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Highly Efficient Synthesis of Digoxin

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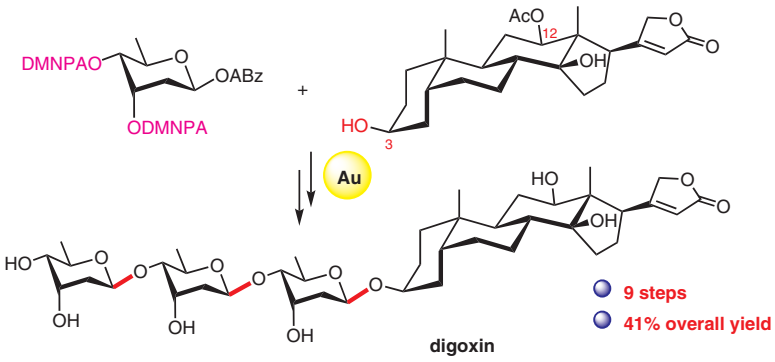

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Abstract Taking advantage of the reliable stereocontrol capability of DMNPA group via long-distance-participation (LDP) effect as well as the mild and efficient deprotection conditions, the first and highly efficient synthesis of digoxin was achieved through a nine-step longest linear sequence with 41% overall yield.

Key words digoxin, cardiac glycosides, synthesis, glycosylation, DMNPA

Represented by digoxin and digitoxin, cardiac glycosides (CGs) have been widely prescribed for the treatment of congestive heart failure and cardiac arrhythmia.[1] Moreover, recent investigations demonstrate that CGs, including digoxin and digitoxin, show impressive antitumoral activities with coveted selectivity between normal and cancer cells.[2] Mechanistically, the impressive pharmaceutical potential of digoxin and digitoxin is closely related to Na^+/K^+-ATPase, a ubiquitous membrane protein responsible for Na^+/K^+ transport.[3] As ligands, digoxin and digitoxin can bind with Na^+/K^+-ATPase, leading to the activation of multiple signal transduction pathways, whereby efficacy of enhancement of heart contraction force and velocity,[4] regulation of cell differentiation, proliferation, survival, and apoptosis is achieved.[5] However, the medical application of digoxin and digitoxin suffers from narrow therapeutic window, which inevitably incurs the frequent occurrence of poising cases.[6] The urgent need for CGs with maintained/improved bioactivity while devoid of toxic side effects calls on highly efficient approaches to access to digoxin/digitoxin and analogues thereof.

Structurally, digoxin/digitoxin CGs belong to steroid saponins with digitoxyl trisaccharide chain appended to the 3-OHs of steroid aglycone, digoxigenin and digitoxigenin, via β-glycosidic linkages (Figure 1). The β-glycosidic linkages in combination with the butenolide entities of the aglycones pose considerable challenge for the synthesis of digoxin/digitoxin and their derivatives, because the 2,6-dideoxy property of digitoxose makes the stereoselective construction of glycosidic linkages extremely difficult in the absence of neighboring group participation (NGP) effect[7] while the highly base-sensitive character of butenolide group dictates a judicious selection of protecting groups (PGs).[8] Intrigued by the clinically demonstrated as well as potential medicinal applications, the synthetic investigation toward digitoxin and its analogues[9] have been extensive conducted, leading to the successful establishment of various approaches to furnish digitoxin.[8,10] Nevertheless, the overall synthetic efficiency of existing methods was compromised either by detour synthetic strategy or by inefficient PGs manipulations. Although theoretically the established synthetic strategies for syntheses of digitoxin and its analogues could also be applicable in the synthesis of digoxin derivatives, the syntheses of digoxin derivatives have only been reported sparsely and the synthesis of digoxin has yet to be achieved.[11] Leveraging on the robust long-distance-participation (LDP) effect as well as mild and efficient deprotection conditions of 2,2-dimethyl-2-(*ortho*-nitro-

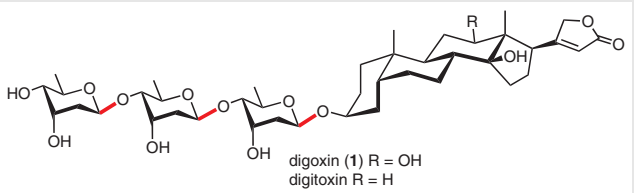

Figure 1 The chemical structures of digoxin and digitoxin

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phenyl)acetyl (DMNPA) group,[12] the first and efficient synthesis of digoxin was presented herein.

