Biologically Potent L-Hexoses and 6-Deoxy-L-Hexoses: Their Syntheses and Applications

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This account describes our recent work in the development of new methodologies to prepare rare and biologically potent L-hexoses and 6-deoxy-L-hexoses, from cheapest D-glucose, via L-hexofuranoses and 1,6-anhydro-β-L-hexopyranoses as key building blocks. Their applications in the syntheses of heparin oligosaccharides, the carbohydrate moiety of bleomycin A_2, and L-acovenose are also summarized here.

Keywords: L-Hexose; 1,6-Anhydro-β-L-hexopyranoses; Bleomycin A_2; Heparin.

INTRODUCTION

L-Hexoses and 6-deoxy-L-hexoses (Fig. 1), which are known as rare sugars from natural sources, are key components of numerous biologically potent oligosaccharides, antibiotics, glycopeptides, steroid glycosides, as well as terpene glycosides.[1] For example, L-idose and its derivatives form an important group of vital structural elements of biomolecules. Heparin, heparan sulfate, and dermatan sulfate, the linear sulfated polysaccharides of glycosaminoglycans covalently bound to a core protein, play significant roles in a diverse set of biological processes, including blood coagulation, cell growth control, inflammation, wound healing, virus infection, tumor metastasis, and diseases of the nervous system.[2] Heparin is widely used as an anticoagulant drug in clinics[3] and contains a trisulfated disaccharide repeating unit **1** as the major component consisting of alternating D-glucosamine and L-iduronic acid with α1→4 linkages. The same unit also occurs in cell surfaced-heparan sulfate as a minor but essential constituent, whereas dermatan sulfate is composed of a D-galactosamine-β1→4-L-iduronic acid disaccharide repeating unit **2**. Neomycin B **3**, an aminoglycoside antibiotic possessing specific interaction with the A site of the prokaryotic 16S *r*RNA[4] and inhibition for the binding of the HIV Rev protein to its viral RNA recognition site (RRE),[5] has 2,6-diamino-2,6-dideoxy-L-idopyranose as the D-ring. 6-Deoxy-L-idopyranose is found as a basic component of the diterpene glycoside **4**, isolated from *Aster spathulifolius maxim*.[6]

Some remarkable examples are presented by L-gulopyranoside-containing compounds. Bleomycin A_2 **5**[7] is a significant antitumor drug exhibiting strong activity through DNA binding and metal-dependent oxidative cleavage of nucleotides in the presence of oxygen. It belongs to a family of glycopeptide antibiotics and contains a disaccharide moiety consisting of a α1→2 linked 3-*O*-carbamoyl-D-mannopyranose with L-gulopyranose. Adenomycin **6**,[8] a nucleoside antibiotic compound, has a L-gulosamine unit β-linked to *chiro*-inositol. Alginate **7**,[9] which is a non-toxic linear polysaccharide extracted from seaweed, comprises various proportions of β-D-mannuronic acid and α-L-guluronic acid jointed by 1→4 linkages. It has shown not only potent antitumor activity *in vivo*[9b] but also antiviral activity against infection by tobacco mosaic virus.[9c]

L-Talose **10** and its derivatives are also found in some natural compounds. Amongst other antibiotics with promising antibacterial properties, capuramycin **8**[10] contains a 3-*O*-methyl-L-talofuranosyl sugar unit, whereas acovenosides[11] and maduralide[12] have 6-deoxy-3-*O*-methyl-L-talopyranose **9** (L-acovenose) as the carbohydrate motif.

Other notable examples include L-altrose **11** and L-mannose **12**. The former is a typical constituent of the extracellular polysaccharides from *Butyrivibrio fibrisolvens* strain CF3.[13] The latter is found in some steroid glycosides,[14] and its phenol derivatives are potent substrates for measuring the α-L-mannosidase activity of commercial naringinase.[15]

Since these frequently encountered L-hexoses and 6-deoxy-L-hexoses are not commercially available, their synthesis has been an area of intense investigation for chemists.[16] To tackle this problem, we planned to first achieve the conversion from D-*gluco* to L-*ido* configuration in the shortest

Dedicated to Professor Sunney I. Chan on the occasion of his 67th birthday and his retirement from professional life.

