this unit cell contained 2 molecules of composition $C_{19}H_{20}O_7$, a perfectly reasonable crystal density of 1.37 g/cm^3 would result. The space group could be either $P1$ or $P\bar{1}$, and the latter centrosymmetric choice was the correct one. All unique diffraction maxima with $2\theta < 114°$ were collected using graphite monochromated Cu K$\bar{\alpha}$ radiation and variable-speed, 1° in ω scans. Of the 2359 unique reflections surveyed in this manner, 1440 (61%) were judged observed [$F_o > 3\sigma(F_o)$].[4] A phasing model was found with the MULTAN series of programs, and the initial E synthesis revealed all of the non-hydrogen atoms. Hydrogens were located on a ΔF synthesis following partial refinement. Block-diagonal least-squares refinements with anisotropic nonhydrogen atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.0416 for the observed reflections. Additional crystallographic details can be found in the supplementary material.

Antimicrobial Activity. A standard in vitro disk (0.25 in.) bioassay was used to assess the antibacterial activity of the annulins. Activities are reported as minimum inhibitory concentrations (MIC) in μg/disk. *Staphylococcus aureus*: A (**3**), 31.5; B (**4**), 7.5. *Bacillus subtilis*: A (**3**), 6.3; B (**4**), 1.5.

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Registry No. **3**, 105335-73-7; **4**, 105335-74-8; **5**, 105335-75-9.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, interatomic angles, and torsional angles for annulin A (**3**) (5 pages). Ordering information is given on any current masthead page.

(4) All crystallographic calculations were done on a PRIME 9950 computer operated by the Cornell University Computing Facility. Principal programs employed: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN 80, and RANTAN 80, systems of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson synthesis) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. Declercq, and M. M. Woolfson, University of York, England, 1980; BLS78A, an aniostropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a locally modified crystalloggaphic illustration program by W. D. S. Motherwell, Cambridge Crystallographic Data Centre, 1978; BOND, a program to calculate molecular parameters and prepare tables written by K. Hiratsu and G. Van Duyne, Cornell University, 1985.

Photochemistry of 5- and 6-Iodouracils in the Presence of Allylsilanes and Alkenes. A Convenient Route to C5- and C6-Substituted Uracils[1]

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The photocoupling reaction of 5- and 6-iodouracil derivatives with allylsilanes and alkenes is presented. Irradiation of 5-iodouridine (**5**) and 5-iodo-2′-deoxyuridine (**6**) in the presence of allyltrimethylsilane in aqueous acetonitrile gave 5-allyluridine (**7**) and 5-allyl-2′-deoxyuridine (**8**), respectively. Irradiation of 6-iodo-1,3-dimethyluracil (**11**) in the presence of allylsilanes and alkyl-substituted olefins produced the corresponding C6-substituted uracil derivatives in good yields. 5-Fluoro-6-iodo-1,3-dimethyluracil (**12**) underwent a similar photocoupling reaction with allylsilanes and alkenes. The photocoupling reaction provides a convenient method for carbon–carbon bond formation at the C5 or C6 position of uracil derivatives. A radical addition mechanism has been proposed for this novel photocoupling reaction.

Synthetic methods for carbon–carbon bond formation at the C5 or C6 position of pyrimidine bases and nucleosides have become increasingly important in recent years because of a broad spectrum of biological activities of these derivatives.[2,3] The palladium-catalyzed coupling of alkenes[4] and alkynes[5] with 5-chloromercuri- or 5-iodouridine derivatives initially described by Bergstrom and co-workers has been widely used for the synthesis of C5-substituted uracil nucleosides with carbon functionalities.[3] Organolithium derivatives of pyrimidine bases and nucleosides have also been used for carbon–carbon bond formation at the C6 position of protected uridine derivatives.[3,6] A different approach utilizing a photochemical reaction as the key step has also been reported.[7,8] For example, photocycloadducts of 5-fluorouracil derivatives with alkenes were utilized for the preparation of C5-substituted uracil derivatives.[8]

In the course of our studies on the organic photochemistry of nucleic acid bases,[9] we recently demonstrated that photoaddition of alkenes and alkynes to 6-cyanouridine provides a useful route to C5-substituted uridines possessing functionalized side chains.[10] We have sought a

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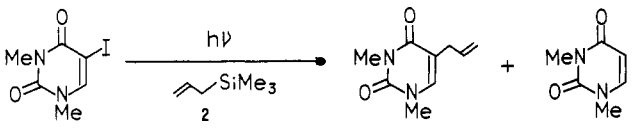
more convenient route to C5 and C6-substituted uracils, starting from readily available iodouracils and alkenes that would be regiospecific with respect to the position of the halogen substituents. Such photoreactions would also be of considerable importance for modification of nucleic acids and their monomeric units containing halogenated uracils. In the present paper we report a new type of photocoupling reaction of 5- and 6-iodouracil derivatives.[11] The scope and limitations of the photocoupling reaction are described.

