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New Method for the Preparation of L-Gulose from D-Mannose: Synthetic Study on the Sugar Moiety of Bleomycin

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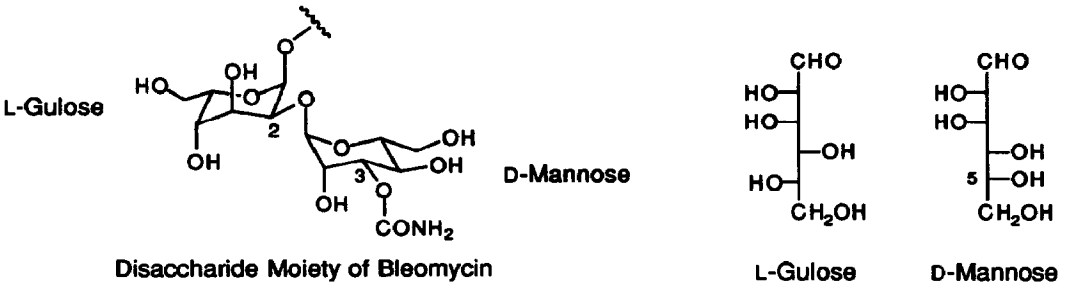
Abstract: *L-Gulose, a key building block of the carbohydrate moiety of antitumor antibiotic bleomycins, is prepared from D-mannose by the inversion at C-5 .*

Antitumor antibiotic bleomycin possesses a quite unique disaccharide moiety, 2-*O*-(3-*O*-carbamoyl-D-mannopyranosyl)-L-gulopyranose. In order to investigate the role of this moiety,[2] it became necessary to develop an efficient method for the preparation of L-gulose. Although several routes to L-gulose have already been reported starting from L-gulono-1,4-lactone or D-glucose,[3] we were interested in the novel route from D-mannose involving the inversion at C-5. (Scheme 1)

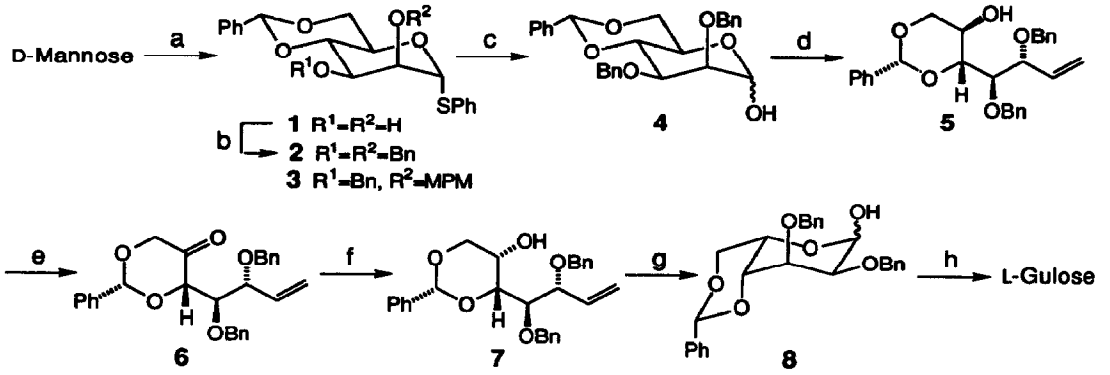
Scheme 1



4,6-*O*-Benzylidene-D-mannothioglycoside **1**, prepared from D-mannose (4 steps, 44% overall yield) was converted to the hemiacetal **4** by benzylation followed by the hydrolysis of thioglycoside in 66% yield. The reaction of **4** with phosphonium ylide generated the free hydroxyl group at C-5[4] with the concurrent protection of the C-1 formyl group as vinyl group,[5] and the resulting β-dioxanol **5** (65% yield, 80% conversion) was oxidized to dioxanone **6** by Swern oxidation. It was anticipated that the reduction of **6** would proceed through the hydride attack from the less hindered β-face to give the desired α-dioxanol **7**. As expected α-dioxanol **7**[6] was exclusively formed by the L-Selectride reduction of **6** in 75% yield (2 steps).[7] Stereochemistry of this compound was determined by the ^{1}H-NMR spectrum[6] as well as the significant NOE observed between the C-4 and the C-5[4] protons. Ozonolysis of the vinyl group generated the aldehyde which was isolated as hemiacetal **8** as an anomeric mixture in 86% yield. In order to further confirm the stereochemistry of **8**, this was deprotected to L-gulose, which was identical with the authentic sample.