Retrosynthetically, digoxin (**1**) could be assembled by digitoxosyl *ortho*-alkynylbenzoate (ABz) **2** and digoxigenin **3**[13] (Figure 2). Given the susceptibility of both the glycosidic linkages of 2-deoxysugars and the aglycone, the Yu glycosylation protocol was preferred.[14] Meanwhile, to secure satisfactory stereocontrol in glycosylation steps, two DMNPA groups with intensified LDP effect and mild deprotection conditions were installed in donor **2**, and a reliable linear synthetic strategy was adopted during the incorporation of the digitoxyl trisaccharide chain.[15]

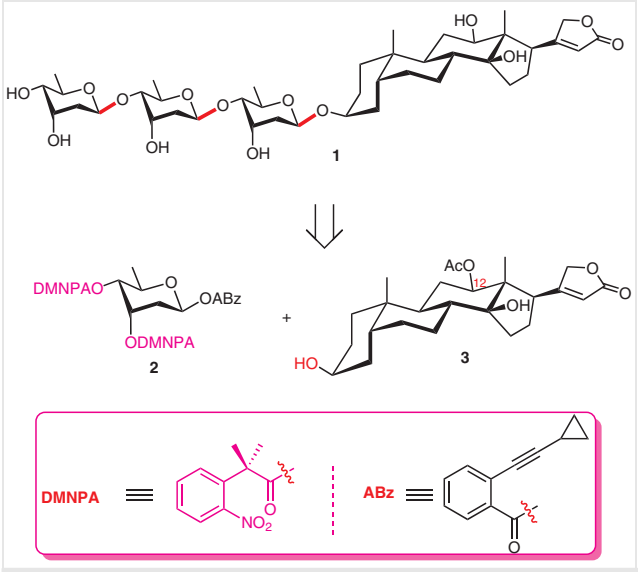
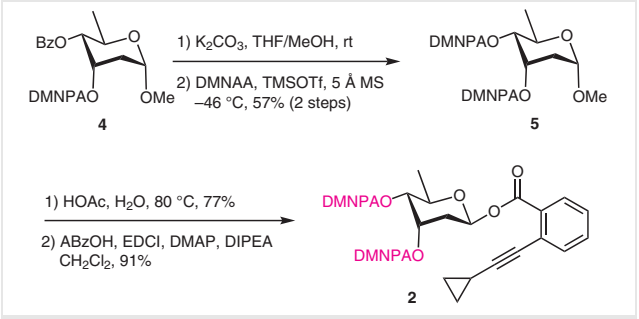


