3)); 6.94, 7.96 (*m*, 4 arom. H). MS: 264 ($C_{16}H_{21}NO_7^+ - CH_3NCO - H_2O$). MS(HR): 264.0987 ($M^+ - CH_3NCO - H_2O$, calc. 264.0998).

(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 2,6-Dideoxy-4-O-(p-methoxybenzoyl)-3-O-(N-methylcarbamoyl)-α- and β-D-ribo-hexopyranoside (**A10**). A mixture of **IV** [6] (50 mg), dry benzene (1.9 ml), CH_2Cl_2 (0.6 ml), **A9** (95 mg) and TsOH (5.3 mg) was stirred for 2.5 h at r.t. The mixture was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, dried over anh. $MgSO_4$ and evaporated *in vacuo*. The crude product was chromatographed on silica gel *G* plates to yield 45 mg (47.47%) of the mixture **A10** which could not be separated, 21 mg (42%) of unreacted **IV**, and 33 mg (34.74%) of unreacted **A9**. IR ($CHCl_3$): 3470 (NH, OH); 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H–C(18')); 0.91 (*s*, 3H–C(19')); 2.76 (*m*, CH_3N); 3.88 (*s*, CH_3O); 4.08 (br. *s*, $W_{1/2} = 9$, H–C(3')); 4.90 (*m*, $W_{1/2} = 20$, H–C(1), H–C(4)); 5.48 (br. *s*, $W_{1/2} = 8$, H–C(3)); 6.49, 7.24, 7.34 (br. *s*, $W_{1/2} = 4$, H–C(21'), H–C(22'), H–C(23')); 6.93, 7.96 (*m*, 4 arom. H). MS: 340 ($C_{39}H_{53}NO_9^+ - C_{16}H_{21}NO_7$). MS(HR): 340.2401 ($M^+ - C_{16}H_{21}NO_7$, calc. 340.2402). *4,7-Dimethyl-3-oxo-2,6-dioxa-4-azabicyclo[3.3.1]non-8-yl* p-*Methoxybenzoate* (**III**; 30 mg) was also isolated from the mixture. It was crystallized from Et_2O/hexane, m.p. 146–148°. IR ($CHCl_3$): 1700 (C=O); no OH and NH. ^{1}H-NMR ($CDCl_3$): 1.31 (*d*, $J = 6$, CH_3–C(7)); 2.26 (*m*, 2H–C(9)); 3.12 (*s*, CH_3N); 3.88 (*s*, arom. CH_3O); 6.94 (*d*, $J = 8$, 2 arom. H); 8.05 (*d*, $J = 8$, 2 arom. H). MS: 321 ($C_{16}H_{19}NO_6^+$). MS(HR): 321.1210 (M^+, calc. 321.1212). Anal. calc. for $C_{16}H_{19}NO_6$ (321.33): C 59.80, H 5.96, N 4.36; found: C 59.43, H 6.02, N 4.37.

(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 2,6-Dideoxy-α- and β-D-ribo-hexopyranoside (**A11b** *and* **A11a**, *resp.*). Compound **A10** (45 mg) was reduced in refluxing THF (3 ml) with $LiAlH_4$ (9 mg) for 10 min. Wet Et_2O was added, and the mixture was filtered through a sintered glass funnel. The residue was washed with MeOH/$CHCl_3$ 1:10 and the filtrate evaporated *in vacuo*. The crude products were chromatographed on silica gel *G* plates with acetone/$CHCl_3$ to yield 3.5 mg (11.22%) of **A11b** and 25.5 mg (78.9%) of **A11a**. Compound **A11b** was crystallized from Et_2O/hexane, m.p. 173–175°, $[\alpha]_D^{22} = +73.79°$ ($c = 1.4$, $CHCl_3$); compound **A11a** was crystallized from $CHCl_3$/Et_2O/hexane, m.p. 189–191°, $[\alpha]_D^{22} = -10.51°$ ($c = 1.45$, $CHCl_3$), and was identical with the sample derived from natural digitoxin *(vide infra)* by mixed m.p., spectral data, and TLC in several solvent systems. Data for **A11b**: IR($CHCl_3$): 3470 (OH). ^{1}H-NMR ($CDCl_3$): 0.72 (*s*, 3H–C(18')); 0.95 (*s*, 3H–C(19')); 1.32 (*d*, $J = 6$, 3H–C(6)); 3.16 (*m*, $W_{1/2} = 22$, H–C(4)); 5.03 (*d*, $J = 4$, H–C(1)); 6.50, 7.24, 7.34 (br. *s*, $W_{1/2} = 4$, H–C(21'), H–C(22'), H–C(23')). MS: 488 ($C_{29}H_{44}O_6^+$). MS(HR): 488.3131 (M^+, calc. 488.3138). Anal. calc. for $C_{29}H_{44}O_6$ (488.64): C 71.28, H 9.08; found: C 71.02, H 9.13.

Data for **A11a**: IR ($CHCl_3$): 3600, 3450 (OH). ^{1}H-NMR ($CDCl_3$): 0.72 (*s*, 3H–C(18')); 0.92 (*s*, 3H–C(19')); 1.30 (*d*, $J = 6$, 3H–C(6)); 3.35 (*m*, $W_{1/2} = 16$, H–C(4)); 3.74 (*m*, $W_{1/2} = 20$, H–C(5)); 4.07 (br. *s*, $W_{1/2} = 8$, H–C(3')); 4.15 (br. *s*, $W_{1/2} = 9$, H–C(3)); 4.91 (*dd*, $J = 3, 10$, H–C(1)); 6.49, 7.24, 7.34 (br. *s*, $W_{1/2} = 4$,

H–C(21'), H–C(22'), H–C(23')). MS: 488 ($C_{29}H_{44}O_6^+$). MS(HR): 488.3138 (M^+, calc. 488.3138). Anal. calc. for $C_{29}H_{44}O_6$ (488.64): C 71.28, H 9.08; found: C 71.16, H 9.10.

