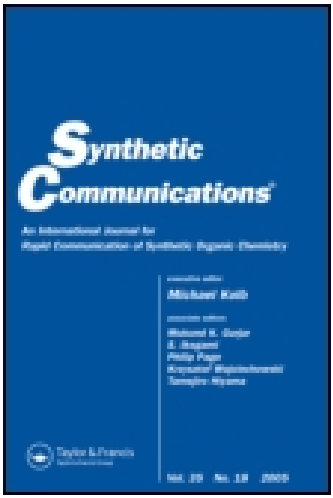


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Mitsunobu Reactions for the Synthesis of Carbocyclic Analogues of Nucleosides: Examination of the Regioselectivity[1]

Akemi Toyota [a] , Nobuya Katagiri [a] & Chikara Kaneko [a]

[a] Pharmaceutical Institute, Tohoku University , Aobayama, Sendai, 980, Japan
Published online: 24 Sep 2006.

To cite this article: Akemi Toyota , Nobuya Katagiri & Chikara Kaneko (1993) Mitsunobu Reactions for the Synthesis of Carbocyclic Analogues of Nucleosides: Examination of the Regioselectivity[1] , Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:9, 1295-1305, DOI: 10.1080/00397919308011216

To link to this article: http://dx.doi.org/10.1080/00397919308011216

SYNTHETIC COMMUNICATIONS, 23(9), 1295-1305 (1993)

MITSUNOBU REACTIONS FOR THE SYNTHESIS OF CARBOCYCLIC ANALOGUES OF NUCLEOSIDES: EXAMINATION OF THE REGIOSELECTIVITY[1]

Akemi Toyota,* Nobuya Katagiri and Chikara Kaneko

Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

ABSTRACT: In order to provide a general synthetic method for carbocyclic nucleosides, regioselectivities in Mitsunobu reaction of purine, pyrimidin-2-one and their substituted derivatives with a variety of alcohols were examined and found to depend upon both substituents of the bases and kind of the alcohols.

Due to intense current interest for carbocyclic nucleosides,[2,3] much efforts have been paid for development of the method generally applicable to the preparation of these analogues. Attachment of cyclopentane or other substituents to purine bases via direct alkylation with cyclopentyl halides and their equivalents (e.g. mesylated cyclopentanols) yields both N^9- and N^7-substituted derivatives.[4] Though vinyl epoxide ring opening by 6-chloropurine (or even adenine) was reported to give the N^9-substituted derivatives selectiviely, this method inevitably gives the products that are hydroxylated in an undesirable position.[5] Since stepwise construction of purine and pyrimidine ring systems from the corresponding cyclopentylamines requires multistep and is tedious,[6] we have chosen the direct introduction of cyclopetane moiety to the purine bases at the N^9-position by the corresponding alcohol as the best choice. To this purpose, two methods have so far been disclosed: 1) Mitsunobu reaction[7] of purines with cyclopentanols and 2) application

of Palladium(0)-catalyzed allylic alkylation[8] of the bases by cyclopentenyl acetates. In this line of works, we previously investigated the Mitsunobu reaction of 6-chloropurine with three alcohols (ethyl alcohol, benzyl alcohol and monosilylated *cis*-2-cyclopentene-1,4-diol) and found that, while the monosilylated diol afforded a single N^9-product (for which we tentatively assigned the 1,4-*trans* structure by an analogy of the well settled S_N2 replacement in the Mitsunobu reactions[7]), the N^7-products were obtained irrespective of the alcohols.[9] By using this alkylation reaction as the key step, we have succeeded in the EPC (enantiomerically pure compounds) synthesis of (-)-BCA [(1*R*,4*S*,5*R*)-9-(4,5-bishydroxymethylcyclopent-2-en-1-yl)-9*H*-adenine)[10] having a potent anti-HIV activity from (-)-Corey lactone in quite short steps.[11] In this case, the N^7-substituted purine was obtained in a small amount (ratio of 9-substituted purine/7-substituted purine = *ca.* 4).

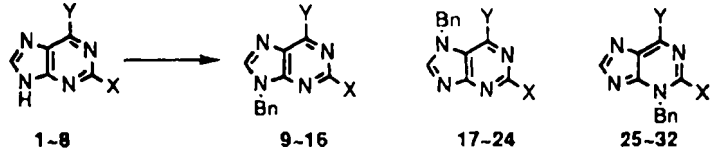
Since the selective 9-alkylation of purine derivatives (6-chloropurine, 2,6-dichloropurine, and even purine itself) was considered as the most important advantage of the Mitsunobu reaction for the preparation of carbocyclic nucleosides,[12] it is important to clarify to what extent one can enhance the regioselecivity (enhancement of the yield of the N^9-substituted purine derivatives) either by altering substituents on the purine ring or by changing the kind of alcohols. In this paper, we will report the detailed result of Mitsunobu reactions of purine bases having fluorine, chlorine, iodine, and other substituents at the 6- and/or 2-positions of purine ring with different kinds of alcohols. The same reaction using 4-ethoxypyrimidin-2-one as the base was also carried out in order to develop a general synthetic method for the pyrimidine nucleosides. The results of these studies are described in the following three items.

