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# Total Synthesis of Spicamycin Amino Nucleoside

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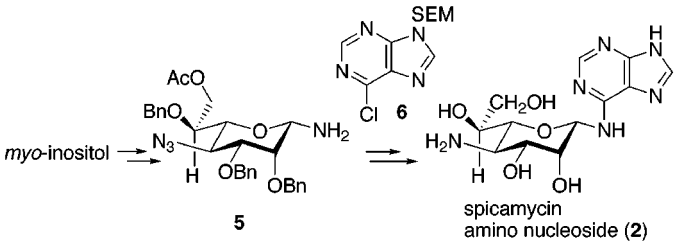
## ABSTRACT




**The first total synthesis of spicamycin amino nucleoside 2 has been achieved. The aminoheptose unit 5 was prepared stereoselectively from *myo*-inositol, and the characteristic *N*-glycoside linkage was constructed by way of Pd-catalyzed coupling reaction of 5 with 6-chloropurine derivative 6.**

In 1983, Hayakawa and co-workers reported the isolation of spicamycin **1** from the culture broth of *Streptomyces alanosinicus* as a potent differentiation inducer of HL-60 human promyelocytic leukemia cells.[1] The structural study by spectral and degradation methods revealed that spicamycin consists of a novel aminoheptose, adenine, glycine, and fatty acids, and is a mixture of several congeners that differ in their fatty acid moieties.[1] Mild acid hydrolysis of spicamycin afforded spicamycin amino nucleoside (SAN, **2**),[2] whose absolute structure was determined by X-ray analysis and copper complex (TACu) method to be 6-(4-amino-4-deoxy-L-*glycero*-$\beta$-L-*manno*-heptopyranosylamino)-9*H*-purine.[3] These studies showed that the structure of **1** is quite unique among the nucleoside antibiotics with respect to the glycosylation site: while conventional adenine-nucleoside antibiotics bear a sugar at the N(9) position, the present compound is glycosylated at the C(6)-amino group of adenine with the $\beta$-manno anomeric configuration.

Extensive structure−activity relationship studies[2,4] of spicamycin analogues prepared by semisynthetic methods employing the condensation of **2** with various amino acids and fatty acids proved that SAN **2** is a useful precursor for the synthesis of spicamycin and its analogues and generated the promising compounds, KRN 5500 **3**[5] and SPM VIII **4**,[2] which showed potent antitumor activities against human gastric cancer SC-9 and COL-1 colon carcinoma xenografts, respectively. Although such significant biological activity and an intriguing structure have attracted the considerable synthetic attention, neither a total synthesis of **1** nor even the preparation of the aminoheptose moiety has been

(1) (a) Hayakawa, Y.; Nakagawa, M.; Kawai, H.; Tanabe, K.; Nakayama, H.; Shimazu, A.; Seto, H.; Otake, N. *J. Antibiot.* **1983**, *36*, 934. (b) Hayakawa, Y.; Nakagawa, M.; Kawai, H.; Tanabe, K.; Nakayama, H.; Shimazu, A.; Seto, H.; Otake, N. *Agric. Biol. Chem.* **1985**, *49*, 2685.

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

(3) Sakai, T.; Shindo, K.; Odagawa, A.; Suzuki, A.; Kawai, H.; Kobayashi, K.; Hayakawa, Y.; Seto, H.; Otake, N. *J. Antibiot.* **1995**, *48*, 899.

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

(5) Kamishohara, M.; Kawai, H.; Sakai, T.; Isoe, T.; Hasegawa, K.; Mochizuki, J.; Uchida, T.; Kataoka, S.; Yamaki, H.; Tsuruo, T.; Otake, N. *Oncol. Res.* **1994**, *6*, 383.