*3β-[(2',6'-Dideoxy-β-*D*-ribo-hexopyranosyl)oxy]-14-hydroxy-5β,14β-card-20(22)-enolide* (**A12**) [3]. Compound **A11a** (24.4 mg) in dry CH_2Cl_2 (1 ml) was treated with AcONa (10.3 mg), AcOH (7.5 mg) and *m*-chloroperbenzoic acid (80%, 23.7 mg) at r.t. for 1.5 h. A drop of Me_2S was added, and the mixture was evaporated at r.t. *in vacuo*. The residue was reduced in THF/MeOH 1:1 (2 ml) with $NaBH_4$ (10 mg) for 3 h at r.t. The mixture was acidified to pH 2 with H_2SO_4 (2N) in an ice bath and extracted with CH_2Cl_2. The extracts were washed with H_2O and brine, dried over anh. $MgSO_4$, and evaporated *in vacuo*. The crude products were chromatographed on silica gel *G* plates to yield 18 mg (71.43%) of **A12**, which was crystallized from $CHCl_3/Et_2O$, m.p. 200–204°, $[\alpha]_D^{22} = -5.62°$ (*c* = 0.55, MeOH). IR ($CHCl_3$): 3430 (OH); 1735 (C=O). ^{1}H-NMR ($CDCl_3$): 0.88 (*s*, 3H–C(18)); 0.93 (*s*, 3H–C(19)); 1.30 (*d*, *J* = 6, 3H–C(6')); 3.73 (*m*, $W_{1/2}$ = 18, H–C(5')); 4.05, 4.14 (br. *s*, $W_{1/2}$ = 8, H–C(3), H–C(3')); 4.83, 5.04 (*d*, *J* = 18, 2H–C(21)); 4.90 (*d*, *J* = 10, H–C(1')); 5.90 (*s*, H–C(22)). MS: 504 ($C_{29}H_{44}O_7^+$).

All data for **A12** agreed with the literature, and the material was identical with an authentic sample.

*4-*O*-Benzyl-2,6-dideoxy-3-*O*-(*N*-methylcarbamoyl)-*D*-ribo-hexose* (**A13**). The unresolved mixture **A6a**/**A6b** (833 mg) in AcOH (2.7 ml) and H_2O (8.1 ml) was heated to 110° for 45 min and worked up as described before (*cf.* prep. of **A9**) to yield 451 mg of **A13** and unreacted **A6a**/**A6b**. After recycling **A6a**/**A6b** twice, a total amount of 611 mg (76.8%) of **A13** was obtained. IR ($CHCl_3$): 3580, 3455 (NH, OH); 1695 (C=O). ^{1}H-NMR ($CDCl_3$): 1.27 (*d*, *J* = 6, 3H–C(6)); 1.70–2.20 (*m*, 2H–C(2)); 2.73 (*m*, $W_{1/2}$ = 13, CH_3N); 5.50 (br. *s*, $W_{1/2}$ = 16, H–C(3)); 7.35 (*s*, 5 arom. H). MS: 277 ($C_{15}H_{21}NO_5^+ - H_2O$). MS(HR): 277.1302 ($M^+ - H_2O$, calc. 277.1314).

*(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 4-*O*-Benzyl-2,6-dideoxy-3-*O*-(*N*-methylcarbamoyl)-α- and β-*D*-ribo-hexopyranoside* (**A14**). TsOH (53 mg) was added to a mixture of **IV** (500 mg) and **A13** (824 mg) in benzene (19 ml)/CH_2Cl_2 (6 ml). The mixture was stirred at r.t. for 40 min, diluted with $CHCl_3$, washed with sat. $NaHCO_3$, dried over anh. $MgSO_4$ and evaporated *in vacuo*. The crude product were chromatographed on silica gel with AcOEt/$CHCl_3$ to yield 422 mg (47.6%) of **A14**, 203 mg (40.6%) of unreacted **IV**, and 320 mg (38%) of unreacted **A13**. The anomeric mixture **A14** could not be separated at this stage. IR ($CHCl_3$): 3470 (OH, NH); 1715 (C=O). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H–C(18')); 0.90 (*s*, 3H–C(19')); 1.24 (*d*, *J* = 6, 3H–C(6)); 2.80 (*m*, $W_{1/2}$ = 12, CH_3N): 6.49, 7.23 (br. *s*, 2H of H–C(21') to H–C(23')); 7.36 (*m*, 1 H of H–C(21') to H–C(23'), 5 arom. H). MS: 578 ($C_{38}H_{53}NO_7^+ - CH_3NCO$). MS(HR): 578.3601 ($M^+ - CH_3NCO$, calc. 578.3595).

*(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 4-*O*-Benzyl-2,6-dideoxy-α- and β-ribo-hexopyranoside* (**A15b** *and* **A15a**, *resp.*). The anomeric mixture **A14** (422 mg) was reduced with $LiAlH_4$ (30 mg) in refluxing THF (10 ml) for 30 min. The excess of the reagent was destroyed with wet Et_2O. The mixture was filtered through a sintered glass funnel, and the residue was washed with MeOH/$CHCl_3$ 1:10. The combined filtrates were evaporated *in vacuo* and chromatographed on silica gel with acetone/$CHCl_3$ to yield 86 mg (22.4%) of **A15b**, which was crystallized from acetone/hexane, m.p. 152–154°, $[\alpha]_D^{22} = +68.25°$ (*c* = 1.10, $CHCl_3$), and 260 mg (67.7%) of **A15a**, which was crystallized from $CHCl_3$/hexane, m.p. 166.5–168°, $[\alpha]_D^{22} = +6.22°$ (*c* = 1.00, $CHCl_3$). Data for **A15b**: IR ($CHCl_3$): 3500 (OH). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H–C(18')); 0.93 (*s*, 3H–C(19')); 1.30 (*d*, *J* = 6, 3H–C(6)); 3.06 (*dd*, *J* = 4, 10, H–C(4)); 4.56, 4.76 (*d*, *J* = 12, PhCH_2); 4.99 (*d*, *J* = 4, H–C(1)); 6.49, 7.23 (br. *s*, 2 H of H–C(21') to H–C(23')); 7.34–7.42 (*m*, 1 H of H–C(21') to H–C(23'), 5 arom. H). MS: 578 ($C_{36}H_{50}O_6^+$). MS(HR): 578.3597 (M^+, calc. 578.3607). Anal. calc. for $C_{36}H_{50}O_6$ (578.76): C 74.70, H 8.71; found: C 74.62, H 8.69.

Data for **A15a**: IR ($CHCl_3$): 3565 (OH). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H–C(18')); 0.91 (*s*, 3H–C(19')); 1.28 (*d*, *J* = 6, 3H–C(6)); 3.17 (*dd*, *J* = 4, 10, H–C(4)); 3.81 (*m*, $W_{1/2}$ = 22, H–C(5)); 4.05 (br. *s*, $W_{1/2}$ = 8, H–C(3')); 4.26 (*m*, $W_{1/2}$ = 8, H–C(3)); 4.54, 4.66 (*d*, *J* = 12, PhCH_2); 4.91 (*d*, *J* = 10, H–C(1)); 6.49, 7.23, 7.34 (br. *s*, H–C(21'), H–C(22'), H–C(23')); 7.39 (br. *s*, 5 arom. H). MS: 578 ($C_{36}H_{50}O_6^+$). MS(HR): 578.3609 (M^+, calc. 578.3607). Anal. calc. for $C_{36}H_{50}O_6$ (578.76): C 74.70, H 8.71; found: C 74.59, H 8.61.

