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Preparation of 2-*O*-(3-*O*-Carbamoyl-α-D-mannopyranosyl)-L-gulopyranose: Synthetic Study on the Sugar Moiety of Antitumor Antibiotic Bleomycin

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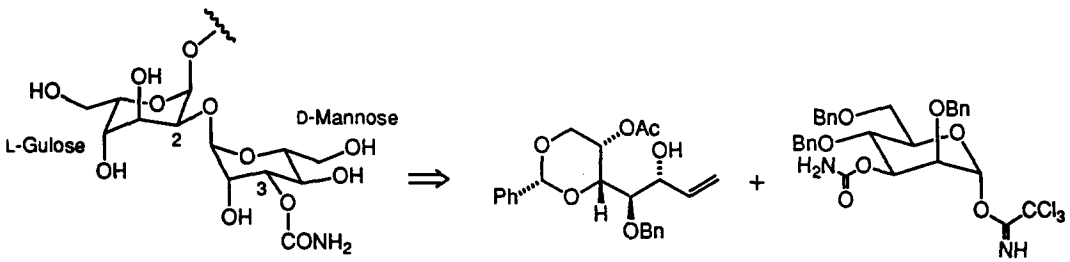
Abstract: *A new practical route to the disaccharide moiety of bleomycin was developed. Both of key building blocks* ***9*** *and* ***16*** *were prepared from* D*-mannose in a regioselective manner by applying stannylene acetal methodology. Glycosylation of the allyl alcohol* ***9*** *with the trichloroacetimidate* ***16*** *proceeded smoothly, and the further incorporation to the disaccharide moiety was successfully accomplished.*

Antitumor antibiotic bleomycin[2] has quite unique disaccharide moiety, 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose. In order to investigate the role of this moiety[3], it became necessary to develop a practical method of the preparation of L-gulose equivalent and 3-*O*-carbamoyl-D-mannose.



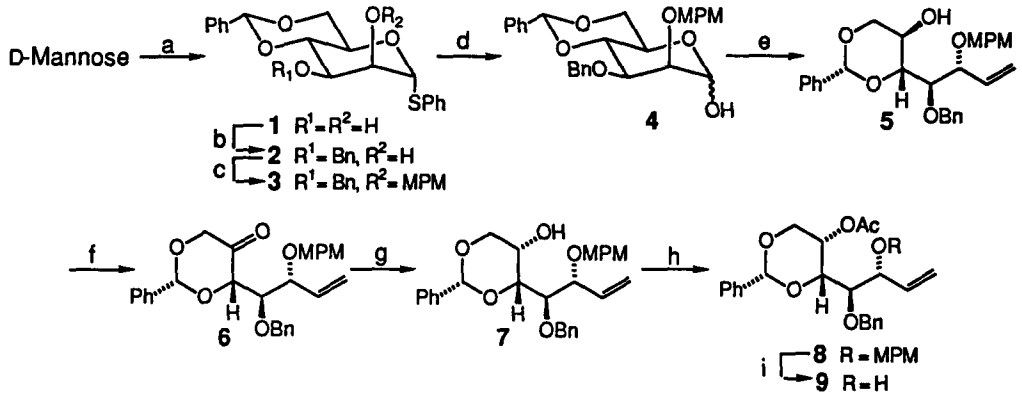
Disaccharide Moiety of Bleomycin

Recently Boger and coworkers reported the total synthesis of bleomycin A_2.[4] During the course of their synthesis, they developed a stereoselective conversion of D-mannose to L-gulose derivative by Rh(I)-catalyzed hydroboration of 6-deoxy-hex-5-enopyranoside derivative.[4d] This prompts us to disclose our own results on the carbohydrate moiety of bleomycin.

In the previous paper[5] we reported a novel method for the conversion of D-mannose to L-gulose. The inversion of the stereochemistry at mannose C-5 was achieved through oxidation-reduction method. Described herein are (1) application of our methodology for the preparation of properly protected L-gulose equivalent, (2) regioselective introduction of carbamoyl group onto mannose C-3 hydroxyl, and finally (3) coupling of each fragment and the further incorporation to the disaccharide moiety of bleomycin.

Scheme 1 shows the preparation of L-gulose equivalent. It was necessary to distinguish the gulose C-2 hydroxyl group for introduction of D-mannose portion, and for this purpose CsF-mediated regioselective alkylation of stannylene acetal[6] was adopted.