Since we also succeeded in obtaining the 2-*O*-MPM derivative **3**,[8] the present methodology would provide an efficient access to the disaccharide moiety of bleomycin. Investigations along this line are under way in our laboratory.

Scheme 2



Reagents and Conditions: **a**: (i) Ac_2O, Pyridine; (ii) PhSH, $SnCl_4$, CH_2Cl_2; (iii) NH_3, MeOH; (iv) $PhCH(OMe)_2$, HBF_4, DMF (overall 44%). **b**: BnBr, NaH, DMF (quant.). **c**: NBS, aq.CH_3CN (66%). **d**: nBuLi (1 equiv.), then $Ph_3P{=}CH_2$ (65%, 80% conversion). **e**: $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2. **f**: LiB(*sec*-Bu)$_3$H, THF, -78 °C (75% from **5**). **g**: O_3, MeOH, -78 °C, then Me_2S (86%). **h**: $Pd(OH)_2$, H_2, MeOH, 10 atm (53%).

References and Notes

1. On leave from Faculty of Pharmaceutical Sciences, University of Tokyo.
2. (a) Sugiura, Y.; Suzuki, T.; Otsuka, M.; Kobayashi, S.; Ohno, M.; Takita, T.; Umezawa, H. *J. Biol. Chem.* **1983**, *258*, 1328-1336. (b) Otsuka, M.; Nishio, T.; Oshitari, T.; Owa, T.; Sugiura, Y.; Maeda, K.; Ohno, M.; Kobayashi, S. *Heterocycles* **1992**, *33*, 27-34. (c) For review, see: Stubbe, J ;Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107-1136.
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4. The carbon numbers are expressed according to the carbohydrate numbering in this paper.
5. For Wittig reaction of hemiacetal with metylenetriphenylphosphorane, see: Pougny, J. -R.; Nassr, M. A. M.; Sinaÿ, P. *J. Chem. Soc. Chem. Commun.* **1981**, 375-376.
6. **7**: mp 101-2°C (Et_2O-hexane). $[\alpha]_D^{20}$ -30.6 (c 1.0, $CHCl_3$). ^{1}H-NMR (400MHz, $CDCl_3$); δ 3.12 (1H, d, *J*=9.6Hz), 3.65 (1H, dddd, *J*=1.1, 1.5, 2.0, 9.6Hz), 3.97 (1H, dd, *J*=4.3, 7.3Hz), 4.00 (1H, dd, *J*=1.5, 11.9Hz), 4.03(1H, dd, *J*=1.1, 7.3Hz), 4.12 (1H, dd, *J*=4.3, 8.1Hz), 4.18 (1H, dd, *J*=2.0, 11.9Hz), 4.43 (1H, d, *J*=11.8Hz), 4.66 (1H, d, *J*=11.8Hz), 4.75 (1H, d, *J*=11.1Hz), 4.80 (1H, d, *J*=11.1Hz,), 5.35 (1H, ddd, *J*=0.8, 1.7, 17.3Hz), 5.40 (1H, ddd, *J*=0.6, 1.7, 10.3Hz), 5.57(1H, s), 6.05(1H, ddd, *J*=8.1, 10.3, 17.3Hz), 7.23-7.40 (13H), 7.50 (2H). Anal; calcd. for $C_{28}H_{30}O_5$ C:75.31 H:6.77, found C:75.33 H:6.75.
7. In sharp contrast, reduction with other reducing reagents such as $NaBH_4$ and DIBAL proceeded in rather non-stereoselective manner with the predominant formation of β-dioxanol **5** (ratio *ca.* 7:3~8:2).
8. **3** was obtained by selective monobenzylation at C-3 hydroxyl group through the stannylene acetal of **1**, followed by *p*-methoxybenzylation at the remaining hydroxyl group at C-2 (86% overall yield). For selective benzylation of stannylene acetal, see: Nagashima, N; Ohno, M. *Chem. Lett.* **1987**, 141-144.

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