Mitsunobu Reaction of Purine and its Derivatives with Benzyl Alcohol

In order to examine how the regioselectivity of the reaction depends upon the substituents, we have carried out Mitsunobu reaction by using benzyl alcohol as the common alkylating reagent to append the heterocyclic rings, purine (**1**), 6-fluoropurine (**2**), 6-chloropurine (**3**), 6-iodopurine (**4**), 6-azidopurine (**5**), 6-dimethylaminopurine (**6**), 2,6-dichloropurine (**7**), or 2-chloro-6-iodopurine (**8**).

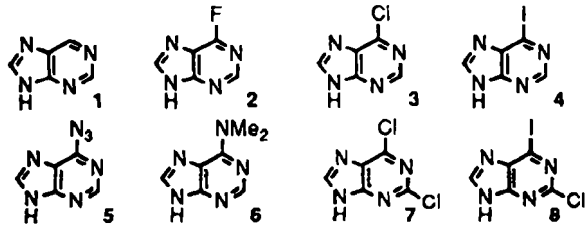
The results of these reactions are shown in Table 1. In order to compare each reaction strictly, all of the reactions were carried out in THF at 0 °C (1 h) and then

Table 1. Mitsunobu reaction of purine (1), its mono- (2~6) and disubstituted derivatives (7 and 8) with benzyl alcohol



1~8 9~16 17~24 25~32

Entry	Substrate	X	Y	Product (%)		
1	1	H	H	9 (70)	17 (9)	25 (21)
2	2	H	F	10 (64)	18 (16)	26 (none)
3	3	H	Cl	11 (67)	19 (23)	27 (9)
4	4	H	I	12 (74)	20 (13)	28 (13)
5	5	H	N_3	13 (24)	21 (69)	29 (none)
6	6	H	NMe_2	14 (64)	22 (none)	30 (36)
7	7	Cl	Cl	15 (69)	23 (26)	31 (none)
8	8	Cl	I	16 (85)	24 (10)	32 (none)



at room temperature for further 10 h. Unlike to other purines, purine (1) was practically insoluble to the solvent. However, as reaction proceeded, all of 1 gradually dissolved and gave three benzylated products (9, 17, and 25) with the yields of 9 > 25 > 17.

The result of Mitsunobu reaction using mono-substituted purines (2-6) shown in Table 1 is summarized as follows: (1) In the mono-halogenated series (Entries 2–4), the yields of 9- (and 3-benzylated) products increase with the order of F < Cl < I. (2) None of the N^7-benzylated product was detected in the reaction using dimethylamino derivative (Entry 6). (3) No N^3-benzylated product was detected in the reactions of 6-fluoro- and 6-azidopurines (Entries 2 and 5). (4) While all the purines except the azidopurine (5) gave the N^9-substituted products as the major ones, 5 gave the N^7-benzylated product as the major one.

The fact that any N^3-benzylated product was not obtained in the reactions of the dihalogenated purines (Entries 7 and 8) indicates that the presence of chlorine at the 2-position prohibited the formation of the N^3-substitution. Like mono-halogenated series, the ratio of N^9-/N^7-benzylated products is higher for **8** than that for **7**. It seems reasonable to assume that the steric factor of iodine at the 6-position has prevented the formation of the N^7-isomer.

Mitsunobu Reaction of 6-Chloro- (3), 6-Iodopurines (4) and their 2-Chloro Derivatives (7 and 8) with a Variety of Alcohols

In order to examine how the kinds of alcohol affect the regioselectivity, the same reactions have then been extended to two purines (**3** and **4**) using a variety of alcohols. These alcohols are classified broadly into two groups: 1) alkanols: ethanol (**b**), ethylene glycol mono *tert*-butyldiphenylsilyl ether (**c**) as the primary alkanol and isopropanol (**d**), cyclopropanol (**e**), and the substituted cyclopropanol (**f**) as the secondary alkanol and 2) secondary allyl alcohols: *cis*-2-cyclopentene-1,4-diol mono *tert*-butyl-dimethylsilyl ether (**g**), and the substituted cyclopentenol (**h**).