Results and Discussion

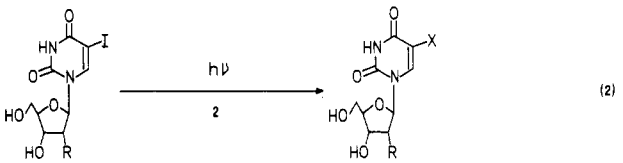
Photoreaction of 5- and 6-Iodouracil Derivatives with Allylsilanes. Mechanistically, the photochemistry of 5- and 6-iodouracil derivatives in the presence of allylsilanes is of special interest, since it provides useful information on the reactive species generated from their excited states. Allylsilanes are known to undergo electrophilic substitution with carbocations accompanied with allylic rearrangement and loss of the trimethylsilyl group,[12] whereas the photoinduced electron-transfer reaction with allylsilanes has been reported to provide the adduct of α-substitution with loss of the trimethylsilyl group as major product.[13] By contrast, the regiochemistry for free radical addition to allylsilanes has not been thoroughly investigated.[12,14] Thus it is conceivable that examination of photoproducts obtained in the photoreaction with substituted allylsilanes would serve as a mechanistic probe for reactive intermediates in the irradiation of iodouracil derivatives. In addition to such mechanistic interest, photoaddition to allylsilanes may provide a convenient method for regioselective carbon–carbon bond formation at the C5 or C6 position of uracil derivatives.

We first examined the photoreaction of 5-iodo-1,3-dimethyluracil (1) in the presence of allyltrimethylsilane (2). Irradiation of 1 in the presence of a large excess of 2 (15 equiv) in acetonitrile–water (10:1) with a high-pressure mercury lamp through a Pyrex filter gave 5-allyl-1,3-dimethyluracil (3) (40%) along with 4 (37%). When the



(1)

photoreaction was conducted in hydrogen-donating solvents such as alcohols or in the absence of 2 in aqueous acetonitrile, the only detectable photoproduct was the dehalogenated product 4. A similar irradiation of commercially available 5-iodouridine (5) and 2 (15 equiv) in acetonitrile–water (5:1) produced 5-allyluridine (7, 61%) together with 9 (30%). Essentially the same result was obtained in the irradiation of 5-iodo-2'-deoxyuridine (6) with 2. Thus the photocoupling reaction to allyltrimethylsilane provides an exceedingly facile route to synthetically useful 5-allyluridine derivatives and has following important features: (i) allylation of *unprotected* uridine can be accomplished in aqueous solvents under neutral

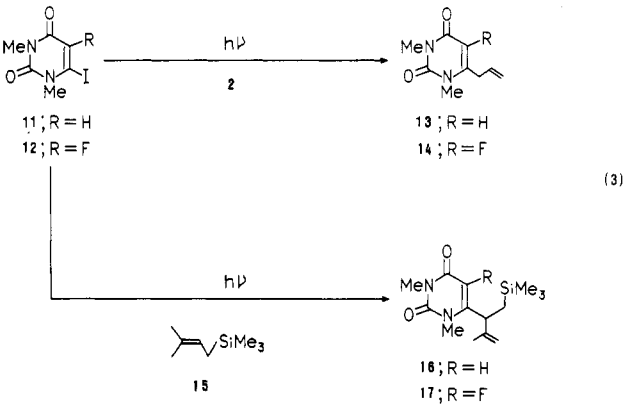


(2)

conditions; (ii) 5-allyluridines 7 and 8 thus formed are easily separable by passing through a short silica gel column due to the relatively high solubility of these products in alcoholic solvents, in contrast to the poor solubility of 9 and 10. However, various attempts to minimize the side reaction leading to the reduction products 9 and 10 have so far been fruitless.

We next turned our attention to the photochemistry of 6-iodouracil derivatives.[15] Among several methods available for transformation of uracil and uridine to C6-substituted analogues, lithiation at C6 with organolithium reagents such as lithium diisopropylamide (LDA) followed by quenching with nucleophiles provides a reliable method for the introduction of carbon substituents.[6] However, the 6-lithio derivative of uridine does not cleanly give the 6-monoallylated product, since the resulting 6-allyl derivative suffers further lithiation and hence further alkylation.[6] On the other hand, 6-iodo derivatives are readily available by the trapping of 6-lithio derivatives with iodine.[15] Irradiation of 6-iodo-1,3-dimethyluracil (11) and allyltrimethylsilane (2) in aqueous acetonitrile proceeded smoothly to result in a clean formation of 6-allyluracil derivative 13 (85%) as a single product, showing the superiority of the photocoupling method over the direct allylation of 6-lithio derivative.

In order to gain further insight into the regioselectivity of the photocoupling reaction, irradiation of 11 and 4-(trimethylsilyl)-2-methyl-2-butene (15) was examined under identical conditions. Unexpectedly, the adduct 16



(3)

coupled at the β position of 15 was formed in 53% yield together with the reduction product 4 (19%): no desilylated product could be detected. Apparently, the mode of adduct formation in the present photoreaction is different from that observed in usual thermal electrophilic substitution of 15. Essentially the same results were obtained in irradiation of 5-fluoro-6-iodo-1,3-dimethyluracil (12) with allylsilane 2 or 15. Again, the only isolable product in irradiation of 12 with 15 was 17 (58%) with no desilylated adduct being detected. The photoaddition

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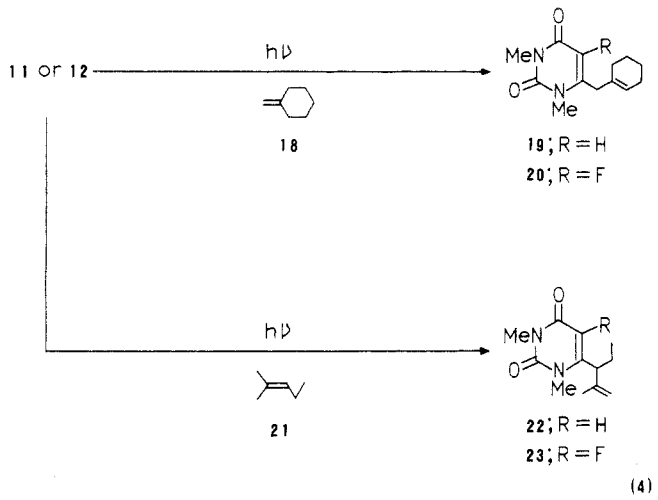
giving rise to **16** and **17** is formally analogous to a so-called ene-type reaction.

