A Concise Synthesis of 3-Hydroxy-4-(β-glucopyranosyl) Benzoate: A New Route to β-*C*-Aryl Glycosides

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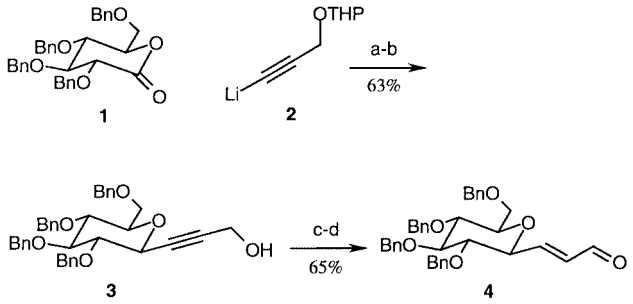
Abstract: A synthesis of specifically substituted β-*C*-aryl glycosides is described. The aromatic moiety is built up starting from the easily available 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone with a benzoannulation reaction as a key step.

Key words: annulation, cyclization, carbohydrates, glycosides, phenols

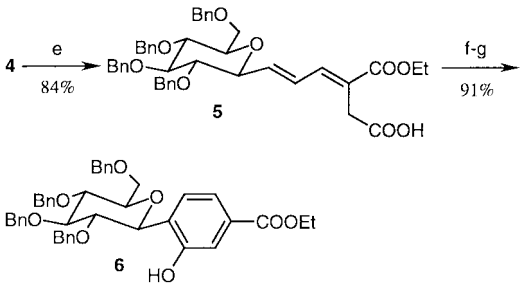
C-Aryl glycosides are an important subclass of *C*-glycosides.[1] Several products containing *C*-aryl glycosidic linkage were isolated from natural sources and their relevant biological interest[2] prompted our study in this field. Many different synthetic approaches have been developed recently[3] and in most cases these methods couple a carbohydrate derivative with a suitable aryl moiety. Since arenes bearing electron-withdrawing groups lack reactivity, some alternate procedures in which the aromatic ring is constructed from a pre-existing *C*-glycoside have been reported.[4] Here, we report a concise preparation of 3-hydroxy-4-(β-glucopyranosyl) benzoic acid ester **6** using the benzoannulation reaction of 3-alkoxycarbonyl-3,5-hexadienoic acids.[5] We have shown that the latter process is very flexible,[6] giving benzoannulated phenols bearing a benzylic stereocentre starting from γ-chiral-α,β-unsaturated aldehydes.[7] In order to extend this cyclization to the synthesis of *C*-aryl-glycosides, we prepared the suitable γ-glucopyranose-α,β-unsaturated aldehyde **4** (Scheme 1).



Reagents and conditions: 2+1 THF, -78 °C, 30 min then 0 °C, 1 h; b) Et_3SiH, $BF_3.Et_2O$, CH_2Cl_2, to -78 °C at r.t, 2 h then H_2O; c) RED-Al, Et_2O, 0 °C, 1 h; d) MnO_2, $CHCl_3$, reflux, 4 h.

Scheme 1

The easy available 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone **1**[8] was condensed with the lithium salt of protected propynol **2** to give an anomeric mixture of the related alcohol in almost quantitative yield. The latter was treated with triethylsilane (3 equiv) and boron trifluoride (3 equiv)[9] to afford exclusively the β-linked propargylic alcohol **3** in 65% yield. Regioselective reduction of the triple bond with sodium bis-(2-methoxyethoxy)aluminium hydride[10] (1.6 eq. based on aluminium) gave us the *trans* allylic alcohol in 86% yield, which was oxidized with MnO_2 (10 equiv) in refluxing $CHCl_3$ to the aldehyde **4** in 75% yield.[11] Its conversion into 6-glucopyranose-3-ethoxycarbonyl-3,5-exadienoic acid **5** was performed by Wittig reaction (Scheme 2) with triphenyl-(α-carbethoxy-β-carboxyethyl)phosphonium betaine.[12]



Reagents and conditions: e) triphenyl-(α-carbethoxy-β-carboxyethyl)phosphonium betaine, $CHCl_3$ reflux 10 h; f) $ClCO_2Et$ 1.5 equiv, Et_3N 2 equiv, r.t. 15 min; g) NaOH/EtOH, 10 min. then HCl aq

