A New Entry to 2-Substituted Purine Nucleosides Based on Lithiation-Mediated Stannyl Transfer of 6-Chloropurine Nucleosides

Keisuke Kato,[†,‡] Hiroyuki Hayakawa,[†,||] Hiromichi Tanaka,*[,†] Hiroki Kumamoto,[†] Satoru Shindoh,[†] Satoshi Shuto,[§] and Tadashi Miyasaka[†]

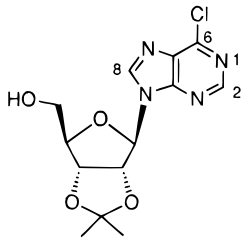
School of Pharmaceutical Sciences, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan, and Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-12 Nishi-6, Kita-ku, Sapporo 060, Japan

Received March 3, 1997[⊗]

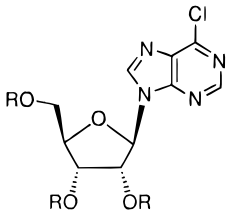
In spite of exclusive lithiation at the 8-position of 9-(2,3,5-tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloropurine (**2**) with LDA, subsequent quenching of its lithiated species with Bu_3SnCl (or TMSCl) results in the formation of 2-substituted products. Under optimized reaction conditions, where LTMP was used as a lithiating agent, 9-(2,3,5-tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-(tributylstannyl)purine (**11**) was formed in quantitative yield. Several experiments carried out to verify the reaction mechanism suggested that an anionic stannyl (or silyl) transfer from the 8- to the 2-position had been involved. Manipulation of the 2-tributylstannyl group in **11** and in its adenine counterpart (**22**) has disclosed a new entry to 2-substituted purine nucleosides. This chemistry was briefly applied to the synthesis of the 2-fluoro analogue of neplanocin A.

Introduction

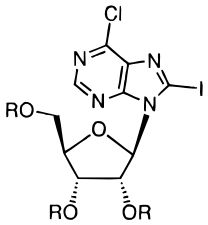
Lithiation (hydrogen−lithium exchange) of purine nucleosides started with the finding by Barton *et al.* that 8-alkylation of *N*-methyl derivatives of 2′,3′-*O*-isopropylideneadenosine can be achieved by way of lithiation with butyllithium followed by alkylation.[1,2] Later, in 1983, we reported an improved method for the synthesis of 8-carbon-substituted purine nucleosides in which 6-chloro-9-(2,3-*O*-isopropylidene-*β*-D-ribofuranosyl)purine (**1**) was used as a substrate for lithiation.[3] In this instance, the use of butyllithium as a lithiating agent appeared to be unsatisfactory due to the intervention of halogen−lithium exchange.[4] The use of LDA for the lithiation of **1**, on the other hand, enabled a clean conversion to the 8-lithiated species to give a yield of more than 80%. Its reaction with carbon electrophiles (such as MeI, PhCHO, EtCHO, Ph_2CO, and Et_2CO), combined with the feasibility of subsequent nucleophilic substitution at the 6-position, has provided a general entry to various types of 8-carbon-substituted purine nucleosides.[5]



1



2 R = TBDMS



3 R = TBDMS

It is well known that, unlike 8-substituted purine nucleosides, the 2-substituted derivatives adopt an *anti*-glycosidic conformation due to the absence of a substituent *ortho* to the glycosyl bond.[6] Therefore, the 2-substituted purine nucleosides are considered to serve as mimics of naturally occurring purine nucleosides. Synthesis of these analogues has previously mostly been accomplished by either the classical condensation method or the ring closure of imidazole nucleoside precursors.[7] Consequently, there have only been a limited number of approaches available for constructing C−C bonds at the 2-position of purine nucleosides. These involve a homolytic methylation[8] and nucleophilic substitution with

* Corresponding author. Phone: 81-3-3784-8187. Fax: 81-3-3784-8252.
† Showa University.
§ Hokkaido University.
‡ Current address: School of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274, Japan.
|| Currrent address: Tsumura Central Research Laboratories, 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-11, Japan.
⊗ Abstract published in *Advance ACS Abstracts*, September 15, 1997.

(1) Barton, D. H. R.; Hedgecock, C. J. R.; Lederer, E.; Motherwell, W. B. *Tetrahedron Lett.* **1979**, 279.
(2) The halogen−lithium exchange of trimethylsilylated 8-bromopurine nucleosides has also been reported: Công-Danh, N.; Beaucourt, J.-P.; Pichat, L. *Tetrahedron Lett.* **1979**, 2385.
(3) Tanaka, H.; Uchida, Y.; Shinozaki, M.; Hayakawa, H.; Matsuda, A.; Miyasaka, T. *Chem. Pharm. Bull.* **1983**, *31*, 787.
(4) There can be seen an inconsistency between our result and the following report, in which 6-chloro-9-(tetrahydropyran-2-yl)purine underwent 8-lithiation with butyllithium and, upon treatment with carbon electrophiles, gave the 8-carbon-substituted derivatives in good yields: Leonard, N. J.; Bryant, J. D. *J. Org. Chem.* **1979**, *44*, 4612.
(5) For the LDA lithiation of naturally occurring purine nucleosides, see: (a) Hayakawa, H.; Haraguchi, K.; Tanaka, H.; Miyasaka, T. *Chem. Pharm. Bull.* **1987**, *35*, 72. (b) Hayakawa, H.; Tanaka, H.; Haraguchi, K.; Mayumi, M.; Nakajima, M.; Sakamaki, T.; Miyasaka, T. *Nucleosides Nucleotides* **1988**, *7*, 121. (c) Hayakawa, H.; Tanaka, H.; Sasaki, K.; Haraguchi, K.; Saitoh, T.; Takai, F.; Miyasaka, T. *J. Heterocycl. Chem.* **1989**, *26*, 189.
(6) Saenger, W. *Principles of Nucleic Acid Structure*; Springer-Verlag: New York, 1984.
(7) For a review article, see: Srivastava, P. C.; Robins, R. K.; Meyer, R. B., Jr. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1988; Vol. 1, pp 113−281.
(8) Maeda, M.; Nushi, K.; Kawazoe, Y. *Tetrahedron* **1974**, *30*, 2677.

S0022-3263(97)00398-8 CCC: $14.00

Table 1. Lithiation of 2 with LTMP and Subsequent Reactions with Electrophiles[a]

entry	LTMP (equiv)	electrophile (equiv)	HMPA (equiv)	products (% yield by isolation)
1	1.2	TMSCl (1.2)		**2** (40), **4** (49), and **5** plus **6** (10, *ca.* 1:2)
2	1.2	Bu_3SnCl (1.2)		**2** (29), **9**, (8), and **10** plus **11** (57, *ca.* 3:2)
3	1.2	CH_3OD (excess)		8-deuterated **2** (98)[b]
4	5.0	TMSCl (1.2)		**2** (43), **4** (23), and **6** (23)
5	5.0	Bu_3SnCl (1.2)		**2** (59), **9** (7), and **11** (32)
6	5.0	CH_3OD (excess)		deuterated **2** (90)[c]
7	5.0	TMSCl (1.2)	10	**2** (5) and **6** (83)
8	5.0	Bu_3SnCl (1.2)	10	**11** (90)
9	5.0	Bu_3SnCl (5.0)		**11** (100)[d]

[a] Purification of the products was carried out by Florisil column chromatography, except for entry 9. [b] Deuterium was incorporated exclusively into the C8-position to the extent of 100% (calculated by ^{1}H NMR spectroscopy). [c] A mixture consisting of **2** (5%), 8-deuterated **2** (84%), and 2,8-dideuterated **2** (11%) (calculated by ^{1}H NMR spectroscopy). [d] Purification of the product was performed by silica gel column chromatography.

cyanide.[9] An apparent drawback of these methods lies in their narrow scope. An alternative and frequently used approach starts with the use of 6-chloro-2-iodopurine nucleosides,[10,11] the preparation of which necessitates guanine precursors for generating the 6-chloropurin-2-yl radical.[12]

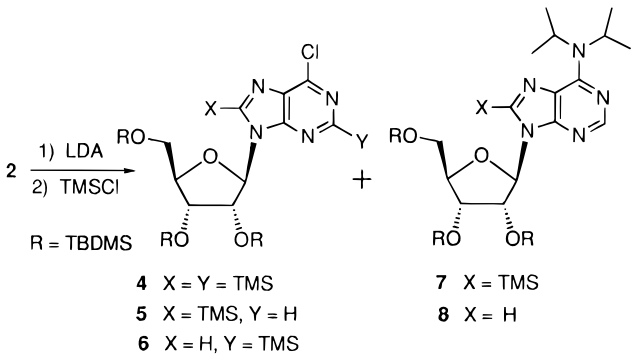
During our continuing studies on lithiation chemistry of nucleosides, we found that quenching of the 8-lithiated species of 9-(2,3,5-tris-*O*-TBDMS-β-D-ribofuranosyl)-6-chloropurine (**2**) with TMSCl (or Bu_3SnCl) gave the corresponding 2-substituted product, as a result of silyl (or stannyl) transfer from the 8- to the 2-position. The present paper describes the details of this reaction as well as the use of the resulting 2-tributylstannyl derivative for the synthesis of 2-substituted purine nucleosides.[13]

Results and Discussion

Lithiation-Based Silyl and Stannyl Transfer from the 8- to the 2-Position. When lithiation of **2** was carried out with LDA (1.2 equiv) in THF below −70 °C and the resulting lithiated species quenched by adding CH_3OD, deuterium was incorporated solely into the 8-position to the extent of 89% (98% recovery). This is fully in accord with the previous result obtained by using **1**.[3] Additional evidence to support the exclusive 8-lithiation of **2** came from the fact that quenching with iodine gave the 8-iodo derivative **3** in 93% yield. The structure of **3** was readily deduced by ^{1}H NMR spectroscopy: anisotropic deshielding by the nitrogen atom at the 3-position, due to the *syn*-glycosidic conformation of **3**, was observed in its H-2′ (δ 5.50) as compared with that of **2** (δ 4.58).

In contrast to this, when the same lithiated species of **2** was treated with TMSCl (1.2 equiv), several products (**4**−**8**) were obtained after Florisil column chromatography along with recovered **2** (33%) (Scheme 1): the 2,8-bis-TMS derivative **4** (15%), an inseparable mixture consisting of **5** plus **6** (*ca.* 4:1, combined yield 10%), **7** (28%), and **8** (14%). The ratio of the products varied significantly when silica gel was used as an adsorbent,

Scheme 1



presumably due to protonolysis of the silyl group during the chromatography.