*(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 4-*O*-Benzyl-2,6-dideoxy-3-*O*-(p-methoxybenzoyl)-β-*D*-ribo-hexopyranoside* (**A16**). Compound **A15a** (272 mg) was treated with *p*-methoxybenzoyl chloride (104.4 mg) and a catalytic amount of 4-(dimethylamino)pyridine (10 mg) in pyridine (5 ml) for 6 h at 60°. Pyridine was removed *in vacuo*, and the residue was dissolved in $CHCl_3$, washed with citric acid (5%) and sat. $NaHCO_3$, dried over anh. $MgSO_4$ and evaporated. The crude products were chromatographed on silica gel to yield 310 mg (92.54%) of foamy **A16**, $[\alpha]_D^{22} = +27.51°$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 1680, 1210 (–COO–). ^{1}H-NMR ($CDCl_3$): 0.70 (*s*, 3H–C(18')); 0.91 (*s*, 3H–C(19')); 1,29 (*d*, *J* = 6, 3H–C(6)); 3.27 (*dd*, *J* = 4, 10, H–C(4)); 3.88 (*s*, CH_3O); 4.00 (*m*, H–C(5)); 4.08 (br. *s*, $W_{1/2}$ = 8, H–C(3')); 4.24, 4.73 (*d*, *J* = 12, PhCH_2); 4.96 (*d*, *J* = 10, H–C(1)); 5.83 (br. *s*, $W_{1/2}$ = 8, H–C(3)); 6.97, 8.06 (*d*, *J* = 9, 4 arom. H); 7.29 (*s*, 5 arom. H). MS: 712 ($C_{44}H_{56}O_8^+$). MS(HR): 712.4001 (M^+, calc. 712.3975).

*(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) 2,6-Dideoxy-3-*O*-(*p*-methoxybenzoyl)-β-*D*-ribo-hexopyranoside* (**A17**). Compound **A16** (296 mg) was debenzylated in EtOH (15 ml) with Pd/C (10%, 74 mg) and H_2 for 40 min. The mixture was filtered through *Celite* and the filtrate was evaporated *in vacuo*. The crude product was chromatographed on silica gel *G* plates to yield 71 mg (24%) of unreacted **A16** and 175 mg (67.67%) of **A17**, which was crystallized from $CHCl_3$/hexane, m.p. 151–153°, $[\alpha]_D^{22} = -7.68°$ ($c = 0.99$, $CHCl_3$). IR ($CHCl_3$): 3590, 3470 (OH); 1695, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 3.56 (*dd*, $J = 4, 10$, H–C(4)); 3.90 (*s*, CH_3O); 4.08 (br. *s*, $W_{½} = 8$, H–C(3)); 6.49, 7.23, 7.34 (br. *s*, H–C(21'), H–C(22'), H–C(23')); 6.98, 8.03 (*d*, $J = 9$, 4 arom. H). MS: 622 ($C_{37}H_{50}O_8^+$). MS(HR): 622.3540 (M^+, calc. 622.3505). Anal. calc. for $C_{37}H_{50}O_8$ (622.77): C 71.35, H 8.09; found: C 71.30, H 8.12.

*Methyl 4-*O*-Benzyl-2,6-dideoxy-3-*O*-(*p*-methoxybenzoyl)-α- and β-*D*-ribo-hexopyranoside* (**B1a** *and* **B1b**, *resp.*). Compound **A5** (2.52 g) in pyridine (20 ml) was treated with *p*-methoxybenzoyl chloride (2.21 g) and 4-(dimethylamino)pyridine (50 mg) for 5 h at 60°. The mixture was worked up as described before (*cf.* **A7a→A8a**). The crude product was chromatographed on silica gel to yield 2.07 g (53.6%) of **B1a**, which was crystallized from $CHCl_3$/hexane, m.p. 81.5–82.5°, $[\alpha]_D^{22} = +160.34$ ($c = 1.48$, $CHCl_3$), and 1.51 g (41%) of oily **B1b**, $[\alpha]_D^{22} = +85.49°$ ($c = 1.22$, $CHCl_3$). Data for **B1a**: IR ($CHCl_3$): no OH; 1680, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.30 (*d*, $J = 6$, 3H–C(6)); 1.99, 2.24 (*m*, 2H–C(2)); 3.26 (*dd*, $J = 4, 10$, H–C(4)); 3.40 (*s*, CH_3O–C(1)); 3.85 (*s*, arom. CH_3O); 4.28 (*m*, H–C(5)); 4.46, 4.75 (*d*, $J = 12$, PhCH_2); 4.73 (*d*, $J = 4$, H–C(1)); 5.71 (br. *s*, $W_{½} = 9$, H–C(3)); 6.95, 8.10 (*d*, $J = 9$, 4 arom. H); 7.30 (*s*, 5 arom. H). MS: 386 ($C_{22}H_{26}O_6^+$). MS(HR): 386.1721 (M^+, calc. 386.1729). Anal. calc. for $C_{22}H_{26}O_6$ (386.43): C 68.38, H 6.78; found: C 68.25, H 6.79.

Data for **B1b**: IR ($CHCl_3$): no OH; 1695, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.37 (*d*, $J = 6$, 3H–C(6)); 1.83, 2.24 (*m*, 2H–C(2)); 3.26 (*dd*, $J = 4, 10$, H–C(4)); 3.52 (*s*, CH_3O–C(1)); 3.86 (*s*, arom. CH_3O); 4.02 (*m*, H–C(5)); 4.44, 4.73 (*d*, $J = 12$, PhCH_2); 4.80 (*d*, $J = 10$, H–C(1)); 5.82 (br. *s*, $W_{½} = 9$, H–C(3)); 6.96, 8.06 (*d*, $J = 9$, 4 arom. H); 7.29 (*s*, 5 arom. H). MS: 386 ($C_{22}H_{26}O_6^+$).

