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# Pd-Catalyzed Coupling Reaction of Glycosylamines with 6-Chloropurines: Synthesis of 6-(β-D-Mannopyranosylamino)-9*H*-purine and its β-D-Gluco Isomer, *N*-Glycoside Models for Spicamycin and Septacidin

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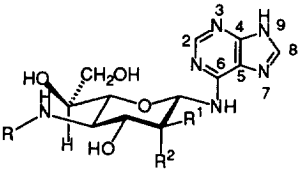
***Abstract:*** The first example of preparation of 6-(β-D-mannopyranosylamino)-9*H*-purine (**8**), whose *N*-glycosidic linkage corresponds to a natural antibiotic, spicamycin, by Pd-catalyzed coupling reaction of a mannopyranosylamine with 9-protected-6-chloropurine, followed by deprotection, is described. Its β-D-gluco isomer (**11**) was also synthesized. This work established the procedure to construct the novel *N*-glycoside, in which the pyranose unit is connected to the amino group at C(6) of adenine moiety.



Spicamycin[1] (**1**) and septacidin[2] (**2**), are two structurally related *Streptomyces* metabolites with potent antitumor activity. Their structures, elucidated by spectral and X-ray analyses of a deacyl congener **3**, spicamycin amino nucleoside (SAN),[1] are unique among the nucleoside antibiotics with respect to the glycosylation site: while conventional adenine-nucleoside antibiotics bear a sugar at the N(9) position,[3] the present compounds are glycosylated at the C(6)-amino group of adenine. Moreover, the sugar portions are novel 4-amino-4-deoxy-heptopyranoses with the β-manno or β-gluco anomeric configurations. Although such an interesting structural feature as well as the promising biological activities have naturally arrested sizable attention of the synthetic community,[4] neither a total synthetic route nor the basic methodology to construct the characteristic *N*-glycoside has not been developed thus far.

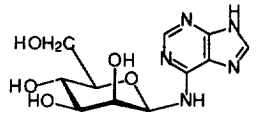
In this communication, we wish to report a viable method for the construction of such a novel *N*-glycoside structure based on the Pd-catalyzed coupling of glycosylamines with 6-halopurine derivatives, which indeed worked for the preparation of manno- (**8**) and glucopyranosylamino-9*H*-purine derivatives (**11**), the model compounds for the synthesis of **1** and **2**, respectively.



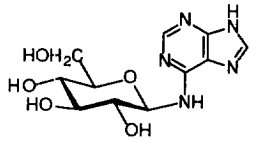
R = $Me_2CH(CH_2)_nCONHCH_2CO$- or $MeCH_2CH_2(CH_2)_nCONHCH_2CO$- (n = 8~14);
$R^1$ = H; $R^2$ = OH: Spicamycin (**1**)

R = $Me_2CH(CH_2)_nCONHCH_2CO$- (n = 8~14);
$R^1$ = OH; $R^2$ = H: Septacidin (**2**)

R = H; $R^1$ = H; $R^2$ = OH: SAN (**3**)



6-(β-D-Mannopyranosylamino)-9*H*-purine (**8**)



6-(β-D-Glucopyranosylamino)-9*H*-purine (**11**)

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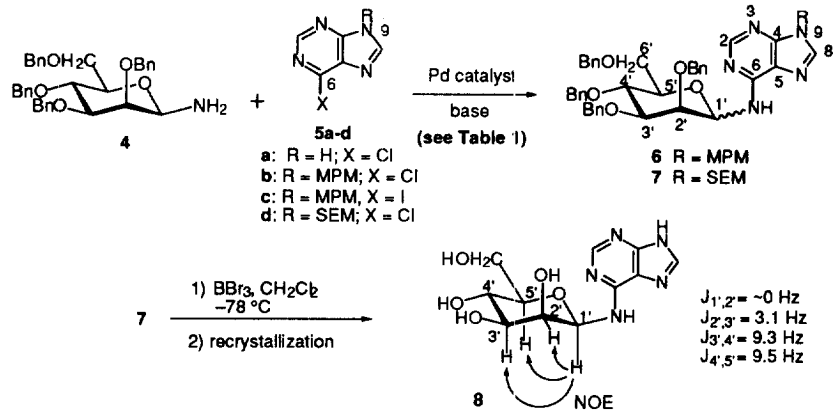
*PII:* S0040-4039(99)00250-6




