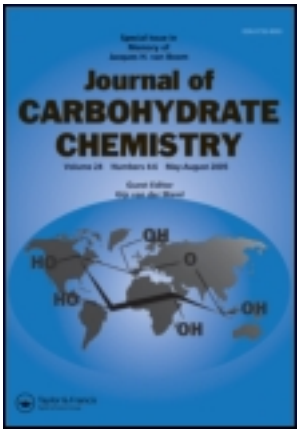

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A Convenient Synthesis of a Cardiac Sugar: "D-Digitalose"

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D-Digitalose (6-deoxy-3-*O*-methyl-D-galactose), a biologically important sugar that is found in some cardiac glycosides, was synthesized from D-galactose via 3-*O*-methyl-1,2,5-*O*-orthodichloroacetyl-α-D-galactofuranose.

Keywords Cardiac sugar; Orthoester; Orthoester hydrolysis; D-Digitalose; D-Galactose

INTRODUCTION

For many years, cardiac glycosides have been studied for their role in improving symptoms in patients with heart failure caused by systolic ventricular dysfunction.[1–4] Cardiac glycosides act by both affecting the availability of intracellular Ca^{2+} for myocardial contraction and increasing the sensitivity of myocardial contractile proteins. They are potent and highly specific inhibitors of the intrinsic plasma membrane Na/K-ATPase, also known as the sodium pump.[5]

In addition to their well-known cardiac activity, cardiac glycosides have also been shown to induce signaling pathways via Na/K-ATPase and have validated anticancer properties.[6,7] It is well known that digitalis has the ability to inhibit the activity of Na/K-ATPase and lead to increased intracellular Ca^{2+}. Deregulation of these ions results in activation of a number of intracellular pathways, leading to changes in cellular structure or gene expression. These molecules render a vast range of therapeutically important biological activities to lots of tumor cell types, the mechanisms of which remain under active investigation by many groups.[7–10] On the other hand, cardiac glycosides in nontoxic concentrations have been shown to induce apoptosis in different malignant cell lines in vitro.[8,10] In light of the pivotal role of apoptosis in cancer

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development and progression, these new experimental findings showed high antitumor capability of the cardiac glycosides.[11]

Cardiac steroids are widely used in the modern treatment of congestive heart failure, but their toxicity remains a serious problem. Much of the interest in the effects of structural modification on cardiotonic activity results from the desire to develop agents with less toxic potential.[6] Toxic effects of cardiac glycosides on the myocardium may be due to excessive inhibition of cardiac Na/K-ATPase, although there is also evidence that effects on the nervous input to the heart may be involved, and it is not clear to what extent such an effect is mediated by inhibition of Na/K-ATPase.[12]

Several studies were conducted to modify glycosides with the purpose of improving their above-mentioned biological properties. However, many of these studies focused on the aglycon portion of glycosides, since it was previously believed that sugar moieties of bioactive glycosides are responsible for properties such as hydrophilicity but do not affect the biological activity of the aglycon directly. Important exceptions to this generalization include the preparations of a number of glycosides and oligosaccharides that have anticancer or other medical properties.[13–17] There are now many known examples of cases where removal of sugar moieties has left an aglycon with little or no activity.[18] Therefore, there is a continuing interest in finding methods by changing the sugar moieties of biologically active glycosides, such as cardiac glycosides, to modify their biological activities. Deoxygenated and/or functionalized sugars such as deoxy and dideoxy sugars and methylated deoxy sugars provide desirable hydrophilic and hydrophobic domains together with modification of the bioactivities of glycosides.[19–23] In this sense, there are many current studies regarding more convenient syntheses of cardiac sugars.[24–26] D-Digitalose is one such desirable monosaccharide that has been obtained from extracts of dried leaves of *Digitalis purpurea*[27] and is found in many antitumor medications.[28–33]