*Methyl 2,6-Dideoxy-3-*O*-(*p*-methoxybenzoyl)-α-*D*-ribo-hexopyranoside* (**B2**). Compound **B1a** (2 g) was debenzylated in EtOH (80 ml) with Pd/C (10%, 0.5 g) and H_2 for 5 h. The mixture was filtered through *Celite*, and the filtrate was evaporated to dryness *in vacuo*. The crude product was crystallized from $CHCl_3$/hexane to yield 1.47 g (96%) of **B2**, m.p. 115–116°, $[\alpha]_D^{22} = +144.04°$ ($c = 0.96$, $CHCl_3$). IR ($CHCl_3$): 3590, 3500 (OH); 1682, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 3.39 (*s*, CH_3O–C(1)); 3.50 (*m*, H–C(4)); 4.11 (*m*, H–C(5)); 4.74 (*d*, $J = 4$, H–C(1)); 5.39 (*m*, $W_{½} = 8$, H–C(3)); 6.96, 8.05 (*d*, $J = 9$, 4 arom. H). MS: 296 ($C_{15}H_{20}O_6^+$). MS(HR): 296.1270 (M^+, calc. 296.1260). Anal. calc. for $C_{15}H_{20}O_6$ (296.31): C 60.80, H 6.80; found: C 60.56, H 6.72.

*Methyl 2,6-Dideoxy-3-*O*-(*p*-methoxybenzoyl)-4-*O*-(*p*-nitrobenzoyl)-α-*D*-ribo-hexopyranoside* (**B3**). Compound **B2** (1.3 g) was stirred in pyridine (10 ml) with *p*-nitrobenzoyl chloride (980 mg) and 4-(dimethylamino)pyridine (100 mg) at 60° for 4 h and worked up as described above (*cf.* **A7a→A8a**). The crude product was crystallized from $CHCl_3$/hexane to yield 1.76 g (90%) of **B3**, m.p. 125–127°, $[\alpha]_D^{22} = +207.7°$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): no OH; 1720, 1250 (–COO–); 1520, 1345 (NO_2). ^{1}H-NMR ($CDCl_3$): 2.46 (*m*, $W_{½} = 8$, 2H–C(2)); 3.48 (*s*, CH_3O–C(1)); 4.32 (*m*, H–C(5)); 4.85 (br. *s*, $W_{½} = 7$, H–C(1)); 5.03 (*dd*, $J = 4, 10$, H–C(4)); 5.72 (*m*, $W_{½} = 8$, H–C(3)); 6.97, 8.02 (*d*, $J = 9$, 4 arom. H); 8.13 (*m*, 4 arom. H). MS: 445 ($C_{22}H_{23}NO_9^+$). MS(HR): 445.1372 (M^+, calc. 445.1372). Anal. calc. for $C_{22}H_{23}NO_9$ (445.41): C 59.32, H 5.21, N 3.14; found: C 59.22, H 5.16, N 3.15.

*2,6-Dideoxy-3-*O*-(*p*-methoxybenzoyl)-4-*O*-(*p*-nitrobenzoyl)-*D*-ribo-hexose* (**B4**). A soln. of **B3** (6 g) in AcOH (50 ml) was heated under reflux. H_2O (120 ml) was added gradually to keep the soln. homogeneous. Reflux was continued for 2 h after which most of the AcOH was distilled off at reduced pressure. The mixture was poured into Et_2O/sat. aq. $NaHCO_3$ and the aq. layer was extracted with more Et_2O. The Et_2O extracts were washed with H_2O and brine, dried over anh. $MgSO_4$ and evaporated *in vacuo* to yield 5.8 g of crude **B4**, which was used for the next step without further purification. IR ($CHCl_3$): 3600 (OH); 1700, 1225 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.32 (*m*, $W_{½} = 20$, 3H–C(6)); 1.98–2.43 (*m*, 2H–C(2)); 3.90, 3.91 (*s*, CH_3O); 4.34, 4.71 (*m*, H–C(5)); 5.02 (*m*, $W_{½} = 18$, H–C(4)); 5.42 (br. *s*, $W_{½} = 18$, H–C(1)); 5.86 (br. *s*, $W_{½} = 10$, H–C(3)). MS: 431 ($C_{21}H_{21}NO_9^+$). MS(HR): 431.1216 (M^+, calc. 431.1216).

*Ethyl 2,6-Dideoxy-3-*O*-(*p*-methoxybenzoyl)-4-*O*-(*p*-nitrobenzoyl)-1-thio-α- and β-*D*-ribo-hexopyranoside* (**B5a** *and* **B5b**, *resp.*). Crude **B4** (5.8 g) was stirred in dry CH_2Cl_2 (70 ml) with ethanethiol (4.6 ml) and TsOH (470 mg) for 24 h at r.t. The soln. was diluted with more CH_2Cl_2, washed with sat. $NaHCO_3$, dried over anh. $MgSO_4$ and evaporated. The crude products were chromatographed on silica gel with hexane/$CHCl_3$/Et_2O to yield 3.23 g (50% after 2 steps) of **B5a** and 2.64 g (41.25% after 2 steps) of **B5b**. Both **B5a**, m.p. 94–95°, $[\alpha]_D^{22} = +214.12°$ ($c = 1.01$, $CHCl_3$), and **B5b**, m.p. 133–135°, $[\alpha]_D^{22} = +170.96°$ ($c = 1.02$, $CHCl_3$), were crystallized from $CHCl_3$/hexane. Data for **B5a**: IR ($CHCl_3$): no OH; 1700 (C=O); 1520 (NO_2). ^{1}H-NMR ($CDCl_3$): 1.28 (*d*, $J = 6$, 3H–C(6)); 1.37 (*t*, $J = 7$, CH_3CH_2S); 2.31, 2.56–2.75 (*m*, 2H–C(2), CH_3CH_2S); 3.91 (*s*, CH_3O); 4.81 (*m*, $W_{½} = 20$, H–C(5)); 5.03 (*dd*, $J = 4, 10$, H–C(4)); 5.40 (*d*, $J = 6$, H–C(1)); 5.78 (*m*, $W_{½} = 8$, H–C(3)); 6.99, 8.05, 8.16, 8.21 (*d*, $J = 9$,

8 arom. H). MS: 414 ($C_{23}H_{25}NO_8S^+ - CH_3CH_2S$). MS(HR): 414.1225 ($M^+ - CH_3CH_2S$, calc. 414.1189). Anal. calc. for $C_{23}H_{25}NO_8S$ (475.53): C 58.09, H 5.30, N 2.94, S 6.74; found: C 58.03, H 5.27, N 2.94, S 6.58.