Apart from the question of why the 2-silylated derivatives **4** and **6** were produced, it is apparent that **7** and **8** resulted from nucleophilic displacement with LDA. The fact that such undesired displacement was not observed during the formation of the 8-iodo derivative **3** suggests that the TMSCl was acting as a Lewis acid to coordinate with the purine ring, for example, at the N1-position. One would readily anticipate that the presence of a more bulky lithium dialkylamide could not allow such a reaction pathway. When LTMP (1.2 equiv) was employed in the above lithiation-based silylation of **2**, only the 6-chloropurine derivatives **4**−**6** were formed (entry 1 in Table 1). As shown in entry 2, the use of Bu_3SnCl as an electrophile gave basically the same result, forming the bis-stannylated (**9**) and monostannylated (**10** and **11**) products. That the initial lithiation had taken place exclusively at the 8-position in entries 1 and 2 was confirmed again by deuterium incorporation (entry 3).

It is interesting to see that, with an increased amount of LTMP (5.0 equiv), recovery of **2** remained much the same (entry 4) or became even higher (entry 5). Also, there can be seen in common in entries 4 and 5 that a higher yield of the 2-substituted product (**6** or **11**) resulted at the expense of the 8-substituted derivative (**5** or **10**). Since the yield of **4** plus **6** (entry 4, 46%) or **9** plus **11** (entry 5, 39%) exceeds the extent of the 2,8-dilithiated species of **2** (entry 6, 11%, see footnote), it would be reasonable to assume that initial introduction of the 8-TMS or 8-$SnBu_3$ groups facilitated further lithiation at the 2-position and that the subsequent reaction leading to the 2-substituted products involves lithiation-based transfer of the silyl or stannyl group from the 8- to the 2-position. We found that a high-yield formation of the 2-substituted derivative (**6** or **11**) can be accomplished either by adding HMPA (10 equiv) as an additive (entries 7 and 8) or by using an increased

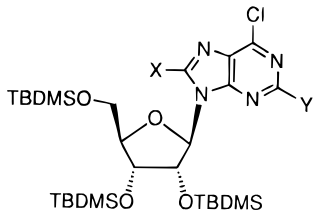
(9) Matsuda, A.; Nomoto, Y.; Ueda, T. *Chem. Pharm. Bull.* **1979**, *27*, 183.

(10) (a) Nair, V.; Lyons, A. G. *Tetrahedron* **1990**, *46*, 7677. (b) Nair, V.; Purdy, D. F. *Tetrahedron* **1991**,*47*, 365. (c) Adah, S. A.; Nair, V. *Tetrahedron Lett.* **1995**, *36*, 6371.

(11) (a) Matsuda, A.; Shonozaki, M.; Miyasaka, T.; Machida, H.; Abiru, T. *Chem. Pharm. Bull.* **1985**, *33*, 1766. (b) Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. *J. Med. Chem.* **1992**, *35*, 241.

(12) (a) Nair, V.; Richardson, S. G. *Synthesis* **1982**, 670. (b) Nair, V.; Young, D. A. *J. Org. Chem.* **1985**, *50*, 406.

(13) A preliminary communication of the present study has been reported: Kato, K.; Hayakawa, H.; Tanaka, H.; Kumamoto, H.; Miyasaka, T. *Tetrahedron Lett.* **1995**, *36*, 6507.



9 X = Y = $SnBu_3$
10 X = $SnBu_3$, Y = H
11 X = H, Y = $SnBu_3$

amount of Bu_3SnCl and then subjecting the reaction mixture to silica gel column chromatography (entry 9) which effects protonolysis of the 8-stannyl group.[14]

Scheme 2

2 —(1) LTMP (5 equiv) / THF / HMPA; (2) **4** (1.0 equiv)→ **2** (12%)[a] + **6** (72%)[a]

[a] Yields were calculated based on the combined amount of **2** plus **4**.

6 —LTMP (5 equiv) / THF / HMPA→ no reaction

5 —LTMP (5 equiv) / THF→ **2** (29%) + **4** (10%) + **5** plus **6** (24%, *ca.* 1 : 1)

Several experiments were carried out to verify the assumption regarding silyl transfer from the 8- to the 2-position (Scheme 2). When the 2,8-bis-TMS derivative **4** (1.0 equiv) was employed as an electrophile in the reaction with the lithiated **2**, the 2-TMS derivative **6** was formed in 72% yield (based on the combined amount of **2** plus **4**). This fact indicates that **6** resulted not only from **4** through direct removal of the 8-TMS group but also from silyl transfer from **4** to **2**. That the 2-TMS group once introduced is stable under these lithiation conditions was confirmed by treating **6** with LTMP. More direct evidence was obtained upon LTMP lithiation of the isolated 8-TMS derivative **5**, resulting in the formation of not only the desilylated product **2** but also the 2-silylated products **4** and **6**. These experimental results enabled us to propose a possible reaction mechanism depicted in Scheme 3,[15] which can be summarized as follows: the inital lithiation occurs at the 8-position (exclusively with LDA, dominantly with LTMP) to give **2a**; the 8-TMS derivative **5** formed upon silylation of **2a** promptly undergoes lithiation at the 2-position with **2a** (or with the lithiating agent) to give **5a**; the reaction between **5a** and **5** gave the 2,8-bis-TMS derivative **4** and regenerated **2a** simultaneously; finally, silyl transfer from **4** to **2a** furnishes **6a** which is stable under the lithiation conditions and thus is accumulated. A high-yield formation of **6** observed in the presence of HMPA would be explicable as a consequence of increased silaphilicity of the lithiated species such as **2a** and **5a**. We believe that the stannylation reaction of **2** follows a similar pathway.[16] It is worth mentioning that the presence of the electronegative 6-chlorine atom plays an important role in this transfer, since the reaction of 2′,3′,5′-tris-*O*-TBDMS-*N*,*N*-dimethyladenosine under the conditions in entry 8 gave the corresponding 8-stannyl derivative as the sole product.[17]

Since stannylated organic molecules undergo further functionalization, for example, through the Stille reaction,[18] the present 2-stannylation method will find wider use for the synthesis of 2-substituted purine derivatives in general, if the sugar moiety has no effect on the reaction.[19] When 6-chloro-9-methylpurine (**12**) was used as a substrate, although concomitant stannylation of the 9-methyl substituent occurred in this instance as shown in Scheme 4, the combined yield of the 2-stannylated products (**13**, 48%; **14**, 44%) suggests that the present method would provide an efficient entry to the synthesis of 2-substituted purine derivatives.

Synthesis of 2-Substituted Purine Ribonucleosides by Manipulation of the 2-Tributylstannyl Group. To show the usefulness of the present chemistry for the synthesis of purine nucleosides variously substituted at the 2-position, several transformations were carried out by using the 2-stannyl derivative **11** as shown in Scheme 5. Compound **11** readily undergoes halogenation in THF when treated with iodine or *N*-halosuccinimides to give **15**−**17**.

Regiochemical assignment of these 2-substituted products was confirmed by $^{13}C-^{1}H$ COLOC (correlation *via* long-range coupling) spectroscopy. Since carbon atoms other than C-5 in the 6-chloropurine ring (and also in the adenine ring) are bound to two electronegative atoms, the ^{13}C resonance of **2** which appeared at the highest field (δ 132.1) is assignable to C-5. When $^{13}C-^{1}H$ COLOC was seen between a ring proton and C-5, the compounds are determined to be 2-substituted derivatives. In the 2-iodo derivative **15**, correlation of a ring proton (δ 8.47) was seen in both C-5 (δ 132.3) and C-4 (δ 151.9), and C-2 appeared at δ 116.3. On the other hand, in the 8-iodo derivative **3**, such a correlation of a ring proton (δ 8.65) was not observed with C-5 (δ 134.8) but with both C-4 and C-6 (δ 151.9 or 149.8), and C-8 appeared at a significantly higher field of δ 109.8 due to the presence of the iodine atom.

It was also possible to prepare the 2-fluoro derivative **18** by using XeF_2 in the presence of AgOTf and 2,6-di(*tert*-butyl)-4-methylpyridine.[20] For C−C bond formation, the Stille reaction was applied. Thus, compounds **19** and **20** were prepared in refluxing THF in the presence of $Pd(PPh_3)_4$/CuI by using BnBr and PhI, respectively. Introduction of a benzoyl group could be performed with

(14) Protonolysis of stannylated heterocycles with silica gel has been reported: Sakamoto, T.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1993**, *41*, 478.

(15) For an example of anionic C−C silyl rearrangement, see: Daney, M.; Lapouyade, R.; Bouas-Laurent, H. *J. Org. Chem.* **1983**, *48*, 5055.

(16) Rearrangement of a stannyl group has been reported recently in the lithiation of a stannylated heterocycle: Kelly, T. R.; Lang, F. *Tetrahedron Lett.* **1995**, *36*, 9293.

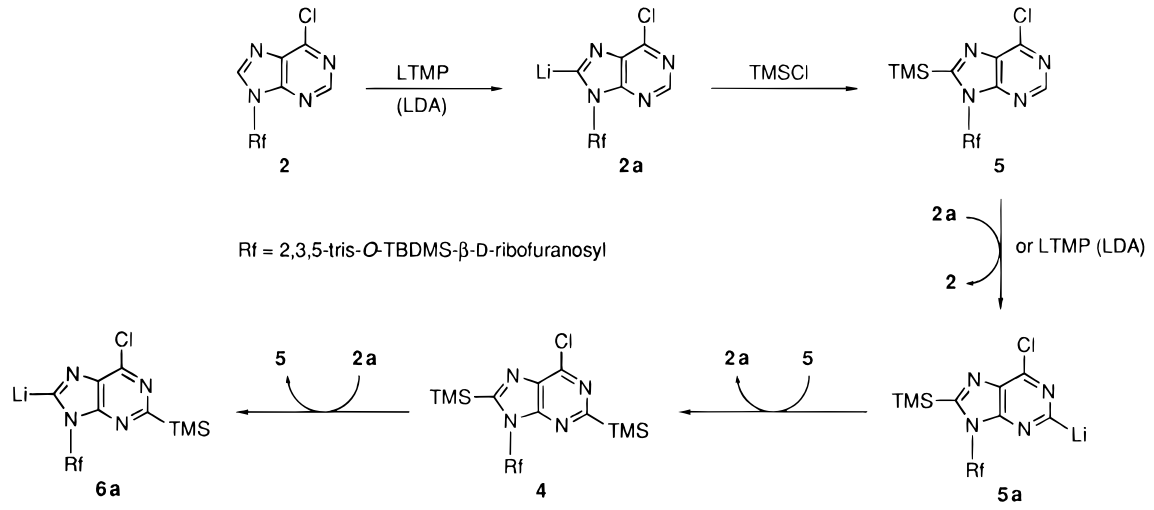
(17) Although almost quantitative formation of the 8-tributylstannyl derivative was apparent from TLC analysis (basic alumina plate, hexane/EtOAc = 10/1) of the reaction mixture, the product was isolated only in 35% yield after Florisil column chromatography, resulting in the formation of the starting material in 50% yield (see the Experimental Section).