Photoreaction of 6-Iodouracil Derivatives with Alkenes. In order to know whether such an ene-like reaction occurs with other olefins, irradiation of **11** in the presence of a large excess of methylenecyclohexane (**18**) and 2-methyl-2-pentene (**21**) was carried out in aqueous acetonitrile under similar conditions. As shown in Eq 4, similar ene-type adducts **19** and **22** were formed in reasonable yields together with the reduction product **4** in both cases. More efficient photoaddition has been observed in irradiation of the 5-fluoro derivative **12** with these olefins. These results indicate that irradiation of 6-iodouracil derivatives (**11**, **12**) and alkyl-substituted olefins in aqueous acetonitrile results in a regiospecific formation of C6-substituted uracil derivatives with a shifted double bond accompanied with the elimination of hydroiodic acid. The formation of hydroiodic acid is apparent from the fact that the photolysate became slightly acidic during irradiation. To our knowledge, such an ene-like reaction with substituted olefins has been unprecedented in the photochemistry of organic halides.[16] Particularly, comparison with the results from 2-methyl-2-pentene (**21**) and the allylsilane **15** clearly indicates that both reactions proceed via a similar mechanism. Such an ene-type photoreaction of 6-iodouracil derivatives with alkyl-substituted olefins constitutes a simple method for the synthesis of C6-substituted uracil derivatives which are hardly accessible by other routes. Especially, 5-fluoro-6-alkyluracil derivatives such as **17**, **20**, and **23** are an intriguing class of compounds because of their potential biological activities. However, it should be mentioned here that irradiation of 6-iodouracils **11** and **12** with less substituted olefins such as



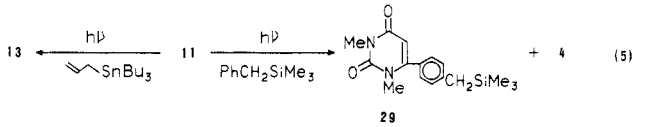
(4)

1-hexene or cyclohexene gave an intractable mixture of products including dehalogenated product.

Mechanistic Interpretation. As already described, irradiation of **11** with the allylsilane **15** gave the adduct retaining the trimethylsilyl group, namely **16**, exclusively. This is clearly different from the result expected from the intervention of carbocationic species. Carbocation **26**, if formed via electron transfer within an initially formed radical pair cage,[16] would give **28** upon reaction with allylsilane **15** (Scheme I, path b).[12] A mechanism involving electron transfer from **15** ($E_{1/2}^{ox}$ 1.07 V vs. Ag/Ag^+)[13a] to photoexcited **11** appears also possible (path c). In fact, such an electron-transfer process has been reported in the photoreaction of imminium salts[13a,b] and cyanoaromatics[13c] with allylsilanes. In these cases, however, the products of α- and/or γ-substitution are usually formed as a consequence of a single electron-transfer-desilylation process.[13] In the present case no indication of formation of **27** and **28** was observed. Thus the product formation is completely different from that expected from the electron-transfer mechanism.

A reasonable explanation for the formation of **16** is a radical addition mechanism (path a). Photoinduced homolysis of carbon–iodide bond of **11** would result in a formation of a radical-pair cage. 6-Uracilyl radical **24** thus formed would attack the less hindered site of the double bond of the allylsilane **15** to give the more stabilized tertiary radical **25** which then undergoes disproportionation with I· to furnish **16** and hydroiodic acid. Regioselectivity for the addition and the double-bond shift to the unconjugated system are consistent with this radical mechanism. Concomitant formation of **4** may be ascribed to the competitive hydrogen abstraction of the 6-uracilyl radical **24**.

In support of this radical mechanism irradiation of **11** and benzyltrimethylsilane produced a radical addition product **29** (26%) along with the reduction product **4** (46%): none of 6-benzyluracil derivative was detected. Neither carbocation **26** nor the electron-transfer mechanism can explain this result. In such cases the 6-benzyluracil derivative should be obtained.[13b,17] A similar radical addition reaction has already been noted in irradiation of **11** in the presence of radical acceptors such as benzene and *N*-alkylpyrroles.[18] Likewise, 6-uracilyl radical **24** would attack the double bond of allyltrimethylsilane (**2**) from the less hindered site to yield **30** (Scheme II). In this case two routes (paths a and b) are possible for the formation of **13**. Path a involves the elimination of $Me_3Si^\bullet$ to give **13** directly, whereas path b gives vinyl silane **31** as an initial product which then undergoes protodesilylation to **13** under slightly acidic aqueous conditions. However, the latter possibility was eliminated by the fact that irradiation of **11** and **2** in acetonitrile–D_2O gave none of the deuterated product **32**. The radical addition–elimination sequence has been postulated in one case for free radical addition to allylsilanes.[14] Interestingly, irradiation of **11** in the presence of allyltributyltin, a typical radical acceptor, under similar conditions resulted in a smooth formation of **13**



