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Synthesis of 48 Disaccharide Building Blocks for the Assembly of a Heparin and Heparan Sulfate Oligosaccharide Library

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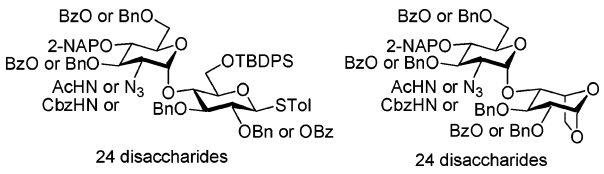
ABSTRACT



An efficient synthesis of the entire set of suitably protected 48 disaccharide building blocks for the assembly of a heparin and heparan sulfate oligosaccharide library is described here.

Heparin (HP) and heparan sulfate (HS) are structurally related linear polyanionic polysaccharides, belonging to the family of glycosaminoglycans, covalently bound to the core proteins of proteoglycans. These naturally occurring, highly sulfonated and acidic biopolymers play crucial roles in numerous biological systems through their interaction with diverse proteins.[1] HP, which occurs exclusively in mast cells, is widely used as an anticoagulant drug in the clinic owing to its high affinity binding with antithrombin III.[2] HS, being ubiquitously distributed on the cell surface and in the extracellular matrix, mediates various physiologically important processes such as viral and bacterial infection, growth factor regulation, inflammatory response, angiogenesis, tumor metastasis, cell adhesion, and lipid metabolism.[3]

HP and HS are both biosynthesized through a unique pathway, which involves the formation of a polysaccharide chain consisting of alternating *N*-acetyl-α-D-glucosamine (GlcNAc) and *β*-D-glucuronic acid (GlcA) residues jointed by 1→4 linkages. This backbone is modified through a series of enzymatic processes, including C5 epimerization of GlcA to L-iduronic acid (IdoA), N-deacetylation of GlcNAc to D-glucosamine ($GlcNH_2$), and sulfonation at the O2 position of GlcA/IdoA and at the N, O3, and/or O6 positions of $GlcNH_2$.[4] Variable substitution patterns of the polysaccharide chain give rise to a large number of complex sequences resulting in microheterogeneity, for example, 48 di-, 48^2 tetra-, 48^3 hexa-, 48^4 octasaccharides, and so on. Of these theoretically possible 48 disaccharide units (Scheme 1), only 23 have been characterized so far.[5] Homogeneous HP and HS materials with well-defined configurations are essential

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(2) (a) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed.* **1993**, *32*, 1671−1690. (b) Petitou, M.; Hérault, J.-P.; Bernat, A.; Driguez, P.-A.; Duchaussoy, P.; Lormeau, J.-C.; Herbert, J.-M. *Nature* **1999**, *398*, 417−422. (c) Petitou, M.; van Boeckel, C. A. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3118−3133. (d) de Kort, M.; Buijsman, R. C.; van Boeckel, C. A. A. *Drug Discovery Today* **2005**, *10*, 769−779.

(3) (a) Iozzo, R. V. *Nat. Rev. Mol. Cell Biol.* **2005**, *6*, 646−656. (b) Häcker, U.; Nybakken, K.; Perrimon, N. *Nat. Rev. Mol. Cell Biol.* **2005**, *6*, 530−541. (c) Fuster, M. M.; Esko, J. D. *Nat. Rev. Cancer* **2005**, *5*, 526−542.

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10.1021/ol062464t CCC: $33.50
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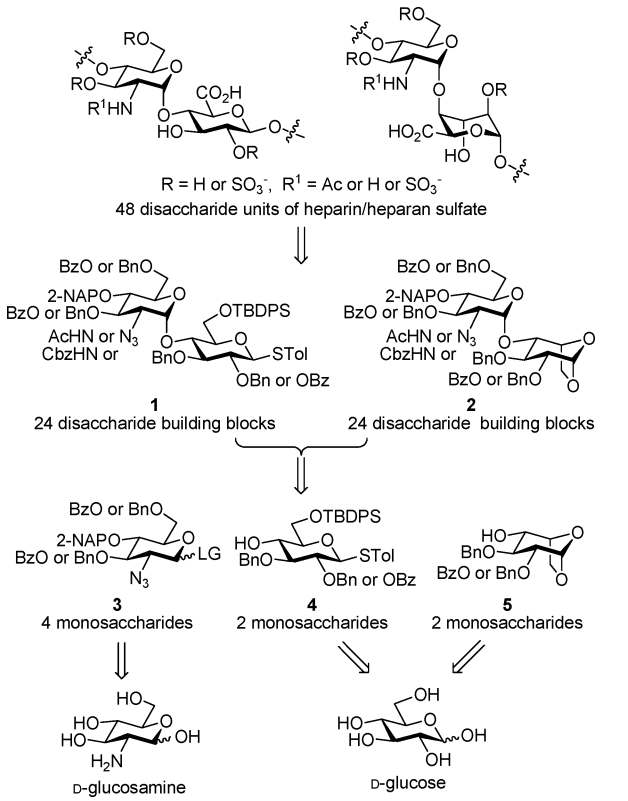
Scheme 1



for determining structure−activity relationships. Such molecules are extremely difficult to acquire from natural sources, and chemical synthesis may offer one of the best options for securing them. Over the past few years, several approaches have been documented in the literature to prepare specific HP and HS saccharide units.[6] Herein, we report a straightforward synthesis of the entire set of 48 disaccharide building blocks needed for the assembly of HP and HS oligosaccharide libraries.

Our retrosynthesis of 48 disaccharide synthons **1** and **2** from two common sugars, D-glucose and D-glucosamine, is outlined in Scheme 1. The O-sulfation pattern in the target molecules called for strategic placement of acyl groups (Bz) to protect those hydroxyls that would be ultimately sulfonated and of permanent benzyl protecting groups (Bn) for those that would remain free. For the generation of exclusive 1,2-*trans*-glycosidic linkages during chain elongation, the same ester functionality at C2 would be expected to offer anchimeric assistance, whereas benzyl ethers at such locations might have the stereochemistry of glycosidation controlled via solvent effects (e.g., CH_3CN).[7] In addition, a temporary protecting group (TBDPS) is needed to mask the primary hydroxyl on the D-glucopyranosyl subunit of **1** to allow oxidation to the corresponding carboxylic acid. The 2-naphthylmethyl group (2-NAP),[8] which was used to block the C4 hydroxy group of the $GlcNH_2$ subunit, would allow mildly chemoselective deprotection for further elongation of the sugar chain, and it could also be simultaneously removed along with other permanent benzyl groups under hydrogenolytic conditions at the final termination process. The C2 amino group of $GlcNH_2$ would typically be protected as an azide owing to its nonparticipating nature in coupling reactions. It would be expected to predominantly lead to the α-anomeric disaccharide building blocks and could be readily transformed into the NHAc and NHCbz groups. At a later stage, the $-N_3$ could be selectively converted to the $-NHSO_3^-$ unit via a combination of Staudinger reaction and N-sulfonation, whereas the −NHCbz could be expected to reveal a free $-NH_2$ upon hydrogenolysis. The 1,6-anhydro-*β*-L-idopyranosyl sugars **5**, which can be prepared from D-glucose through C5 epimerization, serve as highly active glycosyl acceptors because of the rigid conformation and three equatorially substituted groups at C2, C3, and C4. The 1,6-anhydro ring of **2** can be opened, and further functional group modification and glycosylation of the corresponding L-idopyranosyl sugar at C6 and C1 can be carried out, respectively. Thus, four D-glucosamine-derived glycosyl donors **3** may be individually coupled with two D-glucopyranosyl 4-alcohols **4** and two L-idopyranosyl 4-alcohols **5** via Schmidt's trichloroacetimidate method[9] to get two sets of eight disaccharides. These 16 compounds can each be converted into the N-acetylated and N-Cbz-protected derivatives, generating a total of 48 disaccharide synthons **1** and **2**.

