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RECENT IMPROVEMENTS TOWARDS THE SYNTHESIS OF THE C-GLUCURONOSYL CANCER CHEMOPREVENTIVE (β -d-GLUCOPYRANOSYLURONATE)-4-RETINAMIDOPHENYLMETHANE

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COMMUNICATION

RECENT IMPROVEMENTS TOWARDS THE SYNTHESIS OF THE C-
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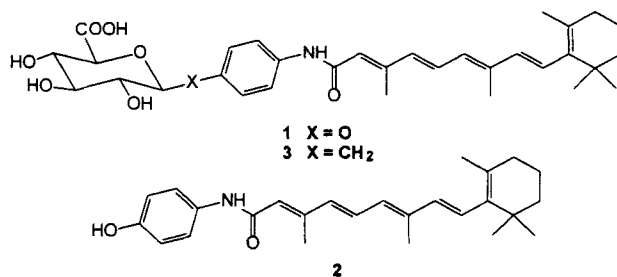
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Evidence suggests that the glucuronide conjugates of retinoids may be active metabolites of the parent compounds with potential utility as drugs.¹ We have recently shown that the *O*-glucuronide metabolite **1** of the synthetic retinoid *N*-4-hydroxyphenylretinamide (**2**) shows reduced toxicity and a significant chemopreventive advantage relative to the parent retinoid in a carcinogen-induced rat mammary cancer model.² In efforts to determine whether these conjugates function as intact molecules or must be hydrolyzed back to **2**, we designed and synthesized a series of C-glycosyl and C-glucuronosyl analogues of **1**.³ Our syntheses of these compounds are lengthy (10-12 steps) and lead to the desired products in less than 4% overall yields. Limitations on the availability of these compounds led us to evaluate them using a modified protocol for the carcinogen-induced rat mammary tumor model. While many of our analogues showed cancer chemopreventive activity in this assay, C-glucuronosyl analogue **3** has proven to be the most effective analogue of **2** we have yet evaluated in this model.⁴ Unfortunately, compound **3** was prepared in the poorest overall yield among these analogues. However, its potent activity and low toxicity make it an important candidate for expanded biological studies. Because additional studies of this important

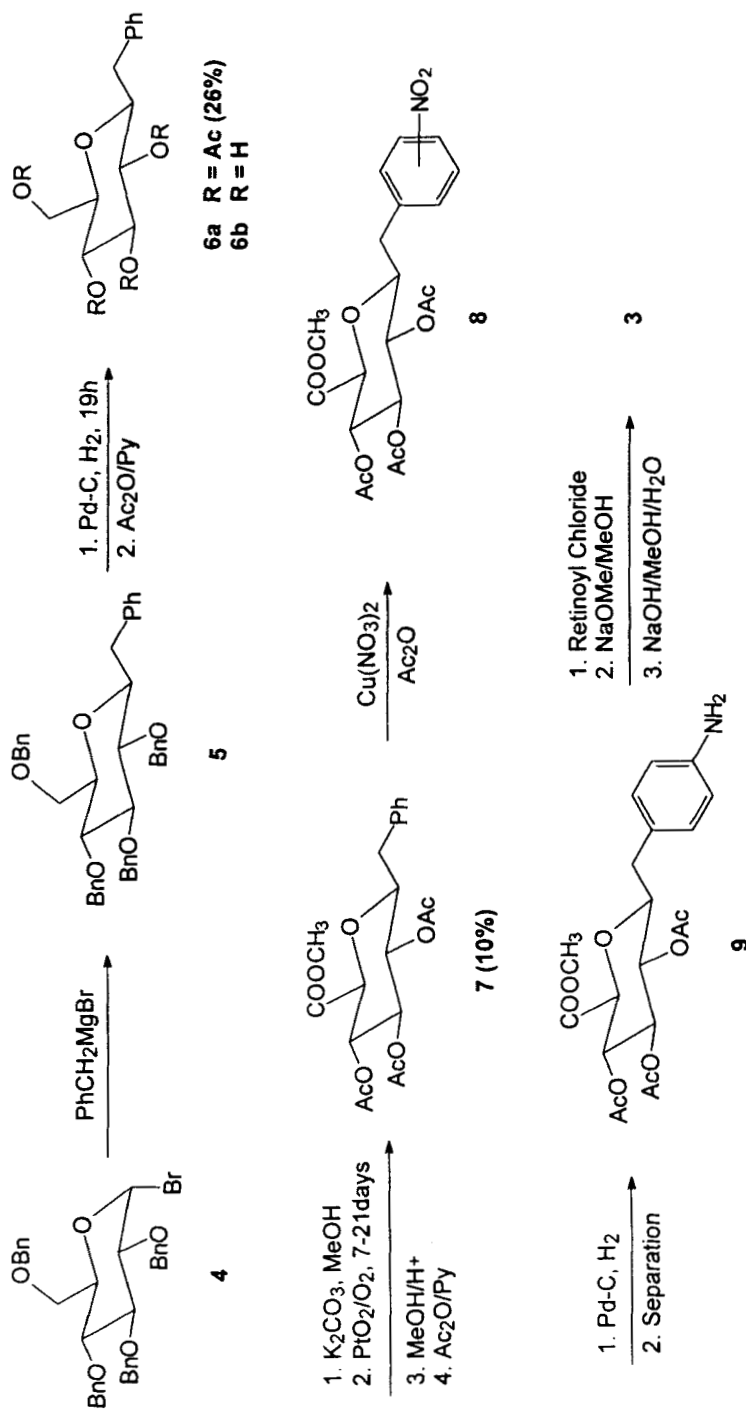
new compound will benefit from improvements in its synthesis, we briefly describe below recent dramatic improvements we have made in the preparation of **3**.



