ORGANIC LETTERS

2002
Vol. 4, No. 14
2401−2403

# Novel Synthesis of L-Ribose from D-Mannono-1,4-lactone

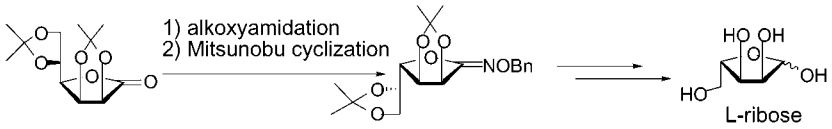
**Hideyo Takahashi, Yoshinori Iwai, Yuko Hitomi, and Shiro Ikegami***

*Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-0195, Japan*

*shi-ike@pharm.teikyo-u.ac.jp*

**Received May 7, 2002**

## ABSTRACT




**D-Mannono-1,4-lactone was efficiently converted into L-ribose in eight steps. A key step of this synthesis is the cyclization of a γ-hydroxyalkoxamate under Mitsunobu conditions. It is noteworthy that the *O*-alkylation product was obtained in 94% yield and that none of the *N*-alkylation product was detected in this cyclization.**

Since Miller reported several efficient biomimetic β-lactam syntheses based on the intramolecular *N*-alkylation of β-hydroxyalkoxamates under Mitsunobu conditions,[1] a considerable number of studies have been conducted on this type of intramolecular cyclization.[2] Recently, we reported the intramolecular *O*-/*N*-alkylation of δ-hydroxyalkoxamates derived from D-glycono-1,5-lactones.[3] In contrast to β-hydroxyalkoxamates, we found that the cyclization of δ-hydroxyalkoxamates resulted mainly in *O*-alkylation rather than *N*-alkylation. Taking advantage of the structural relationship between D-glucose and L-idose, D-galactose and L-altrose, and D-mannose and L-gulose, we utilized the *O*-alkylated products, which had the inverted stereochemistry at C5, as precursors for the corresponding L-sugars and developed a novel, practical synthesis of the rare L-pyranoses (Scheme 1).

These successful results prompted us to investigate the intramolecular *O*-/*N*-alkylation of the γ-hydroxyalkoxamate derived from D-mannono-1,4-lactone in the hope of developing a practical synthesis of L-ribofuranose. In the past decade, the number of reports of L-nucleosides[4] has increased dramatically due to their potent biological activity as antiviral agents.[5] Thus, an efficient method of producing the rare sugar, L-ribofuranose, would be extremely beneficial.[6] Herein we describe the novel and practical conversion of D-mannono-1,4-lactone into L-ribose. The key feature of the sequence is *O*-alkylation of γ-hydroxyalkoxamates with inversion of the stereochemistry at C4 under Mitsunobu conditions.

As shown in Scheme 2, the readily available 2,3,5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone[7] **5** was first converted into the γ-hydroxyalkoxamate **6**. Treatment of **5** with *O*-benzylhydroxyamine (1.4 equiv) in $CH_2Cl_2$ for 30 min,

(1) (a) Mattingly, P. G.; Kerwin, J. F., Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983−3985. (b) Morrison, M. A.; Miller, M. J. *J. Org. Chem.* **1983**, *48*, 4421−4423. (c) Miller, M. J.; Mattingly, P. G. *Tetrahedron* **1983**, *39*, 2563−2570. (d) Farouz, F.; Miller, M. J. *Tetrahedron Lett.* **1991**, *32*, 3305−3308.

(2) For a discussion of *O*-/*N*-alkylation selectivity in Mitsunobu reactions of various amides and carbamates, see: (a) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. Jr. *J. Am. Chem. Soc.* **1980**, *102*, 7026−7032. (b) Bose, A. K.; Sahu, D. P.; Manhas, M. S. *J. Org. Chem.* **1981**, *46*, 1229−1230. (c) Krook, M. A.; Miller, M. J. *J. Org. Chem.* **1985**, *50*, 1126−1128. (d) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807−2810. (e)Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267−6270. (f) Koppel, I.; Koppel, J.; Koppel, I.; Leito, I.; Pihl, V.; Wallin, A.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 2* **1993**, 655−658.