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completed. Only a few reports on syntheses of compounds related to spicamycin have appeared: Fleet reported the synthesis of spicamycin analogues in which the aminoheptose unit was replaced by 4-amino-4-deoxy-L- and D-rhamnose (rhamnospicamycin),[6] and Acton disclosed the preparation of analogues with 4-amino-4-deoxy- and 4-amino-4,6-dideoxy-L-glucose.[7] Both syntheses employed the multistep procedures, in which 6-(pyranosylamino)-4-amino-5-nitroropyrimidines, prepared by the coupling reaction of pyranosylamines with 6-amino-4-chloro-[7] or 4,6-dichloro-5-nitropyrimidine[6] were involved as the key intermediates, for the construction of the *N*-glycosidic structures. Here, we report the first total synthesis of SAN **2** starting from naturally abundant cyclitol, *myo*-inositol.

Our retrosynthetic analysis (Figure 1) suggested that *N*-glycosidic structure in **2** would be constructed by the Pd-catalyzed coupling reaction of protected glycosylamine **5**

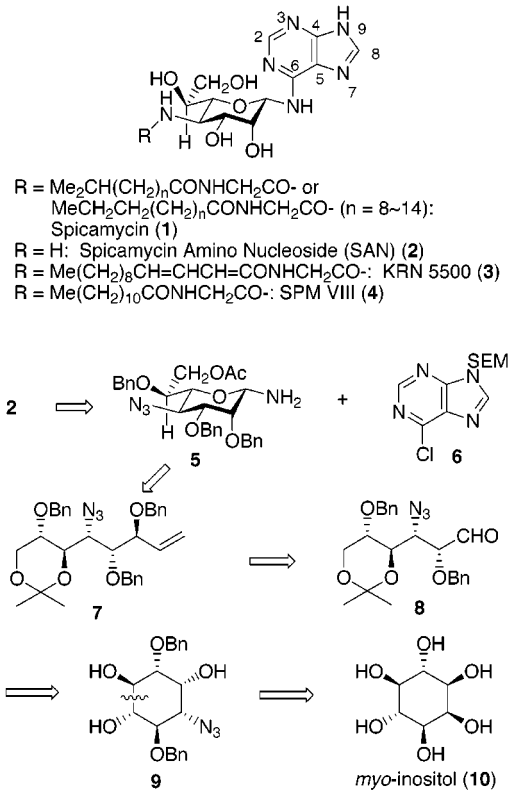
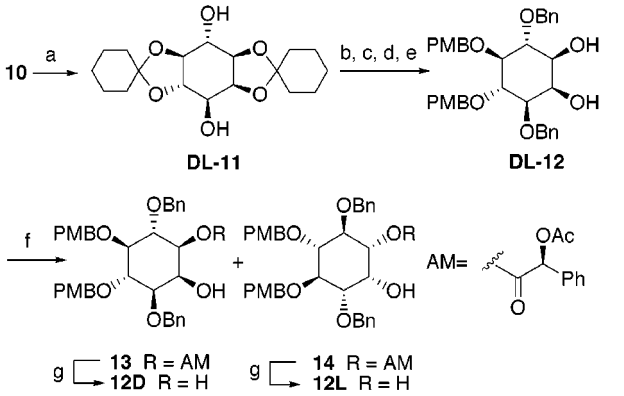



**Figure 1.** Structures of spicamycin and related compounds, and retrosynthetic route to SAN (SEM = 2-(trimethylsilyl)ethoxymethyl).

with 6-chloro-9-SEM-purine **6**. This straightforward methodology, recently reported from this laboratory,[8] was proved to be effective for the construction of the spicamycin-type *N*-glycosides and successfully provided protected 6-(*β*-D-mannopyranosylamino)purine by a one-step reaction in good yield. The amine **5** was planned to be prepared from acyclic precursor **7**, which would be generated by the carbon elongation of aldehyde **8**. The aldehyde **8** would derive from the ring cleavage reaction of a highly functionalized cyclohexane derivative **9**, which was envisioned as arising from *myo*-inositol **10**.