(18) For a review concerning the Stille reaction, see: Mitchell, T. N. *Synthesis* **1992**, 803.

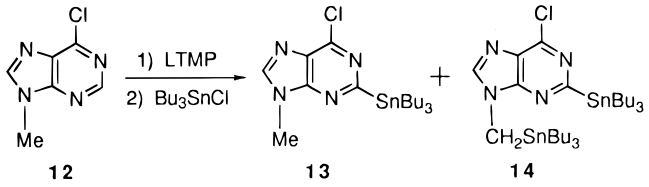
(19) It has been reported that the extent of lithiation at the 6-position of uridine (or acyclouridine) derivatives is affected by the structure of the sugar (or acyclic) moiety: (a) Hayakawa, H.; Tanaka, H.; Maruyama, Y.; Miyasaka, T. *Chem. Lett.* **1985**, 1401. (b) Hayakawa, H.; Tanaka, H.; Obi, K.; Itoh, M.; Miyasaka, T. *Tetrahedron Lett.* **1987**, *28*, 87. (c) Tanaka, H.; Miyasaka, T.; Sekiya, K.; Takashima, H.; Ubasawa, M.; Nitta, I.; Baba, M.; Walker, R. T.; De Clercq, E. *Nucleosides Nucleotides* **1992**, *11*, 447.

(20) (a) Tius, M. A.; Kawakami, J. K. *Synth. Commun.* **1992**, *22*, 1461. (b) Tius, M. A. *Tetrahedron* **1995**, *51*, 6605.

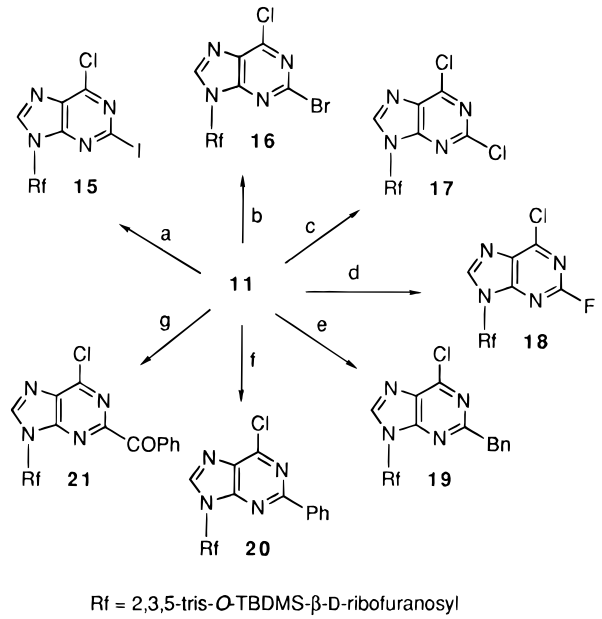
Scheme 3



Scheme 4



Scheme 5[a]



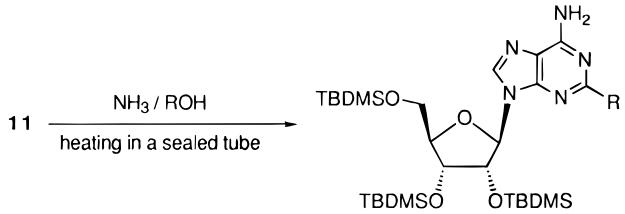
[a] Reagents (isolated yields are shown in parentheses): (a) iodine, THF (97%); (b) NBS, THF (92%); (c) NCS, THF (95%); (d) XeF_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2 (85%); (e) BnBr, $Pd(PPh_3)_4$, CuI, THF (55%); (f) PhI, $Pd(PPh_3)_4$, CuI, THF (41%); (g) PhCOCl, pyridine, toluene (60%).

PhCOCl/pyridine in refluxing toluene to give the 2-benzoyl derivative **21** without using palladium catalysis.[21] These C−C bond-forming reactions required a longer reaction time (for 20−24 h), and in some cases, formation of the destannylated product (**2**) was observed.

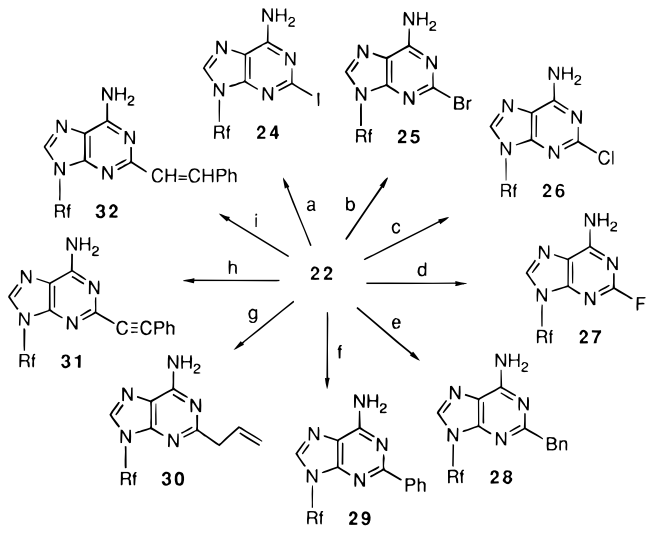
The above series of reactions were also examined after converting **11** to the 2-stannylated adenosine derivative **22**. When this conversion (Scheme 6) was carried out

(21) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 2003.

Scheme 6



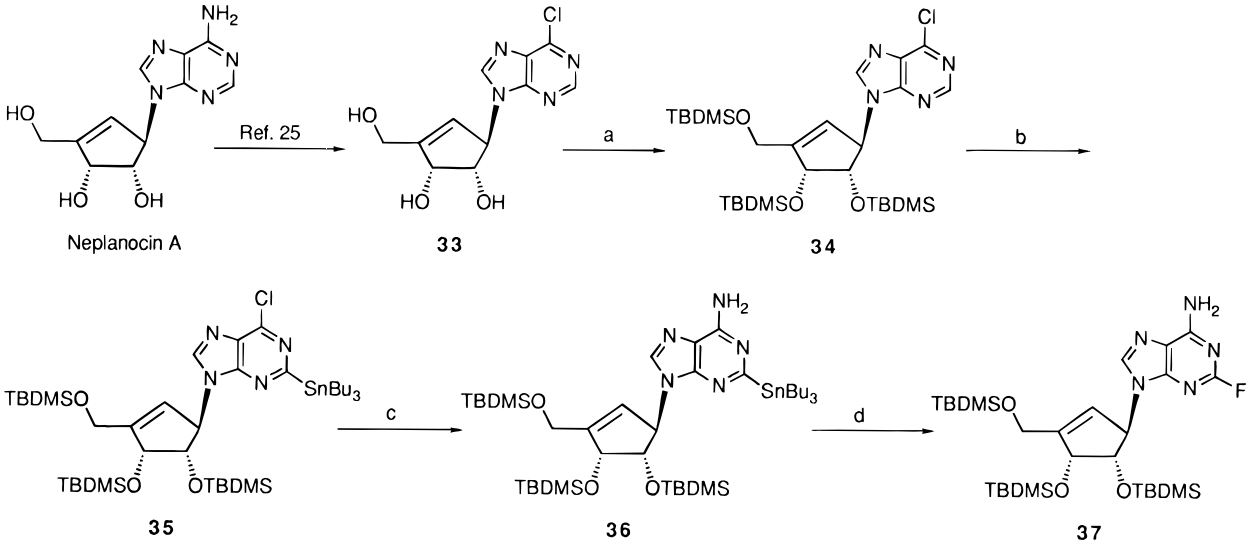
Scheme 7[a]



[a] Reagents (isolated yields are shown in parentheses): (a) iodine, THF (100%); (b) NBS, THF (90%); (c) NCS, THF (70%); (d) XeF_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2 (80%); (e) BnBr, $Pd(PPh_3)_4$, CuI, THF (83%); (f) PhI, $Pd(PPh_3)_4$, CuI, THF (89%); (g) allyl bromide, $Pd(Ph_3)_4$, CuI, THF (63%); (h) PhC≡CI, $Pd(PPh_3)_4$, CuI, THF (72%); (i) PhCH=CHBr, $Pd(PPh_3)_4$, CuI, THF (40%).

by heating with NH_3/MeOH in a sealed tube at 100 °C, **22** was obtained only in moderate yield (50−60%) with concomitant formation of 2′,3′,5′-tris-*O*-TBDMS-adenosine (**23**).[5a,22] Since **11** gave mainly the destannylated product upon treatment with K_2CO_3/MeOH, it was conceivable that methoxide formed in the NH_3/MeOH was responsible for the formation of **23**. When NH_3/2-

Scheme 8[a]



[a] Reagents (isolated yields are shown in parentheses): (a) TBDMSCl, imidazole, DMF (82%); (b) LTMP, THF, and then Bu_3SnCl (100%); (c) NH_3, 2-propanol (78%); (d) XeF_2, AgOTf, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2 (53%).

propanol (*ca.* 5%, saturated at 0 °C) was used for the above ammonolysis of **11**, **22** was obtained in 92% yield with only a small amount (6%) of **23**.

Compounds **24**−**32** were synthesized by using **22** under similar conditions to those employed in the reactions of **11**, as shown in Scheme 7. Compounds **29**−**32** were prepared by the procedure described for the preparation of the 2-benzyl-6-chloropurine derivative **19**. The 2-benzyl (**28**) and 2-phenyl (**29**) derivatives were isolated in slightly higher yields than those obtained from **11**. The preparations of **30** and **31** were carried out by using allyl bromide and iodophenylacetylene, respectively. Compound **32** was obtained as a mixture of two geometrical isomers (*E*/*Z* = 6/1) by the use of *β*-bromostyrene (a mixture of isomers).