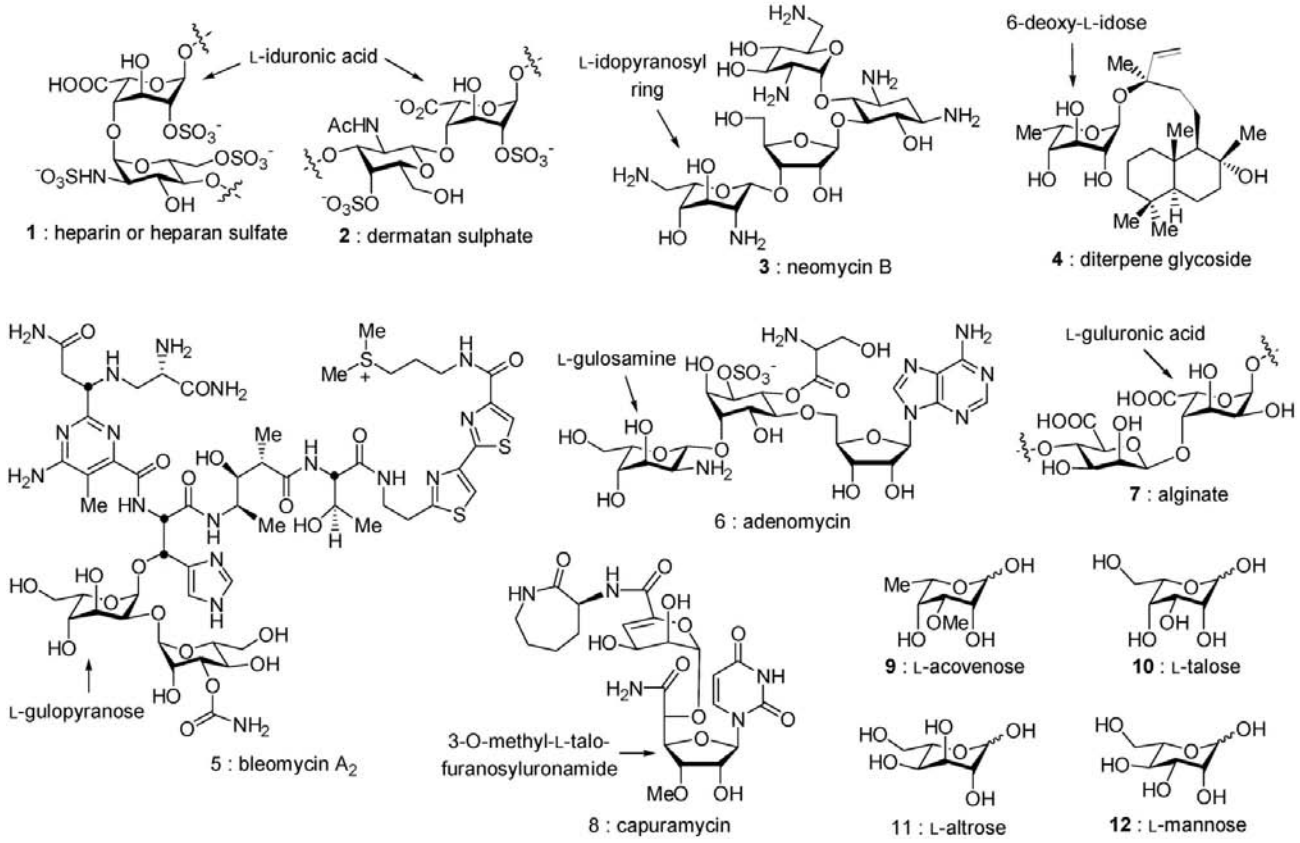


Fig. 1. Structures of some biologically potent compounds containing L-hexoses or 6-deoxy-L-hexoses as key components.

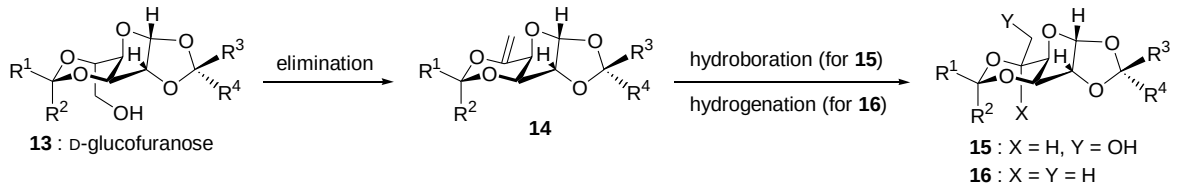
possible way and then carry out the specific epimerization of the L-*ido* sugars at C2, C3 and/or C4 to get to the whole set of L-hexoses. Our idea, as illustrated in Scheme I, was to use double ketal fixation on the 1,2- and 3,5-dihydroxy groups of D-glucose to form the *cis*-*anti*-*cis*-fused tricyclic D-glucofuranose **13**, which may undergo elimination to yield the enol ethers **14** with the requisite 5-*exo*-double bond. Owing to the steric congestion on the α-face, stereoselective hydroboration and hydrogenation of **14** are expected to furnish the desired L-idofuranose **15** and 6-deoxy-L-idofuranose **16**, respectively.