Figure 2 Digoxin and its retrosynthetic analysis

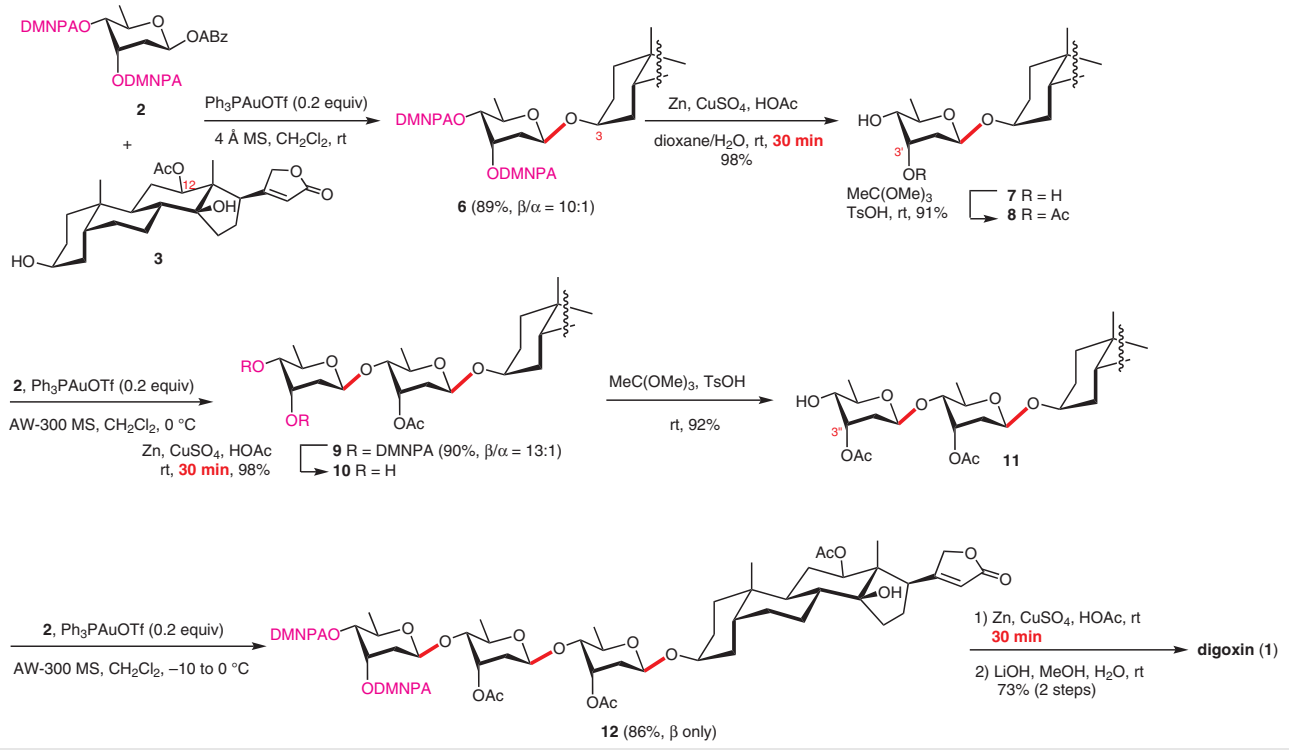
The synthetic investigation commenced with the preparation of digitoxyl ABz donor **2** with **4**[12b] as starting materials (Scheme 1). The introduction of the second DMNPA group on **4** was achieved by selective removal of benzoyl (Bz) group and ensuing acylation with 2,2-dimethyl-2-(*ortho*-nitrophenyl)acetyl anhydride (DMNPAA) under the effect of TMSOTf[12a] to furnish **5** (57%, over 2 steps). It should be pointed out that during the selective cleavage of 4-OBz under basic conditions, partial migration of the 3-ODMNPA was observed, presumably because of the *cis*-vicinal relationship between 3,4-OHs of digitoxose. Nevertheless, the migration of DMNPA group was inconsequential as both regioisomers provided the same product **5** after acylation with DMNPAA. Hydrolysis of methyl glycoside **5** followed by dehydrative acylation with ABzOH under standard conditions[13] to afford β-**2** exclusively.

With donor **2** in hand, now the stage was set for the incorporation of the trisaccharide sugar chain via a linear strategy (Scheme 2). Pleasingly, under the effect of $Ph_3PAuOTf$,[16] the coupling between **2** and digoxigenin (**3**)



Scheme 1 Synthesis of digitoxyl *ortho*-alkynylbenzoate donor **2**

proceeded smoothly, affording monosaccharide glycoside **6** as a α/β mixture with the desired β-isomer as the predominant product (89%, α/β = 1:10). Subsequently, the simultaneous cleavage of the two DMNPA groups in **6** was achieved under the effect of $Zn/CuSO_4$/HOAc, delivering **7** almost quantitatively in only 30 minutes without touching the 12-OAc and the butenolide moiety of the aglycon (98% yield). The resulting diol intermediate **7** was then put to selective discrimination of the axial 3′-OH with an acetyl group via a sequence of 3′,4′-orthoester formation and ensuing acid-mediated regioselective opening of the resulting orthoester to deliver **8** (91%), which was ready for sugar chain extension via 4′-OH. The subsequent sugar chain prolongation entailed coupling of **8** with donor **2**, which was operated in the presence of acid-washed MS-300 at 0 °C to ensure both high stereoselectivity and excellent yield (**9**, 90%, β/α = 13:1). The slight modification of the standard glycosylation conditions was dictated by the lowered reactivity of acceptor **8** than **3** caused by the deactivating effect of the vicinal electron-withdrawing acetyl group.[17] The following deprotection of the two DMNPA groups in **9** was carried out under the standard conditions to yield **10**, while keeping the two 3,12-*O*-acetyl groups and butenolide moiety intact (30 min, 98%). Compound **10** was then put to the identical conditions as those used to convert **7** into **8** to provide acceptor **11** (92%), primed for the appending of the final digitoxyl residue. Thus, under the slightly modified conditions (AW-300 MS, –10 to 0 °C), the condensation between **11** and **2** proceeded without any event, providing **12** exclusively (86% yield). Finally, global deprotection of **12** through successive DMNPA groups removal and acetyl groups cleavage afforded digoxin (**1**, 73%, for 2 steps). The chirality of all freshly fashioned glycosidic linkages was determined by ^{1}H NMR spectra, wherein all anomeric protons appeared at δ = 4.5–4.8 ppm in doublet of doublet (dd) form, with the big *J* values being around 10.0 Hz and small *J* values being around 2.0 Hz, respectively. Additional convincing evidence came from the direct spectroscopic-data comparison of the synthetic **1** with authentic sample, which showed that actually identical spectra were obtained (see the Supporting Information). Counting from the easily available digoxosyl donor



