The New and Efficient Synthesis of a Heptose Moiety of Spicamycin

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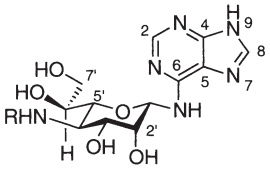
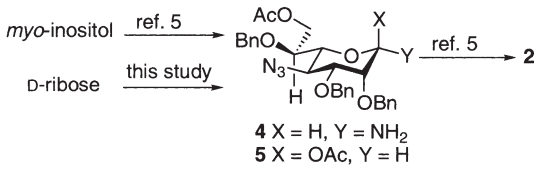
The new and efficient synthesis of 7-*O*-acetyl-4-azido-2,3,6-tri-*O*-benzyl-4-deoxy-L-*glycero*-α-L-*manno*-heptopyranosyl acetate (**5**), a key intermediate for the synthesis of novel anti-cancer antibiotic, spicamycin (**1**), starting from D-ribose is described.

Spicamycin (**1**), isolated by Hayakawa and co-workers from culture broth of *Streptomyces* as a differentiation inducer of HL-60 human promyelocytic leukemia cells, have been reported to show high anti-cancer activities.[1] Spicamycin consists of a novel aminoheptose (4-amino-4-deoxy-L-*glycero*-L-*manno*-heptopyranose), adenine, glycine, and fatty acids. Numerous spicamycin derivatives possessing various fatty acid moieties were prepared[2,3] from spicamycin amino nucleoside **3** (SAN, obtained by acid hydrolysis of natural spicamycin) to generate clinically promising compounds, SPM VIII[2] **2** and KRN 5500.[4]



R = $Me_2CH(CH_2)_nCONHCH_2CO$- or
$MeCH_2CH_2(CH_2)_nCONHCH_2CO$- (n = 8~14):
Spicamycin (**1**)
R = $Me(CH_2)_{10}CONHCH_2CO$-: SPM VIII (**2**)
R = $Me(CH_2)_8CH{=}CHCH{=}CHCONHCH_2CO$-: KRN 5500
R = H: Spicamycin Amino Nucleoside (SAN) (**3**)

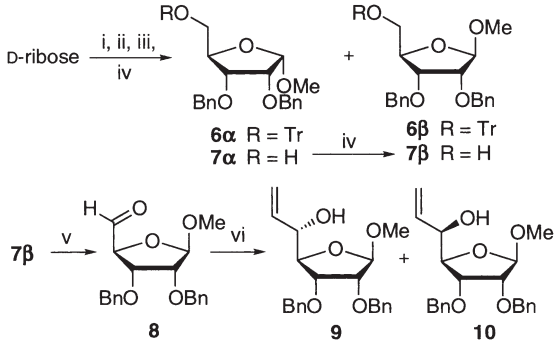
Recently, we reported the first total synthesis of one of spicamycin congeners, SPM VIII **2**,[5] in which Pd-catalyzed coupling reaction[6] of heptopyranosylamine **4** with a 6-chloropurine derivative was employed as the key transformation, and successfully confirmed its proposed absolute structure.[1] The novel heptopyranosylamine **4** with L-*glycero*-L-*manno* configuration was synthesized by stereoselective introduction of an amino function into α-pyranosyl acetate **5**, which was prepared from naturally abundant cyclitol, *myo*-inositol[5] (Scheme 1). Although the first (and to date only) synthesis of **5** from *myo*-inositol, which involved the optical resolution during the synthetic process, was useful for the determination of the synthetically unconfirmed absolute stereochemistry of the natural product, it is now required for us to develop more practical synthetic way to **5** for the large-scale preparation and structure-activity relationship study of novel spicamycin derivatives. It is also an important task to establish an effective synthetic route to heptopyranoses from readily available material, since several seven-carbon sugars structurally related to **5** are known to be constituents of biologically significant antibiotic (septacidin)[7a] and lipopolysaccharides.[7b] In this paper, we report a new and efficient synthesis of **5** starting from D-ribose.