The characteristics derived from the results shown in Table 2 are as follows: (1) use of alkanols resulted in higher ratios of N^9-/N^7-alkylated products than those obtained from the reactions using allyl alcohols and (2) the same ratios also depended upon the kinds of primary and secondary nature of the alcohols. Thus, in both series of compounds (**3** and **4**), the secondary ones gave higher ratios of N^9-/N^7-isomers than those of the corresponding primary ones.

The characteristic (1) probably reflects that the allyl alcohols are more reactive than the saturated alcohols and hence lowers the regioselectivity of the reactions. Since more bulky alcohols in each series gave the lesser amount of the N^7-substituted products, it is reasonable to assume that the N^7-substitution is more

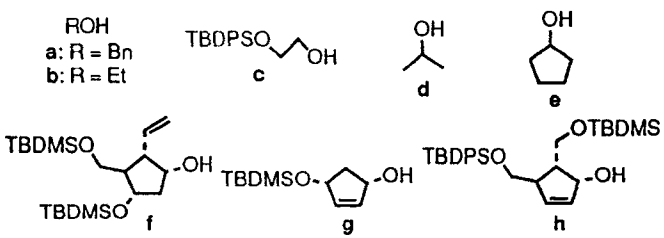
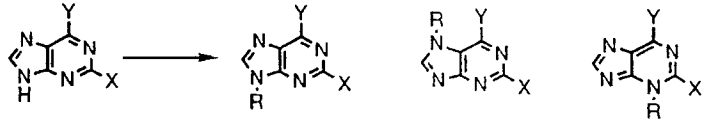


Table 2. Mitsunobu reaction of 6-chloro (3), 6-iodopurines (4) and their 2-chloro derivatives (7 and 8) with a variety of alcohols



3, 4, 7, 8 11,12,15,16 19,20,23,24 27,28,31,32

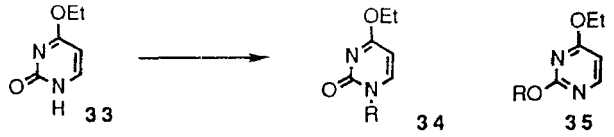
Entry	Substrate Compd	X	Y	Alcohol	Product (%)		
9	3	H	Cl	b	11b (81)	19b (14)	27b(±)
10	3	H	Cl	e	11e (87)	19e (3)	27e (10)
11	3	H	Cl	f	11f (65)	19f (9)	27f (none)
12	3	H	Cl	g	11g (58)	19g (11)	27g (4)
13	3	H	Cl	h	11h (48)	19h (12)	27h (±)
14	4	H	I	c	12c (92)	20c (7)	28c (±)
15	4	H	I	d	12d (87)	20d (4)	28d (9)
16	4	H	I	e	12e (89)	20e (none)	28e (11)
17	7	Cl	Cl	c	15c (81)	23c (9)	31c (none)
18	8	Cl	I	c	16c (91)	24c (3)	32c (none)

sensitive toward steric hindrance caused by the C^6-substituent than the N^9-substitution. The complete lack of the N^3-benzylated products in the reactions of the dihalogenated purines (7 and 8) (cf. Table 1) as well as the above-mentioned characteristic (1) then led us to examine Mitsunobu reaction of these two purine bases (7 and 8) with the monosilylated ethylene glycol (c). As expected, the yields of the N^9-alkylated products increased and the 9-alkylated purine (26c) was obtained in 91% yield.

Mitsunobu Reaction of 4-Ethoxypyrimidin-2-one (33) with a Variety of Alcohols

Mitsunobu reaction of 33 with benzyl alcohol (a) gave the N^1-substituted (34a) and O-substituted products (35a) in 86% and 13% yields, respectively. Though the amounts of the O-alkylation products increased by using primary saturated alcohols (b and c), the O-alkylation products become the major products only when the secondary alcohols (e.g. e and h) were used.

Table 3. Mitsunobu reaction of 4-ethoxypyrimidin-2-one (33) with a variety of alcohols



Entry	Alcohol	Product (%)	
19	a	**34a** (87)	**35a** (13)
20	b	**34b** (53)	**35b** (42)
21	c	**34c** (57)	**35c** (30)
22	e	**34e** (±)	**35e** (96)
23	h	**34h** (13)	**35h** (82)

Conclusion

In summary, the following could be said: 1) The condensation of purines with alkanols by Mitsunobu reaction provides one-step route for the preparation of 9-alkylated purines and, hence, for that of carbocyclic nucleosides. 2) Since the replacement of hydroxyl group of the alcohols occurs in S_N2 fashion, one can use this reaction for the EPC synthesis of carbocyclic nucleosides from chiral cyclopentanols. 3) Though the regioselectivity is not high (formation of the 9-substituted purines as major products with significant amount of the 7-and/or 3-substituted ones), appropriate choice of the purine substituents as well as alcohols could suppress the by-product formation and gives practically selective formation of the 9-substituted purines (for instance, Enties 14 and 18). 4) In case of Mitsunobu and related reactions using triphenylphosphine as one of the reagent for the preparation of alkylated purines, one should take care for the isolation of 7-alkylated purines, because their polarity on silica gel chromatography is nearly the same with triphenylphosphine oxide.