The known racemic diol[9] **DL-11**, prepared from **10** in a one-step reaction, was converted into protected diol **DL-12** in 45% yield from **DL-11** (Scheme 1). The equatorial

**Scheme 1**[a]




[a] Conditions: (a) 1,1-dimethoxycyclohexane, *p*-TsOH, DMF (see ref 9); (b) NaH, BnCl, DMF; (c) *p*-TsOH, EtOH, 45 °C; (d) NaH, PMBCl, $Bu_4NI$, THF−DMF, rt; (e) AcOH−$H_2O$ (4:1), 50 °C; (f) (+)-L-*O*-acetylmandelic acid, DCC, DMAP, $CH_2Cl_2$, −20 °C; (g) NaOMe, MeOH, 50 °C.

hydroxy group in **DL-12** was selectively acylated by a treatment with an equimolar amount of L-*O*-acetyl mandelic acid[10] in the presence of DCC and 4-(dimethylamino)pyridine (DMAP) to provide a pair of chiral diastereoisomers, **13** and **14**, which were easily separated by silica gel chromatography followed by recrystallization, in 41 and 37% isolated yields, respectively. Deacylation of **13** gave **12D** (85% yield) and that of **14** afforded the enantiomer **12L** (89%).[11]

Synthesis of the aminoheptose moiety commenced with **12D** (Scheme 2), whose equatorial hydroxy group was selectively benzoylated, and the remaining hydroxy group was converted into azide via mesylate to give **15** in 72%

(6) (a) Martin, A.; Butters, T. D.; Fleet, G. W. J. *Chem. Commun*. **1998**, 2119. (b) Martin, A.; Butters, T. D.; Fleet, G. W. J. *Tetrahedron Asymmetry* **1999**, *10*, 2343.

(7) Acton, E. M.; Ryan, K. J.; Luetzow, A. E. *J. Med. Chem.* **1977**, *20*, 1362.

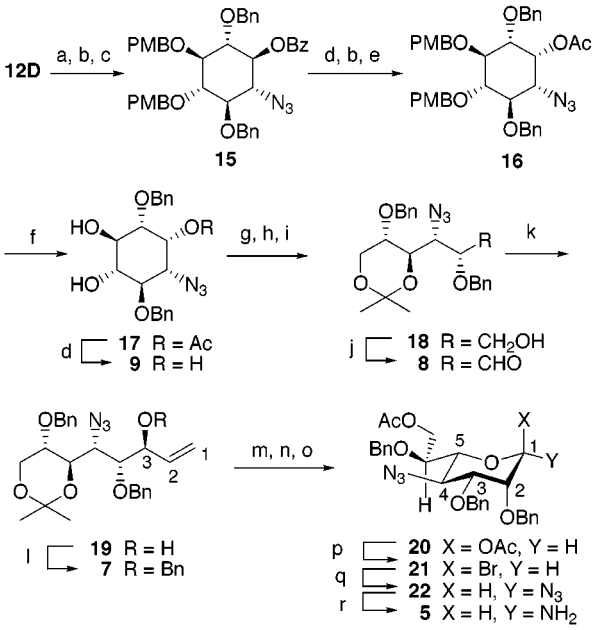
(8) Chida, N.; Suzuki, T.; Tanaka, S.; Yamada, I. *Tetrahedron Lett.* **1999**, *40*, 2573.

(9) (a) Garegg, P. J.; Iversen, T.; Johansson, R.; Lindberg, B. *Carbohydr. Res.* **1984**, *130*, 322. (b) Jiang, C.; Baker, D. *J. Carbohydr. Chem.* **1986**, *5*, 615.

(10) Chida, N.; Yamada, E.; Ogawa, S. *J. Carbohydr. Chem.* **1988**, *7*, 555.

