Regiochemistry and Stereochemistry in Pd(0)-Catalyzed Allylic Alkylation of Nucleoside Bases

Lise-Lotte Gundersen,[a] Tore Benneche,[a,*] Frode Rise,[b] Adolf Gogoll[b] and Kjell Undheim[a]

[a] Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, N-0315 Oslo, Norway and [b] Institute of Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden

Gundersen, L.-L., Benneche, T., Rise, F., Gogoll, A. and Undheim, K., 1992. Regiochemistry and Stereochemistry in Pd(0)-Catalyzed Allylic Alkylation of Nucleoside Bases. – Acta Chem. Scand. 46: 761–771.

Allylic alkylation of amino- and hydroxy-azaheterocycles, in particular nucleoside bases, has been effected using Pd(0)-catalysis. A method has been developed for the preparation of carbocyclic nucleoside analogs such as the antiviral agent Carbovir. The synthesis of an appropriately substituted cyclopentenyl acetate for this reaction is described. Carbocyclic nucleosides of thymine at N-1, of adenine at N-9 and guanine at N-9 are described. Regiochemistry and stereochemistry of the products and intermediates have been determined by NMR studies. The (trimethylsilyl)ethyl group has been found to be an excellent protecting group for the 6-OH group in guanine, and it is readily removed by fluoride ions.

Alkylations of nucleoside bases and related biologically important heteroarene derivatives are frequently carried out on the respective ambident anions.[1,2] The chemoselectivity and regioselectivity depend on factors such as the nature of counter ion and the relative hardness (softness) of the nucleophilic centers in the anion, and on the electronic nature (hardness, softness) and the size of the electrophile, besides the properties of the solvent.

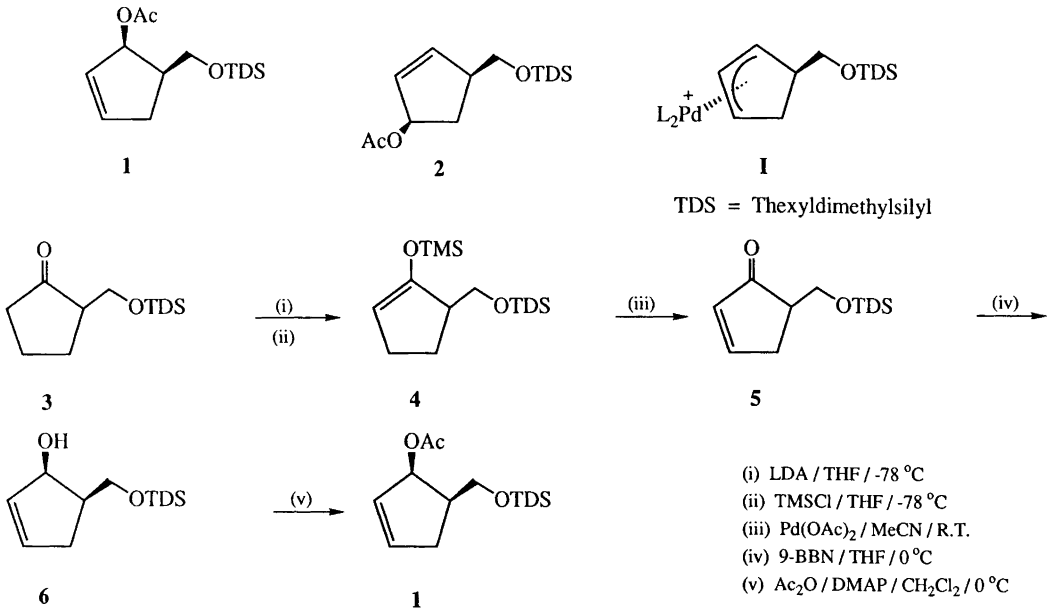
In this report we describe work on alkylation reactions using π-allyl palladium complexes for the purpose of developing methods for regio- and stereo-chemical control in the preparation of carbocyclic nucleosides. Previously we have described the use of π-allylpalladium complexes in the alkylation of 2-pyrimidinone.[3] Since π-allylpalladium complexes are relatively soft electrophiles,[4] alkylation was on the nitrogen which is the softer part of the ambient pyrimidinone anion.[3]

In nucleosides and analogs, β-stereochemistry at the anomeric carbon is a requirement for nucleoside activity. In the syntheses of nucleosides, however, stereochemical control at the anomeric carbon is frequently a major difficulty. We envisaged that the stereochemical course can be controlled by a palladium-catalyzed coupling reaction with an allylic acetate or carbonate since the stereochemistry in such reactions is controlled by the stereochemistry of the Pd(0)-template. The stereochemical outcome with soft nucleophiles is retention of the acetate or carbonate configuration.[4] The product from the coupling reaction has a carbon–carbon double bond which can be further manipulated, e.g. by introduction of one or two hydroxy groups.

The allylic coupling reaction constitutes a promising route for the preparation of antiviral carbocyclic nucleosides containing a cyclopentene ring attached to a heterocyclic moiety in its allylic position.[5,6] In our syntheses of such structures (*vide infra*) the carbocyclic sugar is an appropriately substituted cyclopentenyl acetate. Either the cyclopentenyl acetate **1** or its isomer **2** (Scheme 1) could have been used as starting material for the synthesis, because in Pd(0)-catalyzed allylic alkylations the original positional identity is lost once the leaving group has departed.[4] The same intermediate palladium complex (**I**; Scheme 1) is formed from either isomer. The regioselectivity during the approach by the nucleophilic base is controlled by non-bonded interactions, in the present case from the substituent on the cyclopentene ring. Both the stereochemical and regiochemical assumptions were confirmed in alkylation reactions using the cyclopentenyl acetate **1**.

The cyclopentenyl acetate **1** was prepared from the cyclopentanone **3** which we have previously described.[7] The latter was converted into its trimethylsilyl enol ether **4**, which was oxidized to the α,β-unsaturated ketone **5** by Pd(II) acetate. The use of other oxidants such as benzoquinone or 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of catalytic amounts of palladium was less satisfactory. Reduction of the enone **5** with 9-borabicyclo-[3.3.1]nonane (9-BBN) in THF led almost exclusively to the formation of the *cis*-alcohol **6**. Cerium(III)-catalyzed sodium borohydride reduction of the enone **5** was also tried, but the product was a mixture of saturated *cis*- and *trans*-alcohols and the *trans*-cyclopentenol in addition to the desired *cis*-alcohol **6**. The stereochemical assignment of the product was based on NMR data. NOE studies of the

* To whom correspondence should be addressed.

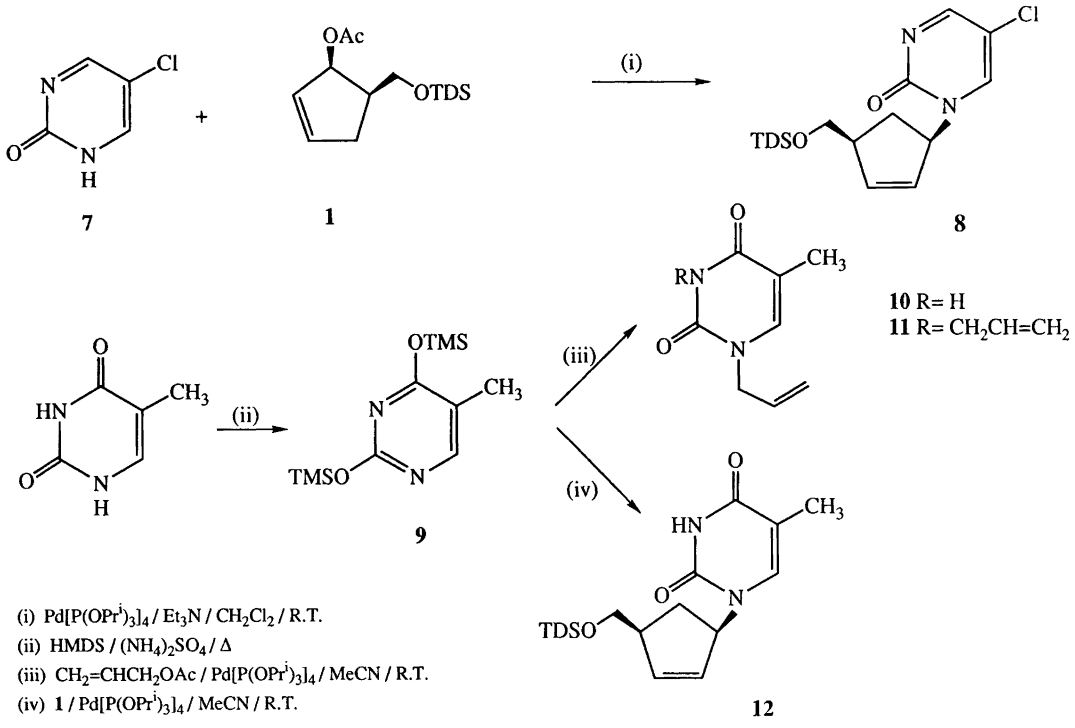


Scheme 1.

