Photocycloaddition of Deoxyuridines to 2,3-Dimethyl-2-butene

Naoki HAGA,* Ichiro ISHIKAWA, Hiroaki TAKAYANAGI, and Haruo OGURA#
School of Pharmaceutical Sciences, Kitasato Univserity, 5-9-1, Shirokane, Minato-ku, Tokyo 108
(Received April 30, 1993)

Direct and ketone (acetone or acetophenone)-sensitized photocycloaddition of 2,3-dimethyl-2-butene to 2′-deoxyuridine (**1a**), thymidine (**1b**), 5-fluoro-2′-deoxyuridine (**1c**), and their 3′,5′-di-*O*-acetyl derivatives **1d**—**1f** by near-UV irradiation have been studied. The triplet excited state of the nucleosides was found to be the major intermeidate by the triplet quenching technique. From the respective reactants, a pair of diastereomeric products having a cyclobutane ring were isolated. The absolute configuration of the bridgehead carbon atoms was identified by X-ray crystallographic analyses with two of them as (1*R*, 6*R*)-isomer **3a** and (1*S*, 6*S*)-isomer **2b** and by ^{1}H NMR. The conformations of the glycosyl bond, the pyrimidine ring, and the sugar portion in solution were identified by ^{1}H NMR and compared with the ones in the crystalline state.

Photoreactions involving the carbon–carbon double bond in pyrimidine nucleosides have been extensively investigated mainly because photodimerization and photohydration of pyrimidine nucleosides in DNA are responsible for their highly mutagenic potential.[1,2] On the other hand, the photoreactions of pyrimidines or pyrimidine nucleosides with simple alkenes receive little attention presumably because cross-photocycloaddition may furnish an intractable mixture. For example, Swenton et al. and Kaneko and co-workers have reported on the regioselective photoreaction of simple olefins with uracils,[3—6] and have compared the ratio of the closure vs. the cleavage of the biradical intermediates with the reaction of α, β-unsaturated carbonyl compounds and alkenes.[7] Charlton and Lai[8] who have studied on the photoreaction of 2′,3′,5′-tri-*O*-acetyluridine with 2,3-dimethyl-2-butene. In addition, no mechanistic studies for these have been found in the literature. However, we considered that these photocyclizations might provide a route to variety of bicyclic pyrimidine nucleosides. It is intriguing to evaluate biological activities of the cyclobutane adducts of this type, especially interaction with repair enzymes. Our recent work has found that two photo-adducts of the cyclobutane type could be isolated from UV-irradiated acetone solution containing uridiens,[9] 2′-deoxyuridiens,[10] or 2,3-dimethyl-2-butene. Interestingly enough, the former showed great differentiation-inducing and growth-inhibitory activities towards HL-60 cells.[11]

In this paper, we deal with the photocycloaddition of 2,3-dimethyl-2-butene to 2′-deoxyuridine (**1a**), thymidine (**1b**), and 5-fluoro-2′-deoxyuridine (**1c**). Elucidation of the reaction pathway and the detailed analyses of the structures including the conformation of these adducts will be dealt with.

Results

Nucleosides **1a**—**1c** used in this work have absorption maxima at 260—270 nm arising from their $\pi\rightarrow\pi^*$ transition. When **1** was irradiated by the high-pressure mercury arc without a filter, not only conversion of **1** into **2** and **3** but also photoreversion has occurred. To avoid this unfavorable photoreversion, direct irradiation of nucleosides was done using a 1.2 mm Pyrex filter, which transmits lines longer than 275 nm of mercury arc to be absorbed. As shown in Fig. 1, only nucleosides, and not the photoproducts **2** and **3** absorb these lines.

Irradiation of a degassed solution of 3—6 mM of **1a** (X=H), **1b** (X=Me), and **1c** (X=F) containing 30 mM of 2,3-dimethyl-2-butene in acetonitrile gave rise to a pair of cyclobutane photoproducts **2** and **3** (1 M=1 mol dm^{-3}). Through this reaction proceeded accompanied with an isosbestic point at 249 nm on the UV spectrum, the conversion ratio was fairly low. For example, more than 50% of **1b** was recovered unchanged after 24 h of irradiation. In the presence of oxygen, 1, 3-pentadiene and 2,5-dimethyl-2,4-hexadiene, the reaction using **1b** was sluggish and more than 90% remained inert even after 12 h of irradiation (Table 1).

To improve the conversion efficiency, we did the reaction in the presence of sensitizers. Nucleobases and nucleosides have these triplet energies (E_T) in the range of 215—240 kJ mol^{-1}.[16] Since both acetone (E_T=235.8 kJ mol^{-1}) and acetophenone (E_T=221.6 kJ mol^{-1}) also have their triplet energy in the same range[17] with those of nucleosides, we conceived that these sensitizers are appropriate to this photoreaction. A high-pressure mercury lamp with a 2 mm of Pyrex filter was the lamp of choice. This set-up allows lines longer than 304 nm of the arc to be absorbed, where neither the nucleosides used in this work nor 2,3-dimethyl-2-butene absorb (Fig. 1).

Irradiation of **1a**, **1b**, and **1c** containing 50 mM of 2,3-dimethyl-2-butene in acetone was done in a similar manner to the direct excitation case. A pair of cyclobutane photoproducts **2** and **3** were produced in more abundantly than in 75% yield (Scheme 1, Table 2). It was found that acetophenone also affords similar results as in acetone, but the efficiency decreased to a considerable extent.

#Present address: Silalic Acids Society, 3-5-604, Kitasuna, Koto-Ku, Tokyo 136.

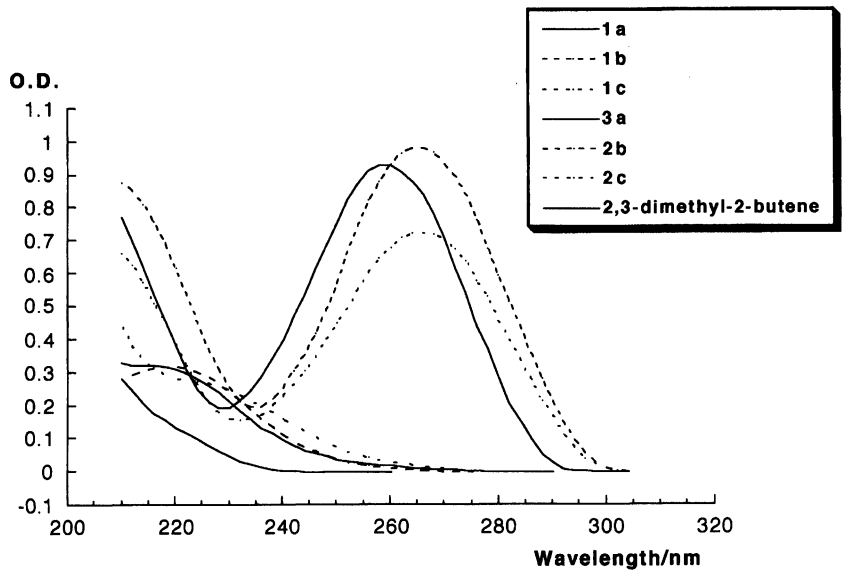
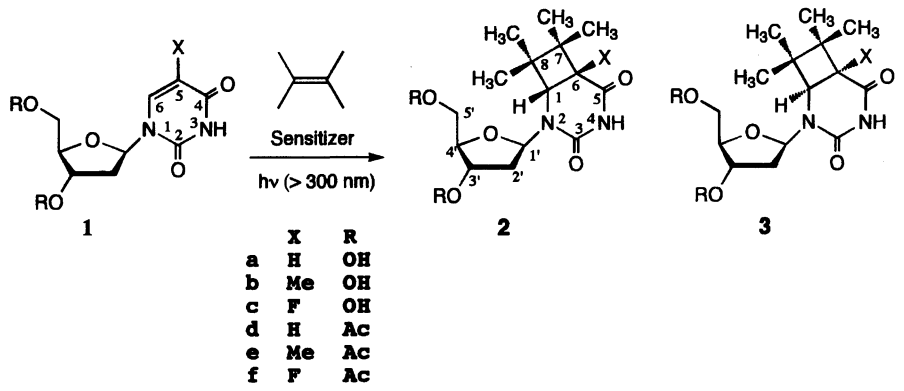


Fig. 1. UV Spectra of **1a** (9.8×10^{-5} mol dm^{-3}), **1b** (8.1×10^{-5} mol dm^{-3}), **1c** (7.6×10^{-5} mol dm^{-3}), **2b** (1.1×10^{-4} mol dm^{-3}), **3a** (1.0×10^{-4} mol dm^{-3}), **4a** (1.1×10^{-5} mol dm^{-3}) and 2,3-dimethyl-2-butene (4.3×10^{-4} mol dm^{-3}).

