1,6-Anhydro-β-L-hexopyranoses as Potent Synthons in the Synthesis of the Disaccharide Units of Bleomycin A_2 and Heparin

Shang-Cheng Hung,*,† Shankar R. Thopate,† Fa-Chen Chi,‡ Shu-Wen Chang,† Jinq-Chyi Lee,‡ Cheng-Chung Wang,† and Yuh-Sheng Wen†

Institute of Chemistry, Academia Sinica Taipei 115, Taiwan
Department of Chemistry, National Tsing Hua University Hsinchu 300, Taiwan

Received September 27, 2000

L-Hexoses are key components of numerous biologically potent oligosaccharides and glycopeptides. For example, bleomycin A_2,[1] a glycopeptide antibiotic with significant antitumor activity, contains a carbohydrate moiety consisting of a $\alpha 1 \rightarrow 2$ linked 3-*O*-carbamoyl-D-mannopyranose with L-gulopyranose (Figure 1). Glycosaminoglycans, for example, heparin, heparan sulfate, and dermatan sulfate, play important roles in a diverse set of biological processes[2] and have L-idopyranosiduronic acids as typical constituents. Finally, L-altrose is a key structural element of the extracellular polysaccharides from *Butyrivibrio fibrisolvens* strain CF3.[3] Given the importance of L-hexoses[4] in the field of glycobiology, and that these rare sugars are not readily accessible from natural sources, we have explored herein a novel and efficient route toward the synthesis of 1,6-anhydro-β-L-gulo, -ido and -altropyranosyl sugars. Finally, we show how these valuable building blocks can be used to prepare the disaccharide units of bleomycin A_2 as well as heparin.

Synthesis of the desired 1,6-anhydro-β-L-hexopyranoses was carried out employing regioselective benzylation, benzoylation, triflation, and nucleophilic substitution of 1,6-anhydro-β-L-idopyranose **2** as key steps (Scheme 1). First, 1,2:3,5-di-*O*-isopropylidene-β-L-idofuranose **1** was prepared in three steps from diacetone α-D-glucose.[5] Hydrolysis in acidic media at refluxing temperature provided **2** (88%), which was selectively benzylated[6] to give the 3-OBn **3** (72%) due to the steric hindrance of C2- and C4-trimethylsilyloxy groups adjacent to the bridge-head atoms. Owing to the inductive effect of the two oxygen atoms at C1, the C2-oxide formed in basic solution reacts predominantly with various electrophiles. Selective benzoylation of **3** at 0 °C led to the 2-OBz **4** as a single isomer (85%). This result allowed the one-pot synthesis of **5** (88%), which was subjected to S_N2 substitutions with sodium nitrite and sodium azide to afford the L-*altro* sugar **6** (84%) and its 4-azido derivative **7** (87%), respectively. A similar strategy was applied to synthesize 1,6-anhydro-β-L-gulopyranosyl sugars and the adducts **8**, **9**, and **10** were respectively isolated in excellent yields. The absolute configurations of **3** (L-*ido*), **7** (L-*altro*), and **10** (L-*gulo*) were determined through their single-crystal X-ray analyses, respectively (see Supporting Information).

With the key synthon **9** in hand, the synthesis of the disaccharide moiety of bleomycin A_2 was carried out (Scheme 2). Carbonylation of **11**[7] furnished the carbonate **12** (68%) which, upon acetolysis[8] with Ac_2O and TFA, provided the diacetate **13** (88%). Treatment with 30% HBr in acetic acid produced the corresponding glycosyl bromide **14** in 94% yield. Silver triflate-activated coupling with the glycosyl acceptor **9** yielded the

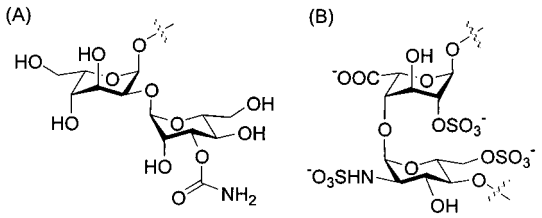
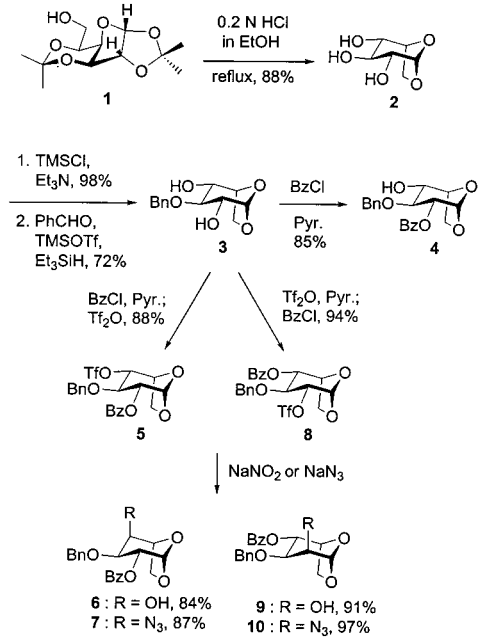


Figure 1. (A) The carbohydrate moiety of bleomycin A_2. (B) The disaccharide repeating unit of heparin.