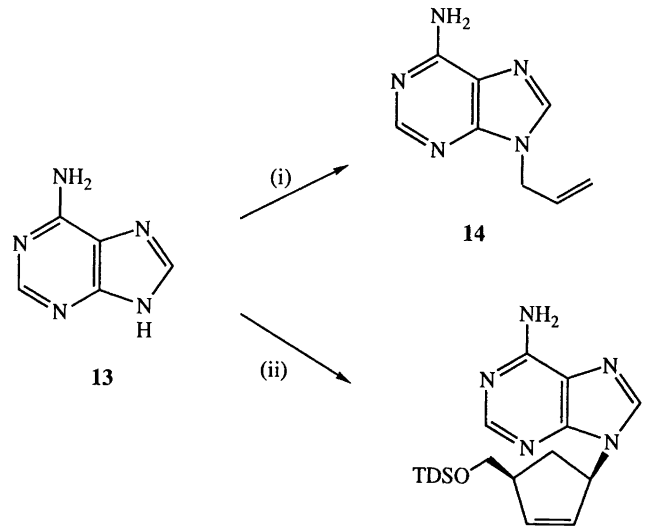
acetate **1** showed that 1-H and 5-H must have a *cis* relationship since irradiation of 1-H gave an 18 % increase of the signal intensity of 5-H whereas irradiation of 5-H gave a 13 % increase in the intensity of the 1-H-signal (Scheme 6).

In the alkylation reactions the reactivity of the cyclopentenyl acetate **1** was qualitatively compared with the reactivity of allyl acetate where there is no substituent to cause steric interference.

π-Allylpalladium acetate reacted with the ambident anion of the 5-chloro-2-pyrimidinone with exclusive formation of the *N*-alkylated product.[3] The same course of reaction was observed with the *cis*-cyclopentenyl acetate **1**, the product being the *N*-alkylated derivative **8** (Scheme 2). The regiochemistry corresponds to alkylation by the less sterically hindered terminal allylic carbon, and the stereochemistry was retained as shown by NOE experiments (*vide infra*).



Scheme 2.



(iii) CH_2=$CHCH_2OAc$ / $Pd(PPh_3)_4$ / Cs_2CO_3 / DMSO / 45 °C
(iv) **1** / $Pd(PPh_3)_4$ / Cs_2CO_3 / DMSO / 45 °C

Scheme 3.

In thymine there are two ambident anionic centers for alkylation. Mono *N*-alkylation can occur at either N-1 or N-3, but in most cases alkylation on N-1 is the faster reaction. In the present work alkylation was run on the bis-activated 2,4-bis(trimethylsilyloxy) derivative **9**. With allyl acetate the product was a mixture of the N-1 mono-alkylated derivative **10** and the 1,3-dialkylated derivative **11**. The non-bonded interaction in the reaction of the cyclopentenyl acetate **1**, however, gave exclusively the N-1 alkylated product, the pyrimidine nucleoside **12**. NOE experiments (Scheme 6) confirmed that the alkylation was on N-1. There was 4% increase in the intensity of the 6-H signal in the heterocycle when 1'-H in the cyclopentene ring was irradiated, and an increase of 2% in the intensity of the 1'-H signal when 6-H was irradiated. The *cis* stereochemistry was also confirmed by NMR (*vide infra*).

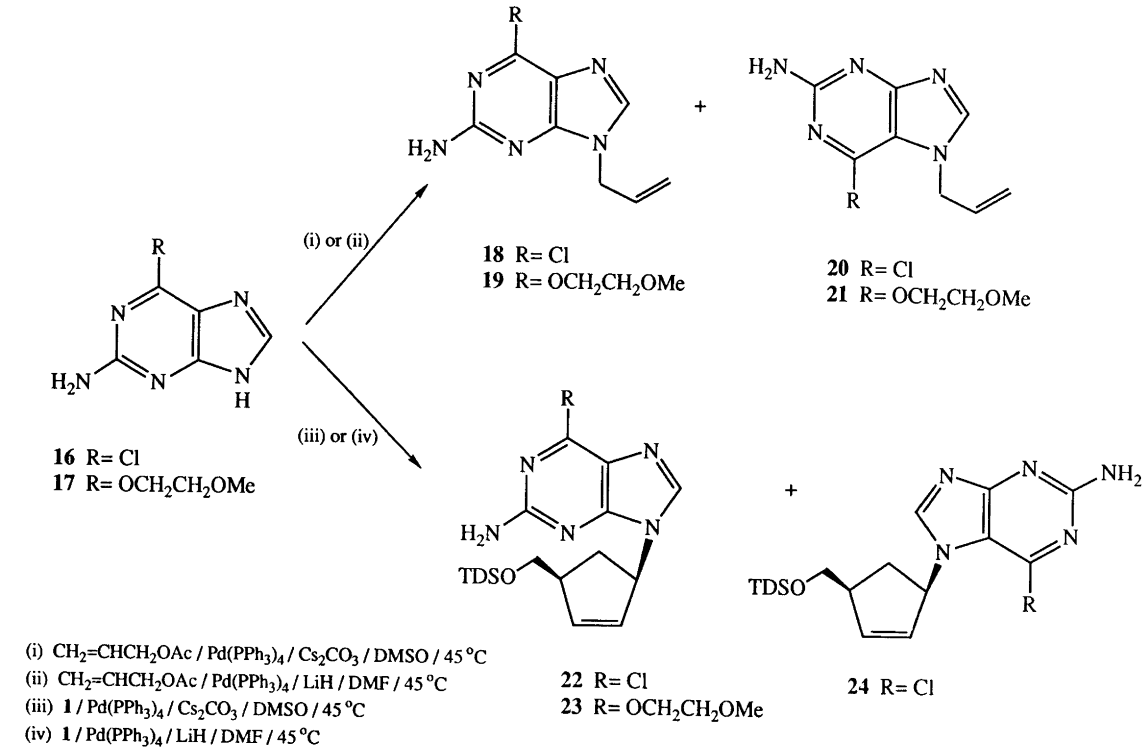
In the alkylation of amino- or hydroxy-purines mixtures of isomeric products are frequently formed. Thus simple alkylation reactions on adenine **13** under basic conditions can give mixtures of N-3, N-7 and N-9 alkylated products with the last isomer as the major product.[2,8] It is therefore notable that exclusive N-9 alkylation (**14**) was observed in the Pd-catalyzed reaction between allyl acetate and adenine **13** as its cesium salt (Scheme 3, Table 1). The cesium salt of adenine was used because of its favourable solubility in DMSO, which was the preferred solvent. The catalyst was tetrakis(triphenylphosphine)palladium and the reaction temperature was 45 °C. The same exclusive N-9 attack was observed for the cyclopentenyl acetate **1** and hence formation of **15**. The regiochemistry of the product was ascertained by a combination of selective INEPT and HETCOR studies in NMR (*vide infra*). For comparison, vinyl epoxides have also been reported to react with adenine in the same regioselective manner under the influence of Pd(0)-catalysis.[9]

The difficulties encountered in regioselective alkylations of guanine have led to the use of various 6-substituted 2-aminopurines as precursor substrates for guanine.[10] In the present study the 5-chloro derivative **16** was reacted with allyl acetate under the influence of Pd(0), and a 1:1 mixture of N-9 (**18**) and N-7 (**20**) alkylated products was formed (Scheme 4). The product from the reaction of **16** with the cyclopentenyl acetate **1** also contained a considerable amount of the N-7 alkylated product (**24**) in addition to the N-9 alkylated isomer (**22**).