**Scheme 1.** Bn = $PhCH_2$-, MPM = (*p*-OMe)$C_6H_4CH_2$-, SEM = $Me_3SiCH_2CH_2OCH_2$-.

The known mannopyranosylamine (**4**)[5,6] was chosen as the substrate, which was subjected to the reactions with 6-halopurine derivatives (**5a-d**). Initial attempts under the base-catalyzed conditions ($Et_3N$ in BuOH, reflux)[7] led only to the decomposition of **4**, presumably due to the instability of the pyranosylamine as well as the reduced nucleophilicity of the amino group by the presence of an endocyclic oxygen. At this juncture we turned our attention to the Pd-catalyzed conditions, which have been recently reported by Buchwald,[8] Hartwig,[9] and Tanaka,[10] to be effective for the coupling of aliphatic and aromatic amines with aryl halides or triflates. Although the reaction of **4** with 6-chloropurine **5a** under the Tanaka's conditions[10] [$Pd(Pcy_3)_2Cl_2$, NaO*t*Bu, toluene, 140 °C] gave no coupling products, we were delighted to find that the use of 9-protected 6-chloropurine **5b**[11] afforded the coupling product **6**, though in only 25% yield, as an inseparable mixture of α- and β-anomers[12] (Table 1, run 1). The dependence on various reaction parameters were then examined and the results were addressed in Table 1. Several points became clear; (i) toluene was the choice for the solvent (runs 1-3), (ii) the use of the 6-iodopurine derivative **5c**[13] (run 4) and Hartwig conditions[9a] (run 6) did not offer much improvement (run 4), (iii) $Pd(Pcy)_3Cl_2$–$Cs_2CO_3$ system and the Buchwald's conditions[8a] gave moderate results (runs 5 and 7). Further improvement was attained under the Buchwald's conditions by employing an excess

**Table 1.** Coupling reaction of mannopyranosylamine (**4**) with halopurines.[a]

| run | purine | catalyst[b] | additive[c] | base | solvent | time/h | molar ratio (**4** : purine) | product[d] | yield[e]/% |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **5b** | $Pd(Pcy_3)_2Cl_2$ | | NaO*t*Bu | toluene | 12 | 1.5 : 1.0 | **6** | 25 |
| 2 | **5b** | $Pd(Pcy_3)_2Cl_2$ | | NaO*t*Bu | *o*-xylene | 50 | 1.5 : 1.0 | **6** | 12 |
| 3 | **5b** | $Pd(Pcy_3)_2Cl_2$ | | NaO*t*Bu | DMF | 12 | 1.5 : 1.0 | — | 0 |
| 4 | **5c** | $Pd(Pcy_3)_2Cl_2$ | | NaO*t*Bu | toluene | 21 | 1.5 : 1.0 | **6** | 35 |
| 5 | **5b** | $Pd(Pcy_3)_2Cl_2$ | | $Cs_2CO_3$ | toluene | 16 | 1.5 : 1.0 | **6** | 41 |
| 6 | **5b** | $Pd_2(dba)_3$ | DPPF | NaO*t*Bu | toluene | 20 | 1.5 : 1.0 | **6** | 28 |
| 7 | **5b** | $Pd_2(dba)_3$ | (–)-BINAP | NaO*t*Bu | toluene | 14 | 1.5 : 1.0 | **6** | 45 |
| 8 | **5b** | $Pd_2(dba)_3$ | (–)-BINAP | NaO*t*Bu | toluene | 14 | 1.0 : 2.0 | **6** | 79 |
| 9 | **5d** | $Pd_2(dba)_3$ | (–)-BINAP | NaO*t*Bu | toluene | 9 | 1.0 : 2.0 | **7** | 74 |
| 10 | **5d** | $Pd_2(dba)_3$ | (+)-BINAP | NaO*t*Bu | toluene | 5 | 1.0 : 2.0 | **7** | 68 |

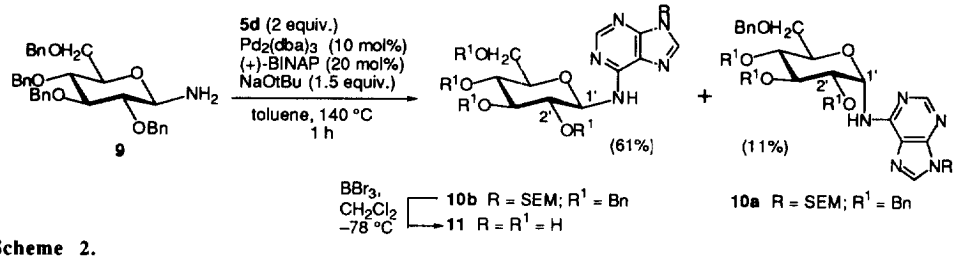
a) All reactions were carried out with purine [40 μmol (run 1-7) or 120 μmol (run 8-10)] and compound **4** (60 μmol) in the presence of catalyst (6 μmol) and base [60 μmol (run 1-7) or 90 μmol (run 8-10)] in solvent (2.5 ml) at 140 °C in a sealed tube; see, ref. 14. b) cy = cyclohexyl; dba = dibenzylideneacetone. c) 200 mol% to catalyst. DPPF = 1,1'-bis(diphenylphosphino)-ferrocene; BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. d) Obtained as an anomeric mixture (α:β = *ca.* 1:5). Ratio was determined with 300 MHz $^1H$ NMR spectra. e) Isolated yield after silica gel chromatography.

amount of purine to afford **6** in 79% yield (run 8). With SEM-protected purine **5d**,[11] which was expected to undergo facile deprotection, the similar reaction conditions[14] provided **7**[15] in 74% yield (run 9). The use of (+)–BINAP gave slightly lower yield (run 10).