Experimental

General Procedure for the Alkylation of Purine Bases (1-8) with a Variety of Alcohols by Mitsunobu Reaction. Diethyl azodicarboxylate (0.05 ml, 0.15 mmol) was added in portions to a mixture of the purine (0.15 mmol), the alcohol (0.3 mmol), and triphenylphosphine (79 mg, 0.3 mmol) in THF (2.7 ml). The mixture was stirred at 0 °C for 1 h and then at room temperature for further 10 h.

Table 4. Physical and spectroscopic data for benzylated purines

Compd. No.	mp (°C)	UV(MeOH) λ_{max} nm	^{1}H-NMR δ(CDCl$_3$)
9-Isomer			
9[13]	96-98	263.5	5.50 (2H, s), 7.38 (5H, s), 8.12, 9.06 and 9.20 (each, 1H, s,
10[14]	__a	248 (248)	5.53 (2H, s), 7.43 (5H, s), 8.18 and 8.77 (each 1H, s, purine-H x 2).
11[15]	__a	265	5.47 (2H, s), 7.35 (5H, br s, C_6H_5), 8.15 and 8.80 (each 1H, s, purine-H x 2).
12[16]	__a	276	5.43 (2H, s), 7.33 (5H, s), 8.12 and 8.66 (each 1H, s, purine-H x 2).
13[17]	__b	253 262 288	5.43 (2H x 3/8, s). 5.58 (2H x 5/8, s), 7.26-7.90 (5H, m), 7. 7.97 (1H x 3/8, s), 8.18 (1H x 5/8, s), 8.71 (1H x 3/8, s), 9. 9.52 (1H x 5/8, s).
14[18]	__b	278	3.53 (6H, s), 5.36 (2H, s), 7.30 (5H, s), 7.40-7.90 (1H, masked by the signals of the phosphine oxide), 8.41 (1H, s).
15[19]	150-152 (146-147)	273	5.43 (2H, s), 7.38 (5H, s), 8.07 (1H, s).
16[c]	163-165	283	5.41 (2H, s), 7.38 (5H, s), 8.08 (1H, s).
7-Isomer			
17[13]	140-142 (144-145)	266 (266)	5.47 (2H, s), 7.40 (5H, m), 8.33, 8.80 and 9.18 (each 1H, s, purine-H x 3).
18[14]	__b	255	5.53 (2H, s), 7.40 (5H, m), 8.30 and 8.80 (each 1H, s, purine-H x 2).
19[15]	__b		5.70 (2H, s), 7.30-7.50 (5H, masked by the signals of the phosphine oxide), 8.35 and 8.87 (each 1H, s, purine x 2).
20	__b	281	5.87 (2H, s), 8.24 and 8.82 (1H each, s, purine-H x 2).
21[17]	__b	254 263 286	5.83 (2H, s), 7.3-7.9 (5H, masked by the signals of the phoshine oxide), 8.30 and 9.56 (each 1H, s, purine-H x 2).
23	128-131	282.	5.70 (2H, s), 7.33 (5H, m), 8.22 (1H, s).
24	__a		5.77 (2H, s), 7.0-7.55 (5H, m), 8.33 (1H, s).
3-Isomer			
25[13]	oil	279 (277.5)	5.86 (2H,s), 7.47 (5H, s), 8.70 (2H, s, purine-H x 2), 9.07 (1H, s, purine-H).
27[d]	oil	282	5.82 (2H, s), 7.47 (5H, s), 8.42 and 8.55 (1H each, s, pur purine-H x 2).
28[e]	oil	297.5	5.75 (2H, s), 7.41 (5H, s), 8.27 and 8.53 (1H each, s, pur purine-H x 2).
30[18]	142-145 (144-145)	299	3.20-4.20 (6H, b), 5.52 (2H, s), 7.35 (5H, s), 7.95 and 8.04 (1H, each, s, purine-H x 2).

a. Contaminated with bis(ethoxycarbonyl)hydrazine.

b. Contaminated with triphenylphosphine oxide.

c. Anal. Calcd for $C_{12}H_8ClN_4I$: C, 38.89; H, 2.18; N, 15.12. Found: C, 39.01; H, 2.21; N, 15.19.

d. High-resolution MS *m/z* Calcd for $C_{12}H_9N_4Cl$ = [244.0515]. Found: [244.0483].

e. High-resolution MS *m/z* Calcd for $C_{12}H_9N_4I$ = [335.9870]. Found: [335.9879].

