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HIGHLY SELECTIVE PHOTOREACTIONS OF α-OXOAMIDES AND α-TROPOLONE ALKYL ETHERS IN CRYSTALLINE INCLUSION COMPLEXES

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Abstract - Control of photocyclization of three α-oxoamides in crystalline inclusion complexes with three kinds of host compounds was studied. In all cases, β-lactams were obtained exclusively. In two cases, cis-β-lactams were formed selectively. By an enantioselective control using an optically active host compound, 1,6-di(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol, optically active β-lactams of high enantiomeric excess were obtained. Irradiation of complexes of α-tropolone alkyl ethers with the above optically active host compound in a solid state, gave the [2+2] photoreaction product, 1-alkoxybicyclo[3.2.0]hepta-3,6-dien-2-one, and its ring-opened derivative, alkyl 4-oxo-2-cyclopentene-1-acetate, in 100 and 72-91% enantiomeric excess, respectively.

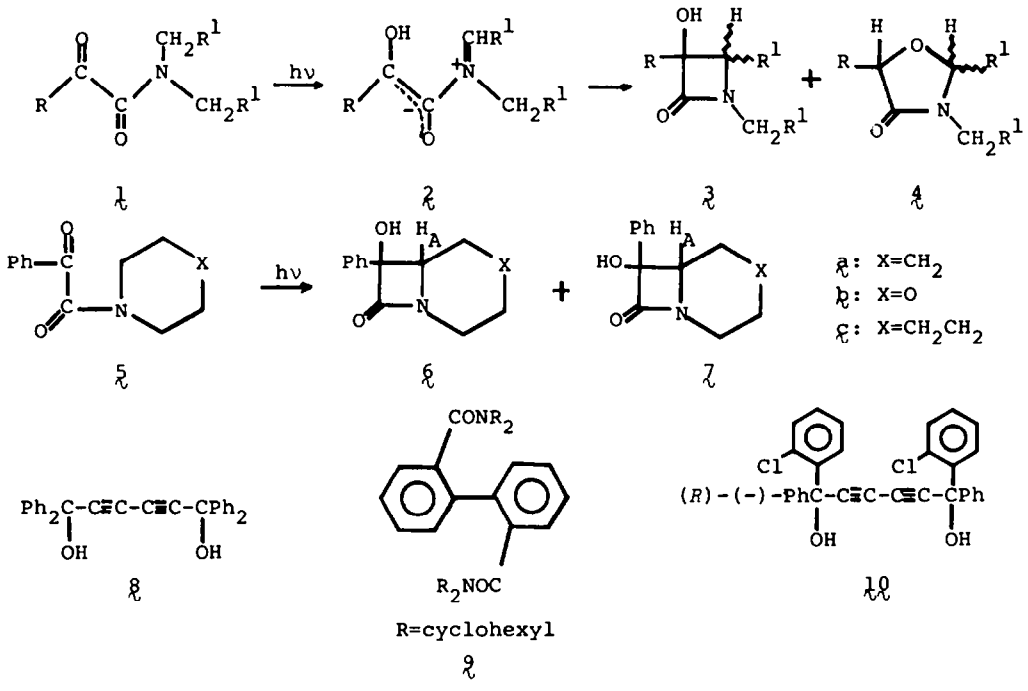
It is important but difficult to control steric and enantiomeric courses of photoreaction. We succeeded to control the course of the title photoreactions by carring out the reaction in crystalline inclusion complexes.

As a synthetic approach to penicillin derivatives, photocyclization of α-oxoamides (1) to β-lactams (3) has long been studied.[1,2] This reaction, however, gives a complex mixture of racemic cis- and trans-isomers of β-lactams and of oxazolidin-4-ones (4), since the reaction proceeds via a zwitterionic intermediate (2).[3] Of these isomers, only the optically active β-lactams is the useful compound. Some severe controls of the photocyclization are necessary to obtain the optically active β-lactam selectively.

Some attempts of such control have been tried. Irradiation of 1 in a solid state gave 3 selectively,[4] but this method was not applicable to α-oxoamide derived from a cyclic amine such as N-benzoylformylpiperidine (5a).[4] Furthermore, no stereoselective control was achieved by this method and it gave a mixture of cis- and trans-isomers of (3).[4] Of course, no efficient enantioselective control of the photocyclization has yet been reported, although 15% ee 3 has been obtained by irradiation of 1 in an inclusion complex with deoxycholic acid.[5]

We now report the highly selective photocyclizations of three α-oxoamides (5a-c) in complexes with three host compounds, 1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol (8),[6-8] N,N,N',N'-tetracyclohexyl-2,2'-biphenyldicarboxamide (9),[9] and (*R*)-(-)-1,6-di(o-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol (10).[10] The nine complexes prepared from 5a-c and 8-10 are shown in Table 1.