Table 1. Photoreaction of 2′-Deoxyuridines **1** with 2,3-Dimethyl-2-butene by Direct Excitation of **1**

	X	Quencher (M^{-1})	Time/h	Yield/%	**2**/**3**	Recoverry of **1**
1a	H	—	12	41	1.0	50
1b	CH_3	—	12	21	2.6	68
1b	CH_3	—	24	29	2.7	52
1b	CH_3	Oxygen[b)]	12	0	—	93
1b	CH_3	1,3-Pentadiene (0.01)	12	0	—	90
1b	CH_3	2,5-Dimethyl-2,4-hexadiene (0.01)	12	0	—	97
1c	F	—	12	40	1.8	39

a) Yields as a mixture of **2** and **3**. b) Oxygen gas was bubbled into the solution throughout the time of the irradiation.



Scheme 1.

In every case, photoproducts could not be cleanly separated by silica-gel chromatography. It was found, however, that **3a** from **1a** and **2b** form **1b** could be crystallized from methanol and ethyl acetate in pure form on concentration of the eluate. Concentration of each eluate containing **3a** or **2b**, obtained by a flash chromatography afforded a residue which in turn was crystallized form methanol and ethyl acetate. On the basis of elemental analysis, FAB-MS, UV and 400 MHz ^{1}H NMR spectral properties, each product was unambiguously identified as a cyclobutane photoproduct that was formed by linking nucleosides to 2,3-dimethyl-2-butene across positions 5 and 6 of the pyrimidine ring. Products **2c** and **3c** from **1c** could not be separated by means of recrystallization. Accordingly, they were isolated via 3′,5′-di-*O*-acetyl derivatives (see below).

Table 2. [a]Photocycloaddition of 2′-Deoxyuridines to 2,3-Dimethyl-2-butene by Sensitized Excitation

	X	Sensitizer	Time/h	Yield/%[a]	2 : 3	Recovery of 1
1a	H	Acetone	7.5	79	0.9	0
1a	H	Acetophenoene	12	74	1.0	10
1b	CH_3	Acetone	8.0	86	2.7	0
1b	CH_3	Acetophenoene	12	68	2.4	19
1c	F	Acetone	1.0	76	2.0	0
1c	F	Acetophenoene	1.5	81	1.8	0

a) Yields as a mixture of **2** and **3**.

Further evidence for supporting the structure assignment of **3a** and **2b** was obtained from X-ray crystallographic analyses. Stereodiagrams of the 2′-deoxyuridine photoproduct **2b** and the thymidine photoproduct **3a** are shown in Fig. 2. The absolute configuration of 1-C and 6-C were turned out to be *R* for **3a** and *S* for **2b**.

NMR spectra of the mother liquor of the photo-products from **1a** and **1b** after collection of crylstals of **2b** and **3a** had very similar profiles to those of **2b** and **3a**. That is, they bear a 2-deoxyribofuranosyl moiety, and showed the presence of a 5,6-saturated pyrimidine ring and four methyl groups originating from 2,3-dimethyl-2-butene. Similarly, other products from **1a** and **1b** were assigned as the (1*S*,6*S*)-isomer **2a** and (1*R*,6*R*)-isomer **3b**, respectively. The ratio of **2** to **3** was calculated on the basis of the integration of the anomeric proton in the NMR spectra. In each case, except **1a**, the stereoselectivity was observed, though the extent was not so great.

The chemical shift values and coupling constants of six photoproducts **2a**—**2c** and **3a**—**3c**, together with those of **1a**—**1c**, are listed in Tables 3 and 4, respectively. The assignment of the ^{1}H NMR spectra of all six photoproducts was done by comparison with those of **1a**—**1c** and by analysis of the double resonance technique. The resonances of deoxyribofuranosyl protons of the photoproducts **2** and **3** are quite similar to those in **1**. Compounds **2a** and **2b** are characterized by the upfield and downfield chemical shift by 0.2 ppm of a signal owing to 2′-CH and 1-CH resonance, respectively, compared to **3a** and **3b**. This is presumably due to the anisotropy of the carbonyl group at position 3. Though the products **2c** and **3c** obtained from the reaction mixture of **1c** failed to crystallize in a suitable form for X-ray diffraction, we deduced the absolute configuration at positions 1 and 6 and the ratio of **2c** and **3c** on the basis of the NMR property of 1- and 2′-CH resonance.

To analyze the spatial relationship of protons, nuclear Overhouser effect (NOE) of these six photoproducts was measured. A summary of the NOE relationship is listed in Table 5. Observed NOE's are between 1-CH and 2′-CH; 1-CH and 1′-CH; and 1′-CH and 4′-CH.

To facilitate isolation and purification of the photoproducts, nucleosides **1a**—**1c** were acetylated to give the corresponding 3′,5′-di-*O*-acetyl derivatives **1d** (X=H), **1e** (X=Me), **1f** (X=F). They were irradiated in a similar manner as in the case of **1a**—**1c**. From each of the reactants, a pair of disastereomers, **2d** (X=H), **2e** (X=Me), **2f** (X=F), and **3d**—**3f**, were formed and isolated in excellent yields by silica-gel chromatography. The results are given in Table 6. Their structures were identified on the basis of ^{1}H NMR and FAB-MS. The upfield chemical shift by 0.2 ppm of a signal owing to 2′-CH resonance and the downfield shift by 0.2 ppm of that owning to 1-CH were used to diagnose the absolute configurations at the bridgehead carbon as in the case

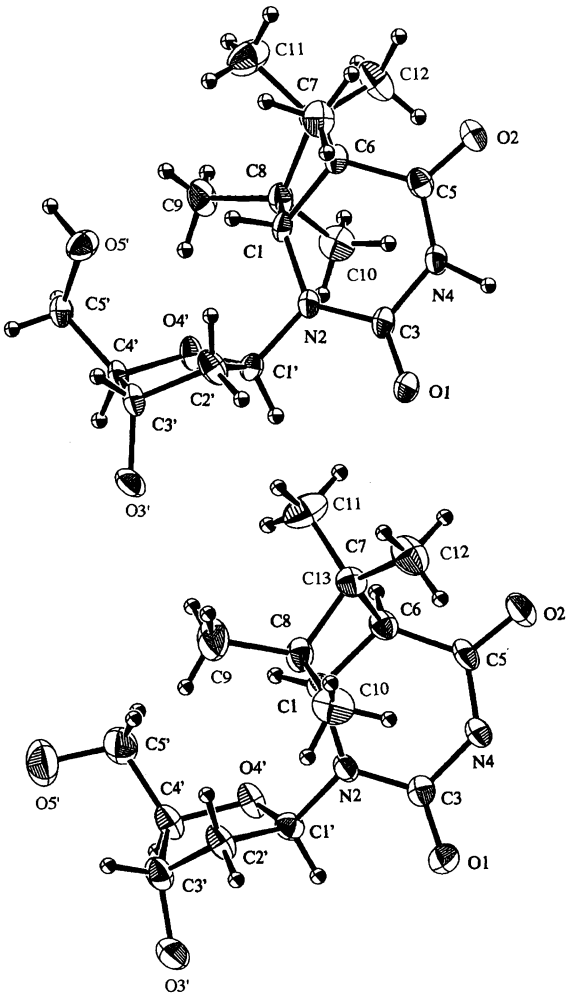


Fig. 2. Stereoscopic View of **2b** (top) and **3a** (bottom).

Table 3. Chemical Shifts in ppm (from TMS) of All Six Photoproducts **2a**—**2c** and **3a**—**3c** as Well as 2′-Deoxyuridines **1a**—**1c** at 23°C in DMSO-d_6.