(3) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995−3000.

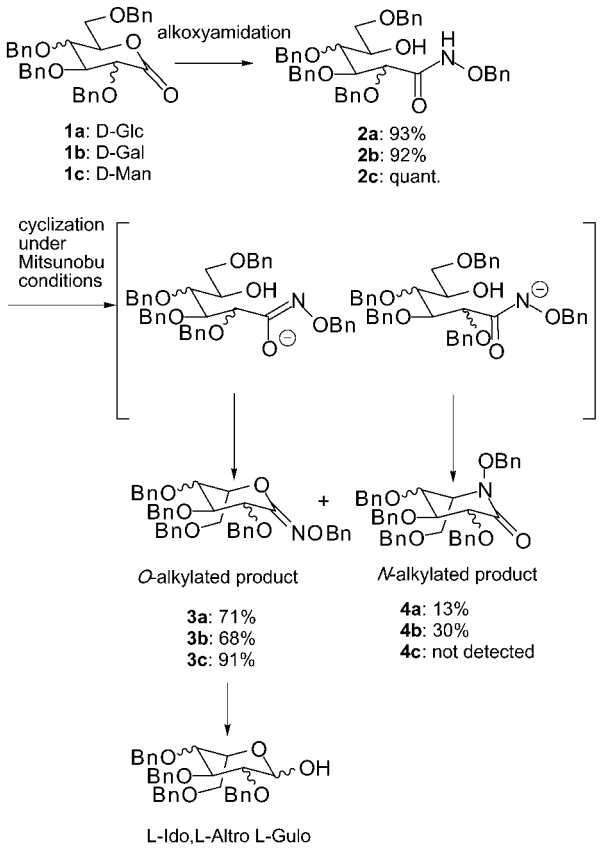
(4) L-RNA: (a) Ashley, G. W. *J. Am. Chem. Soc.* **1992**, *114*, 9731−9736. L-DNA: (b) Damha, M. J.; Giannaris, P. A.; Marfey, P. Biochemistry **1994**, *33*, 7877−7885. (c) Hashimoto, Y.; Iwanami, N.; Fujimori, S.; Shudo, K. *J. Am. Chem. Soc.* **1993**, *115*, 9883−9887. (d) Fujimori, S.; Shudo, K.; Hashimoto, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7436−7438.

(5) Mansuri, M. M.: Farina, V.; Starrett, J. E. Jr.; Benigni, D. A.; Brankovan, V.: Martin, J. C. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 65−68

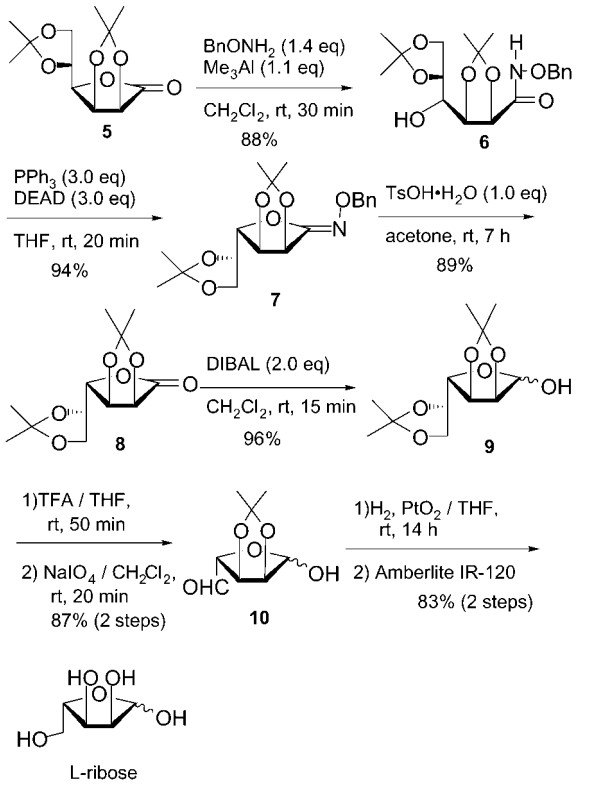
(6) For other syntheses of L-ribose, see: (a) Shi, Z.-D.; Yang, B.-H.; Wu, Y.-L. *Tetrahedron Lett.* **2001**, *42*, 7651−7653. (b) Sivets, G. G.; Klennitskaya, T. V.; Zhernosek, D. V.; Mikhailopulo, I. A. *Synthesis* **2002**, 253−259. (c) Jung, M. E.; Xu, Y. *Tetrahedron Lett.* **1997**, *38*, 4199−4202.