(5)

(80%) probably via a radical chain process. Free-radical addition to allyltributyltin via a chain process has been well documented.[19]

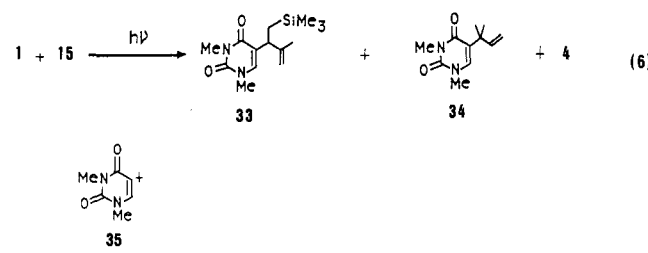
While further work is apparently necessary for full elucidation of the detailed mechanism of the photocoupling of 6-iodouracil to allylsilanes, available evidence is consistent with the radical addition mechanism. It is also conceivable that a similar radical process is involved in the photoreaction of 5-iodouracil derivative **1** with allyltrimethylsilane. In fact, irradiation of **1** and allylsilane **15** produced a similar radical addition product **33** (15%) together with **34** (27%) and **4** (46%). In this case, however, the formation of a considerable amount of **34** suggests the coexistence of an alternative pathway in competition to the radical process. Carbocation **35** formed via electron

(16) Kropp, P. J. *Acc. Chem. Res.* **1984**, *17*, 131, and references therein.

(17) Lan, A. J. Y.; Quillen, S. L.; Heuckeroth, R. O.; Mariano, P. S. *J. Am. Chem. Soc.* **1984**, *106*, 6439.

(18) Ikehira, H.; Matsuura, T.; Saito, I. *Tetrahedron Lett.* **1985**, *26*, 1743.

(19) For example: Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.



transfer within a radical pair cage[16] or an electron transfer from **15** to photoexcited **1**[20] may be responsible for the formation of **34**.

In summary, we demonstrated a novel ene-type photoreaction between 5- or 6-iodouracil derivatives and alkenes including allylsilanes. Such photocoupling reactions provide an exceedingly facile route to C5 and C6 alkyl-substituted uracil derivatives. A radical addition mechanism has been proposed for the photocoupling of 6-iodouracil derivatives to allylsilanes and alkenes.

Experimental Section

Melting points were determined on a Yanagimoto micro-melting-point apparatus and are uncorrected. Ultraviolet spectra were recorded with a Shimadzu UV-200 spectrometer. Infrared spectra were recorded on a JASCO IRA-1 spectrometer. ^{1}H NMR spectra were obtained on a Varian T-60 or FT-80A spectrometer employing Me_4Si as an internal standard. High-resolution mass spectra were obtained on a JEOL LMS-DX 300 spectrometer. Silica gel column chromatography was performed with Wako gel C-200. TLC was performed on Merck silica gel 60 PF_{254}. Irradiations were made with a 100-W high-pressure mercury lamp with the use of a Pyrex vessel fitted with a water-cooling jack at ambient temperature under nitrogen atmosphere, unless otherwise stated.

Preparation of 6-Iodo-1,3-dimethyluracil (11). To a stirred, cooled (−78 °C) solution of *n*-butyllithium (3.66 mL, 5.71 mmol) in hexane was added 0.84 mL (6.00 mmol) of diisopropylamine. The resulting solution of lithium diisopropylamide (LDA) was evaporated to dryness to give a white solid. Freshly distilled THF (10 mL) was added to the solid at −78 °C. To this solution was added dropwise a solution of 1,3-dimethyluracil (**4**)(400 mg, 2.86 mmol) in 10 mL of dry THF, and the mixture was stirred for 1 h at 0 °C. To a solution of iodine (1.52 g, 6.00 mmol) in 30 mL of dry DMF at −78 °C was added dropwise the THF solution of lithiated **4**. The mixture was stirred for 10 min at −78 °C and 1 h at room temperature. After the mixture was quenched with a saturated aqueous solution of ammonium chloride and the solvent evaporated, the residue was dissolved in 150 mL of ethyl acetate. The solution was washed successively with saturated aqueous sodium thiosulfate, water, and brine and dried over anhydrous magnesium sulfate. Silica gel column chromatography gave 295 mg (39%) of **11** and 291 mg (26%) of 5,6-diiodo-1,3-dimethyluracil by eluting with ethyl acetate–chloroform 10:1. **11**: mp 174 °C; ^{1}H NMR ($CDCl_3$) δ 3.29 (s, 3 H), 3.62 (s, 3 H), 6.47 (s, 1 H); IR (Nujol) 1630, 1150 cm^{-1}; UV (EtOH) λ_{max} 273 nm (ε 6890); exact mass calcd for $C_6H_7N_2O_2I$ 265.9555, found 265.9558. 5,6-Diiodo-1,3-dimethyluracil: mp 224–225 °C; ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 3 H), 3.90 (s, 3 H); UV (EtOH) λ_{max} 288 nm (ε 11200); exact mass calcd for $C_6H_6N_2O_2I_2$ 391.8522, found 391.8497.