	X	Bridge head	1-CH	6-CH	1′-CH	2′-CH	2″-CH	3′-CH	4′CH
2a	H	(1*S*,6*S*)	4.00(d)	2.78(d)	6.01(dd)	2.03(ddd)	1.72(ddd)	4.05(dddd)	3.62(dt)
3a	H	(1*R*.6*R*)	4.24(d)	2.81(d)	6.13(dd)	1.80(dd)	1.80(dd)	4.17(dddd)	3.62(dt)
2b	CH_3	(1*S*,6*S*)	3.64(s)	—	6.04(dd)	1.97(ddd)	1.73(ddd)	4.05(dddd)	3.62(dt)
3b	CH_3	(1*R*.6*R*)	3.87(s)	—	6.11(dd)	1.81(ddd)	1.78(ddd)	4.10(dddd)	3.67(dt)
2c	F	(1*S*,6*S*)	4.28(d)	—	6.04(dd)	1.99(ddd)	1.78(ddd)	4.10(dddd)	3.67(dt)
3c	F	(1*R*,6*R*)	4.49(d)	—	6.10(dd)	1.83(dd)	1.83(dd)	4.19 (ddt)	3.66(dt)
1a	H		7.86(d)	5.63(d)	6.15(t)	2.10(ddd)	2.05(ddd)	4.22(dddd)	3.77(dt)
1b	CH_3		7.69(s)	—	6.16(dd)	2.09(ddd)	2.04(ddd)	4.23(dddd)	3.76(dt)
1c	F		8.21(d)	—	6.12(dt)	2.10(dd)	2.10(dd)	4.25(ddt)	3.78(dt)

	X	Bridge head	5′-CH	5″-CH	3′-OH	5′-OH	4-NH	CH_3
2a	H	(1*S*,6*S*)	3.47(ddd)	3.41(ddd)	5.09(d)	4.75(t)	10.2(br s)	1.17, 0.93, 0.85, 0.85
3a	H	(1*R*,6*R*)	3.47(dd)		5.13(d)	4.86(t)	10.3(br s)	1.17, 0.97, 0.87, 0.86
2b	CH_3	(1*S*,6*S*)	3.45(dd)	3.43(dd)	5.11(d)	4.75(t)	10.1(br s)	1.14, 1.04, 0.91, 0.86, 0.86
3b	CH_3	(1*R*,6*R*)	3.48(ddd)	3.44(ddd)	5.11(d)	4.83(t)	10.2(br s)	1.12, 1.04, 0.94, 0.87, 0.86
2c	F	(1*S*,6*S*)	3.47(dd)		5.14(d)	4.83(t)	11.0(br s)	1.14, 1.05, 0.92, 0.81
3c	F	(1*R*,6*R*)	3.49(dd)		5.14(d)	4.83(t)	11.0(br s)	1.14, 1.05, 0.92, 0.81
1a	H		3.58(ddd)	3.52(ddd)	5.24(d)	5.01(t)	11.3(br s)	—
1b	CH_3		3.58(ddd)	3.53(ddd)	5.23(d)	5.02(t)	11.3(br s)	1.75(s)
1c	F		3.62(ddd)	3.56(ddd)	3.25(d)	5.15(t)	11.8(br s)	—

Table 4. Coupling Constants (J/Hz) for Furanosyl Moiety of Photoproducts **2a**—**2c** and **3a**—**3c** together with **1a**—**1c** at 23 °C in DMSO-d_6

	X	Bridge head	1′2′	1′2″	2′2″	2′3′	2″3′	3′4′	4′5′	4′5″	5′5″
2a	H	(1*S*,6*S*)	8.4	5.6	12.8	6.7	5.3	2.8	5.3	5.3	11.2
3a	H	(1*R*,6*R*)	8.1	6.5	—	5.2	3.2	2.3	4.8	4.8	—
2b	CH_3	(1*S*,6*S*)	8.8	5.6	12.6	6.1	2.8	2.6	5.2	5.2	—
3b	CH_3	(1*R*,6*R*)	8.4	6.4	12.8	4.8	3.1	2.4	4.5	4.5	11.4
2c	F	(1*S*,6*S*)	8.7	6.0	13.2	6.8	2.4	1.6	4.5	4.5	—
3c	F	(1*R*,6*R*)	8.3	6.3	—	4.4	4.4	1.7	4.6	4.6	—
1a	H		6.6	6.5	13.2	5.2	4.0	3.2	4.0	4.0	—
1b	CH_3		7.2	6.4	13.4	5.6	3.2	2.8	4.8	4.8	11.6
1c	H		6.8	6.8	—	4.8	4.8	4.0	3.6	3.6	11.2

Table 5. NOE Data (in %) of **2** and **3**

	X	Bridge head	C1-H→C2′-H	C1-H→ C1′-H	C1′-H→C4′-H	C3′-OH→C2″-H	C5′-H→C1′-H
2a	H	(1*S*,6*S*)	1.1	1.3	2.0	1.5	Absent
3a	H	(1*R*,6*R*)	1.5	1.2	a)	2.8	Absent
2b	CH_3	(1*S*,6*S*)	2.6	2.0	a)	2.2	Absent
3b	CH_3	(1*R*,6*R*)	2.7	3.7	2.4	1.2	Absent
2c	F	(1*S*,6*S*)	2.5	1.5	4.2	2.7	Absent
3c	F	(1*R*,6*R*)	1.6	1.5	2.5	2.5	Absent

a) NOE could not be measured because signals of C4′ overlapped on other ones.

of **1a**—**1c**. In each case, stereoselectivity, albeit not so great, was observed.

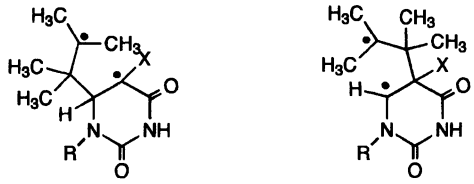
Finally, they were deacetylated in methanolic sodium methoxide to give the corresponding deprotected products. They were identical to **2a**—**2c** and **3a**—**3c** obtained by irradiation of **1a**—**1c**.

Discussion

Reaction Pathway. It is amply demonstrated that pyrimidine nucleosides proceed via the triplet excited state of the pyrimidine.[1] In the photoreaction of 1,3-dimethyl-2-butene and nucleosides **1**, irradiation in the absence of sensitizers with lines longer than 275 nm converted **1** into the photoadducts **2** and **3**. Triplet quenchers such as oxygen, 1,3-pentadiene, and 2,5-dimethyl-2,4-hexadiene significantly retarded this reaction rate (Table 1), but in the sensitized reaction of 1,3-dimethyl-2-butene and **1** in the presence of acetone or acetophenone, irradiation with lines longer than 304 nm, where neither nucleosides **1** nor 2,3-dimethyl-2-butene absorb significantly, converted **1** to the photoadducts **2** and **3**. This indicates that the triplet ex-

Table 6. Photocycloaddition of 3′,5′-Di-*O*-acetyl-2′-Deoxyuridines to 2,3-Dimethyl-2-butene in Acetone

	X	Time/h	Yield/%		2:3
			2	3	
1d	H	2.0	58	26	2.2 : 1.0
1e	CH_3	7.0	60	12	5.0 : 1.0
1f	F	0.8	72	23	3.1 : 1.0



Scheme 2.

cited states of **1** are undoubtedly major species of the reaction. In the sensitized reaction, a somewhat longer irradiation time was required for reaction of the **1b** than that of **1a**, though **1a** has a higher triplet energy (237.5 kJ mol^{-1}) than **1b** (219.9 kJ mol^{-1}).[16] This is due presumably to the steric hindrance of the methyl group at position 5 of **1b**. When position 5 is occupied by an electronic fluorine atom (**1c** and **1f**), a much shorter irradiation time was enough to comple the reaction (Table 1). This results clearly indicates that the reaction efficiency depends on the nature of the C–C double bond of **1** rather than difference in the triplet energy between **1** and the sensitizers. That is, electron-withdrawing fluorine atom increases the reactivity toward the electron-rich 2,3-dimethyl-2-butene. Because to our knowledge no data for the triplet energy are available for **1c** or 5-fluoroacil, we cannot analyze quantitatively the correlation of the difference in triplet energy between neucleosides and sensitizers vs. reactivity. Further work is required for the access to the detailed mechanism of this reaction. The measurement of quantum yield of the photoreaction and flash-photolytic analyses of **1** will be shortly described.