The synthesis of four glycosyl donors **15**−**18** is shown in Scheme 2. First, D-glucosamine-derived 1,3-diol **6**[10] was converted to the *β*-1,3-dibenzoate **7** (BzCl, Et_3N, 92%). The corresponding 3-OBn derivative **8** was obtained in 77% overall yield via anomeric benzoylation (Bz_2O, Et_3N) followed by O3 benzylation (Ag_2O, BnBr). A highly regioselective borane-reductive O6 ring opening of 4,6-*O*-naphthylidene acetals **7** and **8** in the presence of 5 mol % of $Cu(OTf)_2$[11] cleanly afforded the individual 6-alcohols **9** (89%) and **10** (86%), which were subsequently benzoylated to give the 6-OBz derivatives **11** and **12** in 95% and 92% yields, respectively. Benzylation of **9** or **10** employing BnBr/Ag_2O or BnBr/NaH did not succeed. Alternatively, TMSOTf-

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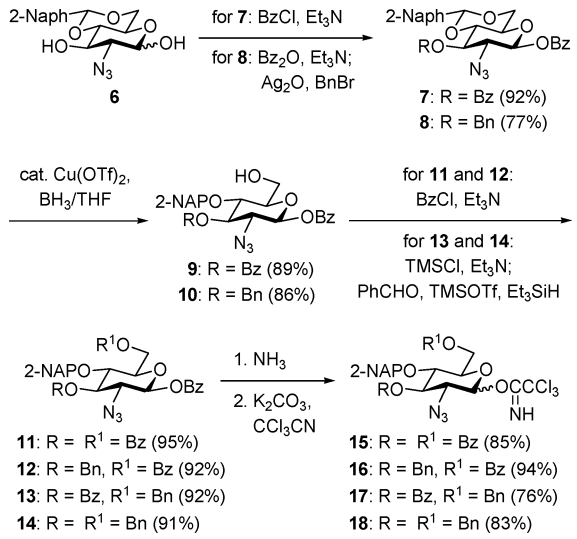
(8) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169−172.

(9) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.

(10) Lu, X.-A.; Chou, C.-H.; Wang, C.-C.; Hung, S.-C. *Synlett* **2003**, 1364−1366.

(11) Shie, C.-R.; Tzeng, Z.-H.; Kulkarni, S. S.; Uang, B.-J.; Hsu, C.-Y.; Hung, S.-C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1665−1668.

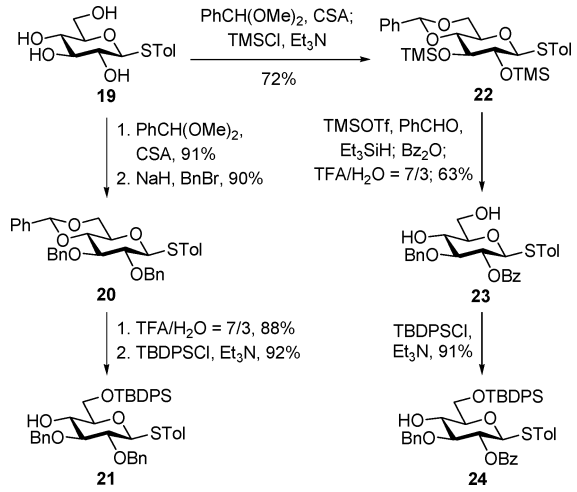
Scheme 2



activated Et_3SiH-reductive etherification[21] of the corresponding 6-*O*-trimethylsilyl derivatives with benzaldehyde led to the expected 6-OBn compounds **13** (92%) and **14** (91%), respectively. These four anomeric benzoates **11**−**14**, upon facile nucleophilic displacement with ammonia, were concomitantly transformed into the glycosyl trichloroacetimidates **15**−**18** in high overall yields, respectively.

Scheme 3 illustrates our efficient preparation of thioglycosides **21** and **24**. Tetraol **19** underwent sequential 4,6-O-benzylidenation (91%) and 2,3-di-O-benzylation (90%) to yield the ether derivative **20**, which was subjected to acid hydrolysis followed by regioselective silylation at O6 to furnish the 4-alcohol **21** (92%). A three-step protocol from tetraol **19** was employed for the synthesis of compound **24**. First, one-pot 4,6-O-benzylidenation and 2,3-di-O-silylation of **19** provided the bis-OTMS ether **22** (72%). Regioselective O3 benzylation[12] of **22** followed by O2 benzoylation under the prevailing acidic environment and concomitant hydrolysis

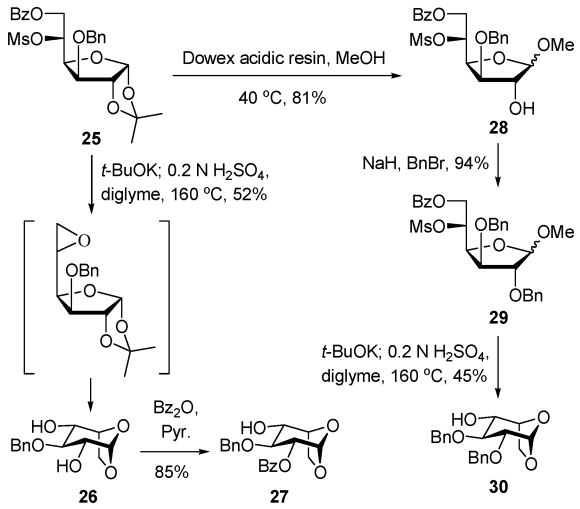
Scheme 3



of the 4,6-*O*-benzylidene acetal in a single flask gave the 4,6-diol **23** (63%), which was similarly protected at the O6 position to afford the corresponding silyl ether **24** in 91% yield.

