Efficient Synthesis of Diverse Monosaccharide Derivatives in the Solid Phase

Shū Kobayashi,*,† Takeshi Wakabayashi, and Masaru Yasuda

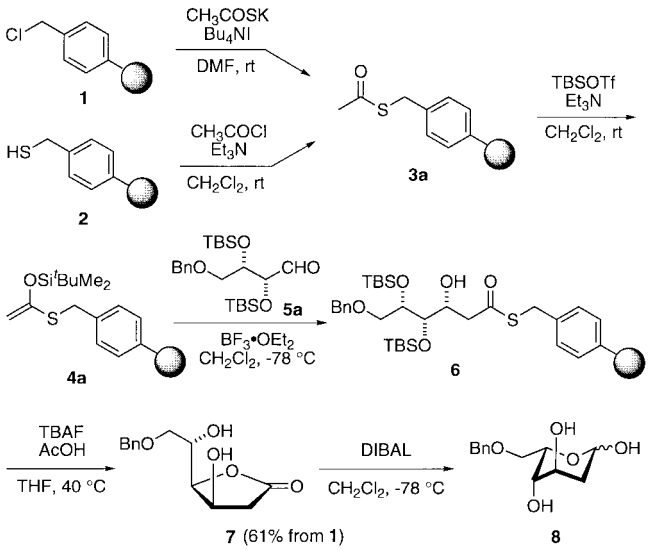
Department of Applied Chemistry, Faculty of Science, Science University of Tokyo (SUT), and CREST, Japan Science and Technology Corporation (JST), Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Received February 18, 1998

While there are many biologically important compounds containing sugars, monosaccharides are the smallest sugar unit and are known to play important roles in their biological activities.[1] To obtain compounds having unique biological activity as well as to refine specific molecular interactions, it is desirable to be able to easily optimize the structure of monosaccharides, and therefore, development of new methods for the synthesis of diverse monosaccharide derivatives is in great demand.

While monosaccharides have rather simple structures, they may contain four, five, six, or seven (higher sugars) asymmetric centers, and the combination of various substituents at each chiral center provides a great number of structurally different monosaccharide derivatives. Three major methods have been reported so far for the synthesis of monosaccharides. The first method is the traditional one, that is, the synthesis of rare sugars from the common sugars such as glucose, mannose, galactose, etc.[2] One drawback of this method is that it requires tedious long transformations and protection and deprotection of the hydroxyl groups of the monosaccharides. The second method is to utilize stereoselective reactions of three-carbon or four-carbon alkoxyaldehydes (glyceraldehyde or threose derivatives prepared from mannitol or tartaric acids) with carbon nucleophiles such as allylmetals or enolates[3] or hetero Diels−Alder reactions.[4] Finally, efficient methods for the synthesis of monosaccharides from simple achiral compounds using asymmetric synthesis have been reported recently.[5] While these syntheses provide useful methods for the preparation of specific rare sugars, much time and manpower are required for the synthesis of a diverse monosaccharide library according to these methods.

Scheme 1. Solid-Phase Synthesis of 6-*O*-Benzyl-2-deoxy-L-gulose (8)



Our approach reported herein is based on solid-phase synthesis.[6] Organic synthesis on solid supports has advantages over conventional liquid-phase approaches in its particularly simple reaction procedures. Therefore, application to automated systems and library construction are promising using solid-phase protocols. An example, the synthesis of a rare sugar, 6-*O*-benzyl-2-deoxy-L-gulose, is shown in Scheme 1. The starting material, chloromethylated resin **1** or thiol resin **2**, was converted to thioester resin **3a**. Treatment of **3a** with *tert*-butyldimethylsilyl triflate (TBSOTf) and triethylamine in dichloromethane at room temperature (rt) provided polymer-supported silyl enol ether (PSSEE) **4a**.[7] A key reaction is the aldol condensation of **4a** with a chiral aldehyde (**5a**) using a Lewis acid promoter,[8] which proceeded smoothly in dichloromethane at −78 °C (20 h) to afford the desired adduct with perfect stereoselectivity (>98/2). Deprotection of the TBS group of the aldol adduct (**6**) using tetrabutylammonium fluoride (TBAF)/acetic acid in THF at 40 °C for 6 h induced spontaneous lactone formation and, hence, cleavage from the polymer support. The yield was determined to be 61% from **1** (four steps) at this stage. It is noted that all transformations in the solid-phase were carried out in one pot. Finally, reduction of **7** with diisobutylaluminum hydride (DIBAL) gave 6-*O*-benzyl-2-deoxy-L-gulose (>80%).

Similarly, four monosaccharide derivatives (lactones) were prepared using the combination of chiral alkoxy aldehydes and PSSEEs in the solid-phase (Scheme 2). The 2-deoxy series and 2-benzyloxy series were prepared from PSSEE **4a** and **4b**, respectively. It is noted that the stereochemistry of the stereogenic center at the C-3 position can be controlled by choice of the protective groups of the alkoxyaldehydes. The diversity of the monosaccharide derivatives obtained according to this protocol depends on the numbers and kinds of alkoxy aldehydes and PSSEEs. We have already reported a preparation method for PSSEEs, according to which various types can be prepared.[7] On the other hand, many alkoxy aldehydes have been synthesized from natural sources such as mannitol and tartaric acid.[3,9] Alternatively, we have developed an efficient method for the synthesis of alkoxy aldehydes using asymmetric aldol reactions. Recently, we have developed tin(II)-mediated highly diastereo- and enan-

† Present address: Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan.