10.1021/ol026141i CCC: $22.00 
**Published on Web 06/18/2002**

**Scheme 1.** Synthesis of L-Pyranoses from D-Glycono-1,5-lactones




**Scheme 2.** Synthesis of L-Ribose from D-Mannono-1,4-lactone




followed by addition of $Me_3Al$ (1.1 equiv) at room temperature, afforded the corresponding $\gamma$-hydroxybenzyloxamate **6** in 88% yield.[8] We next examined the cyclization of **6** under Mitsunobu conditions[9] (3.0 equiv of TPP and 3.0 equiv of DEAD[10]). Fortunately, **7** was obtained as the sole product in 94% yield. It is noteworthy that none of the *N*-alkylated product was detected. Treatment of the *O*-cyclized oxime compound **7** with *p*-TsOH monohydrate (1.0 equiv) in acetone at room temperature gave L-gulono-1,4-lactone **8** in 89% yield. Compound **8** crystallized, and the inversion of stereochemistry at C4 was shown by X-ray crystallography. The carbonyl moiety of **8** was reduced by excess DIBAL to provide 96% of 2,3,5,6-di-*O*-isopropylidene-L-gulofuranose **9**. Compound **9** was partially hydrolyzed to the diol, which was treated with $NaIO_4$ to provide **10** in 87% yield. Of the methods examined for the reduction of the aldehyde moiety of **10**, hydrogenolysis using $PtO_2$ as a catalyst gave the best results. Finally, acidic hydrolysis to deprotect the isopropylidene group afforded L-ribose in 83% yield from **10**. Thus, the conversion of D-mannono-1,4-lactone to L-ribose was accomplished efficiently in 50% overall yield.

Having obtained these successful results, we next turned our attention to the ratio of *O*-/*N*-alkylated products in the reaction of $\gamma$-hydroxyalkoxamates under Mitsunobu conditions. In a previous paper, we reported that the significant difference in the ratios of *O*-/*N*-alkylation was dependent on the stereochemistry of the D-sugars: the $\delta$-hydroxyalkoxamates (**2a**, **2b**) derived from D-glucono-1,5-lactone **1a** and D-galactono-1,5-lactone **1b** provided a mixture of *O*-/*N*-alkylated products, whereas the $\delta$-hydroxyalkoxamate **2c** derived from D-mannono-1,5-lactone **1c** afforded the *O*-cyclized compound **3c** as the sole product. As for the $\gamma$-hydroxyalkoxamate **6**, we observed complete specificity for the *O*-alkylated product **7** as shown in the above synthesis. Next, we carried out studies on the selectivity of the *O*-/*N*-alkylation using different protective groups in order to determine if the configuration of the $\gamma$-hydroxyalkoxamates was important (Scheme 3).

The $\gamma$-hydroxyalkoxamate **11** derived from 2,3-di-*O*-methoxymethyl-D-mannono-1,4-lactone was easily converted into the *O*-alkylated product **12**. Similarly, the reaction of the $\gamma$-hydroxyalkoxamate **13** derived from 2,3-di-*O*-benzyl-D-mannono-1,4-lactone proceeded to give the *O*-alkylated product **14**. It is interesting to note that no *N*-alkylated