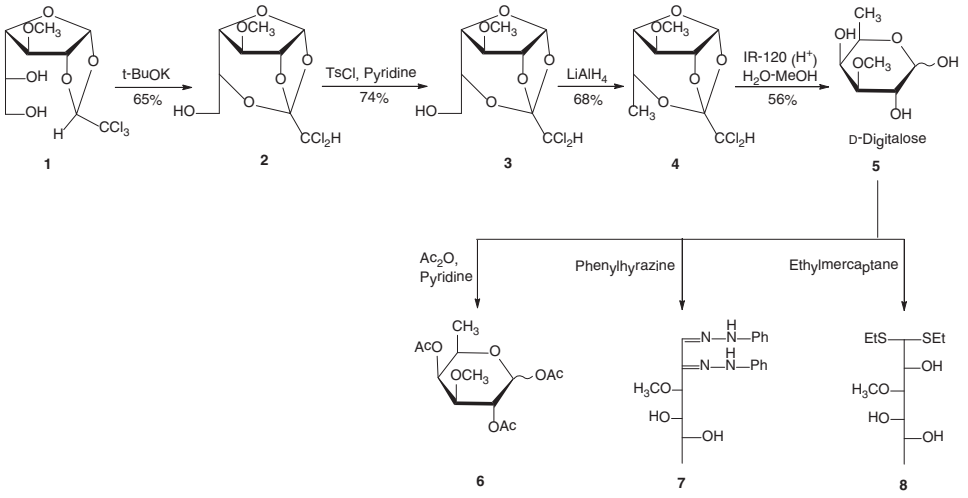
There have been four different syntheses for D-digitalose in the literature to date. However, all of these syntheses have disadvantages, such as the requirements of many steps,[34–37] and some of them also involve configuration changes or use of expensive sugars as the starting compounds. Therefore, we thought it would be useful to find an alternative synthesis of this important sugar. Herein, we describe a convenient new method, the first step of which is the preparation of 1,2-*O*-trichloroethylidene-α-D-galactofuranose (galactochloralose).

RESULTS AND DISCUSSION

Our synthesis used D-galactose as starting material. Galactochloralose can be easily prepared from D-galactose through its reaction with anhydrous chloral, using sulfuric acid as catalyst. Furthermore, it can be isolated and purified

without the need for tedious chromatographic separation steps. Isopropylidenation of galactochloralose with either acetone or 2,2-dimethoxypropane gives the 5,6-*O*-isopropylidene derivative, which can be subjected to further methylation and acid hydrolysis to afford 3-*O*-methyl-1,2-*O*-trichloroethylidene-α-D-galactofuranose (**1**) as described previously.[38] This can then be converted to the tricyclic orthoester, 3-*O*-methyl-1,2,5-*O*-orthodichloroacetyl-α-D-galactofuranose (**2**) (Sch. 1), by dehydrochlorination of the trichloroethylidene acetal group using potassium *tert*-butoxide.[39] The orthoester **2** has a free hydroxyl group on C-6, which can be tosylated to afford **3**. Reduction of the 6-*O*-tosyl group can be carried out using $LiAlH_4$ in toluene or diethyl ether to afford the 6-deoxy derivative **4**. Ether is the preferred solvent because a by-product is obtained with toluene as solvent. The final step involved the convenient removal of the orthoester moiety from compound **4** by acidic hydrolysis, using ion-exchange resin Amberlite IR-120 (H^+). Hydrolysis of dichloroacetyl orthoester has not been mentioned in the literature previously. This new method also demonstrates that dichloroacetyl derivatives can be used conveniently as a suitable protecting group.

The syrupy raw D-digitalose (**5**) was purified by silica gel column chromatography. To further characterize **5**, it was acetylated with acetic anhydride in pyridine. ^{1}H NMR spectrum of the acetylated sugar **6** as an anomeric mixture indicated an α/β ratio of 37/63. Crystallization of **6** gives the crystals of the pure β-anomer, m.p. 98–100°C (lit. m.p. 96–97°C). The syrupy D-digitalose was also characterized by formation of its phenylosazone **7**, m.p. 178–179°C (lit. m.p. 177–178°C) and its diethyldithioacetal derivative **8**, m.p. 97–98°C (lit.