Synthesis of the 2-Fluoro Derivative of Nucleoside Antibiotic Neplanocin A. Among the vast number of nucleoside antibiotics, including carbocyclic nucleosides, compounds having adenine as a nucleobase constitute the largest family.[23] Their 2-substituted analogues have mostly been synthesized by condensation of the base and sugar (or carbocyclic) moiety,[24] due to the lack of an appropriate method for functionalizing the 2-position of intact purine nucleosides. We briefly applied the present method to the synthesis of the 2-fluoro analogue of neplanocin A (Scheme 8).

The preparation of 6-chloro-9-[(1*R*,2*S*,3*R*)-4-(hydroxymethyl)-2,3-dihydroxy-4-cyclopenten-1-yl]purine (**33**) from neplanocin A has a precedent.[25] Protection of the hydroxyl groups of **33** with TBDMS gave **34**. Lithiation-based stannylation of **34** was carried out under the reaction conditions shown in entry 9 in Table 1 to give the corresponding 2-tributylstannylated product **35** in quantitative yield. Ammonolysis of **35** furnished the adenine derivatives **36**. The 2-fluoroneplanocin A (**37**) was prepared from **36** by using XeF_2 as mentioned in the preparation of **18**.

Conclusion

Although the initial lithiation of 6-chloropurine nucleoside with lithium dialkylamides takes place at the 8-position, it was found in the present study that reaction of the 8-lithiated species with tin and silicon electrophiles furnished 2-functionalized products. Several experiments were carried out to verify that the mechanism involved an anionic transfer of a stannyl or silyl group from the 8- to the 2-position. The resulting 2-stannylated product obtained in quantitative yield can be used for further transformations. This constitutes a new entry into 2-substituted purine nucleosides which previously have been difficult to synthesize starting from naturally occurring nucleosides. An application of this approach to the synthesis of the 2-fluoro analogue of neplanocin A was also accomplished.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured at 23 °C (internal standard, Me_4Si) at either 400 or 500 MHz. ^{13}C NMR chemical shifts are shown only for purine ring carbons. Mass spectra (MS) were taken in the FAB mode (*m*-nitrobenzyl alcohol as a matrix). For compounds containing Cl and/or Sn, ion peaks corresponding to ^{35}Cl and/or ^{120}Sn are shown. Column chromatography was carried out on Florisil (Merck) or silica gel (silica gel 60, Merck). Thin layer chromatography (TLC) was performed on basic alumina (precoated plate, aluminum oxide 60 F_{254}, type E, Merck) or silica gel (precoated silica gel plate F_{254}, Merck).

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloropurine (2). A mixture of 6-chloro-9-(*β*-D-ribofuranosyl)purine (14.3 g, 49 mmol), TBDMSCl (40.2 g, 250 mmol), and imidazole (25.4 g, 340 mmol) in DMF (200 mL) was stirred at room temperature for 15 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column (hexane/EtOAc = 30/1). This gave **2** (30.1 g, 98%) as a foam. Crystallization from hexane gave an analytical sample (mp 138 °C): UV (MeOH) λ_{max} 265 nm (ϵ

(22) Destannylation with aqueous ammonia has been reported in the reaction of a stannylated heterocycle: Uchiyama, D.; Yabe, M.; Kameyama, H.; Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1996**, *43*, 1301.

(23) For a review article concerning nucleoside antibiotics, see: Isono, K. *J. Antibiot.* **1988**, *41*, 1711.

(24) For a recent example, see: Obara, T.; Shuto, S.; Saito, Y.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E.; Matsuda, A. *J. Med. Chem.* **1996**, *39*, 3847.

(25) Shuto, S.; Obara, T.; Toriya, M.; Hosoya, M.; Snoeck, R.; Andrei, G.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1992**, *35*, 324.

9400), λ_{min} 227 nm (ϵ 3100); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03, −0.02, 0.09, 0.10, 0.15, and 0.16 (18H, each as s), 0.79, 0.93, and 0.96 (27H, each as s), 3.80 (1H, dd, J = 11.6, 2.6 Hz), 4.02 (1H, dd, J = 11.6, 3.6 Hz), 4.15−4.17 (1H, m), 4.30 (1H, dd, J = 4.5, 3.7 Hz), 4.58 (1H, dd, J = 5.1, 4.5 Hz), 6.13 (1H, d, J = 5.1 Hz), 8.55 (1H, s), 8.74 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 132.1, 144.1, 151.0, 151.5, 151.9; FAB-MS m/z 629 ($M^+ + H$). Anal. Calcd for $C_{28}H_{53}ClN_4O_4Si_3$: C, 53.42; H, 8.48; N, 8.90. Found: C, 53.58; H, 8.75; N, 8.89.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-8-iodopurine (3). To a THF (5 mL) solution of LDA (0.6 mmol) was added **2** (314 mg, 0.5 mmol) in THF (3 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. The mixture was stirred for 5 min and then treated with iodine (152.4 mg, 0.6 mmol as I_2) in THF (3 mL). After being stirred at below −70 °C for 0.5 h, the reaction mixture was diluted with 5% aqueous $Na_2S_2O_3$ and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and chromatographed on a silica gel column (hexane/EtOAc = 50/1). This afforded **3** (351 mg, 93%) as a syrup: UV (MeOH) λ_{max} 276 nm (ϵ 14 200), λ_{min} 240 nm (ϵ 7700); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.37, −0.05, −0.02, 0.04, 0.18, and 0.19 (18H, each as s), 0.81, 0.84, and 0.99 (27H, each as s), 3.74 (1H, dd, J = 11.0, 4.0 Hz), 4.03 (1H, dd, J = 11.0, 8.0 Hz), 4.09−4.11 (1H, m), 4.59 (1H, dd, J = 4.4, 3.0 Hz), 5.50 (1H, dd, J = 6.0, 4.4 Hz), 5.98 (1H, d, J = 6.0 Hz), 8.65 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 109.8, 134.8, 149.8, 151.2, 151.9; FAB-MS m/z 755 ($M^+ + H$). Anal. Calcd for $C_{28}H_{52}ClIN_4O_4Si_3$: C, 44.52; H, 6.94; N, 7.42. Found: C, 44.86; H, 7.15; N, 7.06.

Lithiation of 2 with LDA and Subsequent Silylation: Formation of 4−8. To a THF (10 mL) solution of LDA (0.6 mmol) was added **2** (315 mg, 0.5 mmol) in THF (5 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. After the mixture was stirrred for 5 min, TMSCl (140 μL, 0.6 mmol) was added, and stirring was further continued for 0.5 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Florisil column chromatography of the organic layer gave **4** (elution with hexane/EtOAc = 100/1, syrup, 58 mg, 15%), a mixture of **5** plus **6** (elution with hexane/EtOAc = 50/1, syrup, 35 mg, *ca.* 4:1, 10%), and **2** (elution with hexane/EtOAc = 30/1, 104 mg, 33%). Further elution with hexane/EtOAc = 10/1 gave **7** (syrup, 107 mg, 28%) and then **8** (foam, 49 mg, 14%).

Physical data of **4** are as follows: UV (MeOH) λ_{max} 275 nm (ϵ 11 000), λ_{min} 239 nm (ϵ 4000); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.51, −0.21, 0.08, 0.09, 0.14, and 0.18 (18H, each as s), 0.40 and 0.53 (18H, each as s), 0.66, 0.92, and 0.96 (27H, each as s), 3.70 (1H, dd, J = 10.5, 4.4 Hz), 3.98 (1H, t, J = 10.5 Hz), 4.06 (1H, dd, J = 10.5, 4.2 Hz), 4.31 (1H, d, J = 4.0 Hz), 5.77 (1H, dd, J = 8.4, 4.0 Hz), 6.11 (1H, d, J = 8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) δ 132.7, 150.0, 152.6, 164.9, 173.7; FAB-MS m/z 773 ($M^+ + H$). Anal. Calcd for $C_{34}H_{69}ClN_4O_4Si_5 \cdot H_2O$: C, 51.57; H, 9.04; N, 7.08. Found: C, 51.86; H, 9.04; N, 6.90.

For physical data of **5** and **6**, see the individual part given below.

Due to the instability of **7** under chromatographic conditions, its analytically pure sample could not be obtained. Physical data of **7** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.18, −0.06, 0.05, 0.12, and 0.14 (18H, each as s), 0.38 (9H, s), 0.80, 0.90, and 0.94 (27H, each as s), 1.24, 1.26, 1.33, and 1.36 (each as d, J = 7.0 Hz), 3.55 (1H, t, J = 10.5 Hz), 3.64−3.70 (1H, m), 3.69 (1H, dd, J = 10.3, 4.4 Hz), 3.89 (1H, dd, J = 10.3, 4.4 Hz), 4.16 (1H, d, J = 4.4 Hz), 4.83 (1H, sept, J = 7.0 Hz), 5.35 (1H, dd, J = 8.8 Hz), 5.82 (1H, d, J = 8.8 Hz), 8.17 (1H, s); FAB-MS m/z 767 ($M^+ + H$).

Physical data of **8** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.20, −0.05, 0.08, 0.11, and 0.12 (18H, each as s), 0.80, 0.91, and 0.94 (27H, each as s), 1.24, 1.25, 1.31, and 1.32 (12H, each as d, J = 7.0 Hz), 3.63 (1H, sept, J = 7.0 Hz), 3.73 (1H, dd, J = 11.3, 2.2 Hz), 3.83 (1H, dd, J = 11.3, 3.2 Hz), 3.99−4.02 (1H, m), 4.16−4.19 (1H, m), 4.20 (1H, dd, J = 10.2, 4.4 Hz), 4.67 (1H, sept, J = 7.0 Hz), 5.86 (1H, d, J = 6.2 Hz), 7.55 (1H, s), 8.27 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 94.8, 118.4, 131.9, 151.3, 152.8; FAB-MS m/z 695 ($M^+ + H$). Anal. Calcd for $C_{24}H_{67}N_5O_4Si_3 \cdot 2H_2O$: C, 55.65; H, 9.81; N, 9.59. Found: C, 55.92; H, 9.80; N, 9.59.