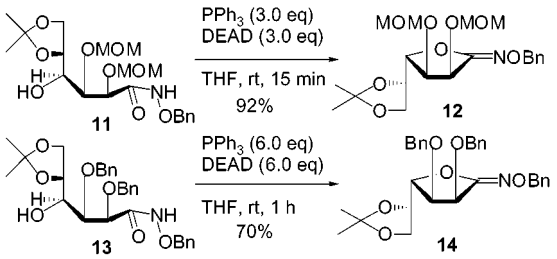
(7) (a) Standring, D. N.; Bridges, E. G.; Placidi, L.; Faraj, A.; Loi, A. G.; Pierra, C.; Dukhan, D.; Gosselin, G.; Imbach, J.-L.; Hernandez, B.; Juodawlkis, A.; Tennant, B.; Korba, B.; Cretton-Scott, E.; Schinazi, R. F.; Myers, M.; Bryant, M. L.; Sommadossi, J.-P. *Antiviral Chem. Chemother.* **2001**, *12*, 119−129. (b) Anderson, K. S. *Antiviral Chem. Chemother.* **2001**, *12*, 13−17. (c) Gumina, G.; Song, G.-Y.; Chu, C. K. *FEMS Mirobiol. Lett.* **2001**, *202*, 9−15. (d) Chen, S.-H. *Front. Biotechnol. Pharm.* **2001**, *2*, 307−328. (e) Graciet, J.-C. G.; Schinazi, R. F. *Adv. Antiviral Drug Des.* **1999**, *3*, 1−68.

(8) We found that the later addition of $Me_3Al$ resulted in more enormous acceleration of the reaction than the use of the preceding formation of $Me_3$-Al-alkoxyamine complex to be considered as an active species. For earlier studies on amidation, see: Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174.

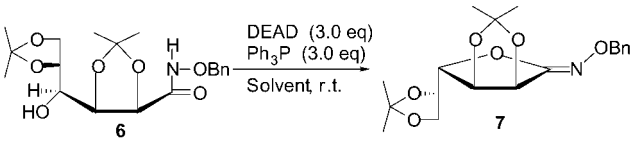
(9) Review: Mitsunobu, O. *Synthesis* **1981**, 1−28.

(10) To execute the reaction completely, excess amount of Mitsunobu reagent is used.

**Scheme 3.** Effect of Protective Groups on the Ratio of *O*-/*N*-Alkylation




**Scheme 4.** Solvent Effect on Selectivity of *O*-/*N*-Alkylation




| Entry | Solvent | Time | Yield |
|---|---|---|---|
| 1 | THF | 20 min | 93.7 % |
| 2 | toluene | 20 min | 89.4 % |
| 3 | $CH_2Cl_2$ | 20 min | 88.6 % |
| 4 | DMSO | 60 min | 74.3 % |

product was detected in either case. These results indicated that the steric requirement of the protective groups at C2 and C3 did not affect the selectivity of the *O*-/*N*-alkylation. We next investigated the effect of solvent on this cyclization (Scheme 4).

The reactions proceeded smoothly in all solvents (THF, toluene, $CH_2Cl_2$, DMSO) and provided the *O*-alkylated product **7** in good yields: the *N*-alkylated product was never observed. It must be recalled here that the *δ*-hydroxyalkoxamate **2c** derived from the D-mannono-1,5-lactone **1c** gave similar results: none of the *N*-alkylated product was detected in that case. One explanation for this result may be that the axially oriented substituent at C2 in mannose causes the *O*-alkylation under Mitsunobu conditions to be much more favorable.

In conclusion, we have established a novel and efficient method for the conversion of D-mannono-1,4-lactone into L-ribose. This is the first application of the Mitsunobu-type cyclization for the synthesis of an L-furanose. Work on the transformation of D-sugars to other L-sugars based on similar concepts and controlling the ratios of *O*-/*N*-alkylation are in progress.

**Acknowledgment.** We thank Dr. Moto Shiro, Rigaku Corp., Matsubara, Akishima, Tokyo, for providing X-ray crystallographic data. We are grateful to Misses J. Shimode and M. Kitsukawa for spectroscopic measurements. The generous financial support for this research from the Ministry of Education, Science, Sports and Culture of Japan, The Fujisawa Foundation, and Hayashi Memorial Foundation for Female Natural Scientists is gratefully acknowledged.

**Supporting Information Available:** Representative experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026141I