Table 5. Physical and spectroscopic data for alkylated purines

Compd. No.	mp (°C)	UV(MeOH) λ_{max} nm	^{1}H-NMR δ ($CDCl_3$)
9-Isomer			
11b[9]	__b	265	1.60 (3H, t, J = 8 Hz), 4.38 (2H, q, J = 8 Hz), 8.17 and 8.77 (each 1H, s, purine-H x 2).
11e	__a	266	1.96 (8H, m), 5.03 (1H, m), 8.20 and 8.75 (each 1H, s, purine-H x 2).
11f[20,f]	oil	264	0.07 and 0.08 (each 6H, s), 0.90 and 0.93 (each 9H, s), 1.70-2.55 (3H, m, $C_{3'}$-H, $C_{5'}$-H x 2), 3.10 (1H, dd, J = 18, 10 Hz, $C_{2'}$-H), 3.73 (2H, t, J = 4 Hz, CH_2OTBDMS), 4.57 (1H, m, $C_{4'}$-H), 5.00 (3H, m, $C_{1'}$-H, $C_{7'}$-H x 2), 5.77 (1H, m, C_6-H), 8.13 and 8.73 (each 1H, s, purine-H x 2).
11g[9,g]	126-127	266	0.119 and 0.121 (each 3H, s, $SiMe_2$), 0.92 (9H, s, CMe_3), 2.34 (1H, ddd, J =13.5, 7.5, 4 Hz, $C_{5'}$-H), 2.48 (1H, ddd, J = 13.5, 9, 4 Hz, $C_{5'}$-H), 5.25 (1H, m, CH-O), 5.95 (1H, m, CH-N), 6.05 (1H, ddd, J = 5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.35 (1H, ddd, J = 5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.03 and 8.77 (each 1H, s, purine-H x 2).
11h[12,h]	oil	266	0.02 (6H, s, $SiMe_2$), 0.82 and 1.07 (each 9H, s, t-Bu x 2), 2.35 (1H, m, $C_{5'}$-H), 2.91 (1H, m, $C_{4'}$-H), 3.75 (1H, m, CHH'OTBDPS), 3.78 (2H, m, CH_2OTBDMS), 3.83 (1H, m, CHH'OTBDPS), 5.73 (1H, m, $C_{1'}$-H), 5.78 and 6.13 (each 1H, m, olefinic-H x 2), 7.40 and 7.63 (each 5H, m, Ph x 2), 8.10 and 8.69 (each 1H, s, purine-H x 2).
12c[i]	130-132	275	0.99 (9H, s, t-Bu), 3.98 (2H, m, -OCH_2), 4.30 (2H, m, NCH_2), 7.33 (10H, m), 8.20 and 8.47 (each 1H, s, purine-H x 2).
12d	__a	276.	1.68 (6H, d, J = 6.5 Hz), 4.96 (1H, qq, J = 6.5 Hz), 8.26 and 8.66(each 1H, s, purine-H x 2).
12e	__a	276	1.97 (8H, m), 5.00 (1H, m), 8.17 and 8.61 (each 1H, s, purine-H x 2).
15c[j]	100-102	273	1.02 (9H, s), 4.03 (2H, m), 4.33 (2H, m), 7.35 (10H, m), 8.13 (1H, s).
16c	125-128	284	1.02 (9H, s), 4.01 (2H, m), 4.27 (2H, m), 7.33 (10H, m), 8.12 (1H, s).
24c	__a	292	1.02 (9H, s), 4.33 (2H, m), 4.58 (2H, m), 7.38 (10H, m), 8.31 (1H, s).
7-Isomer			
19b[9]	121-122 (122-123)		1.63 (3H, t, J = 11 Hz), 4.58 (2H, q, J =11 Hz), 8.30 and 8.87 (each 1H, s, purine-H x 2).
19e	__b		1.93 (8H, m), 5.30 (1H, m), 8.35 and 8.87 (each 1H, s, purine-H x 2).
19f[20,k]	oil	271	0.10 (12H, s), 0.92 and 0.95 (each 9H, s), 1.73-2.87 (3H, m), 2.97 (1H, dd, J = 18, 9 Hz), 3.78 (2H, t, J = 4 Hz), 4.42 (1H, m), 4.88 (1H, dd, J = 9, 3 Hz, $C_{7'}$-H_{cis}), 5..12 (1H, d, J = 3 Hz, $C_{7'}$-H_{trans}), 5.63 (2H, m, $C_{1'}$-H, $C_{6'}$-H), 8.42 and 8.90 (each 1H, s, purine-H x 2).
19g[9]	__a	269	0.103 and 0.11 (each 3H, s, $SiMe_2$), 0.91 (9H, s, CMe_3), 2.27 (1H, ddd, J = 15, 7.5, 3.5 Hz, $C_{5'}$-H), 2.50 (1H, ddd, J =15, 7.5, 5 Hz, $C_{5'}$-H), 5.14 (1H, m, CH-O), 6.14 (1H, ddd, J = 5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.23 (1H, m, CH-N), 6.38 (1H, ddd, J = 5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.18 and 8.90 (each 1H, s, purine-H x 2).
19h	oil	272	0.15 (6H, s, $SiMe_2$), 0.94 and 1.25 (each 9H, s, t-Bu x 2), 2.51 (1H, m, $C_{5'}$-H).3.13 (1H, m, $C_{4'}$-H), 4.03 (4H, m, CH_2OSi x 2),

