***cis*-3-Ethoxy-3-(trifluoromethyl)-5-phenyl-1,2,4-trioxolane (*cis*-7f)**: mp 66–68 °C; ^{1}H NMR δ 1.34 (t, J = 7.10 Hz, 3 H), 4.06 (qm, J = 7.81 and 2.26 Hz, 2 H), 6.42 (s, 1 H), 7.37–7.64 (m, 5 H); ^{13}C NMR (at −10 °C) δ 14.61 (qt, J = 127.5 and 2.8 Hz), 59.83 (tq, J = 146.2 and 4.5 Hz), 106.72 (dt, J = 176.7 and 4.5 Hz), 114.72 (q, J = 36.8 Hz), 119.83 (q, J = 286.9 Hz), 128.52 (t, J = 7.3 Hz), 128.90 (dd, J = 162.4 and 7.2 Hz), 128.38 (d, J = 163.0 Hz), 131.69 (dt, J = 161.3 and 7.3 Hz).

Reduction of Ozonide 7f. Solutions containing 40 mg of either *cis*-7f or *trans*-7f in 0.3 mL of $CDCl_3$ were admixed with 0.1 mL of $CDCl_3$ solutions containing triphenylphosphine and kept in an NMR tube at rt for 15 h and 2 d, respectively. ^{1}H NMR analysis showed in each case the presence of **6b** (δ 1.37, t, J = 7.15 Hz; 4.39, q, J = 7.16 Hz) and of benzaldehyde (**9**) (δ 10.03, s) in a molar ratio of ca. 1:1.

(b) Ozonolysis in Pentane. A solution of 1.18 g (5.46 mmol) of **11a** in 80 mL of pentane was ozonized at −75 °C. The solvent was evaporated at rt and 13 Torr to leave 1.1 g of a residue. ^{1}H NMR analysis showed the presence of 10% of *cis*-7f (δ 6.32, s), 74% of *trans*-7f (δ 6.42, s), 8% of *cis*-10 (δ 6.33, s), and 8% of *trans*-10 (δ 6.36, s). Separation by column chromatography (conditions as above) gave 14 mg (1%) of *cis*-7f, 145 mg (10%) of *trans*-7f, and 84 mg of a mixture consisting of *cis*-7f, *cis*-10, and *trans*-10 in a ratio of 1:4:5.

Ozonolysis of 11b. (a) Ozonolysis on Polyethylene. A 0.30-g (1.67-mmol) sample of **11b**[11] on 24 g of polyethylene was ozonized at −75 °C for 2 h, and the products were worked up as described above for **11a** to leave 190 mg of a residue. ^{1}H NMR analysis showed the presence of **12** (65%, δ 4.85, d, J = 47.11 Hz), **9** (23%; δ 10.02, s), and benzoic acid (12%).

(b) Ozonolysis in Pentane. A solution of 150 mg (0.83 mmol) of **11b** in 40 mL of pentane was ozonized at −75 °C, and the product was worked up as described above for **11a** to leave 127 mg of a residue. ^{1}H NMR analysis showed the presence of **12** (65%), *cis*-**10** (10%), *trans*-**10** (12%), **13** (8%; δ 6.93, s) and **9** (5%). Separation by column chromatography (column 3 × 60 cm; 20 g of silica gel; pentane/ether, 20:1) gave 42.4 mg (48%) of **12** (δ 1.32, t, J = 7.15 Hz, 3 H; 4.29, q, J = 7.15 Hz, 2 H; 4.85, d, J = 47.11 Hz, 2 H), 25 mg (13%) of a 3:7 mixture of *cis*-**10** (δ 6.33, s) and *trans*-**10** (δ 6.36, s), 6 mg (3%) of **13** (mp 201–202 °C; δ 6.93, s, 2 H; 7.40–7.54, m, 10 H), and 3 mg (4%) of **9** (δ 7.47–7.67, m, 3 H; 7.88–7.90, m, 2 H; 10.02, s, 1 H).

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Registry No. **1a**, 109-92-2; **1b**, 4747-15-3; **1c**, 66051-10-3; **1d**, 120872-41-5; **1e**, 19096-89-0; **4a**, 90150-47-3; **5a**, 97674-27-6; **6a**, 431-47-0; **6b**, 383-63-1; **6c**, 598-99-2; **7a**, 140928-35-4; **7b** (isomer 1), 140928-36-5; **7b** (isomer 2), 140928-44-5; **7c**, 140928-37-6; **7d**, 140928-38-7; **7f**-*trans*, 140928-39-8; **7f**-*cis*, 140928-40-1; **7a** (isomer 1), 140928-41-2; **7a** (isomer 2), 140928-45-6; **7h**, 140928-42-3; **7i**, 140928-43-4; **8**, 183-84-6; **9**, 100-52-7; *cis*-**10**, 21072-45-7; *trans*-**10**, 21072-46-8; **11a**, 5942-75-6; **11b**, 6043-54-5; **12**, 459-72-3; **13**, 16204-37-8; $PhCO_2H$, 65-85-0.