The Stereoselectivity. Variation in the ratio of **2** to **3** may be a reflection of the substituent effect on stereoselectivity. That is, in the case of **1b** and **1c**, the more stable tertiary biradical intermediate **4** would be predominant, as compared to the secondary biradical **5**, which would suffer from more steric hindrance from furanose. In the case of **1a**, both biradicals are secondary, so the attack of 2,3-dimethyl-2-butene would occur exclusively at the position 5 to **5**, which would not suffer so much steric hindrance from furanose, as compared to **4** (Scheme 2). In the case of 2′-deoxyuridine **1a**, little stereoselectivity was observed, but much more stereoselectivity was observed when its *O*-acetylated derivative **1d** was irradiated. This suggests that the di-*O*-acetylated furanoside also influences on the selectivity of the attack at position 5.

Conformation Study. The X ray crystallography (Fig. 2 and Table 7) provides us with an unambiguous picture of the torsion angle about the glycosyl bond. The dihedral angles are O4′–C1′–N2–C3: −121.4° (**3a**), −148.1° (**2b**); O4′–C1′–N2–C1: 54.2° (**3a**), 34.6° (**2b**). That is, both **3a** and **2b** in crystals are in the *ac* conformation; typical of pyrimidine nucleosides (Fig. 2). On the other hand, a similar magnitude of NOE in solution was observed not only between 1-CH and 2′-CH, but also between 1-CH and 1′-CH for six photoproducts (Table 5). If the *ac* conformation predominates in the solution as well as in crystals, NOE between 1-CH and 1′-CH would fail to be observed. This suggests that in the solution the *sc* and *ac* conformations equilibrate.

In crystals, the cyclobutane ring is not coplanar, but puckered with a dihedral angle defined by C6–C1–C8–C7: 11.6° for **3a**, −15.9° for **2b** (Table 7), which are more planar than those in diemthylthymidyl-thymidine (−27°)[18] and thymidyl (3′-5′-) thymidine cyanoethyl ester (−28°).[19] Saturation of the C5–C6 bonds of **1** leads to half-chair puckering of the pyrimidine bases. That is, for **3a** base, the N4–C5–C6–C1 portion defines a four-atom plane whose dihedral angle is 2.1°, from which N2 and C3 are deviated to the opposite direction. For **2b** base, N4–C3–N2–C1 portion defines a plane whose dihedral angle is 3.9°, from which C5 and C6 are deviated to the opposite direction (Table 7).

For the furanose, both for **3a** and for **2b** in crylstals the C1′–O4′–C7′–C3′ portion defines a four-atom plane whose dihedral angle is −7.2° for **3a** and 4.0° for **2b**, from which C2′ are deviated toward the pyrimidine ring. This shows that the sugar conformation of **3a** and **2b** in crylstals are in ^2E type, which agrees with the situation associated with thymidyl (3′-5-) thymi-

Table 7. A Summary of Dihedral Angle (degree)[a] in Photoproducts **3a** and **2b**

		3a	**2b**
Glycosyl bond	(O4′–C1′–N2–C3)	−121.4	−148.1
	(O4′–C1′–N2–C1)	54.2	34.6
Cyclobutane ring	(C6–C1–C8–C7)	11.6	−15.9
Saturated pyrimidine	(N4–C5–C6–C1)	2.1	
ring	(N2–C1–C6–C5)	−17.2	
	(C6–C5–N4–C3)	12.3	
	(N2–C3–N4–C5)		8.5
	(N4–C3–N2–C1)		3.9
	(C3–N2–C1–C6)		−21.7
Furanose	(C2′–C1′–O4′–C4′)	−17.6	
	(O4′–C4′–C3′–C2′)	29.0	16.2
	(C1′–O4′–C4′–C3′)	−7.2	
	(C3′–C4′–O4′–C1′)		4.0
	(C4′–O4′–C1′–C2′)		−22.7

a) The sign is positive if when looking from atom 2 to atom 3 a clockwise motion of atom 1 would superimpose it on atom 4.

dine cyanoethyl ester.[18] On the other hand, sugar conformations in solution can be deduced on the bases of coupling constants. The sum of $J_{1'2'}$ and $J_{3'4'}$ are roughly close to the typical value (10.8±0.4 Hz) for deoxyribonucleoside.[20] Thus, the proportion of these furanose conformers can be calculated by the method of Chen and Sarma.[21] The results are shown in Table 8. In solution, as well as in crystals, ^2E is predominant for all of six photoproducts. However NOEs between 1'-CH and 4'-CH were observed for all of six photoproducts (Table 5). This shows that the sugar puckering is ^4E for all of these six products. That is, though the predominant sugar conformation in solution is ^2E, the sugar is not fixed in one conformation in solution.

Table 8. Conformation and Population of Conformers for Sugar Moiety

	$J_{1'2'}+J_{3'4'}$	% ^2E[a]
2a(1*S*,6*S*)	11.2	74
3a(1*R*,6*R*)	10.3	79
2b(1*S*,6*S*)	11.4	76
3b(1*R*,6*R*)	10.8	78
2c(1*S*,6*S*)	10.4	85
3c(1*R*,6*R*)	10.4	84
dUrd	9.8	70
Thd	10.0	74
5-FdUrd	10.8	63

a) Calculated by using $J_{1'2'}+J_{3'4'}=10.8$ Hz.

Conclusion

Direct or sensitized photoreaction of 2'-deoxyuridine, thymidine, and 5-fluoro-2'-deoxyuridine with 2,3-dimethyl-2-butene was found to produce a pair of cyclobutane photoproducts. Their structures were identified on the basis of X-ray crystallographic analyses and NMR properties. From the triplet quenching experiment, the triplet excited state of nucleosides was proved to be the key intermediate. X-Ray crystallographic analyses showed that the predominant conformation of the photoproducts in crystals is of the *ac* type for the glycosyl bond of the half-chair type for the pyrimidine ring, and of the ^2E type for the furanose. An NMR study showed that the equilibrium is established among some conformations: *sc* and *ac* for glycosyl bonds and ^2E and ^4E for the furanose ring.

Experimental

Melting points were obtained on a Mitamura micro hot plate and are not corrected. ^{1}H NMR spectra were taken with a Varian UNITY 400 spectrometer in solvents, with tetramethylsilane as an internal reference. UV spectra were obtained on a Hitachi UV-vis 340 spectrophotometer. Low-resolution whole-molecule ion mass spectra were taken on a JMS-DX 300. High-resolution mass spectra were taken on a JMS AX 505 HA. Flash column chromatography was done on silica gel (Merck Art 9385 Kieselgel 60). Thin layer chromatography was done on silica gel (Merck Art 11696 TLC-Kieselgel 60 HF). Microanalyses were done in the microanalytical laboratory of our school.

Materials. Commercially available 2'-deoxyuridine (**1a**) and thymidine (**1b**) were used for photoreaction without purification.

2'-Deoxy-3',5'-di-*O*-acetyluridine (1d): A mixture of 2.28 g (10.0 mmol) of **1a** and 20.5 g (100 mmol, 5 equiv) of acetic anhydride in 20 ml of pyridine was stirred at ambient temperature for 22 h. The solvent was removed under reduced pressure to dryness and the residue was subsequently treated with 200 ml of dichloromethane and washed with 1 mol dm^{-3} HCl, then 1 mol dm^{-3} $NaHCO_3$, and finally brine. The organic phase was dried over magnesium sulfate and evaporated to give 92% **1d**. Recrystallization from ethyl acetate–hexane gave colorless plates, mp 109.0—111.0 °C. Anal. Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97%. Found: C, 49.74; H, 5.09; N, 8.88%. Electron ionization (EI)-MS *m/z* 312 (M^+). ^{1}H NMR ($CDCl_3$) δ=9.23 (s, 1H, 3-NH), 7.49 (d, 1H, *J*=8.1 Hz, 6-CH), 6.25 (dd, 1H, *J*=8.5, 6.0 Hz, 1'-CH), 5.78 (d, 1H, *J*=8.1 Hz, 6-CH), 5.21 (dt, 1H, *J*=6.0, 2.4 Hz, 3'-CH), 4.34 (dd, 1H, *J*=12.0, 4.8 Hz, 5'-CH), 4.30 (dd, 1H, *J*=12.0, 3.6 Hz, 5''-CH), 4.26 (ddd, 1H, *J*=4.8, 3.6, 2.4 Hz, 4'-CH), 2.53 (ddd, 1H, *J*=13.8, 6.0, 2.4 Hz, 2'-CH), 2.15 (ddd, 1H, *J*=13.8, 8.5, 6.0 Hz, 2''-CH), 2.11, 2.10 (each, s, 3H, 3',5'-OAc).