Table 5 Continued

			6.07 (1H, m, olefinic-H), 6.37 (2H, m, $C_{1'}$-H and olefinic-H), 7.73 (10H, m, Ph x 2), 8.56 and 9.10 (each 1H , s, purine-H x 2).
20c	__a	280	1.00 (9H, s), 4.30 (2H, m), 4.60 (2H, m), 7.30 (10H, m), 8.27 and 8.70 (each 1H, s, purine-H x 2).
20d	__b	280	1.73 (6H, d, J = 6.5 Hz), 4.83 (1H, m), 8.43 and 8.73 (each 1H, s, purine-H x 2).
23c	oil	283	1.01 (9H, s), 4.04 (2H, m), 4.54 (2H, m), 7.37 (10H, br s), 8.27 (1H, s).
24c	__a	292	1.02 (9H, s), 4.33 (2H, m), 4.58 (2H, m), 7.38 (10H, m), 8.31 (1H, s).
3-Isomer			
27e	oil	281.5	2.05 (8H, m), 5.35 (1H, m), 8.46 and 8.48 (each 1H, s, purine-H x 2).
27g[9]	oil	280	0.118 and 0.125 (each 3H, s, $SiMe_2$), 0.92 (9H, s, CMe_3), 15, 8, 4 Hz, $C_{5'}$-H), 5.23 (1H, m, CH-O), 6.10 (1H, ddd, J = 5, 2, 1 Hz, $C_{2'}$- or $C_{3'}$-H), 6.41 (1H, m, CH-N). 6.46 (1H, ddd, J = 5, 2, 2 Hz, $C_{2'}$- or $C_{3'}$-H), 8.32 and 8.55 (each 1H, s, purine-H x 2). MS m/z (M^+): 350.
28d	oil	294	1.79 (6H, d, J = 7 Hz), 5.28 (1H, qq, J = 7 Hz), 8.37 and 8.51 (each 1H, s, purine-H x 2).
28e	oil	297.5	2.07 (8H, m), 5.40 (1H, m), 8.42 and 8.55 (each 1H, s, purine-H x 2).

a,b. The same as in Table 4.

f. High-resolution MS m/z Calcd for $C_{25}H_{43}N_4O_2Si_2Cl$ (M^+): 522..2614. Found: 522.2650.

g. Anal. Calcd for $C_{16}H_{23}ClN_4OSi$ $1/4H_2O$: C, 54.07; H, 6.66; N, 15.77. Found: C, 53.96; H, 6.36; N, 15.62.

h. High-resolution MS m/z Calcd for $C_{30}H_{36}ClN_4O_2Si_2$ (M^+-t-Bu): 575.2063. Found: 575.2021.

i. Anal. Calcd for $C_{23}H_{25}N_4IOSi$: C, 52.27; H, 4.77; N, 10.60. Found: C, 52.51; H, 4.75; N, 10.52.

j. Anal. Calcd for $C_{23}H_{24}Cl_2N_4OSi$: C, 58.59; H, 5.13; 11.88. Found: C, 58.59; H, 5.16; N, 11.86.

k. High-resolution MS m/z Calcd for $C_{25}H_{44}N_4O_2Si_2Cl$ (M^+ + H): 523.2629. Found: 523.2675.

After removal of the solvent *in vacuo*, the product was separated by flash chromatography (silica gel). Elution was carried out in the order of hexane-ethyl acetate, ethyl acetate, ethyl acetate-methanol, and chloroform-methanol as the solvents. As a result, the products were eluted in the following order: the 9-alkylated derivatives, then, 7-alkylated derivatives, and finally the 3-alkylated derivatives. The yields of the products using benzyl alcohol are given in Table 1 and those derived from the other alcohols in Table 2. The yields of products that correspond to footnotes a and b were calculated from the intensity of the ^{1}H-NMR signals. Melting points and chemical analysis data as well as spectroscopic data (UV and ^{1}H-NMR) are given in Tables 4 and 5.