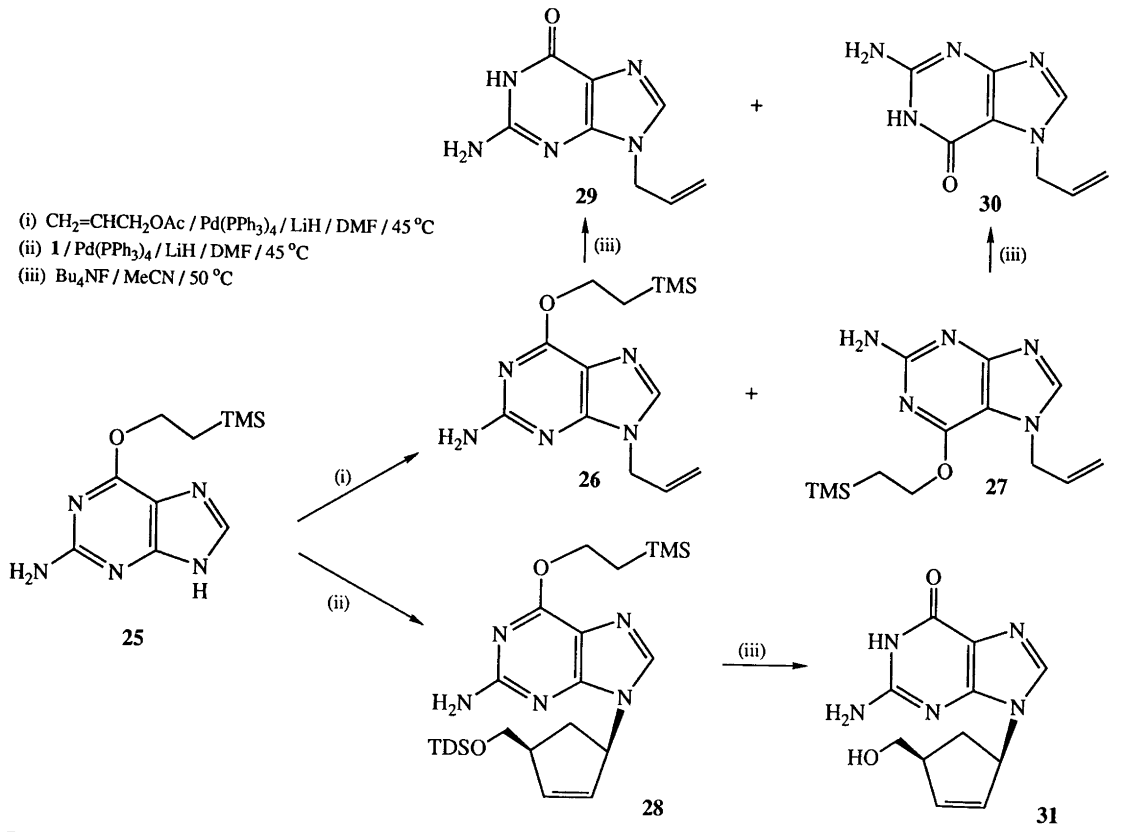
O^6-Alkylguanines can be alkylated preferentially at N-9.[10] For our study we required an alkyl group on the 6-hydroxy oxygen which can be removed under relatively mild conditions once the *N*-alkylation has been achieved. An appropriate substrate is the 6-methoxyethoxy derivative **17** where the 6-substituent has a pronounced N-9 directing effect in simple alkylations.[10a] The Pd(0)-catalyzed reaction with allyl acetate, however, produced both the N-9 (**19**) and the N-7 (**21**) allyl isomers (Table 1); with cesium carbonate as the base, in DMSO, the isomer ratio (N-9/N-7) was 1.4:1.0; with lithium hydride in DMF the isomer ratio was 2.1:1.0. With the more bulky cyclopentenyl acetate **1**, however, the reaction took place in the desired manner at N-9 with **23** as the only isolated product.

Removal of the methoxyethyl group on the oxygen in the 6-position requires acidic conditions which are incompatible with the carbocyclic nucleoside structure **23** where the purine base is in an allylic position and therefore acid sensitive. This is overcome in those cases where it is desired to saturate the double bond before removal of the protecting group. For the retention of the double bond, however, we have found the 2-trimethylsilylethyl group to be a good choice for protection of the 6-hydroxy group. The 2-trimethylsilylethyl group has been used widely as a protecting function for carbohydrates and carboxylic acids; it is readily removed by fluoride ion.[11]

The guanine derivative **25** (Scheme 5) was available from



Scheme 4.



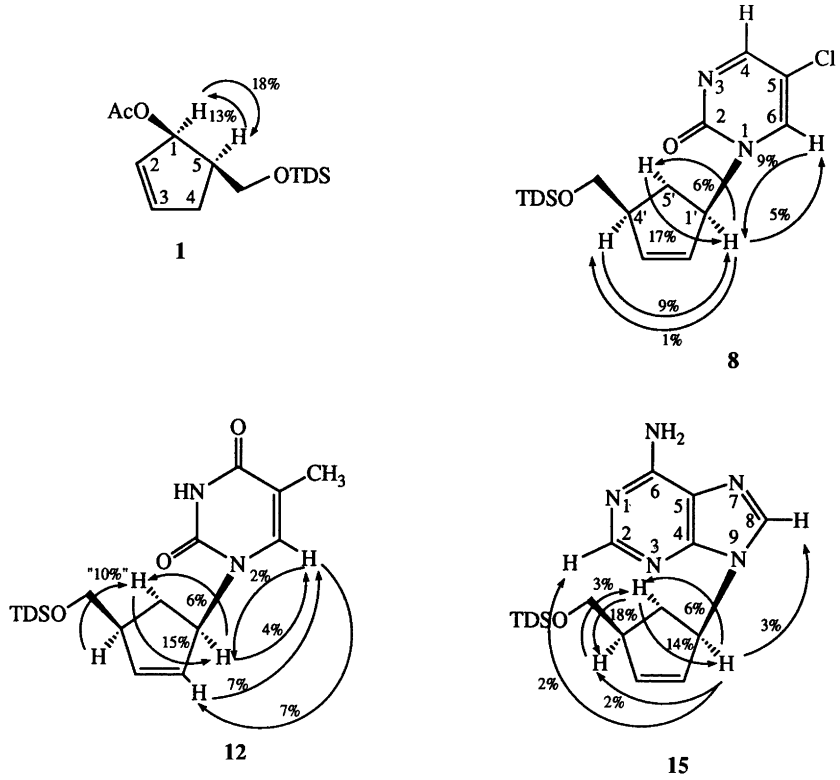
Scheme 5.

Table 1. Pd(0)-catalyzed allylation of the purines **13**, **16**, **17** and **25** with allyl acetate and **1**.

Entry	Comp.	Acetate	Product	Base/Solvent	N-9/N-7 ratio	Yield (%)
1	**13**	Allyl acetate	**14**	Cs_2CO_3/DMSO	Only N-9	68
2	**13**	**1**	**15**	Cs_2CO_3/DMSO	Only N-9	54
3	**16**	Allyl acetate	**18, 20**	Cs_2CO_3/DMSO	1:1.1	38
4	**16**	**1**	**22, 24**	Cs_2CO_3/DMSO	4.6:1	28
5	**17**	Allyl acetate	**19, 21**	Cs_2CO_3/DMSO	1.4:1	64
6	**17**	Allyl acetate	**19, 21**	LiH/DMF	2.1:1	76
7	**17**	**1**	**23**	LiH/DMF	Only N-9	55
8	**25**	Allyl acetate	**26, 27**	LiH/DMF	1:1	82
9	**25**	**1**	**28**	LiH/DMF	Only N-9	54

the reaction between 2-amino-6-chloropurine **16** and the sodium salt of 2-trimethylsilylethanol. Its reaction with allyl acetate using Pd-catalysis led to equimolar formation of N-9 (**26**) and N-7 (**27**) alkylated products. The important finding, however, is that only the N-9 alkylated product **28** was formed from the cyclopentenyl acetate **1**. The silylethyl group was removed simply by reaction with tetrabutylammonium fluoride in acetonitrile at 50 °C. The product **31**, which was formed from **28**, is the antiviral compound Carbovir.[6] Thus in general the trimethylsilylethyl group should be a very useful protecting group for the oxygen in the guanine 6-position during alkylation reactions directed at N-9.

The assignments of the regiochemistry and stereochemistry of the products were based on NMR. NOE data are given in Scheme 6. In the product **8** from the reaction between the cyclopentenyl acetate **1** and 5-chloro-2-pyrimidinone **7** (Scheme 2), the regiochemistry was confirmed by a 9 % NOE from 6-H to 1′-H and a 5 % enhancement in the opposite direction. In the subsequent stereochemical assignment the relative chemical shift of the 5′-methylene protons was established by 6 % and −1 % NOE from 1′-H to the methylene protons. The former effect is due to the α-H, the latter to the β-H. In the reverse direction 5′α-H had a 17 % effect on 1′-H. The effect of 4′-H on 5′β-H was a small indirect negative one (probably via 5′α-H) in accordance with a *trans* relationship. The separation between the signals from 4′-H and 5′α-H was too small for selective irradiation of either one for the confirmation experiment. Thus attempted irradiation of 4′-H also resulted in irradia-



Scheme 6.

tion of 5′α-H and a positive NOE on 5′β-H. The α-H configuration at 4′-position, however, was confirmed by a 9% NOE to 1′-H and an 1% intensity increase in the opposite direction. The small effect from 1′-H on 4′-H probably arises because 4′-H is quite well relaxed by protons on the side chain while 1′-H is not.[12]

The regiochemistry of the carbocyclic thymine derivative **12** (Scheme 2) followed from the positive NOE from 1′-H to 6-H (4%) and from 6-H to 1′-H (2%). The stereochemical assignment was based on a positive NOE from 1′-H to 5′α-H (6%) and from 5′α-H to 1′-H (15%). The NOE from 4′-H to 5′α-H could not be measured accurately because of the small difference in chemical shift between 4′-H and 5′α-H, which resulted in partial cancellation of the 5′α-H signal by off-resonance effects. An NOE of 10%, however, was determined by irradiation for 60 s at very low power to avoid most of the off-resonance effect. The findings correlate well with NOE data for a similar compound which was prepared by a different route.[13]

The point of attachment of the carbocycle to adenine in **15** (Scheme 3) was revealed by long-range selective INEPT studies[14] after prior assignments of the ^1H and ^{13}C NMR signals. The highest field signal in the ^{13}C NMR of adenine derivatives is due to C-5.[2] By analogy, the signal at the highest field in the downfield region is tentatively assigned to C-5 in **15**. Applying the selective proton pulses to the signal at 7.89 ppm showed this to be due to 8-H because of correlation with C-5 (119.8 ppm) and with the signal at 149.8 ppm which was therefore assigned to C-4. Selective proton pulses to the remaining purine singlet at 8.38 ppm showed correlation with C-4 at 149.8 ppm and with the signal at 155.5 which therefore must be due to C-6. One-bond heteronuclear multiple quantum coherence (HMQC) experiments,[14] connected the signals at 7.89 (8-H) and 139.2 ppm (C-8), and the signals at 8.38 (2H) and 152.7 ppm (C-2). The point of attachment of the carbocycle was subsequently determined by applying selective proton pulses to the 1′-H multiplet (5.75 ppm) which was found to be correlated to C-4 and C-8 in the purine ring. The stereochemistry ws further clarified by NOE experiments as shown in Scheme 6. In particular, 1′-H and 4′-H have a *cis* relationship.

