Synthesis of Silicon Analogues of Acyclonucleotides Incorporable in Oligonucleotide Solid-Phase Synthesis

Jacques Thibon, Laurent Latxague, and Gérard Déléris*

Laboratoire de Chimie Bio-Organique, Université Victor Segalen Bordeaux 2, 146 rue Léo Saignat, F-33076 Bordeaux Cedex, France

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The synthesis of the four silicon analogues of acyclonucleosides was described. In every case, the silicon atom was introduced onto an allyl group on the natural nucleobase following a hydrosilylation reaction. Diols obtained were protected as 4,4′-dimethoxytrityl ethers and subsequently activated as 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite in order to be suitable for oligonucleotide solid phase synthesis.

Introduction

Modulation of gene expression as a therapeutic approach has generated much interest in recent years. Two main strategies, which both use oligodeoxynucleotides (ODNs), are currently studied: antigene agents that bind to a double-strand DNA and then, form a localized triplex preventing gene transcription[1] and antisense agents which target messenger RNA (mRNA) to form a duplex preventing translation.[2] Antisense ODNs act through specific hybridization to coding (sense) sequences in the mRNA by Watson−Crick base pairing; such ODNs can be made of a small number of nucleotides (<20) with enough specificity.[3] However, the use of natural ODNs is restricted by their low cellular uptake and their susceptibility to enzymatic degradation. Several chemical modifications have been performed to date to overcome these difficulties. Two ways,[2,4] phosphodiester linkage and nucleoside modifications (either of sugar or heterocyclic bases), have been investigated.

Among the earliest and most widely used ODN analogues are the phosphorothioates[5] (one sulfur atom replaces a nonbinding phosphate oxygen) which exhibit a better stability to nucleases or the methylphosphonates[6] (a methyl group replaces a negatively charged phosphate oxygen) with an improved lipophily, and in the most recent approach, the whole phosphodiester was replaced by a guanidinium linkage, affording a positively charged ODN.[7]

On the other hand, little work has been devoted to the replacement of the carbohydrate moiety of the nucleoside by an acyclic chain, which can be thought as another way to increase the enzymatic stability of ODNs.[8] Thus, Schneider et al.[9] report the use of glycerol-like chains in ODN analogues and Vandendriessche et al.[10] the use of dihydroxyalkyl or methoxydihydroxyalkyl chains, with improved results.

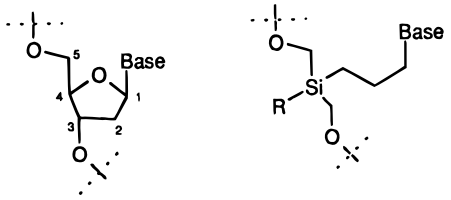

Figure 1. Natural nucleoside *vs* our proposed acyclic sila analogue. R = Me or may be modified to add new functionalities.

Our strategy uses a bis(hydroxymethyl)silicon chain in order to improve the overall lipophily of the resulting ODN and to take advantage of the wide range of reactions permitted by silicon. So far, silicon has been seldom used in ODN analogues synthesis, except for alkoxysilane internucleoside linkage,[11] but the known sensitivity of the alkoxysilane moiety to both acids and bases restricts its use *in vivo*. In our work, a silicon atom replaced carbon-4′ of the deoxyribose, while carbon-2′ and the carbohydrate oxygen were removed; finally, to avoid potential β-elimination during the course of the synthesis, a propyl chain (instead of an ethyl) separates the heterocyclic base from silicon (Figure 1).

We here describe the synthesis of the phosphoramidites synthons corresponding to the four protected silicon nucleoside analogues bearing cytosine, guanine, thymine, and adenine nucleobases.

Results and Discussion

Owing to the diverse reactivities of the four nucleobases, their nucleoside analogues had to be synthesized in slightly different ways. However, every time the key step involved a hydrosilylation reaction in order to introduce the silicon atom onto the molecule.

For this purpose, we used two silanes, bis(chloromethyl)methylsilane (**1a**) and (chloromethyl)dimethylsilane (**1b**), readily obtained from hydride reduction of the corresponding chlorosilanes (Scheme 1).

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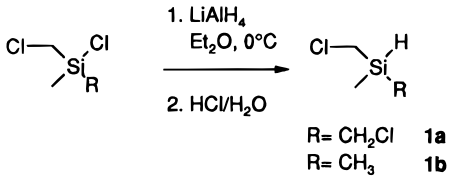
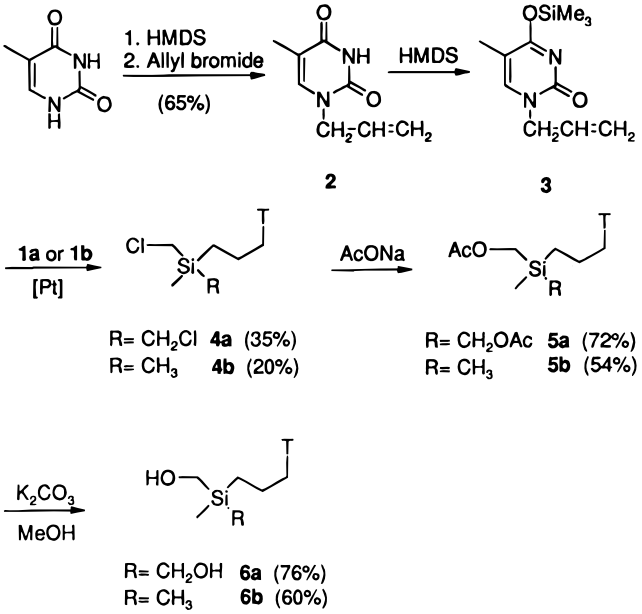
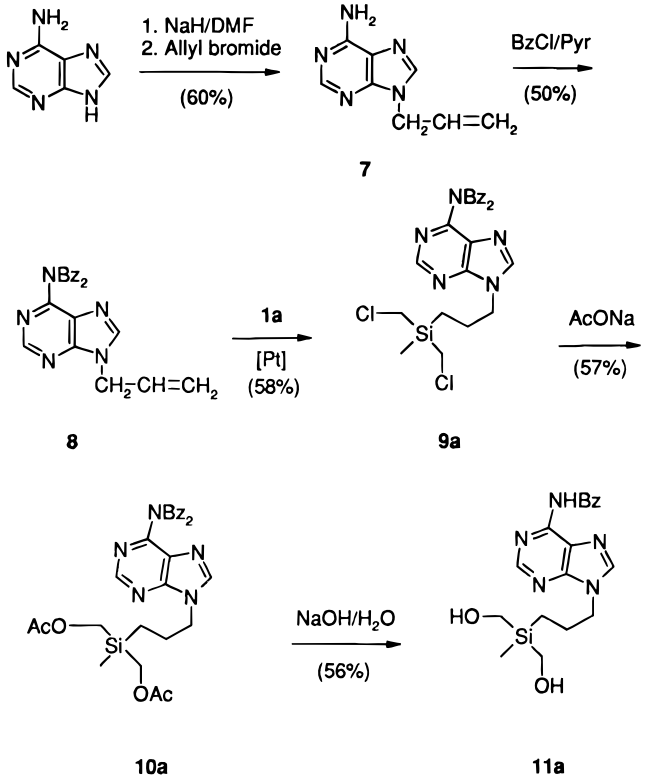
Scheme 1



Scheme 2



Scheme 3



Compounds **1a** and **1b** were then reacted with an allylic precursor of the nucleoside analogues to give the hydrosilylated key synthetic intermediates. We used either a solution of chloroplatinic acid in isopropyl alcohol or tetrabutylammonium hexachloroplatinate as catalyst. Both gave similar results in hydrosilylation product, but we found the use of the later preferable to H_2PtCl_6 which is very sensitive to moisture and light exposure. Finally, as already emphasized in a preliminary work,[12] most of the labile protons had to be masked by a suitable protective group prior to hydrosilylation.

Thymidine Analogues. The previously known *N*-1-allylthymine[13,14] (**2**) was prepared from thymine by reacting its 2,4-bis((trimethylsilyl)oxy) derivative with allyl bromide in DMF (Scheme 2); *N*,*N*-1,3-bis(allyl)-thymine (15%) was also isolated as a byproduct. Several unsuccessful hydrosilylations of unprotected **2** led us to mask its N-3 labile proton to afford the trimethylsilyl ether **3** which gave moderate yields of the desired compounds **4a** and **4b**. Acetoxylation of the later gave compounds **5a** and **5b** subsequently saponified under anhydrous conditions (K_2CO_3/methanol) to afford the hydroxylated compounds **6a** and **6b**.