A practical route for the synthesis of rare 1,6-anhydro-β-L-idopyranosyl 4-alcohols **27** and **30** is depicted in Scheme 4. Compound **25**, generated from diacetone α-D-glucose in

Scheme 4



three known steps,[6g] upon treatment with *t*-BuOK followed by addition of a 1:2 mixture of 0.2 N $H_2SO_{4(aq)}$ and diglyme and subsequent heating at 160 °C in a one-pot manner afforded the 2,4-diol **26** (52%), which was regioselectively benzoylated to yield the 2-OBz **27** (85%). Direct benzylation of **26** under various conditions gave a mixture of 2,3-di-OBn **30** (low yield), 3,4-di-OBn, and 2,3,4-tri-OBn, which was tedious for separation of the first two regioisomers. Alternatively, methanolysis of the ketal **25** furnished the methyl glucofuranoside **28** (81%), which underwent benzylation at O2 to get the product **29** in 94% yield. Similar conversion of compound **29** into the 1,6-anhydro sugar was carried out, and the desired product **30** (45%) was obtained.

The assembly of eight monosaccharide units to prepare the entire set of 48 disaccharide synthons is summarized in Scheme 5. AgOTf- or TMSOTf-promoted coupling of the donors **15**−**18** with the acceptors **21**, **24**, **27**, and **30** led to the disaccharides **31**−**46**, respectively. The O6 benzoyl group had a marked influence on the stereoselectivity of the glycosylation reaction, yielding the D-*gluco*-disaccharides (**31**, **33**, **35**, and **36**) in only α-form and the L-*ido*-disaccharides (**39**, **41**, **43**, and **44**) as major α-isomers. In contrast, the benzyl ethers at the C6 position of **17** and **18** reflected lower α/β selectivity. Finally, treatment of **31**−**46** with thioacetic acid[13] gave the N-acetylated products **47**−**62** in excellent yields, respectively. A two-step transformation of **31**−**46**, individually, via consecutive Staudinger

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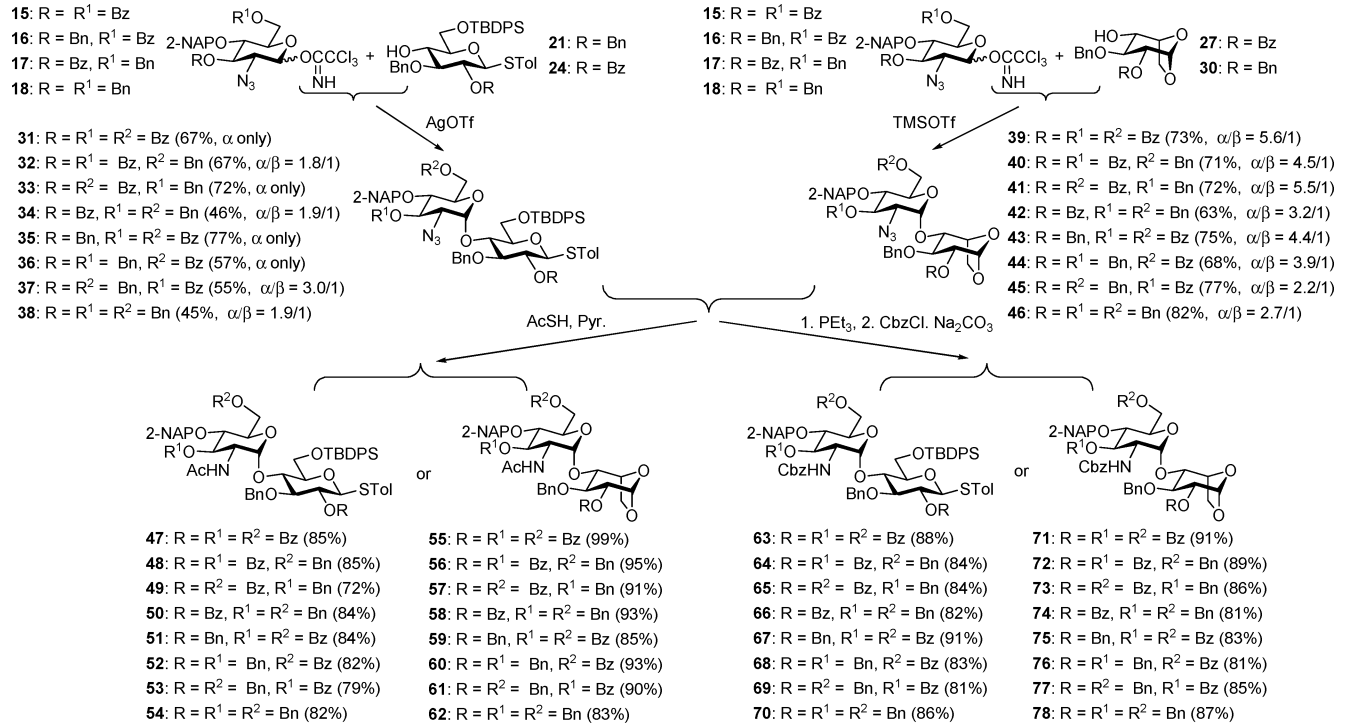
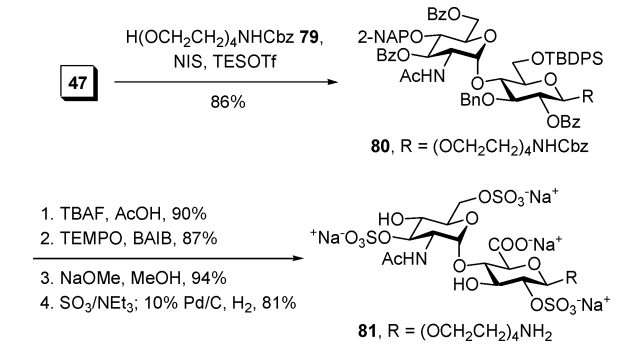
Scheme 5



reaction and Cbz protection afforded the corresponding N-Cbz derivatives **63**−**78** in good yields.

Transformations of two representative synthons into the linker-attached HP/HS disaccharides are exemplified in Schemes 6 and 7. Coupling of **47** with the alcohol **79**

Scheme 6



furnished the *β*-isomer **80**, which underwent desilylation, TEMPO oxidation, debenzoylation, O-sulfonation, and hydrogenolysis to give the desired molecule **81**. Acetolysis of **39** followed by anomeric conversion and subsequent coupling with **79** led to the α-isomer **82**, which was subjected to deacetylation, TEMPO oxidation, debenzoylation, azido reduction, N- and O-sulfonation, and hydrogenolysis to yield the expected disaccharide **83**.