Scheme 1

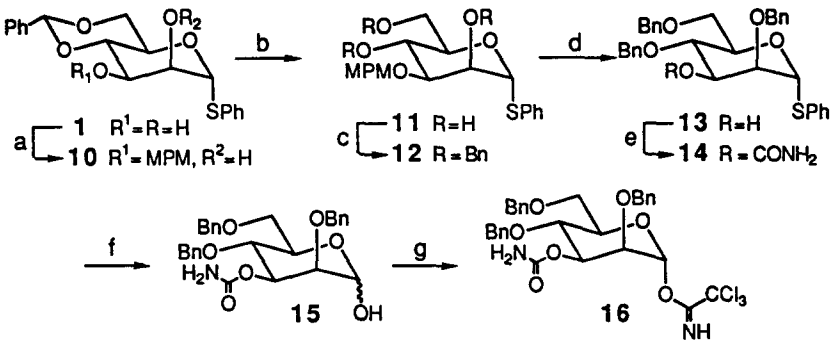


Reagents and Conditions: **a** (i) Ac_2O, Pyridine; (ii) PhSH, $SnCl_4$, CH_2Cl_2; (iii) NH_3, MeOH; (iv) $PhCH(OMe)_2$, HBF_4, DMF (overall 44%), **b** *n*-Bu_2SnO, PhMe, reflux; BnBr, CsF, DMF (91%), **c** NaH, MPMCl, DMF (98%), **d** NBS, aq.acetone (50%, 90% conversion), **e** $Ph_3P^+CH_3\ Br^-$ (2.7 equiv.), *n*-BuLi (2.5 equiv.) (66%), **f** $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, **g** LiB(*sec*-Bu)$_3$H, THF, -78 °C (83% from **5**), **h** Ac_2O, Pyridine (94%), **i** DDQ, aq.CH_2Cl_2 (91%).

Thus, 4,6-*O*-benzylidene-D-mannothioglycoside **1**, prepared from D-mannose (4 steps, 44% overall yields), was converted to 3-*O*-benzyl-2-*O*-MPM derivative **3** through selective benzylation of the stannylene acetal of **1** followed by *p*-methoxybenzylation at the remaining hydroxyl group at C-2. After oxidative hydrolysis of phenylthioglycoside, the resulting hemiacetal **4** was reacted with phosphonium ylide to obtain the hydroxyolefin **5**. It was expected that the protection of the C-1[7] formyl group as vinyl group would result in increasing a nucleophilicity of the hydroxyl group at C-2[7]. The β-dioxanol **5** was oxidized to dioxanone **6** by Swern oxidation. L-Selectride reduction of **6** gave the desired α-dioxanol **7** as a single isomer in 83% yield from the β-dioxanol **5**. Protection of C-5 hydroxyl group as an acetate followed by oxidative hydrolysis of MPM ether[8] provided the allyl alcohol **9**[9], which serves as the glycosyl acceptor for the disaccharide formation.

The synthesis of 3-*O*-carbamoyl-α-D-mannose portion is shown in Scheme 2. The stannylene acetal method was again employed to distinguish the C-3 hydroxyl of mannose. In this case MPM group was introduced into *O*-3. Alkylation of the stannylene acetal with MPMBr (generated *in situ* from MPMCl and *n*-Bu_4NBr) and CsF afforded 3-*O*-MPM ether **10** in 94% yield. Deprotection of benzylidene acetal followed by benzylation of the triol gave **12**. After oxidative cleavage of MPM group, the resulting alcohol **13** was converted to the 3-*O*-carbamoyl derivative **14** by the conventional method (*p*-$NO_2C_6H_4OCOCl$, Et_3N, then NH_3). Oxidative hydrolysis of thioglycoside with NBS afforded the hemiacetal **15**, which was converted to the trichloroacetimidate **16**[9] by treatment with trichloroacetonitrile and a catalytic amount of DBU.

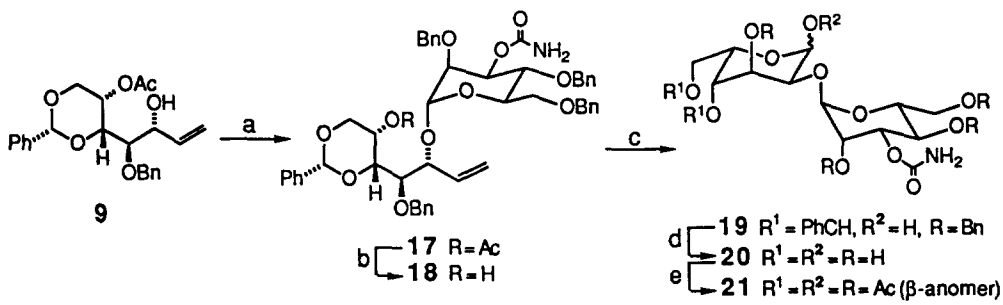
Scheme 2



Reagents and Conditions: **a** *n*-Bu_2SnO, PhMe, reflux; MPMCl, *n*-Bu_4NBr, CsF, DMF (94%), **b** 1%H_2SO_4 in MeOH, 0°C, 45 min (90%), **c** NaH, BnBr, DMF (99%), **d** DDQ, aq.CH_2Cl_2, rt, 2.5 hr (83%), **e** *p*-$NO_2C_6H_4OCOCl$, Et_3N, 4-DMAP, THF; NH_3 (92%), **f** NBS, aq.acetone (74%), **g** CCl_3CN, DBU(cat.) (92%).

