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A novel synthesis of β-phenylglucuronides using the Mitsunobu reaction; an application of phenolic chromium tricarbonyl complexes

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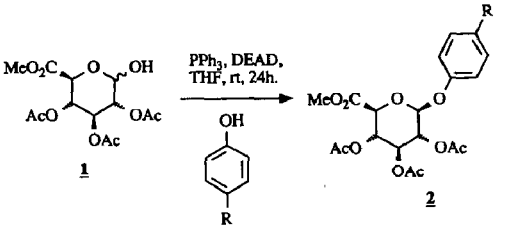
Abstract

Methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate reacts with phenols under Mitsunobu conditions to give β-phenylglucuronides. Improved yields are obtained with *p*-methyl and *p*-methoxyphenol by prior complexation to the chromium tricarbonyl residue, which serves to increase the acidity of the phenol.

Introduction

The need to assay glucuronides of drug substances and metabolites in body fluids has led us to examine new methods for their preparation. The methods currently



2	R	yield(%)	Lit. Ref.
a	NO_2	49	12
b	Br	41	13
c	Cl	26	13
d	H	26	2
e	Me*	10	13
f	MeO*	trace	-

* Reaction allowed to proceed for 72h.

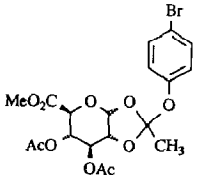
Scheme 1

available have recently been reviewed [1], and while the Koenigs–Knorr reaction is the most frequently used, a number of problems with this approach have been highlighted by Fischer et al. [2]. These workers developed an alternative method for glucuronidation which employs the stable hemiacetal **1** as a starting material and trimethylsilyltrifluoromethanesulphonate as an activating agent; the method is applicable to a number of alcohols and to phenols with pK_a's of < 10.

Our interest has focused on the use of the Mitsunobu reaction [3] for the synthesis of β-phenylglucuronides e.g. **2**. The synthesis of phenyl glycosides [4] and, more recently, acyl glucuronides [5], by use of such methodology has been reported, but as far as we are aware it has not been applied to glucuronide synthesis. The mechanism of the Mitsunobu reaction itself is currently attracting considerable attention [6,7].

Results and discussion

The hemiacetal **1** was prepared by the method described by Tietze and Seele [8], and was used (as obtained), as an 8/1 mixture of the α- and β-isomers. The Mitsunobu reaction was carried out by pre-mixing triphenylphosphine and diethyl azodicarboxylate (DEAD) in tetrahydrofuran (THF) at room temperature and then adding the phenolic component followed by **1**. The reagents were used in an approximate molar ratio of 2/2/2/1. The initial experiments were carried out with *p*-bromophenol and the desired β-phenylglucuronide (**2b**) was isolated in 41% yield, accompanied by 26% of the orthoester **3**. The outcome of the reaction showed some dependence on order of addition and molar ratios of reagents.



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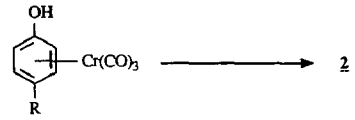
A range of phenols were then employed in the reaction and the results are summarised in Scheme 1. A number of by-products other than the corresponding orthoesters were also observed, including small quantities of α-glucuronides. The most interesting feature of the results, however, is an apparent trend towards an increase in the yield with increasing acidity of the phenolic component.

We were intrigued by the possibility of increasing the acidity of the phenol by π-bonding to a metal, and hence improving the yields of the Mitsunobu reaction. The increased acidity of benzylic protons in arenechromium tricarbonyl complexes is well established [9], and phenolic chromium tricarbonyl complexes have been prepared and shown to undergo deprotonation [10,11]. *p*-Methoxyphenol and *p*-methylphenol were selected for examination, since in these cases the yields of the Mitsunobu reactions are particularly poor.

The complexes were prepared by refluxing a solution of the phenol and an excess of chromium hexacarbonyl in THF/di-n-butyl ether (Bu_2O) 2/5. The solvent and excess of chromium hexacarbonyl were removed, the yellow residue was redissolved in THF and the solution used immediately in the Mitsunobu reaction. The chro-



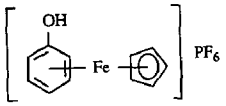
complex	R	product	yield(%)
4	Me	2e	35
5	MeO	2f	21

Scheme 2

mium carbonyl complexes of the glucuronides **2** were not isolated, but could be detected by thin layer chromatography. At the end of the reaction period, exposure of the solution to air effected decomplexation, and the β-phenylglucuronide formed was then purified by column chromatography.

The yields of the β-phenylglucuronides obtained by this method are summarised in Scheme 2 and are significantly higher than those previously reported, indicating the operation of expected enhancement of the phenol acidity in the chromium tricarbonyl complexes. The Mitsunobu approach therefore provides a general method for the preparation of β-phenylglucuronides.

The iron(II) complex **6** [12] was also prepared and its behaviour in the Mitsunobu reaction examined, but decomplexation of the phenol from the metal occurred and the β-phenylglucuronide was not formed.



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Experimental

The ^{1}H NMR spectra were recorded on a Bruker AM 250 or Bruker AM 200 instrument with Me_4Si as internal standard. Mass spectra were recorded on a VA 7070F instrument. IR spectra were recorded on a Perkin Elmer 298 spectrophotometer. Elemental analyses were obtained with a CEC 240 XA elemental analyser. Melting points were determined in open capilliary tubes and are uncorrected. All experiments were conducted under nitrogen. The β-phenylglucuronides all gave melting points and spectroscopic data consistent with the literature values.