Adenosine Analogues. Under alkaline conditions using sodium hydride in DMF, adenine was alkylated with allyl bromide to afford *N*-9-allyladenine (**7**) as the major product[15] (Scheme 3). Prior to the hydrosilylation step, the exocyclic 6-amino group of the purine ring was protected with benzoyl chloride to give compound **8** allowing a good yield for hydrosilylation step to product **9a**. The later was acetoxylated to give **10a** which was saponified in an aqueous sodium hydroxide solution to give compound **11a** with one remaining benzoyl group. Interestingly, there was no need to remove it, since it is also a suitable protective group during the oligonucleotide synthesis.

An alternative way, starting from 6-chloropurine, is described in Scheme 4.

Similar to adenine, 6-chloropurine reacted with allyl bromide to give 9-allyl-6-chloropurine (**12**). Hydrosilylation of this compound with **1a** or **1b** afforded respectively **13a** and **13b** which after acetoxylation yielded **14a** and **14b**.

Displacement of chlorine with NH_2 in **14a** and **14b** was conducted by ammoniolysis in a steel bomb (overnight at 90 °C) to yield directly the hydroxylated coumpounds **15a** and **15b**.

Benzoyl chloride reaction gave exclusively the peracylated compound which was further treated with a 1 N NaOH solution to cleave one of the amino benzoyl groups to give **11a**.

Cytidine Analogues. In a first attempt, we directly synthesized a protected *N*-1-allylcytosine by reacting cytosine with *N*,*N*-dimethylformamide diallyl acetal in anhydrous DMF according to Helfer et al.[16] Unfortunately, hydrosilylation of the resulting 1-allyl-*N*-4-[(dimethylamino)methylene]cytosine led to a complex mixture of various products we were unable to identify. A direct allylation of cytosine using sodium hydride and allyl bromide, or *via* the activated 2,4-bis((trimethylsilyl)-oxy)cytosine, was unsuccessfull in our hands.

Thus, we used an indirect pathway starting from uracil. Actually, *N*-1-allyluracil (**16**) was readily obtained

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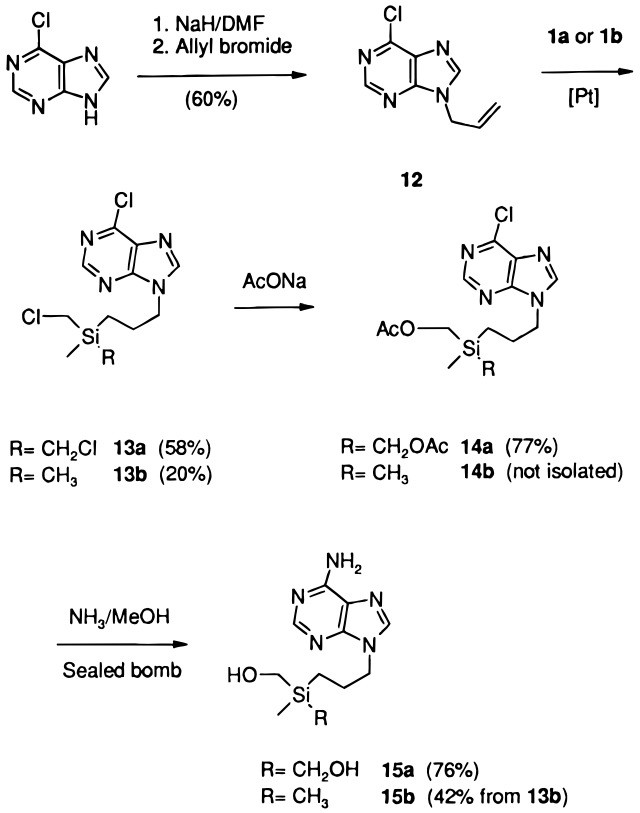
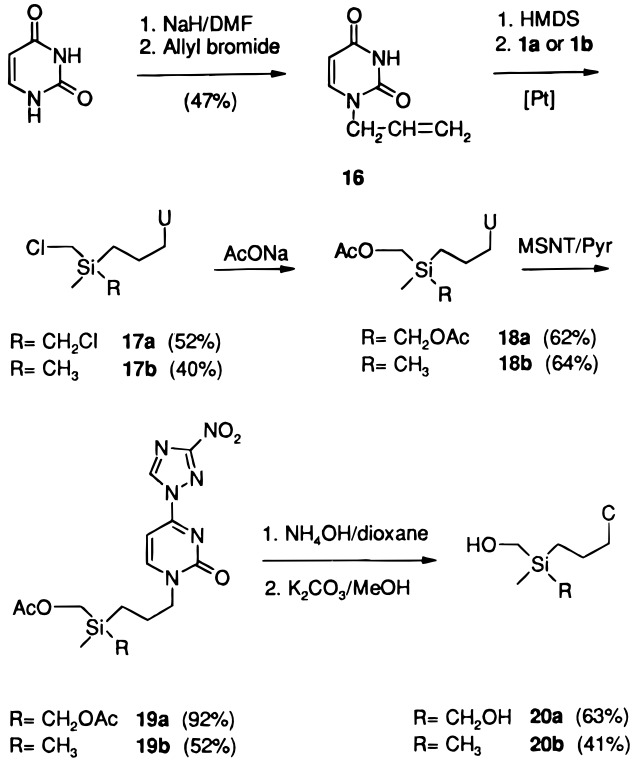
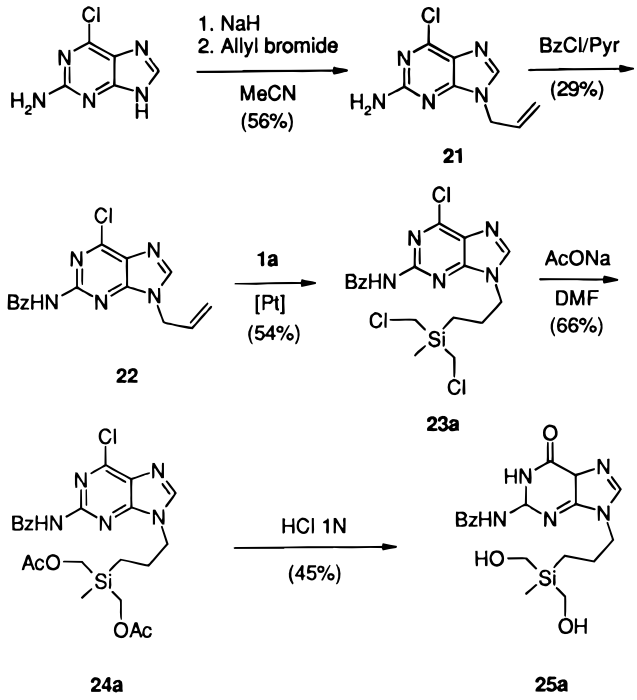
Scheme 4



Scheme 5



Scheme 6



and subjected to hydrosilylation yielding **17a** and **17b** followed by acetoxylation to yield **18a** and **18b** (Scheme 5). At this stage of the synthesis, we underwent the uracil−cytosine transformation *via* 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole (MSNT), known as a condensing reagent in oligonucleotide synthesis. Reese et al.[17,18] reported that MSNT, when reacted with tri-*O*-acetyluridine, afforded 4-(3-nitro-1,2,4-triazolo)pyrimidinone which further gave cytidine when treated with ammonium hydroxide. Thus, reaction of **18a** and **18b** with MSNT in pyridine at room temperature afforded **19a** and **19b** in high yields. Subsequent treatment with aqueous ammonia in dioxane, followed by saponification of the acetoxy moiety, afforded **20a** and **20b**.

Guanosine Analogues. Commercially available 2-amino-6-chloropurine was alkylated in dry acetonitile with sodium hydride/allyl bromide to afford its *N*-9-allyl derivative **21** (Scheme 6).

The exocyclic 2-amino group was protected with benzoyl chloride to give **22** which was reacted with **1a** in the presence of tetrabutylammonium hexachloroplatinate to yield compound **23a**. The later was acetoxylated and refluxed with hydrochloric acid to give in a single step the dihydroxylated guanosine analogue **25a** in a 45% yield.