Data for **B5b**: IR ($CHCl_3$): no OH; 1700 (C=O); 1520 (NO_2). ^{1}H-NMR ($CDCl_3$): 1.32 (*d*, *J* = 6, 3H–C(6)); 1.36 (*t*, *J* = 7, CH_3CH_2S); 2.14–2.36 (*m*, 2H–C(2)); 2.82 (*q*, *J* = 7, CH_3CH_2S); 3.92 (*s*, CH_3O); 4.24 (*m*, $W_{1/2}$ = 20, H–C(5)); 5.01 (*dd*, *J* = 4, 10, H–C(4)); 5.11 (*dd*, *J* = 4, 10, H–C(1)); 5.82 (*m*, $W_{1/2}$ = 8, H–C(3)); 7.00, 7.99, 8.02, 8.21 (*d*, *J* = 9, 8 arom. H). MS: 414 ($C_{23}H_{25}NO_8S^+ - CH_3CH_2S$). Anal. calc. for $C_{23}H_{25}NO_8S$ (475.53): C 58.09, H 5.30, N 2.94, S 6.74; found: C 57.85, H 5.36, N 2.94, S 6.69.

(21′,23′-Epoxy-14′-hydroxy-24′-nor-5′β,14′β-chola-20′,22′-dien-3′β-yl) O-*[2″,6″-Dideoxy-3″*-O-(p-*methoxybenzoyl)-4″*-O-(p-*nitrobenzoyl)-α- and β-*D-ribo-*hexopyranosyl]-(1→4)-[2,6-dideoxy-3-*O-(p-*methoxybenzoyl)-β-*D-ribo-*hexopyranoside]* (**B6b** *and* **B6a**, *resp.*). A mixture of **A17** (186.6 mg), $CdCO_3$ (105 mg), two drops of DMF, **B5a** (142.5 mg), and $HgCl_2$ (81 mg) in dry CH_2Cl_2 (6 ml) was stirred at r.t. for 18 h after which time more **B5a** (142.5 mg) and $HgCl_2$ (81 mg) were added. Stirring was continued for a further 22 h, and the mixture was filtered through *Celite*. The filtrate was evaporated *in vacuo*, and the crude products were chromatographed on silica gel *G* plates with hexane/$CHCl_3$/acetone 6:3:1 to yield 182 mg (58.6%) of **B6a**, $[\alpha]_D^{22}$ = +112.00° (*c* = 1.04, $CHCl_3$), 7 mg (2.3%) of **B6b**, $[\alpha]_D^{22}$ = +40.48° (*c* = 0.42, $CHCl_3$), 51 mg (27.33%) of unreacted **A17**, 49 mg of unreacted **B5a**, 21 mg of newly formed **B5b**, and 33 mg of **B4**.

In the same way as described above, **A17** (62.6 mg) was treated with **B5b** (2 × 47.5 mg) in CH_2Cl_2 (2 ml) in the presence of $CdCO_3$ (35 mg), a drop of DMF, and $HgCl_2$ (2 × 27 mg). After 48 h stirring, work up, and separation by chromatography, 54 mg (52%) of **B6a**, 2 mg (2%) of **B6b**, 17.5 mg (28%) of **A17**, 15 mg of **B5b**, 5 mg of **B5a**, and 13 mg of **B4** were obtained. Both compounds **B6b** and **B6a** remained as foam. Data for **B6b**: IR ($CHCl_3$): 1690, 1225 (–COO–); 1520 (NO_2). ^{1}H-NMR ($CDCl_3$): 0.72 (*s*, 3H–C(18′)); 0.93 (*s*, 3H–C(19′)); 1.24, 1.36 (*d*, *J* = 6, 3H–C(6), 3H–C(6″)); 3.67 (*dd*, *J* = 4, 10, H–C(4)); 3.83, 3.91 (*s*, $2CH_3O$); 4.13 (br. *s*, H–C(3′)); 4.54 (*m*, $W_{1/2}$ = 20, H–C(5″)); 5.00 (*m*, $W_{1/2}$ = 16, H–C(1), H–C(4″)); 5.15 (br. *s*, $W_{1/2}$ = 8, H–C(1″)); 5.57, 5.78 (br. *s*, $W_{1/2}$ = 8, H–C(3), H–C(3″)); 6.47, 7.24, 7.34 (br. *s*, H–C(21′), H–C(22′), H–C(23′)); 6.80, 6.88, 7.81, 7.89, 8.07, 8.22 (*d*, *J* = 9, 12 arom. H).

Data for **B6a**: IR ($CHCl_3$): 1690, 1220 (–COO–); 1510 (NO_2). ^{1}H-NMR ($CDCl_3$): 0.70 (*s*, 3H–C(18′)); 0.91 (*s*, 3H–C(19′)); 1.16, 1.35 (*d*, *J* = 6, 3H–C(6), 3H–C(6″)); 3.52 (*dd*, *J* = 4, H–C(4)); 3.90, 3.92 (*s*, 2 CH_3O); 4.86 (*m*, $W_{1/2}$ = 20, H–C(1), H–C(4″)); 5.06 (*d*, *J* = 10, H–C(1″)); 5.68, 5.76 (br. *s*, $W_{1/2}$ = 8, H–C(3), H–C(3″)); 6.48, 7.22, 7.34 (br. *s*, H–C(21′), H–C(22′), H–C(23′)); 6.99, 7.96, 8.03, 8.18 (*m*, 12 arom. H).

(21′,23′-Epoxy-14′-hydroxy-24′-nor-5′β,14′β-chola-20′,22′-dien-3′β-yl) O-*[2″,6″-Dideoxy-3″*-O-(p-*methoxybenzoyl)-β-*D-ribo-*hexopyranosyl]-(1→4)-[2,6-dideoxy-3-*O-(p-*methoxybenzoyl)-β-*D-ribo-*hexopyranoside]* (**B7**) and *(21′,23′-Epoxy-14′-hydroxy-24′-nor-5′β,14′β-chola-20′,22′-dien-3′β-yl)* O-*[2″,6″-Dideoxy-4″*-O-(p-*methoxybenzoyl)-β-*D-ribo-*hexopyranosyl]-(1→4)-[2,6-dideoxy-3-*O-(p-*methoxybenzoyl)-β-*D-ribo-*hexopyranoside]* (**B8**). Compound **B6a** (104 mg) in CH_2Cl_2 (0.5 ml) was treated with sat. NH_3/MeOH (3 ml) at r.t. for 30 min, and then the soln. was evaporated *in vacuo*. The crude products were chromatographed on silica gel *G* plates to yield 59 mg (66.59%) of **B7** and 20 mg (22.5%) of **B8.** This last compound was stirred with sat. NH_3/MeOH (0.8 ml) for 30 min and yielded another 13 mg of **B7** and 5 mg of **B8**. Both **B7**, $[\alpha]_D^{22}$ = +16.73° (*c* = 1.01, $CHCl_3$), and **B8**, $[\alpha]_D^{22}$ = +91.50° (*c* = 2.00, $CHCl_3$), were obtained as foam. Data for **B7**: IR ($CHCl_3$): 3590 (OH); 1690, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 0.70 (*s*, 3H–C(18′)); 0.90 (*s*, 3H–C(19′)); 1.22, 1.30 (*d*, *J* = 6, 3H–C(6), 3H–C(6″)); 3.47 (*m* $W_{1/2}$ = 22, H–C(4), H–C(4″)); 3.89, 3.90 (*s*, 2 CH_3O); 4.88 (*m*, $W_{1/2}$ = 8, H–C(1), H–C(1″)); 5.45, 5.64 (br. *s*, $W_{1/2}$ = 8, H–C(3), H–C(3″)); 6.98, 8.03 (*m*, 8 arom. H).