4 X = H, Y = NH_2
5 X = OAc, Y = H

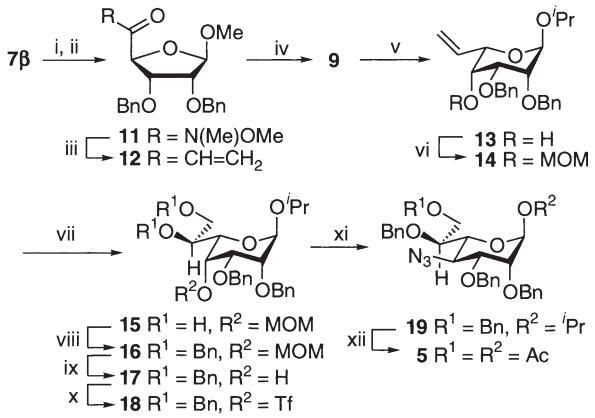
Scheme 1. Bn = $-CH_2Ph$.

The known methyl 2,3-di-*O*-benzyl-β-D-ribofuranoside[8] (**7β**), chosen as the starting material, was prepared from D-ribose in 4 step reactions (Scheme 2). Thus, *O*-benzylation of an anomeric mixture of methyl 6-*O*-trityl-α- and β-riborufanosides (obtained from D-ribose in quantitative yield, α:β = 1:3.7), followed by chromatographic separation afforded **6β** and **6α** in 74% and 20% isolated yields, respectively. Deprotection of a trityl ether in **6β** with *p*-TsOH in MeOH gave **7β** in 91% yield along with the isomerized product **7α** in 4% yield. Similar treatment of **6α** also gave **7β** (90%) and **7α** (9%), respectively, and further amount of **7β** was obtained in 88% yield by acid-catalyzed isomerization of **7α**. An aldehyde **8**[9] derived from alcohol **7β** by Swern oxidation (94%) was subjected to the two-carbon homologation by reactions with vinylmagnesium bromide or vinyllithium. However, low yields of the desired product **9** and observed poor stereoselectivities (up to 65% combined yields, **9**:**10** = 1:3–1.3:1) led us to explore other approaches.



Scheme 2. Tr = $-CPh_3$. *Reagents and conditions*: i HCl–MeOH, 0 °C; ii TrCl, pyridine, DMAP, rt; iii BnCl, NaH, DMF, rt; iv *p*-TsOH·H_2O, MeOH, rt; v DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C to −50 °C then Et_3N, −50 °C; vi $CH_2{=}CHMgBr$ or $CH_2{=}CHLi$.

Jones oxidation of **7β**, followed by condensation with MeONHMe·HCl provided Weinreb's amide **11** in 80% yield from **7β** (Scheme 3). The amide **11** was then treated with vinylmagnesium bromide to afford **12** in 98% yield. Stereoselective reduction of **12** was achieved with $NaBH_4$–$CeCl_3{\cdot}7H_2O$ at −78 °C to provide allylic alcohols **9** and **10** in 85% and 11%



Scheme 3. MOM = $-CH_2OMe$, ^iPr = $-CHMe_2$, Tf = $-SO_2CF_3$. *Reagents and conditions*: i Jones reagent, acetone, 0 °C; ii MeONHMe·HCl, WSC, HOBt, $^iPr_2NEt$, DMF, rt; iii CH_2=CHMgBr, THF, −78 °C; iv $NaBH_4$, $CeCl_3·7H_2O$, MeOH–CH_2Cl_2, (1/1), −78 °C; v CSA, ^iPrOH, 120 °C, in a sealed tube, 48 h; vi MOMCl, NaH, THF, 0 °C; vii $K_2OsO_4·2H_2O$, NMO, ^tBuOH–H_2O (3/1), rt; viii BnBr, NaH, Bu_4NI, DMF, rt; ix 4 mol/l aqueous HCl–THF (1/2), rt; x Tf_2O, DMAP, pyridine, CH_2Cl_2, 0 °C; xi Me_3SiN_3, KF, 18-crown-6-ether, MeCN, rt; xii Ac_2O, AcOH, $FeCl_3·6H_2O$, H_2SO_4, rt.