Scheme 1: Synthesis of D-digitalose.

m.p. 95–96°C). All reactions were carried out smoothly and with reasonable yields. All of the derivatives were also characterized by NMR spectroscopy.

In conclusion, we have developed an alternative and convenient method for the synthesis of a cardiac sugar, D-digitalose (**5**). Starting from 3-*O*-methyl-1,2,5-*O*-orthodichloroacetyl-α-D-galactofuranose (**1**), the target compound was obtained in four separate steps in an overall yield of 18.3%. Further studies on preparations of various glycoside derivatives of this sugar are in progress and will be reported.

EXPERIMENTAL

General Methods

^{1}H NMR spectra (400 MHz) were recorded on a Varian AS 400 instrument. TLC and column chromatography were performed on precoated aluminium plates (Merck 5554) and silica gel G-60 (Merck 7734), respectively. All solvent removal operations were carried out under reduced pressure. Optical rotations were recorded on a Rudolph Autopol-1 Automatic Polarimeter. Melting points were recorded on a Gallenkamp Melting Point Device 350BM2.5.

3-*O*-Methyl-1,2-*O*-trichloroethylidene-α-D-galactofuranose (1)[38]

D-Galactose (27.45 g, 152 mmol) was added to chloral (84 mL, 861 mmol) under continuous stirring. After conc. H_2SO_4 (1 mL, d = 1.84) was added, the mixture was refluxed for 3 h. Then, the solids were dissolved in dichloromethane. Excess chloral and dichloromethane were evaporated, and dark syrup was obtained, which was entirely dissolved in methanol (200 mL). This solution was decolorized with activated charcoal, and the filtered solution was concentrated to afford 1,2-*O*-trichloroethylidene-α-D-galactofuranose (galactochloralose) as colorless crystals (35.46 g, 75%), m.p. 205–207°C, $[\alpha]_D^{21}$ –31.25 (c 0.4 in MeOH).

Crystalline galactochloralose (20 g, 64.8 mmol) was dissolved in DMF (30 mL). This solution was stirred with 2,2-dimethoxypropane (20 mL, 162.2 mmol) and *p*-toluenesulfonic acid (10 mg) for 24 h at rt. Then, the reaction mixture was neutralized with saturated aqueous sodium bicarbonate. The solvent was removed under reduced pressure, and the residue was crystallized from methanol at 0°C to give the pure 5,6-O-isopropylidene-1,2-*O*-trichloroethylidene-α-D-galactofuranose (18.12 g, 81%), m.p. 215–217°C (dec), $[\alpha]_D^{21}$ +17.1 (c 4.8 in pyridine).

A solution of 5,6-*O*-isopropylidene-1,2-*O*-trichloroethylidene-α-D-galact ofuranose (10.4 g, 30.28 mmol) in DMF (72 mL) was stirred with BaO (6 g, 39.12 mmol) and MeI (10 mL, 160.6 mmol) at rt for 24 h. The reaction mixture was filtered. The solvent was removed, and the residue was extracted with

dichloromethane (3 × 20 mL). The organic phase was decolorized with diluted sodium thiosulphate solution and washed with water (3 × 50 mL). The dried dichloromethane solution was evaporated to give the methylated product (9.6 g, 89%). $[\alpha]_D^{21}$ –35.8 (*c* 2.4 in $CHCl_3$).