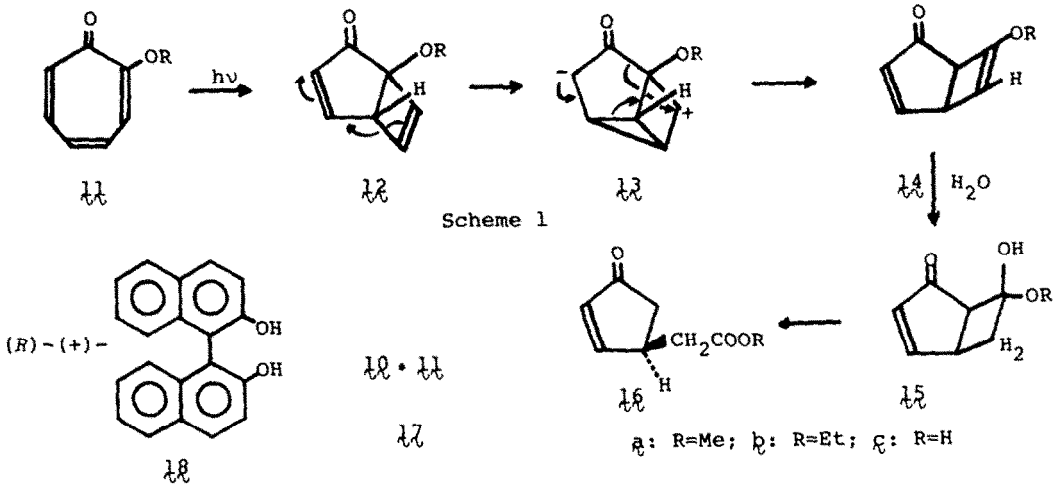
In all photocyclizations, only the β-lactams were obtained and no oxazolidin-4-one was produced. In most photocyclizations in the complex with 8 and 10, cis-β-lactams (6) were formed predominantly. Furthermore, in the photocyclization in the complex with 9, 6 was formed exclusively. However, the complex of 5b and



9 (**23**) was inert to the irradiation.

Irradiation of the complex of **5** and **10** (**21**, **24**, and **27**) gave optically active **6** and **7** (Table 2). Irradiation of **21** gave 62.4% ee **6a** and 95% ee **7a** in the yields shown in Table 2. Irradiation of **24** gave 55.5% ee **6b** and optically active **7b**, but the optical purity of the latter could not be determined. Similar irradiation of **27** gave 11.2% ee **6c** and racemic **7c**.

The enantioselective control of photoreaction in crystalline inclusion complex with **10** was found to be applicable more effectively to the photoreaction of α-tropolone alkyl ether (**11**) which gives 1-alkoxybicyclo[3.2.0]hepta-3,6-dien-2-one (**12**) and alkyl 4-oxo-2-cyclopentene-1-acetate (**16**). The photoreaction of α-tropolone methyl ether (**11a**) in solution to 1-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (**12a**), 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (**14a**), and methyl 4-oxo-2-cyclopentene-1-acetate (**16a**) has been reported[11] and the mechanism shown in Scheme 1 has been postulated for the reaction.[11] Nonetheless, no optically pure compound has been obtained, although optically active **12**, **14**, and **16** are useful compounds as chiral synthons. Only two attempts of the enantioselective synthesis of these compounds have been done so far. Irradiation of racemic **12a** with circular polarized light gave **12a** and **14a** of very low optical purity (up to 1.6% ee),[12-14] and irradiation of β-cyclodextrin complex of **11a** as a water dispersion gave 62% ee **12a**.[15] Contrarily, irradiation of a 1:1 complex of **11** and **10** in a solid state gave 100% ee **12** and 72-91% ee **16**. Interestingly, however, a 1:1 complex of **11a** with (*R*)-(+)-2,2'-dihydroxy-1,1'-binaphthyl (**18**) was inert to irradiation in the solid state. Although α-tropolone itself (**11c**) also gives **12c** and some other products by an irradiation in solution,[16] irradiation of a 1:2 complex of **10** and **11c** (**17c**) in a solid state gave an unidentified oily product.