3',5'-Di-*O*-acetyltheymidine (1e): In a similar manner for **1a**, **1b** was acetylated to give 89% **1e**. Recrystallization from benzne gave colorless plates, mp 126.0—127.0 °C (lit,[12] 126.0—127.0 °C). Anal. Calcd for $C_{14}H_{18}N_2O_7$: C, 51.44; H, 5.49; N, 8.53%. Found: C, 51.53; H, 5.56; N, 8.59%. EI-MS *m/z* 326 (M^+). ^{1}H NMR ($CDCl_3$) δ=9.11 (br s, 1H, 4-NH), 7.27 (d, 1H, *J*=1.6 Hz, 6-CH), 6.33 (dd, 1H, *J*=8.4, 5.2 Hz, 1-CH), 5.21 (ddd, 1H, *J*=6.4, 2.0, 1.6 Hz, 3'-CH), 4.37 (dd, 1H, *J*=11.2, 4.0 Hz, 5'-CH), 4.33 (dd, 1H, *J*=11.2, 3.6 Hz, 5''-CH), 4.24 (ddd, 1H, *J*=4.0, 3.6, 1.6 Hz, 4'-CH), 2.46 (ddd, 1H, *J*=14.0, 5.2, 2.0 Hz, 2''-CH), 2.16 (ddd, 1H, *J*=14.0, 8.4, 6.4 Hz, 2'-CH), 2.13, 2.11 (each, s, 3H, 3',5'-OAc), 1.93 (d, 3H, *J*=1.6 Hz, 5-CCH_3).

2'-Deoxy-5-fluorouridine (1c) and 3',5'-Di-*O*-acetyl-5-fluorouridine (1f): They were prepared from 5-fluorouracil[13] as described by Brokes et al.[20] Spectral data are as follows;

1f: Recrystallized from ethanol. Colorless plates, mp 150.5—152.5 °C (lit,[14] 151.5—152.0 °C). Anal. Calcd for $C_{13}H_{15}FN_2O_7$: C, 47.28; H, 4.58; F, 5.75; N, 8.48%. Found: C, 47.11; H, 4.57; F, 5.75; N, 8.34%. Fast atom bombardment (FAB)-MS (*m*-nitrobenzylamine (*m*-NBA) as a matrix) *m/z* 331 (M^++H). ^{1}H NMR ($CDCl_3$) δ=8.8—8.9 (br s, 1H, 3-NH), 7.66 (d, 1H, *J*=6.4 Hz, 6-CH), 6.30 (ddd, 1H, *J*=8.0, 6.0, 1.6 Hz, 1'-CH), 5.22 (ddd, 1H, *J*=7.2, 5.6, 2.8 Hz, 3'-CH), 4.41 (dd, 1H, *J*=12.0, 4.0 Hz, 5'-H), 4.31 (dd, 1H, *J*=12.0, 3.6 Hz, 5''-CH), 4.27 (m, 1H, 4'-CH), 2.53 (ddd, 1H, *J*=14.4, 6.0, 2.8 Hz, 2'-CH), 2.14 (m, 1H, 2'-CH), 2.15, 2.13 (each s, 3H, 3',5'-OAc).

1c: Recrystallized from methanol. Colorless prisms, mp 142—143 °C. Anal. Calcd for $C_9H_{11}FN_2O_5$: C, 43.91; H, 4.50; F, 7.72; N, 11.38%. Found: C, 43.87; H, 4.51; F, 7.81; N, 11.31%. FAB-MS (*m*-NBA as a matrix) *m/z* 246 (M^++H). ^{1}H NMR (DMSO-d_6) δ=11.82 (br s, 1H, 3-NH), 8.21 (d, 1H, *J*=7.6 Hz, 6-CH), 6.12 (dt, 1H, *J*=6.8, 2.4 Hz, 1'-CH), 5.25 (d, 1H, *J*=4.4 Hz, 3'-OH), 5.15 (t, 1H, *J*=5.2 Hz, 5'-OH), 4.25 (dt, 1H, *J*=4.8, 4.0 Hz, 3'-CH), 3.78 (dt,

Table 9. Atomic Coordinates ($\times 10^4$) and Equivalent Temperature Factors (B_{eq}) of **3a**

Atom	x	y	z	B_{eq}
C1	0.7709(5)	0.1117(2)	0.2197(9)	3.2(3)
N2	0.8244(4)	0.0836(2)	0.0429(7)	3.1(2)
C3	0.7529(5)	0.0602(2)	−0.105(1)	3.1(2)
O1	0.7928(3)	0.0432(2)	−0.2636(6)	4.1(2)
N4	0.6233(4)	0.0565(2)	−0.0734(7)	3.1(2)
C5	0.5641(4)	0.0660(3)	0.102(1)	3.4(3)
O2	0.4529(3)	0.0535(2)	0.1195(7)	5.1(2)
C6	0.6357(5)	0.0941(2)	0.268(1)	3.3(3)
C7	0.6062(5)	0.1631(2)	0.316(1)	3.6(3)
C8	0.7348(5)	0.1815(2)	0.222(1)	3.8(3)
C9	0.6002(8)	0.1709(3)	0.540(1)	6.0(4)
C10	0.4875(6)	0.1909(3)	0.231(1)	5.5(3)
C11	0.8175(6)	0.2234(3)	0.346(1)	7.2(4)
C12	0.7223(7)	0.2083(3)	0.015(1)	5.5(4)
C1′	0.9587(5)	0.0756(3)	0.0265(9)	3.2(3)
C2′	1.0368(5)	0.1342(3)	0.026(1)	3.9(3)
C3′	1.1625(5)	0.1124(3)	0.099(1)	4.0(3)
O3′	1.2310(4)	0.0843(2)	−0.0549(7)	5.3(2)
C4′	1.1239(5)	0.0662(3)	0.260(1)	4.2(3)
O4′	1.0029(3)	0.0422(2)	0.1971(6)	3.8(2)
C5′	1.1065(7)	0.0958(4)	0.468(1)	5.9(4)
O5′	1.2191(5)	0.1163(3)	0.5381(8)	7.9(3)

Table 10. Atomic Coordinates ($\times 10^4$) and Equivalent Temperature Factors (B_{eq}) of **2b**

Atom	x	y	z	B_{eq}
C1	0.0417(5)	0.1233(3)	−0.0779(5)	2.8(2)
N2	0.0446(4)	0.1455(2)	0.0664(4)	3.0(2)
C3	0.0761(5)	0.2246(3)	0.1147(6)	3.4(3)
O1	0.0825(5)	0.2473(2)	0.2345(4)	4.9(2)
N4	0.0995(4)	0.2884(2)	0.0138(4)	3.4(2)
C5	0.0811(5)	0.2834(3)	−0.1236(6)	3.1(3)
O2	0.0985(4)	0.3474(2)	−0.1951(4)	4.2(2)
C6	0.302(5)	0.1996(3)	−0.1799(5)	2.9(2)
C7	0.1210(6)	0.1481(3)	−0.2778(6)	3.5(3)
C8	0.1567(5)	0.0893(3)	−0.1516(6)	3.3(3)
C9	0.1644(6)	−0.0078(3)	−0.1778(6)	4.7(3)
C10	0.2726(6)	0.1167(4)	−0.0799(7)	4.7(3)
C11	0.2242(6)	0.1976(4)	−0.3468(7)	5.2(3)
C12	0.0504(7)	0.0989(4)	−0.3902(7)	6.1(4)
C13	0.2242(6)	0.1976(4)	−0.3468(7)	5.2(3)
C1′	0.0067(5)	0.0815(3)	0.1702(5)	2.9(2)
C2′	−0.1296(5)	0.0766(3)	0.1873(6)	3.8(3)
C3′	−0.1527(5)	−0.0159(3)	0.2270(6)	3.3(3)
O3′	−0.1484(4)	−0.0311(2)	0.3715(4)	4.2(2)
C4′	−0.0488(5)	−0.0641(3)	0.1581(5)	2.9(2)
O4′	0.0425(3)	−0.0012(2)	0.1209(4)	3.1(2)
C5′	−0.0812(6)	−0.1160(3)	0.0341(6)	3.8(3)
O5′	−0.1431(4)	−0.0640(2)	−0.0645(4)	4.2(2)

1H, J=4.0 H, 3.6 Hz, 4′-CH), 3.62 (ddd, 1H, J=11.2, 5.6, 3.6 Hz, 5′-CH), 3.56 (ddd, 1H, J=11.2, 5.6, 3.6 Hz, 5″-CH), 2.10 (dd, 2H, J=6.8, 4.8 Hz, 2′,2″-CH). UV (MeCN) 265 (ε 6290), 207 nm (6050).