Lithiation of 2 with LTMP (1.2 equiv) and Subsequent Stannylation: Formation of 9−11 (Table 1, entry 2). To a THF (10 mL) solution of LTMP (0.6 mmol) was added **2** (315 mg, 0.5 mmol) in THF (5 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. After the mixture was stirred for 5 min, Bu_3SnCl (400 μL, 0.6 mmol) was added, and stirring was further continued for 0.5 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Florisil column chromatography (hexane/EtOAc = 100/1) of the organic layer gave **9** (syrup, 48 mg, 8%) and a mixture of **10** plus **11** (syrup, 261 mg, *ca.* 3:2, 57%). The starting material **2** (91 mg, 29%) was recovered by elution with hexane/EtOAc = 30/1.

Compounds **9** and **10** were unstable, and their pure samples could not be obtained. For physical data of **11**, see the corresponding part given below.

Partial ^{1}H NMR data of **9** are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.47, −0.19, −0.18, 0.15, 0.17, and 0.18 (18H, each as s), 0.86−0.97, 1.17−1.21, 1.29−1.42, and 1.50−1.57 (54H, each as m), 3.70−3.74 (1H, m), 3.90 (1H, t, J = 10.2 Hz), 3.97−4.01 (1H, m), 4.28 (1H, t, J = 3.3 Hz), 5.74−5.82 (2H, m).

Physical data of **10** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.41, −0.19, 0.07, 0.08, 0.15, and 0.17 (18H, each as s), 0.69, 0.91, and 0.98 (27H, each as s), 0.88−0.90, 1.26−1.50, and 1.59−1.65 (27H, each as m), 3.71 (1H, dd, J = 9.2, 3.2 Hz), 4.02 (1H, t, J = 9.2 Hz), 4.04−4.07 (1H, m), 4.38 (1H, t, J = 4.0 Hz), 5.74−5.80 (2H, m), 8.60 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 134.8, 149.7, 150.2, 153.0, 171.4; FAB-MS m/z 919 ($M^+ + H$).

Preparation of 9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-8-(trimethylsilyl)purine (5). To a THF (10 mL) solution of 2,2,6,6-tetramethylpiperidine (250 μL, 1.5 mmol) kept below −70 °C were added **2** (315 mg, 0.5 mmol) in THF (5 mL) and TMSCl (130 μL, 0.6 mmol) successively under a positive pressure of dry Ar. To this mixture was added BuLi (800 μL, 0.6 mmol, hexane solution) dropwise, while maintaining the reaction temperature below −70 °C. After stirring for 5 min, saturated aqueous $NaHCO_3$ was added to the reaction mixture. Extraction with CH_2Cl_2 followed by Florisil column chromatography (hexane/EtOAc = 100/1) gave **5** (213 mg, 61%) as an oil. Due to the instability of **5** under chromatographic conditions, its analytically pure sample could not be obtained: ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.43, −0.16, 0.09, 0.10, 0.16, and 0.18 (18H, each as s), 0.55 (9H, s), 0.70, 0.92, and 0.98 (27H, each as s), 3.72−3.76 (1H, m), 4.01−4.10 (2H, m), 4.39 (1H, d, J = 4.0 Hz), 5.74 (1H, dd, J = 7.7, 4.0 Hz), 6.09 (1H, d), 8.67 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 133.4, 150.6, 150.7, 153.8, 165.4; FAB-MS m/z 701 ($M^+ + H$).

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-(trimethylsilyl)purine (6). As a typical example for the preparation of this compound, the procedure used in entry 7 in Table 1 is shown below. To a mixture of LTMP (2.5 mmol) and HMPA (900 μL, 5.0 mmol) in THF (5 mL) was added **2** (315 mg, 0.5 mmol) in THF (3 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. After stirring for 5 min, TMSCl (77 μL, 0.6 mmol) was added to the lithiated mixture, and stirring was continued for 0.5 h below −70 °C. The reaction was quenched by adding aqueous NH_4Cl, and the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. Florisil column chromatography (hexane/EtOAc = 50/1) of the organic layer gave **6** (290 mg, 83%) as a syrup. Compound **2** (16 mg, 5%) was recovered by elution with hexane/EtOAc = 10/1. Physical data of **6**: UV (MeOH) λ_{max} 267 nm (ϵ 9000), λ_{min} 234 nm (ϵ 3700); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.20, −0.03, 0.09, 0.11, 0.14, and 0.16 (18H, each as s), 0.39 (9H, s), 0.79, 0.93, and 0.96 (27H, each as s), 3.82 (1H, dd, J = 11.4, 2.5 Hz), 4.03 (1H, dd, J = 11.4, 4.4 Hz), 4.12−4.15 (1H, m), 4.32 (1H, t, J = 4.4 Hz), 4.64 (1H, t, J = 4.4 Hz), 6.14 (1H, d, J = 4.4 Hz), 8.49 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.0, 143.7, 150.0, 150.7, 174.8; FAB-MS m/z 701 ($M^+ + H$). Anal. Calcd for

$C_{31}H_{61}ClN_4O_4Si_4 \cdot 2H_2O$: C, 50.48; H, 8.88; N, 7.59. Found: C, 50.14; H, 8.65; N, 7.22.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-(tributylstannyl)purine (11). As a typical example for the preparation of this compound, the procedure used in entry 9 in Table 1 is shown below. To a THF (5 mL) solution of LTMP (2.5 mmol) was added **2** (315 mg, 0.5 mmol) in THF (3 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. After stirring for 5 min, Bu_3SnCl (670 μL, 2.5 mmol) was added to the lithiated mixture, and stirring was continued for 0.5 h below −70 °C. The reaction was quenched by adding aqueous NH_4Cl, and the mixture was partitioned between saturated aqueous $NaHCO_3$ and EtOAc. Silica gel column chromatography (hexane/EtOAc = 80/1) of the organic layer gave **11** (457 mg, 100%), which was crystallized from MeOH (mp 66−68 °C): UV (MeOH) λ_{max} 270 nm (ϵ 9200), λ_{min} 236 nm (ϵ 7700); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.20, −0.02, 0.09, 0.10, 0.15, and 0.17 (18H, each as s), 0.88 (9H, t, J = 7.3 Hz), 0.90, 0.93, and 0.97 (27H, each as s), 1.19−1.21, 1.29−1.38, and 1.54−1.64 (18H, each as m), 3.82 (1H, dd, J = 11.3, 1.9 Hz), 4.01 (1H, dd, J = 11.3, 3.3 Hz), 4.14−4.16 (1H, m), 4.30 (1H, t, J = 4.4 Hz), 4.50 (1H, t, J = 4.4 Hz), 6.19 (1H, d, J = 4.4 Hz), 8.47 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 130.6, 142.4, 149.2, 150.7, 181.9; FAB-MS m/z 919 (M^+ + H). Anal. Calcd for $C_{40}H_{79}ClN_4O_4Si_3Sn$: C, 52.30; H, 8.67; N, 6.10. Found: C, 52.27; H, 8.82; N, 5.95.

Preparation of 2′,3′,5′-Tris-*O*-TBDMS-*N*,*N*-dimethyl-8-(tributylstannyl)adenosine. To a THF (4 mL) solution of LTMP (4.85 mmol) was added 2′,3′,5′-tris-*O*-TBDMS-*N*,*N*-dimethyladenosine (620 mg, 0.97 mmol) in THF (4 mL) dropwise under a positive pressure of dry Ar, while maintaining the reaction temperature below −70 °C. After stirring for 5 min, Bu_3SnCl (1.25 mL, 4.85 mmol) was added to the lithiated mixture, and stirring was continued for 0.5 h below −70 °C. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Florisil column chromatography of the organic layer gave 2′,3′,5′-tris-*O*-TBDMS-*N*,*N*-dimethyl-8-(tributylstannyl)adenosine (elution with hexane, 329 mg, 35%) as a syrup and the starting material (elution with hexane/EtOAc = 60/1, 310 mg, 50%). Due to the instability of the product under chromatographic conditions, its analytically pure sample could not be obtained: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.40, −0.18, 0.06, 0.08, 0.14, and 0.15 (18H, each as s), 0.88 (9H, t, J = 7.3 Hz), 0.72, 0.90, and 0.97 (27H, each as s), 1.23−1.27, 1.30−1.38, and 1.59−1.65 (18H, each as m), 3.53 (6H, s), 3.68 (1H, dd, J = 4.9, 10.3 Hz), 4.00 (1H, dd, J = 4.9, 10.3 Hz), 4.16 (1H, t, J = 10.3 Hz), 4.34 (1H, d, J = 4.2 Hz), 5.68 (1H, d, J = 7.2 Hz), 5.91 (1H, dd, J = 7.2, 4.2 Hz), 8.19 (1H, s); FAB-MS m/z 928 (M^+ + H).

6-Chloro-9-methyl-2-(tributylstannyl)purine (13) and 6-Chloro-2-(tributylstannyl)-9-[(tributylstannyl)methyl]purine (14). These compounds were prepared from **12** (170 mg, 1.0 mmol) by the procedure described for the preparation of **11**. The following amounts of reagents were used: LTMP (5.0 mmol) in THF (5 mL) and Bu_3SnCl (1.3 mL, 5.0 mmol). After addition of Bu_3SnCl, the reaction was continued for 1 h. Compounds **13** (220 mg, 48%) and **14** (327 mg, 44%) were isolated after extractive workup (aqueous $NaHCO_3/CH_2Cl_2$) followed by Florisil column chromatography (hexane/EtOAc = 20/1 for **14**, hexane/EtOAc = 10/1 for **13**).

Physical data of **13** obtained as a syrup are as follows: UV (MeOH) λ_{max} 270 nm (ϵ 6400), λ_{min} 243 nm (ϵ 5200); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (9H, t, J = 7.3 Hz), 1.19−1.22, 1.31−1.38, and 1.58−1.70 (18H, each as m), 3.91 (3H, s), 7.98 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 129.5, 144.0, 149.0, 151.2, 181.6; FAB-MS m/z 459 (M^+ + H). Anal. Calcd for $C_{18}H_{31}ClN_4Sn$: C, 47.24; H, 6.83; N, 12.24. Found: C, 47.39; H, 6.96; N, 12.22.