isolated yields, respectively. Conversion of methyl furanoside **9** into a pyranoside form was successfully carried out by transglycosylation of **9** with 2-propanol in the presence of CSA[10] (120 °C in a sealed tube) to give α-pyranoside **13** as the major product in 60% yield along with its β-furanoside isomer (35% yield).[11] Protection of the hydroxy function in **13** as a methoxymethyl ether afforded **14** in 84% yield.

Dihydroxylation of **14** with catalytic amount of potassium osmate in the presence of *N*-methylmorpholin-*N*-oxide (NMO) proceeded stereoselectively to afford **15** and its diastereomer in 82% and 18% isolated yields, respectively. Diol **15** was transformed into tetra-*O*-benzyl ether **16** in 93% yield. Deprotection of a MOM ether in **16** gave **17**, and the resulting hydroxy group in **17** was transformed into an inverted azide via trifluoromethanesulfonate[12] **18** to give **19** in 52% yield from **16**. Treatment of **19** with AcOH–Ac_2O in the presence of sulfuric acid and $FeCl_3$[13] induced the acetolysis of the anomeric center as well as the primary benzyl ether to furnish the known α-pyranosyl acetate **5** in 64% yield. Spectral and physical data of **5**[14] were fully identical with those of the authentic sample prepared from *myo*-inositol.[5] Compound **5** had been converted into SPM VIII **2** via **4** in 7 step reactions.[5b]

In summary, the new synthetic way to α-pyranosyl acetate **5**, a key intermediate for the synthesis of spicamycin, starting from D-ribose has been established. The present synthesis, proceeded in 16 steps and in 7.3% overall yield from D-ribose, is more efficient than our previous approach[5] (24 steps, 0.4% overall yield from *myo*-inositol), and provides a practical method for the synthesis of novel spicamycin derivatives possessing various heterocyclic bases with an exocyclic amino group (guanine, cytosine, and so on), which are expected to show clinically interesting activities. Further studies on preparation and biological assessment of such derivatives are currently underway and will be reported in due course. Moreover, it is noteworthy that the synthetic method developed in this work should be applicable to preparation of other biological important natural heptopyranoses starting from readily available carbohydrates.

References and Notes

1 a) Y. Hayakawa, M. Nakagawa, H. Kawai, K. Tanabe, H. Nakayama, A. Shimazu, H. Seto, and N. Otake, *J. Antibiot.*, **36**, 934 (1983). b) Y. Hayakawa, M. Nakagawa, H. Kawai, K. Tanabe, H. Nakayama, A. Shimazu, H. Seto, and N. Otake, *Agric. Biol. Chem.*, **49**, 2685 (1985). c) T. Sakai, K. Shindo, A. Odagawa, A. Suzuki, H. Kawai, K. Kobayashi, Y. Hayakawa, H. Seto, and N. Otake, *J. Antibiot.*, **48**, 899 (1995).

2 M. Kamishohara, H. Kawai, A. Odagawa, T. Isoe, J. Mochizuki, T. Uchida, Y. Hayakawa, H. Seto, T. Tsuruo, and N. Otake, *J. Antibiot.*, **46**, 1439 (1993).

3 a) M. Kamishohara, H. Kawai, A. Odagawa, T. Isoe, J. Mochizuki, T. Uchida, and N. Otake, *J. Antibiot.*, **47**, 1305 (1994). b) T. Sakai, H. Kawai, M. Kamishohara, A. Odagawa, A. Suzuki, T. Uchida, T. Kawasaki, T. Tsuruo, and N. Otake, *J. Antibiot.*, **48**, 504 (1995). c) T. Sakai, H. Kawai, M. Kamishohara, A. Odagawa, T. Tsuruo, and N. Otake, *J. Antibiot.*, **48**, 1467 (1995).

