Pergamon

Tetrahedron Letters 42 (2001) 3811–3814

TETRAHEDRON LETTERS

Synthesis and transformations of D-glucuronic and L-iduronic acid glycals

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Received 10 April 2001; accepted 12 April 2001

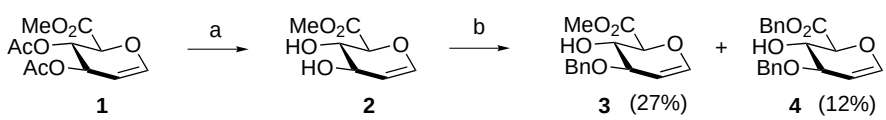
Abstract—D-Glucuronic acid glycals can be efficiently synthesized from diacetone glucose or tri-*O*-acetyl glycal and can be transformed into D-glucuronic acid donors and acceptors in high yields. Base catalyzed epimerization of D-glucuronic acid glycals provides access to the corresponding L-iduronic acid glycals. Both D-glucuronic and L-iduronic acid glycals were transformed into glycosylating agents for use in the synthesis of glycosaminoglycan oligosaccharides. © 2001 Elsevier Science Ltd. All rights reserved.

Glycosaminoglycans (GAGs) such as heparin, heparan sulfate and dermatan sulfate are components of connective tissues and are found on the cell surface. These linear sulfated polymers of 2-amino sugars and hexuronic acids bind and regulate the activity of a large number of proteins.[1] Chemical synthesis of defined oligosaccharide sequences provides a powerful tool to study the structure–activity relationship of GAGs but poses a host of challenges.[2] Access to the hexuronic acids constituents of GAGs, D-glucuronic and L-iduronic acid is often difficult. In particular, L-iduronic acid is not readily accessible from natural sources and requires lengthy synthetic routes. Although numerous reports on the synthesis of L-iduronic acid synthons have been disclosed, the need for efficient routes for the preparation of differentially protected L-iduronic acid building blocks persists.[3] Most of the currently available methods use a selective inversion of the C5 configuration of D-glucofuranose derivatives. Transformation of the resulting L-idofuranose derivatives into their L-idopyranose counterparts remains a challenge.

Glycals have proven versatile intermediates in the synthesis of oligosaccharides and glycosylated natural products as they facilitate protecting group manipulations and may be readily converted into a host of glycosylating agents.[4–6] Here we report the preparation of differentially protected hexuronic acid building blocks using glycal intermediates. Particular attention focused on the use of D-glucuronic acid glycals as precursors to both L-iduronic acid and D-glucuronic acid building blocks.[7]

Two strategic considerations were kept in mind in deciding upon the differentially protected key glycal intermediates. The 3-hydroxyl of hexuronic acid in glycosaminoglycans commonly bears a permanent benzyl protecting group, while a transient protecting group at the 4-hydroxyl ensures a handle for chain elongation. Mindful of this framework we initially focused on the preparation of glycal **3** as a central vantage point for further synthetic explorations.

Several routes for the synthesis of **3** presented themselves. The seemingly most straightforward route relying on deacetylation and selective benzylation of readily available glycal **1**[8] proved unpractical (Scheme 1). After acetate removal at low temperature provided diol **2** in excellent yield without epimerization, the selective benzylation of the 3-hydroxyl group[9] resulted in a mixture of **3** and **4** due to transesterification.



1 **2** **3** (27%) **4** (12%)

Scheme 1. (a) NaOMe, MeOH, –20°C, 98%; (b) i. Bu_2SnO, benzene, reflux, 5 h, ii. BnCl, Bu_4NI, benzene, reflux, 8 h.

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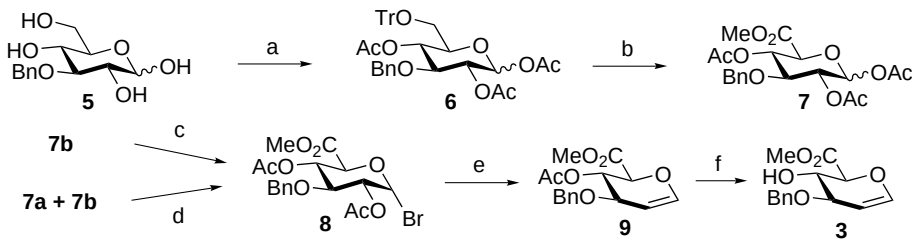
PII: S0040-4039(01)00607-4

The second approach to the synthesis of **3** was based on transformations starting from 3-*O*-benzyl glucose **5** that is readily available from diacetone glucose.[10] Introduction of a 6-*O*-trityl group was followed by acetylation[11] to yield an anomeric mixture of triacetate **6**. Conversion of glucose to glucuronic acid was accomplished by Jones oxidation and subsequent methyl ester formation to fashion **7**.[3f] Exclusively β-acetate **7b** reacted with titanium(IV) bromide[3f] to obtain glycosyl bromide **8** after crystallization. Alternatively, a mixture of anomeric acetates **7a** and **7b** was converted to **8** by selective anomeric deacetylation[12] followed by reaction with $(PhO)_3P/Br_2$.[13] Reductive elimination of **8** using a Zn–vitamin B_{12} mixture[14] provided glucuronic acid glycal **9** in 90% yield. Removal of the 4-*O*-acetate to fashion **3** was effected at low temperature to avoid epimerization (Scheme 2).