Scheme 1



* To whom correspondence should be addressed. Phone: 886-2-2789-8646. Fax: 886-2-2783-1237. E-mail: schung@chem.sinica.edu.tw.
† Institute of Chemistry.
‡ Department of Chemistry.

(1) (a) Hecht, S. M. *J. Nat. Prod.* **2000**, *63*, 158−168. (b) Boger, D. L.; Cai, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 448−476. (c) Claussen, C. A.; Long, E. C. *Chem. Rev.* **1999**, *99*, 2797−2816. (d) Burger, R. M. *Chem. Rev.* **1998**, *98*, 1153−1169. (e) Takita, T.; Umezawa, Y.; Saito, S.; Morishima, H.; Naganawa, H.; Umezawa, H.; Tsuchiya, T.; Miyake, T.; Kageyama, S.; Umezawa, S.; Muraoka, Y.; Suzuki, M.; Otsuka, M.; Narita, M.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1982**, *23*, 521−524. (f) Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J.; Chang, L.-H.; Hecht, S. M. *J. Am. Chem. Soc.* **1982**, *104*, 5537−5538. (g) Boger, D. L.; Honda, T. *J. Am. Chem. Soc.* **1994**, *116*, 5647−5656. (h) Boger, D. L.; Ramsey, T. M.; Cai, H.; Hoehn, S. T.; Stubbe, J. *J. Am. Chem. Soc.* **1998**, *120*, 9139−9148. (i) Abraham, A. T.; Zhou, X.; Hecht, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 1982−1983. (j) Katano, K.; An, H.; Aoyagi, Y.; Overhand, M.; Sucheck, S. J.; Stevens, W. C.; Hess, C. D.; Zhou, X.; Hecht, S. M. *J. Am. Chem. Soc.* **1998**, *120*, 11285−11296.

(2) (a) Conrad, H. E. *Heparin-Binding Proteins*; Academic Press: New York, 1998. (b) Lindahl, U. *Pure Appl. Chem.* **1997**, *69*, 1897−1902. (c) Iozzo, R. V. *Annu. Rev. Biochem.* **1998**, *67*, 609−652. (d) Sinay, P.; Jacquinet, J.-C. *Carbohydr. Res.* **1984,** *132*, C5−C9. (e) van Boeckel, C. A. A.; Petitou, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1671−1690. (f) Tabeur, C.; Mallet, J.-M.; Bono, F.; Herbert, J.-M.; Petitou, M.; Sinaÿ P. *Bioorg. Med. Chem.* **1999**, *7*, 2003−2012.

(3) Stack, R. J. *FEMS Microbiol. Lett.* **1987**, *48*, 83−87.

(4) Some selected synthetic papers: (a) Alper, P. B.; Hendrix, M.; Sears, P.; Wong, C.-H. *J. Am. Chem. Soc.* **1998**, *120*, 1965−1978. (b) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995−3000. (c) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949−951. (d) Hung, S.-C.; Wang, C.-C.; Thopate, S. R. *Tetrahedron Lett.* **2000**, *41*, 3119−3122. (e) Adinolfi, M.; Barone, G.; De Lorenzo, F.; Iadonisi, A. *Synlett* **1999**, 336−338.

(5) Hung, S.-C.; Puranik, R.; Chi, F.-C. *Tetrahedron Lett.* **2000**, *41*, 77−80.

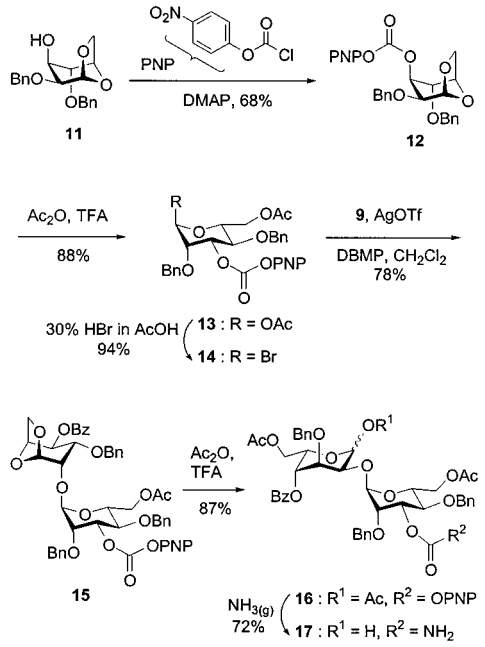
(6) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 4367−4370.