Physical data of **14** obtained as a syrup are as follows: UV (MeOH) λ_{max} 270 nm (ϵ 5700), λ_{min} 255 nm (ϵ 4900); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83 (9H, t, J = 7.3 Hz), 0.89 (9H, t, J = 7.3 Hz), 0.87−0.93, 1.23−1.40, 1.28−1.37, 1.38−1.44, and 1.58−1.68 (36H, each as m), 3.99 (2H, t, J = 11.3 Hz), 7.90 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 130.0, 144.1, 148.9, 151.0, 180.8; FAB-MS m/z 747 (M^+ + H). Anal. Calcd for $C_{30}H_{57}ClN_4Sn_2$: C, 48.26; H, 7.70; N, 7.50. Found: C, 48.40; H, 7.83; N, 7.40.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-iodopurine (15). A solution of **11** (450 mg, 0.49 mmol) and iodine (190.5 mg, 0.75 mmol as I_2) in THF (5 mL) was stirred at room temperature for 4 h. The reaction mixture was diluted with 5% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The extract was washed with brine, dried ($MgSO_4$), and chromatographed on a silica gel column (hexane/EtOAc = 50/1). This afforded **15** (370 mg, 97%) as a syrup: UV (MeOH) λ_{max} 282 nm (ϵ 9700), λ_{min} 249 nm (ϵ 7300); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.16, 0.01, 0.09, 0.10, 0.15, and 0.17 (18H, each as s), 0.84, 0.93, and 0.96 (27H, each as s), 3.80 (1H, dd, J = 11.5, 2.2 Hz), 4.04 (1H, dd, J =11.5, 4.0 Hz), 4.15−4.17 (1H, m), 4.29 (1H, dd, J = 4.0, 4.4 Hz), 4.54 (1H, dd, J = 4.0, 4.4 Hz), 6.02 (1H, d, J = 4.4 Hz), 8.47 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 116.3, 132.3, 144.2, 150.4, 151.9; FAB-MS m/z 755 (M^+ + H). Anal. Calcd for $C_{28}H_{52}ClIN_4O_4Si_3$: C, 44.52; H, 6.94; N, 7.41. Found: C, 44.92; H, 7.01; N, 7.29.

2-Bromo-9-(2,3,5-tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloropurine (16). A solution of **11** (102 mg, 0.11 mmol) and NBS (61 mg, 0.33 mmol) in THF (5 mL) was stirred for 0.5 h at room temperature. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Silica gel column chromatography (hexane/EtOAc = 50/1) of the extract gave **16** (67 mg, 92%) as a solid (mp 59−61 °C): UV (MeOH) λ_{max} 276 nm (ϵ 11 300), λ_{min} 239 nm (ϵ 6800); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.19, −0.01, 0.09, 0.10, 0.15, and 0.16 (18H, each as s), 0.82, 0.92, and 0.95 (27H, each as s), 3.79 (1H, dd, J = 11.9, 2.6 Hz), 4.03 (1H, dd, J = 11.9, 3.8 Hz), 4.15−4.17 (1H, m), 4.29 (1H, t, J = 4.4 Hz), 4.55 (1H, t, J = 4.4 Hz), 6.03 (1H, d, J = 4.4 Hz), 8.52 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.7, 143.0, 144.5, 151.4, 152.4; FAB-MS m/z 707 and 709 (M^+ + H). Anal. Calcd for $C_{28}H_{52}BrClN_4O_4Si_3$: C, 47.48; H, 7.40; N, 7.91. Found: C, 47.68; H, 7.55; N, 7.89.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-2,6-dichloropurine (17). A mixture of **11** (102 mg, 0.11 mmol) and NCS (50 mg, 0.33 mmol) in THF (5 mL) was stirred at room temperature for 23 h. The reaction mixture was partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. Silica gel column chromatography (hexane/EtOAc = 50/1) of the organic layer gave **17** (69 mg, 95%) as a solid (mp 121−122 °C): UV (MeOH) λ_{max} 274 nm (ϵ 10 700), λ_{min} 237 nm (ϵ 5700); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02, 0.00, 0.09, 0.10, 0.14, and 0.16 (18H, each as s), 0.82, 0.93, and 0.95 (27H, each as s), 3.79 (1H, dd, J = 11.3, 2.6 Hz), 4.03 (1H, dd, J = 11.3, 3.7 Hz), 4.15−4.17 (1H, m), 4.29 (1H, t, J = 4.6 Hz), 4.56 (1H, t, J = 4.6 Hz), 6.04 (1H, d, J = 4.6 Hz), 8.53 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 131.5, 144.8, 151.7, 152.6, 153.0; FAB-MS m/z 663 (M^+ + H). Anal. Calcd for $C_{28}H_{52}Cl_2N_4O_4Si_3$: C, 50.66; H, 7.90; N, 8.44. Found: C, 50.81; H, 8.09; N, 8.40.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-fluoropurine (18). A CH_2Cl_2 (5 mL) solution containing **11** (102 mg, 0.11 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (23 mg, 0.11 mmol), XeF_2 (51 mg, 0.30 mmol), and silver triflate (50 mg, 0.30 mmol) was stirred for 5 min under a positive pressure of dry Ar. Usual workup (see that for **16**) followed by silica gel column chromatography (hexane/EtOAc = 60/1) gave **18** (61 mg, 85%) as a solid (mp 121−124 °C): UV (MeOH) λ_{max} 269 nm (ϵ 9700), λ_{min} 237 nm (ϵ 4800); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.23, −0.01, 0.09, 0.10, 0.15, and 0.16 (18H, each as s), 0.80, 0.93, and 0.96 (27H, each as s), 3.79 (1H, dd, J = 11.0, 3.3 Hz), 4.01 (1H, dd, J = 11.0, 4.2 Hz), 4.15−4.17 (1H, m), 4.29 (1H, t, J = 4.4 Hz), 4.54 (1H, t, J = 4.4 Hz), 6.02 (1H, d, J = 4.4 Hz), 8.52 (1H, s); ^{13}C NMR (500 Hz, $CDCl_3$) δ 130.8 (J = 5.2 Hz), 144.7 (J = 3.1 Hz), 152.7 (J = 16.8 Hz), 153.2 (J = 16.8 Hz), 157.1 (J = 221.2 Hz); FAB-MS m/z 647 (M^+ + H). Anal. Calcd for $C_{28}H_{52}ClFN_4O_4Si_3$: C, 51.94; H, 8.10; N, 8.65. Found: C, 51.77; H, 8.25; N, 8.57.

2-Benzyl-9-(2,3,5-tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloropurine (19). A THF (2 mL) solution containing **11** (102 mg, 0.11 mmol), $Pd(PPh_3)_4$ (6.5 mg, 5.5 μmol, 5 mol %), CuI (4.4 mg, 22 μmol, 20 mol %), and benzyl bromide (16 μL, 0.13 mmol) was refluxed for 9 h under a positive pressure of dry Ar. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. Silica gel column chromatography

(hexane/EtOAc = 20/1) of the extract gave **19** (43 mg, 55%) as an oil: UV (MeOH) λ_{max} 269 nm (ϵ 11 100), λ_{min} 234 nm (ϵ 5600); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.20, −0.04, 0.09, 0.10, 0.14, and 0.16 (18H, each as s), 0.80, 0.93, and 0.96 (27H, each as s), 3.80 (1H, dd, J = 11.0, 2.6 Hz), 4.04 (1H, dd, J = 11.0, 4.0 Hz), 4.12−4.15 (1H, m), 4.29 (2H, s), 4.29−4.31 (1H, m), 4.54 (1H, t, J = 4.4 Hz), 6.06 (1H, d, J = 4.4 Hz), 7.18−7.39 (5H, m), 8.47 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 130.2, 143.7, 150.7, 151.9, 164.0; FAB-MS m/z 719 (M^+ + H). Anal. Calcd for $C_{35}H_{59}ClN_4O_4Si_3 \cdot {}^1/_2H_2O$: C, 57.70; H, 8.30; N, 7.69. Found: C, 57.80; H, 8.37; N, 7.55.

9-(2,3,5-Tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloro-2-phenylpurine (20). This compound was prepared from **11** (102 mg, 0.11 mmol) and iodobenzene (45 μL, 0.33 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 24 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 60/1) gave **20** (32 mg, 41%) as a solid (mp 55−59 °C): UV (MeOH) λ_{max} 285 (ϵ 16 300) and 243 nm (ϵ 17 300), λ_{min} 219 nm (ϵ 8600); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.18, −0.02, 0.11, 0.14, 0.15, and 0.17 (18H, each as s), 0.80, 0.95, and 0.96 (27H, each as s), 3.84 (1H, dd, J = 12.0, 2.6 Hz), 4.05 (1H, dd, J = 12.0, 4.0 Hz), 4.17−4.18 (1H, m), 4.36 (1H, t, J = 4.4 Hz), 4.65 (1H, t, J = 4.4 Hz), 6.20 (1H, d, J = 4.4 Hz), 7.47−7.50 (3H, m), 8.48−8.49 (2H, m), 8.54 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 130.6, 144.2, 151.0, 152.3, 159.3; FAB MS m/z 705 (M^+ + H). Anal. Calcd for $C_{34}H_{57}ClN_4O_4Si_3 \cdot H_2O$: C, 56.44; H, 8.22; N, 7.74. Found: C, 56.52; H, 8.17; N, 7.51.

2-Benzoyl-9-(2,3,5-tris-*O*-TBDMS-*β*-D-ribofuranosyl)-6-chloropurine (21). A toluene (10 mL) solution containing **11** (102 mg, 0.11 mmol) and benzoyl chloride (22 μL, 0.15 mmol) was refluxed for 0.5 h under a positive pressure of dry Ar. After addition of pyridine (10 μL, 0.20 mmol) to this solution, the reaction mixture was further refluxed for 20 h. Usual workup (see that for **16**) followed by silica gel column chromatography (hexane/EtOAc = 40/1) gave **21** (44 mg, 60%) as a syrup: UV (MeOH) λ_{max} 263 nm (ϵ 13 600), λ_{min} 238 nm (ϵ 10 600); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.27, −0.06, 0.06, 0.08, 0.14, and 0.15 (18H, each as s), 0.75, 0.91, and 0.96 (27H, each as s), 3.79 (1H, dd, J = 13.0, 3.2 Hz), 4.03 (1H, dd, J = 13.0, 3.3 Hz), 4.12−4.14 (1H, m), 4.29 (1H, t, J = 4.8 Hz), 4.54 (1H, t, J = 4.8 Hz), 6.14 (1H, d, J = 4.8 Hz), 7.50 (2H, t, J = 7.3 Hz), 7.64 (1H, t, J = 7.3 Hz), 8.01 (2H, d, J = 7.3 Hz), 8.75 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 132.5, 145.8, 151.0, 151.2, 156.2; FAB-MS m/z 734 (M^+ + H). Anal. Calcd for $C_{35}H_{57}ClN_4O_5Si_3 \cdot {}^1/_2H_2O$: C, 56.61; H, 7.87; N, 7.55. Found: C, 56.96; H, 8.27; N, 7.53.