Preparation of 5-Fluoro-6-iodo-1,3-dimethyluracil (12). To a solution of LDA (5.71 mmol) in THF (20 mL) was added dropwise a solution of 5-fluoro-1,3-dimethyluracil (81 mg, 2.86 mmol) in dry THF (10 mL) at −78 °C, and the mixture was stirred for 1 h at 0 °C. To a solution of iodine (1.52 g, 6.00 mmol) in dry DMF (10 mL) at −78 °C was added dropwise a THF solution of the lithiated 5-fluoro-1,3-dimethyluracil. The mixture was stirred for 10 min at −78 °C and 1 h at room temperature. Aqueous workup as described above followed by silica gel column chromatography (ethyl acetate–chloroform 20:1) gave 35 mg (43%) of **12**. **12**: ^{1}H NMR ($CDCl_3$) δ 3.37 (S, 3 H), 3.67 (s, 3 H), 3.67 (s, 3 H); UV (acetonitrile) λ_{max} 271 nm (ε 5860); exact mass calcd for $C_6H_6N_2O_2FI$ 283.9460, found 283.9451.

Irradiation of 5-Iodo-1,3-dimethyluracil (1) in the Presence of Allyltrimethylsilane (2). A solution of **1** (70 mg, 0.263 mmol) and **2** (0.63 mL, 3.95 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated with a 100-W high-pressure mercury lamp in Pyrex reaction vessel at ambient temperature under nitrogen for 10 h. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium thiosulfate and dried over anhydrous magnesium sulfate. Purification by preparative TLC (silica gel, ethyl acetate–chloroform 1:5) gave **3** (19 mg, 40%) and **4** (14 mg, 37%). **3**: ^{1}H NMR ($CDCl_3$) δ 3.10 (d, 2 H, J = 6 Hz), 3.40 (s, 6 H), 4.91–5.38 (m, 2 H), 5.60–6.06 (m, 1 H), 6.93 (s, 1 H); IR (neat) 1640, 1500, 1350 cm^{-1}; exact mass calcd for $C_9H_{12}N_2O_2$ 180.0898, found 180.0898.

Irradiation of 5-Iodouridine (5) in the Presence of Allyltrimethylsilane (2). A solution of **5** (70 mg, 0.19 mmol) and **2** (0.40 mL, 2.52 mmol) in acetonitrile–water (4:1, 200 mL) was irradiated with a 400-W high-pressure mercury lamp in a Pyrex reaction vessel as described above for 10 h. After removal of the solvent, the residue was chromatographed on silica gel with ethanol–ethyl acetate (1:10) to give **7** (33 mg, 61%) and **9** (14 mg, 30%). **7**: ^{1}H NMR (CD_3OD) δ 3.00 (d, 2 H, J = 6 Hz), 3.70–3.81 (m, 2 H), 3.90–4.10 (m, 1 H), 4.10–4.21 (m, 2 H), 4.85–5.22 (m, 2 H), 5.63–6.10 (m, 1 H), 5.82 (br s, 1 H), 7.75 (s, 1 H); IR (Nujol) 3500, 1690, 1300 cm^{-1}; exact mass calcd for $C_{12}H_{16}N_2O_6$ 284.1008, found 284.0996.

Irradiation of 5-Iodo-2′-deoxyuridine (6) in the Presence of Allyltrimethylsilane (2). A solution of **6** (70 mg, 0.20 mmol) and **2** (0.40 mL, 2.52 mmol) in acetonitrile–water (4:1, 200 mL) was irradiated under the same conditions as described above for 10 h. After removal of the solvent, the residue was chromatographed on a silica gel column with ethyl acetate to give **8** (26 mg, 49%) and **10** (14 mg, 31%). **8**: ^{1}H NMR (CD_3OD) δ 2.19–2.41 (m, 2 H), 3.09 (d, 2 H, J = 6 Hz), 3.70–3.85 (m, 2 H), 3.85–4.03 (m, 1 H), 4.03–4.55 (m, 1 H), 4.90–5.30 (m, 2 H), 5.50–6.00 (m, 1 H), 6.30 (t, 1 H, J = 6 Hz), 7.75 (s, 1 H); IR (Nujol) 3470, 1700, 1300 cm^{-1}; exact mass calcd for $C_{12}H_{16}N_2O_5$ 268.1063, found 268.1046.