Data for **B8**: IR ($CHCl_3$): 3595 (OH); 1690, 1210 (–COO–). ^{1}H-NMR ($CDCl_3$): 0.70 (*s*, 3H–C(18′)); 0.90 (*s*, 3H–C(19′)), 1.12, 1.34 (*d*, *J* = 6, 3H–C(6), 3H–C(6″)); 3.47 (*dd*, *J* = 4, 10, H–C(4)); 3.87, 3.89 (*s*, 2 CH_3O); 4.29 (br. *s*, $W_{1/2}$ = 8, H–C(3″)); 4.68 (*dd*, *J* = 4, 10, H–C(4″)); 4.85, 5.00 (*d*, *J* = 10, H–C(1), H–C(1″)); 5.63 (br. *s*, $W_{1/2}$ = 8, H–C(3)); 6.96, 8.02 (*m*, 8 arom. H).

(21′,23′-Epoxy-14′-hydroxy-24′-nor-5′β,14′β-chola-20′,22′-dien-3′β-yl) O-*[2″,6″-Dideoxy-β-*D-ribo-*hexopyranosyl]-(1→4)-[2,6-dideoxy-β-*D-ribo-*hexopyranoside]* (**B9**). Compound **B7** (22 mg) in dry THF (3 ml) was reduced with $LiAlH_4$ (10 mg) for 30 min at r.t., and the excess reagent was destroyed with wet Et_2O. The mixture was filtered through a sintered glass funnel, and the residue was washed repeatedly with MeOH/$CHCl_3$ 1:10. The combined filtrates were evaporated *in vacuo*, and crystallization of the crude product from $CHCl_3$/Et_2O gave 13 mg (85%) of **B9**, m.p. 185–187°, $[\alpha]_D^{22}$ = +16.99° (*c* = 0.99, $CHCl_3$), which was identical with a sample derived from natural digitoxin *(vide infra)* by mixed m.p., spectral data, and TLC in several solvent systems. IR ($CHCl_3$): 3575 (OH); 1060 (C–O). ^{1}H-NMR ($CDCl_3$): 0.69 (*s*, 3H–C(18′)); 0.91 (*s*, 3H–C(19′)); 1.23, 1.29 (*d*, *J* = 6, 3H–C(6), 3H–C(6″)); 3.28 (*m*, $W_{1/2}$ = 24, H–C(4), H–C(4″)); 3.80 (*m*, $W_{1/2}$ = 8, H–C(3′), H–C(3), H–C(3″)); 4.91 (*m*, $W_{1/2}$ = 20, H–C(1), H–C(1″)); 6.49, 7.23, 7.33 (br. *s*, H–C(21′), H–C(22′), H–C(23′)). MS: 618 ($C_{35}H_{54}O_9^+$). MS (HR): 618.3767 (M^+, calc. 618.3759). Anal. calc. for $C_{35}H_{54}O_9$ (618.78): C 67.94, H 8.80; found: C 67.85, H 8.78.

*Methyl 2,6-Dideoxy-3,4-bis-*O*-(*p*-methoxybenzoyl)-α-*D*-ribo-hexopyranoside* (**C2**). Compound **C1** [11] (2.2 g) was treated with *p*-methoxybenzoyl chloride (5.3 g) in pyridine for 6 h at r.t. and worked up as described before (*cf.* **A7a**→**A8a**). After crystallization of the crude product from $CHCl_3$/hexane, 5.5 g (94%) of **C2**, m.p. 134–135°, $[\alpha]_D^{22} = +114.61°$ (*c* = 1.00, $CHCl_3$), were obtained. IR ($CHCl_3$): no OH; 1680, 1230 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.28 (*d*, *J* = 6, 3H–C(6)); 2.24 (*m*, $W_{1/2}$ = 18, 2H–C(2)); 3.44 (*s*, CH_3O–C(1)); 3.84, 3.89 (*s*, 2 arom. CH_3O); 4.50 (*m*, H–C(5)); 4.83 (*d*, *J* = 3, H–C(1)); 5.01 (*dd*, *J* = 4, 10, H–C(4)); 5.65 (*m*, $W_{1/2}$ = 8, H–C(3)); 6.84, 6.96, 7.87, 8.05 (*d*, *J* = 9, 8 arom. H). MS: 430 ($C_{23}H_{26}O_8^+$). MS (HR): 430.1631 (M^+, calc. 430.1627). Anal. calc. for $C_{23}H_{26}O_8$ (430.44): C 64.17, H 6.09; found: C 63.87, H 6.06.

*2,6-Dideoxy-3,4-bis-*O*-(*p*-methoxybenzoyl)-*D*-ribo-hexose* (**C3**). Compound **C2** (5 g) was treated with AcOH (40 ml) and H_2O (100 ml) in the way described above (*cf.* **B3**→**B4**) to yield 4.7 g of crude **C3**, which was used for the next step without further purification. IR ($CHCl_3$): 3435 (OH); 1710, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.32 (*m*, 3H–C(6)); 2.02, 2.35 (*m*, 2H–C(2)); 3.83, 3.88, 3.90 (*s*, 2 CH_3O); 4.33, 4.68 (*m*, H–C(5)); 4.99 (*m*, H–C(4)); 5.37 (*m*, $W_{1/2}$ = 14, H–C(1)); 5.79 (br. *s*, $W_{1/2}$ = 8, H–C(3)); 6.84, 6.98, 7.86, 8.02 (*m*, 8 arom. H). MS: 416 ($C_{22}H_{24}O_8^+$). MS (HR): 416.1474 (M^+, calc. 416.1471).