Table 6. Physical and spectroscopic data for the alkylation products of 4-ethoxypyrimidin-2-one (33) with a variety of alcohols

Compd. No.	mp (°C)	UV(MeOH) λ_{max} nm	^{1}H-NMR δ ($CDCl_3$)
1-Alkyl-4-O-ethyluracil			
34a[21]	oil	277	1.34 (3H, t, *J* = 7Hz), 4.43 (2H, q, *J* = 7 Hz), 5.03 (2H, s), 5.80(1H, d, *J* = 7.2 Hz), 7.31 (5H, s), 7.35 (1H, d, *J* = 7.2 Hz).
34b[22]	—[b]	277	1.37 (6H, t, *J* = 7 Hz), 3.91 (2H, q, *J* = 7 Hz), 4.45 (2H, q, *J* = 7 Hz), 5.87 (1H, d, *J* = 7 Hz), 7.43 (1H, d, *J* = 7 Hz).
34c	—[a]	276	1.03 (9H, s), 1.38 (3H, t, *J* = 7 Hz), 3.97 (4H, s), 4.47 (2H, q, *J* = 7 Hz), 5.80 (1H, d, *J* = 7 Hz), 7.27-7.70 (11H, m).
34h	—[a]	280	0.03 (6H, s), 0.85 (9H, s), 1.08 (9H, s), 1.33 (3H, t, *J* = 7Hz), 2.10 (1H, m), 2.90 (1H, m), 3.70 (4H, m), 4.37 (2H, q, *J* = 7 Hz), 5.60 (2H, d, *J* = 7 Hz), 5.70 (2H, m, olefinic-H and $C_{1'}$-H), 6.07 (1H, m), 7.27-7.77 (11H, m).
2-O-Alkyl-4-O-ethyluracil			
35a[21]	oil	259	1.38 (3H, t, *J* = 7 Hz), 4.38 (2H, q, *J* = 7 Hz), 5.45 (2H, s), 6.36(1H, d, *J* = 5 Hz), 7.44 (5H, m), 8.23 (1H, d, *J* = 5 Hz).
35b[22]	oil	260	1.38 (3H, t, *J* = 7 Hz), 1.42 (3H, t, *J* = 7 Hz), 4.48 (4H, q, *J* = 7 Hz), 6.38 (1H, d, *J* = 6 Hz), 8.23 (1H, d, *J* = 6 Hz).
35c	oil	260	1.07 (9H, s), 1.36 (3H, t, *J* = 7 Hz), 4.01 (2H, m), 4.50 (2H, m), 4.52 (2H, q, *J* = 7 Hz), 6.30 (1H, d, *J* = 5.5 Hz), 7.23-7.80 (10H, m), 8.33 (1H, d, *J* = 5.5 Hz).
35e[21]	oil	261	1.50 (3H, t, *J* = 7 Hz), 1.98 (8H, m), 4.40 (2H, q, *J* = 7Hz), 5.43 (1H, m), 6.33 (1H, d, *J* = 6 Hz), 8.22 (1H, d, *J* = 6 Hz).
35h	oil	260.5	0.06 (6H, s), 0.87 (9H, s), 1.10 (9H, s), 1.37 (3H, t, *J* = 7 Hz), 2.37 (1H, m), 2.87 (1H, m), 3.78 (2H, d, *J* = 6 Hz), 3.89 (2H, d, *J* = 5 Hz), 4.43 (2H, q, *J* = 7 Hz), 5.98 (2H, m, olefinic-H x 2), 6.03 (1H, m), 6.32 (1H, d, *J* = 5.5 Hz), 7.30-7.83 (10H, m), 8.18 (1H, d, *J* = 5.5 Hz).

a,b. The same as in Tables 3 and 4.

General Procedure for the Alkylation of 4-Ethoxypyrimidin-2-one (33) with a Variety of Alcohols by Mitsunobu Reaction. Diethyl azodicarboxylate (0.05 ml, 0.15 mmol) was added in portions to a mixture of the pyrimidinone (0.15 mmol), the alcohol (0.3 mmol), and triphenylphosphine (79 mg, 0.3 mmol) in THF (2.7 ml) at 0 °C. The mixture was stirred at the same temperature for 1 h and then at room temperature for further 10 h. After removal of the solvent *in vacuo*, the product was separated by flash chromatography (silica gel). Elution was carried out by hexane-ethyl acetate as the solvents. The O-alkylated products were eluted first and then 1-substituted ones followed. The yields of the products are given in Table 3. Melting points and chemical analysis data as well as spectroscopic data (UV and ^{1}H-NMR) are given in Table 6.