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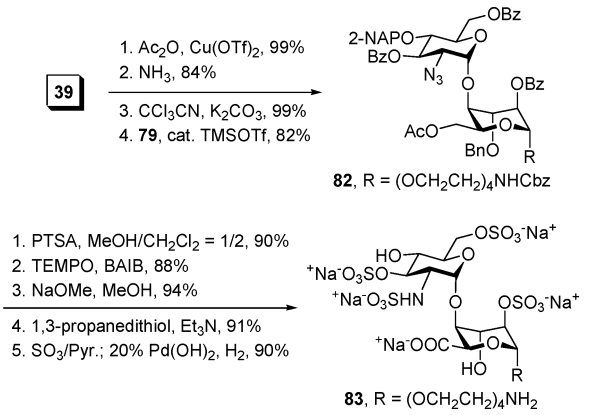
In conclusion, we have synthesized 48 HP- and HS-related disaccharide building blocks. These synthons can be used to prepare HP and HS oligosaccharides in chemically pure form for screening against various proteins.

Scheme 7



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Supporting Information Available: Experimental procedures and ^{1}H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Synthesis of Heparin Oligosaccharides

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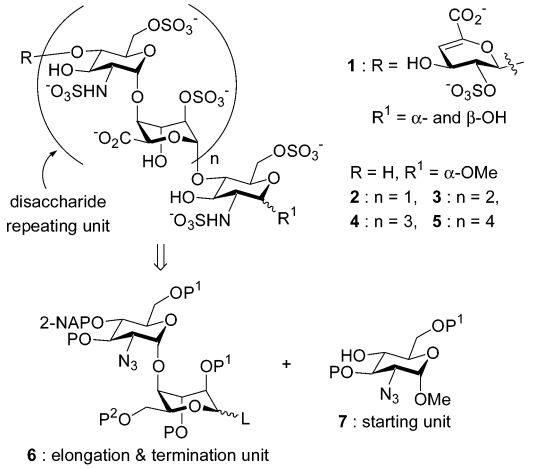
Heparin and its structurally related heparan sulfate, the linear sulfated polysaccharides belonging to the family of glycosaminoglycans, play significant roles in a diverse set of biological processes, including blood coagulation, virus infection, cell growth, inflammation, wound healing, tumor metastasis, lipid metabolism, and diseases of the nervous system.[1] Heparin is widely used as an anticoagulant drug in clinic[2] and contains a trisulfated disaccharide repeating unit (Scheme 1) as the major component consisting of alternating D-glucosamine and L-iduronic acid with α1 → 4 linkages. Enzymatic degradation of heparin with heparinase gives a mixture of oligosaccharides **1** with even sugar units invariably having an unsaturated D-glucuronic acid residue at the nonreducing end.[3] Effort has been invested to determine the minimal structural requirements, mostly involving tetra- ($n = 1$) to decasaccharide ($n = 4$), for biological activities.[4] With the discovery of increasing numbers of heparin-binding proteins, there is a need to characterize the molecular properties, within the proteins and heparin, responsible for specific recognition. Toward fulfilling this goal, we have explored herein the synthesis of heparin oligosaccharides **2**−**5**.

The frequently encountered problems in the synthesis of heparin molecules[5] include the generation of rare L-idose,[6] the differentiation of all hydroxy groups on each sugar residue, the stereocontrol in the construction of all α-glycosidic bonds, the cleavage of multi-protecting groups, and the transformation of multifunctional groups. Our retrosynthetic plan of target compounds **2**−**5** entails two building blocks, an elongation and termination disaccharide unit **6** and a starting D-glucosamine unit **7**. The 2-naphthylmethyl group (2-NAP),[7] which is used to block the C4′-hydroxyl of **6**, allows chemoselective deprotection with DDQ during chain-enhancement and simultaneous removal along with the permanent benzyl groups (P) in the final termination process. The ester protecting groups (P^1) not only offer anchimeric assistance to generate exclusive 1,2-*trans*-glycosidic linkages, but also can be selectively removed to free those hydroxyls which would ultimately carry sulfonate groups. In addition, a temporary protection (P^2) is needed to mask the primary hydroxyl on L-idose that could be oxidized to carboxylic acid.

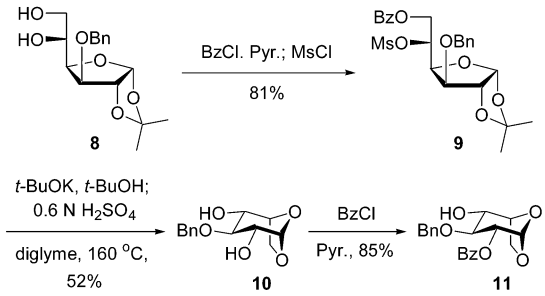
An efficient synthesis of the L-idopyranosyl sugar **11** is illustrated in Scheme 2. The 5,6-diol **8**,[8] generated from commercially available diacetone α-D-glucose in two known steps, underwent one-pot benzoylation-mesylation to yield the corresponding furanose **9** (81%) as a single isomer. Treatment of compound **9** with *t*-BuOK in *t*-BuOH followed by addition of a 1:2 mixture of 0.6 N $H_2SO_{4(aq)}$ and diglyme and subsequent heating at elevated temperature (160 °C) for 16 h led to the 2,4-diol **10** (52%) in a one-pot manner. The formation of **10** presumably takes place through an intramolecular S_N2 substitution to produce the C5-epimerized L-ido epoxide,[9] which concomitantly gets hydrolyzed in acidic media[10] and eliminates a water molecule via 3-*O*-benzyl-L-idopyranose intermediate. Regioselective benzoylation of **10** provided the corresponding 2-ester **11**[11] in 85% yield, exclusively.

Scheme 1



L = leaving group; 2-NAP = 2-naphthylmethyl group; P, $P^1$and P^2 are permanent, ester and temporary protecting groups, respectively.