RESULTS AND DISCUSSION

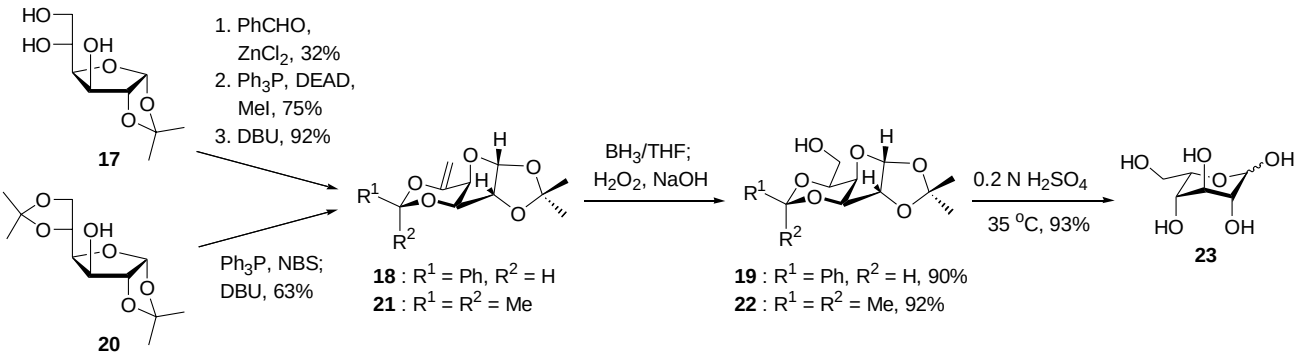
Synthesis of L-Idose

Scheme II outlines our efficient synthesis of L-idose. In the initial attempt,[17] 3,5-*O*-benzylidenation (PhCHO, $ZnCl_2$, 32%) of 1,2-*O*-isopropylidene-α-D-glucofuranose **17** followed by sequential Mitsunobu-type iodination (Ph_3P, DEAD, MeI, 75%) and β-elimination (DBU, 92%) furnished the olefin **18** in three steps. As per our expectation, hydroboration of compound **18** led to the β-L-idofuranosyl sugar **19** (90%) as a single diastereoisomer in excellent selectivity. Although the

Scheme I



Scheme II



strategy works well, there are certain disadvantages of this route, including (1) it takes four steps to generate the desired L-*ido* product **19**, (2) tedious purification of each intermediate is necessary, (3) the overall 22% yield from **17** to **18** is low, and (4) the starting material **17** is more expensive than common D-glucose derivatives. To improve these unsatisfactory results, we have developed another convenient and practical synthesis of L-idose **23** from commercially available and cheap diacetone α-D-glucose **20** in only three steps.[18,19] Consecutive treatment of **20** with triphenylphosphine (PPh_3), *N*-bromosuccinimide (NBS), and DBU provided the enol ether **21** (63%) in a one-pot manner via a tandem isopropylidene rearrangement, regioslective C6-bromination, and β-elimination.[19] Hydroboration of compound **21** proceeded well with expected high selectivity, and the corresponding alcohol **22** was obtained in 92% yield. Hydrolysis of **22** in 0.2 N $H_2SO_{4(aq)}$ at 35 °C successfully afforded L-idose **23** in excellent yield (93%).

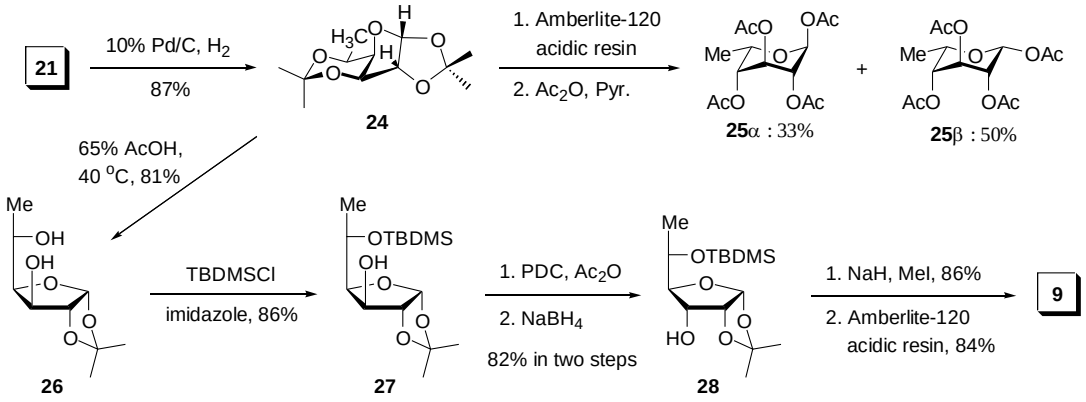
Synthesis of 6-Deoxy-L-idose and L-Acovenose