Phosphoramidite Synthesis. Solid support synthesis of oligonucleotides requires the functional protection of the 5′-hydroxy function of nucleosides. For this purpose, the 4,4′-dimethoxytrityl (DMTr) group is one of the most popular; however, the exocyclic amino function of cytosine, adenine, or guanine nucleosides must be protected first, in order to prevent undesired tritylation. Among our proposed nucleoside analogues, the adenosine **11a** and guanidine **25a** analogues were already protected during the course of the synthesis. The cytidine analogue **20a** was protected with benzoyl chloride (Scheme 7). Yields of the subsequent tritylation step were lowered by the presence of two identical primary hydroxy groups. Therefore, **27a**, **28a**, **29a**, and **30a** were obtained as mixtures of mono- and diprotected derivatives, along with unreacted starting material. Nevertheless, following purification on silica gel, the diprotected derivatives could be recovered and treated with trifluoroacetic acid in

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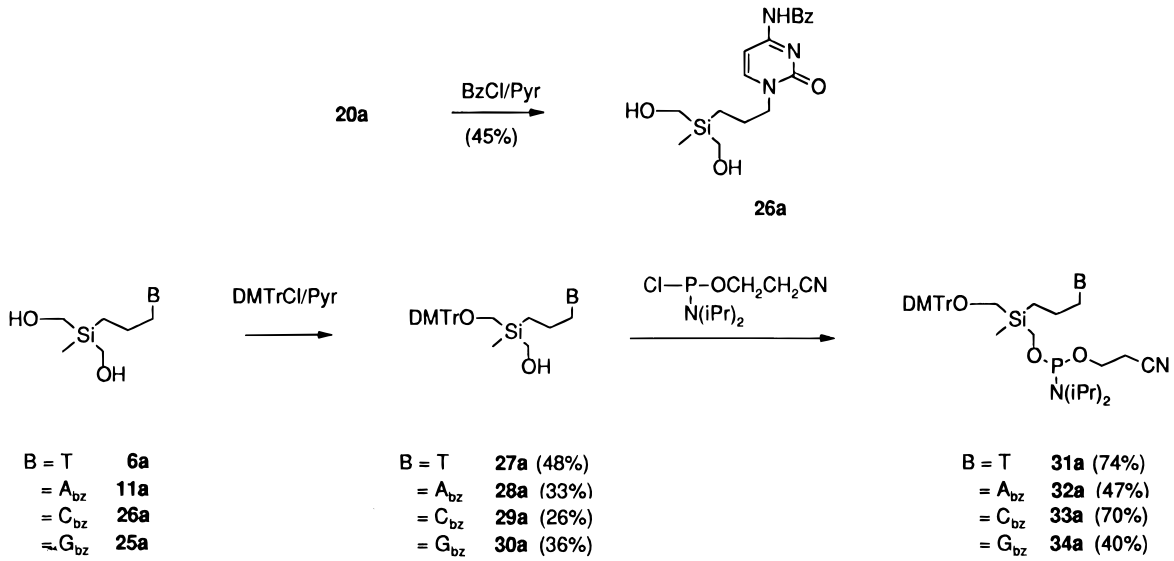
Scheme 7



dichloromethane to give another crop of dihydroxylated compounds.

Finally, a coupling reaction of the remaining hydroxy group with 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite led to the four end products **31a**, **32a**, **33a**, and **34a**.

Summary of the Results. In conclusion, the synthesis of the four novel silicon analogues of acyclonucleosides was achieved. In every case, silicon was introduced onto the heterocyclic moiety following a hydrosilylation reaction. In order to be suitable for use in solid phase oligonucleotide synthesis, nucleoside analogues were protected as 4,4′-dimethoxytrityl ethers and subsequently activated as 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidites. Insertion of the obtained analogues of nucleotides within oligonucleotides (17 mer) is now in progress, and the physico-chemical properties for hybridization either with DNA or RNA complementary sequences will be determined.

Experimental Section

General. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded at 200, 50, and 81 MHz, respectively; chemical shifts are given in ppm from tetramethylsilane (^{1}H and ^{13}C) or H_3PO_4 (^{31}P) as an internal standard. Infrared spectra were measured using neat samples on NaCl plates for liquids or using the KBr technique for solids. Melting points were taken on a hot stage apparatus and are uncorrected. Mass spectra were obtained under FAB conditions. Thin layer chromatography (TLC) was carried out on aluminum-backed silica gel 60 F_{254} 0.25 mm plates (Merck). Column chromatography was performed using silica gel (70−230 mesh) and flash column chromatography using silica gel (230−400 mesh) at 0.4 bar.

Bis(chloromethyl)methylsilane (1a). To a solution of bis(chloromethyl)methylchlorosilane (5 mL, 0.03 mol) in anhydrous ether (30 mL) stirred at 0 °C under nitrogen was added lithium aluminum hydride (0.76 g, 0.02 mol) over a period of 4 h. The suspension was stirred for 3 h at 0 °C and then 1 h at room temperature and carefully hydrolyzed with a 1 N HCl solution (2.5 mL) and stirred for a further 12 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure and then distilled off to yield 4.05 g of **1a** (93%) as a colorless liquid: bp 53 °C/25 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.33 (d, 3H, J = 7.2 Hz), 2.98 (d, 4H, J = 3 Hz), 4.13−4.19 (m, 1H); IR (film) 2935, 2153, 1394, 1264, 873 cm^{-1}.

(Chloromethyl)dimethylsilane (1b). Under similar conditions, compound **1b** was obtained in 78% yield starting from (chloromethyl)dimethylchlorosilane: colorless liquid, bp 82−83 °C/760 mmHg; ^{1}H NMR ($CDCl_3$) δ 0.20 (d, 6H, J = 3.6 Hz), 2.80 (d, 2H, J = 2.4 Hz), 3.90−4.10 (m, 1H); IR (film) 2947, 2131, 1394, 1255, 882 cm^{-1}.

General Procedure for the Preparation of Allyl Derivatives. To a stirred suspension of nucleobase in dry dimethylformamide (DMF) was added in small portions sodium hydride (80% in oil) at room temperature. After 2 h of stirring, freshly distilled allyl bromide was added dropwise, and the mixture was heated to 70 °C for 2 h. The clear reaction mixture was concentrated to dryness under reduced pressure, the remaining solid was washed with dichloromethane and filtrated, and the filtrate was concentrated to an oil purified on a silica gel column. *N*-1-Allylthymine was prepared differently *via* its bis(trimethylsilyl) derivative.

***N*-9-Allyladenine (7).** Following the general procedure, adenine (5 g, 0.037 mol) treated with sodium hydride (0.9 g, 0.037 mol) and allyl bromide (7 g, 0.058 mol) gave **7** separated from *N*-7-allyladenine on a silica gel column using ethyl acetate as eluant: yield 3.87 g (59%); ^{1}H NMR (DMSO-d_6) δ 4.77 (d, 2H, J = 6 Hz), 5.09 (m, 2H), 5.95−6.14 (m, 1H), 7.25 (s, 2H), 8.10 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 44.89, 117.34, 118.60, 133.17, 140.68, 149.40, 152.53, 155.98.

***N*-9-Allyl-6-chloropurine (12).** Following the general procedure, 6-chloropurine (5 g, 0.032 mol) was treated with sodium hydride (1.36 g, 0.056 mol) and allyl bromide (7 g, 0.058 mol) The reaction gave a mixture of *N*-9-allyl-6-chloropurine (**12**) and *N*-7-allyl-6-chloropurine which were separated on a silica gel column using ethyl acetate as eluant: yield 3.8 g (60%); ^{1}H NMR ($CDCl_3$) δ 4.88 (d, 2H, J = 5.8 Hz), 5.18−5.36 (m, 2H), 5.92−6.11 (m, 1H), 8.10 (s, 1H), 8.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.35, 101.68, 120.05, 130.91, 131.55, 145.01, 151.10, 152.07.

***N*-1-Allyluracil (16).** Following the general procedure, uracil (10.5 g, 0.093 mol) treated with sodium hydride (2.5 g, 0.104 mol) and allyl bromide (15 g, 0.123 mol) gave **16** separated from *N*1,*N*3-bis(allyl)uracil on recrystallization in propan-2-ol: yield 7.5 g (47%); ^{1}H NMR ($CDCl_3$) δ 4.30 (d, 2H, J = 8 Hz), 5.19−5.31 (m, 2H), 5.91−5.69 (m, 2H), 7.24 (d, 1H, J = 8 Hz), 9.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.91, 102.42, 119.37, 131.44, 143.81, 150.96, 164.06.

***N*-1-Allylthymine (2).** A mixture of thymine (10.4 g, 0.038 mol), 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 10 mL), and a few milligrams of of ammonium sulfate was refluxed under an inert atmosphere until a clear solution was obtained. The excess of HMDS was coevaporated with toluene, and to the resulting 2,4-bis(trimethylsilyl)thymine was added dry DMF (25 mL) and allyl bromide (25 mL). The mixture was stirred for 3 days at 80 °C under an inert atmosphere. After removal of the solvent and excess allyl bromide, the remaining oil was flash chromatographed (CH_2Cl_2−MeOH 98:2) to leave a pale yellow solid recrystallized from toluene: yield 4.08 g (64%);

mp 112 °C; ^{1}H NMR ($CDCl_3$) δ 1.90 (d, 3H, J = 1 Hz), 4.30 (d, 2H, J = 6 Hz), 5.20−5.30 (m, 2H), 5.70−5.90 (m, 1H), 6.90 (d, 1H, J = 1 Hz), 9.00 (large s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.2, 49.6, 110.8, 118.9, 131.7, 139.8, 151.2, 164.7; IR (KBr) 3146, 2980, 1710, 1650, 1480, 1413, 1362, 1245, 902 cm^{-1}; MS (EI 70 eV) m/e 166 (M^+), 151 ($M^+ - 15$), 147, 123, 110, 94.