2′,3′,5′-Tris-*O*-TBDMS-2-(tributylstannyl)adenosine (22). Compound **11** (500 mg, 0.54 mmol) in THF (5 mL) was reacted with NH_3/2-propanol (45 mL, saturated at 0 °C, containing *ca.* 5% NH_3) in a sealed tube at 105 °C for 60 h. After being evaporated, the reaction mixture was purified by silica gel column chromatography. Elution with hexane/EtOAc = 10/1 gave **22** (454 mg, 92%) as a syrup. Compound **23**[5a] (20 mg, 6%) was also isolated by elution with hexane/EtOAc = 5/1. Physical data for **22**: UV (MeOH) λ_{max} 263 nm (ϵ 11 600), λ_{min} 241 nm (ϵ 8800); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.13, −0.02, 0.08, 0.09, 0.13, and 0.15 (18H, each as s), 0.81, 0.93, and 0.96 (27H, each as s), 0.88 (9H, t, J = 7.7 Hz), 1.12 (6H, t, J = 9.5 Hz), 1.32−1.35 (6H, m), 1.54−1.58 (6H, m), 3.79 (1H, dd, J = 11.3, 4.3 Hz), 4.01 (1H, dd, J = 11.3, 4.3 Hz), 4.10−4.13 (1H, m), 4.30 (1H, t, J = 4.4 Hz), 4.60 (1H, t, J = 4.4 Hz), 5.44 (2H, br), 6.06 (1H, d, J = 4.4 Hz), 8.13 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.2, 138.6, 149.2, 153.4, 180.6; FAB-MS m/z 900 (M^+ + H). Anal. Calcd for $C_{40}H_{81}N_5O_4Si_3Sn$: C, 53.44; H, 9.08; N, 7.79. Found: C, 53.73; H, 9.27; N, 7.68.

2′,3′,5′-Tris-*O*-TBDMS-2-iodoadenosine (24). The iodination of **22** (102 mg, 0.11 mmol) was carried out for 0.5 h by the procedure described for the preparation of **15**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 4/1) gave **24** (98 mg, 100%) as a syrup: UV (MeOH) λ_{max} 267 nm (ϵ 15 200), λ_{min} 237 nm (ϵ 6000); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.13, 0.00, 0.09, 0.10, 0.14, and 0.15 (18H, each as s), 0.93, 0.94, and 0.95 (27H, each as s), 3.78 (1H, dd, J = 11.4, 2.9 Hz), 4.03 (1H, dd, J = 11.4, 5.1 Hz), 4.10−4.13 (1H, m), 4.29 (1H, t, J = 4.4 Hz), 4.66 (1H, t, J = 4.4 Hz), 5.89 (1H, d, J = 4.4 Hz), 6.03 (2H, br), 8.06 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.5, 120.0, 139.7, 149.8, 155.1; FAB-MS m/z 736 (M^+ + H). Anal. Calcd for $C_{28}H_{54}IN_5O_4Si_3$: C, 45.70; H, 7.40; N, 9.52. Found: C, 45.71; H, 7.39; N, 9.24.

2-Bromo-2′,3′,5′-tris-*O*-TBDMS-adenosine (25). The bromination of **22** (102 mg, 0.11 mmol) was carried out for 0.5 h by the procedure described for the preparation of **16**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 3/1) gave **25** (68 mg, 90%) as an oil: UV (MeOH) λ_{max} 263 nm (ϵ 12 000), λ_{min} 235 nm (ϵ 6200); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.16, −0.01, 0.09, 0.10, 0.13, and 0.15 (18H, each as s), 0.83, 0.92, and 0.95 (27H, each as s), 3.78 (1H, dd, J = 11.4, 2.9 Hz), 4.04 (1H, dd, J = 11.4, 4.8 Hz), 4.10−4.13 (1H, m), 4.30 (1H, t, J = 4.4 Hz), 4.66 (1H, t, J = 4.4 Hz), 5.92 (1H, d, J = 4.4 Hz), 6.18 (2H, br), 8.11 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.3, 139.9, 144.7, 150.4, 155.9; FAB-MS m/z 690 (M^+ + H). Anal. Calcd for $C_{28}H_{54}BrN_5O_4Si_3$: C, 48.82; H, 7.90; N, 10.17. Found: C, 49.06; H, 8.01; N, 9.99.

2′,3′,5′-Tris-*O*-TBDMS-2-chloroadenosine (26). The chlorination of **22** (50 mg, 0.056 mmol) was carried out for 6 h by the procedure described for the preparation of **17**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 3/1) gave **26** (26 mg, 70%) as a solid (mp 125−127 °C): UV (MeOH) λ_{max} 261 nm (ϵ 9700), λ_{min} 229 nm (ϵ 1300); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.17, −0.02, 0.09, 0.10, 0.13, and 0.14 (18H, each as s), 0.82, 0.92, and 0.95 (27H, each as s), 3.37 (1H, dd, J = 11.4, 2.9 Hz), 4.04 (1H, dd, J = 11.4, 4.4 Hz), 4.11−4.14 (1H, m), 4.30 (1H, t, J = 4.4 Hz), 4.66 (1H, t, J = 4.4 Hz), 5.93 (1H, d, J = 4.4 Hz), 6.09 (2H, br), 8.16 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.0, 140.3, 150.8, 154.1, 155.8; FAB-MS m/z 644 (M^+ + H). Anal. Calcd for $C_{28}H_{54}ClN_5O_4Si_3$: C, 52.18; H, 8.45; N, 10.87. Found: C, 52.10; H, 8.72; N, 10.79.

2′,3′,5′-Tris-*O*-TBDMS-2-fluoroadenosine (27). The fluorination of **22** (164 mg, 0.18 mmol) was carried out for 15 min by the procedure described for the preparation of **18**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 5/1) gave **27** (90 mg, 80%) as a solid (mp 210−211 °C): UV (MeOH) λ_{max} 261 nm (ϵ 12 700), λ_{min} 223 nm (ϵ 2700); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.20, −0.03, 0.09, 0.10, 0.12, and 0.13 (18H, each as s), 0.81, 0.92, and 0.95 (27H, each as s), 3.77 (1H, dd, J = 11.3, 2.9 Hz), 4.02 (1H, dd, J = 11.3, 4.4 Hz), 4.10−4.13 (1H, m), 4.30 (1H, t, J = 4.4 Hz), 4.63 (1H, t, J = 4.4 Hz), 5.91 (1H, d, J = 4.4 Hz), 6.27 (2H, br), 8.11 (1H, s); ^{13}C NMR (500 Hz, $CDCl_3$) δ 119.0 (J = 4.2 Hz), 139.6 (J = 3.1 Hz), 151.2 (J = 19.6 Hz), 157.1 (J = 19.8 Hz), 159.0 (J = 211.0 Hz); FAB-MS m/z 628 (M^+ + H). Anal. Calcd for $C_{28}H_{54}FN_5O_4Si_3 \cdot H_2O$: C, 52.06; H, 8.74; N, 10.84. Found: C, 52.31; H, 9.00; N, 10.79.

2-Benzyl-2′,3′,5′-tris-*O*-TBDMS-adenosine (28). This compound was prepared from **22** (102 mg, 0.11 mmol) and benzyl bromide (16 μL, 0.13 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 9 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 5/1) gave **28** (65 mg, 83%) as a syrup: UV (MeOH) λ_{max} 261 nm (ϵ 10 200), λ_{min} 233 nm (ϵ 3500); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.08, −0.04, 0.09, 0.10, 0.12, and 0.13 (18H, each as s), 0.80, 0.92, and 0.94 (27H, each as s), 3.80 (1H, dd, J = 11.0, 3.1 Hz), 4.07 (1H, dd, J = 11.0, 4.8 Hz), 4.11−4.15 (1H, m), 4.10 (2H, s), 4.31 (1H, t, J = 4.0 Hz), 4.68 (1H, t, J = 4.0 Hz), 5.57 (2H, br), 5.96 (1H, d, J = 4.0 Hz), 7.19−7.35 (5H, m), 8.11 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 118.5, 139.5, 150.1, 155.3, 163.9; FAB-MS m/z 700 (M^+ + H). Anal. Calcd for $C_{35}H_{61}N_5O_4Si_3 \cdot {}^3/_2H_2O$: C, 57.81; H, 8.87; N, 9.63. Found: C, 57.51; H, 8.59; N, 9.41.

2′,3′,5′-Tris-*O*-TBDMS-2-phenyladenosine (29). This compound was prepared from **22** (80 mg, 0.09 mmol) and iodobenzene (10 μL, 0.1 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 15 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 5/1) gave **29** (55.1 mg, 89%) as crystals (mp 199 °C): UV (MeOH) λ_{max}

240 nm (ϵ 17 000), λ_{min} 235 nm (ϵ 11 700); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.13, −0.03, 0.11, 0.12, and 0.14 (18H, each as s), 0.82, 0.94, and 0.95 (27H, each as s), 3.83 (1H, dd, *J* = 11.0, 3.0 Hz), 4.07 (1H, dd, *J* = 11.0, 5.1 Hz), 4.14−4.16 (1H, m), 4.37 (1H, t, *J* = 4.6 Hz), 4.88 (1H, t, *J* = 4.6 Hz), 5.58 (2H, br), 6.08 (1H, d, *J* = 4.6 Hz), 7.42−7.43 (3H, m), 8.18 (1H, s), 8.39−8.40 (2H, m); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.2, 140.3, 150.9, 155.1, 159.4; FAB-MS *m*/*z* 686 (M^+ + H). Anal. Calcd for $C_{34}H_{59}N_5O_4Si_3$: C, 59.52; H, 8.67; N, 10.21. Found: C, 59.23; H, 8.70; N, 9.98.