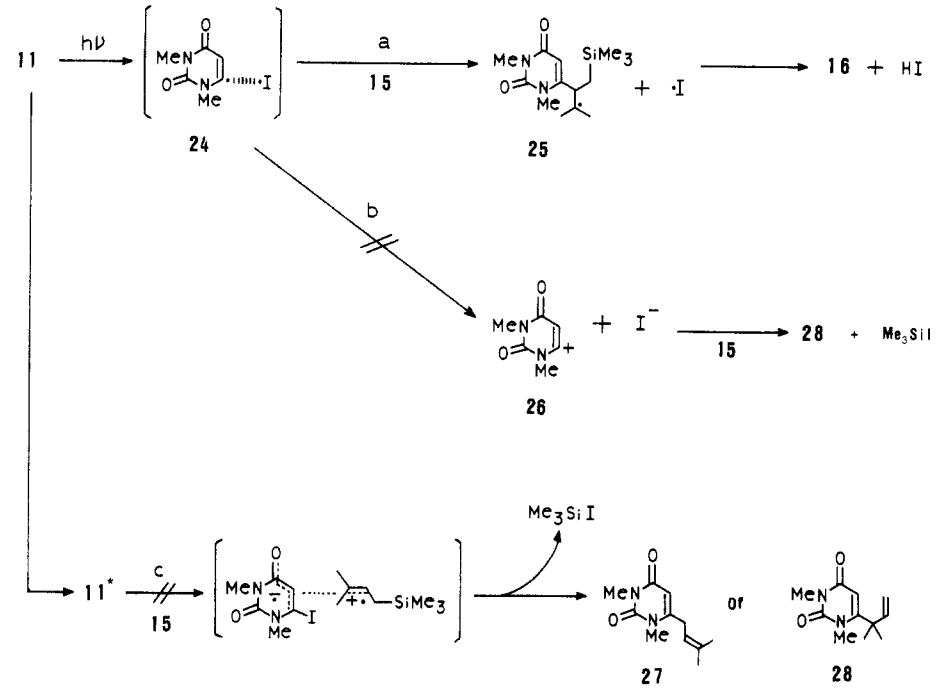
Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of Allyltrimethylsilane (2). A solution of **11** (70 mg, 0.26 mmol) and **2** (0.27 mL, 3.95 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated with a 100-W high-pressure mercury lamp under the standard conditions for 10 h. After removal of the solvent, the residue was extracted with ethyl acetate. The extract was washed with aqueous sodium thiosulfate solution and dried over anhydrous magnesium sulfate. Purification by preparative TLC (silica gel, ethyl acetate–chloroform 1:5) gave **13** (40 mg, 85%). **13**: ^{1}H NMR ($CDCl_3$) δ 3.23 (d, 2 H, J = 6 Hz), 3.31 (s, 3 H), 3.39 (s, 3 H), 4.93–5.35 (m, 2 H), 5.50–5.89 (m, 1 H), 5.55 (s, 1 H); IR (neat) 1700, 1650 cm^{-1}; exact mass calcd for $C_9H_{12}N_2O_2$ 180.0898, found 180.0897.

Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of 4-(Trimethylsilyl)-2-methyl-2-butene (15). A solution of **11** (70 mg, 0.26 mmol) and **15** (374 mg, 2.63 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated under the standard conditions for 10 h. After removal of the solvent, the residue was extracted with ethyl acetate. After being washed with aqueous sodium thiosulfate, the residue was purified by preparative TLC (silica gel, ethyl acetate–hexane 1:1) to give **16** (39 mg, 53%) and **4** (7 mg, 19%). **16**: ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 0.99 (d, 2 H, J = 7 Hz), 1.67 (s, 3 H), 3.18–3.47 (m, 1 H), 3.28 (s, 3 H), 3.39 (s, 3 H), 4.90 (d, 2 H, J = 6 Hz), 5.65 (s, 1 H); IR (neat) 1700, 1660, 1430 cm^{-1}; exact mass calcd for $C_{12}H_{24}N_2O_2Si$ 280.1607, found 280.1564.

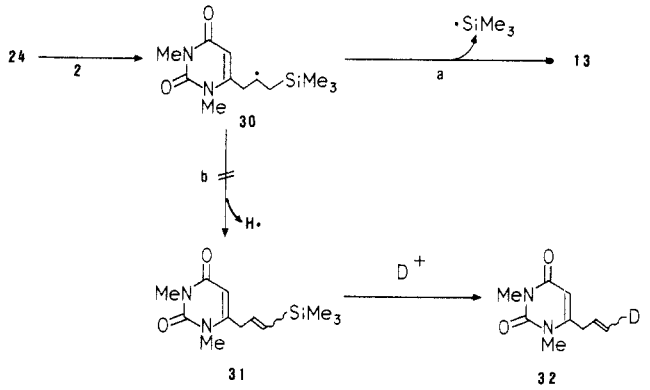
Irradiation of 5-Fluoro-6-iodo-1,3-dimethyluracil (12) in the Presence of Allyltrimethylsilane (2). A solution of **12** (71 mg, 0.25 mmol) and **2** (290 mg, 2.50 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 9 h. After removal of the solvent, the residue was dissolved in ethyl acetate. The extract was washed with aqueous sodium thiosulfate and dried over magnesium sulfate. The crude product was purified by preparative TLC (silica gel, ethyl acetate–chloroform 1:3) to give **14** (37 mg, 74%). **14**: ^{1}H NMR ($CDCl_3$) δ 3.30–3.53 (m, 2 H), 3.40 (s, 6 H), 5.10 (d, 1

(20) For a related electron-transfer with 5-bromouracil: (a) Ito, S.; Saito, I.; Matsuura, T. *J. Am. Chem. Soc.* **1980**, *102*, 7535. (b) Koch, T. H.; Swanson, B. J.; Kutzer, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 1274.

Scheme I



Scheme II



H, J = 10 Hz), 5.20–5.40 (m, 1 H), 5.50–6.00 (m, 1 H); IR (neat) 1700, 1640, 1360 cm^{-1}; exact mass calcd for $C_9H_{11}N_2O_2F$ 198.0805, found 198.0814.