6-(*N*,*N*-Dibenzoylamino)-*N*-9-allylpurine (8). To a stirred solution of *N*-9-allyladenine (5 g, 0.028 mol) in pyridine (100 mL), protected from moisture with a drying tube and cooled in an ice bath, was added benzoyl chloride (40 g, 0.284 mol) dropwise. After 2 h, the mixture was left at room temperature for 1 h and was hydrolyzed with a 1 N $NaHCO_3$ solution (100 mL) followed by water (100 mL). After concentration under reduced pressure, the mixture was dissolved in methylene chloride, and the solution was washed twice with a 1 N $NaHCO_3$ solution and dried on sodium sulfate. The crude product was chromatographed on a silica gel column using a stepwise gradient of methanol−methylene chloride (0:100−5:95) to afford **8** recrystallized in propan-2-ol: yield 5 g (50%); ^{1}H NMR ($CDCl_3$) δ 4.83 (d, 2H, J = 6 Hz), 5.19−5.35 (m, 2H), 5.95−6.09 (m, 1H), 7.31−7.45 (m, 6H), 7.82 (m, 4H), 8.04 (s, 1H), 8.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.09, 119.81, 127.21, 128.62, 129.37, 131.04, 132.89, 134.04, 144.65, 151.66, 152.14, 153.05, 172.25.

***N*-9-Allyl-*N*-2-amino-6-chloropurine (21).** To a stirred suspension of 2-amino-6-chloropurine (1 g, 0.0060 mol) in dry acetonitrile (120 mL) was added at room temperature sodium hydride (60% dispersion in mineral oil, 0.26 g, 0.0065 mol), and the solution was stirred for 1 h under a nitrogen atmosphere. To this mixture was slowly added a solution of allyl bromide (8 mL) in dry acetonitrile (15 mL). The reaction mixture was stirred at room temperature for 24 h and filtered, and the yellow filtrate was evaporated to dryness. The residue was purified on a flash silica gel column using CH_2Cl_2/CH_3OH (95/5) as the eluant to yield the title compound as a yellow amorphous solid, whose NMR spectra was identical to previously reported data.[19] Yield: 700 mg (56%).

***N*-9-Allyl-2-(*N*-benzoylamino)-6-chloropurine (22).** To a cold (0 °C) solution of coumpound **21** (1.2 g, 0.0057 mol) in dry pyridine (15 mL) was slowly added benzoyl chloride (1 mL). The resulting mixture was stirred 1 h at 0 °C and washed with a saturated solution of $NaHCO_3$ (10 mL) followed by 10 mL of water. The organic layer was extracted with methylene chloride, washed with a saturated solution of $NaHCO_3$, dried ($MgSO_4$), and filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified on a flash silica gel column using CH_2Cl_2/CH_3OH (98/2) as the eluant to yield the title compound: yield 520 mg (29%); ^{1}H NMR ($CDCl_3$) δ 4.68 (d, 2H, J = 6.7 Hz), 5.09−6.00 (m, 2H), 5.78−5.97 (m, 1H), 7.20−7.45 (m, 3H), 7.85−7.93 (m, 2H), 8.00 (s, 1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.07, 119.95, 127.57, 128.02, 128.52, 130.90, 132.32, 133.74, 144.76, 150.54, 152.06 152.38, 165.05.

General Procedure for Hydrosilylation. To a stirred solution of the protected allylnucleobase in anhydrous THF heated to reflux was added **1a** or **1b** under a nitrogen atmosphere, followed by 0.1 mL of a 0.1 M solution of H_2PtCl_6 in propan-2-ol or a few milligrams of $(Bu_4N)_2PtCl_6$. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95:5).

After concentration under reduced pressure, the residue was hydrolyzed, the product was extracted with methylene chloride, and the combined extracts were dried with sodium sulfate. The crude product was chromatographed on a silica gel column using ethyl acetate as eluting solvent or a stepwise gradient of methanol−methylene chloride (0:100−5:95).

Bis(chloromethyl)methyl[3-[*N*-9-(6-(*N*,*N*-dibenzoylamino)purinyl)]propyl]silane (9a). Following the general procedure for hydrosilylation, a mixture of **8** (0.5 g, 0.00013 mol) in THF (15 mL, 0.184 mol) and an excess of **1a** (1 g, 0.0069 mol) was reacted with hexachloroplatinic acid at 60 °C for 2 h: yield 0.400 g (58%); ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 3H), 0.74−0.83 (m, 2H), 1.96−2.04 (m, 2H), 2.88 (s, 4H), 4.25 (t, 2H), 7.24−7.46 (m, 6H), 7.82 (m, 4H), 7.85 (m, 1H), 8.05 (s, 1H), 8.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.43, 8.26, 23.91, 26.73, 46.83, 127.23, 128.60, 129.36, 132.87, 134.03, 144.85, 151.61, 152.01, 153.13, 172.23.

Bis(chloromethyl)methyl[3-[*N*-1-(2,4-dioxopyrimidinyl)]propyl]silane (17a). A mixture of allyluracil **16** (1.2 g, 0.0079 mol), HMDS (5 mL), trimethylchlorosilane (0.5 mL), and a few crystals of ammonium sulfate was heated at reflux, under inert atmosphere, for 5 h; then, HMDS in excess was removed by distillation under reduced pressure. To the protected allyluracil was added THF (20 mL), bis(chloromethyl)methylsilane (1.5 g, 0.0103 mol), and hexachloroplatinic acid as described in the general procedure for hydrosilylation: yield 1.2 g (52%); ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 3H), 0.73−0.82 (m, 2H), 1.68−1.84 (m, 2H), 2.90 (s, 4H), 3.67−3.74 (t, 2H), 5.67 (d, 1H, J = 7.8 Hz), 7.12 (d, 1H, J = 7.8 Hz), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.40, 7.91, 22.92, 26.80, 51.33, 102.17, 144.29, 150.75, 163.63; IR (film) 3052.9, 2358.9, 1681.9, 1455.8, 1258.6, 816.7 cm^{-1}.

Bis(chloromethyl)methyl[3-[*N*-9-(6-chloropurinyl)]propyl]silane (13a). Following the general procedure for hydrosilylation, a mixture of *N*-9-allyl-6-chloropurine (**12**) (0.800 g, 0.0041 mol) in THF (20 mL) and bis(chloromethyl)methylsilane (**1a**) (1 g, 0.0069 mol) stirred in the presence of hexachloroplatinic acid (0.2 mL) at 60 °C for 2 h yielded 0.400 g (58%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 3H), 0.75−0.84 (m, 2H), 1.94−2.10 (m, 2H), 2.88 (s, 4H), 4.30 (t, 2H), 8.11(s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.43, 151.86, 151.75, 150.99, 145.01, 131.55, 47.02, 26.80, 23.92, 8.27.

(Chloromethyl)dimethyl[3-[*N*-9-(6-chloropurinyl)]propyl]silane (13b). Following the general procedure for hydrosilylation, a mixture of *N*-9-allyl-6-chloropurine (**12**) (0.500 g, 0.0025 mol) in anhydrous THF (20 mL) and (chloromethyl)-dimethylsilane (**1b**) (1 g, 0.0093 mol) stirred in the presence of hexachloroplatinic acid (0.2 mL) at 60 °C for 2 h yielded 0.158 g (20%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.57−0.68 (m, 2H), 1.85−2.01 (m, 2H), 2.83 (s, 2H), 4.26 (t, 2H), 8.10 (s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.67, 10.79, 24.34, 29.71, 47.32, 145.20, 151.00, 151.92.

(Chloromethyl)dimethyl[3-[*N*-1-(2,4-dioxopyrimidinyl)]propyl]silane (17b). Allyluracil **16** (3 g, 0.0197 mol) was protected as described for compound **17a** using HMDS (30 mL), trimethychlorolsilane (0.5 mL), and ammonium sulfate. THF (40 mL), (chloromethyl)dimethylsilane (**1b**) (2.3 g, 0.0213 mol), and hexachloroplatinic acid were then added according to the general procedure for hydrosilylation to give **17b**: yield 2 g (40%); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.57−0.66 (m, 2H), 1.65−1.77 (m, 2H), 2.75 (s, 2H), 3.65−3.73 (t, 2H), 5.66 (d, 1H, J = 7.8 Hz), 7.12 (d, 1H, J = 7.8 Hz), 9.29 (s, 1H); ^{13}C NMR (MeOD) δ −3.89, 12.02, 25.05, 31.30, 53.31, 102.94, 148.30, 153.70, 167.68; IR (film) 3052.9, 2358.98, 1681.9, 1455.8, 1258.6, 816.7 cm^{-1}.