Experimental

The ^1H NMR spectra were recorded at 300 MHz with either a Varian XL-300 (manual) or at 200 MHz with a Varian Gemini 200 instrument. The ^{13}C NMR spectra were recorded at 75 or 50 MHz using the above-mentioned spectrometers. The nuclear Overhauser difference experiments, the selective INEPT[14] experiments, the HETCOR[15] and the reverse detection[16] experiments were performed on a Varian VXR-300 and on a Varian XL-300 automatic instrument both equipped with 5 mm ^1H/broad-band switchable probes. The samples were dissolved in $CDCl_3$ and were degassed with a flow of helium gas for several minutes, before being capped. The nuclear Overhauser experiments were run with long build-up times of 30, 40 or 60 s to ensure close to steady-state conditions. On the VXR the relevant resonance(s) were irradiated at low power for this period, the decoupler was then gated off, the ^1H broad-band pulse applied, and 32 or 64 FIDs were acquired. The process was repeated with the decoupler set at a frequency remote from any resonance, and the FID resulting from the latter experiment was subtracted from the former. The Overhauser experiments performed with the XL-300 automatic instrument were identical except that a delay of 2 ms (D2) was introduced between the end of the selective irradiation and the proton pulse (Ref. 15, p. 236). The mass spectra under electron impact conditions were recorded at 70 eV ionizing potential and ammonia, isobutane or methane was used for chemical ionization (CI); the spectra are presented as *m/z* (% rel. int.).

cis-*1-Acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene* **1**. Acetic anhydride (0.40 ml, 4.2 mmol) in dry dichloromethane (10 ml) was added dropwise with stirring to a solution of *cis*-5-dimethylthexylsilyloxy-2-cyclopentenol (**6**) (900 mg, 3.5 mmol) and 4-*N,N*-dimethylaminopyridine (535 mg, 4.4 mmol) in dry dichloromethane (10 ml) at 0 °C under N_2. The mixture was stirred for 1 h at 0 °C and 15 min at ambient temperature, diluted with dichloromethane and washed with sat. aq. $CuSO_4$ (× 4), sat. aq. $NaHCO_3$ (× 2) and brine (× 1). The dried ($MgSO_4$) solution was evaporated and the crude product purified by flash chromatography using EtOAc–hexane (1:15); yield 950 mg (91%). Anal. $C_{16}H_{30}O_3Si$: C,H. ^1H NMR ($CDCl_3$, 300 MHz): 0.02 (SiMe), 0.78 (Me in thexyl), 0.82 (d, *J* 6.9 Hz, Me in thexyl) 1.56 (m, *J* 6.9 Hz, CH in thexyl), 1.96 (MeCO), 2.21 (1 H, ddt, *J* 16.7, 6.9 and 2.2 Hz, H *trans* to 5-H, CH_2), 2.41 (1 H, ddt, *J* 16.7, 7.9 and 2.2 Hz, H *cis* to 5-H, CH_2), 2.52 (m, 5-H), 3.53 (1 H, dd, *J* 9.8 and 7.1 Hz, H_A, CH_2O), 3.71 (1 H, dd, *J* 9.8 and 7.6 Hz, H_B, CH_2O), 5.68 (dt, *J* 6.8 and 2.2 Hz, 1-H), 5.86 (ddt, *J* 6.8, 5.8 and 2.2 Hz, 2-H), 6.09 (dt, *J* 5.8 and 2.2 Hz, 3-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 (SiMe), 18.2 and 20.4 (Me in thexyl), 21.3 (*Me*CO), 25.2 (C in thexyl), 34.4 (CH in thexyl), 34.8 (CH_2), 43.5 (C-5), 61.9 (CH_2O), 78.9 (C-1), 130.1 and 137.7 (CH=), 171.2 (CO). MS (CI–NH_3): 316 (46, *M*+18), 299 (66, *M*+1), 256 (16), 239 (28), 215 (24), 172 (51), 155 (100), 106 (44), 89 (28), 79 (94).

5-Dimethylthexylsilyloxymethyl-1-trimethylsilyloxycyclopentene **4**. 2-(Dimethylthexylsilyloxymethyl)cyclopentanone[7] (2.56 g, 10.0 mmol) in dry tetrahydrofuran (5 ml) was added dropwise to a stirred solution of lithium diisopropylamide [prepared *in situ* by addition of butyllithium (6.60 ml of a 1.6 M solution in hexane, 10.6 mmol) to diisopropylamine (1.68 ml, 12.0 mmol) in tetrahydrofuran (10 ml) at −78 °C] under N_2 at −78 °C. After 1 h, chlorotrimethylsilane (2.15 ml, 17.0 mmol) was added and the solution was stirred for 15 min at −78 °C and for 45 min at ambient temperature. The reaction mixture was evaporated, pentane added to the residue and lithium

chloride removed by filtration. Evaporation of the filtrate gave crude **4** which was used without further purification; yield 3.12 g (95%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.03 (OTMS), 0.06 (SiMe), 0.83 (Me in thexyl), 0.87 (d, *J* 6.9 Hz, Me in thexyl), 1.60 (m, *J* 6.9 Hz, CH in thexyl), 2.1–2.6 (5 H, m, CH_2 and CH), 3.49 (1 H, dd, *J* 9.7 and 6.7 Hz, H_A, CH_2O), 3.65 (1 H, dd, *J* 9.7 and 3.7 Hz, H_B, CH_2O), 4.58 (m, CH=). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 and −3.4 (SiMe), 0.1 (OTMS), 18.5 and 20.5 (Me in thexyl), 24.7 (C in thexyl), 25.0 and 27.0 (CH_2), 34.2 (CH in thexyl), 47.8 (CH), 63.9 (CH_2O), 102.3 (CH=), 154.5 (OC=). MS (CI–isobutane): 329 (58, *M*+1), 313 (11), 243 (100), 229 (5), 209 (7), 171 (12), 169 (44), 147 (26), 89 (18), 73 (64).

5-Dimethylthexylsilyloxymethyl-2-cyclopentenone **5**. A solution of palladium(II) acetate (2.13 g, 9.5 mmol) in dry acetonitrile (100 ml) was added to crude 5-dimethylthexylsilyloxymethyl-1-trimethylsilyloxycyclopentene (3.12 g, 9.5 mmol). The mixture was stirred for 4 h at ambient temperature under N_2 and filtered and the filtrate was evaporated. The residue was purified by flash chromatography using EtOAc–hexane (1:10); yield 1.80 g (71% from **3**). Anal. $C_{14}H_{26}O_2Si$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.04 (SiMe), 0.75 (Me in thexyl), 0.80 (d, *J* 6.9 Hz, Me in thexyl), 1.52 (m, *J* 6.9 Hz, CH in thexyl), 2.41 (m, CH), 2.7–2.8 (m, CH_2), 3.78 (1 H, dd, *J* 9.7 and 3.6 Hz, H_A, CH_2O), 3.87 (1 H, dd, *J* 9.7 and 4.8 Hz, H_B, CH_2O), 6.15 and 7.70 (m, CH=). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.8 (SiMe), 18.3 and 20.1 (Me in thexyl), 24.9 (C in thexyl), 32.8 (CH_2), 34.1 (CH in thexyl), 47.1 (CH), 61.9 (CH_2O), 134.1 and 164.5 (CH=), 210.5 (CO). MS (CI–NH_3): 255 (100, *M*+1), 239 (5), 216 (5), 196 (4), 169 (41), 139 (2), 111 (2), 106 (7), 95 (7), 91 (8), 81 (3), 74 (10).