As anticipated, the high stereoselectivity observed in the hydroboration of **21** was also realized in its hydrogenation, and the 6-deoxy-β-L-idofuranose derivative **24** was obtained as a single diastereoisomer in high yield (87%).[18] This result was exploited to synthesize two important 6-deoxy-L-hexoses, as depicted in Scheme III.[20] Compound **24** upon hydrolysis in the presence of an acidic resin provided the expected 6-deoxy-L-idose, which was directly per-*O*-acetylated to its tetraacetate derivatives **25**α (33%) and **25**β (50%), in order to circumvent its possible inter-conversion to 6-deoxy-L-sorbose. Alternatively, selective hydrolysis of **24** under mild acidic conditions gave the 3,5-diol **26** (81%), which underwent regioselectively silylation at O5 to furnish the corresponding alcohol **27** (TBDMSCl, imidazole, 86%). The C3-epimerisation was then achieved through an oxidation-reduction sequence to afford the 6-deoxy-β-L-talofuranosyl sugar **28** (82% in two steps). 3-*O*-Methylation of compound **28** (NaH, MeI, 86%) followed by hydrolysis (Amberlite-120 acidic resin, 84%) yielded the desired target molecule L-acovenose **9**.

Synthesis of L-Talose, L-Altrose, and L-Mannose

For the preparation of other L-hexoses, it was realized that the free hydroxy group at the C6 position of the L-ido-

Scheme III



furanose **22** makes it an unsuitable precursor due to the difficulties in epimerisation of the remaining chiral centers. Regioselective hydrolysis of **22** followed by 5,6-*O*-isopropylidenation furnished the 3-alcohol **29** in 65% overall yield in two steps. With the appropriate synthon **29** in hand, the synthesis of various L-hexoses (Scheme IV) was successfully carried out taking advantage of the 5,5-*cis*-fused ring configuration that allows the nucleophilic and electrophilic additions only from the β-face.

Since L-talose **10** is a C3-epimer of L-idose **23**, we employed a simple oxidation-reduction protocol for inversion of compound **29** at C3. Oxidation of **29** with pyridinium dichromate and acetic anhydride led to the ketone **30** (98%), which was subjected to sodium borohydride reduction to give 1,2:5,6-di-*O*-isopropylidene-β-L-talofuranose **31** in 92% yield. Hydrolysis of **31** using Amberlite-120 acidic resin smoothly afforded L-talose **10**[19] in quantitative yield. On the other hand, methylation of **31** allowed us to introduce a methyl group at O3, and the ether **32** was obtained in 93% yield. Consecutive removal of the 5,6-*O*-isopropylidene group (64% $HOAc_{(aq)}$, 92%) and regioselective 6-*O*-silylation (TBDPSCl, cat. DMAP, Et_3N, 77%) furnished the corresponding 5-alcohol, which is a key intermediate for the total synthesis of capuramycin.[10b]

The difference between L-altrose **11** and L-idose **23** is only at the C4 position. Epimerization of the 3-alcohol **29** to the corresponding L-altrofuranosyl sugar was thought feasible via elimination of a water molecule to form a double bond at C3 and C4 followed by stereoselective hydroboration of the resulting olefin. Reaction of **29** with diethylaminosulfur trifluoride (DAST) and pyridine afforded the enol ether **33** (51%), which upon hydroboration yielded the expected L-altrofuranosyl sugar **34** (78%) as a single diastereoisomer. Acidic hydrolysis of the alcohol **34** in the presence of Amberlite-120 resin led to L-altrose **11**[21] in excellent yield.

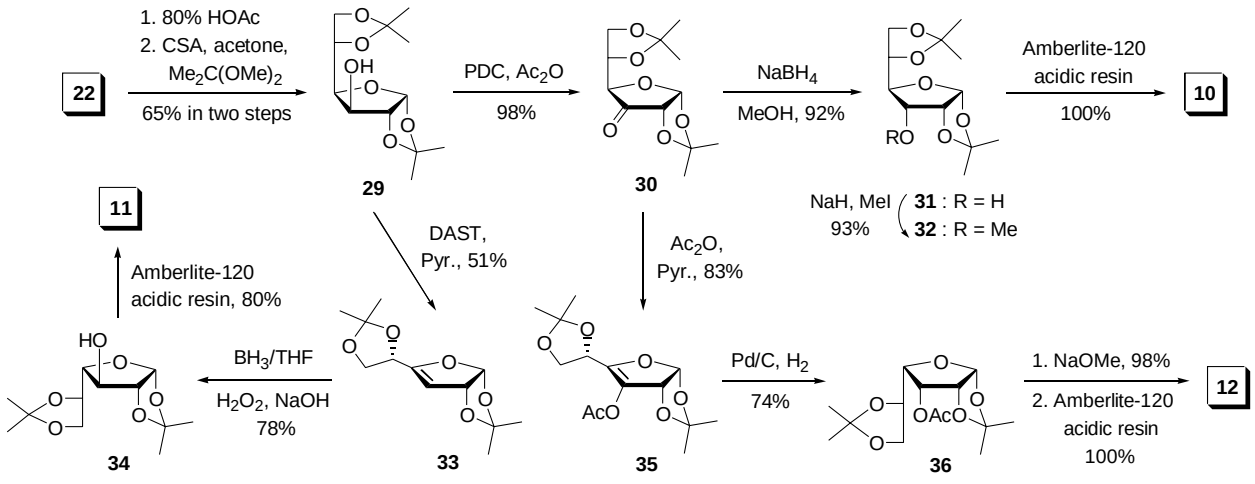
It was envisioned that the L-*manno* sugars could be accessed via simultaneous epimerisation of **29** at both C3 and C4 chiral centers. Enolization of the ketone **30** with acetic anhydride in pyridine provided the enol acetate **35** (83%), which was hydrogenated stereoselectively to provide the L-mannofuranosyl derivative **36** (74%). Sequential deacetylation (98%) and acidic hydrolysis (100%) of **36** gave the desired L-mannose **12**.[21]