(11) The absolute configuration and the optical purity of **12D** and **12L** were determined by their transformation into the known compounds, 1D- and 1L-1,4,5,6-tetra-*O*-benzyl-*myo*-inositol, respectively. For 1D-isomer prepared from **12D**: mp 144−145 °C.; $[\alpha]^{23}_D$ +25 (*c* 1, $CHCl_3$), lit. (Shvets, V. I.; Klyashchitskii, B. A.; Stepanov, A. E.; Evstgneeva, R. P. *Tetrahedron*, **29**, *1973*, 331) mp 140−142 °C, $[\alpha]^{20}_D$ +25 (*c* 0.18, $CHCl_3$). For 1L-isomer from **12L**: mp 144−145 °C.; $[\alpha]^{25}_D$ −24 (*c* 1, $CHCl_3$), lit. mp 141−143 °C; $[\alpha]^{20}_D$ −24.3 (*c* 1.3, $CHCl_3$). The optical purity of **12D** and **12L** were also confirmed to be >98% ee, respectively, by chiral column analysis (chiralcel OD).

**Scheme 2**[a]



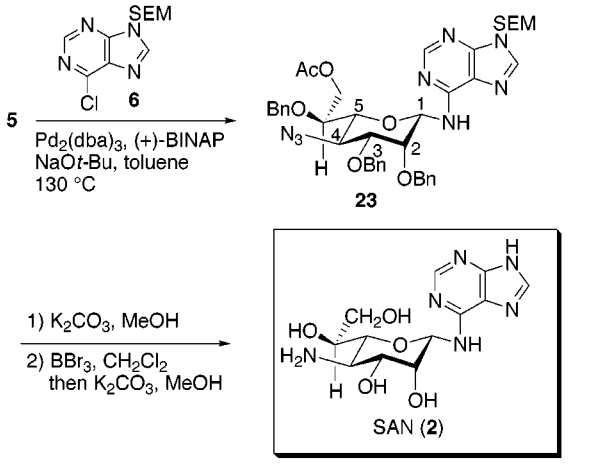

[a] Conditions: (a) BzCl, pyridine, rt; (b) MsCl, pyridine, rt; (c) $NaN_3$, DMF, 100 °C; (d) NaOMe, MeOH, rt; (e) KOAc, 18-crown-6, DMF, 100 °C; (f) DDQ, wet $CH_2Cl_2$, 0 °C; (g) $NaIO_4$, MeOH−$H_2O$, rt; (h) $NaBH_4$, MeOH, 0 °C; (i) 2,2-dimethoxypropane, *p*-TsOH, DMF, rt; (j) DMSO, DCC, TFA, pyridine, PhH, rt; (k) $CH_2$═CHLi, $Et_2O$, −115 °C; (l) NaH, BnBr, DMF, 0 °C; (m) $O_3$, $CH_2Cl_2$, −78 °C, then $Me_2S$; (n) *p*-TsOH, MeOH, 0 °C; (o) $Ac_2O$, pyridine, rt; (p) TMSBr, $CHCl_3$, rt; (q) $TMSN_3$, $Bu_4NF$, THF, rt; (r) $H_2$ (1 atm), Lindlar catalyst, toluene, rt.

yield. After deprotection of the benzoyl group in **15**, the resulting alcohol was transformed into inverted acetate **16**[12] (64%). Removal of *O*-PMB and *O*-acetyl groups in **16** gave triol **9** in 95% yield.

Periodate oxidation of **9**, followed by reduction with $NaBH_4$, and subsequent treatment with 2,2-dimethoxypropane provided azidoalditol **18** in 80% yield from **9**. Moffatt oxidation of **18** gave unstable aldehyde **8**, which, without isolation, was immediately reacted with vinyllithium[13] in $Et_2O$ at −115 °C to afford Felkin−Anh product **19** as the major isomer.[14] Protection of the hydroxy group in **19** provided tri-*O*-benzyl ether **7** in 68% yield from **18**. Ozonolysis of **7** ($Me_2S$ workup), followed by acid hydrolysis and subsequent treatment with acetic anhydride and pyridine, afforded 4-azidoheptopyranosyl acetate **20**[15] as the single α-anomer in 81% yield. Treatment of **20** with trimethylsilyl bromide[16] gave unstable α-bromoheptose derivative **21**, which was then reacted with trimethylsilyl azide in the presence of TBAF[17] to afford β-anomeric azide **22**[18] in 81% yield from **20**. When diazide compound **22** was subjected to hydrogenation conditions in the presence of Lindlar catalyst in toluene, only anomeric azide group was reduced to give β-heptopyranosylamine **5**[15,18] in 78% yield.