A solution of the methylated compound (2.58 g, 7.33 mmol) in methanol (40 mL) was stirred with Amberlite IR-120(H+) resin (15 mL) and water 20 mL for 24 h, by which time TLC indicated the complete hydrolysis of the compound. After the filtration of the mixture, the filtrate was neutralized with aq. sodium bicarbonate solution. Methanol was removed and the residue was extracted with dichloromethane (3 × 50 mL). The dried dichloromethane solution was evaporated to give **1** as syrup (2.05 g, 89%). $[\alpha]_D^{21}$ –55,1 (c 5.1 in MeOH) ^{1}H NMR (DMSO-d_6): δ 3.31 (s, 3H, OCH_3), 3.37–3.47 (m, 2H, H-6, H-6′), 3.50 (m, 1H, H-5), 3.96–4.02 (m, 2H, H-3, H-4), 4.66 (t, 1H, $J_{6,OH}$ = 5.2 Hz, OH), 4.88 (d, 1H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 0 Hz, H-2), 4.91 (d, 1H, $J_{5,OH}$ = 5.2 Hz, OH), 5.67 (s, 1H, CCl_3CH), 6.15 (d, 1H, H-1); ^{13}C NMR (DMSO-d_6): δ 108.74 C_a, 107.27 C_1, 99.90 CCl_3, 63.31 C_6, 57.54 OCH_3; Anal. Calcd for $C_9H_{13}Cl_3O_6$: C, 33.40; H, 4.05. Found: C, 33.37; H, 4.14.

3-*O*-Methyl-1,2,5-*O*-orthodichloroacetyl-α-D-galactofuranose (2)

A mixture of 3-*O*-Methyl-1,2-*O*-trichloroethylidene-α-D-galactofuranose (**1**) (9.7 g, 29.98 mmol) and potassium *tert*-butoxide (10.03 g, 90 mmol, 3 equivalent) in *tert*-butanol (300 mL) was refluxed for 1 h. The mixture was filtered while hot, and the filtrate was evaporated to give syrup, which was crystallized from CH_2Cl_2 to afford the title compound **2** (5.6 g, 65%). m.p. 67–68°C; $[\alpha]_D^{21}$ +25.5 (*c* 1.65 in MeOH); ^{1}H NMR (DMSO-d_6): δ 3.34 (s, 3H, OCH_3), 3.40–3.60 (m, 2H, H-6, H-6'), 3.96 (s, 1H, $J_{3,4}$ = 0 Hz, H-3), 3.96 (dd, 1H, $J_{5,6}$ = 6.8 Hz, H-5), 4.61 (dd, 1H, $J_{4,5}$ = 2 Hz, H-4), 4.83 (dd, 1H, $J_{2,4} \sim$ 1.6 Hz (W coupling), $J_{2,3}$ = 0 Hz, H-2), 4.86 (t, 1H, $J_{6,OH}$ = 5.2 Hz, OH), 6.11 (d, 1H, $J_{1,2}$ = 4.0 Hz, H-1), 6.42 (s, 1H, CCl_2H); ^{13}C NMR ($CDCl_3$): δ 119.87 C_a, 104.42 C_1, 85.76 CCl_2H, 62.51 C_6, 57.53 OCH_3; Anal. Calcd for $C_9H_{12}Cl_2O_6$: C, 37.65; H, 4.21. Found: C, 37.63; H, 4.22.

3-*O*-Methyl-1,2,5-*O*-orthodichloroacetyl-6-*O*-tosyl-α-D-galactofuranose (3)

A solution of compound **2** (5.30 g, 18.48 mmol) and *p*-toluensulphonyl chloride (10.58 g, 55.50 mmol) in dry pyridine (30 mL) was stirred for 1 h at rt. The mixture was poured onto crushed ice (50 g) and extracted with CH_2Cl_2 (3 × 100 mL). The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated to give a residue, which was crystallized from an ethyl acetate-hexane mixture to give pure **3** (6.04 g, 74%). m.p. 115–116°C; $[\alpha]_D^{21}$ +34.0 (*c* 0.48 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 3H, Ar-CH_3), 3.42 (s, 1H, OCH_3), 3.95 (s,

1H, $J_{3,4} = 0$ Hz, H-3), 4.15–4.30 (m, 3H, H-5, H-6, H-6'), 4.59 (dd, 1H, $J_{4,5} = 2.4$ Hz, H-4), 4.70 (dd, 1H, $J_{2,4} \sim 1.6$ Hz (W coupling), $J_{2,3} = 0$ Hz, H-2), 5.56 (s, 1H, CCl_2H), 5.96 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1), 7.62 (d, 2H, $J = 8.0$ Hz, Ar-H), 7.80 (d, 2H, $J = 8.0$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$): δ 119.89 C_a, 104.55 C_1, 69.21 C_6, 68.07 CCl_2H, 57.61 OCH_3, 21.87 Ar-CH_3; Anal. Calcd for $C_{16}H_{18}Cl_2O_8S$: C, 43.55; H, 4.11; S, 7.27. Found: C, 43.77; H, 4.06; S, 7.19.