Synthesis of 1,6-Anhydro-β-L-hexopyranoses

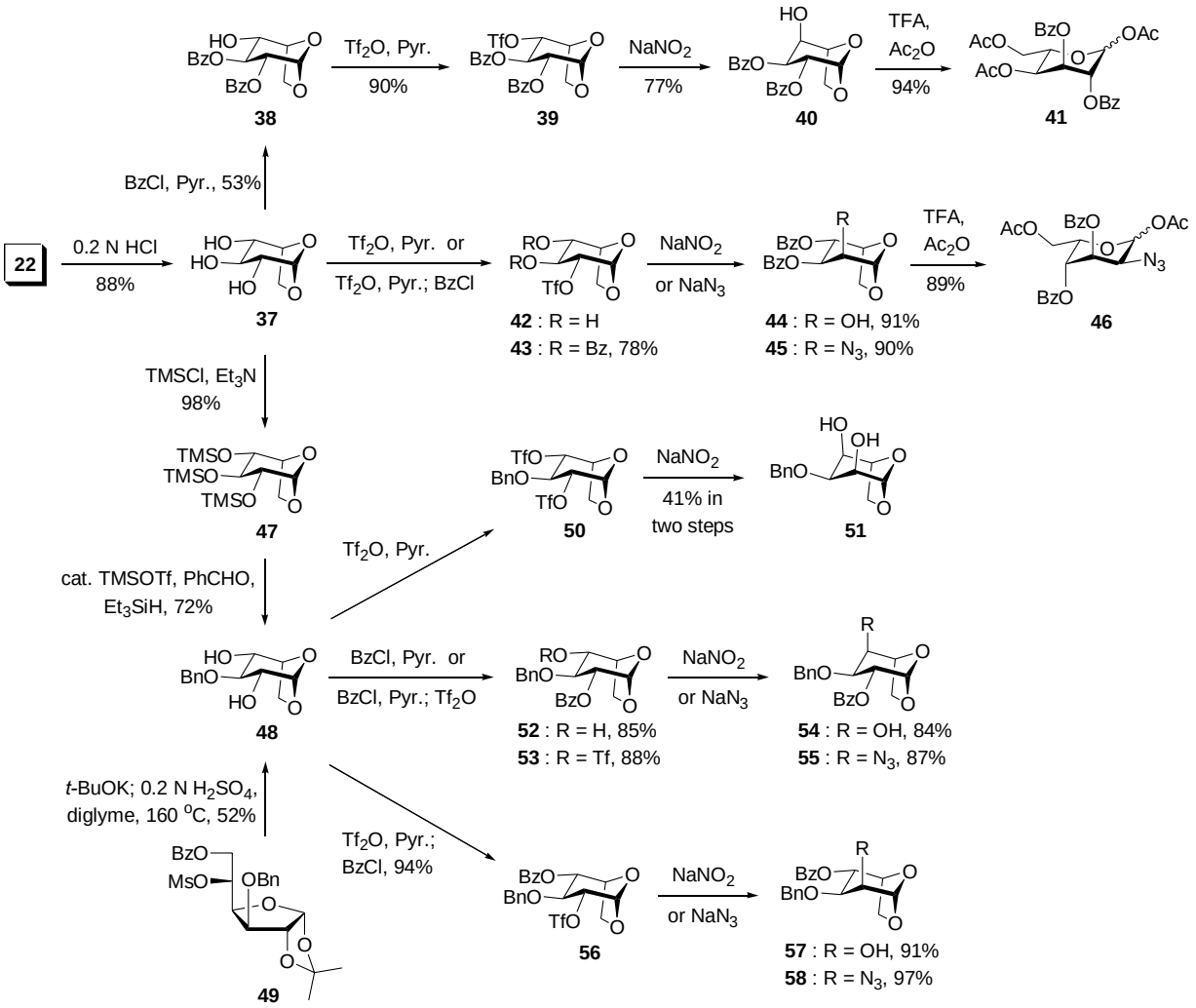
The D- and L-form 1,6-anhydro-β-hexopyranoses are valuable building blocks in the synthesis of oligosaccharides, glycoconjugates, as well as natural products.[22] A straightforward synthesis of various rare 1,6-anhydro-β-L-hexopyranosyl sugars is summarized in Scheme V. Reflux of compound **22** in a 0.2 N ethanolic solution of HCl yielded the 1,6-anhydro-β-L-idopyranose **37** (88%) as a single product.[23] Subsequently, we developed efficient protocols for regioselective protection and selective epimerisation of individual chiral centers in the triol **37** that paved the way to other rare 1,6-anhydro sugars and consequently to L-hexoses.[19,24]