As expected, glycosylation of the allyl alcohol **9** with the trichloroacetimidate **16** proceeded smoothly at -15°C within 10 minutes to obtain the desired α-mannosyl derivative **17** in 84% yield. After deprotection of the acetate, **18** was subjected to ozonolysis to obtain **19** as an anomeric mixture (α:β=*ca* 2:1). Hydrogenolysis using $Pd(OH)_2$ gave free 2-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulose **20**[9], which was converted to heptaacetate **21** as a single isomer (β-anomer; $J_{1,2}$=8.4 Hz). Spectral data ($[\alpha]_D$, MS, ^1H and ^{13}C NMR) of **21**[9] were identical to those reported by Bogar *et al.*[4d]

Scheme 3



Reagents and Conditions: **a** **16** (1.2 equiv), BF_3-OEt_2 (2.0 equiv), CH_2Cl_2, -15 °C, 10 min (84%), **b** K_2CO_3, MeOH, 60°C, 10 min (93%), **c** O_3, MeOH, -78 °C; Me_2S (94%) **d** 20% $Pd(OH)_2$ on carbon (cat), H_2, MeOH, 5 hr (97%), **e** Ac_2O, Pyridine (92%).

In conclusion, we have developed a new practical route to the disaccharide moiety of bleomycin. The key features of the present synthesis are as follows: (1) olefination of C-1 formyl group of **4** not only served as the temporal protection but also increased the nucleophilicity of the hydroxyl group at gulose *O*-2; and that (2) stannylene acetal methodology was successfully applied for the preparation of both fragments.

Acknowledgement

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8. (a) For the oxidative cleavage, see Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* , **1986**, *42*, 3021-3028. (b) Without protection of the free hydroxyl, DDQ oxidation of **7** afforded the 3,5,9,11-tetraoxabicyclo[5.4.0]undecane derivative instead of the desired diol. For a related intramolecular acetalization, see Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.*, **1983**, *24*, 4037-4040.
9. **9**: $[a]_D^{20}$ +22.5° (*c* 1.12, $CHCl_3$), IR(neat) 3452, 3034, 2862, 1738, 1454 cm^{-1}; CI-MS *m/z* 399 ($M+H^+$); ^{1}H-NMR (400MHz, $CDCl_3$) δ 2.18 (3H, s), 2.36 (1H, br), 3.93 (1H, dd, *J*=3.7, 8.4 Hz), 4.04 (1H, dd, *J*=1.6, 13.1 Hz), 4.09 (1H, m), 4.12 (1H, dd, *J*=1.6, 8.4 Hz), 4.31 (1H, dd, *J*=1.6, 13.1 Hz), 4.69 (1H, d, *J*=11.3 Hz), 4.80 (1H, ddd, *J*=1.6, 1.6, 1 6 Hz), 4.95 (1H, d, *J*=11.3 Hz), 5.26 (1H, ddd, *J*=1.1, 1.2, 10.4 Hz), 5.35 (1H, ddd, *J*=1.2, 1.2, 17.3 Hz), 5.63 (1H, s), 5.97 (1H, ddd, *J*=7.2, 10.4, 17.3 Hz), 7.27-7.41 (8H, m), 7.52 (2H, m); Anal calcd. for $C_{23}H_{26}O_6$ C: 69.33 H: 6.58, found C: 69.09 H: 6.54. **16**: IR (neat) 3493, 3381, 3339, 3032, 2918, 2870, 1728, 1672, 1599, 1496, 1454, 1358, 1278, 1101, 1064, 970, 925, 835, 796, 736, 698, 646 cm^{-1}; ^{1}H-NMR (400MHz, $CDCl_3$) δ 3.72 (1H, dd, *J*=1.9, 11.3Hz), 3.82 (1H, dd, *J*=4.0, 11.3Hz), 4.03 (1H, ddd, *J*=1.9, 4.0, 9.7Hz), 4.12 (1H, dd, *J*=2.4, 3.3 Hz), 4.14 (1H, dd, *J*=9.0, 9.7Hz), 4.52 (1H, d, *J*=12.0 Hz and 1H, d, *J*=11.1 Hz), 4.60-4.71 (5H, m), 4.76 (1H, d, *J*=12.1 Hz), 5.21 (1H, dd, *J*=3.2, 9.0 Hz), 6.37 (1H, d, *J*=2.4 Hz), 7.20-7.38 (15H, m), 8.59 (1H, s).
20: ^{13}C-NMR (100MHz, $CDCl_3$) of the major anomer δ 60.5, 60.8, 63.9, 67.7, 68.5, 69.1, 72.5, 73.1, 73.5, 74.2, 92.4, 96.6, 157.6; ^{13}C-NMR (100MHz, $CDCl_3$) of the minor anomer δ 60.7, 64.1, 65.3, 68.6, 69.4, 69.7, 71.3, 73.1, 73.3, 74.1,93.1, 99.6, 157.5; SIMS (NaCl, 3-NBA) *m/z* 408 (M^++Na). The specific rotation of **21**: $[a]_D^{20}$ +35.5° (*c* 0.95, $CHCl_3$); lit.[4d] $[a]_D^{25}$ +35.4° (*c* 0.07, $CHCl_3$).

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