cis-*5-Dimethylthexylsilyloxymethyl-2-cyclopentenol* **6**. A 0.5 M solution of 9-borabicyclo[3.3.1]nonane in tetrahydrofuran (14.4 ml, 7.2 mmol) was added dropwise to a stirred solution of 5-dimethylthexylsilyloxy-2-cyclopentenone (1.52 g, 6.0 mmol) in dry tetrahydrofuran (6 ml) at 0 °C under N_2. The resultant solution was stirred at 0 °C for 5 h and at ambient temperature for 3 h, before 3 drops of methanol were added and the reaction mixture was evaporated. The residue was dissolved in pentane, ethanolamine (0.43 ml, 7.2 mmol) was added, the mixture was filtered and the filtrate evaporated. The crude product was purified by flash chromatography using EtOAc–hexane (1:7); yield 1.01 g (66%). Anal. $C_{14}H_{28}O_2Si$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.12 and 0.13 (SiMe), 0.85 (Me in thexyl), 0.88 (d, *J* 6.9 Hz, Me in thexyl), 1.62 (m, *J* 6.9 Hz, CH in thexyl), 2.1–2.2 (1 H, m, H *trans* to 5-H, CH_2), 2.3–2.5 (2 H, m, H *cis* to 5-H, CH_2 and 5-H), 2.94 (br s, OH), 3.77 (1 H, dd, *J* 10.0 and 7.5 Hz, H_A, CH_2O), 3.86 (1 H, dd, *J* 10.0 and 4.7 Hz, H_B, CH_2O), 4.86 (m, 1-H), 5.84 and 5.94 (m, CH=). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.6 and −3.5 (SiMe), 18.6 and 20.4 (Me in thexyl), 25.2 (C in thexyl), 34.3 (CH_2), 34.4 (CH in thexyl), 42.7 (C-5), 63.4 (CH_2O), 78.1 (C-1), 133.5 and 134.6 (CH=). MS (CI–NH_3): 274 (2, *M*+18), 257 (34, *M*+1), 239 (25), 204 (4), 172 (34), 155 (155), 106 (29), 89 (26), 79 (48), 75 (27).

cis-*5-Chloro-1-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-2(1H)-pyrimidinone* **8**. Triethylamine (0.16 ml, 1.12 mmol) was added to a suspension of 5-chloro-2(1*H*)-pyrimidinone (146 mg, 1.12 mmol) in dry dichloromethane (8 ml) and the mixture was stirred for 10 min at ambient temperature under N_2 before *cis*-1-acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (334 mg, 1.12 mmol), palladium(II) acetate (13 mg, 0.06 mmol) and triisopropyl phosphite (0.11 ml, 0.45 mmol) were added. The mixture was stirred for 44 h, diluted with dichloromethane and washed with brine (×2). The dried ($MgSO_4$) solution was evaporated and the crude product purified by flash chromatography using EtOAc–hexane (1:1); yield 186 mg (45%). Anal. $C_{18}H_{29}ClN_2O_2Si$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.07 and 0.09 (SiMe), 0.83 (Me in thexyl), 0.86 (d, *J* 6.9 Hz, Me in thexyl), 1.46 (1 H, dt, *J* 13.9 and 6.4 Hz, 5′β-H), 1.60 (m, *J* 6.9 Hz, CH in thexyl), 2.82 (1 H, dt, *J* 13.9 and 6.9 Hz, 5′α-H), 2.95 (m, 4′-H), 3.54 (1 H, dd, *J* 10.3 and 4.6 Hz, H_A, CH_2O), 3.74 (1 H, dd, *J* 10.3 and 4.1 Hz, H_B, CH_2O), 5.65 (dt, *J* 5.7 and 2.1 Hz, 2′-H), 5.81 (m, 1′-H), 6.18 (dt, *J* 5.7 and 2.0 Hz, 3′-H), 7.77 (d, *J* 3.4 Hz, 6-H), 8.47 (d, *J* 3.4 Hz, 4-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 and −3.4 (SiMe), 18.5, 18.6, 20.3 and 20.4 (Me in thexyl), 25.3 (C in thexyl), 34.0 (CH_2), 34.1 (CH in thexyl), 47.5 (C-4′), 64.4 (C-1′), 64.4 (CH_2O), 111.2 (C-5), 128.6 (C-2′), 141.8 (C-3′), 142.1 (C-6), 154.8 (C-2), 164.3 (C-4). MS (CI–NH_3): 371/369 (26/68, *M*+1), 317 (10), 283 (10), 205 (30), 187 (44), 155 (18), 131 (48), 106 (24), 89 (28), 79 (100).

1-Allylthymine **10**[17] *and 1,3-diallylthymine* **11**.[17] A mixture of thymine (378 mg, 3.0 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (15 ml) was heated at reflux under N_2 until the solution became clear (1.5 h). The solution was evaporated and the residue dissolved in dry acetonitrile (5 ml). Allyl acetate (0.32 ml, 3.0 mmol), palladium(II) acetate (33 mg, 0.15 mmol) and triisopropyl phosphite (0.30 ml, 1.2 mmol) were added and the resultant mixture was stirred at ambient temperature under N_2 for 21 h. The reaction mixture was evaporated and the products separated by flash chromatography using EtOAc–hexane (1:1).

10: Yield 52 mg (10%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.90 (d, *J* 1.2 Hz, Me), 4.32 (d, *J* 5.7 Hz, NCH_2), 5.23 (1 H, d, *J* 17.2 Hz, CH in CH_2=), 5.28 (1 H, d, *J* 9.8 Hz, CH in CH_2=), 5.8–5.9 (m, CH=), 6.97 (q, *J* 1.2 Hz, 6-H), 9.90 (br s, NH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.9 (Me), 50.3 (CH_2N), 111.5 (C-5), 119.6 (CH_2=), 132.3 (CH=), 140.3 (C-6), 151.6 (C-2), 165.1 (C-4). MS (CI–CH_4): 167 (100, *M*+1), 166 (15, *M*), 139 (1), 124 (5), 123 (10), 96 (1), 95 (2), 81 (1).

11: Yield 268 mg (43%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ

1.87 (d, *J* 1.2 Hz, Me), 4.30 [d, *J* 5.8 Hz, N(1)CH_2], 4.51 [d, *J* 5.7 Hz, N(3)CH_2], 5.1–5.2 (4 H, m, 2 × CH_2=), 5.7–5.9 (2 H, m, 2 × CH=), 6.95 (q, *J* 1.2 Hz, 6-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.5 (Me), 43.9 and 51.2 (CH_2N), 110.5 (C-5), 118.2 and 118.4 (CH_2=), 132.2 and 132.4 (CH=), 138.4 (C-6), 151.5 (C-2), 163.8 (C-4). MS (CI–CH_4): 207 (100, *M*+1), 206 (49, *M*), 191 (35), 179 (1), 165 (5), 151 (2), 137 (1), 123 (9), 94 (13).

cis-*1-[4-(Dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-thymine* **12**. A mixture of thymine (164 mg, 1.3 mmol) and ammonium sulfate (10 mg) in hexamethyldisilazane (5 ml) was heated at reflux under N_2 until the solution became clear (1 h). The solution was evaporated and the residue dissolved in dry acetonitrile (7 ml). *cis*-1-Acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (298 mg, 1.2 mmol), palladium(II) acetate (11 mg, 0.05 mmol) and triisopropyl phosphite (0.10 ml, 0.4 mmol) were added and the resultant mixture was stirred at ambient temperature under N_2 for 41 h. The reaction mixture was evaporated and the product purified by flash chromatography using EtOAc–hexane (3:4); yield 186 mg (51 %). Anal. $C_{19}H_{32}N_2O_3Si$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 and 0.09 (SiMe), 0.83 (Me in thexyl), 0.87 (d, *J* 6.9 Hz, Me in thexyl), 1.42 (1 H, dt, *J* 13.6 and 7.4 Hz, 5′β-H), 1.62 (m, *J* 6.9 Hz, CH in thexyl), 1.91 (d, *J* 1.2 Hz, Me), 2.61 (1 H, dt, *J* 13.6 and 8.3 Hz, 5′α-H), 2.89 (m, 4′-H), 3.56 (1 H, dd, *J* 10.1 and 4.9 Hz, H_A, CH_2O), 3.71 (1 H, dd, *J* 10.1 and 4.7 Hz, H_B, CH_2O), 5.63 (dt, *J* 5.6 and 2.2 Hz, 2′-H), 5.72 (m, 1′-H), 6.08 (dt, *J* 5.6 and 2.2 Hz, 3′-H), 7.08 (q, *J* 1.2 Hz, 6-H), 8.88 (br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 (SiMe), 12.8 (Me), 18.5 and 20.3 (Me in thexyl), 25.2 (C in thexyl), 33.3 (CH_2), 34.1 (CH in thexyl), 47.3 (C-4′), 61.1 (C-1′), 64.7 (CH_2O), 110.9 (C-5), 129.7 (C-2′), 136.8 (C-6), 139.8 (C-3′), 151.1 (C-2), 163.9 (C-4). MS (CI–CH_4): 365 (30, *M*+1), 279 019), 204 (26), 201 (34), 181 (25), 155 (63), 127 (95), 89 (95), 79 (100).