Scheme 2



With the key synthon **11** in hand, we proceeded to synthesize heparin oligosaccharides **2**−**5**, as outlined in Scheme 3. The cheaply available D-glucosamine hydrochloride was first transformed into the 1,3-diol **12** (75%) employing a combination of amino-azido conversion at C2 and 4,6-*O*-naphthylidenation. Regioselective O1-benzoylation of compound **12** with 1-*N*-(benzyloxy)benzotriazole (BzOBT)[12] followed by O3-benzylation afforded the product **13**, which was subjected to sequential O6-ring opening,[13] O6-benzoylation, and anomeric debenzoylation to provide the 1-alcohol **14**. Transformation of **14** into the corresponding trichloroacetimidate and further coupling with the acceptor **11** led to the α-linked disaccharide **15α** and its *β*-isomer **15*β*** in 61% and 11% yields, respectively. The absolute configuration of **15*β*** was unambiguously determined through its X-ray single-crystal analysis (see Supporting Information). $Cu(OTf)_2$-catalyzed acetolysis of **15α** delivered the 1,6-diacetate **16** (88%), which upon selective O1-deacetylation using ammonia was similarly converted to the imidate **17** (77%). The 4-alcohol **18**, prepared by selective O6-benzoylation (Bz_2O, Et_3N,

[†] Academia Sinica.
[‡] National Tsing Hua University.

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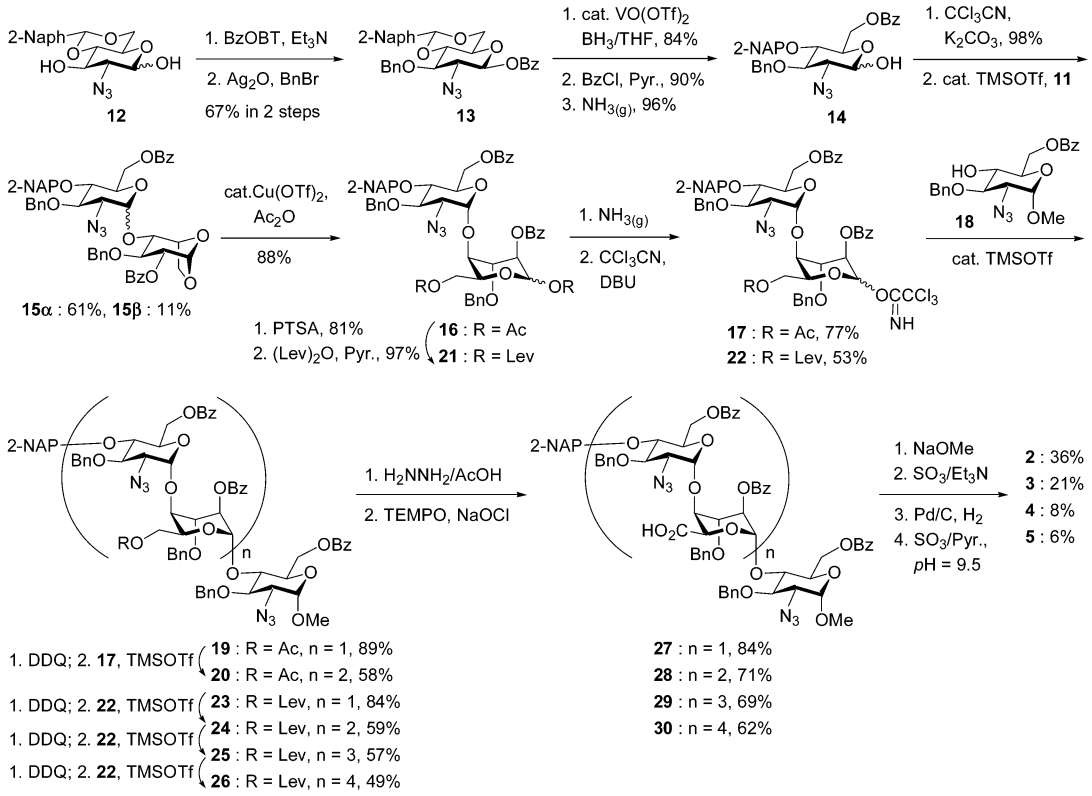
Scheme 3



97%) of methyl 2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside,[14] was coupled with **17** to provide the α-linked trisaccharide **19** (89%) as a single isomer. Further chain-elongation sequence, involving removal of the O4-NAP using DDQ and subsequent glycosylation with the disaccharide donor **17**, posed no problems and furnished the pentasaccharide **20** (58%), exclusively. While reaction of compound **19** with $HBF_4 \cdot Et_2O$[15] gave the corresponding 6′-alcohol in excellent yield, simultaneous removal of two acetyl groups in **20** proved testing and compelled us to rethink our present strategy.

Levulinoyl (Lev) esters were thought to be better options for our purpose. Direct levulinolysis of **15α** did not work. Alternatively, deacetylation[16] of **16** afforded the 1,6-diol (81%), which was reacted with Lev_2O in pyridine to get the ester **21** (97%). A similar reaction sequence of anomeric deprotection and imidate formation led to the glycosyl donor **22** (53% in two steps), which was coupled with **18** in a likewise manner to construct the α-linked trisaccharide **23** (84%). The elongation cycle was then repeated thrice to assemble the penta-, hepta-, and nonasaccharides **24**, **25**, and **26**, respectively. Cleavage of the Lev groups in **23**−**26** followed by oxidation using TEMPO,[17] individually, furnished the acids **27**−**30** in good overall yields. The corresponding *O*-sulfates, obtained by consecutive deacetylation and *O*-sulfonation of **27**−**30**, underwent hydrogenolysis to reduce the OBn, O-2-NAP, and N_3 groups and subsequent *N*-sulfonation to provide the desired target molecules **2**−**5**, respectively.

In summary, we successfully developed a straightforward synthesis of the L-idopyranosyl sugar **11** as a valuable building block and carried out the total synthesis of heparin oligosaccharides **2**−**5**.

Acknowledgment. We thank Professor Chun-Chen Liao for his helpful discussions. This work was supported by the National Science Council of Taiwan R.O.C. (NSC 91-2113-M-001-004).

Supporting Information Available: Experimental procedures, ^1H NMR spectra, and X-ray structural information for compound **15*β*** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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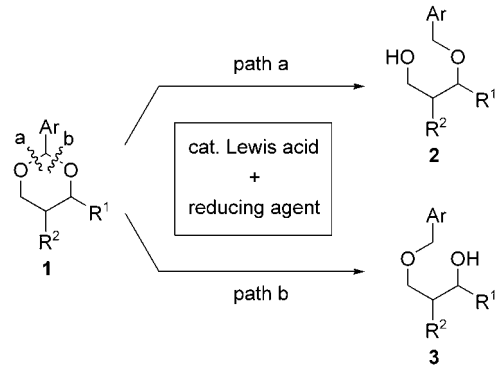
Synthetic Methods

$Cu(OTf)_2$ as an Efficient and Dual-Purpose Catalyst in the Regioselective Reductive Ring Opening of Benzylidene Acetals**

*Chi-Rung Shie, Zheng-Hao Tzeng, Suvarn S. Kulkarni, Biing-Jiun Uang, Ching-Yun Hsu, and Shang-Cheng Hung**