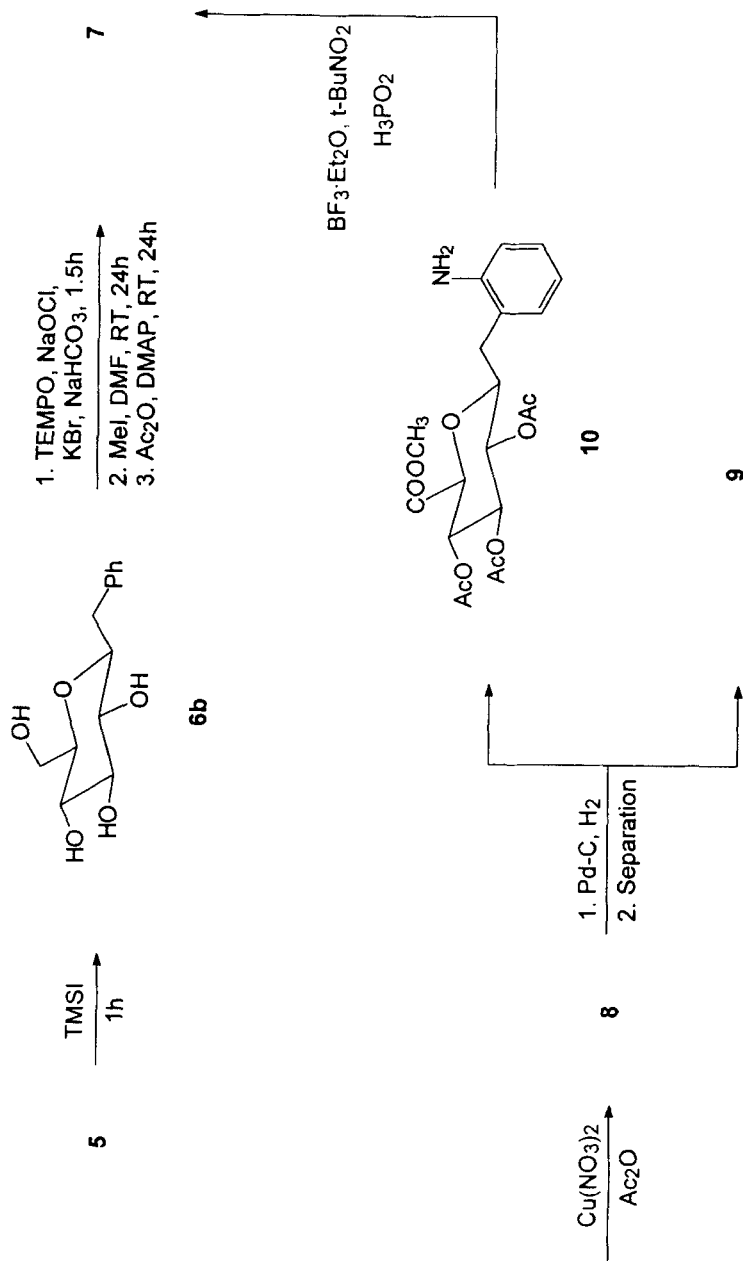
Scheme 1 provides the full details of our originally described synthesis of **3**.³ As can be seen, the low yield of **3** is primarily due to poor yields in removing the benzyl protecting groups, difficult oxidation to the uronic acid, and the production of an inseparable 3:2 mixture of the *p*- and *o*-nitro isomers of **8**. Catalytic hydrogenation of **5** over Pd-C proceeds sluggishly and in modest yield to **6a**. While we subsequently found catalytic transfer hydrogenation of **5** to **6a** (Pd(OH)₂/cyclohexene/toluene)⁵ proceeded in better yields, the reaction required 7 days and also utilized expensive catalysts. In our hands, oxidation to the uronic acid over platinum (IV) oxide was also variable in terms of time to completion (1-3 weeks) and proceeded in poor yield. Fortunately, the mixture of nitration products **8** were separable chromatographically after reduction to anilines **9** and **10** (Scheme 2).

The synthetic steps leading to an improved yield of intermediate compounds **7** and **9** are outlined in Scheme 2. While oxidative methods are known for benzyl ether cleavage (e.g. CrO₃/CH₃COOH),⁶ we were concerned about the potential for benzylic oxidation at the 1-position. Other reductive methods in addition to hydrogenation, such as Na/NH₃(*l*), have also been used,⁷ however, we wished to apply a method more readily amenable to large scale processes. Therefore, removal of the benzyl protecting groups from intermediate **5** was accomplished in one hour using trimethylsilyl iodide (TMSI)⁸ with a 50% yield of **6b**.⁹ This is a significant improvement in efficiency compared to Scheme 1 and avoids the use of relatively expensive catalysts.