9-Allyladenine **14**.[2] A mixture of adenine (135 mg, 1.0 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (5 ml) was stirred for 15 min at 45 °C under N_2 and cooled to ambient temperature before allyl acetate (0.11 ml, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 23 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The crude product was purified by flash chromatography using $CHCl_3$–MeOH (6:1); yield 119 mg (68 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.79 (d, *J* 5.4 Hz, NCH_2), 5.04 (1 H, dd, *J* 17.2 and 1.4 Hz, CH in CH_2=), 5.19 (1 H, dd, *J* 10.3 and 1.4 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 7.25 (br s, NH_2), 8.12 and 8.15 (H in adenine). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 45.8 (CH_2N), 117.5 (CH_2=), 118.8 (C-5), 133.5 (CH=), 140.6 (C-8), 149.3 (C-4), 152.3 (C-2), 155.8 (C-6). MS (EI): 175 (69, M^+), 174 (100), 148 (25), 147 (26), 135 (16), 121 (11), 120 (12), 108 (25), 80 (14), 67 (16).

cis-*9-[4-(Dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-adenine* **15**. A mixture of adenine (176 mg, 1.3 mmol) and cesium carbonate (424 mg, 1.3 mmol) in DMSO (5 ml) was stirred for 15 min at 45 °C under N_2 and cooled to ambient temperature before *cis*-1-acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (298 mg, 1.0 mmol) in DMSO (1 ml) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 20 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The crude product was purified by flash chromatography using $CHCl_3$–MeOH (20:1); yield 202 mg (54 %). Anal. $C_{19}H_{31}N_5OSi$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.08 (SiMe), 0.84 (Me in thexyl), 0.87 (d, *J* 6.9 Hz, Me in thexyl), 1.6–1.7 (2 H, m, 5′β-H and H in thexyl), 2.80 (1 H, dt, *J* 13.7 and 8.6 Hz, 5′α-H), 3.01 (m, 4′-H), 3.60 (1 H, dd, *J* 10.0 and 5.6 Hz, H_A, CH_2O), 3.70 (1 H, dd, *J* 10.0 and 5.6 Hz, H_B, CH_2O), 5.75 (m, 1′-H), 5.88 (dt, *J* 5.6 and 2.1 Hz, 2′-H), 6.14 (br s, NH_2), 6.18 (dt, *J* 5.6 and 2.0 Hz, 3′-H), 7.89 (8-H), 8.38 (2-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 (SiMe), 18.5 and 20.4 (Me in thexyl), 25.2 (C in thexyl), 34.1 (CH_2), 35.0 (CH in thexyl), 47.8 (C-4′), 59.5 (C-1′), 64.4 (CH_2O), 119.8 (C-5), 128.1 (C-2′), 138.8 (C-3′), 139.2 (C-8), 149.8 (C-4), 152.7 (C-2), 155.5 (C-6). MS (CI–CH_4): 374 (100, *M*+1), 358 (14), 289 (21), 288 (80), 210 (27), 164 (16), 136 (24), 89 (5), 79 (11), 75 (8).

2-Amino-6-(2-methoxyethoxy)purine **17**.[10a] 2-Methoxyethanol (0.95 ml, 12.0 mmol) was added to a 50 % oil suspension of sodium hydride (576 mg, 12.0 mmol) in dry dioxane (40 ml). After 15 min of stirring under N_2 at ambient temperature, 2-amino-6-chloropurine (1.02 g, 6.0 mmol) was added and the resultant mixture was refluxed for 18 h. The solvent was evaporated and the residue was dissolved in water (20 ml) and extracted with diethyl ether (× 2). The water layer was acidified to pH 5 with 20 % acetic acid. After cooling, the solid was removed by filtration and recrystallized from ethanol–water (1:1); yield 890 mg (71 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.33 (Me), 3.70 and 4.53 (t, *J* 4.5 Hz, CH_2), 6.26 (br s, NH_2), 7.85 (8-H).

9-Allyl-2-amino-6-chloropurine **18**[18] *and 7-allyl-2-amino-6-chloropurine* **20**. A mixture of 2-amino-6-chloropurine (170 mg, 1.0 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (5 ml) was stirred for 15 min at 45 °C under N_2 and cooled to ambient temperature before allyl acetate (0.11 ml, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 23 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The products were separated by flash chromatography using $CHCl_3$–MeOH (10:1). Compound **18** was purified by flash chromatography using EtOAc.

18: Yield 37 mg (18 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.71 (d, *J* 5.0 Hz, NCH_2), 5.00 (1 H, d, *J* 17.1, CH in CH_2=), 5.21 (1 H, d, *J* 10.3 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.96 (br s, NH_2), 8.13 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 44.8 (CH_2N), 117.3 (CH_2=), 123.1 (C-5), 132.8 (CH=), 143.0 (C-8), 149.3 (C-6), 153.9 (C-4), 159.8 (C-2). MS (EI): 211/209 (30/100, M^+), 182 (4), 174 (17), 168 (18), 147 (7), 141 (21), 134 (12), 114 (10), 54 (12), 53 (23).

20: Yield 42 mg (20 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 4.92 (1 H, d, *J* 15.1, CH in CH_2=), 4.97 (d, *J* 2.9 Hz, NCH_2), 5.23 (1 H, d, *J* 10.6 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.69 (br s, NH_2), 8.41 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 49.2 (CH_2N), 107.1 (C-5), 118.8 (CH_2=), 132.4 (CH=), 139.6 (C-6), 150.6 (C-8), 152.9 (C-2), 154.1 (C-4). MS (EI): 211/209 (32/100, M^+), 182 (12), 174 (16), 169 (8), 168 (9), 147 (11), 141 (18), 134 (19), 132 (12), 114 (9), 54 (12), 53 (17).

9-Allyl-2-amino-6-(2-methoxyethoxy)purine **19** *and 7-allyl-2-amino-6-(2-methoxyethoxy)purine* **21**. *Method A.* A mixture of 2-amino-6-(2-methoxyethoxy)purine (209 mg, 1.0 mmol) and cesium carbonate (326 mg, 1.0 mmol) in DMSO (5 ml) was stirred for 15 min at 45 °C under N_2 and cooled to ambient temperature before allyl acetate (0.11 ml, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 6 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The products were separated by flash chromatography using $CHCl_3$–MeOH (13:1).

19: Yield 93 mg (37 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.32 (Me), 3.70 and 4.54 (t, *J* 4.8 Hz, CH_2O), 4.67 (d, *J* 5.1 Hz, NCH_2), 4.95 (1 H, dd, *J* 17.2 and 1.1 Hz, CH in CH_2=), 5.17 (1 H, d, *J* 10.8 and 1.1 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.45 (br s, NH_2), 7.86 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 45.5 (CH_2N), 58.9 (Me), 65.4 and 70.8 (CH_2O), 113.8 (C-5), 117.1 (CH_2=), 133.5 (CH=), 139.5 (C-8), 154.0 (C-4), 159.5 (C-6), 160.0 (C-2). MS (EI): 249 (32, M^+), 234 (1), 219 (6), 204 (3), 191 (100), 174 (8), 164 (7), 149 013), 134 (5), 121 (27).

21: Yield 68 mg (27 %). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.32 (Me), 3.69 and 4.52 (t, *J* 4.3 Hz, CH_2O), 4.81 (d, *J* 5.2 Hz, NCH_2), 5.11 (1 H, dd, *J* 17.8 and 1.3 Hz, CH in CH_2=), 5.19 (dd, *J* 10.9 and 1.3 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.15 (br s, NH_2), 8.09 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 49.4 (CH_2N), 58.8 (Me), 65.2 and 70.6 (CH_2O), 106.0 (C-5), 117.8 (CH_2=), 134.2 (CH=), 145.2 (C-8), 156.5 (C-4), 159.5 (C-6), 163.8 (C-2). MS (EI): 249 (54, M^+), 218 (2), 204 (2), 191 (100), 174 (17), 164 (16), 150 (19), 134 (4), 122 (11), 108 (6).

Method B. A mixture of 2-amino-6-(2-methoxyethoxy)-purine (209 mg, 1.0 mmol) and lithium hydride (15 mg, 2.0 mmol) in dry DMF (25 ml) was stirred for 30 min at ambient temperature under N_2 before allyl acetate (0.11 ml, 1.0 mmol) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 6 h. Water (2 ml) was added and the mixture evaporated. Methanol (10 ml) was added to the residue, the mixture filtered and the filtrate evaporated. The products were separated by flash chromatography using $CHCl_3$–MeOH (13:1); yield 129 mg (52 %) of **19** and 61 mg (24 %) of **21**.

cis-*2-Amino-6-chloro-9-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]purine* **22** *and* cis-*2-amino-6-chloro-7-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]purine* **24**. A mixture of 2-amino-6-chloropurine (220 mg, 1.3 mmol) and cesium carbonate (424 mg, 1.3 mmol) in DMSO (5 ml) was stirred for 15 min at 45 °C under N_2 and cooled to ambient temperature before *cis*-1-acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (298 mg, 1.0 mmol) in DMSO (1 ml) and tetrakis(triphenylphosphine)palladium (58 mg, 0.05 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 22 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The products were separated by flash chromatography using $CHCl_3$–MeOH (40:1).