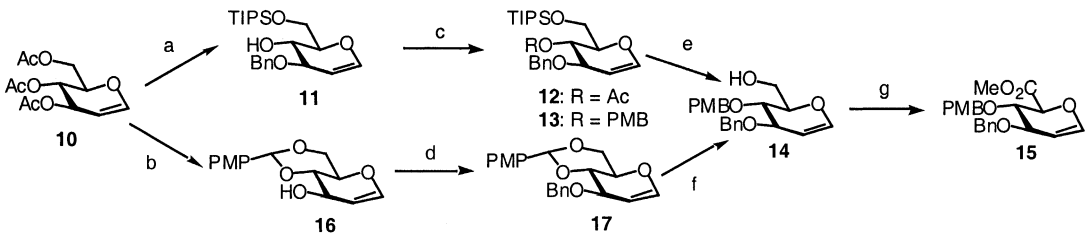
Our final approach for the preparation of differentially protected glucuronic acid glycals such as **15** relied exclusively on the use of glycal intermediates. The differentially protected key glycal **14** was obtained via two routes. Glucal **10** was deprotected, 6-*O*-silylated and selectively benzylated at the 3-position.[15] Removal of the 6-*O*-TIPS ether from **12** (derived from **11** by acetylation of the C4 hydroxyl) was low yielding. This problem was overcome by introduction of a 4-*p*-methoxybenzyl ether to yield **13** that was smoothly transformed into glycal **14**. Alternatively, **14** was obtained from **10** via 4,6-*O*-*p*-methoxybenzylidene derivative **16**,[16] 3-*O* benzylation to yield **17**, followed by regioselective ring opening[17]. Glucal **14** was oxidized via a two-step procedure: Dess–Martin-oxidation[18] initially yielded an aldehyde, which was further oxidized to the acid before esterification provided **15** (Scheme 3).[19]

With the D-glucuronic acid glycals in hand, transformations to glucuronic acid building blocks such as thioethyl and *n*-pentenyl glycosides were studied. Epoxidation of glycals **15** and **18** (derived from **3** by 4-*O* silylation) with DMDO was followed by conversion to thioglycosides (**19**, **20**) or *n*-pentenyl glycosides (**21**, **22**) via one-pot procedures. Removal of the 4-OH protecting groups yielded glycosyl acceptors **25** and **28** (Scheme 4).

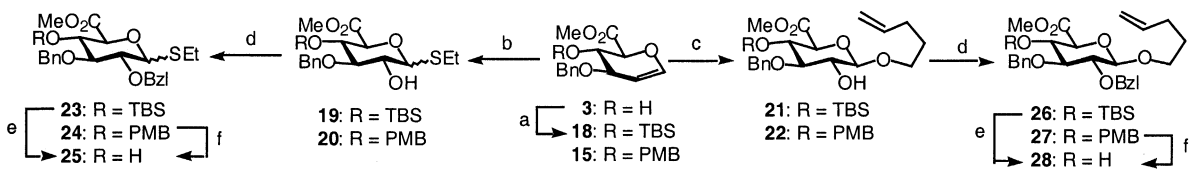
The observation that base-catalyzed epimerization of D-glucuronic acid glycal **29** results mainly in the formation of iduronic acid glycal **30** (**30**:**29** = 4:1) reported by



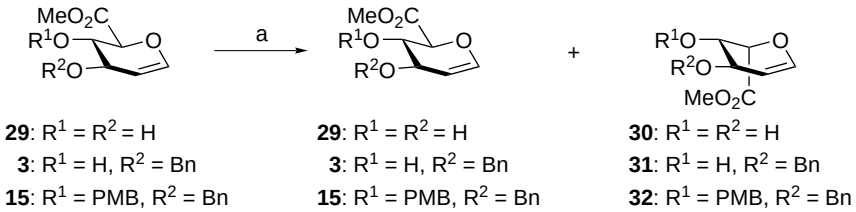
Scheme 2. (a) i. TrCl, pyridine, 80°C, ii. Ac_2O, pyridine, 86%; (b) i. CrO_3, 3 M H_2SO_4, acetone, ii. $TMSCHN_2$, CH_2Cl_2/MeOH, 56%; (c) $TiBr_4$, CH_2Cl_2/EtOAc, 88%; (d) i. hydrazine acetate, DMF, 76%, ii. $P(OPh)_3$, Br_2, pyridine, CH_2Cl_2, 71%; (e) Zn, vitamin B_{12}, MeOH, NH_4Cl, 90%; (f) NaOMe, MeOH, –20°C, 90%.