11 12 13 14 15 16 17 18

Scheme 1

10 • 11

a: R=Me; b: R=Et; c: R=H

EXPERIMENTAL

Preparation of α-Oxoamides. N-Benzoylformylpiperidine (5a), N-benzoylformylmorpholine (5b), and N-benzoylformylhexamethyleneimine (5c) were prepared according to the literature procedure.[17] 5a is the known compound of mp 103-105 °C.[1,4] 5b: mp 58-60 °C; νCO (Nujol mull) 1680 and 1640 cm^{-1}; Found C, 65.51, H, 5.90, N, 6.51%. Calcd C, 65.74, H, 5.98, N, 6.39%. 5c: mp 45-46 °C; νCO (Nujol mull) 1680 and 1635 cm^{-1}; Found C, 72.42, H, 7.54, N, 5.87%. Calcd C, 72.70, H, 7.41, N, 6.06%.

Preparation of Inclusion Complexes of α-Oxoamides. Inclusion complexes of 5a-c with 8 or 10 were prepared by crystallization of host and guest compounds from ether-petrol ether. Complexes of 5a-c with 9 were prepared by similar crystallizations of the components from di-n-butyl ether. The complex of 5a with 10 could be prepared by crystallizing these from ether-petrol ether-benzene, and the benzene containing complex in a 1:1:1 ratio was obtained. These complexes are summarized in Table 1.

Irradiation of the Complex of α-Oxoamide. Irradiation of the complex was carried out by high-pressure Hg-lamp at room temperature in a powdered solid state. Irradiation time is shown in Table 2.

Isolation of Photocyclization Products of α-Oxoamides. From the irradiation product of the complex with 8 and 10, host compound, recovered α-oxoamide, and β-lactam were separated by column chromatography on silica gel using benzene-ethyl acetate as solvent. In the case of the complex with 9, a 1:1 acetone complex of 9 crystallized out by dissolving the crude reaction product in acetone. From the acetone solution left after separation of the complex, cis-β-lactams, 6a and 6c were obtained in pure state. Only in the cases of 6b and 7b, they were separated by silica gel chromatography. However, neither 6a and 7a nor 6c and 7c were separable by the chromatotography. Therefore, these ratios and enantiomeric excess of optically active β-lactams were determined by HPLC on Chiralcel.[18] These data are shown in Table 2.

Table 1. Compound numbers, melting points, and elemental analyses of the host-guest inclusion complexes of 8-10 with 5a-c

Guest	Host[a] 8		9		10	
	Number	Mp (°C)	Number	Mp (°C)	Number	Mp (°C)
	Found C, H, N (%)		Found C, H, N (%)		Found C, H, N (%)	
	Calcd C, H, N (%)		Calcd C, H, N (%)		Calcd C, H, N (%)	
5a	19	98-101	20	nc[b]	21	75-79[c]
	81.76, 5.97, 2.24		78.01, 8.89, 5.11		75.36, 5.39, 1.66	
	81.75, 5.90, 2.22		77.92, 8.59, 5.35		75.57, 5.31, 1.80	
5b	22	94-96	23	nc	24	65-70
	75.85, 5.69, 3.37		75.98, 8.46, 5.38		73.08, 4.82, 2.14	
	76.04, 5.67, 3.28		76.20, 8.31, 5.33		72.80, 4.73, 1.99	
5c	25	113-115	26	nc	27	84-87
	81.53, 6.10, 2.03		78.35, 8.57, 5.18		73.24, 5.76, 2.99	
	81.83, 6.09, 2.17		78.06, 8.69, 5.25		73.64, 5.75, 2.96	

a) Host:guest molar ratios are 1:1 except the case of 22 and 27 (1:2), and 21 consists of 5a, 10, and benzene in a 1:1:1 ratio. b) nc means not clear.
c) Measured in a sealed capillary.