The structures of the coupling products were established from their $^1$H NMR spectra. The major isomer of **7** showed its anomeric proton at δ 5.76 as a broad singlet, whereas that of the minor isomer appeared at δ 6.41 (broad s). When the broad signal at δ 7.10 (NH, exchangeable with $D_2O$) was irradiated, the signal of the anomeric proton sharpened, implying the connectivity of the C-1' carbon in mannose to the amino group at C-6 of the adenine moiety. The observed NOE in the major isomer between H-1' and H-3', H-1' and H-5', and H-1' and H-2' showed its β-manno configuration.

Treatment of **7** (α/β mixture) with $BBr_3$ in $CH_2Cl_2$ at –78 °C removed all the protecting groups to afford a mixture of the α- and β-D-mannopyranosylamino-9*H*-purine, quantitatively, from which the pure β-anomer **8**[15] was isolated in 81% yield by recrystallization (water)[16]. The coupling constants and NOE observed in the $^1$H NMR of **8** (Scheme 1) again supported the β-manno configuration.

The coupling procedure proved to be applicable also to the *gluco* isomer (Scheme 2). Thus, the reaction of glucopyranosylamine **9**[17] with excess **5d** under the Buchwald's conditions using (+)–BINAP[18] (140 °C, 1 h) provided β-gluco derivative **10b**[15] and its α-anomer **10a** in 61 and 11% isolated yields, respectively. The observed coupling constants ($J_{1',2'}$ ~ 8 Hz for **10b**, and ~ 4 Hz for **10a**) clearly revealed their anomeric configurations. Deprotection of **10b** gave 6-(β-D-glucopyranosylamino)-9*H*-purine (**11**)[15] in 85% yield.




**Scheme 2.**

In summary, a viable method has been developed for constructing the novel *N*-glycoside structures of spicamycin and septacidin. The present results, successful coupling of glycosylamines with 6-chloropurine derivatives, greatly expands the scope of Pd-catalyzed amination to the preparation of structurally complex *N*-glycosides. Further studies directed toward the synthesis of spicamycin and septacidin are now under investigation.

**Acknowledgments**: We thank Professors Mitsuo Sekine and Keisuke Suzuki (Tokyo Institute of Technology, Japan) for useful information and suggestions.