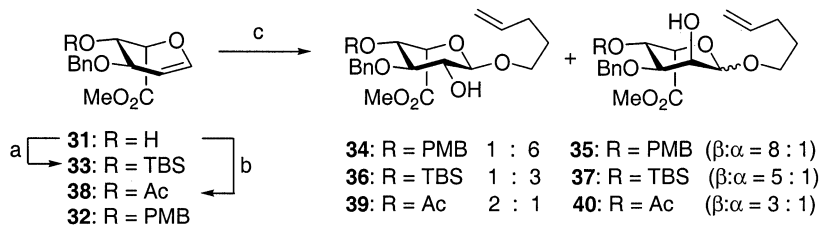
Scheme 3. (a) i. NaOMe, MeOH, ii. TIPSCl, imidazole, DMF, iii. Bu_2SnO, toluene, iv. BnBr, Bu_4NI, 67%; (b) i. NaOMe, MeOH, ii. *p*-$OMePhCH(OMe)_2$, PPTS, THF, 64%; (c) PMBCl, NaH, THF, 77% or Ac_2O, DMAP, pyridine, CH_2Cl_2, 79%; (d) BnBr, NaH, THF, 90%; (e) R = Ac: TBAF, THF, 48%, R = PMB: TBAF, AcOH, THF, 95%; (f) DIBAL-H, CH_2Cl_2, 87%; (g) i. Dess–Martin periodinane, CH_2Cl_2, ii. $NaClO_2$, 2-methyl-2-butene, *t*BuOH, NaH_2PO_4, H_2O, iii. MeI, $KHCO_3$, DMF, 79%.



Scheme 4. (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 89%; (b) i. DMDO, acetone, 0°C, ii. EtSH, $(F_3CCO)_2O$, CH_2Cl_2, R = TBS: 55% (α/β = 2/8), R = PMB: 58% (α/β = 1/9); (c) i. DMDO, acetone, 0°C, ii. 4-pentenol, $ZnCl_2$, CH_2Cl_2, R = TBS: 82%; R = PMB: 57%; (d) BzCl, DMAP, CH_2Cl_2, quant.; (e) HF–pyridine, THF, 98%; (f) CAN, MeCN/H_2O (9:1), 92%.



Scheme 5. (a) NaOMe, MeOH, rt, 80%.



Scheme 6. (a) TBSCl, imidazole, CH_2Cl_2, 85%; (b) Ac_2O, pyridine, 86%; (c) i. DMDO, acetone, 0°C, ii. 4-pentenol, $ZnCl_2$, CH_2Cl_2, 25–30%.

Thiem[7] prompted us to investigate if D-glucuronic acid glycals could serve as key intermediates for the preparation of L-iduronic acid building blocks. Exploitation of such an epimerization strategy would allow ready access to these otherwise cumbersome to prepare differentially protected synthons. Treatment of protected glycals **3** and **15** with concentrated solutions of sodium methoxide[7] resulted in complete degradation of the starting glycals. Lower concentrations of base and shorter reaction times resulted in 1:1 mixtures of **3**/**31** and **15**/**32**, respectively (80% yield in both cases, Scheme 5). Silica column chromatography readily facilitated the separation of the mixtures to provide pure L-iduronic acid glycals **31** and **32**.

In order to access differentially protected L-iduronic acid building blocks, the conversion of L-iduronic acid glycals **32** and **33** to *n*-pentenyl glycosides was investigated. Transformation of **32** and **33** into the corresponding *n*-pentenyl glycosides under the conditions for D-glucuronic acid glycals resulted in a mixture of the desired L-iduronic acid glycosides (**34** and **36**) and L-glucuronic acid derivatives (**35** and **37**) with a preference for the latter. Reaction of 4-*O*-acetate protected glycal **38** furnished preferentially L-iduronic acid *n*-pentenyl glycoside **39**. The steric and electronic features of the O-4 protecting group strongly influence the conformation of the glycals and thus reactions involving such species. The epoxides derived from L-iduronic acid glycals are less stable than those derived from D-glucuronic acid glycals leading to lower yields and anomeric mixtures in the preparation of *n*-pentenyl glycosides (Scheme 6).

In summary, we have disclosed different synthetic routes to differentially protected D-glucuronic acid glycals that may serve as intermediates en route to a variety of natural products. The conversion of these glycals into thioethyl and *n*-pentenyl glycoside donors has also been demonstrated.

Acknowledgements

This work was supported by grants from the National Institutes of Health (1RO1HL64799). Financial support from the DAAD (German Academic Exchange Service) for a postdoctoral fellowship for P.S. and FOMEC for a postdoctoral fellowship for H.A.O. is gratefully acknowledged. Funding for the MIT-DCIF Inova 501 was provided by NSF (Award # CHE-9808061) and for an INOVA 501 by NSF (DBI-9729592).

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