*Methyl (p-bromophenyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (**2b**)*

Diethyl azodicarboxylate (42 mg, 0.24 mmol) was dissolved in dry THF (3 ml) and the solution stirred at room temperature under nitrogen. To the stirred solution was added triphenylphosphine (76 mg, 0.29 mmol) followed by *p*-bromophenol (50 mg, 0.29 mmol), and the mixture was stirred at ambient temperature for 5 min. Methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate (50 mg, 0.15 mmol) was added and stirring continued at room temperature under nitrogen for 24 h. The solvent was then removed in vacuo and the residue subjected to column chromatography on silica with gradient elution (starting ethyl acetate/hexane 1/4 increasing to ethyl acetate/hexane 1/2). This afforded the product **2b** (30 mg, 41%) as a white solid. Recrystallisation from ethyl acetate/hexane afforded white needles, m.p. 162.5°C

(lit. 162–163.5°C) [13]). ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3, Ac) 2.05 (s, 3, Ac) 2.06 (s, 3, Ac) 3.73 (s, 3, OMe) 4.17 (m, 1, H5) 5.09 (d, J 5.6 Hz, 1, H1) 5.22–5.38 (m, 3, H2,3,4) 6.88 (m, 2, ArH) 7.40 (m, 2, ArH).

Also isolated was methyl (3,4-di-*O*-acetyl-1-2-(4-bromophenoxy)ethylidene-β-D-glucopyranosid)uronate (**3**) (18 mg, 25%). ^{1}H NMR ($CDCl_3$): δ 1.81 (s, 3, CMe), 2.09 (s, 3, Ac), 2.12 (s, 3, Ac), 3.78 (s, 3, OMe), 4.23 (m, 1, H2), 4.30 (d, J 7.9 Hz, 1, H5), 5.16 (m, 1, H4), 5.26 (m, 1, H3), 5.84 (d, J 4.8 Hz, 1, H1), 7.02 (m, 2, ArH), 7.40 (m, 2, ArH). ^{13}C NMR ($CDCl_3$): δ 20.70 ($COCH_3$, x2), 21.85 (CCH_3), 52.82 (OCH_3), 68.04 (C3), 68.15 (C4), 68.89 (C5), 72.76 (C2), 96.20 (C1), 117.28 (ArC-Br), 122.96 (COR_3), 123.59 (ArCH, x2), 132.36 (ArCH, x2), 152.01 (ArCO) 168.59, 168.82, 169.29 (Ac x2, COOMe).

Methyl (p-methoxyphenyl 2,3,4-tri-O-acetyl-β-D-glucopyranosid)uronate (2f)

(i) *p*-Methoxyphenol (77 mg, 0.61 mmol) and chromium hexacarbonyl (530 mg, 2.41 mmol) were dissolved in a deoxygenated mixture of THF (2 ml) and Bu_2O (5 ml). The solution was refluxed for 4 h, allowed to cool, diluted with deoxygenated ether (20 ml), and filtered through Hy-Flo. The solvent was removed in vacuo, the residue dissolved in dry, deoxygenated THF (2 ml), and used immediately as outlined below.

(ii) To a solution of PPh_3 (157 mg, 0.6 mmol) in dry, deoxygenated THF was added, successively, DEAD (104 mg, 0.6 mmol), the solution prepared as in (i) above, and methyl 2,3,4-tri-*O*-acetyl-D-glucopyranuronate (102 mg, 0.31 mmol). The mixture was stirred for 72 h at room temperature in the absence of light and then for 48 h in the presence of air and light. The mixture was diluted with dichloromethane (10 ml) and filtered through Hy-Flo. The filtrate was washed successively with water, 2*M* aqueous NaOH, and water, then dried over sodium sulphate. The solvent was removed in vacuo and the residue purified by sequential flash chromatography on silica gel using the following eluants: 20/1 dichloromethane/hexane; 1/1 ethyl acetate/hexane and 20/1 dichloromethane/hexane. This afforded **2f** (28 mg, 21%) as a white, crystalline solid contaminated with trace amounts of the α-phenylglucuronide (as evidenced by its NMR spectrum). An analytical sample was prepared by recrystallisation from dichloromethane/ether/hexane, which gave white needles, m.p. 150–150.5°C. Anal. Found: C, 54.31; H, 5.52. $C_{20}H_{24}O_{11}$ calc.: C, 54.54; H, 5.49%. IR ($CHCl_3$): ν_{max} 1760 cm^{-1}. Mass spectrum *m/e* (relative intensity) 440 (M^+, 0.1), 411 (2), 317 (2), 257 (3), 220 (2), 215 (2), 155 (27), 127 (29), 124 (14), 43 (100). ^{1}H NMR ($CDCl_3$): δ 2.04 (s, 3, Ac), 2.05 (s, 3, Ac), 2.08 (s, 3, Ac), 3.74 (s, 3, OMe), 3.77 (s, 3, OMe), 4.09 (m, 1, H5), 4.99 (d, J 7 Hz, 1, H1), 5.20–5.40 (m, 3, H2,3,4), 6.78 (m, 2, ArH), 6.93 (m, 2, ArH).

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