(1) For leading references, see: *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G., Eds.; ACS Symposium Series 386; Amrican Chemical Society: Washington, DC, 1989. Thiem, J.; Klaffke, W. *Top. Curr. Chem.* **1990**, *154*, 285. *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer: Heidelberg, 1990. Kawano, T.; Cui, J.; Koezuka, Y.; Toura, I.; Kaneko, Y.; Motoki, K.; Ueno, H.; Nakagawa, R.; Sato, H.; Kondo, E.; Koseki, H.; Taniguchi, M. *Science* **1997**, *278*, 1626.

(2) For example, see: Prentice, N.; Cundet, L. J.; Smith, F. *J. Am. Chem. Soc.* **1956**, *78*, 4439. Kuhn, R.; Baschang, G. *Liebigs Ann. Chem.* **1960**, *633*, 164.

(3) For example, McGarvey, G. J.; Kimura, M.; Oh, T. *J. Carbohydr. Chem.* **1984**, *3*, 125. Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 265.

(4) For example: Danishefsky, S. J.; DeNinno, M. P. In *Trends in Synthetic Carbohydrate Chemistry*; Horton, D., Hawkins, L. D., McGarvey, G., Eds.; ACS Symposium Series 386; Amrican Chemical Society: Washington, DC, 1989; pp 176−181.

(5) Ko, S. Y.; Lee, W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245. Mukaiyama, T.; Shiina, I.; Kobayashi, S. *Chem. Lett.* **1990**, 2201. Jung, M. E.; Castro, C.; Gardiner, J. M. *Tetrahedron Lett.* **1991**, *32*, 5717. Kobayashi, S.; Kawasuji, T. *Synlett* **1993**, 911.

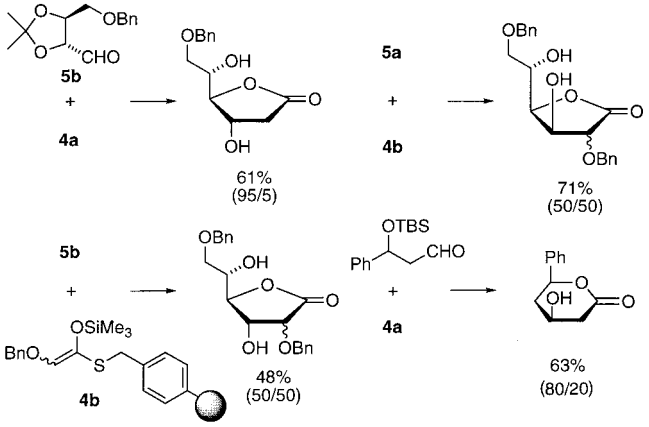
(6) Merrifield, R. R. *J. Am. Chem. Soc.* **1963**, *85*, 2149; Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science* **1993**, *260*, 1307; Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555, and references therein.

(7) Kobayashi, S.; Hachiya, I.; Suzuki, S.; Moriwaki, M. *Tetrahedron Lett.* **1996**, *37*, 2809.

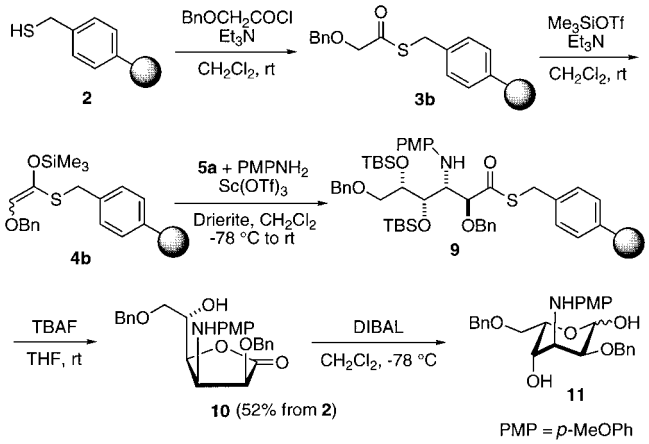
(8) Kobayashi, S.; Hachiya, I.; Yasuda, M. *Tetrahedron Lett.* **1996**, *37*, 5569.