Photoreaction of 1a, 1b, and 1c with 2,3-Diemthyl-2-butene by Direct Irradiation. A general procedure was noted by use of the reaction of photoreaction of **1b** with 2,3-dimethyl-2-butene as a representative. After 30 min nitrogen bubbling before the irradiation, a solution of 365 mg (1.5 mmol) of **1b** and 1.26 g (15.0 mmol, 10 equiv) of 2,3-dimethyl-2-butene in acetonitrile (500 ml) was irradiated with a 400 W high-pressure mercury lamp with a 1.2 mm Pyrex filter. Throughout the irradiation, nitrogen bubbling was continued. Because the reaction proceeded sluggishly, irradiation was stopped after 36 h. The solvent was removed under reduced pressure to dryness and the residue was subsequently treated with 3 ml of hot hexane to remove nonpolar material. The pale yellow amorphous residue (480 mg) was flash chromatographed (eluent: chloroform–ethanol 7:1) to give 191 mg (39%) of a mixture consisted of **2b** and **3b** (R_f: 0.3), and 121 mg (50%) of **1b** (R_f: 0.15). A small amount of undefined materials were eluted and discarded. For **1a** and **1c**, irradiation was done similarly as shown in Table 1, (for experimental conditions, see below).

Table 11. Intramolecular Distances of **3a** Involving the Nonhydrogen Atoms

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
O2	C5	1.223(6)	C6	C1	1.528(7)
O1	C3	1.219(6)	C6	C7	1.564(7)
O4′	C1′	1.442(6)	C1	C8	1.562(7)
O4′	C4′	1.455(6)	C8	C7	1.563(8)
O5′	C5′	1.366(8)	C8	C12	1.522(9)
O3′	C3′	1.412(7)	C8	C11	1.518(8)
N4	C5	1.358(7)	C7	C10	1.517(8)
N4	C3	1.402(6)	C7	C9	1.523(9)
N2	C1	1.458(7)	C1′	C2′	1.520(7)
N2	C1′	1.447(6)	C3′	C4′	1.534(8)
C5	C6	1.489(8)	C4′	C5′	1.560(1)

Photoreaction of 1a, 1b, and 1c with 2,3-Dimethyl-2-butene by Acetone- or Acetophenone-Sensitized Excitation. A general procedure was noted by use of the reaction of photoreaction of **1a** with 2,3-dimethyl-2-butene as a representative. Before the irradiation, nitrogen gas was bubbled through the reaction. A solution of 343 mg (1.5 mmol) of **1a** and 1.26 g (15.0 mmol, 10 equiv) of 2,3-dimethyl-2-butene in acetone (or 0.01 mol dm^{-3} of acetophenone in acetonitrile) was irradiated with a 400 W high-pressure mercury lamp with a 2.0 mm Pyrex filter for period given in Table 2. Throughout the irradiation, nitrogen bubbling was continued. The solvent was removed under reduced pressure to dryness and the amorphous residue was treated with hot hexane to remove nonpolar material. The pale yellow gummy residue (630 mg) was flash chromatographed (solvent system: chloroform–ethanol 7:1) to give 370 mg of mixture of **2a** and **3a** as a pale yellow solid. Recrystallization from methanol–ethyl acetate afforded a first crop of **3a** as colorless prisms. For the reaction of **1b** and **1c**, irradiation was done similarly. The results are given in Table 2, (for experimental conditions, see below).

Photoreaction of 1d, 1e, and 1f with 2,3-Dimethyl-2-butene by Acetone-Sensitized Excitation. A general procedure was noted by use of the reaction of photoreaction of **1d** with 2,3-dimethyl-2-butene as a representative. A solution of 468 mg (1.5 mmol) of **1d** and 1.26 g (15 mmol, 10 equiv) of 2,3-dimethyl-2-butene in acetone was irradiated for 2.0 h through a Pyrex filter. (Before and throughout the

Table 12. Intramolecular Distances of **2b** Involving the Nonhydrogen Atoms

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
O3′	C3′	1.425(6)	C3′	C2′	1.504(6)
O5′	C5′	1.424(6)	C2′	C1′	1.514(7)
O4′	C4′	1.446(5)	C1	C6	1.546(7)
O4′	C1′	1.421(5)	C1	C8	1.548(7)
O1	C3	1.203(6)	C5	C6	1.515(7)
O2	C5	1.223(6)	C6	C13	1.515(8)
N2	C1′	1.474(6)	C6	C7	1.594(7)
N2	C1	1.445(6)	C7	C11	1.526(8)
N2	C3	1.354(6)	C7	C12	1.542(8)
N4	C3	1.414(6)	C7	C8	1.577(7)
N4	C5	1.352(7)	C8	C9	1.524(6)
C4′	C3′	1.522(7)	C8	C10	1.516(8)
C4′	C5′	1.491(7)			

time of the irradiation, nitrogen gas was bubbled into the reaction system.) The solvent was removed under reduced pressure to dryness and the residue was treated with hot hexane. A colorless amorphous residue obtained was flash chromatographed (eluent: ethyl acetate) to give 344g (58%) of **2a** and 154 mg (26%) of **3a** as a colorless oil. For the reaction of **1b** and **1c**, irradiation was done similarly.

(1*S*, 6*S*)-3′,5′-Di-*O*-acetyl-7,7,8,8-tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]-octane-3,5-dione (2d): Colorless oil. FAB-MS (*m*-NBA as a matrix) *m/z* 397 (M^++H), ^{1}H NMR ($CDCl_3$) δ=7.58 (br, s, 1H, 4-NH), 6.13 (dd, 1H, *J*=8.0, 6.8 Hz, 1′-CH), 5.12 (dt, 1H, *J*=6.4, 2.8 Hz, 3′-CH), 4.27 (dd, 1H, *J*=12.4, 4.0 Hz, 5′-CH), 4.23 (dd, 1H, *J*=12.4, 5.2 Hz, 5″-CH), 4.09 (ddd, 1H, *J*=5.2, 4.0, 2.8 Hz, 4′-CH), 3.88 (d,1H, *J*=9.6 Hz, 1-CH), 2.92 (d, 1H, *J*=9.6 Hz, 6-CH), 2.10, 2.09 (each s, 3H, OAc), 1.25, 1.01, 1.00, 0.96 (each s, 3H, 7,7,8,8-CH_3).

(1*R*, 6*R*)-3′,5′-Di-*O*-acetyl-7,7,8,8-tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo-[4.2.0]octane-3,5-dione (3d): Colorless oil. FAB-MS (*m*-NBA as a matrix) *m/z* 397 (M^++H). ^{1}H NMR ($CDCl_3$) δ=7.74 (br s, 1H, 4-NH), 6.26 (dd, 1H, *J*=9.2, 5.4 Hz, 1′-CH), 5.13 (dt, 1H, *J*=6.0, 2.2 Hz, 3′-H), 4.29 (dd, 1H, *J*=12.4, 5.2 Hz, 5′-CH), 4.22 (dd, 1H, *J*=12.0, 4.0 Hz, 5″-CH), 4.10 (ddd, 1H, *J*=5.2, 4.0, 2.2 Hz, 4′-CH), 4.08 (d, 1H, *J*=10.0 Hz, 1-CH), 2.96 (d, 1H, *J*=10.0 Hz, 6-CH), 2.11, 2.09 (each s, 3H, 3′,5′-OAc), 2.0—2.6 (m, 2H, 2′2″-CH), 1.28, 1.08, 1.01, 0.98 (each s, 3H, 7,7,8,8-CH_3).

(1*S*, 6*S*)-3′,5′-Di-*O*-acetyl-6,7,7,8,8-Pentamethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo-[4.2.0]octane-3,5-dione (2e): Cololress oil. FAB-MS (*m*-NBA as a matrix) *m/z* 411 (M^++H). ^{1}H NMR ($CDCl_3$) δ=7.69 (br s, 1H, 4-NH), 6.19 (dd, 1H, *J*=8.6, 5.7 Hz, 1′-CH), 5.10 (dt, 1H, *J*=6.0, 2.8 Hz, 3′-CH), 4.24 (d. 2H, *J*=4.2 Hz, 5′-CH_2), 4.08 (dt, 1H, *J*=4.5, 2.8 Hz, 4′-CH), 3.43 (s, 1H, 1-CH), 2.01—2.18 (m, 2H, 2′-2″-CH), 2.05, 2.04 (each s, 3H, OAc), 1.24, 1.05, 1.00, 0.96 (each s, 3H, 7,7,8, 8-CH_3).