Asymmetric Type-II Photocyclization of Acrylylureas

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Type-II photocyclization is an important and well-studied photochemical reaction.[1] An asymmetric version of this type of reaction in the crystalline state is quite remarkable.[2] Yet in solution, there has been no conclusive results on asymmetric type-II cyclization. Some preliminary investigations on asymmetric type-II photocyclization of chiral ketones bearing asymmetric centers on γ-positions were carried out in solution.[3]

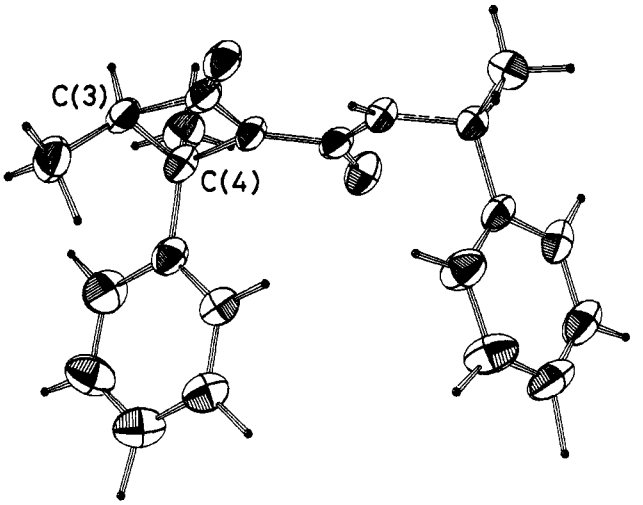

Figure 1. ORTEP view of **2a**.

In order to have a better understanding of the mechanism of type-II photocyclization in solution, and also to achieve a complete retention of the original configuration of the γ-carbon atom after cyclization, we designed photocyclization of acrylylureas **1a–11**[4] bearing two chiral (1-phenylethyl)amino groups. One of the chiral centers connected to the imido nitrogen atom is for the reaction site, the attached hydrogen to this chiral center will be abstracted by the excited enone double bond, and the remaining chiral 1-phenylethylamino group is for determination of the absolute configuration of the photoproducts.

As reported for α,β-unsaturated amides, photocyclization gave 2-azetidinones.[5] The cyclization was efficiently sensitized by benzophenone or *p*-methoxyacetophenone in benzene externally irradiated in a Pyrex test tube by a 450-W high-pressure mercury lamp under bubbling of

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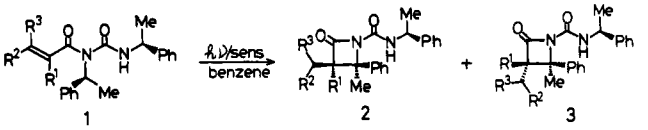
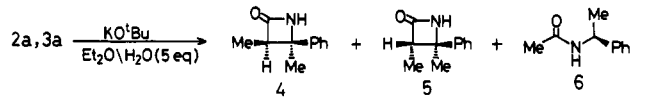
argon. Irradiation of **1a** for 4 h with 1 equiv of benzophenone afforded 2-azetidinones **2a** and **3a** (80%) as a 3:2 diastereomeric mixture which was separated by preparative HPLC. In the absence of sensitizer, no reaction was observed. Similarly, benzophenone-sensitized photocyclization of **1b** gave **2b** (81%) as a single diastereomer.