Structure Elucidation of β-Lactams. Structures of 6 and 7 were elucidated on the basis of IR and NMR spectra, and elemental analyses. In IR spectra, all showed a typical carbonyl absorption of β-lactam ring at about 1735 cm^{-1}. The structure of 6b was confirmed by a direct comparison of its melting point with that of an authentic sample.[1] The cis- and trans-structures of 6c and 7c, respectively, were determined on the basis of their NMR spectra. The H_A of 7c appeared at a higher magnetic field (as two doublets centered at 3.46 ppm), due to a shielding effect by the phenyl ring, than did H_A of 6c (as two doublets centered at 3.75 ppm). However, cis- and trans-configurations of the other β-lactams could not be determined by NMR spectra. The trans-structure was tentatively assigned to the isomer which appears as a relatively sharp peak in a shorter retention time in HPLC on the Chiralcel, since 7b appears as a sharp peak in a shorter retention time than does 6b. (6b) mp 151-152 °C; νCO (Nujol mull) 1730 cm^{-1}; Found C, 66.06, H, 6.19, N, 6.29%. Calcd C, 65.74, H, 5.98, N, 6.39%. (7b) mp 144-145 °C; νCO (Nujol mull) 1740 cm^{-1}; Found C, 65.54, H, 6.05, N, 6.52%. Calcd C, 65.74, H, 5.98, N, 6.39. (6c) mp 120-122 °C; νCO (Nujol mull) 1735 cm^{-1}; Found C, 72.73, H, 7.33, N, 6.12%. Calcd C, 72.70, H, 7.41, N, 6.06%.

Separation and Purification of Optically Active 6b and 7b. The product obtained by an irradiation of 24 followed by a silica gel chromatography was found to be a 78:22 mixture of 55.8% ee (-)-6b and an optically active (-)-7b (Table 2). When an acetone solution of the product (1.0 g) was kept at room temperature for 2 days, racemic 6b crystallized out (0.17 g). The acetone solution left after filtration of the racemic 6b was worked up by a chromatography on silica gel using benzene-ethyl acetate as solvent, and 85% ee (-)-6b ($[\alpha]_D$ -164.2°, 0.35 g) and an optically active (-)-7b ($[\alpha]_D$ -48.7°, 0.05 g) were obtained. However, optical purity of the latter could not be determined.

Table 2. Irradiation time and yields and ratios of products

Complex	Irradiation time (h)	Yield[a] (%)	Product ($[\alpha]_D$ value (°)[b] and optical purity (% ee)[c])	Ratio of 6:7
19	55	41	6a and 7a	77 : 23
20	30	73	6a --	100 : 0
21	100	67	(-)-6a and (-)-7a[d]	57 : 43
			(-62.4, 62.5) (-62.4, 95)	
22	40	38	6b and 7b	77 : 23
23[e]	50	--	-- --	-- --
24	50	49	(-)-6b and (-)-7b	78 : 22
			(-107.8, 55.8) (-48.7)	
25	25	82	6c and 7c	91 : 9
26	10	74	6c --	100 : 0
27	30	67	(+)-6c and 7c[f]	49 : 51
			(+22.6, 11.2) (0, 0)	

a) Yield of a mixture of 6 and 7 which was separated from the crude photocyclization product by a silica gel chromatography. b) All $[\alpha]_D$ values were measured in $CHCl_3$ at c 1.0. c) Optical purity was determined by HPLC on Chiralcel.[18] d) Since optically active 6a and 7a could not be separated, it is not clear whether both the enantiomers are (-)-ones or not. Therefore, both are tentatively shown as (-)-enantiomers. Since $[\alpha]_D$ value of each enantiomer is also not clear, $[\alpha]_D$ value of the mixture is shown. e) 23 was inert to the irradiation. f) When an acetone solution of the mixture of (+)-6c and 7c was kept, racemic 7c crystallized out, mp 135-137 °C.

Preparation of Inclusion Complexes of 11. When a solution of 10 (9.66 g, 20 mmol) and 11a (2.76 g, 20 mmol) in benzene-n-hexane (1:1) (50 ml) was kept at room temperature for 12 h, a 1:1 complex of 10 and 11a was obtained as colorless needles (10.40 g, 84% yield); mp 69-71 °C; $[\alpha]_D$ -92.2°; νOH 3180 cm^{-1}, νCO 1590 and 1520 cm^{-1}. Found C, 73.61; H, 4.65%. Calcd C, 73.67, H, 4.55%.

By a similar method, a 1:1 complex of 10 and 11b was obtained as colorless prisms in 97% yield; mp 135-137 °C; $[\alpha]_D$ -104°; νOH 3200 cm^{-1}, νCO 1590 and 1520 cm^{-1}. Found C, 73.64; H, 4.83%. Calcd C, 73.93, H, 4.77%.