*Ethyl 2,6-Dideoxy-3,4-bis-*O*-(*p*-methoxybenzoyl)-1-thio-α- and β-*D*-ribo-hexopyranoside* (**C4a** *and* **C4b**, *resp.*). Crude **C3** (4.7 g) was stirred with ethanethiol (3.8 ml) and TsOH (420 mg) in dry CH_2Cl_2 (60 ml) for 20 h at r.t. and worked up as described previously (*cf.* **B4**→**B5**). The crude products were chromatographed on silica gel with Et_2O/$CHCl_3$/hexane to yield 2.9 g (54% after 2 steps) of **C4a** and 1.9 g (35.5% after 2 steps) of **C4b**. Both **C4a**, m.p. 104–105°, $[\alpha]_D^{22} = +266.51°$ (*c* = 0.88, $CHCl_3$), and **C4b**, m.p. 104–105°, $[\alpha]_D^{22} = +164.55°$ (*c* = 0.99, $CHCl_3$), were crystallized from $CHCl_3$/hexane. Data for **C4a**: IR ($CHCl_3$): no OH; 1695, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.28 (*d*, *J* = 6, 3H–C(6)); 1.35 (*t*, *J* = 7, CH_3CH_2S); 2.32, 2.53–2.75 (*m*, 2H–C(2), CH_3CH_2S); 3.84, 3.90 (*s*, 2 CH_3O); 4.79 (*m*, H–C(5)); 5.02 (*dd*, *J* = 4, 10, H–C(4)); 5.38 (*d*, *J* = 6, H–C(1)); 5.72 (*m*, $W_{1/2}$ = 8, H–C(3)). MS: 399 ($C_{24}H_{28}SO_7^+ - CH_3CH_2S$). MS (HR): 399.1446 ($M^+ - CH_3CH_2S$, calc. 399.1444). Anal. calc. for $C_{24}H_{28}SO_7$ (460.55): C 62.59, H 6.13, S 6.96; found: C 62.50, H 6.19, S 6.81.

Data for **C4b**: IR ($CHCl_3$): no OH; 1695, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 1.32 (*d*, *J* = 6, 3H–C(6)); 1.34 (*t*, *J* = 7, CH_3CH_2S); 2.13–2.37 (*m*, 2H–C(2)); 2.80 (*q*, *J* = 7, CH_3CH_2S); 3.83, 3.91 (*s*, 2 CH_3O); 4.23 (*m*, H–C(5)); 4.98 (*dd*, *J* = 4, 10, H–C(4)); 5.07 (*dd*, *J* = 3, 12, H–C(1)); 5.75 (*m*, $W_{1/2}$ = 8, H–C(3)). MS: 399 ($C_{24}H_{28}SO_7^+ - CH_3CH_2S$). Anal. calc. for $C_{24}H_{28}SO_7$ (460.55): C 62.59, H 6.13, S 6.96; found: C 62.40, H 6.05, S 6.83.

(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) O-*[2''',6'''-Dideoxy-3''',4'''-bis-*O*-(*p*-methoxybenzoyl)-β-*D*-ribo-hexopyranosyl]-(1→4)-*O*-[2'',6''-dideoxy-3''-*O*-(*p*-methoxybenzoyl)-β-*D*-ribo-hexopyranosyl]-(1→4)-[2,6-dideoxy-3-*O*-(*p*-methoxybenzoyl)-β-*D*-ribo-hexopyranoside]* (**C5**). A mixture of **B7** (74 mg) in dry CH_2Cl_2 (2 ml), $CdCO_3$ (29 mg), one drop of DMF, **C4a** (38.4 mg), and $HgCl_2$ (22.5 mg) was stirred at r.t. for 36 h, during which time more **C4a** (2 × 38.4 mg) and $HgCl_2$ (2 × 22.5 mg) were added at 12-h intervals. The mixture was filtered through *Celite*, and the filtrate was evaporated *in vacuo*. The crude product was chromatographed on silica gel *G* plates with hexane/$CHCl_3$/Et_2O 1:1:0.3 to yield 62 mg (57.8%) of **C5**, which was crystallized from $CHCl_3$/hexane, m.p. 159–161°, $[\alpha]_D^{22} = +112.92°$ (*c* = 1.05, $CHCl_3$), 13 mg of **C4b**, 30 mg of **C4a**, 27 mg of **C3**, and 18.5 mg of unreacted **B7**. IR ($CHCl_3$): 1690, 1220 (–COO–). ^{1}H-NMR ($CDCl_3$): 0.70 (*s*, 3H–C(18')); 0.90 (*s*, 3H–C(19')); 1.14, 1.21, 1.26 (*d*, *J* = 6, 3H–C(6), 3H–C(6''), 3H–C(6''')); 3.41 (*m*, $W_{1/2}$ = 20, H–C(4), H–C(4'')); 3.81, 3.89, 3.90 (4 CH_3O); 4.82 (*m*, $W_{1/2}$ = 20, H–C(4'''), H–C(1), H–C(1'')); 4.96 (*d*, *J* = 10, H–C(1''')); 5.39, 5.67 (br. *s*, $W_{1/2}$ = 8, 12, H–C(3), H–C(3''), H–C(3''')); 6.48, 7.22, 7.33 (br. *s*, H–C(21'), H–C(22'), H–C(23')); 6.81, 6.98, 7.80, 7.98, 8.05 (*m*, 16 arom. H). Anal. calc. for $C_{73}H_{88}O_{20}$ (1285.50): C 68.21, H 6.90; found: C 68.09, H 6.91.

(21',23'-Epoxy-14'-hydroxy-24'-nor-5'β,14'β-chola-20',22'-dien-3'β-yl) O-*[2''',6'''-Dideoxy-β-*D*-ribo-hexopyranosyl]-(1→4)-[2'',6''-dideoxy-β-*D*-ribo-hexopyranosyl]-(1→4)-[2,6-dideoxy-β-*D*-ribo-hexopyranoside]* (**C6**). Compound **C5** (50 mg) in dry THF (5 ml) was reduced with $LiAlH_4$ (20 mg) for 40 min at r.t. Excess reagent was destroyed with wet Et_2O, the mixture was filtered through a sintered glass funnel, and the residue was washed with MeOH/$CHCl_3$ 1:10. The combined filtrates were evaporated, and the crude product was crystallized from acetone/hexane to yield 25 mg (86.2%) of **C6**, m.p. 240–241°, $[\alpha]_D^{22} = +12.05°$ (*c* = 1.00, $CHCl_3$), which was identical with the sample derived from natural digitoxin *(vide infra)* by mixed m.p., all spectral data, and TLC in several solvent systems. IR ($CHCl_3$): 3570 (OH); 1065 (C–O). ^{1}H-NMR ($CDCl_3$): 0.71 (*s*, 3H–C(18')); 0.92 (*s*, 3H–C(19')); 1.25, 1.31 (*d*, *J* = 6, 3H–C(6), 3H–C(6''), 3H–C(6''')); 3.28 (*m*, $W_{1/2}$ = 26, H–C(4), H–C(4''), H–C(4''')); 3.81 (*m*, $W_{1/2}$ = 24, H–C(5), H–C(5''), H–C(5''')); 4.91 (*m*, $W_{1/2}$ = 20, 3 anom. H); 6.49, 7.23, 7.34 (br. *s*, H–C(21'), H–C(22'), H–C(23')). Anal. calc. for $C_{41}H_{64}O_{12}$ (748.96): C 65.75, H 8.61; found: C 65.62, H 8.61.