(7) Paulsen, H.; Lebuhn, R. *Liebigs Ann. Chem.* **1983**, 1047−1072.

(8) (a) Černý, M.; Staněk, J. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 23−177. (b) Zottola, M.; Rao, B. V.; Fraser-Feid, B. *J. Chem. Soc.. Chem. Commun.* **1991**, 969−970.

10.1021/ja003508a CCC: $20.00
Published on Web 03/13/2001

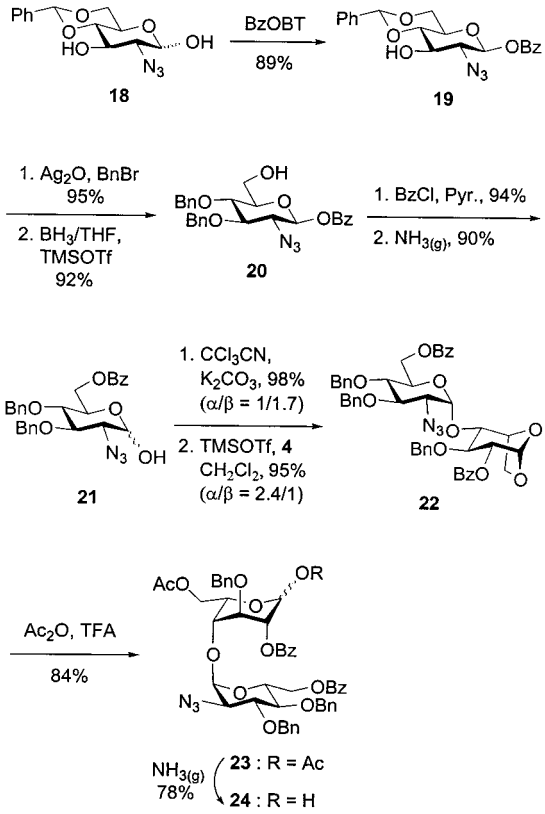
Scheme 2



disaccharide **15** (78%) with α-configuration as determined by the nuclear Overhauser enhancement between the anomeric proton with the benzyl protons at O2 in D-mannopyranosyl unit. Ring opening under acetolysis condition gave the triacetate **16** in 87% yield. One-pot substitution of carbonate and selective anomeric deacetylation with ammonia gas[9] afforded the desired alcohol **17** (72%), which is believed to be a suitable intermediate for the total synthesis of bleomycin A_2, according to the elegant work reported by Hecht and co-workers.[1j]

Application of the synthon **4** in the construction of heparin's disaccharide skeleton is summarized in Scheme 3. Regioselective benzoylation of the diol **18**[10] with benzoyloxybenzotriazole (BzOBT)[11] in Et_3N and CH_2Cl_2 at room temperature led to the 1-β-OBz **19** in 89% yield. Due to the kinetic stereoelectronic effect and 1,3-diaxial repulsion,[12] the anomeric oxide was selectively formed and oriented toward the equatorial position, yielding the β-benzoate as a single anomer. Benzylation[13] and regioselective opening of benzylidene[14] furnished the alcohol **20** in two steps in 87% overall yield. The absolute structures of **19** and **20** were firmly secured by their single-crystal X-ray analyses, respectively (see Supporting Information). Benzoylation (94%) followed by removal of the anomeric benzoyl group (90%) gave the alcohol **21**, which was transformed into the corresponding

Scheme 3



trichloroacetimidate (α/β = 1/1.7, 98%) and further coupled with **4** in the presence of TMSOTf to provide the α-linked disaccharide **22** ($J_{1,2}$ = 3.6 Hz, 60%) and its β-isomer (25%), respectively. The 1,6-anhydro-β-L-idopyranosyl ring of **22** was opened under acetolysis condition, and the diacetate **23** was obtained in 84% yield. Regioselective removal of anomeric acetate afforded the expected alcohol **24** (78%). Its application in the synthesis of heparin-like oligosaccharides is currently under investigation, and the detail results will be published elsewhere.

In conclusion, we have successfully developed a convenient route to prepare the 1,6-anhydro-β-L-hexopyranoses and demonstrated that these L-form sugars offer potent synthons toward the construction of the disaccharide moieties of bleomycin A_2 and heparin.

Acknowledgment. We thank Professor Sunney I. Chan for his helpful discussion and the National Science Council of Republic of China for financial support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and X-ray structural information for compounds **3**, **7**, **10**, **19**, and **20** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA003508A

(9) Dondoni, A.; Marra, A.; Massi, A. *J. Org. Chem.* **1997**, *62*, 6261−6267.
(10) Palme, M.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 959−969.
(11) Kim, S.; Chang, H.; Kim, W. J. *J. Org. Chem.* **1985**, *50*, 1751−1752.
(12) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21−123.
(13) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945−5948.
(14) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355−358.