Bis(chloromethyl)methyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (4a). Allylthymine **2** (1g, 0.006 mol) was protected as described for compound **17a** using HMDS (10 mL), trimethychlorolsilane (1 mL), and ammonium sulfate. Then, THF (10 mL), bis(chloromethyl)methylsilane (**1a**) (1.14 g, 0.008 mol), and hexachloroplatinic acid were added according to the general procedure for hydrosilylation. Compound **4a** was isolated as a white amorphous solid: yield 650 mg (35%); mp 156 °C; ^{1}H NMR ($CDCl_3$) δ 0.24 (s, 3H), 0.73−0.80 (m, 2H), 1.58−1.79 (m, 2H), 1.91 (d, 3H, J = 1 Hz), 2.91 (s, 4H), 3.67 (t, 2H), 6.97 (d, 1H, J = 1 Hz), 8.36 (large s); ^{13}C NMR ($CDCl_3$) δ 7.90, 12.30, 22.94, 26.85, 51.00, 110.71, 140.25, 150.95, 164.38.

(Chloromethyl)dimethyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (4b). Allylthymine **2** (1g, 0.006 mol) was treated as described for compound **4a**, using (chloromethyl)dimethylsilane (**1b**) (0.65 g, 0.006 mol) according to the general procedure for hydrosilylation. Compound **4b** was isolated as a white amorphous solid: yield 340 mg (20%); mp 147 °C; ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 6H), 0.57−0.66 (m, 2H), 1.60−1.77 (m, 2H), 1.91 (s, 3H), 2.77 (s, 2H), 3.66 (t, 2H, J = 7.3 Hz), 6.96 (s, 1H).

(19) Gundersen, L. L.; Benneche, T.; Rise, F.; Gogoll, A.; Undheim, K. *Acta Chem. Scand.* **1992,** *46,* 761.

Bis(chloromethyl)methyl[3-[*N*-9-(2-(*N*-benzoylamino)-6-chloropurinyl)]propyl]silane (23a). A stirred solution of compound **22** (520 mg, 0.00165 mol) in dry THF (25 mL) and bis(chloromethyl)methylsilane (**1a**) (286 mg, 0.002 mol) was heated at 65 °C under a nitrogen atmosphere. A catalytic amount of tetrabutylammonium hexachloroplatinate was added, and the mixture was kept at 60−70 °C for 24 h. After concentration under reduced pressure, the residue was purified on a flash silica gel column using CH_2Cl_2/CH_3OH (96/4) as the eluant to give the title compound as a pale yellow oil: yield 410 mg (54%); ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 3H), 0.62−0.71 (m, 2H), 1.85−2.05 (m, 2H), 2.80 (s, 4H), 4.14 (t, 2H, J = 6.8 Hz), 7.32−7.45 (m, 3H), 7.87−7.91 (m, 2H), 8.00 (s, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.31, 8.23, 23.64, 27.00, 47.01, 127.72, 128.42, 128.84, 132.57, 134.06, 145,09, 150,79,152.13, 152.83, 164.98.

General Procedure for Acetoxylation. A mixture of the chloro derivative, freshly dried sodium acetate, and dry DMF was stirred at 100−140 °C for 24 h under an inert atmosphere. The solvent was removed by distillation, the residue was washed with water, and the product was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Flash chromatography afforded the pure acetoxy compounds.

Bis(acetoxymethyl)methyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (5a). Compound **4a** (1 g, 0.0032 mol) was treated according to the general procedure with sodium acetate (1.05 g, 0.0128 mol) and DMF (25 mL). Flash chromatography using ethyl acetate−toluene (9:1) gave the title compound which slowly crystallized as white needles in cold (4 °C) diethyl ether: yield 820 mg (72%); mp 72 °C; ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.60−0.69 (m, 2H), 1.62−1.74 (m, 2H), 1.89 (d, 3H, J = 0.8 Hz), 2.01 (s, 6H), 3.64 (t, 2H, J = 7.3 Hz), 3.83 (s, 4H), 6.96 (d, 1H), 9.27 (large s, 1H); ^{13}C NMR ($CDCl_3$) δ −8.07, 7.73, 11.88, 20.21, 22.55, 50.51, 53.84, 109.95, 140.15, 150.81, 164.37, 171.07.

(Acetoxymethyl)dimethyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (5b). Compound **4b** (340 mg, 0.00123 mol) was treated according to the general procedure with sodium acetate (201 mg, 0.0024 mol) and DMF (20 mL). Flash chromatography using dichloromethane−methanol (98:2) gave the title compound as a light yellow solid: yield 200 mg (54%); mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.50−0.58 (m, 2H), 1.57−1.73 (m, 2H), 1.89 (d, 3H, J = 1.3 Hz), 2.01 (s, 3H), 3.64 (t, 2H), 3.74 (s, 2H), 6.96 (d, 1H), 9.34 (large s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.92, 10.56, 12.27, 20.72, 23.31, 51.22, 56.36, 110.48, 140.39, 150.87, 164.36, 171.76.

Another run starting from **3**, conducted without isolation of **4b**, gave better results (22% overall yield from **3**).

Bis(acetoxymethyl)methyl[3-[*N*-9-(6-chloropurinyl)]-propyl]silane (14a). Following the general procedure for acetoxylation, compound **13b** (2.5 g, 0.0074 mol) was stirred overnight at 70 °C with sodium acetate (2 g, 0.024 mol) in DMF (50 mL) to provide the title compound: yield 2.2 g (77%); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.62−0.71 (m, 2H), 1.97 (m, 8H), 3.81 (s, 4H), 4.23 (t, 2H), 8.12 (s, 1H), 8.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.45, 8.48, 20.53, 23.85, 47.09, 54.08, 131.65, 145.37, 151.00, 151.74, 171.2.

Bis(acetoxymethyl)methyl[3-[*N*-9-(6-(*N*,*N*-dibenzoylamino)purinyl)]propyl]silane (10a). Compound **9a** (0.900 g, 0.0017 mol) treated according to the general procedure with sodium acetate (0.600 g, 0.0072 mol) in DMF (20 mL) was purified by column chromatography using ethyl acetate to give the title compound: yield 0.510 g (57%); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.62−0.71 (m, 2H), 1.97 (m, 8H), 3.81 (s, 4H), 4.09 (t, 2H), 7.29−7.35 (m, 6H), 7.79−7.83 (m, 4H), 8.03 (s, 1H), 8.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.70, 8.67, 20.60, 23.98, 46.90, 54.15, 126.91, 128.22, 129.34, 132.86, 134.04, 144.86, 151.59, 151.96, 153.17, 171.48, 172.24.

Bis(acetoxymethyl)methyl[3-[*N*-1-(2,4-dioxopyrimidinyl)]propyl]silane (18a). Compound **17a** (2.8 g, 0.0095 mol) treated according to the general procedure with sodium acetate (3 g, 0.037 mol) in DMF (90 mL) was purified by column chromatography using ethyl acetate to give the title compound: yield 2 g (62%); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 3H), 0.60−0.69 (m, 2H), 1.69−1.76 (m, 2H), 2.00 (s, 6H), 3.64−3.72 (t, 2H), 3.85 (s, 4H), 5.66 (d, 1H, J = 7.8 Hz), 7.12 (d, 1H, J = 7.8 Hz), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.73, 8.18, 20.61, 22.95, 51.33, 54.18, 102.08, 144.35, 150.77, 163.75, 171.57; IR (KBr): 3188.1, 3054.2, 2955.5, 2251.7, 1674.5, 1456.4, 1368.5, 1219.0, 1030.4, 915.3, 806.1, 725.9 cm^{-1}.

(Acetoxymethyl)dimethyl[3-[*N*-1-(2,4-dioxopyrimidinyl)]propyl]silane (18b). Compound **17b** (0.9 g, 0.0035 mol) treated according to the general procedure with sodium acetate (0.640 g, 0.0078 mol) in DMF (20 mL) was purified by column chromatography using ethyl acetate to give the title compound: yield 0.630 g (64%); ^{1}H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.41−0.50 (m, 2H), 1.54−1.62 (m, 2H), 1.92 (s, 3H), 3.56−3.65 (m, 4H), 5.56 (d, 1H, J = 7.8 Hz), 7.10 (d, 1H, J = 7.8 Hz), 10.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.00, 10.43, 20.61, 23.16, 51.36, 56.30, 101.84, 144.65, 151.08, 164.39, 171.63.