Having finished the preparation of the heptopyranosylamine unit **5** with correct stereocenters, we explored the construction of the characteristic *N*-glycoside (Scheme 3).

**Scheme 3**




Reaction of amine **5** with **6** in the presence of $Pd_2(dba)_3$ (10 mol %), (*R*)-(+)-BINAP (20 mol %), and NaO*t*Bu (150 mol %) in toluene at 130 °C in a sealed tube for 2.5 h[8,19] gave the desired coupling product, fully protected 6-(β-pyranosylamino)-9-SEM-purine **23**[15,18] in 65% yield.[20] Deacylation of **23**, followed by treatment with excess $BBr_3$ in $CH_2Cl_2$ at

(12) All new compounds described in this paper were characterized by 300 MHz $^1$H NMR, 75 MHz $^{13}$C NMR, IR, and mass spectrometric and/or elemental analyses.

(13) Vinyllithium was prepared by the procedure reported by Seyferth and Weiner; see, Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583.

(14) Although the formation of C(3) epimer of **19** was detected in the $^1$H NMR spectrum (**19**/(C(3) epimer: >8/1), this could not be isolated.

(15) Selected data for **20**: $[\alpha]^{22}_D$ −47 (*c* 0.72, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 2.01, 2.04 (2s, each 3 H), 3.66 (dd, 1 H, *J* = 1.3 and 10.0 Hz), 3.67 (dd, 1 H, *J* = 2.0 and 2.9 Hz,), 3.72 (dd, 1 H, *J* = 2.9 and 10.0 Hz), 3.89 (ddd, 1 H, *J* = 1.3, 4.4, and 7.1 Hz), 4.16 (dd, 1 H, *J* = 10.0 and 10.0 Hz), 4.24 (dd, 1 H, *J* = 7.1 and 12.0 Hz), 4.34 (dd, 1 H, *J* = 4.4 and 12.0 Hz), 4.57 and 4.70 (2s, each 2 H), 4.62 and 4.71 (2d, each 2 H, *J* = 12.0 Hz), 6.17 (d, 1 H, *J* = 2.0 Hz), 7.26−7.39 (m, 15 H); $^{13}$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. For **5**: $[\alpha]^{22}_D$ +7 (*c* 1, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.99 (s, 3 H), 2.33 (bs, 2 H), 3.30 (dd, 1 H, *J* = 1.5 and 10.1 Hz), 3.47 (dd, 1 H, *J* = 2.7 and 9.8 Hz), 3.85−3.90 (m, 2 H), 3.91 (dd, 1 H, *J* = 9.8 and 10.1 Hz), 4.05 (d, 1 H, *J* = 1 Hz), 4.23 (dd, 1 H, *J* = 6.8 and 12.0 Hz), 4.35 (dd, 1 H, *J* = 4.4 and 12.0 Hz), 4.41−5.04 (m, 6 H), 7.28−7.40 (m, 15 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.9, 58.7, 63.8, 72.2, 72.5, 74.9, 75.4, 75.8, 77.1, 82.9, 83.4, 127.7, 128.0, 128.1, 128.3, 128.3, 128.6, 137.2, 137.9, 138.3, 170.7. For **23**: $[\alpha]^{22}_D$ +4 (*c* 0.84, $CHCl_3$); $^1$H NMR (300 MHz, MeOH-$d_4$ at 55 °C) δ −0.06 (s, 9 H), 0.90 (t, 2 H, *J* = 7.8 Hz), 1.96 (s, 3 H), 3.61 (dd, 1 H, *J* = 1.7 and 10.0 Hz), 3.65 (t, 2 H, *J* = 7.8 Hz), 3.85 (dd, 1 H, *J* = 2.7 and 10.0 Hz), 3.92 (ddd, 1 H, *J* = 1.7, 4.4, and 7.1 Hz), 4.04 (dd, 1 H, *J* = 10.0 and 10.0 Hz), 4.20 (dd, 1 H, *J* = 2.7 and <1 Hz), 4.20 (dd, 1 H, *J* = 7.1 and 11.7 Hz), 4.29 (dd, 1 H, *J* = 4.4 and 11.7 Hz), 4.53−5.02 (m, 6 H), 5.61 (s, 2 H), 5.85 (bs, 1 H, *J* < 1 Hz), 7.20−7.48 (m, 15 H), 8.21 and 8.34 (2s, each 1 H); $^{13}$C NMR (75 MHz, MeOH-$d_4$, rt) δ −1.5, 14.2, 20.9, 58.4, 60.4, 64.1, 67.2, 72.0, 72.6, 73.6, 73.9, 74.6, 76.2, 77.6, 82.7, 119.7, 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 137.1, 137.7, 138.1, 140.8, 150.4, 153.0, 153.3, 170.7; FAB-MS, *m/z* 795 (M + H)$^+$.