Digitoxin (= *3β-{*O*-[2''',6'''-Dideoxy-β-*D*-ribo-hexopyranosyl]-(1→4)-*O*-[2'',6''-dideoxy-β-*D*-ribo-hexopyranosyl]-(1→4)-[2',6'-dideoxy-β-*D*-ribo-hexopyranosyl]}oxy-14-hydroxy-5β,14β-card-20(22)-enolide*; **C7**). Com-

pound **C6** (37.4 mg) in CH_2Cl_2 (1 ml) was treated with AcONa (10.3 mg), AcOH (7.5 mg), and *m*-chloroperbenzoic acid (80%, 23.7 mg) at r.t. for 2 h. After this time, a drop of Me_2S was added to destroy the excess peracid. The mixture was evaporated *in vacuo*, and the residue was separated on silica gel *G* plates giving 33.5 mg of crude lactal. This material was reduced in THF/MeOH 1:1 (1 ml) with $NaBH_4$ (10 mg) for 3 h at r.t. The mixture was then neutralized with H_2SO_4 (2N) in an ice bath and acidified to pH 3–4 with citric acid (5%). The suspension was extracted with $CHCl_3$, and the extracts were washed with citric acid (5%), sat. $NaHCO_3$, dried over anh. $MgSO_4$, and evaporated to dryness. The crude product was chromatographed on silica gel *G* plates with $CHCl_3/Et_2O$/acetone 1:1:0.5 to yield 28.5 mg (74.6%) of **C7**, which was crystallized from acetone/hexane, m.p. 236–237°, and was identical with natural digitoxin by mixed m.p., spectral data, and TLC in several solvent systems. IR ($CHCl_3$): 3560 (OH); 1725 (C=O). ^{1}H-NMR ($CDCl_3$): 0.87 (*s*, 3H–C(18)); 0.92 (*s*, 3H–C(19)); 3.26 (*m*, $W_{1/2}$ = 36, H–C(4'), H–C(4''), H–C(4''')); 3.81 (*m*, $W_{1/2}$ = 28, H–C(5'), H–C(5''), H–C(5''')); 4.05, 4.15, 4.27 (br. *s*, $W_{1/2}$ = 8, H–C(3), H–C(3'), H–C(3''), H–C(3''')); 4.82, 5.03 (*d*, *J* = 18, 2H–C(21)); 4.91 (*m*, $W_{1/2}$ = 20, 3 anom. H); 5.89 (br. *s*, $W_{1/2}$ = 4, H–C(22)).

'Isodigitoxin' (= *3β-*{O-*[2''',6'''-Dideoxy-β-*D-ribo-*hexopyranosyl]-(1→4)-*O-*[2'',6''-dideoxy-β-*D-ribo-*hexopyranosyl]-(1→4)-[2',6'-dideoxy-β-*D-ribo-*hexopyranosyl]}oxy-21,23-epoxy-14-hydroxy-24-nor-5β,14β-chol-20(22)-en-23-one;* **C8**). NaOAc (11.5 mg) and NBS (17.8 mg) were added to a soln. of **C6** (74.8 mg) in dioxane/H_2O 20:1 (1 ml). The mixture was stirred at r.t. for 15 min, diluted with $CHCl_3$, washed with Na_2SO_3 (5%) and $NaHCO_3$ (5%), dried over anh. $MgSO_4$ and evaporated *in vacuo*. The crude product was chromatographed on silica gel *G* plates to give 49.6 mg (64.9%) of **C8**, which was crystallized from acetone/hexane, m.p. 214–216° (m.p. before vigorous drying of ether of crystallization, 149–150°), $[\alpha]_D^{22}$ = +8.65° (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 3580, 3480 (OH); 1745 (C=O). ^{1}H-NMR ($CDCl_3$): 0.82 (*s*, 3H–C(18)); 0.92 (*s*, 3H–C(19)); 1.25, 1.31 (*d*, *J* = 6, 3H–C(6'), 3H–C(6''), 3H–C(6''')); 3.25 (*m*, $W_{1/2}$ = 24, H–C(4'), H–C(4''), H–C(4''')); 3.78 (*m*, $W_{1/2}$ = 24, H–C(5'), H–C(5''), H–C(5''')); 4.81 (*d*, *J* = 2, 2H–C(23)); 4.91 (*m*, $W_{1/2}$ = 20, 3 anom. H); 7.30 (br. *s*, H–C(22)). Anal. calc. for $C_{41}H_{64}O_{13}$ (764.96): C 64.38, H 8.43; found: C 64.27, H 8.45.

C6 *from Natural Digitoxin* (**C7**). Natural digitoxin (**C7**; 1.528 g) was reduced in dry THF (50 ml) with diisobutyl aluminum hydride (1M, 24 ml) at −70° under N_2 for 1 h. The excess reagent was destroyed with H_2O, and the mixture was carefully neutralized with H_2SO_4 (2N) in an ice bath. The mixture was extracted with CH_2Cl_2, and the extracts were washed with citric acid (5%), $NaHCO_3$ (5%), dried over anh. $MgSO_4$, and evaporated to dryness. The crude product was chromatographed on silica gel to yield 1.29 g (86%) of 'natural' **C6**, which was crystallized from $Et_2O/CHCl_3$, m.p. 240–242°. The 'natural' **C6** was identical with the synthetic sample by mixed m.p., all spectral data, and TLC in several systems.

Partial Hydrolysis of **C6**. A soln. of 'natural' **C6** (1 g) and TsOH (80 mg) in CH_2Cl_2/H_2O 4:1 (100 ml) was stirred at r.t. for 36 h and then diluted with more CH_2Cl_2. The CH_2Cl_2 layer was separated, washed with $NaHCO_3$ (5%) and brine, dried over anh. $MgSO_4$, and evaporated *in vacuo*. The crude products were purified by chromatography on silica gel with $CHCl_3/Et_2O$/acetone to give 20 mg (4.2%) of **IV**, 25 mg (3.83%) of 'natural' **Alla** (m.p. 189–191°), 205 mg (24.8%) of 'natural' **B9** (m.p. 185–187°), and 650 mg of unreacted **C6**. Both the monodigitoxoside **Alla** and bisdigitoxoside **B9** were identical with the respective synthetic samples by all spectral and chromatographic criteria and mixed m.p.

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