A 1:2 complex of 10 and 11c was also obtained by a similar method as colorless prisms in 97% yield; mp 94-96 °C; νOH 3350 and 3200 cm^{-1}, νCO 1600 and 1535 cm^{-1}. Found C, 72.60, H, 4.52%. Calcd C, 72.63, H, 4.43%.

When a solution of 9 (2.86 g, 10 mmol) and 11a (1.38 g, 10 mmol) in MeOH (10 ml) was kept at room temperature for 12 h, a 1:1 complex of 9 and 11a was obtained as colorless prisms (4.00 g, 94% yield); mp 137-143 °C; $[\alpha]_D$ +15.1°; νOH 3530 and 3120 cm^{-1}, νCO 1590 and 1550 cm^{-1}. Found C, 79.28, H, 5.43%. Calcd C, 79.60, H, 5.25%. In all complexes, ratios of the components were determined by NMR spectra.

Irradiation of the Complex of 11. All the irradiations were carried out at room temperature in a solid state under grinding every 6 h by an agate mortar and pestle using a high-pressure Hg-lamp. Irradiations were continued until a half of the complex had reacted.

Purification of Reaction Products. The crude reaction products were purified by chromatography on silica gel using $CHCl_3$ as solvent to give 12 and 16 as colorless oils in the yields shown in Table 3. For example, silica gel chromatography of the crude product obtained by irradiation of a 1:1 complex of 10 and 11a (17a) gave 10, 12a, 16a, and unreacted 11a, in 98, 11, 26, and 47% yields, respectively. Yields of 12a and 16a are calcurated based on the reacted 11a.

Determination of Structure and Optical Purity of 12 and 16. The structure of 12 and 16 were elucidated by comparing their spectral data with those reported.[11] The optical purity of 12 and 16 was determined by HPLC method using a column containing an optical active solid phase, Chiralcel.[18] The optical purity of 16a was also confirmed by referring its reported $[\alpha]_D$ value.[13] All $[\alpha]_D$ values are shown in Table 3.

Although the structure of the oily material obtained by irradiation of a 1:2 complex of 10 and 11c (17c) could not be determined, its physical data (νOH 3350 and 3200 cm^{-1}, νCO 1600 and 1535 cm^{-1}; bp could not be determined because of its thermal instability) were not identical with those of 12c and its derivatives reported in the literature.[16]

Photoreaction of 12 to 16 in Aqueous MeOH. When a solution of 100% ee 12a or 100% ee 12b in 2% aqueous MeOH was irradiated at room temperature for 4 h, 45% ee 16a and 35% ee 16b were obtained, respectively, in almost quantitative yields.

Racemization of 16a and 16b by Irradiation in Aqueous MeOH. When a solution of 91% ee 16a or 72% ee 16b in 2% aqueous MeOH was irradiated at room temperature for 4 h, 34% ee 16a and 27% ee 16b were obtained, respectively, in almost quantitative yields.

Table 3. Irradiation products of 11 in a crystalline inclusion complex

Complex	Irradiation[a] time (h)	Product	Yield[b] (%)	$[\alpha]_D$ (MeOH, c 0.2) (°)	Optical purity (% ee)
10·11a (17a)	72	12a	11	-168	100
		16a	26	+89.5	91
10·11b (17b)	83	12b	12	-189	100
		16b	14	+59.3	72
10·11c (17c)	90	an oily material[c]	43	0	--
18·11a	178[d]	--	--	--	--

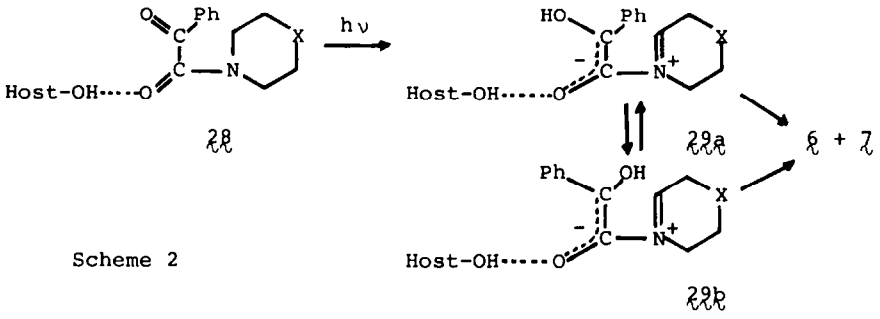
a) The time for about 50% conversion. b) Calcurated based on reacted 11. c) Structure was not determined. d) No reaction occurred.