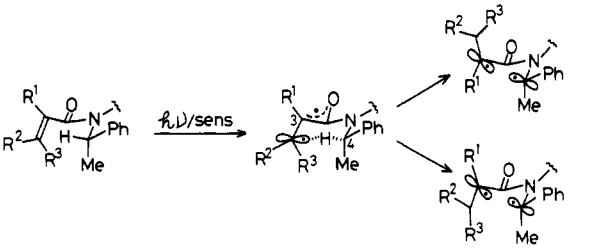
Single-crystal X-ray diffraction analysis of **2a**[6] established the relative configuration of three asymmetric carbon atoms to be either 3*R*, 4*R*, and (*S*)-(1-phenylethyl)carbamoyl or 3*S*, 4*S*, and (*R*)-(1-phenylethyl)carbamoyl because there would be a possibility of epimerization on a carbamoyl moiety by hydrogen abstraction. Therefore we decided to hydrolyze **2a** to confirm the stereochemistry of the carbamoyl moiety which was a marker to indicate the configuration of the other asymmetric carbon atoms. The hydrolysis was carried out in ether with 10 equiv of KO^{t}Bu and 5 equiv of H_2O.[7] Since *N*-acetyl-1-phenylethylamine[8] (**6**, 15%) derived from the acetylation of the hydrolyzed amine showed an agreeable $[\alpha]_D$ value to that corresponding to the *S*-configuration, the carbamoyl moeity remained intact during the photoreaction. Consequently, the three asymmetric carbon atoms of **2a** were determined to be 3*R*, 4*R*, and (*S*)-(1-phenylethyl)carbamoyl. Due to an epimerization at C(3), two epimeric 2-azetidinones **4** (11%) and **5** (16%) were also obtained as hydrolysis products.

Assignments of C(3) configurations of **4** and **5** were based on the ^{1}H NMR chemical shifts of C(3) methyl groups. An upfield shift for C(3) methyl of **4** suggests that it is syn to the phenyl group. Hydrolysis of **3a** and subsequent acetylation gave **6** (26%) together with **4** (19%) and **5** (17%). The results indicated that **3a** was epimeric to **2a** at C(3), and its absolute configuration was assigned as 3*S*, 4*R*, and (*S*)-(1-phenylethyl)carbamoyl, accordingly. Similar hydrolysis of **2b** revealed that it had the (*S*)-(1-phenylethyl)carbamoyl group. In this case **6** (29%) was obtained together with N-acetylated 2-azetidinone (**7**, 70%). The absolute configuration of C(4) of **2b** was determined by methylation of **2a** at C(3). The resulting *gem*-dimethyl derivative (70%) showed an NMR spectrum and an agreeable value of $[\alpha]_D$ identical to that of **2b**. Therefore, **2b** was assigned the 4*S* configuration.



From the above-mentioned determination of absolute configuration of **2a**, **3a**, and **2b**, it was confirmed that the photocyclizations of **1a** and **1b** proceeded stereospecifically with retention of stereochemistry at C(4). These results indicate that the type-II mechanism of this cyclization involves neither a zwitterionic[5j] nor an intramolecular charge-transfer exciplex[5g] intermediate initialy formed via an electron transfer. Photocyclizations according to these two mechanisms should afford the products, epimeric at C(4). A diradical formed directly via hydrogen abstraction[1] by an excited enone β-carbon atom seems to be the most probable intermediate in this case. The combination of the resulting diradical was faster than the inversion of stereochemistry at C(4) and the radical at C(4) was chiral during the reaction time scale, so that the retention of the stereochemistry at C(4) was achieved. The other radical at C(3) would be easily enolized and lose its stereochemistry in the six-membered transition state[9] of the hydrogen atom abstraction process (Scheme I). An alternative explanation that accounts for the lack of stereochemical control at C(3) involves the diastereofacial interaction in the initial photoexcited intermediate, as represented by A and B in Scheme II, which provides azetidinones **2** and **3** whiout epimerization at C(3). Pherhaps the steric interactions in such transition states govern product control.[10]

Scheme I



Scheme II

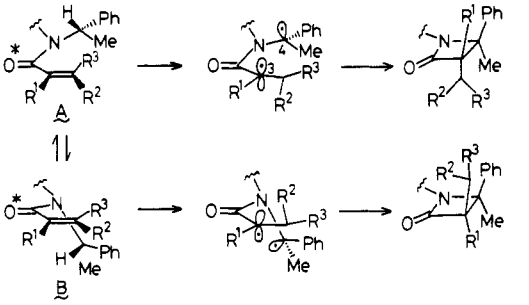


Table I. Yields of 2-Azetidinones

entry	compd	R^1	R^2	R^3	yield (%)	2:3[a]
1	**1a**	H	H	H	80	60:40
2	**1b**	Me	H	H	81	
3	**1c**	*i*-Pr	H	H	74	26:74
4	**1d**	H	Me	H	75	60:40
5	**1e**	H	Et	H	78	70:30
6	**1f**	H	*n*-Pr	H	70	60:40
7	**1g**	H	*i*-Pr	H	66	52:48
8	**1h**	Me	Me	H	73	58:42
9	**1i**	H	Me	Me	80	63:37
10	**1j**	Me	Me	Me	79	63:37
11	**1k**	$-(CH_2)_3-$		H	77	
12	**1l**	$-(CH_2)_4-$		H	57	

[a] Ratios (2:3) were determined from the integration of appropriate peaks in the ^{1}H NMR spectra of diastereomeric mixtures after flash column chromatography. These two diastereomers were separated by preparative HPLC.