The use of the 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in selective, rapid oxidation of monosaccharide derivatives to uronic acids has recently been developed.¹⁰ This method is mild and less time consuming than other methods used for achieving this oxidation, especially by eliminating the need for selective manipulation of protecting groups on the secondary hydroxyl moieties. The reaction is



Scheme 1



Scheme 2

mediated by oxyammonium ions, which are continuously regenerated from the nitroxyl radical by hypochlorite. A catalytic amount of TEMPO is used and the hypochlorite source is commercially available bleaching solution (Clorox, The Clorox Company, Oakland, CA). Despite the presence of non-essential compounds in the bleaching solution, we found it to be very effective and much less expensive than the hypochlorite solution available from chemical reagent suppliers. Thus, synthesis of intermediate compound **7**¹¹ was accomplished by TEMPO oxidation of **6b** (Scheme 2) and *in situ* reprotection to give **7**.¹² Compared to the same step shown in Scheme 1 which required 7-21 days and expensive PtO₂, which rapidly lost its catalytic activity, the TEMPO oxidation was completed within 2 hours. Using the above modifications, the overall yield of **7** starting from **5** is now 34% which is 10 times greater than for the same steps shown in Scheme 1.

Removal of the amino group from the phenyl ring of **10** would allow recovery of a useful synthetic intermediate. Thus we also find that **10** can be smoothly converted to valuable intermediate **7** using nonaqueous dediazotizing conditions (BF₃·Et₂O, *t*-butylnitrite; H₃PO₂)¹³ in 56% yield,¹⁴ further improving the overall efficiency of synthesizing **3**.

In conclusion, we have successfully improved the syntheses of intermediate compounds **7** and **9** leading to the potent cancer chemopreventive agent **3** which should permit its preparation for further biological evaluation.

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9. **β -D-Glucopyranosylphenylmethane (6b)**. To a stirring solution of 1 g (1.63 mmol) of **5¹⁵** in 10 mL CH₂Cl₂ was added TMSI (1 mL, 7.03 mmol) and the resulting reaction mixture stirred for 30 min at room temperature. The reaction was then quenched by adding 20 mL of anhydrous methanol and stirred for a further 30 min. Evaporation of solvent gave a dark red oil which was dissolved in ether and extracted with 4x50 mL water. The combined aqueous extract was concentrated to an oil which was chromatographed with 1:1 ethyl acetate/acetone to yield 0.21 g (50%) **6b** as a light brown oil which was used as obtained: ¹H NMR (acetone-*d*₆): δ 7.14-7.31 (m, 5H), 4.17-4.30 (m, 2H), 3.10-3.68 (m, 6H), 2.01-2.12 (m, 1H); HRMS calcd for C₁₃H₁₈O₅ 254.1154, found 254.1155.
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11. **(Methyl 2,3,4-tri-O-acetyl- β -D-glucopyranosyluronate)phenylmethane (7)**. Oil **6b** (0.21 g, 0.82 mmol), KBr (15 mg, 0.13 mmol) and TEMPO (15 mg) were dissolved in 10 mL of saturated NaHCO₃. Clorox (10 mL, 5.25% hypochlorite) was added into the aqueous mixture over a period of 30 min. The resulting mixture was stirred for a further 1 h. The reaction mixture was then washed with 50 mL CH₂Cl₂ and the aqueous layer was concentrated to dryness. Anhydrous DMF (10 mL) was added to the resulting solid mass followed by CH₃I (0.13 g, 0.92 mmol) and the mixture was stirred for 24 h. Acetic anhydride (0.3 g, 2.94 mmol) and catalytic DMAP (60 mg) were then added and stirring was continued for another 24 h. Water (100 mL) was then added and the aqueous solution was extracted with 2x100 mL of ethyl acetate. The organic extract was dried (MgSO₄) and evaporation of solvent afforded a dark red liquid which was chromatographed with 6:4 ethyl acetate/hexane to yield 0.23 g (68%) **7** as a solid with physical and spectral properties identical to our previous report.³
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14. **Dediazotization of 10 to 7**. To BF₃·Et₂O (0.61 mL, 4.95 mmol) at -78 °C was added a solution of (methyl 2,3,4-tri-O-acetyl- β -D-glucopyranosyluronate)-2'-aminophenylmethane (**10**) (1.40 g, 3.30 mmol) in CH₂Cl₂. A solution of *t*-butyl nitrite (0.47 mL, 3.30 mmol) in CH₂Cl₂ was then added dropwise and the mixture stirred for 30 min, warmed to room temperature and a cold solution of 50% H₃PO₂ (50 mL) was added dropwise. The reaction mixture was stirred at room temperature overnight. The aqueous layer was separated and extracted with CH₂Cl₂ which was combined with the organic layer. Removal of solvent yielded a solid which was recrystallized from 2-propanol to afford 0.76 g (56% yield) of **7** identical in all respects with previously isolated **7**.³
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