Benzoylation of the triol **37** afforded the 2,3-di-OBz **38** (53%) as a major compound. Triflation of the 4-alcohol **38** furnished the corresponding 4-OTf product **39** (90%), which underwent nucleophilic substitution with $NaNO_2$ in HMPA to provide the expected 1,6-anhydro-β-L-altropyranosyl sugar **40** (77%). Acetolysis of compound **40** proceeded very well, and the fully protected L-altrose derivative **41**[23] was obtained in 94% yield.

Scheme IV



Scheme V



Reaction of compound **37** with one equiv of trifluoromethanesulfonic anhydride in pyridine led to the 2-OTf compound **42** as a single isomer in excellent selectivity. One-pot triflation-benzoylation of **37** successfully yielded the corresponding ester **43** (78%), which was treated with $NaNO_2$ or NaN_3 to give the 1,6-anhydro-β-L-gulopyranose **44** and its 2-azido derivative **45**. Conversion of **45** into the ring opened adduct **46** (89%) was similarly carried out under acetolysis conditions. It is believed that the fully protected L-gulosamine derivative **46**[23] could be a potential precursor in the synthesis of adenomycin **6**.[8]

On the other hand, regioselective 3-*O*-benzylation of the potent synthon **37** employing TMSOTf-catalyzed Et_3SiH-reductive etherification of its *O*-trimethylsilylated ether **47** (98%) gave the corresponding 3-OBn **48** (72%) in very good selectivity.[24,25] Alternatively, treatment of the 5-OMs-6-OBz compound **49** with *t*-BuOK in *t*-BuOH followed by heating in a 1:2 mixture of 0.2 N $H_2SO_{4(aq)}$ and diglyme at elevated temperature (160 °C) led to **48** in a moderate 52% yield in a one-pot manner.[26] Similarly, consecutive triflation and nucleophilic substitution of the diol **48** via the 2,4-di-OTf **50** as an intermediate furnished the corresponding L-*allo* 2,4-diol **51** in 41% overall yield in two steps.

In comparison with compound **37**, the regioselectivity observed in the benzoylation and/or triflation of the diol **48** is extremely high wherein the O3 position is fixed with a benzyl group. Selective benzoylation of **48** with BzCl in pyridine at 0 °C led to the 2-OBz **52** (85%) as a single isomer. One-pot benzoylation-triflation of **48** provided the 2-OBz-4-OTf derivative **53** (88%), which was subjected to S_N2 substitutions with $NaNO_2$ and NaN_3 to afford the 1,6-anhydro-β-L-altropyranosyl sugar **54** (84%) and its 4-azido derivative **55**

(97%), respectively. A mere reversal in the order of reagent addition to the diol **48** (Tf_2O, then BzCl) resulted in the formation of the 2-OTf-4-OBz compound **56** (95%). Similar substitutions were applied to synthesize the 1,6-anhydro-β-L-gulopyranosyl sugars **57** and its 2-azido derivative **58** in 91% and 97% yields, respectively.

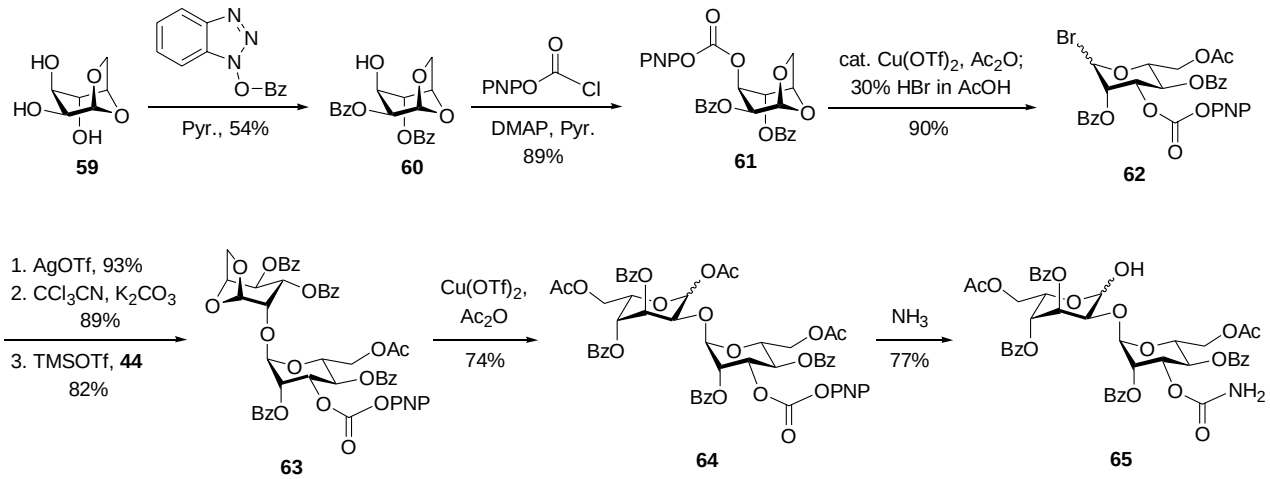
Synthesis of the Carbohydrate Moiety of Bleomycin A_2