Irradiation of 5-Fluoro-6-iodo-1,3-dimethyluracil (12) in the Presence of 4-(Trimethylsilyl)-2-methyl-2-butene (15). A solution of **12** (71 mg, 0.25 mmol) and **15** (355 mg, 2.50 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 9 h. A similar aqueous workup followed by evaporation of the solvent as described above gave a solid residue. Purification of the crude product by preparative TLC (silica gel, ethyl acetate–chloroform 1:5) gave **17** (43 mg, 58%). **17**: ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 1.00–1.33 (m, 2 H), 1.70 (br s, 3 H), 3.34 (s, 6 H), 3.60–4.00 (m, 1 H), 4.86–5.07 (m, 2 H); IR (neat) 1700, 1650, 1480 cm^{-1}; exact mass calcd. for $C_{14}H_{23}N_2O_2FSi$ 298.1512, found 298.1508.

Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of Methylenecyclohexane (18). A solution of **11** (70 mg, 0.26 mmol) and **18** (252 mg, 2.63 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 10 h. A similar aqueous workup followed by preparative TLC gave **19** (30 mg, 49%). **19**: ^1H NMR δ 1.40–1.77 (m, 4 H), 1.77–2.21 (m, 4 H), 3.05 (br s, 2 H), 3.30 (s, 3 H), 3.33 (s, 3 H), 5.32–5.60 (m, 1 H), 5.57 (s, 1 H); IR (neat) 1700, 1440 cm^{-1}; exact mass calcd for $C_{13}H_{18}N_2O_2$ 234.1367, found 234.1348.

Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of 2-Methyl-2-pentene (21). A solution of **11** (70 mg, 0.26 mmol) and **21** (220 mg, 2.63 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 10 h. A similar aqueous workup followed by preparative TLC gave **22** (19 mg, 33%). **22**: ^1H NMR δ 1.02 (t, 3 H, J = 6 Hz), 1.50–2.01 (m, 2 H), 1.75 (s, 3 H), 3.12 t, 1 H, J = 6 Hz), 3.33 (s, 3 H), 3.42 (s, 3 H), 4.86 (br s, 1 H), 5.00 (br s, 1 H), 5.67 (s, 1 H); IR (neat) 1700, 1650, 1440 cm^{-1}; exact mass calcd for $C_{12}H_{18}N_2O_2$ 222.1369, found 222.1386.

Irradiation of 5-Fluoro-6-iodo-1,3-dimethyluracil (12) in the Presence of Methylenecyclohexane (18). A solution of **12** (71 mg, 0.25 mmol) and **18** (240 mg, 2.50 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 9 h. Aqueous workup followed by preparative TLC gave **20** (43 mg, 68%). **20**: ^1H NMR ($CDCl_3$) δ 1.50–1.79 (m, 4 H), 1.79–2.16 (m, 4 H), 3.20–3.50 (m, 2 H), 3.37 (s, 6 H), 5.37–5.60 (m, 1 H); IR (neat) 1700, 1660, 1360 cm^{-1}; exact mass calcd for $C_{13}H_{17}N_2O_2F$ 252.1275, found 252.1300.

Irradiation of 5-Fluoro-6-iodo-1,3-dimethyluracil (12) in the Presence of 2-Methyl-2-pentene (21). A solution of **12** (71 mg, 0.25 mmol) and **21** (210 mg, 2.50 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 9 h. Aqueous workup followed by preparative TLC (silica gel, ethyl acetate–chloroform 1:5) gave **23** (32 mg, 54%). **23**: ^1H NMR δ 0.97 (t, 3 H, J = 7 Hz), 1.61–2.00 (m, 2 H), 1.77 (br s, 3 H), 3.40 (s, 6 H), 3.40–3.75 (m, 1 H), 4.90–5.12 (m, 2 H); IR (neat) 1700, 1650, 1480 cm^{-1}; exact mass calcd for $C_{12}H_{17}N_2O_2F$ 240.1273, found 240.1251.

Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of Benzyltrimethylsilane. A solution of **11** (70 mg, 0.26 mmol) and benzyltrimethylsilane (431 mg, 2.63 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated for 10 h under the standard conditions. After removal of the solvent, the residue was dissolved in ethyl acetate. After being washed with aqueous sodium thiosulfate, the residue was purified by preparative TLC (silica gel, ethyl acetate) to give **29** (21 mg, 26%) and **4** (13 mg, 46%). **29**: ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H), 2.14 (s, 2 H), 3.21 (s, 3 H), 3.40 (s, 3 H), 5.68 (s, 1 H), 6.98–7.40 (m, 4 H); IR ($CHCl_3$) 1700, 1660, 1440 cm^{-1}; exact mass calcd for $C_{16}H_{22}N_2O_2Si$ 302.1449, found 302.1425.

Irradiation of 6-Iodo-1,3-dimethyluracil (11) in the Presence of Allyltributyltin. An emulsion of **11** (70 mg, 0.26 mmol) and allyltributyltin (1.30 g, 3.95 mmol) in acetonitrile–water (10:1, 100 mL) was irradiated under the standard conditions for 10 h. After removal of the solvent, the residue was extracted with ethyl acetate. The extract was washed with aqueous solution of sodium thiosulfate and dried over anhydrous magnesium sulfate. Purification of the residue by preparative TLC (silica gel, ethyl acetate–chloroform 1:5) gave **13** (38 mg, 80%).