(1*R*, 6*R*)-3′,5′-Di-*O*-acetyl-6,7,7,8,8-Pentamethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo-[4.2.0]octane-3,5-dione (3e): Colorless oil. FAB-MS (*m*-NBA as a matrix) *m/z* 411 (M^++H). ^{1}H NMR ($CDCl_3$) δ=7.54 (br s, 1H, 4′-NH), 6.24 (dd, 1H, *J*=9.2, 5.2 Hz, 1′-CH), 5.11 (dt, 1H, *J*=6.4, 2.4 Hz, 3′-CH), 4.33 (dd, 1H, *J*=12.4, 5.6 Hz, 5′-CH), 4.19 (dd, 1H, *J*=12.4, 4.4 Hz, 5″-CH), 4.08 (ddd, 1H,*J*=5.6, 4.4, 2.4 Hz, 4′-CH), 2.11, 2.10 (each s, 3H, 3′,5′-OAc), 1.28, 1.13, 1.05, 0.99 (each 3H, CH_3).

(1*S*, 6*S*)-3′,5′-Di-*O*-acetyl-6-fluoro-7,7,8,8-tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (2f): Colorless oil. FAB-MS (*m*-NBA as a matrix) *m/z* 415 (M^++H). ^{1}H NMR ($CDCl_3$) δ=7.66 (br s, 1H, 4-NH), 6.19 (dd, 1H, *J*=9.6, 5.2 Hz, 1′-CH), 5.14 (dt, 1H, *J*=6.8, 2.3 Hz, 3′-CH), 4.28 (d, 1H, *J*=4.4 Hz, 5′-CH), 4.27 (dt, 1H, *J*=4.4 Hz, 5″-CH), 4.15 (dt, 1H, *J*=4.4, 2.3 Hz, 4′-CH), 3.98 (d, 1H, *J*=22.4 Hz, 1-CH), 2.24 (ddd, 1H, *J*=13.6, 5.2, 1.2 Hz, 2′-CH), 2.05 (ddd, 1H, *J*=13.6, 5.2, 2.3 Hz, 2″-CH), 2.12, 2.10 (each s, 3H, 3′,5′-OAc), 1.22 (d, 1H, *J*=4.0 Hz, 7-CH_3), 1.07, 1.06, 0.95 (each s, 3H, 7,8,8-CH_3).

(1*R*, 6*R*)-3′,5′-Di-*O*-acetyl-6-fluoro-7,7,8,8-tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (3f): Colorless oil. FAB-MS (*m*-NBA as a matrix) *m/z* 415 (M^++H). ^{1}H NMR ($CDCl_3$) δ=8.05 (br s, 1H, 4-NH), 6.12 (dd, 1H, *J*=8.0, 6.1 Hz, 1′-CH), 5.16 (dt, 1H, *J*=6.8, 2.2 Hz, 3′-CH), 4.20—4.35 (m, 3H, 4′,5′,5″-CH), 4.13 (d, 1H, *J*=22.4 Hz, 1-CH), 2.38 (ddd, 1H, *J*=13.8, 8.0, 7.0 Hz, 2′-CH), 2.15 (ddd, 1H, *J*=13.8, 6.1, 5.6 Hz, 2″-CH), 2.11, 2.10 (each s, 3H, 3′,5′-OAc), 1.25 (d, 3H, *J*=4.0 Hz, 7-CH_3), 1.19, 1.16, 0.95 (each s, 3H, 7,8,8-CH_3).

Methanolysis of 2d—2f and 3d—3f. A solution of 340 mg (0.86 mmol) of **2d** and 330 mg of 28% sodium methoxide (1.72 mmol) in 5 ml of methanol was stirred at ambient temperature for one hour. The solution was neutralized with Dowex 50 (H^+) resin and filtered. The filtrate was concentrated to give **2a** quantitatively. Other diacetyl derivatives were deacetylated in a similar manner.

(1*S*, 6*S*)-7, 7, 8, 8-Tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (2a): Recrystallized methanol–ethyl acetate. High-resolution (HR) FAB-MS: Found: *m/z* 313.1774 (M^++H). Calcd for $C_{15}H_{23}FN_2O_5$: (M^++H), 313.1763. ^{1}H NMR: See Tables 3 and 4.

(1*R*, 6*R*)-7, 7, 8, 8-Tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (3a): Recrystallized methanol–ethyl acetate. Mp 178.0—179.0 °C. Colorless prisms. Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.69; H, 7.69; N, 8.98%. Found: C, 57.60; H, 7.78; N, 8.89%. FAB-MS (*m*-NBA) *m/z* 313 (M^++H). ^{1}H NMR: See Tables 3 and 4. UV (MeCN) 218 nm (ε 3010).

(1*S*, 6*S*)-6,7,7,8,8-Pentamethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (2b): Recrystallized methanol–ethyl acetate. Mp 222.0 °C. Colorless prisms. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.95; H, 8.04; N, 8.59%. Found: C, 58.93; H, 8.05; N, 8.52%. FAB-MS (*m*-NBA) *m/z* 327 (M^++H). ^{1}H NMR: See Tables 3 and 4. UV (MeCN) 219 nm (ε 3150).

(1*R*, 6*R*)-6,7,7,8,8-Pentamethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (3b): Recrystallized methanol–ethyl acetate. Mp 182.0—184.0 °C. Colorless prisms. Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.95; H, 8.04; N, 8.59%. Found: C, 58.84; H, 8.10; N, 8.50%. FAB-MS (*m*-NBA) *m/z* 327 (M^++H). ^{1}H NMR: See Tables 3 and 4.

(1*S*, 6*S*)-6-Fluoro-7,7,8,8-pentamethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-

Table 13. Intramolecular Bond Angles of **3a** Involving the Nonhydrogen Atoms

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C1′	O4′	C4′	110.1(4)	C7	C8	C12	113.1(5)
C5	N4	C3	125.6(5)	C7	C8	C11	116.2(6)
C1	N2	C3	122.7(4)	C12	C8	C11	109.1(6)
C1	N2	C1′	120.0(5)	C6	C7	C8	89.0(4)
C3	N2	C1′	117.2(5)	C6	C7	C10	118.0(5)
O2	C5	N4	120.2(6)	C6	C7	C9	108.7(5)
O2	C5	C6	121.0(6)	C8	C7	C10	118.6(5)
N4	C5	C6	118.8(4)	C8	C7	C9	114.3(6)
C5	C6	C1	115.2(5)	C10	C7	C9	107.3(6)
C5	C6	C7	116.4(5)	O4′	C1′	N2	108.8(5)
C1	C6	C7	89.7(4)	O4′	C1′	C2′	104.0(4)
N2	C1	C6	116.1(5)	N2	C1′	C2′	116.3(5)
N2	C1	C8	120.7(5)	C1′	C2′	C3′	103.0(4)
C6	C1	C8	90.4(4)	O3′	C3′	C2′	110.8(5)
O1	C3	N4	117.3(5)	O3′	C3′	C4′	112.2(5)
O1	C3	N2	124.9(5)	C2′	C3′	C4′	101.4(4)
N4	C3	N2	117.8(5)	O4′	C4′	C5′	107.7(5)
C1	C8	C12	112.4(5)	C3′	C4′	C5′	113.7(5)
C1	C8	C11	116.4(5)	O5′	C5′	C4′	110.2(6)