2-Allyl-2′,3′,5′-tris-*O*-TBDMS-adenosine (30). This compound was prepared from **22** (102 mg, 0.11 mmol) and allyl bromide (25 μL, 0.22 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 18 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 10/1) gave **30** (42 mg, 59%) as a syrup: UV (MeOH) λ_{max} 263 nm (ϵ 11 600), λ_{min} 233 nm (ϵ 7400); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.14, −0.02, 0.08, 0.10, 0.12 and 0.13 (18H, each as s), 0.81, 0.92, and 0.94 (27H, each as s), 3.56 (2H, d, *J* = 6.9 Hz), 3.78 (1H, dd, *J* = 11.0, 3.3 Hz), 4.06 (1H, dd, *J* = 11.0, 4.2 Hz), 4.10−4.13 (1H, m), 4.32 (1H, t, *J* = 4.4 Hz), 4.73 (1H, t, *J* = 4.4 Hz), 5.09 (1H, dd, *J* = 1.7, 9.9 Hz), 5.16 (1H, dd, *J* = 1.7, 17.0 Hz), 5.69 (2H, br), 5.95 (1H, d, *J* = 4.4 Hz), 6.14 (1H, ddt, *J* = 17.0, 9.9, 6.9 Hz), 8.10 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 118.5, 139.6, 150.4, 155.2, 163.6; FAB-MS *m*/*z* 651 (M^+ + H). Anal. Calcd for $C_{31}H_{59}N_5O_4Si_3$: C, 57.27; H, 9.15; N, 10.77. Found: C, 57.44; H, 9.43; N, 10.71.

2′,3′,5′-Tris-*O*-TBDMS-2-(phenylethynyl)adenosine (31). This compound was prepared from **22** (102 mg, 0.11 mmol) and iodophenylacetylene (30 mg, 0.13 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 10.5 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 2/1) gave **31** (56.3 mg, 72%) as a syrup: UV (MeOH) λ_{max} 260 nm (ϵ 14 600), λ_{min} 238 nm (ϵ 10 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.11, 0.01, 0.10, 0.11, 0.12, and 0.14 (18H, each as s), 0.85, 0.93, and 0.94 (27H, each as s), 3.80 (1H, dd, *J* = 12.5, 2.9 Hz), 4.05 (1H, dd, *J* = 12.5, 4.3 Hz), 4.12−4.14 (1H, m), 4.54 (1H, t, *J* = 4.8 Hz), 4.70 (1H, t, *J* = 4.8 Hz), 5.87 (2H, br), 6.04 (1H, d, *J* = 4.8 Hz), 7.35−7.36 (3H, m), 7.62−7.63 (2H, m), 8.20 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 119.5, 140.5, 149.9, 155.0, 155.1; FAB-MS *m*/*z* 710 (M^+ + H). Anal. Calcd for $C_{36}H_{59}N_5O_4Si_3$: C, 60.89; H, 8.37; N, 9.86. Found: C, 60.64; H, 8.51; N, 9.69.

2′,3′,5′-Tris-*O*-TBDMS-2-(β-styryl)adenosine (32). This compound was prepared from **22** (102 mg, 0.11 mmol) and β-bromostyrene (17 μL, 0.13 mmol) by the procedure described for the preparation of **19**. The reaction was continued for 22 h at refluxing temperature. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 2/1) gave **32** (30.3 mg, 40%, *E*/*Z* = *ca.* 6/1) as a syrup. Further purification by HPLC (hexane/EtOAc = 2/1) gave an analytically pure *E*-isomer: UV (MeOH) λ_{max} 265 nm (ϵ 13 800), λ_{min} 241 nm (ϵ 8100); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.07, 0.01, 0.10, 0.12, 0.14, and 0.16 (18H, each as s), 0.85, 0.94, and 0.96 (27H, each as s), 3.82 (1H, dd, *J* = 11.5, 2.6 Hz), 4.09 (1H, dd, *J* = 11.5, 4.4 Hz), 4.13−4.16 (1H, m), 4.36 (1H, t, *J* = 4.4 Hz), 4.68 (1H, t, *J* = 4.4 Hz), 5.61 (2H, br), 6.06 (1H, d, *J* = 4.4 Hz), 7.00 (1H, d, *J* = 15.8 Hz), 7.30 (1H, t, *J* = 7.4 Hz), 7.38 (2H, t, *J* = 7.4 Hz), 7.58 (2H, t, *J* = 7.4 Hz), 7.87 (1H, d, *J* = 15.8 Hz), 8.19 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 118.9, 139.8, 150.6, 154.9, 159.4; FAB-MS *m*/*z* 712 (M^+ + H). Anal. Calcd for $C_{36}H_{61}N_5O_4Si_3 \cdot {}^1/_2H_2O$: C, 59.96; H, 8.67; N, 9.71. Found: C, 60.05; H, 8.76; N, 9.32.

9-[(1*R*,2*S*,3*R*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3-bis[(*tert*-butyldimethylsilyl)oxy]-4-cyclopenten-1-yl]-6-chloropurine (34). A mixture of **33** (70 mg, 0.25 mmol), TBDMSCl (210 mg, 1.25 mmol), and imidazole (140 mg, 1.75 mmol) in DMF (4 mL) was stirred at room temperature for 18 h. The reaction mixture was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried (Na_2SO_4), evaporated, and chromatographed on a silica gel column (hexane/EtOAc = 20/1) to give **34** (130 mg, 82%) as a solid (mp 120−122 °C): UV (MeOH) λ_{max} 266 nm (ϵ 6300), λ_{min} 232 nm (ϵ 1100); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.61, −0.16, 0.10, 0.11, and 0.12 (18H, each as s), 0.74, 0.91, and 0.93 (27H, each as s), 4.34−4.35 (2H, m), 4.41 (1H, dd, *J* = 5.6, 4.4 Hz), 4.51 (1H, d, *J* = 4.4 Hz), 5.51−5.57 (1H, m), 5.79 (1H, d, *J* = 1.8 Hz), 8.10 (1H, s), 8.72 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 132.1, 144.5, 151.1, 151.8, 152.4; FAB-MS *m*/*z* 625 (M^+ + H). Anal. Calcd for $C_{29}H_{53}ClN_4O_3Si_3$: C, 55.69; H, 8.54; N, 8.96. Found: C, 55.49; H, 8.83; N, 8.83.

9-[(1*R*,2*S*,3*R*)-4-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3-bis[(*tert*-butyldimethylsilyl)oxy]-4-cyclopenten-1-yl]-6-chloro-2-(tributylstannyl)purine (35). This compound was prepared from **34** (100 mg) under the reaction conditions shown in entry 9 of Table 1. The procedure used is similar to that described for the preparation of **6**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 30/1) gave **35** (148 mg, 100%) as a syrup: UV (MeOH) λ_{max} 273 nm (ϵ 7300), λ_{min} 247 nm (ϵ 4600); ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.55, −0.18, 0.09, 0.11, and 0.12 (18H, each as s), 0.71, 0.91, and 0.93 (27H, each as s), 0.88 (9H, t, *J* = 7.3 Hz), 1.14−1.23, 1.27−1.39, and 1.56−1.63 (18H, each as m), 4.32 (1H, t, *J* = 2.2 Hz), 4.34 (1H, t, *J* = 2.2 Hz), 4.40 (1H, dd, *J* = 4.8, 5.9 Hz), 4.49 (1H, d, *J* = 4.8 Hz), 5.63−5.64 (1H, m), 5.77 (1H, d, *J* = 1.9 Hz), 7.97 (1H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 132.1, 142.5, 149.3, 151.2, 181.7; FAB-MS *m*/*z* 915 (M^+ + H). Anal. Calcd for $C_{41}H_{79}ClN_4O_3Si_3Sn$: C, 53.85; H, 8.71; N, 6.13. Found: C, 53.91; H, 8.78; N, 5.99.

2′,3′,6′-Tris-*O*-TBDMS-2-(tributylstannyl)neplanocin A (36). This compound was prepared from **35** (140 mg) by the procedure similar to that described for the preparation of **22**. The reaction was carried out at 105 °C for 49 h. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 5/1) gave **36** (106 mg, 78%) as a syrup together with the starting material **35** (21 mg, 15%): UV (MeOH) λ_{max} 263 nm (ϵ 9600), λ_{min} 240 nm (ϵ 5900); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.48, −0.18, 0.08, 0.11, and 0.12 (18H, each as s), 0.74, 0.91, and 0.93 (27H, each as s), 0.88 (9H, t, *J* = 7.1 Hz), 1.09−1.13, 1.29−1.33, and 1.54−1.59 (18H, each as m), 4.27−4.30 (1H, m), 4.33−4.37 (1H, m), 4.43 (1H, t, *J* = 4.9 Hz), 4.50 (1H, d, *J* = 4.9 Hz), 5.50 (2H, br), 5.53−5.55 (1H, m), 5.75 (1H, d, *J* = 1.8 Hz), 7.67 (1H, s); ^{13}C NMR (500 MHz, $CDCl_3$) δ 119.3, 138.5, 148.7, 153.4, 180.7; FAB-MS *m*/*z* 896 (M^+ + H). Anal. Calcd for $C_{41}H_{81}N_5O_3Si_3Sn$: C, 55.02; H, 9.12; N, 7.82. Found: C, 55.17; H, 9.35; N, 7.75.

2′,3′,6′-Tris-*O*-TBDMS-2-fluoroneplanocin A (37). The fluorination of **36** (103 mg, 0.11 mmol) was carried out for 20 min by the procedure described for the preparation of **18**. After workup of the reaction mixture, silica gel column chromatography (hexane/EtOAc = 3/1) gave **37** (28 mg, 53%) as a solid (mp 245−247 °C): UV (MeOH) λ_{max} 263 nm (ϵ 10 200), λ_{min} 227 nm (ϵ 3000); ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.49, −0.13, 0.09, and 0.11 (18H, each as s), 0.78 and 0.91 (27H, each as s), 4.28−4.32 (2H, m), 4.37 (1H, t, *J* = 3.9 Hz), 4.49 (1H, d, *J* = 3.9 Hz), 5.39−5.40 (1H, m), 5.73 (1H, s), 6.11 (2H, br), 7.73 (1H, s); ^{13}C NMR (500 Hz, $CDCl_3$) δ 118.3 (*J* = 4.3 Hz), 149.2, 152.0 (*J* = 19.7 Hz), 157.0 (*J* = 20.7 Hz), 159.6 (*J* = 210.0 Hz); FAB-MS *m*/*z* 624 (M^+ + H). Anal. Calcd for $C_{29}H_{54}FN_5O_3Si_3$: C, 55.82; H, 8.72; N, 11.22. Found: C, 56.10; H, 8.97; N, 10.91.

Acknowledgment. Financial support from the Ministry of Education, Science and Culture (Grant-in-Aid No. 08772034 to K.K. and No. 09672159 to H.T.) is gratefully acknowledged. The authors thank Professor Takao Sakamoto, Tohoku University, for helpful correspondence about destannylation of stannylated heterocycles.

JO970398Q