Bis(acetoxymethyl)[3-[*N*-9-(2-(*N*-benzoylamino)-6-chloropurinyl)]propyl]silane (24a). To a stirred solution of compound **23a** (410 mg, 0.0009 mol) in dry DMF (20 mL) was added freshly dried sodium acetate (0.3 g, 0.0036 mol). The mixture was heated at 120 °C for 21 h under a nitrogen atmosphere and filtered, and the filtrate was evaporated *in vacuo* to yield an oil purified on a flash silica gel column using CH_2Cl_2/CH_3OH (95/5) as the eluant to give the title compound as a viscous yellow oil: yield 300 mg (60%); ^{1}H NMR ($CDCl_3$) δ −0.09 (s, 3H), 0.42−0.50 (m, 2H), 1.60−1.71 (m, 2H), 1.78 (s, 6H), 3.66 (s, 4H), 3.82 (t, 2H, J = 7 Hz), 7.20−7.39 (m, 3H), 7.48 (s, 1H), 7.82−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −8.13, 7.47, 20.12, 23.33, 45.80, 53.71, 120.29, 127.61, 128.12, 131.24, 132.78, 138.76, 147.40, 148.03, 155.16, 168.23, 171.29.

Bis(acetoxymethyl)methyl[3-[*N*-1-(2-oxo-4-(3-nitro-1,2,4-triazolo)pyrimidinyl)]propyl]silane (19a). Compound **18a** (2 g, 0.0058 mol) was coevaporated twice with 20 mL of dry pyridine and then stirred under a nitrogen atmosphere with 1-(2-mesitylenesulfonyl)-3-nitro-1,2,4-triazole (MSNT, 2.4 g, 0.008 mol) and a solution of diphenyl phosphate (0.4 g, 0.0016 mol) in pyridine (20 mL) for 72 h at room temperature. Water (20 mL) was added, and the solvent evaporated under reduced pressure; the residue was coevaporated twice with toluene (40 mL) and purified on a silica gel column using a stepwise gradient of methanol−dichloromethane (0:100−5:95): yield 2.3 g (92%); ^{1}H NMR (DMSO-d_6) δ 0.07 (s, 3H), 0.60−0.68 (m, 2H), 1.75 (m, 2H), 1.98 (s, 6H), 3.81 (s, 4H), 3.88−3.95 (t, 2H), 6.97 (d, 1H, J = 7.8 Hz), 8.55 (d, 1H, J = 7.8 Hz), 9.71 (s, 1H); ^{13}C NMR (DMSO-d_6) δ −7.57, 7.68, 20.44, 22.08, 53.28, 54.19, 93.33, 145.90, 153.88, 154.57, 157.88, 163.09, 170.98; IR: 2358.9, 2340.7, 1732.6, 1682.5, 1558.3, 1300.7, 820.4, 794.6 cm^{-1}.

(Acetoxymethyl)dimethyl[3-[*N*-1-(2-oxo-4-(3-nitro-1,2,4-triazolo)pyrimidinyl)]propyl]silane (19b). Compound **18b** (0.650 g, 0.0021 mol), treated like **18a** with MSNT (1 g, 0.0033 mol) and diphenyl phosphate (0.1 g, 0.0004 mol) in pyridine (5 mL) for 24 h at room temperature, afforded the title compound: yield 0.450 g (52%); ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6H), 0.52−0.61 (m, 2H), 1.81 (m, 2H), 1.97 (s, 3H), 3.71 (s, 2H), 3.91-3.98 (t, 2H), 7.00 (d, 1H, J = 7.8 Hz), 7.98 (d, 1H, J = 7.8 Hz), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.97, 10.73, 20.67, 23.07, 54.88, 56.30, 93.80, 144.38, 152.23, 154.14, 158.11, 163.48, 171.63.

General Procedure for Hydroxylation. A stirred solution of the acetoxylated compound in anhydrous methanol was reacted with dry potassium carbonate under an inert atmosphere at room temperature. After completion of the reaction (monitored by TLC), a 1 N HCl solution was added. The resulting neutral solution was concentrated under reduced pressure, and the residue was taken up in dichloromethane, dried ($MgSO_4$), and filtered. The filtrate was evaporated to an oil applied to a silica gel column eluted with dichloromethane−methanol (9:1) to afford the pure hydroxylated compounds.

Bis(hydroxymethyl)methyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (6a). Compound **5a** (820 mg, 0.0023 mol) treated according to the general procedure with potassium carbonate (636 mg, 0.0046 mol) in methanol (50 mL) and 9.2 mL of 1 N HCl solution was purified by flash chromatography to give an oil which slowly crystallized *in vacuo* as a white amorphous solid: yield 476 mg (76%); mp

116 °C; ^{1}H NMR (CD_3OD) δ 0.07 (s, 3H), 0.62−0.71 (m, 2H), 1.66−1.82 (m, 2H), 1.85 (d, 3H, J = 1 Hz), 3.43 (s, 4H), 3.69 (t, 2H, J = 7.3 Hz), 7.42 (d, 1H); ^{13}C NMR (CD_3OD) δ −8.25, 8.34, 12.20, 24.17, 52.13, 52.50, 110.86, 143.22, 152.82, 166.76; MS (FAB), *m*/*e* (rel intensity) 273.1 (90, M + 1), 241.1 (100).

(Hydroxymethyl)dimethyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (6b). Compound **5b** (200 mg, 0.67 mmol) treated according to the general procedure with potassium carbonate (92 mg, 0.67 mmol) in methanol (20 mL) and 1.3 mL of a 1 N HCl solution was purified by flash chromatography to give **6b** as a white amorphous solid: yield 100 mg (60%); mp 138 °C; ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.49−0.58 (m, 2H), 1.64−1.70 (m, 2H), 1.84 (d, 3H, J = 1 Hz), 3.35 (s, 2H), 3.62 (t, 2H, J = 7.4 Hz), 6.98 (d, 1H); ^{13}C NMR ($CDCl_3$) δ −5.16, 10.35, 12.32, 23.54, 51.41, 54.89, 110.47, 140.55, 150.88, 164.19; MS (FAB), *m*/*e* (rel intensity) 257.1 (100, M + 1), 225.1 (88).

Bis(hydroxymethyl)methyl[3-[*N*-9-(*N*-6-benzamidopurinyl)]propyl]silane (11a). A solution of compound **10a** (0.400 g, 0.0007 mol) in ethanol (8 mL) was stirred for 1 h with a 2 N NaOH solution (4 mL). The mixture was neutralized with aqueous ammonium chloride and concentrated under reduced pressure. The aqueous solution was extracted with dichloromethane, and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified on a silica gel column using a stepwise gradient of methanol−methylene chloride (0:100−15:85): yield 0.150 g (56%); ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3H), 0.64−0.72 (m, 2H), 2.01 (m, 2H), 2.74 (s, 2H), 3.53 (s, 4H), 4.25 (t, 2H), 7.46 (m, 3H), 8.00 (m, 3H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −8.03, 8.12, 24.31, 46.81, 53.50, 122.76, 128.18, 129.79, 132.67, 133.52, 143.13, 149.50, 151.96, 152.26, 165.14.

Bis(hydroxymethyl)methyl[3-[*N*-9-(6-aminopurinyl)]propyl]silane (15a). Compound **14a** (0.550 g, 0.0014 mol) was dissolved in 20 mL of methanol and then chilled at −80 °C in a steel bomb, and liquid ammonia (10 g) was then added. The mixture was stirred at 90 °C overnight. Solvent was evaporated, and the residue was purified on a silica gel column using a stepwise gradient of methanol−methylene chloride (5:95−25:75, v/v): yield 0.330 g (76%); ^{1}H NMR (D_2O) δ −0.04 (s, 3H), 0.46−0.54 (m, 2H), 1.77 (m, 2H), 3.34 (s, 4H), 4.00 (t, 2H), 7.93 (s, 1H), 7.95 (s, 1H); ^{13}C NMR (D_2O) δ −6.86, 9.39, 26.13, 49.32, 53.74, 144.77, 151.00, 153.35, 153.65, 156.92; ^{13}C NMR (DMSO-d_6) δ −7.93, 7.74, 24.11, 45.91, 50.22, 118.71, 141.11, 149.48, 151.84, 155.55; IR 998.0, 1249.0, 1417.0, 1475.0, 1601.0, 1651.0, 2884.0, 3198.0, 3345.0 cm^{-1}; HRMS calcd 282.1386, found 282.1388.

(Hydroxymethyl)dimethyl[3-[*N*-9-(6-aminopurinyl)]propyl]silane (15b). Following the general procedure for acetoxylation, compound **13b** (0.270 g, 0.00089 mol) was stirred overnight at 100 °C with sodium acetate (0.320 g, 0.0039 mol) in DMF (20 mL). The solvent was evaporated under reduced pressure and the residue dissolved in 30 mL of methanol. The solution was chilled at −80 °C in a steel bomb, and liquid ammonia (20 g) was then added. The mixture was stirred at 90 °C overnight. The solvent was evaporated, and the residue was purified on a silica gel column using a stepwise gradient of methanol−methylene chloride (5:95−25:75, v/v): yield 0.100 g (42%); ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.55−0.63 (m, 2H), 1.86−201 (m, 3H), 3.40 (s, 2H), 4.19 (t, 2H), 5.76 (large exchanged with D_2O, 2H), 7.79 (s, 1H), 8.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.18, 10.56, 24.74, 46.69, 54.40, 140.41, 152.84, 155.33; MS (FAB), *m*/*e* (rel intensity) 266.1 (100, M + 1); HRMS calcd 266.1437, found 266.1439.