22: Yield 93 mg (23 %). Anal. $C_{19}H_{30}ClN_5OSi$: C,H. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (SiMe), 0.81 (Me in thexyl), 0.84 (d, *J* 6.9 Hz, Me in thexyl), 1.57 (m, *J* 6.9 Hz, CH in thexyl), 1.64 (1 H, dt, *J* 13.6 and 6.4 Hz, 5′β-H), 2.72 (1 H, dt, *J* 13.6 and 8.6 Hz, 5′α-H), 2.98 (m, 4′-H), 3.57 (1 H, dd, *J* 10.0 and 5.5 Hz, H_A, CH_2O), 3.67 (1 H, dd, *J* 10.0 and 5.3 Hz, H_B, CH_2O), 5.38 (br s, NH_2), 5.56 (m, 1′-H), 5.81 (dt, *J* 5.6 and 2.2 Hz, 2′-H), 6.14 (dt, *J* 5.6 and 2.0 Hz, 3′-H), 7.83 (8-H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −3.5 (SiMe), 18.4, 20.2 and 20.3 (Me in thexyl), 25.2 (C in thexyl), 34.1 (CH in thexyl), 34.7 (CH_2), 47.8 (C-4′), 59.3 (C-1′), 65.2 (CH_2O), 125.4 (C-5), 129.0 (C-2′), 139.4 (C-3′), 140.7 (C-8), 151.0 (C-6), 153.4 (C-4), 158.9 (C-2). MS (CI–CH_4): 410/408 (38/97, M+1), 392 (3), 372 (12), 322 (30), 244 (89), 198 (32), 170 (100), 89 (42), 79 (94), 75 (38).

24: Yield 19 mg (5 %). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.04 (SiMe), 0.81 (Me in thexyl), 0.84 (d, *J* 6.9 Hz, Me in thexyl), 1.5–1.5 (2 H, m, CH in thexyl and 5′β-H), 2.80 (1 H, dt. *J* 13.7 and 8.5 Hz, 5′α-H), 3.00 (m, 4′-H), 3.51 (1 H, dd, *J* 9.9 and 5.9 Hz, H_A, CH_2O), 3.61 (1 H, dd, *J* 9.9 and 5.4 Hz, H_B, CH_2O), 5.16 (br s, NH_2), 5.8–5.9 (2 H, m, 1′-H and 2′-H), 6.27 (dt, *J* 5.6 and 1.9 Hz, 3′-H), 8.06 (8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −2.7 (SiMe), 19.2 and 21.0 (Me in thexyl), 25.9 (C in thexyl), 34.8 (CH in thexyl), 36.9 (CH_2), 48.7 (C-4′), 63.2 (C-1′), 66.0 (CH_2O), 113.2 (C-5), 128.3 (C-2′), 138.9 (C-6), 141.2 (C-3′), 146.4 (C-8), 159.6 (C-2), 164.8 (C-4). MS (CI–CH_4): 410/408 (39/93, M+1), 392 (9), 372 (18), 321 (98), 256 (14), 244 (48), 198 (29), 170 (100), 79 (61), 75 (51).

cis-*2-Amino-9-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-6-(2-methoxyethoxy)purine* **23**. A mixture of 2-amino-6-(2-methoxyethoxy)purine (815 mg, 3.9 mmol) and lithium hydride (45 mg, 6.0 mmol) in dry DMF (75 ml) was stirred for 30 min at ambient temperature under N_2

before *cis*-1-acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (894 mg, 3.0 mmol) in DMF (1 ml) and tetrakis(triphenylphosphine)palladium (174 mg, 0.15 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 19 h. Water (2 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The product was purified by flash chromatography using EtOAc; yield 742 mg (55 %). Anal. $C_{22}H_{37}N_5O_3Si$: C,H. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.02 (SiMe), 0.78 (Me in thexyl), 0.81 (d, *J* 6.9 Hz, Me in thexyl), 1.5–1.6 (2 H, m, CH in thexyl and 5′β-H), 2.67 (1 H, dt, *J* 13.6 and 8.6 Hz, 5′α-H), 2.91 (m, 4′-H), 3.37 (Me), 3.52 (1 H, dd, *J* 9.8 and 5.7 Hz, H_A, CH_2O), 3.63 (1 H, dd, *J* 9.8 and 5.7 Hz, H_B, CH_2O), 3.75 and 4.59 (t, *J* 5.0 Hz, CH_2O), 5.11 (br s, NH_2), 5.51 (m, 1′-H), 5.78 (dt, *J* 5.5 and 2.1 Hz, 2′-H), 6.07 (dt, *J* 5.5 and 2.0 Hz, 3′-H), 7.62 (8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −1.2 (SiMe), 18.9 and 20.7 (Me in thexyl), 25.5 (C in thexyl), 34.4 (CH in thexyl), 35.2 (CH_2), 48.0 (C-4′), 59.0 (C-1′ and Me), 65.5 ($CH_2O \times 2$), 70.5 (CH_2O), 115.1 (C-5), 129.1 (C-2′), 136.8 (C-8), 137.9 (C-3′), 153.1 (C-4), 158.4 (C-6), 160.2 (C-2). MS (CI–CH_4): 448 (100, *M*+1), 432 (15), 416 (8), 362 (48), 296 (4), 284 (14), 238 (13), 210 (50), 178 (10), 515 (10).

2-Amino-6-(2-trimethylsilylethoxy)purine **25**. 2-(Trimethylsilyl)ethanol (3.42 ml, 24.0 mmol) was added to a 50 % oil suspension of sodium hydride (1.15 g, 24.0 mmol) in dry dioxane (60 ml). After 15 min of stirring under N_2 at ambient temperature, 2-amino-6-chloropurine (2.04 g, 12.0 mmol) was added and the resultant mixture refluxed for 19 h. The solvent was evaporated and the residue was dissolved in water (40 ml) and extracted with diethyl ether (× 2). The water layer was acidified to pH 5 with 20 % acetic acid. After cooling, the solid was removed by filtration and purified by flash chromatography using MeOH–$CHCl_3$ (1:8); yield 1.98 mg (69 %). Anal. $C_{10}H_{17}N_5OSi$: C,H. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.08 ($SiMe_3$), 1.14 (t, *J* 8.2 Hz, CH_2Si), 4.56 (t, *J* 8.2 Hz, CH_2O), 6.18 (br s, NH_2), 7.81 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ −0.9 ($SiMe_3$), 17.5 (CH_2Si), 63.7 (CH_2O), 113.2 (C-5), 138.3 (C-8), 155.6 (C-4), 159.9 (C-6), 160.1 (C-2). MS (EI): 251 (8, M^+), 236 (2), 223 (32), 208 (100), 191 (4), 166 (6), 151 (7), 134 (8), 99 (8), 73 (389).

9-Allyl-2-amino-6-(2-trimethylsilylethoxy)purine **26** *and 7-allyl-2-amino-6-(2-trimethylsilylethoxy)purine* **27**. A mixture of 2-amino-6-(2-trimethylsilylethoxy)purine (753 mg, 3.0 mmol) and lithium hydride (45 mg, 6.0 mmol) in dry DMF (60 ml) was stirred for 30 min at ambient temperature under N_2 before allyl acetate (0.33 ml, 3.0 mmol) and tetrakis(triphenylphosphine)palladium (174 mg, 0.15 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 22 h. Water (5 ml) was added and the mixture was evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The products were separated by flash chromatography using $CHCl_3$–MeOH (30:1) and **26** was purified by flash chromatography using EtOAc–hexane (2:1).

26: Yield 347 mg (40 %). Anal. $C_{13}H_{21}N_5OSi$: C,H. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.07 ($SiMe_3$), 1.14 (t, *J* 8.1 Hz, CH_2Si), 4.51 (t, *J* 8.1 Hz, CH_2O), 4.66 (d, *J* 5.0 Hz, NCH_2), 4.66 (d, *J* 17.2 Hz, CH in CH_2=), 5.17 (d, *J* 10.3 Hz, CH in CH_2=), 5.9–6.1 (m, CH=), 6.39 (br s, NH_2), 7.82 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ −0.8 ($SiMe_3$), 17.6 (CH_2Si), 45.0 (NCH_2), 63.9 (CH_2O), 114.1 (C-5), 117.2 (CH_2=), 133.7 (CH=), 139.6 (C-8), 154.2 (C-4), 160.0 (C-6), 160.6 (C-2). MS (EI): 291 (11, M^+), 277 (19), 263 (52), 248 (100), 222 (17), 207 (23), 191 (12), 167 (11), 149 (32), 73 (48).