Regioselective ring opening of benzylidene acetals is one of the major challenges in carbohydrate and natural product syntheses.[1] Substituted and unsubstituted benzylidene acetals are valuable protecting groups to block 1,3-diols. Arylidene acetals **1** can be opened selectively under appropriate reaction conditions (Scheme 1) to yield primary **2** (path a) or

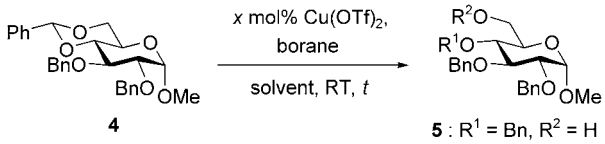


Scheme 1. Lewis acid catalyzed regioselective reductive ring opening of benzylidene acetals **1** to give primary alcohols **2** (path a) or secondary alcohols **3** (path b).

secondary alcohols **3** (path b). A number of effective reagents have been reported for the regioselective ring opening of 4,6-*O*-benzylidene acetals in hexopyranosides. Of these, AlH_3[2] and iBu_2AlH,[3] which are commonly used to cleave at the O6 position, often lack chemoselectivity when substrates contain base-sensitive functionalities. Alternatively, traditional acid-promoted reductive cleavage has been reported to open benzylidene acetals at either the O6[4] or O4 position.[4a,c,f,5] However, these traditional acids have to be used stoichiometrically or in excess and can lead to hydrolysis of the acetal ring as a major side reaction. Often when these protocols have been used, a mixture of regioisomers is obtained that can be difficult to purify by chromatographic techniques. The development of new Lewis acids as efficient catalysts for ring cleavage in a highly selective manner may offer a good solution (Scheme 1). No Lewis acid catalyzed ring openings of 4,6-*O*-benzylidene acetals at the O4 position have been published to date. So far only a reductive cleavage at O6 to the give corresponding 6-alcohol using borane and with $[V(O)(OTf)_2]$ (Tf = trifluoromethanesulfanyl) as the catalyst has been reported, and here the required amount of catalyst was 15 mol%.[6] Herein, we have developed $Cu(OTf)_2$ as an efficient and dual-purpose catalyst that can be used in catalytic quantities; it effects the regioselective reductive ring opening of benzylidene acetals at the O4 or O6 position by merely altering the reactivity of the reducing agent.

Compound **4** was selected for model studies. We examined the cleavage at O6 by employing various boranes in combination with $Cu(OTf)_2$ at room temperature; the results are outlined in Table 1. Initially, treatment of **4** with BH_3·THF in

Table 1: $Cu(OTf)_2$-catalyzed regioselective borane-reductive O6-ring opening of 4,6-*O*-benzylidene acetal **4** to the corresponding 6-alcohol **5** at room temperature.



Entry	*x*	Borane	Solv.	*t* [h]	Yield [%] 5	6
1	15	BH_3·THF[a]	CH_2Cl_2	0.75	94	0
2	15	BH_3·THF	–	0.75	92	0
3	10	BH_3·THF	–	1.5	93	0
4	5	BH_3·THF	–	2.5	95	0
5	1	BH_3·THF	–	27	70	0
6	5	BH_3·Me_2S[b]	–	10	78	3
7	5	BH_3·Me_3N	CH_2Cl_2	25	0	40
8	5	9-BBN[c]	–	27	40	0

[a] 1 M solution in THF. [b] 2 M solution in THF. [c] 0.5 M solution in THF, 9-BBN = 9-borabicyclo[3.3.1]nonane.

the presence of 15 mol% of catalyst in CH_2Cl_2 rapidly furnished the expected ring-opened product **5**[7] in excellent yield (entry 1, 45 min, 94%). Exclusion of CH_2Cl_2 gave similar results (entry 2, 92%). Lowering the concentration of catalyst to 10 mol% and 5 mol% (entries 3 and 4) led to similar selectivity and yields, while decreasing it to 1 mol% extended the reaction time and resulted in a drop in yield (entry 5).

We then tested various borane reagents in tandem with 5 mol% of $Cu(OTf)_2$ to study the effect of ligation and bulk

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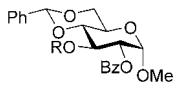
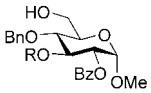
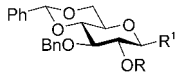
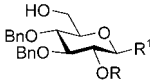
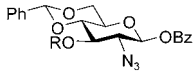
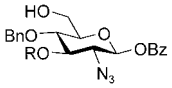
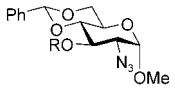
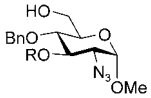
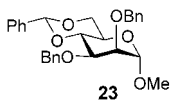
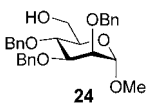
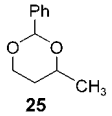
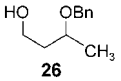
on the regiochemical outcome of the reactions. In entry 6, use of the $BH_3{\cdot}Me_2S$ complex with **4** afforded product **5** (78%) along with a minor 4-alcohol **6** (3%). Interestingly, the mode of regioselection was markedly shifted when $BH_3{\cdot}NMe_3$ was used as the reductant (entry 7); compound **6** was formed in 40% yield as the sole product, and some starting material was recovered (55%). A bulkier reagent, 9-borabicyclo[3.3.1]nonane (9-BBN), was sluggish to react (entry 8), and overnight stirring was needed to furnish **5** in a modest yield (40%) together with the hydrolyzed 4,6-diol (40%) and starting material (15%).