3-*O*-Methyl-1,2,5-*O*-orthodichloroacetyl-6-deoxy-α-D-galactofuranose (4)

A solution of compound **3** (1.45 g, 3.28 mmol) in dry ether (30 mL) was cooled in an ice bath, and then $LiAlH_4$ (0.25 g, 6.56 mmol) was added gradually. The mixture was permitted to reach rt and refluxed for 24 h. TLC indicated that the reaction was not complete; thus, more $LiAlH_4$ (0.25 g, 6.56 mmol) was added and the mixture was refluxed for another 24 h. Excess $LiAlH_4$ was quenched by addition of water (2 mL) and the mixture was filtered. The filtrate was concentrated and the residue was dissolved in hot ethyl acetate. The solvent was removed to afford a crude product that was purified by column chromatography on silica gel eluted with hexane/ethyl acetate (2:1) to give compound **4** as syrup, which was crystallized from ethyl acetate-hexane to afford pure **4** as a solid (0.61 g, 68%): m.p. 77–78°C; $[\alpha]_D^{21}$ +21.8 (c 0.6 in CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.35 (d, 3H, Me), 3.35 (s, 3H, OMe), 3.89 (s, 1H, $J_{3,4} = 0$ Hz, H-3), 4.18 (m, 1H, H-5), 4.26 (dd, 1H, $J_{4,5} = 2.4$ Hz, H-4), 4.63 (dd, 1H, $J_{2,4} \sim 1.6$ Hz (W coupling), $J_{2,3} = 0$ Hz, H-2), 5.63 (s, 1H, CCl_2H), 5.96 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1); ^{13}C NMR ($CDCl_3$): δ 119.79 C_a, 104.49 C_1, 69.84 CCl_2H, 57.45 OCH3, 18.77 C_6; Anal. Calcd for $C_9H_{12}Cl_2O_5$: C,39.87; H, 4.46. Found: C, 40.45; H, 4.42.

Hydrolysis of the Orthoester 3 to D-Digitalose (5)

To a solution of **4** (300 mg, 1.11 mmol) in a mixture of ethanol (4 mL) and water (15 mL), ion-exchange resin (Amberlite IR-120, H^+ form, 0.3 g) was added, and the mixture was stirred at rt for 2 d. The solvent was removed and the residue was purified on a silica gel column eluted with toluene-methanol (8:2) to afford syrupy D-digitalose (**5**) as an anomeric mixture (110 mg, 56%): $[\alpha]_D^{21}$ +107.3 (c 0,6 in H_2O) Anal. Calcd for $C_7H_{14}O_5$: C, 47.18; H, 7.92. Found: C, 47.27; H, 7.99.

DERIVATIVES OF D-DIGITALOSE

Triacetate (6)

An anomeric mixture of D-digitalose (55 mg, 0.308 mmol) was acetylated in pyridine-acetic anhydride to give the triacetate **6** (58 mg, 61.7%) as an

anomeric mixture, which was crystallized from petroleum ether (40–60°C) according to the literature[36] to afford the pure β-anomer (23 mg) as needles. m.p. 98–100°C (lit m.p. 96–97); $[\alpha]_D^{21}$ +48.9 (c 0.46 in $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.23 (s, 3H, H-6), 2.07, 2.10, 2.18 (3s, 3 × OAc), 3.37 (s, 3H, OCH_3), 3.41 (dd, 1H, $J_{3,4} = 3.2$ Hz, H-3), 3.86 (m, 1H, $J_{5,6} = 6.4$ Hz, H-5), 5.19 (dd, 1H, $J_{2,3} =$ 10 Hz, H-2), 5.36 (dd, 1H, $J_{4,5} \sim 1$ Hz, H-4), 5.63 (d, 1H, $J_{1,2} = 8$ Hz, H-1); ^{13}C NMR (DMSO-d_6): δ 170.89, 169.80, 169.62 triacetyl C=O, 92.51 C_1, 58.13 OCH_3, 21.09, 20.67, 20.61 triacetyl-CH_3; Anal. Calcd for $C_{13}H_{20}O_8$: C, 51.31; H, 6.62. Found: C, 51.23; H, 6.59.