The construction of the disaccharide subunit in bleomycin A_2 requires the assembly of 3-*O*-carbamoyl-D-mannopyranosyl donor and L-gulopyranosyl acceptor with a α1→2 linkage. Scheme VI describes our concise synthesis of this carbohydrate moiety using the 1,6-anhydro-β-L-gulopyranosyl alcohol **44** as a key synthon.[19] Commercially available 1,6-anhydro-β-D-mannopyranose **59** was treated with benzoyloxybenzotriazole (BzOBT) to yield the expected 2,4-di-OBz adduct **60** (54%) as a major isomer, which was converted into the corresponding 3-carbonate **61** (89%). $Cu(OTf)_2$, a cheap, water-stable, and reusable catalyst, can be used for a variety of transformations.[27] $Cu(OTf)_2$-catalyzed acetolysis[28] of compound **61** with Ac_2O followed by addition of 30% HBr in acetic acid gave the glycosyl bromide **62** (90%) in a one-pot manner. Hydrolysis of this crude compound **62** with AgOTf in water provided the 1-alcohol (93%) which, upon sequential imidation (K_2CO_3, CCl_3CN, 89%) and coupling with **44** furnished the α-linked disaccharide **63** in 82% yield, exclusively. Acetolysis of **63** in the presence of $Cu(OTf)_2$ as the catalyst afforded the expected diacetate **64** (74%), which underwent one-pot nucleophilic displacement with ammonia to get the desired product **65** (77%), a suitable precursor for the total synthesis of bleomycin A_2.[7]