We then proceeded to investigate the compatibility of various substrates under these optimized conditions (1M $BH_3{\cdot}THF$ in THF, 5 mol% $Cu(OTf)_2$, without additional solvent, room temperature; Table 2). The 2-benzoyl-protected D-glucose derivative **7** successfully furnished the expected 4-benzyl-protected product **8** (entry 1, 4.5 h, 87%), while the 2,3-dibenzoyl-protected compound **9** gave the corresponding 6-alcohol **10**[4a] in 53% yield after 23 h (entry 2). When 15 mol% of $Cu(OTf)_2$ was used, the latter transformation was carried out over a short period (5 h), affording compound **10** in a high yield (entry 3, 91%). The electron-withdrawing groups in the substrates **7** and **9** made their reaction much slower than that of the 2,3-dibenzyl analogue **4** (0.75 h). The reaction rate is closely associated with the nucleophilicity of the oxygen atom at the C6 position and the Lewis acid catalyst. In the $LiAlH_4$–$AlCl_3$ system, the congestion of the protecting group at O3 in D-glucopyranosides plays an important role, and the presence of a bulkier substituent at C3 has been found to favor a higher proportion of O6-opened product.[2b] However, no such steric dependence was observed in our system, and only O4-benzyl ethers were obtained in high yields irrespective of their nature (H, Bn, or Bz).[4b] Similarly, the methyl β-pyranoside **11** (entry 4), β-thioglycoside **13** (entry 5), D-mannose-derived acetal **23** (entry 14), and non-sugar substrate **25** (entry 15) underwent a high-yielding facile ring fission to provide 6-OH derivatives **12**[8] (92%), **14** (93%), **24**[9] (84%), and **26**[10] (90%), respectively. In the D-glucosamine series, the β-benzoyl 3-benzyl-protected **15** led to the desired product **16** in 82% yield (entry 6). Its structure was determined by single-crystal X-ray structure analysis.[11] The 3-benzoyl analogue **17**, although sluggish to react under the optimized conditions (entry 7, 63%), did furnish the expected compound **18** rapidly and in excellent yield (90%) when 15 mol% of $Cu(OTf)_2$ was used (entry 8). When the α-form 3-benzyl **19** (entry 9) and 3-benzoyl **21** (entry 12) were employed, the expected ring-opened products **20** and **22** were obtained in 55 and 56% yields, respectively. Increasing the catalyst concentration to 15 mol% and the reaction temperature to 0°C improved the yield remarkably in case of the former (entry 11, 86%), whereas a substantial amount of the 4,6-diol (30%) from hydrolysis was present in the latter (entry 13, 57%).

Table 2: Reductive ring opening of various benzylidene acetals at the O6 position using $BH_3{\cdot}THF$ and *x* mol% of $Cu(OTf)_2$ as the catalyst.

Entry	Acetal	*x* [mol%]	*t* [h]	Product	Yield [%]
					
1	**7**: R = H	5	4.5	**8**: R = H	87
2	**9**: R = Bz	5	23	**10**: R = Bz	53
3	**9**	15	5	**10**	91
					
4	**11**: R = Bz, R^1 = OMe	5	4	**12**: R = Bz, R^1 = OMe	92
5	**13**: R = Bn, R^1 = STol	5	3.5	**14**: R = Bn, R^1 = STol	93
					
6	**15**: R = Bn	5	3	**16**: R = Bn	82
7	**17**: R = Bz	5	21	**18**: R = Bz	63
8	**17**	15	4.5	**18**	90
					
9	**19**: R = Bn	5	6.5	**20**: R = Bn	55
10	**19**	15	3.5	**20**	67
11	**19**	15[a]	14	**20**	86
12	**21**: R = Bz	5	5	**22**: R = Bz	56
13	**21**	15[a]	9	**22**	57
14	 **23**	5	3.5	 **24**	84
15	 **25**	5	1.5	 **26**	90

[a] The reaction was conducted in an ice bath. Bz = Benzoyl, Bn = benzyl, OMe = methoxy, Tol = tolyl.

With success in the $Cu(OTf)_2$-catalyzed borane-induced reductive O6-ring opening of benzylidene acetals, we then explored the catalytic properties of $Cu(OTf)_2$ for silane-induced reductive cleavage at the O4 position, including the effects of the solvent, silane agent, and catalyst concentration (Table 3). The catalyst was added at 0°C, and the reaction mixture was gradually warmed up to room temperature. When 1 mol% of $Cu(OTf)_2$ was used together with triethylsilane in CH_2Cl_2 (entry 1), the reaction took 15 h to provide the secondary alcohol **6**[5b] (62%) as the only regioisomer. A smaller reducing agent, Me_2EtSiH, offered a marginally improved yield of **6** in a much shorter reaction time (entry 2, 9 h, 65%). Employment of a more polar solvent like nitromethane speeded up the reaction of **4** with Et_3SiH (entry 3, 1 h) and Me_2EtSiH (entry 4, 1 h), which afforded **6** as the sole product in 60% and 68% yields, respectively. Although no other regioisomer was detected, hydrolysis of compound **4** to the corresponding 4,6-diol seemed to become a dominant factor limiting the yield. Less polar solvents, for example, THF and toluene, gave disappointing results. Nevertheless, reduction of **4** in acetonitrile using Et_3SiH (entry 5,

Table 3: $Cu(OTf)_2$-catalyzed reductive ring opening of compound **4** in various solvents with silanes to give the corresponding 4-alcohol **6**.

$$\mathbf{4} \xrightarrow[\text{solvent, } 0\,^{\circ}C \rightarrow RT]{x\ \text{mol\%}\ Cu(OTf)_2,\ 2\ \text{equiv silane}} \mathbf{5} + \mathbf{6}$$

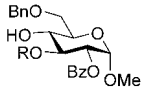
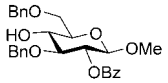
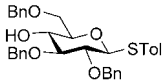
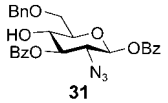
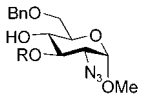
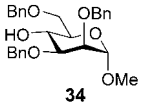
Entry	x	Silane	Solv.	t [h]	Yield [%]	
					5	**6**
1	1	Et_3SiH	CH_2Cl_2	15	0	62
2	1	Me_2EtSiH	CH_2Cl_2	9	0	65
3	1	Et_3SiH	CH_3NO_2	1	0	60
4	1	Me_2EtSiH	CH_3NO_2	1	0	68
5	1	Et_3SiH	CH_3CN	1	7	76
6	1	Me_2EtSiH	CH_3CN	0.5	0	84
7	0.5	Me_2EtSiH	CH_3CN	4	3	75
8	5	Me_2EtSiH	CH_3CN	0.5	3	80
9	10	Me_2EtSiH	CH_3CN	0.5	2	82

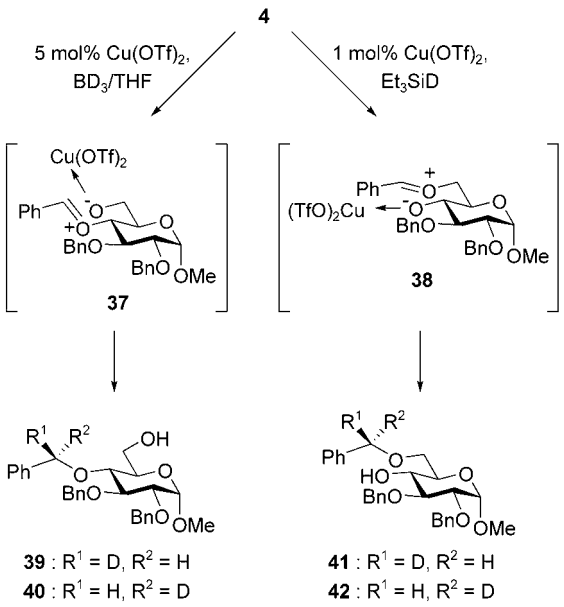
1 h) readily furnished the expected compound **6** (76%) along with the minor isomer **5** (7%), while Me_2EtSiH led to **6** in 84% yield (entry 6, 0.5 h), exclusively. In these cases the hydrolyzed product was recovered in up to 10% yield. In entry 7, when the catalyst concentration was halved, the transformation took place gradually (4 h) to afford compound **6** in 75% yield. In contrast, increasing the concentration of catalyst to 5 mol% or 10 mol% (entries 8 and 9) did not improve the yields of **6** (80–82%).