27: Yield 364 mg (42 %). Anal. $C_{13}H_{21}N_5OSi$: C,H. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 0.08 ($SiMe_3$), 1.14 (t, *J* 8.3 Hz, CH_2Si), 4.46 (t, *J* 8.3 Hz, CH_2O), 4.84 (d, *J* 5.1 Hz, NCH_2), 5.03 (d, *J* 18.1 Hz, CH in CH_2=), 5.19 (d, *J* 9.5 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.09 (br s, NH_2), 8.06 (8-H). ^{13}C NMR (DMSO-d_6, 50 MHz): δ −0.9 ($SiMe_3$), 17.6 (CH_2Si), 48.9 (NCH_2), 64.1 (CH_2O), 106.0 (C-5), 117.6 (CH_2=), 134.5 (CH=), 145.2 (C-8), 157.0 (C-4), 159.9 (C-6), 163.9 (C-2). MS (EI): 291 (24, M^+), 276 (4), 263 (54), 248 (66), 235 (6), 222 (11), 208 (25), 191 (12), 174 (7), 73 (100).

cis-*2-Amino-9-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-6-(2-trimethylsilylethoxy)purine* **28**. A mixture of 2-amino-6-(2-trimethylsilylethoxy)purine (427 mg, 1.7 mmol) and lithium hydride (26 mg, 3.4 mmol) in dry DMF (25 ml) was stirred for 30 min at ambient temperature under N_2 before *cis*-1-acetoxy-5-dimethylthexylsilyloxymethyl-2-cyclopentene (387 mg, 1.3 mmol) in DMF (1 ml) and tetrakis(triphenylphosphine)palladium (81 mg, 0.07 mmol) were added. The resultant solution was stirred at 45 °C under N_2 for 19 h. Water (2 ml) was added and the mixture evaporated. Methanol (10 ml) was added to the residue, the mixture was filtered and the filtrate evaporated. The product was purified by flash chromatography using EtOAc–hexane (1:2); yield 346 mg (54 %). Anal. $C_{24}H_{43}N_5O_2Si_2$: C,H. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.02 ($SiMe_2$), 0.03 ($SiMe_3$), 0.79 (Me in thexyl), 0.82 (d, *J* 6.8 Hz, Me in thexyl), 1.18 (t, *J* 8.4 Hz, CH_2Si), 1.5–1.6 (2 H, m, CH in thexyl and 5′β-H), 2.68 (1 H, dt, *J* 13.6 and 8.5 Hz, 5′α-H), 2.91 (m, 4′-H), 3.59 (1 H, dd, *J* 9.9 and 4.7 Hz, H_A, CH_2O), 3.61 (1 H, dd, *J* 9.9 and 5.7 Hz, H_B, CH_2O), 4.53 (t, *J* 8.4 Hz, CH_2O), 5.05 (br s, NH_2), 5.51 (m, 1′-H), 5.78 (dt, *J* 5.6 and 2.0 Hz, 2′-H), 6.07 (dt, *J* 5.6 and 2.0 Hz, 3′-H), 7.61 (8-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −3.0 and −0.9 (SiMe), 18.1 (CH_2Si), 19.0 and 20.8 (Me in thexyl), 25.7 (C in thexyl), 34.6 (CH in thexyl), 36.5 (CH_2), 48.3 (C-4′), 59.4 (C-1′), 65.2 and 66.1 (CH_2O), 116.3 (C-5), 129.1 (C-2′), 137.7 (C-3′), 139.1 (C-8), 154.0 (C-4), 159.8 (C-6), 161.9 (C-2). MS (CI–CH_4): 490 (88, *M*+1), 474 (18), 462 (11), 446 (12), 404 (15), 376 (41), 298 (25), 224 (21), 208 (25), 73 (100).

9-Allylguanine **29**.[19] A 0.5 M solution of tetrabutylammonium fluoride in dry acetonitrile (4 ml) was added to 9-allyl-2-amino-6-(2-trimethylsilylethoxy)purine (251 mg, 1.0 mmol) and the mixture was stirred at 50 °C under N_2 for 2 h before water (2 ml) was added. The pH was adjusted to 5 with acetic acid and the mixture was evaporated. The product was purified by flash chromatography using Et_3N–MeOH–$CHCl_3$ (1:20:100); yield 151 mg (79 %). ^1H NMR (DMSO-d_6, 200 MHz): δ 4.56 (d, *J* 5.0 Hz, NCH_2), 4.96 (d, *J* 17.6, CH in CH_2=), 5.16 (d, *J* 9.9, CH in CH_2=), 6.0–6.1 (m, CH=), 7.23 (br s, NH_2), 7.48 (8-H).

7-Allylguanine **30**.[19] Compound **30** was prepared from 7-allyl-2-amino-6-(2-trimethylsilylethoxy)purine as described for **29** above; yield 77 %. ^1H NMR (DMSO-d_6, 200 MHz): δ 4.85 (d, *J* 5.0 Hz, NCH_2), 5.01 (d, *J* 17.0 Hz, CH in CH_2=), 5.14 (d, *J* 10.3 Hz, CH in CH_2=), 6.0–6.1 (m, CH=), 6.67 (br s, NH_2), 7.71 (8-H).

cis-*[4-(Hydroxymethyl)-2-cyclopentenyl]guanine* **31**.[6] A 0.5 M solution of tetrabutylammonium fluoride in dry acetonitrile (4.9 ml) was added to *cis*-2-amino-9-[4-(dimethylthexylsilyloxymethyl)-2-cyclopentenyl]-6-(2-trimethylsilylethoxy)-purine (298 mg, 0.61 mmol) and the mixture was stirred at 50 °C under N_2 for 3 h before water (2 ml) was added. The pH was adjusted to 5 with acetic acid and the mixture was evaporated. The product was purified by flash chromatography using Et_3N–MeOH–$CHCl_3$ (1:20:100); yield 105 mg (70 %). ^1H NMR (DMSO-d_6, 200 MHz): δ 1.57 (1 H, dt, *J* 13.6 and 5.6 Hz, 5′β-H), 2.60 (1 H, dt, *J* 13.6 and 8.8 Hz, 5′α-H), 2.97 (m, 4′-H), 3.45 (t, *J* 5.3 Hz, CH_2O), 4.75 (t, *J* 5.3, OH), 5.36 (m, 1′-H), 5.87 (m, 2′-H), 6.13 (m, 3′-H), 6.47 (br s, NH_2), 7.61 (8-H), 10.61 (br s, NH).

References

1. Reutov, O. A., Beletskaya, I. P. and Kurts, A. L. *Ambident Anions*, Consultants Bureau, New York 1983, Chap. 6.
2. Platzer, N., Galons, H., Bensaid, Y., Miocque, M. and Bram, G. *Tetrahedron 43* (1987) 2101, and references therein.
3. Falck-Pedersen, M. L., Benneche, T. and Undheim, K. *Acta Chem. Scand. 43* (1989) 251.
4. Trost, B. M. *Acc. Chem. Res. 13* (1980) 385.
5. (a) Marquez, V. E. and Lim, M. *Med. Res. Rev. 6* (1986) 1; (b) Biggadike, K., Borthwick, A. D. and Exall, A. M. *J. Chem. Soc., Chem. Commun.* (1990) 458; (c) Bodenteich, M. and Marquez, V. E. *Tetrahedron Lett. 30* (1989) 4909; (d) Coe, D. E., Hilpert, H., Noble, S. A., Peel, M. R., Roberts, S. M. and Storer, R. *J. Chem. Soc., Chem. Commun.* (1991) 312; (e) Tseng, C. K. H. and Marquez, V. E. *Tetrahedron Lett. 26* (1985) 3669.
6. Vince, R. and Hua, M. *J. Chem. Med. 33* (1990) 17.
7. Antonsen, Ø., Benneche, T., Gundersen, L.-L. and Undheim, K. *Acta Chem. Scand. 46* (1992) 177.
8. Rasmussen, M. and Hope, J. M. *Aust. J. Chem. 35* (1982) 525.
9. Trost, B. M., Kuo, G.-H. and Benneche, T. *J. Am. Chem. Soc. 110* (1988) 621.
10. (a) Kjellberg, J. and Johansson, N. G. *Nucleosides Nucleotides 8* (1989) 225; (b) Raju, N., Robins, R. K. and Vaghefi, M. M. *J. Chem. Soc. Chem. Commun.* (1989) 1769; (c) Kjellberg, J., Liljenberg, M. and Johansson, N. G. *Tetrahedron Lett. 27* (1986) 877.
11. (a) Sieber, P. *Helv. Chim. Acta 60* (1977) 2711; (b) Gerlach, H. *Helv. Chim. Acta 60* (1977) 3039; (c) Still, W. C. and Ohmizu, H. *J. Org. Chem. 46* (1981) 5242; (d) Lipshutz, B. H., Pegram, J. J. and Morey, M. C. *Tetrahedron Lett. 22* (1981) 4603; (e) Jansson, K., Ahlfors, S., Frejd, T., Kihlberg, J. and Magnusson, G. *J. Org. Chem. 53* (1988) 5629.
12. Neuhaus, D. and Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*. VCH, New York 1989, pp. 81–85.
13. van Maarschalkerwaart, D. A. H., Willard, N. P. and Koomen, G. J. *Nucleosides Nucleotides 9* (1990) 787.
14. Bax, A. *J. Magn. Reson. 57* (1984) 314.
15. Wilde, J. A. and Bolton, P. H. *J. Magn. Reson. 59* (1984) 343.
16. (a) Summers, M. F., Marzilli, L. G. and Bax, A. *J. Am. Chem. Soc. 108* (1986) 4285; (b) Cavenagh, J., Hunter, C. A., Jones, D. N. M., Keeler, J. and Sanders, J. K. M. *Magn. Reson. Chem. 26* (1988) 876.
17. Tateoka, Y., Kimura, T., Watanabe, K., Yamamoto, I. and Ho, I. K. *Chem. Pharm. Bull. 35* (1987) 4928.
18. Masoliver, C. E. and Fermin, I. L. Span. ES 519,897 (1984); *Chem. Abstr. 107* (1987) 236374d.
19. Leonard, N. J. and Frihart, C. R. *J. Am. Chem. Soc. 96* (1974) 5894.

Received November 6, 1991.