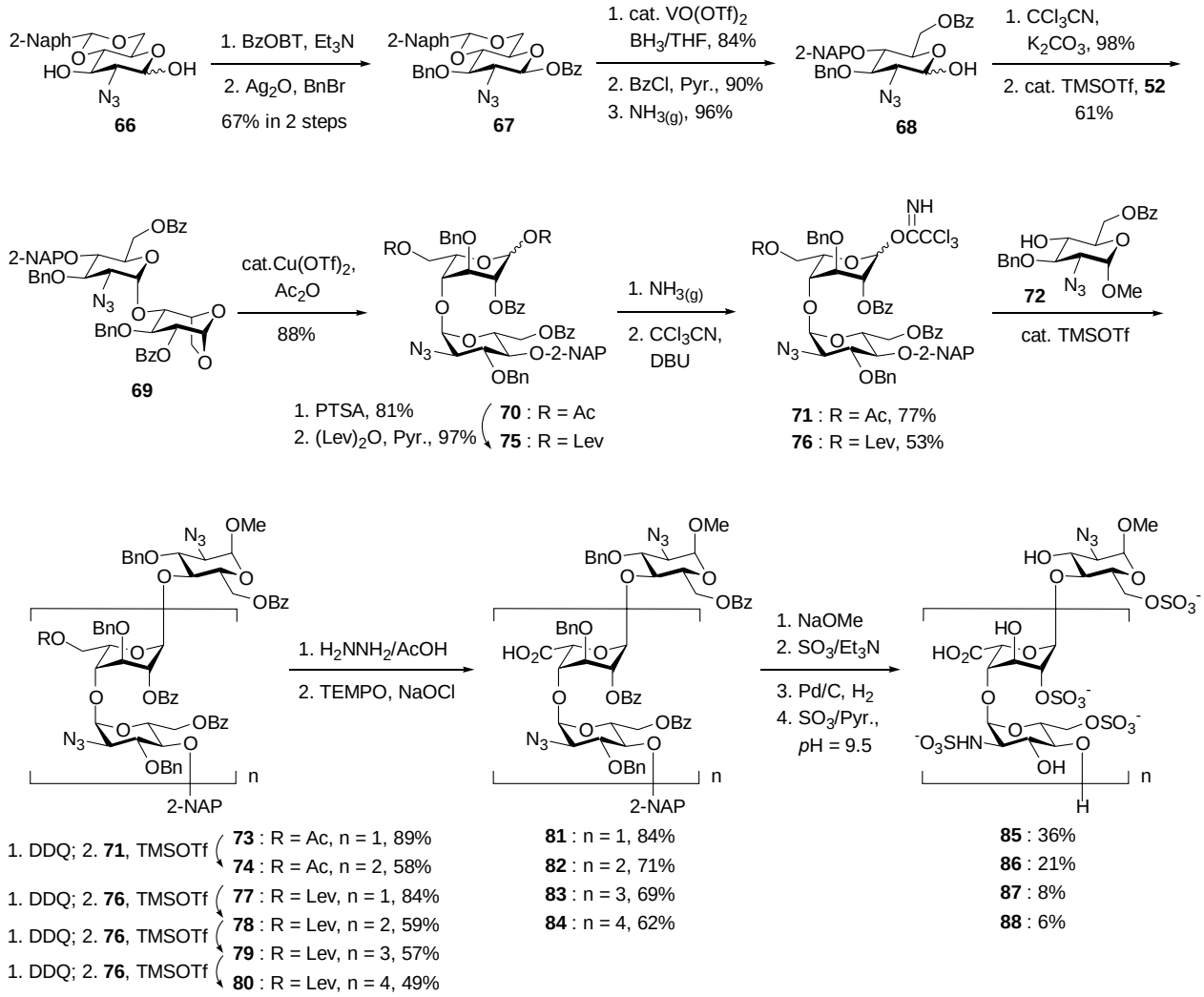
Synthesis of Heparin Oligosaccharides

The application of the versatile synthon **52** in the synthesis of heparin oligosaccharides **85-88** is illustrated in Scheme VII.[26] The 1,3-diol **66**, derived from D-glucosamine via a two-stepped combination of amino-azido conversion and 4,6-*O*-naphthylidenation, underwent consecutive O1-benzoylation[29] and O3-benzylation to afford the fully protected compound **67** (67% from **66**). A highly regioselective borane-reductive ring opening of the 4,6-*O*-benzylidene acetals to the corresponding 4-OBn-6-OH derivatives employing $VO(OTf)_2$ as the catalyst was recently developed by us.[30] Reaction of **67** under the same conditions provided the desired 6-alcohol (84%), which was subjected to O6-benzoylation (90%) followed by O1-debenzoylation (96%) to furnish the 1-alcohol **68**. Transformation of **68** into the corresponding trichloroacetimidate and further coupling with **52** led to the expected α-linked disaccharide **69** in 61% yield. $Cu(OTf)_2$-catalyzed acetolysis of **69** with acetic anhydride gave the 1,6-diacetate **70** (88%) which, upon O1-deacetylation and imidation yielded the desired glycosyl donor **71** (77%). The 4-alcohol **72**, prepared from the known methyl 2-azido-3-*O*-benzyl-2-deoxy-α-D-glucopyranoside by selective benzoylation at O6,[31] was coupled with **71** to get the α-linked trisaccharide **73** (89%) as a single isomer. Further chain-elongation sequence, involving selective removal of the O4-NAP using DDQ and subsequent glycosylation with the disaccharide donor **71**, was successfully carried out, and the pentasaccharide **74** was obtained in 58% yield. While re-

Scheme VI



Scheme VII



action of compound **73** with $HBF_4 \bullet Et_2O$ afforded the corresponding 6′-alcohol in excellent yield, simultaneous removal of two acetyl groups in **74** did not provide us the expected 6,6′-diol.

At this stage, we switched the acetyl groups to levulinoyl (Lev) esters. Thus, deacetylation of compound **70** furnished the 1,6-diol (81%), which was reacted with Lev_2O in pyridine to yield the ester **75** (97%). A similar reaction sequence of anomeric deprotection and imidate formation led to the glycosyl donor **76** (53% in 2 steps), which was coupled with **72** in a likewise manner to construct the α-linked trisaccharide **77** (84%). The elongation cycle was then repeated thrice to assemble the penta-, hepta- and nonasaccharides **78**, **79**, and **80**, respectively. Cleavage of the Lev groups in **77**-**80** followed by TEMPO oxidation, individually, furnished the acids **81**-**84** in good overall yields. The corresponding *O*-sulfates, obtained by consecutive deacetylaion and *O*-sulfonation of **81**-**84**, underwent hydrogenolysis to reduce the OBn, O-2-NAP, and N_3 groups simultaneously and subsequent *N*-sulfonation to give the target molecules **85**-**88**, respectively.

CONCLUSIONS

We have successfully developed a straightforward route to prepare the biologically important and rare L-hexoses and 6-deoxy-L-hexoses from the most abundant D-glucose via their corresponding furanosyl and 1,6-anhydropyranosyl derivatives as key intermediates. The method, being amenable to scale-up operation, is expected to find a wide use and provide a steady supply of rare sugars to those in its con-

stant need. Conceptually, in this synthetic endeavor, we also have uncovered some interesting facets and reactivity patterns exhibited by these conformationally biased synthons. Applications of these new developments to the syntheses of heparin oligosaccharides, the disaccharide moiety of bleomycin A_2, and L-acovenose have been demonstrated.

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