The ^1H NMR signals of the α- and β-anomers were well resolved. The following data of the α-anomer were deduced from the spectrum of the mixture: ^1H NMR ($CDCl_3$): δ 1.16 (s, 3H, H-6), 3.39 (s, 3H, OCH_3), 2.05, 2.14, 2.17 (3s, 3 × OAc), 3.68 (dd, 1H, $J_{3,4} = 3.2$ Hz, H-3), 4.17 (m, 1H, $J_{5,6} = 6.4$ Hz, H-5), 5.20 (dd, 1H, $J_{2,3} = 10$ Hz, H-2), 5.42 (dd, 1H, $J_{4,5} \sim 1$ Hz, H-4), 6.30 (d, 1H, $J_{1,2} = 3.6$ Hz, H-1).

Osazone (7)

An anomeric mixture of D-digitalose (84 mg, 0.47 mmol) was reacted with phenyl hydrazine according to the literature[32] to afford the osazone **7** (77.3 mg, 46%). m.p. 178–179°C (lit m.p. 177–178); ^1H NMR ($CDCl_3$): δ 1.28 (d, 3H, H-6), 3.37 (s, 3H, OCH_3), 3.62 (dd, 1H, H-4), 3.89 (m, 1H, H-5), 4.03 (d, 1H, $J_{3,4} = 6$ Hz, H-3), 6.8–7.4 (m, 10H, 2 × Ph), 7.61 (s, 1H, NH), 7.92 (s, 1H, NH), 12.34 (s, 1H, H-1); ^{13}C NMR ($CDCl_3$): δ 133.04 C_1, 131.59 C_2, 84.40 C_3, 76.72 C_4, 67.61 C_5, 57.24 OCH_3, 19.60 C_6; Anal. Calcd for $C_{19}H_{24}N_4O_3$: C,64.03; H, 6.79. Found: C, 63.96; H, 6.69.

Diethyldithioacetal (8)

An anomeric mixture of D-digitalose (80 mg, 0.45 mmol) was reacted with ethylmercaptane according to literature[32] to afford the diethyldithioacetal derivative **8** (91 mg, 71%). m.p. 97–98°C (Lit[32] m.p. 95–96); $[\alpha]_D^{21}$ +12,1 (c 0.5 in pyridine); ^{13}C NMR ($CDCl_3$): δ 59.34 OCH_3, 55.75 C_1, 27.43 S-CH_2, 14.65 Et-CH_3; Anal. Calcd for $C_{11}H_{24}O_4S_2$: C, 46.45; H, 8.50. Found: C, 46.69; H, 8.59.

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REFERENCES

1. Hauptman, P.J.; Garg, R.; Ralph, A.K. Cardiac glycosides in the next millennium. *Prog. Cardiovasc. Dis.* **1999**, *41*, 247–254.

2. Elderfield, R.C. Carbohydrate component of the cardiac glycosides. *Adv. Carbohyd. Chem. Biochem.* **1945**, *1*, 147–173.

3. Reichstein, T.; Weiss, E. The sugars of the cardiac glycosides. *Adv. Carbohyd. Chem. Biochem.* **1962**, *17*, 65–130.

4. Heller, M. Cardiac glycosides: new/old ideas about old drugs. *Biochem. Pharmacol.* **1990**, *40*, 919–925.

5. Offermans, S.; Rosenthal, W. *Encyclopedia of Molecular Pharmacology*. Springer, Heidelberg, **2008**, 325–328.

6. Foye, W.O.; Lemke, T.L.; Williams D.A. *Foye's Principles of Medicinal Chemistry*. Wiley, Baltimore, **2008**, 348–360.