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(17) Soli, E. D.; Manoso, A. S.; Patterson, M. C.; DeShong, P.; Favor, D. A.; Hirschmann, R.; Smith, A. B., III. *J. Org. Chem.* **1999**, *64*, 3171.

(18) The observed NOE between H-1 and H-2, H-1 and H-3, and H-1 and H-5 in the sugar portion clearly supported the β-manno configuration.

(19) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

−78 °C to 0 °C ($K_2CO_3$−MeOH workup) provided SAN **2** in 58% yield after purification with silica gel chromatography and reverse-phase chromatography. It is noteworthy that azide group in **23** was unexpectedly reduced to amine under the $BBr_3$ conditions. The $^1H$ NMR spectra[18,21] as well as physical properties of synthetic **2** {mp 154−156 °C (dec) (DMF-toluene); $[\alpha]^{23}_D$ +21.5 (*c* 0.14, DMF): authentic sample, mp 154−156 °C (dec) (DMF−toluene)[22]; $[\alpha]^{25}_D$ +21.7 (*c* 0.36, DMF)[22]} were fully identical with those of SAN, prepared from spicamycin by degradation.

In summary, the first total synthesis of SAN **2** starting from *myo*-inositol was accomplished. This synthesis fully confirmed the proposed unique structure of the biologically important natural product and established the synthetic pathway to spicamycin and its analogues. The efficiency of the Pd-catalyzed coupling reaction of glycosylamines with 6-chloropurine is also noteworthy for the construction of the novel *N*-glycoside.

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(20) When this reaction was terminated at 1 h, a mixture of **23** and its α-anomer (3:1) was obtained in 40% yield, revealing that anomerization of **5** and **23** had taken place during the coupling reaction, and *β*-anomer **23** is the thermodynamically favored product.

(21) $^1H$ NMR (300 MHz, MeOH-$d_4$) $\delta$ 3.02 (dd, 1 H, $J$ = 10.0 and 10.0 Hz, H-4′), 3.43 (dd, 1 H, $J$ = 6.4 and 10.0 Hz, H-5′), 3.52 (dd, 1 H, $J$ = 3.2 and 10.0 Hz, H-3′), 3.61 (d, 2 H, $J$ = 4.2 Hz, H-7′), 3.79 (dt, 1 H, $J$ = 4.2 and 6.4 Hz, H-6′), 3.94 (dd, 1 H, $J$ = 3.2 and <1 Hz, H-2′), 5.64 (bs, 1 H, H-1′), 8.12 (s, 1 H, H-8), 8.29 (s, 1 H, H-2); $^{13}C$ NMR {75 MHz, MeOH-$d_4$−DMF (1: 1 v/v)} $\delta$ 53.0, 64.6, 71.4, 75.9, 76.4, 77.3, 80.3, 119.2, 143.0, 150.5, 153.1, 154.0; FAB-MS, *m*/*z* 327 $(M + H)^+$.

(22) These data of SAN were measured in our laboratory on material of natural origin, kindly supplied by Dr. Akimoto (Kirin Brewery Co., Ltd.).