S0022-3263(98)00277-1 CCC: $15.00
Published on Web 06/27/1998

Scheme 2. Synthesis of Monosaccharide Derivatives (Lactones) in the Solid Phase



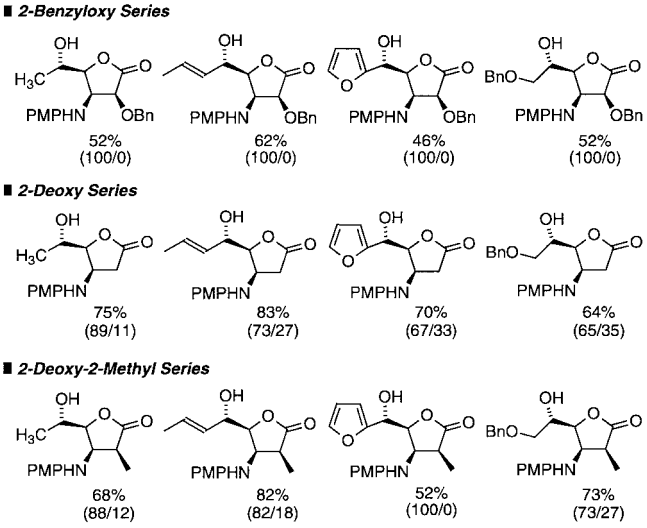
Scheme 3. Solid-Phase Synthesis of 11



tioselective aldol reactions of silyl enol ethers with carbonyl compounds.[10] Various types of β-hydroxy thioesters have been prepared starting from simple achiral compounds using these asymmetric reactions. After protection of the β-hydroxy groups of the aldol adducts, treatment of these protected adducts with DIBAL gave the desired alkoxy aldehydes in excellent yields with excellent diastereo- and enantioselectivities.[11]

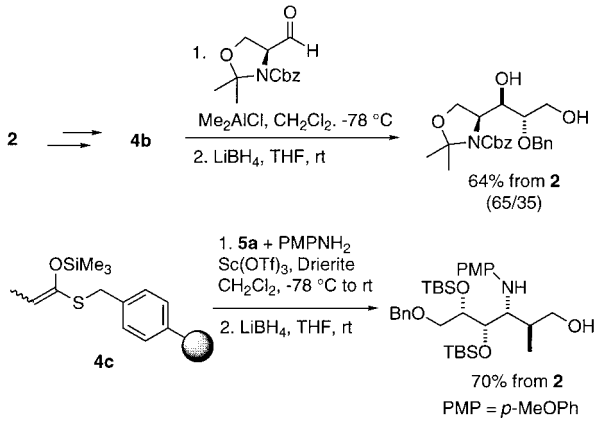
We then synthesized 3-amino sugars in the solid-phase. In nature, there are many biologically interesting compounds containing 3-amino sugars such as daunosamine, acosamine, ristosamine, etc.[12] An example of our solid-phase synthesis of 3-amino sugars is shown in Scheme 3. Thiol resin **2** was converted to thioester resin **3b**, which was silylated to give PSSEE **4b**. The key three-component reaction of an aldehyde, an amine, and **4b** proceeded smoothly in the presence of a catalytic amount of scandium triflate ($Sc(OTf)_3$) in dichloromethane at −78 °C to room temperature over 15 h to afford the corresponding adduct (**9**) with perfect stereoselectivity (>98/2).[13] Also in this case, deprotection of the TBS group (rt, 12 h) induced a spontaneous cyclization to give lactone **10**, which was reduced with DIBAL to produce 3-amino sugar derivative **11** in an 82% yield. Similarly, 2-benzyloxy series, 2-deoxy series, and 2-deoxy-2-methyl series of 3-amino sugars were successfully prepared in the solid phase (Scheme 4).

Scheme 4. Synthesis of 3-Amino Sugar Derivatives (Lactones) in the Solid Phase[a−c]



[a] All yields are from **2**. [b] PMP = *p*-MeOPh. [c] Diastereomer ratios (major/minor) are shown in parentheses.

Scheme 5. Solid-Phase Synthesis of Alditol Derivatives



Finally, the present method was successfully applied to the synthesis of alditol derivatives (the reduced forms of monosaccharides). Reductive cleavage from the support instead of deprotection of the TBS groups gave alditol derivatives in good yields (Scheme 5). Since we have already demonstrated that basic cleavage (NaOMe) from the same support affords carboxylic acids,[8,13] uronic acid (the oxidized forms of monosaccharides) formation would be possible simply by changing the cleavage method.

In summary, a new method for the synthesis of monosaccharide derivatives in the solid phase has been developed. Several transformations in the solid phase have been performed in one pot, and application to an automated system is possible. Moreover, since various kinds of PSSEEs and alkoxyaldehydes are available, this solid-phase synthesis provides a useful method for the synthesis of monosaccharide libraries.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan, and a SUT Special Grant for Research Promotion.

Supporting Information Available: Text describing the experimental procedure and selected physical data of products (7 pages).

JO9802776

(9) Mukaiyama, T.; Yamada, T.; Suzuki, K. *Chem. Lett.* **1983**, 173.
(10) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455. Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472 and references therein.
(11) See the Supporting Information.
(12) Sibi, M. P.; Lu, J.; Edwards, J. *J. Org. Chem.* **1997**, *62*, 5864. Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35.
(13) Kobayashi, S.; Moriwaki, M.; Akiyama, R.; Suzuki, S.; Hachiya, I. *Tetrahedron Lett.* **1996**, *37*, 7783.