Bis(hydroxymethyl)methyl[3-[*N*-1-(4-amino-2-oxopyrimidinyl)]propyl]silane (20a). A solution of compound **19a** (2.3 g, 0.0052 mol) in dioxane (20 mL) was stirred overnight with ammonium hydroxide (40 mL) at room temperature. After concentration under reduced pressure the resulting brown oil was disolved in methanol (40 mL) and reacted with potassium carbonate (1 g, 0.0072 mol) for 12 h at room temperature and neutralized with a 1 N HCl solution, and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column using methanol−dichloromethane−ethyl acetate (33:33:33) as eluant: yield 0.850 g (63%); ^{1}H NMR (DMSO-d_6) δ −0.05 (s, 3H), 0.44−0.52 (m, 2H) 1.58−1.61 (m, 2H), 3.19 (s, 4H), 3.56 (t, 2H), 3.98 (s, 2H), 5.61 (d, 1H, J = 7 Hz), 6.92 (s, 2H), 7.52 (d, 1H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ −7.90, 7.53, 23.17, 50.25, 51.61, 92.93, 146.27, 155.57, 165.70; HRMS (FAB+) calcd 258.12739, found 258.1279.

(Hydroxymethyl)dimethyl[3-[*N*-1-(4-amino-2-oxopyrimidinyl)]propyl]silane (20b). A solution of compound **19b** (0.400 g, 0.001 mol) in dioxane (2 mL) treated as described for compound **19a** with ammonium hydroxide (4 mL), methanol (20 mL), and potassium carbonate (0.400 g, 0.0029 mol) gave the crude product purified on a silica gel column using methanol−dichloromethane−ethyl acetate (20:40:40): yield 100 mg (41%); ^{1}H NMR (DMSO-d_6) δ −0.05 (s, 6H), 0.39−0.47 (m, 2H), 1.50−1.59 (m, 2H), 3.11 (s, 2H), 3.56 (t, 2H), 3.98 (s, 1H), 5.59 (d, 1H, J = 7 Hz), 6.94 (s, 2H), 7.52 (d, 1H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ −4.81, 10.10, 23.26, 51.61, 52.28, 92.90, 146.11, 155.79, 165.88; MS (FAB), *m*/*e* (rel intensity) 241.1 (100, M + 1).

Bis(hydroxymethyl)methyl[3-[*N*-9-(2-(*N*-benzoylamino)-6-oxopurinyl)]propyl]silane (25a). A mixture of **24a** (300 mg, 0.0006 mol), in hydrochloric acid (1 N, 10 mL), was heated under refux for 1 h. The cooled solution was neutralized by addition of aqueous NaOH (1 N) and evaporated *in vacuo* to dryness. The crude product was taken up in isopropyl alcohol and filtered, and the filtrate was evaporated *in vacuo* to an oil purified on a silica gel column using CH_2Cl_2/CH_3OH (90/10) as the eluant to give the title compound as a white solid: yield 110 mg (45%); ^{1}H NMR (CD_3OD) δ -0.02 (s, 3H), 0.53−0.81 (m, 2H), 1.77−1.92 (m, 2H), 3.34 (s, 4H), 4.00 (t, 2H, J = 7.0 Hz), 7.32−7.51 (m, 3H), 7.79−7.84 (m, 4H); ^{13}C NMR (CD_3OD) δ −8.15, 8.76, 25.47, 47.84, 52.51, 121.09, 129.22, 129.88, 133.28, 134.28, 141.53, 149.26, 150.32, 157.27, 170.73.

Bis(hydroxymethyl)methyl[3-[1-(2-oxo-4-benzamidopyrimidinyl)]propyl]silane (26a). Compound **20a** (0.700 g, 0.0027 mol) was coevaporated twice with 20 mL of dry pyridine and dissolved in the same solvent (25 mL) under an inert atmosphere. To this solution cooled in an ice bath was added dropwise trimethylchlorosilane (2 g, 0.018 mol), and the mixture was stirred for 1 h, followed by the carefull addition of benzoyl chloride (3 g, 0.021 mol). The ice bath was removed, and the mixture was stirred at room temperature overnight. The medium was chilled again (ice bath), and cold water (10 mL) was added followed after 15 min by ammonium hydroxide (10 mL). After 1 h, the solvent was removed under reduced pressure, and the product was dissolved in isopropyl alcohol and filtered. The filtrate was concentrated under reduced presure and the crude product purified on a silica gel column using a stepwise gradient of dichloromethane−methanol (95:5−90:10): yield 0.450 g (45%); ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3H), 0.66−0.75 (m, 2H), 1.87 (m, 2H), 3.58 (s, 4H), 3.88 (t, 2H), 7.50 (m, 5H), 7.90 (m, 3H); ^{13}C NMR ($CDCl_3$) δ −7.96, 7.89, 23.14, 53.03, 53.76, 97.09, 127.92, 128.71, 132.86, 132.98, 149.36, 156.09, 162.79, 167.12.

General Procedure for Monotritylation. The dihydroxylated derivatives were coevaporated twice with dry pyridine and then dissolved in the same solvent. The solution was stirred with 4,4′-dimethoxytrityl chloride at room temperature for 4 h, the mixture was hydrolyzed with water (10 mL), the solvent was evaporated under reduced pressure, and the monotritylated compounds were separated from the ditritylated derivatives on a silica gel column.

(Hydroxymethyl)(((4,4′-dimethoxytrityl)oxy)methyl)methyl[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]silane (27a). Compound **6a** (0.500g, 0.0018 mol) treated according to the general procedure with pyridine (15 mL) and 4,4′-dimethoxytrityl chloride (0.680 g, 0.002 mol) was hydrolyzed with water (10 mL). The crude product was chromatographed on a silica gel column using ethyl acetate−triethylamine (98:2) as eluant: yield 0.500 g (48%); ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.60−0.70 (m, 2H), 1.70 (m, 2H), 1.89 (s, 3H), 2.86 (s, 2H), 3.53 (s, 2H), 3.55−3.69 (m, 3H), 3.79 (s, 6H), 6.80 (m, 5H), 7.22 (m, 9H).

(Hydroxymethyl)(((4,4′-dimethoxytrityl)oxy)methyl)methyl[3-[*N*-9-(6-benzamidopurinyl)]propyl]silane (28a). Compound **11a** (0.200 g, 0.00052 mol) treated according to the general procedure with pyridine (5 mL) and 4,4′-dimethox-

ytrityl chloride (0.110 g, 0.00032 mol) was hydrolyzed with water (10 mL). The crude product was chromatographed on a silica gel column using a stepwise gradient of dichloromethane−triethylamine−methanol (98:2:0−93:2:5): yield 0.120 g (33%); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.64−0.73 (m, 2H), 1.93 (m, 2H), 2.81 (s, 2H), 3.52 (s, 2H), 3.75 (s, 6H), 4.21 (t, 2H), 6.75 (m, 4H), 7.20 (m, 10H), 7.49 (m, 3H), 8.00 (m, 3H), 8.75 (s, 1H).

(Hydroxymethyl)(((4,4′-dimethoxytrityl)oxy)methyl)-methyl[3-[*N*-1-(2-oxo-4-benzamidopyrimidinyl)]propyl]-silane (29a). Compound **26a** (0.360 g, 0.001 mol) treated according to the general procedure with pyridine (10 mL) and 4,4′-dimethoxytrityl chloride (0.370 g, 0.0011 mol) at room temperature for 4 h was hydrolyzed with water (10 mL). The crude product was chromatographed on a silica gel column using a stepwise gradient of dichloromethane−triethylamine−methanol (98:2:0−93:2:5): yield 0.170 g (26%); ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 3H), 0.64−0.73 (m, 2H), 1.77 (m, 2H), 2.83 (s, 2H), 3.53 (s, 2H), 3.75 (s, 6H), 3.83 (t, 2H), 6.77 (m, 4H), 7.58 (m, 15H), 7.85 (m, 2H).

(Hydroxymethyl)(((4,4′-dimethoxytrityl)oxy)methyl)-methyl[3-[*N*-9-(2-(*N*-benzoylamino)-6-oxopurinyl)]propyl]-silane (30a). Compound **25a** (0.100 g, 0.00023 mol) treated according to the general procedure with pyridine (5 mL) and 4,4′-dimethoxytrityl chloride (0.080g, 0.000236 mol) was hydrolyzed with water (5 mL). The crude product was chromatographed on a silica gel column using a stepwise gradient of ethyl acetate−triethylamine−methanol (98:2:0−78:2:20): yield 0.080 g (45%); ^{1}H NMR (CD_3OD) δ 0.06 (s, 3H), 0.65−0.82 (m, 2H), 2.02 (m, 2H), 2.85 (s, 2H), 3.53 (s, 2H), 3.75 (s, 6H), 4.00−4.07 (t, 2H, J = 6.8 Hz), 6.72−6.77 (m, 4H), 7.18−7.61 (m, 19H).