Acknowledgment: This work is supported in part by a Grant-in-Aid for Scientific Research on Priority Areas No. 03242104 from the Ministry of Education, Science and Culture, Japan

References and Notes:

1. This paper forms part 30 of "Synthesis of nucleosides and related compounds". For Part 29, see, reference 11.
2. Kaneko, C.; Katagiri, N.; Nomura, M.; Sato, H., *Israel J. Chem.*, 1992, **31**, 247.
3. Roberts, S. M., *Chem. in Brit.*, **1991**, 518.
4. (a) Jones, M. F.; Roberts, S. M., *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2927. (b) Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2479.
5. Biggadike, K.; Borthwick, A. D.; Exall, A. M., Kirk, B. E.; Roberts, S. M.; Ypuns, P., *J. Chem. Soc. Chem. Commun.*, **1987**, 1083.
6. (a) Katagiri, N.; Muto, M.; Nomura, M.; Higashikawa, T.; Kaneko, C., *Chem. Pharm. Bull.*, 1991, **39**, 1112. (b) Vince, R.; Hua, M., *J. Med. Chem.*, 1990, **33**, 17.
7. Reviews for Mitsunobu reaction: Mitsunobu, O., *Synthesis*, **1981**, 1.
8. (a) Trost, B. M.; Verhoeven, T. R., Comprehensive Organometallic Chemistry, Pergamon, Oxford, 1982, Vol. 8, p 799. (b) Gunderson, L-L.; Benneche, T.; Undheim, K., *Tetrahedron Lett.*, 1992, **33**, 1085. (c) Roberts S. M.; Shoberu, K. A., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2605.
9. Toyota, A.; Katagiri, N.; Kaneko, C., *Chem. Pharm. Bull.*, 1992, **40**, 1039.
10. Katagiri, N.; Nomura, M.; Sato, H.; Kaneko, C.; Yusa, K.; Tsuruo, T., *J. Med. Chem.*, **1992, 35**, 1882.
11. Katagiri, N.; Toyota, A.; Shiraishi, T.; Sato, H.; Kaneko, C., *Tetrahedron Lett.*, **1992, 33**, 3507.
12. Regioselective formation of 9-alkylated purines from 6-chloropurine by Mitsunobu reaction as the key step was reported by several groups: (a) Jenny, T. F.; Perisani, N.; Benner, S. A., *Tetrahedron Lett.*, 1991, **32**, 7029. (b) Bestmann, H. J.; Roth, D., *Angew. Chem. Int. Ed. Engl.*, 1990, **29**, 99. (c) Marquez, V. E.; Tseng, C. K. H.; Treanor, S. P.; Driscoll, J. S., *Nucleosides & Nucleotides*, 1987, **6**, 239. (d) Iwakawa, M.; Pinto, B. M.; Szarek, W. A., *Can. J. Chem.*, 1978, **56**, 326. (e) Pinto, B. M.; Vyas, D. M.; Szarek, W. A., *Can. J. Chem.*, 1977, **55**, 937. (f) Szalek, W. A.; Epew, C. D.; Jarrell, H. C.; Jones, J. K. N., *J. Chem. Soc. Chem. Comm.*, **1975**, 648.
13. Miyaki, M.; Shimizu, B., *Chem. Pharm. Bull.*, 1970, **18**, 1446.
14. Beaman, A. G.; Robins, R. K. *J. Org. Chem.*, 1963, **28**, 2310.
15. Montgomery, J. A.; Temple, C. Jr., *J. Am. Chem. Soc.*, 1961, **83**, 630.
16. McKenzie, T. C.; Epstein, J. W., *J. Org. Chem.*, 1982, **47**, 4881.
17. Temple, C. Jr.; Kussner, C. L.; Montgomery, J. A., *J. Org. Chem.*, 1966, **31**, 2210.
18. Itaya,T.; Matsumoto, H.; Ogawa, K., *Chem. Pharm. Bull.*, 1980, **28**,1920.
19. Naito, T.; Nakagawa, S.; Okita; T.; Yamashita, H.; Yamasaki, T.; Kamei, H.; Tomatsu, K.; Imanishi, H.; Kawaguchi, H., *Chem. Pharm. Bull.*, 1982, **30**, 2011.
20. Katagiri, N.; Sato, H.; Arai, S.; Toyota, A; Kaneko, C., *Heterocycles*, 1992, **34**, 1097.
21. Kaspersen, F. M.; Pandit, U. K., *J. Chem. Soc., Perkin I*, **1975**, 1798.
22. Wong, J. L.; Fuchs, D. S., *J. Org. Chem.*, 1970, **35**, 3786.

(Received in Japan 1 October 1992)