Similar photocyclization of acrylylureas **1c–1j** resulted in the formation of two diastereomeric 2-azetidinones in 59–78% yields. Their C(3) configurations were assigned based on ^{1}H NMR chemical shifts of C(3) substituents. Reasonable upfield shifts were observed for the substituents syn to the phenyl group due to its shielding effect. Photocyclization of **1k** and **1l** afforded spiro-2-azetidinone

(6) Colorless crystals of **2a** are monoclinic, the space group is $P2_12_12_1$ with a = 10.833 (20) Å, b = 18.525 (15) Å, c = 9.294 (10) Å, V = 1865 Å, Z = 4, and d_{calcd} = 1.148 g/cm^3, the final residuals were R = 0.053 for 1256 data with $F(o) > 3\sigma(F_o)$.

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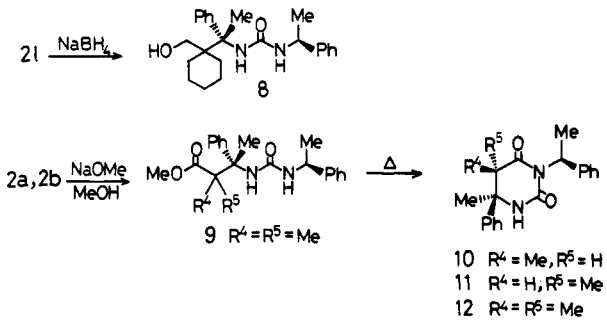
(10) We thank one of the reviewers for suggesting this mechanism.

in 57% and 77% yields, respectively, as a single diastereomer.

Due to the aforementioned reason, we cannot expect to achieve stereochemical control at C(3), but there is a slight preference for the formation of syn isomers in contrast to the predominant formation of anti isomers in the reported cyclization of achiral benzylic system.[5e] This might be caused by the slightly greater steric hinderance between the bulkier group at C(3) and 4-methyl rather than between the former and 4-phenyl (Scheme I). To examine the magnitude of the steric hindrance and also an epimerization of the radical site at C(3), photocyclizations of **1c** and **1j** were carried out (entries 3 and 10). These two acrylylureas should afford the same two diastereomeric 2-azetidinones with syn preference since an abstraction of the hydrogen atom by the enone double bond generates the same substituents at C(3). Though the diastereoselectivity at C(3) was slightly different, both gave the syn isomer with predomination, which agreed with the hypothesis.

Since the obtained 2-azetidinones had three amide bonds, we carried out some reductive and base-catalyzed hydrolytic cleavage of these bonds. As mentioned already, hydrolysis with 10 equiv of potassium *tert*-butoxide and 5 equiv of water resulted in the elimination of carbamoyl moiety. Reduction of **1k** with sodium borohydride resulted in the formation of alcohol **8** (60%). Methanolysis of **2b** with sodium methoxide at room temperature afforded ester **9** (68%). When this methanolysis was carried out in refluxing methanol, cyclized products **10** (10%), **11** (46%), and **12** (88%) were obtained from **2a** and **2b**, respectively. Configurations of **10** and **11** at C(5) were deduced from the NOE relations between C(5) and C(6) substituents in their NOESY spectra.



In conclusion, type-II photocyclization of chiral acrylylureas proceeds with complete retention of the configuration of the reaction site, γ-position to the enone double bond.

Experimental Section

General Procedures. Reaction solutions were concentrated on a rotary evaporator at 15–20 mmHg. Chromatographic separations were accomplished by flash column chromatography on silica gel (Fuji gel BW 200). Separation of diastereomers was carried out by a preparative HPLC run; column Merk LiChrosorb Si60 (7 μm, 10 × 250 mm), *n*-hexane/ethyl acetate as eluent. Acrylylureas **1** were prepared as reported,[4] and spectral data of those new compounds and all reaction products are available as supplementary material.

General Procedure for Type-II Photocyclization of Acrylylureas. Acrylylurea **1** (0.5–1.0 mmol) and benzophenone or *p*-methoxyacetophenone (1 equiv) in benzene (15 mL) in a Pyrex test tube were irradiated by a high-pressure mercury lamp (USHIO 450W). The reaction vessel was cooled in a water bath. The progress of the reaction was monitored by silica gel TLC. After complete disappearence of the starting urea, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate). Diastereomeric 2-azetidinones were separated by HPLC.