Scheme2

Cyclization of **5** in THF solution with $ClCO_2Et$, followed by addition of Et_3N, gave the phenol **6** together with a small amount of its carboxyethyl derivative. Quick treatment of the latter mixture with an excess of ethanolic NaOH (2 eq.) gave the β-*C*-glycoside **6** in 91% yield.[13]

Many different lactones can be used in the preparation of *C*-glycosyl compounds by the Kraus method. Thus, our synthetic approach may be applicable for the preparation of different *C*-aryl-glycosides showing the 3-hydroxy-4-(gluco) benzoate ester substitution pattern. This kind of compound has been already used as starting material for the synthesis of some pyranonaphthoquinone antibiotics.[14] Moreover, the preparation of **6** itself might hold some general significance in the preparation of the *C*-linked glycopeptides, a class of compounds of current interest.[15] Indeed, simple functional group manipulation and *C*-2 chain elongation should allow the conversion of the ester **6** into 3-hydroxy-4-(gluco) phenyalanine, a product conceivably not so directly accessible through the usual *C*-arylation methods.

Acknowledgement

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References and Notes

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(11) Compound **4**: Anal. Calcd for $C_{37}H_{38}O_6$: C, 76.84; H, 6.57. Found: C, 76.65; H, 6.55. mp. 67-69 °C; $[\alpha]_D^{20}$ = -38.6° (c 2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (1H, t, J = 9.2Hz), 3.51 (1H, dt, J = 3, 9.7Hz), 3.63-3.80 (4H, m), 4.01 (1H, ddd, J = 1.5, 4.3, 9.7Hz), 4.53-4.65 (4H, m), 4.82-4.89 (2H, m), 4.94 (2H, s), 6.37 (1H, ddd, J = 1.5, 8, 15.7Hz), 6.70 (1H, dd, J = 4.3, 15.7Hz), 7.20-7.45 (20H, m), 9.39 (1H, d, J = 8Hz); MALDI 600.2 (M^+-1+Na), 616.1 (M^+-1+K); FT-IR (neat): ν (cm^{-1}) 700, 755, 1065, 1095, 1360, 1454, 1497, 1688, 2863, 3030.
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(13) Ethyl chloroformate (4 mmol) was added to a THF solution of acid **5** (2 mmol, 0.1 M) and then Et_3N (6 mmol) was added slowly, while the temperature was kept under 20 °C. The reaction mixture was stirred for 10 min., was treated with an excess of 5% aq, HCl and was extracted with ethyl acetate. The organic phase was concentrated in vacuo, to give a residual mixture of **6** and its carboxyethyl derivative. The latter was treated with ethanolic NaOH (6 mmol) at room temperature for 10 min. The mixture was diluted with an excess of 5% aq HCl and was extracted with ethyl acetate. The organic phase was dried (Na_2SO_4), and was concentrated in vacuo. The residue was chromatographed on a silica gel column eluted with hexane-ethyl acetate (10:1-2:1) to give in 91% yield the phenol **6** with the following analytical data: Anal. Calcd for $C_{43}H_{44}O_8$: C, 75.02; H, 6.39. Found: C, 74.95; H, 6.40. mp 123-124 °C (hexane); $[\alpha]_D^{20}$ = -15.8° (c 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (3H, t, J = 7.2Hz), 3.59 (1H, dt, J = 9.7, 2Hz), 3.66-3.82 (4H, m), 3.84-3.94 (2H, m), 4.38 (2H, q, J = 7.2Hz), 4.42-4.52 (3H, m), 4.54-4.62 (2H, m), 4.85 (1H, d, J = 10.9Hz), 4.87-4.97 (2H, m), 6.93-7.00 (2H, m), 7.12-7.40 (20H, m), 7.56 (1H, dd, J = 7.8, 1.6Hz), 7.6 (1H, d, J = 1.6Hz); MALDI 710.3 (M^+-1+Na), 726.4 (M^+-1+K); FT-IR (neat): ν (cm^{-1}) 697, 737, 1093, 1216, 1288, 1360, 1455, 1500, 1578, 1716, 2904, 3336.
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