4 a) M. Kamishohara, H. Kawai, T. Sakai, T. Isoe, K. Hasegawa, J. Mochizuki, T. Uchida, S. Kataoka, H. Yamaki, T. Tsuruo, and N. Otake, *Oncol. Res.*, **6**, 383 (1994). b) M. Kamishohara, H. Kawai, T. Sakai, T. Uchida, T. Tsuruo, and N. Otake, *Cancer Chemother. Pharmacol.*, **38**, 495 (1996).

5 a) T. Suzuki, S. Tanaka, I. Yamada, Y. Koashi, K. Yamada, and N. Chida, *Org. Lett.*, **2**, 1137 (2000). b) T. Suzuki, S. T. Suzuki, I. Yamada, Y. Koashi, K. Yamada, and N. Chida, *J. Org. Chem.*, **67**, 2874 (2002).

6 N. Chida, T. Suzuki, S. Tanaka, and I. Yamada, *Tetrahedron Lett.*, **40**, 2573 (1999).

7 a) H. Agahigian, G. D. Vickers, M. H. von Saltza, J. Reid, A. I. Cohen, and H. Gauthier, *J. Org. Chem.*, **30**, 1085 (1965). b) J. F. Kenedy and C. A. White, "Bioactive Carbohydrates: In Chemistry, Biochemistry and Biology," Ellis Horwood Limited, Chichester (1983), Chap. 8, p 172.

8 a) R. R. Schmidt and A. Gohl, *Chem. Ber.*, **112**, 1689 (1979). b) E. Kawashima, K. Umabe, and T. Sekine, *J. Org. Chem.*, **67**, 5142 (2002).

9 All new compounds were characterized by ^1H and ^{13}C NMR, IR, and mass spectrometric and/or elemental analyses.

10 When this reaction was carried out in MeOH (CSA, 100 °C, in a sealed tube for 60 h), the desired methyl α-pyranoside was obtained as the minor product (33% yield), and the starting methyl furanoside **9** was recovered in 57% yield.

11 Acidic treatment (CSA in ^iPrOH, 120 °C) of β-furanoside gave additional **13** in 50% yield (28% recovery of the starting β-furanoside).

12 A. Martìn, T. D. Butters, and G. W. J. Fleet, *Tetrahedron: Asymmetry*, **10**, 2343 (1999).

13 D. R. McPhail, J. R. Lee, and B. Fraser-Reid, *J. Am. Chem. Soc.*, **114**, 1905 (1992).

14 Data for **5**: $[\alpha]^{23}_D$ −50 (*c* 0.43, $CHCl_3$) {lit.[5b] $[\alpha]^{22}_D$ −47 (*c* 0.72, $CHCl_3$)}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 and 2.04 (2s, each 3H), 3.66 (dd, 1H, J = 1.3 and 10.0 Hz), 3.67 (dd, 1H, J = 2.0 and 2.9 Hz), 3.72 (dd, 1H, J = 2.9 and 10.0 Hz), 3.89 (ddd, 1H, J = 1.3, 4.4 and 7.1 Hz), 4.16 (dd, 1H, J = 10.0 and 10.0 Hz), 4.24 (dd, 1H, J = 7.1 and 12.0 Hz), 4.34 (dd, 1H, J = 4.4 and 12.0 Hz), 4.57 and 4.70 (2s, each 2H), 4.62 and 4.71 (2d, each 1H, J = 12.0 Hz), 6.17 (d, 1H, J = 2.0 Hz), 7.26–7.39 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 21.0, 57.8, 64.0, 71.8, 71.9, 72.5, 72.9, 73.9, 77.4, 77.5, 91.5, 127.6, 127.8, 127.9, 128.0, 128.0, 128.3, 128.5, 137.2, 137.4, 137.9, 168.7, 170.7. HRMS (EI) Calcd for $C_{32}H_{35}O_8N_3(M^+)$: 589.2424, Found: m/z 589.2436.