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6. Compound **4** was prepared by hydrogenation of 2,3,4,6-tetra-*O*-benzyl-β-D-mannopyranosyl azide in the presence of Pd-$CaCO_3$ catalyst in EtOH at room temperature. Interestingly, when α-azide isomer was subjected to the same reaction condition, rapid anomerization of pyranosylamine took place to afford **4** as the sole product, and the α-anomer of **4** could not be detected in the reaction mixture.
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11. Compound **5b** and **5d** were prepared from commercially available 6-chloropurine by essentially the same procedure as that reported for the preparation of 9-benzyl-6-chloropurine (MPMCl or SEMCl was employed instead of BnCl). See, Gundersoen, L.; Bakkestuen, A. K.; Aasen, A. J.; Overas, H.; Rise, F. *Tetrahedron* **1994**, *50*, 9743-9756.
12. Under the reaction conditions described here, the ratio of α- and β-anomers stayed almost the same (α : β = *ca.* 1 : 5). Formation of the α-anomer suggested that partial anomerization of **4** might had occurred during the coupling step. A similar phenomenon has been reported by Fraser-Reid in the acylation of **4** with 2-chlorobenzoyl chloride in pyridine (α-amide and β-amide were obtained in a ratio of 1 : 4.7); see ref. 5.
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14. Representative procedure: To a mixture of compounds **4** (32 mg, 60 μmol) and **5d** (33 mg, 120 μmol), $Pd_2(dba)_3$ (5.5 mg, 6.0 μmol), (–)-BINAP (7.5 mg, 12 μmol), and NaO*t*Bu (8.6 mg, 90 μmol) in toluene (2.5 mL) was bubbled a stream of Ar for 15 min. The reaction mixture was then heated at 140 °C in a sealed tube for 9 h. After cooling, the mixture was diluted with $Et_2O$ and washed with brine, and dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (4 g), with EtOAc-toluene (1:3) to afford compound **6** as an anomeric mixture (α : β = *ca.* 1 : 5).
15. Selected data for **7**: $^1$H NMR (300 MHz, $CDCl_3$, for the major isomer) δ –0.04 (s, 9 H), 0.91 and 3.57 (2t, each 2 H, J = 8.3 Hz), 3.61-3.98 (m, 4 H), 4.02 (bs, 1 H), 4.10 (dd, 1 H, J = 9.4, 9.4 Hz), 4.46-5.15 (m, 8 H), 5.52 (s, 2 H), 5.76 (bs, 1 H), 7.01 (bs, 1 H; exchangeable with $D_2O$), 7.20-7.50 (m, 20 H), 7.94 and 8.49 (2s, each 1 H). HRMS (EI) Calcd for $C_{45}H_{53}N_5O_6Si$ ($M^+$), 787.3765. Found 787.3776. Anal. Calcd for $C_{45}H_{53}N_5O_6Si$: C, 68.59; H, 6.78; N, 8.89. Found: C, 68.66; H, 6.83; N, 8.66. For **8**: mp 194-196 °C; $[\alpha]_D^{28}$ –24 (*c* 0.6, DMF); $^1$H NMR (300 MHz, $D_2O$, 50 °C) δ 3.79 (ddd, 1 H, J = 1.7, 5.5, 9.3 Hz), 3.88 (dd, 1 H, J = 9.3, 9.5 Hz), 3.95 (dd, 1 H, J = 5.6, 12.1 Hz), 4.00 (dd, 1 H, J = 3.1, 9.5 Hz), 4.10 (dd, 1 H, J = 1.7, 12.1 Hz), 4.33 (d, 1 H, J = 3.1 Hz), 5.89, 8.39 and 8.51 (3s, each 1 H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 61.7, 67.3, 71.3, 74.7, 78.0, 79.1, 119.5, 140.9, 150.8, 152.8, 153.4. HRMS (FAB, glycerol) Calcd for $C_{11}H_{16}N_5O_5$ ($M^+$+H), 298.1151. Found 298.1137. Anal. Found: C, 39.91; H, 5.59; N, 21.01. Calcd for $C_{11}H_{15}N_5O_5 \cdot 2H_2O$: C, 39.64; H, 5.75; N, 21.01. For **10b**: $[\alpha]_D^{28}$ –10 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$, 50 °C) δ –0.04 (s, 9 H), 0.92 (t, 2 H, J = 8.1 Hz), 3.55 (dd, 1 H, J = 8.3, 8.8 Hz), 3.62 (t, 2 H, J = 8.1 Hz), 3.71-3.80 (m, 4 H), 3.85 (dd, 1 H, J = 8.5, 8.8 Hz), 4.40-4.93 (m, 8 H), 5.53 (s, 2 H), 5.90 (bdd, J = 8.3, 8.3 Hz; changed to d, J = 8.3 Hz on addition of $D_2O$), 6.44 (b, 1 H; exchangeable with $D_2O$), 7.09-7.23 (m, 20 H), 7.96 and 8.46 (2s, each 1 H). HRMS (EI) Calcd for $C_{45}H_{53}N_5O_6Si$ ($M^+$), 787.3765. Found 787.3780. For **11**: mp 197-199 °C; $[\alpha]_D^{28}$ –39 (*c* 0.8, $H_2O$); $^1$H NMR (300 MHz, $D_2O$, 55 °C) δ 3.77-3.88 (m, 3 H), 3.93 (dd, 1 H, J = 9.0, 9.0 Hz), 3.94 (dd, 1 H, J = 5.4, 12.2 Hz), 4.09 (dd, 1 H, J = 2.2, 12.2 Hz), 5.65 (d, 1 H, J = 8.5 Hz), 8.31 and 8.42 (2s, each 1 H); $^{13}$C NMR (75 MHz, $D_2O$) δ 61.7, 70.4, 73.3, 77.6, 78.1, 81.8, 118.0, 142.4, 151.3, 152.8, 153.8. HRMS (FAB, glycerol) Calcd for $C_{11}H_{16}N_5O_5$ ($M^+$+H), 298.1151. Found 298.1162.
16. The $^1$H NMR of the mother liquor showed that the ratio of **8** and its α-anomer was *ca.* 2 : 1, implying the anomerization (α → β) had took place during the recrystallization.
17. Compound **9** was synthesized from 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl azide by hydrogenation. see, Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47*, 281-285. They also noted that the hydrogenation of α-azide anomer gave a mixture of **9** and its α-anomer. Indeed, hydrogenation of the α-azide anomer (Pd-$CaCO_3$, EtOH, room temp.) for long reaction time (24 h) induced the complete anomerization and provided **9** as the single β-anomer.
18. In contrast to the results obtained in the coupling of **4** with **5d**, the use of (–)-BINAP significantly reduced the rate of the reaction of **9** with **5d** (140 °C, 36 h), and afforded compounds **10b** and **10a** in lower (44 and 14%) yields.