Scheme 2 Synthesis of digoxin with donor **2**

2, the first total synthesis of digoxin was achieved via a longest linear sequence (LLS) of nine steps with 41% overall yield.

In summary, capitalizing on the robust stereocontrol capability as well as the mild and efficient deprotection process of DMNPA group, the first and highly efficient synthesis of digoxin was accomplished via a nine-step longest linear sequence in 41% overall yield.[18,19] The established protocol exquisitely solves the drawbacks inherent to the existing synthesis of CGs, including unsatisfactory stereoselectivity in glycosylation reaction, harsh reaction conditions, as well as sluggish deprotection process, accordingly may find broad application in synthesis of digoxin/digitoxin and analogues thereof in the future.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1346-5650.

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(18) **General Procedure for the Digitoxosylation**
To a solution of donor **2** (0.05 mmol) and digoxigenin (2.0 equiv) in dry CH_2Cl_2 (2.0 mL) was added freshly activated 4 Å MS or AW MS at room temperature under N_2 atmosphere. After being stirred at the same temperature for 30 min, $Ph_3PAuOTf$ (0.2 equiv) was added at room temperature (or 0 °C and –10 °C) under N_2 atmosphere. The stirring was continued at room temperature (or at 0 °C) until TLC showed that all donor was consumed. Filtration was followed by concentration under reduced pressure to give a residue, which was further purified by silica gel column chromatography to provide the glycosylation products.

(19) **Analytic Data for Digoxin (1)**
White solid; $[\alpha]_D^{25}$ +3.0 (*c* 0.4, $CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 5.82 (t, *J* = 1.6 Hz, 1 H), 4.93 (AB, 2 H), 4.82 (dd, *J* = 2.0, 9.2 Hz, 2 H), 4.78 (dd, *J* = 2.0, 9.6 Hz, 1 H), 4.62–4.59 (m, 3 H), 4.25 (dd, *J* = 1.2, 3.2 Hz, 1 H), 4.19 (dd, *J* = 0.8, 2.8 Hz, 1 H), 4.10 (s, 1 H), 4.06–4.03 (m, 2 H), 3.89 (br s, 1 H), 3.86–3.83 (m, 1 H), 3.75–3.60 (m, 3 H), 3.26–3.20 (m, 2 H), 3.14 (dt, *J* = 2.0, 9.6 Hz, 2 H), 3.02 (ddd, *J* = 2.8, 6.8, 9.6 Hz, 1 H), 1.98–1.29 (m, 23 H), 1.17–1.02 (m, 3 H), 1.13 (d, *J* = 6.4 Hz, 3 H), 1.12 (d, *J* = 6.4 Hz, 3 H), 1.10 (d, *J* = 6.0 Hz, 3 H), 0.84 (s, 3 H), 0.65 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 176.9, 174.0, 115.8, 99.1, 99.0, 95.3, 84.3, 81.9, 81.6, 73.3, 73.0, 72.7, 72.1, 69.1, 67.6, 67.5, 67.0, 66.3, 66.1, 55.7, 45.2, 40.5, 38.4, 38.3, 37.9, 36.3, 34.7, 32.4, 31.6, 30.2, 29.7, 29.6, 26.8, 26.4, 26.0, 23.7, 21.3, 18.4, 18.0, 9.4. HRMS (ESI): *m/z* calcd for $C_{41}H_{64}O_{14}Na$ $[M + Na]^+$: 803.4188; found: 803.4184.