Table 14. Intramolecular Bond Angles of **2b** Involving the Nonhydrogen Atoms

Atom	Atom	Atom	Angle	Atom	Atom	Atom	Angle
C4′	O4′	C1′	109.4(4)	O2	C5	N4	119.5(5)
C1′	N2	C1	119.9(4)	O2	C5	C6	122.9(5)
C1′	N2	C3	116.2(4)	N4	C5	C6	117.4(5)
C1	N2	C3	123.9(4)	C1	C6	C5	112.9(4)
C3	N4	C5	128.2(5)	C1	C6	C13	117.1(4)
O4′	C4′	C3′	107.8(3)	C1	C6	C7	87.2(4)
O4′	C4′	C5′	115.9(5)	C5	C6	C7	114.2(4)
O3′	C3′	C4′	109.1(5)	C13	C6	C7	119.5(5)
O3′	C3′	C2′	113.8(4)	C6	C7	C11	118.8(4)
C4′	C3′	C2′	103.0(4)	C6	C7	C12	110.6(5)
C3′	C2′	C1′	104.1(4)	C6	C7	C8	88.9(4)
O4′	C1′	N2	107.1(4)	C11	C7	C12	108.2(5)
O4′	C1′	C2′	105.5(4)	C11	C7	C8	116.4(5)
N2	C1′	C2′	113.0(5)	C12	C7	C8	113.2(4)
O5′	C5′	C4′	110.9(4)	C1	C8	C7	87.7(4)
N2	C1	C6	116.3(4)	C1	C8	C9	117.2(5)
N2	C1	C8	120.8(5)	C1	C8	C10	112.5(4)
C6	C1	C8	91.7(4)	C7	C8	C9	116.8(5)
O1	C3	N2	124.8(5)	C7	C8	C10	114.0(5)
O1	C3	N4	119.4(5)	C9	C8	C10	107.8(5)
N2	C3	N4	115.8(5)				

3,5-dione (2c): Recrystallized ethyl acetate. Mp 188.0 °C. Colorless fibers. Anal. Calcd for $C_{15}H_{23}FN_2O_5$: C, 54.54; H, 7.02; F, 5.75; N, 8.48%. Found: C, 54.66; H, 7.07; F, 5.72; N, 8.29%. HRFAB-MS: Found: m/z 331.1640 ($M^+ + H$). Calcd for $C_{15}H_{23}FN_2O_5$:($M^+ + H$), 331.1670. ^{1}H NMR: See Tables 3 and 4. UV (MeCN) 222 nm (ε 2410).

(1*R*, 6*R*)-6-Fluoro-7,7,8,8-tetramethyl-2-(β-D-2-deoxyribofuranosyl)-*cis*-2,4-diazabicyclo[4.2.0]octane-3,5-dione (3c): Colorless amorphous. HRFAB-MS: $M^+ + 1 = m/z$ 331.1671. (Calcd for $C_{15}H_{23}FN_2O_5$: ($M^+ + 1$), 331.1670). ^{1}H NMR: See Tables 3 and 4.

Photoreaction of 1b with 2,3-Dimethyl-2-butene in the Presence of Triplet Quencher. A solution of 243 mg (1.0 mmol) of **1b**, 840 mg (10 mmol, 10 equiv) of 2,3-dimethyl-2-butene and 340 mg (5.0 mmol) of 1,3-pentadiene of 552 mg (5.0 mmol) of 2,5-dimethyl-2,4-hexadiene in acetonitrile was irradiated as described in the reaction by direct irradiation. When oxygen was used as a quencher, oxygen was bubbled throughout the irradiation. Removal of the solvent followed by isolation by flash chromatography afforded **1b** and/or **2** and **3**. The results are listed in Table 1.

X-Ray Crystallographic Analysis of 3a and 2b. A crystal having approximate dimensions of 0.2×0.4×0.4 mm (**3a**) and 0.2×0.4×0.3 mm (**2b**) were used for the analysis. The cell dimension and diffraction intensities were measured on a Rigaku AFC-5R diffractometer using graphite monochromated Cu $K\alpha$ radiation (λ=1.54178 Å) and a 12 kW rotaing anode generator at 23 °C. Crystal data are as

follows.

3a: Empirical formula; $C_{15}H_{24}O_5N_2$. Crystal system; orthorombic. Lattice parameters; $a=10.669(3)$, $b=21.690(2)$, $c=6.76(2)$ Å, $V=1564.4(5)$ Å^3. Space group; $P2_12_12_1$. Z value; 4. Density (calculated); 1.326 g cm^{-3}.

2b: Empirical formula; $C_{16}H_{26}O_5N_2$. Crystal system; orthorombic. Lattice paramers; $a=11.026(3)$, $b=15.453(2)$, $c=9.721(2)$ Å, $V=1656.2(5)$ Å^3. Space group; $P2_12_12_1$. Z value; 4. Density (calculated); 1.372 g cm^{-3}. The data were collected using of the ω–2θ scan technique in the range of $2\theta<140.1°$. Scans of $(1.57+0.30\tan\theta)°$ at a speed of 32.0° min^{-1} for **3a** and $(0.89+0.30\tan\theta)°$ by a speed 8.0° for **2b** were made. A total 1626 refelections for **3a** and 1809 reflactions for **2b** were collected for Lorents and polarization factors but not for absorption. The structure was elucidated by a direct method using TEXSAN.[15] The non-hydrogen atoms were refined anisotropically by the full-matrix least-squares refinement. A difference Fourier synthesis was calculated and the positions of all hydrogen atoms were found. Then they were refined isotropically. The final R value was 6.5% for **3a** and 5.7% for **2b**, where $R=\Sigma||F_o|-|F_c||/\Sigma|F_o|$. The final R_w value was 6.3% for **3a** and 5.4% for **2b**, where $R_w=[(\Sigma w(||F_o|-|F_c|)^2/\Sigma wF_o^2)]^{1/2}$. The final atomic parameters, bond length and bond angles for **3a** are given in Tables 9, 11, and 13, respectively. Also, those for **2b** are given in Tables 10, 12, and 14.

One of the authors (N.H.) is grateful to Dr.Yoshihisa Mizuno (professor emeritus of Hokkaido University)for revision of this manuscript and helpful discussions.

References

1) For reviews on photoreaction of nucleic acids, see : a) G. J. Fisher and H. E. Johns, "Photochemistry and Photobiology of Nucleic Acid," ed by S. Y. Wang, Academic Press, New York (1976), Vol. 1, pp. 225—294; b) J. Cadet, "Bioorganic Photochemistry," ed by H. Morrison, John Wiley & Sons, New York (1990), Vol. 1, pp. 1—272.

2) A. A. Lamola, *Pure Appl. Chem.*, **34**, 281 (1973).

3) A. J. Wexler, J. A. Hyatt, P. W. Raynolds, C. Cotrell, and J. S. Swenton, *J. Am. Chem. Soc.*, **100**, 512 (1978).

4) A. Wexler and J. S. Swenton, *J. Am. Chem. Soc.*, **98**, 1602 (1976).

5) A. J. Wexler, R. J. Balchunis, and J. S. Swenton, *J. Org. Chem.*, **49**, 2733 (1984).

6) C. Kaneko and N. Shimomura, *Tetrahedron Lett.*, **24**, 2571 (1982).

7) T. G. Savino, L. K. Chenard, and J. S. Swenton, *Tetrahedron Lett.*, **24**, 4055 (1983).

8) J. L. Charlton and H. K. Lai, *Can.J.Chem.*, **54**, 1445 (1976).

9) I. Ishikawa, T. Itoh, H. Takayanagi, J. Ohshima, N. Kawahara, Y. Mizuno, and H. Ogura, *Chem. Pharm. Bull.*, **38**(8), 1922 (1991).

10) N. Haga, I. Ishikawa, M. Kinumura, H. Takayanagi, and H. Ogura, *Heterocycles*, in press (1993).

11) Y. Honma, T. Ikuta, T. Kasukabe, M. Hozumi, T. Itoh, and H. Ogura, *Anticancer Res.*, **8**, 695 (1988).

12) P. T. Gilham and H. G. Khorama, *J. Am. Chem. Soc.*, **80**, 6212 (1958).

13) S. Mieno, M. Inomata, and F. Fukuoka, *Chem. Pharm. Bull.*, **26** (10), 2990 (1978).

14) J. Brokes, H. Hrebabecky, and J. Beranek, *Collect. Czech. Chem. Commun.*, **44**, 439 (1979).

15) TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).

16) A. A. Lamla, M. Gueron, T. Yamane, J. Eisignan, and R. G. Shulam, *J. Chem. Phy.*, **47**, 2210 (1967).

17) "Handbook of Photochemistry," ed by S. L. Murov, Marcel Dekker, Inc., New York (1973).

18) N. Camerman and A. Camerman, *J. Am. Chem. Soc.*, **92**, 2523 (1970).

19) J. Cadet, L. Voituriez, F. E. Hruska, and A. Grand, *Biopolymers*, **24**, 897 (1985).

20) L. Kan, L. Voituriez, and J. Cadet, *Biochemistry*, **27**, 5796 (1988).

21) D. M. Chen and R. H. Sarma, *J. Am. Chem. Soc.*, **99**, 7333 (1977).