Irradiation of 5-Iodo-1,3-dimethyluracil (1) in the Presence of 4-(Trimethylsilyl)-2-methyl-2-butene (15). A solution of **1** (70 mg, 0.26 mmol) and **15** (374 mg, 2.63 mmol) in acetonitrile–water (10:1, 60 mL) was irradiated under the standard conditions for 10 h. Aqueous workup followed by preparative TLC (silica gel, ethyl acetate–hexane 1:2) gave **33** (11 mg, 15%), **34** (15

mg, 27%), and 4 (17 mg, 46%). **33**: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 1.27 (d, 2 H, J = 9 Hz), 1.60 (s, 3 H), 3.27 (s, 3 H), 3.30 (s, 3 H), 3.10–3.22 (m, 1 H), 4.74–4.90 (m, 2 H), 6.80 (s, 1 H); IR (neat) 1700, 1660, 1450 cm^{-1}; exact mass calcd for $C_{14}H_{24}N_2O_2Si$ 280.1606, found 280.1599. **34**: ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6 H), 3.30 (s, 3 H), 3.36 (s, 3 H), 5.00 (d, 1 H, J = 17 Hz), 5.03 (d, 1 H, J = 9 Hz), 6.04 (dd, 1 H, J = 9, 17 Hz), 6.92 (s, 1 H); IR (neat) 1700, 1650, 1350 cm^{-1}; exact mass calcd for $C_{11}H_{16}N_2O_2$ 208.1211, found 208.1201.

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Registry No. **1**, 40738-83-8; **2**, 762-72-1; **3**, 105183-69-5; **4**, 874-14-6; **4** (5-fluoro), 3013-92-1; **5**, 1024-99-3; **6**, 54-42-2; **7**, 59240-49-2; **8**, 73-39-2; **9**, 58-96-8; **10**, 951-78-0; **11**, 21428-19-3; **11** (R = I), 21418-68-8; **12**, 105183-68-4; **13**, 99044-61-8; **14**, 105183-70-8; **15**, 18293-99-7; **16**, 99044-62-9; **17**, 105183-76-4; **18**, 1192-37-6; **19**, 105183-71-9; **20**, 105183-73-1; **21**, 625-27-4; **22**, 105183-72-0; **23**, 105183-74-2; **29**, 105183-75-3; **33**, 99044-64-1; **34**, 99044-63-0; $PhCH_2SiMe_3$, 770-09-2; $(Me(CH_2)_3)_3SnCH_2CH{=}CH_2$, 24850-33-7.

Preparation of β,β-Dialkyl Analogues of Cysteine Suitable for Peptide Synthesis

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A general method is described for the preparation of cysteine derivatives that are substituted with one or two alkyl groups at the β-carbon. The synthesis is based on the sulfenylation of N^{α}-formyl-α,β-dehydro amino acid esters. The protected dehydro esters were synthesized by the condensation of ethyl isocyanoacetate with a ketone. The sulfenylation of these compounds was accomplished by refluxing with phosphorus pentasulfide to form the intermediate thiazoline, which can be hydrolyzed to the hydrochloride salt of the free sulfhydryl amino acid by heating in acid. The free sulfhydryl amino acid salt was protected as the *S*-*p*-methylbenzyl thioether, isolated as the zwitterion. The S-protected amino acids were then protected as the N^{α}-*tert*-butyloxycarbonyl derivatives and are suitable for use in solution- or solid-phase peptide synthesis.

Peptides comprise a large class of biologically active molecules, which, until recently, have been difficult to prepare synthetically. Within the past several years, advances in the chemistry of both solid- and solution-phase peptide synthesis have greatly facilitated the preparation of specific peptide analogues.[1] Additionally, rational design of peptide hormones to possess specific biological properties (i.e., increased potency, prolonged activity, antagonism, and receptor specificity) is now feasible.[2,3] Since peptide hormones are generally highly flexible molecules, with a myriad of possible conformations—of which only one or a limited number may be responsible for the observed biological response—it is often necessary to reduce the number of possible conformations in order to induce a specific biological response or property.

For the past several years, we have attempted to design "biologically specific" peptide hormones through conformational restriction of the mobility of the molecule (e.g., side-chain or backbone restriction). Specific examples of conformational restriction include the substitution of nonproteinogenic rigid or semirigid amino acids into a peptide hormone[4] and cyclization of a peptide, either between individual side chains[5] or between the N- and the C-terminus.[6] In general, for an amino acid substitution to impart significant conformational constraint on a peptide, the amino acid itself must be conformationally restricted. This approach has been expanded upon and employed in our laboratory for the preparation of conformationally restricted disulfide-linked peptides by the substitution of β,β-dimethylcysteine (penicillamine) for cysteine in enkephalin,[7] somatostatin,[8] and oxytocin.[9] Specifically in enkephalin, this substitution led to the preparation of a receptor-specific peptide hormone, [D-Pen^2,D-Pen^5]enkephalin (DPDPE), the most δ-selective enkephalin agonist known.[7] In this molecule, conformational restriction is induced by disulfide bond formation between the penicillamine (β,β-dimethylcysteine) residues in positions 2 and 5 and by the geminal dimethyl groups. This method of conformational restriction has also been used in fragments of somatostatin to prepare analogues that exhibit a high degree of antagonistic activity at the μ opioid receptor.[8] As part of an investigation aimed at preparing more highly constrained sulfur amino acids for incorporation into peptide hormones, we report a general and relatively simple synthesis of nonproteinogenic β,β-disubstituted sulfur amino acids. These amino acids have been subsequently orthogonally protected at the α amine and the sulfur functionalities, such that they are suitable

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