With these optimized reaction conditions (1 mol% $Cu(OTf)_2$, Me_2EtSiH, CH_3CN, 0°C→room temperature), we examined a number of α- and β-hexopyranosides bearing different protecting groups to check the generality of this protocol (Table 4). In entries 1–8, reactions of the D-glucose-derived benzoates **7** and **9**; β-glucopyranoside **11** and β-thioglycoside **13**; D-glucosamine-derived acetals **17**, **19**, and **21**; and D-mannopyranosyl sugar **23**[12] led to O4-opened products **27**–**34** in 71, 85, 74, 79, 87, 80, 83, and 70% yield, respectively. These experiments revealed that the electron-withdrawing group at the O3 position does not affect the reactivity of substrates, in contrast to the observations of the reductive O6-opening reactions with borane. In the case of the non-carbohydrate compound **25** (entry 9), regioisomeric benzyl ethers **26** (22%) and **35** (24%) were generated along with 1,3-dibenzyl ether **36** (36%) as the major product.

To examine the reaction pathway in greater depth, we performed two experiments using deuterated reducing agents (Scheme 2). Reductive ring opening of **4** with BD_3·THF furnished primary alcohols **39** and **40** in unequal proportions (5:1 ratio), as judged from the signals of the O4-benzylic protons in the ^1H NMR spectrum of the mixture with those of compound **5** (see the Supporting Information). The $Cu(OTf)_2$ catalyst may first coordinate with the more accessible O6 atom and lead to a zwitterionic species **37**, which can be reduced by the reactive borane reagent. The reaction essentially follows the S_N1 pathway, and the stereochemical bias is perhaps offered by the chirality at C4, which is reflected in the observed product ratio. On the other hand, the ring fission of **4** with Et_3SiD generated a 1:1 diastereomeric mixture of secondary alcohols **41** and **42**. The hindered O4-benzyl cation of the intermediate **37** cannot be reduced as the silane reagent is bulky and less reactive than borane and

Table 4: Regioselective reductive ring opening of various benzylidene acetals in acetonitrile employing Me_2EtSiH and with 1 mol% of $Cu(OTf)_2$ as the catalyst.

Entry	Acetal	t [h]	Product	Yield [%]
				
1	**7**	1	**27**: R = H	71
2	**9**	1	**28**: R = Bz	85
3	**11**	0.5	 **29**	74
4	**13**	1.5	 **30**	79
5	**17**	0.5	 **31**	87
				
6	**19**	1	**32**: R = Bn	80
7	**21**	0.5	**33**: R = Bz	83
8	**23**	1	 **34**	70
9	**25**	2	**26**: R^1 = H, R^2 = Bn	22
			35: R^1 = Bn, R^2 = H	24
			36: R^1 = R^2 = Bn	36



Scheme 2. The treatment of **4** with deuterated reducing agents. Bn = Benzyl.

an equilibrium is soon established between the O6- and O4-coordinated complexes, which leads to another zwitterionic species **38**. The silane agent can approach the intermediate **38** at the well-exposed O6-benzyl cation from either side to generate equal amounts of diastereomers.

In conclusion, we have successfully developed $Cu(OTf)_2$ as an excellent dual-purpose catalyst for highly regioselective reductive ring opening of various benzylidene acetals with BH_3 and Me_2EtSiH to furnish the corresponding primary and secondary alcohols, respectively. The reaction conditions are mild, and various protecting groups in the substrates are tolerated. The isotope studies provide the first experimental evidence that neither O6- nor O4-cleavage of the benzylidene ring proceeds through the S_N2 reaction pathway when borane or triethylsilane attacks the acetal carbon center.

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參加「第 23 屆國際醣會議」報告

報告人：洪上程，國立清華大學化學系（95 年 7 月 23 日至 7 月 28 日）

第 23 屆國際醣會議於加拿大 Whistler 舉行，來自全世界不同國家的專家學者共襄盛舉，約有 800 多人參加。會議內容共可分成合成、結構分析和酵素等三個主要議程，讓自己能藉此機會學習不同學科的知識及拓展跨領域的研究方向。茲將幾位重要學者的演講重點摘錄如下：

禽流感是目前威脅全世界的嚴重問題之一，美國 Scripps 研究院 James Paulsen 教授在此次會議報導最新的禽流感資訊及利用醣晶片作為篩選 H5N1 病毒的可能性。此外，澳大利亞 Mark von Itzstein 也分享他們在對抗流感病毒課題新藥研發的歷程及最新的研究動態。

德國的 Richard R. Schmidt 教授則應用他發展的醣鏈鍵生成方法製備許多醣共軛分子，包括複雜的寡醣、glycosphingolipids、glycopeptides 和 glycosylphosphatidyl inositols 等等。此外，他亦結合固相合成的方法製備複雜的 *N*-glycoproteins，是當代的醣化學合成大師。

日本 RIKEN 的 Yukishige Ito 教授則發表一系列 high-mannose *N*-glycans 的合成及其對 calnexin 和 calreticulin 的調控，從合成的角度切入，克服β-1,2-mannosylation 的問題，製備許多不同的衍生物，配合生物方面的活性分析，內容深入且引人入勝，是非常成功的跨領域研究典範。

美國 Texas Austin 大學的劉鴻文教授則對於自然界製備不尋常醣(unusual sugars)的生物機制，提出精闢且深入的解釋，他指出許多自然界二級代謝產物中不尋常醣單元的重要性，例如萬古黴素(vancomycins)和紅黴素 (erythromycins)等抗生素，當醣單元被移除後，非醣的部份完全沒有生物活性，相同的現象也在一些中草藥的重要成份上被發現，如 terpene glycosides 和 steroid glycosides 等分子，而這些作用機制

至今仍不明瞭。

此次我個人亦受到大會邀請發表演講，將我們實驗室在肝素寡醣分子庫的合成經驗作詳細報導，引起許多共鳴，演講完後，有三位研究學者對我們的工作非常感興趣，並提出日後在生物活性方面相互合作的可能性。

醣化學及醣生物學在近幾年來的研究發展愈來愈重要，許多前瞻性的研究大都需要跨領域的合作，希望整合型的研究計畫能發揮功能，真正達到解決問題的目的。