7. Mijatovic, T.; Quaquebeke, E.; Delest, B.; Debeir, O.; Darro, F.; Kiss, R. Cardiotonic steroids on the road to anti-cancer therapy. *Biochim. Biophys. Acta* **2007**, *1776*, 32–57.

8. Haux, J. Digitoxin is a potential anticancer agent for several types of cancer. *Med. Hypotheses* **1999**, *53*, 543–548.

9. Newman, R.A.; Yang, P.; Pawlus, A.D.; Block, K.I. Cardiac glycosides as novel cancer therapeutic agents. *Mol. Interv.* **2008**, *8*, 36–49.

10. Prassas, I.; Diamandis, E.P. Novel therapeutic applications of cardiac glycosides. *Nat. Rev. Drug Discov.* **2008**, *7*, 926–935.

11. Winnicka, K.; Bielawski, K.; Bielawska, A. Cardiac glycosides in cancer research and cancer therapy. *Acta Pol. Pharm.* **2006**, *63*, 109–115

12. Aronson, J.K. *Meyler's Side effect of Cardiovascular Drugs*. Elsevier, Amsterdam, **2009**, 326–338.

13. Langenhan, J.M.; Peters, N.R.; Guzei, I.A.; Hoffmann, M.; Thorson, J.S. Enhancing the anti-cancer properties of cardiac glycosides via neoglycorandomization. *Proc. Natl. Acad. Sci. U S A* **2005**, *102*, 12305–12310.

14. Zhou, M.; O'Doherty, G.A. The de novo synthesis of oligosaccharides: application to the medicinal chemical study of digitoxin. *Curr. Top. Med. Chem.* **2008**, *8*, 114–125.

15. Iyer, A.; Zhou, M.; Azad, N.; Elbaz, H.; Wang, L.; Rogalsky, D.K.; Rojanasakul, Y.; O'Doherty, G.A.; Langenhan, J.M. A Direct Comparison of the Anticancer Activities of Digitoxin MeON-Neoglycosides and O-Glycosides. *ACS Med. Chem. Lett.* **2010**, *1*, 326–330

16. Wang, H.Y.L.; Wu, B.; Zhang, Q.; Rojanasakul, Y.; O'Doherty, G.A. C5′-Alkyl substitution effects on digitoxigenin lung cancer cells cytotoxicity. *ACS Med. Chem. Lett.* **2011**, *2*, 259–263.

17. Wang, H.Y.L.; Rojanasakul, Y.; O'Doherty, G.A. Synthesis and evaluation of the α-D-/α-L-rhamnosyl and amicetosyl digitoxigenin oligomers as anti-tumor agents. *ACS Med. Chem. Lett.* **2011**, *2*, 264–269.

18. Wong, C.H. *Carbohydrate-based Drug Discovery*. John Wiley and Sons: New-York, **2003**, 1–35.

19. Dixon, J. T.; Van Heerden, F.R. Preparation of an analogue of orbicuside A, an unusual cardiac glycoside. *Tetrahedron Asymmetr.* **2005**, *16*, 393–401.

20. Fullerton, D.S.; Kihara, M.; Deffo, T.; Kitatsuji, E.; Ahmed, K.; Simat, B.; From, A.H.L.; Rohrer, D.C. Cardiac glycosides. 1. A Systematic study of digitoxigenin D-glycosides. *J. Med. Chem.* **1984**, *27*, 256–261.

21. Rathore, H.; Hashimoto, T.; Igarashi, K.; Nukaya, H.; Fullerton, S. Cardiac glycosides: 5. Stereoselective syntheses of digitoxigenin α-D, β-D, α-L, β-L-glucosides. *Tetrahedron* **1985**, *41*, 5427–5438.

22. Chiu, F.C.K.; Watson, T.R. Conformational factors in cardiac glycoside activity. *J. Med. Chem.* **1985**, *28*, 509–515.