Hydrolysis and Consecutive Acetylation of 2a and 3a. To a ethereal suspension (15 mL) of KO^{t}BU (486 mg, 4.33 mmol) containing water (39 mg, 2.16 mmol) was slowly added 140 mg (0.43 mmol) of **2a**, and the resulting mixture was stirred for 3 days at room temperature. The dark yellow suspension was diluted with CH_2Cl_2 (20 mL) and filtered. The filtrate was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, the residue was dissolved in benzene (15 mL) and heated at reflux for 6 h with 1 mL of pyridine and 3 mL of acetic anhydride. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed with aqueous 1 N NaOH solution and then with brine. Chromatography on silica gel (*n*-hexane/ethyl acetate = 3/1) and further purification by HPLC afforded **4** (8.0 mg, 11%), **5** (12 mg, 16%), and **6** (10.2 mg, 15%, $[\alpha]^{23}_D$ = −139.1° (*c* = 0.33, $CHCl_3$) and $[\alpha]^{23}_D$ = −143.4° (*c* = 0.70, $CHCl_3$)).

In the same manner, **3a** was hydrolyzed and subsequently acetylated to give **4** (18%), **5** (17%), and **6** (26%, $[\alpha]^{23}_D$ = −136.1° (*c* = 0.13, $CHCl_3$)).

Hydrolysis and Consecutive Acetylation of 2b. By a procedure similar to that for **2a** and **3a**, **7** (112 mg, 70%) was obtained together with 33 mg (29%) of **6** ($[\alpha]^{23}_D$ = −136.7° (*c* = 0.33, $CHCl_3$)) starting from 234 mg (0.70 mmol) of **2b**.

Methylation of 2a. A solution of 40 mg (0.12 mmol) of **2a** in 1.5 mL of THF was added dropwise to a stirred THF–hexane solution (1.15 mmol) at −78 °C. After the solution was stirred for an additional 45 min, 0.072 mmol (1.15 mL) of methyl iodide was added, and the resulting mixture was stirred for 8 h at −78 °C and then allowed to warm to room temperature overnight. The solvent was removed under reduced pressure and replaced by CH_2Cl_2. After being washed with water, the organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane/ethyl acetate = 3/1) to afford 29 mg (70%) of **2b** together with 11 mg (28%) of recovered **2a**.

Sodium Borohydride Reduction of 2l. To a solution of 43 mg (0.11 mmol) of **2l** in THF (2 mL) and water (1 mL) was added 30 mg (0.79 mmol) of $NaBH_4$ at room temperature. The resulting mixture was stirred for an additional 0.5 h. Water (15 mL) was added, and the product was extracted into ether. After being dried over $MgSO_4$, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate = 3/1) to give **10** (25.2 mg, 60%).

Methanolysis of 2b. Sodium methoxide (0.4 mmol) in 0.8 mL of methanol was added dropwise to an ice-cooled solution of **2b** (11.0 mg, 0.032 mmol) in 1.2 mL of methanol under nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, stirred overnight, and acidified with 2 N HCl solution (0.2 mL). The solvent was removed under reduced pressure. The residue was diluted with 5 mL of water and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate = 3/1) to afford 8.0 mg (68%) of **9**. Refluxing of **2b** (32 mg, 0.095 mmol) in methanol (5 mL) with 1.0 mmol of sodium methoxide for 8 h gave **12** (28 mg, 88%) purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 3/1).

Methanolysis of 2a. To a refluxing solution of **2a** (52 mg, 0.16 mmol) in 20 mL of methanol was added NaOMe (2.0 mmol) in 0.6 mL of methanol, and reflux was continued for 5 h. The solvent was replaced by CH_2Cl_2. After the solution was over $MgSO_4$, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (*n*-hexane/ethyl acetate = 3/1) to afford a mixture of **10** and **11**. They were separated by HPLC to give 5 mg (9%) of **10** and 24 mg (46%) of **11**.

Acknowledgment. We thank Dr. Koreharu Ogata, Chemical Analysis Center of Chiba University, for the X-ray crystallographic analysis.

Supplementary Material Available: Spectral data for acrylylureas **1c–1e**, **1h–1l**, and all reaction products, X-ray data for **2a**, and ^1H (and ^{13}C in some cases) NMR spectra of all new compounds (79 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.