General Procedure for the Nucleoside Analogues Synthesis. The monotritylated derivative was coevaporated twice with dry pyridine, stored under vacuum overnight, and then dissolved under a nitrogen atmosphere, in a solution of freshly distilled dichloromethane and diisopropylethylamine. Cyanoethyl diisopropylchlorophosphoramidite in dichloromethane was added dropwise at room temperature to the stirred solution. After 1 h, methanol was added to neutralize the chlorophosphoramidite excess, followed by ethyl acetate and triethylamine. The solution was washed with a 1 N solution of sodium hydrogenocarbonate and brine and was dried on sodium sulfate before concentration under reduced pressure. The crude product was purified on a silica gel column.

Silathymidine Analogue Phosphoramidite (1-*O*-DMT-2-methyl-2-[3-[*N*-1-(2,4-dioxo-5-methylpyrimidinyl)]propyl]-2-silapropanol 3-*O*-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite)) (31a). Compound **27a** (0.500 g, 0.00087 mol) was treated according to the general procedure with dichloromethane (4 mL), diisopropylethylamine (0.8 mL), and cyanoethyl diisopropylchlorophosphoramidite (0.424 g, 0.0018 mol) dissolved in dichloromethane (1 mL). After 1 h of stirring, methanol (0.030 mL) and triethylamine (2 mL) in ethyl acetate (40 mL) were added before washing with $NaHCO_3$ (20 mL) and brine (20 mL). The title product was purified on a silica gel column using ethyl acetate−hexane−triethylamine (68:30:2) as eluant: yield 0.500 g (74%); ^{31}P NMR ($CDCl_3$) δ 151.38; ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 3H), 0.64−0.72 (m, 2H), 0.95−1.15 (m, 12H), 1.67 (m, 2H), 1.85 (s, 3H), 2.53 (t, 2H), 2.75 (s, 2H), 3.22−3.67 (m, 9H), 3.77 (s, 6H), 6.77 (m, 5H), 7.20−7.35 (m, 9H); ^{13}C NMR ($CDCl_3$) δ −7.42, 8.37, 12.19, 20.29, 20.41, 23.41, 24.62, 42.75, 43.00, 51.15, 51.88, 52.85, 55.12, 58.06, 58.46, 87.41, 110.24, 112.88, 126.56, 127.62, 128.22, 130.16, 135.86, 140.53, 144.81, 150.63, 158.30, 164.12; MS (FAB), *m*/*e* (rel intensity) 774.1 (100, M − 1).

Silaadenosine Analogue Phosphoramidite (1-*O*-DMT-2-methyl-2-[3-[*N*-9-(6-benzamidopurinyl)]propyl]-2-silapropanol 3-*O*-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (32a). Compound **28a** (0.180 g, 0.00026 mol) was treated according to the general procedure with dichloromethane (1 mL), diisopropylethylamine (0.2 mL), and cyanoethyl diisopropylchlorophosphoramidite (0.100 g, 0.00042 mol) dissolved in dichloromethane (0.25 mL). After 1 h of stirring, methanol (0.008 mL) and triethylamine (2 mL) in ethyl acetate (40 mL) were added before washing with $NaHCO_3$ (20 mL) and brine (10 mL). The title product was purified on a silica gel column using ethyl acetate−dichloromethane−triethylamine (45:45:10) as eluant: yield 0.110 g (47%); ^{31}P NMR ($CDCl_3$) δ 151.41; ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.66−0.74 (m, 2H), 0.95−1.15 (m, 12H), 1.93 (m, 2H), 2.51 (t, 2H), 2.75 (s, 2H), 3.20−3.52 (m, 4H), 3.75 (s, 8H), 4.20 (t, 2H), 6.75 (m, 4H), 7.20−7.35 (m, 9H), 7.49−7.65 (m, 3H), 7.93−8.03 (m, 3H), 8.75 (s, 1H), 8.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −7.39, 8.73, 20.28, 20.40, 22.86, 24.55, 42.74, 42.99, 46.87, 51.78, 52.78, 55.12, 58.03, 58.39, 87.41, 112.84, 122.85, 126.55, 127.58, 127.79, 128.22, 128.76, 130.13, 132.61, 133.70, 135.83, 142.95, 144.71, 149,32, 151.96, 152.26, 158.26, 164.69; MS (FAB), *m*/*e* (rel intensity) 888.9 (40, M + 1), 448.3 (100).

Silacytidine Analogue Phosphoramidite (1-*O*-DMT-2-methyl-2-[3-[*N*-1-(2-oxo-4-benzamidopyrimidinyl)]propyl]-2-silapropanol 3-*O*-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite) (33a). Compound **29a** (0.100 g, 0.00015 mol) was treated according to the general procedure with dichloromethane (1 mL), diisopropylethylamine (0.2 mL), and cyanoethyl diisopropylchlorophosphoramidite (0.080 g, 0.00033 mol) dissolved in dichloromethane (0.25 mL). After 1 h of stirring, methanol (0.006 mL) and triethylamine (2 mL) in ethyl acetate (15 mL) were added before washing with $NaHCO_3$ (20 mL) and brine (10 mL). The title product was purified on a silica gel column using ethyl acetate−dichloromethane−triethylamine (45:45:10) as eluant: yield 0.090 g (70%); ^{31}P NMR ($CDCl_3$) δ 151.38; ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 3H), 0.64−0.74 (m, 2H), 0.95−1.16 (m, 12H), 1.67−1.82 (m, 2H), 2.54 (t, 2H), 2.76 (s, 2H), 3.20−3.55 (m, 4H), 3.76 (m, 10H), 6.77 (m, 4H), 7.22−7.40 (m, 11H), 7.49−7.65 (m, 3H), 7.86−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ −7.39, 8.40, 20.32, 23.26, 24.62, 42.75, 42.99, 51.85, 52.79, 53.46, 55.12, 58.12, 58.49, 87.44, 97.09, 112.88, 126.56, 127.43, 127.62, 128.22, 128.98, 130.16, 132.86, 133.07, 135.83, 144.75, 149.36, 158.27, 161.91, 156.09, 167.13; MS (FAB), *m*/*e* (rel intensity) 862.4 (62, M + 1), 404.6 (100).

Silaguanosine Analogue Phosphoramidite (1-*O*-DMT-2-methyl-2-[3-[*N*-9-(2-(*N*-benzoylamino)-6-oxopurinyl)]-propyl]-2-silapropanol 3-*O*-(2-cyanoethyl *N*,*N*-diisopropylphosphoramidite)) (34a). Compound **30a** (0.080 g, 0.00011 mol) was treated according to the general procedure with dichloromethane (0.5 mL), diisopropylethylamine (0.1 mL), and cyanoethyl diisopropylchlorophosphoramidite (0.047 g, 0.0002 mol) dissolved in dichloromethane (0.25 mL). After 1 h of stirring, methanol (0.010 mL) and triethylamine (1 mL) in ethyl acetate (6 mL) were added before washing with $NaHCO_3$ (10 mL) and brine (10 mL). The title product was purified on a silica gel column using ethyl acetate−triethylamine−methanol (98:2:0−88:2:10) as eluant: yield 0.080 g (77%); ^{31}P NMR ($CDCl_3$) δ 151.38; ^{1}H NMR (CD_3OD) δ 0.075 (s, 3H), 0.71−0.88 (m, 2H), 1.03−1.12 (m, 12H), 2.02 (m, 2H), 2.48−2.54 (m, 2H), 2.75 (s, 2H), 3.26−3.50 (m, 4H), 3.73 (s, 7H), 4.00−4.08 (t, 2H, J = 6.8 Hz), 6.71−6.76 (m, 4H), 7.17−7.70 (m, 19H); ^{13}C NMR ($CDCl_3$) δ −7.36, 8.97, 20.28, 20.40, 24.43, 24.58, 24.98, 42.71, 42.96, 47.08, 52.18, 52.57, 52.75, 55.12, 58.00, 58.33, 87.47, 112.84, 117.69, 126.67, 127.34, 127.61, 128.22, 128.73, 128.82, 130.16, 135.82, 131.31, 132.22, 133.28, 135.83, 144.92, 147.04, 148.20, 155.56, 158.32, 167.18, 167.63; MS (FAB), *m*/*e* (rel intensity) 901.7 (100, M − 1), 903.4 (84.8), 903.0 (83.4), 903.9 (66).

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Supporting Information Available: NMR, IR MS, and HRMS spectra (70 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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