23. Rathore, H.; From, A.H.L.; Ahmed, K.; Fullerton, D.S. Cardiac glycosides: 7. Sugar stereochemistry and cardiac glycoside activity. *J. Med. Chem.* **1986**, *29*, 1945–1952.

24. Zhou, M.; O'Doherty, G.A. De novo asymmetric synthesis of digitoxin via a palladium catalyzed glycosylation reaction. *Org. Lett.* **2006**, *8*, 4339–4342.

25. Zhou, M.; O'Doherty, G.A. De novo asymmetric syntheses of digioxose and digitoxin. *J. Org. Chem.* **2007**, *72*, 2485–2493.

26. Hung, S.C.; Thopate, S.R.; Puranik, R. Synthesis of 6-deoxy-L-idose and L-acovenose from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. *Carbohydr. Res*. **2001**, *331*, 369–374.

27. Killiani, H. Digitalin verum. *Arch. Pharm.* **1892**, *230*, 250–261.

28. Leach, B.E.; Calhoun, K.M.; Johnson, L.E.; Teeters, C.M.; Jackson, W.G. Chartreusin, a new antibiotic produced by Streptomyces chartreusis, a new species. *J. Am. Chem. Soc.* **1953**, *75*, 4011–4012.

29. Takai, M.; Uehara, Y.; Beisler, J.A. Synthesis and antitumor activity of analogs of the antitumor antibiotic chartreusin. *J. Med. Chem.* **1980**, *23*, 549–553.

30. Lam, K.S.; Veitch, J.A.; Forenza, S.; Combs, C.M.; Colson, K.L. Biosynthesis of elsamicin A, a novel antitumor antibiotic. *J. Nat. Prod.*, **1989**, *52*, 1015–1021.

31. Sugawara, K.; Tsunakawa, M.; Konishi, M.; Kawaguchi, H.; Krishnan, B.; He, C. H.; Clardy, J. Elsamicins A and B, new antitumor antibiotics related to chartreusin. 2. Structures of elsamicins A and B. *J. Org. Chem.* **1987**, *52*, 996–1001.

32. Sternbach, L.H.; Kaiser, S.; Goldberg, M.W. Degradation of chartreusin (antibiotic X-465A). *J. Am. Chem. Soc.* **1958**, *80*, 1639–1647.

33. Fleck, W.; Strauss, D.; Prauser, H.; Jungstand, W.; Heinecke, H.; Gutsche, W.; Wohlrabe, K. Lambdamycin, ein Antibioticum aus dem Stamm IMET 31118 von Streptomyces glaucoachromogenes. *Z. Allg. Mikrobiol*. **1976**, *16*, 521–528.

34. Reber, F.; Reichstein, T. Synthese der Digitalose. *Helv. Chim. Acta* **1946**, *29*, 343–352.

35. Schmidt, O.S.; Wernicke, E. Die Synthese der Digitalose. *Eur. J. Org. Chem.* **1947**, *558*, 70–80.

36. Tamm, C. Eine weitere Synthese der D-Digitalose sowie Bereitung krystallisiereter Digitalose-acetate. Desoxyzucker. *Helv. Chim. Acta* **1949**, *32*, 163–172.

37. Brimacombe, J.S.; Da'Aboul, I.; Tucker, L.C.N. Syntheses of L-vallarose (6-deoxy-3-*O*-methyl-L-altrose) and D-digitalose (6-deoxy-3-*O*-methyl-D-galactose). *J. Chem. Soc. C* **1971**, 3762–3765.

38. Anil, H.; Yuceer, L.; Yuceer, T. 1,2-*O*-Trichloroethylidene-α-D-galactofuranose. *Carbohydr. Res.* **1983**, *123*, 153–156

39. Salman, Y.G.; Makinabakan, O.; Yuceer, L. Tricyclic ortho ester formation from trichloroethylidene acetals of sugars via ketene acetals. *Tetrahedron Lett.* **1994**, *35*, 9233–9236.