DISCUSSION

In all irradiations of 19-27, the β-lactam derivatives (6a-c and 7a-c) were produced exclusively. Reason for the efficient control in the inclusion complexes with 8-10 is not clear. A plausible interpretation is that crystal fields of the inclusion complexes are too small to produce oxazolidin-4-ones which have a relatively large five-membered ring, and give β-lactams which have a relatively small four-membered ring.[19]

Stereochemical control of the photocyclization of 5a and 5c to 6a and 6c, respectively, was achieved by the irradiation of their complex with 9 (Table 2). Contrarily, the stereochemical control in the complex with 8 and 10 is relatively not efficient. A plausible interpretation for the difference is as follows: In the complex with 8 and 10, there is a hydrogen bond between the carbonyl oxygen of amide group of 5 and the hydroxyl group of the host compound as is depicted in 28 of Scheme 2.[20] The zwitterionic intermediate[3] which is formed on irradiation is stabilized by a similar hydrogen bond as is shown in 29 of Scheme 2. This stabilization makes easy an interconversion between 29a and 29b through the equilibrium, and the cyclization proceeds less stereoselectively to afford a mixture of 6 and 7. No such stabilization is expected for the zwitterionic intermediate formed in the complex of 5 with 9. In this case, the intermediate

cyclizes immediately after the formation, and gives 6 exclusively. In fact, photocyclization reaction of 5 in the complex with 8 and 10 is much slower than that with 9 (Table 2).[19]



Scheme 2

Enantioselective photocyclization of 5 occurred efficiently in the complex with 10. Especially, the selectivity is very high in the case of 5a. However, the control is not efficient in the 1:2 complex of 10 and 5c (27). The host:guest ratio probably depends on the packing of these components in crystals. The packing is related to the selectivity of the reaction in a solid state. Therefore, the selectivity would be influenced by the ratio.[19] In the case of 1:1 complex of 10 and 5a containing one mole of benzene (21), this benzene molecule probably works as an important spacer in the crystals in the photocyclization reaction.[19]

In order to control both the stereochemistry and enantioisomerism of the photocyclization product, design of a good host compound is necessary. It seems adequate to design an optically active 2,2'-biphenyldicarboxamide derivative, since 9 is very useful for the stereochemical control of the photocyclization of 5. Preparation of such a host compound is in progress.

The high enantioselectivity of the photoreaction of 11a and 11b shows that a disrotatory photocyclization[21] occurs in one direction in their inclusion complexes with 10. Since (-)-12a and (-)-12b have a (1*S*,5*R*)-configuration,[13,14] the disrotatory cyclization of 11a and 11b should occur in the A direction (Figure 1). In the complex with 10 of (*R*)-configuration,[10,22] 11a and 11b are probably fixed so as not to rotate toward the B direction, as is depicted in Figure 1.

Formation of 91% ee 16a and 72% ee 16b in the photoreaction of 17a and 17b, respectively, shows that the conversion of 12 to 16 proceeds with relatively low enantioselectively. This is probably due to a small amount of water contaminated in the complex, because the irradiation of 100% ee 12a and 100% ee 12b in 2% aqueous MeOH gave 45% ee 16a and 35% ee 16b, respectively. It was also disclosed that this low enantioselective conversion of 12 into 16 is due to a photochemical recemization of 16 *via* its reversible enolization. Irradiation of a 2% aqueous MeOH solution of 91% ee 16a and 72% ee 16b for 4 h gave 34% ee 16a and 27% ee 16b, respectively. However, the racemization occurs very slowly in a dry MeOH solution. Contrarily, the results would support that the photochemical course from 12 to 16 does not contain any racemization step. However, the enantioselectivity of the conversion of 12 to 16 in a crystalline inclusion complex could not be confirmed, since 12 did not form a complex with 10.

Photoreaction of α-tropolone in a 1:2 inclusion complex with 10 (17c) gave an unidentified oily material which does not show any $[\alpha]_D$ value. This result is different from that in solution which gives 2-hydroxybicyclo[3.2.0]hepta-3,6-dien-2-one (12c), 4-oxocyclopent-2-enylacetic acid (16c), and some other products.[16] The photochemical behavior of 17c is also different from that of the 1:1 complex,

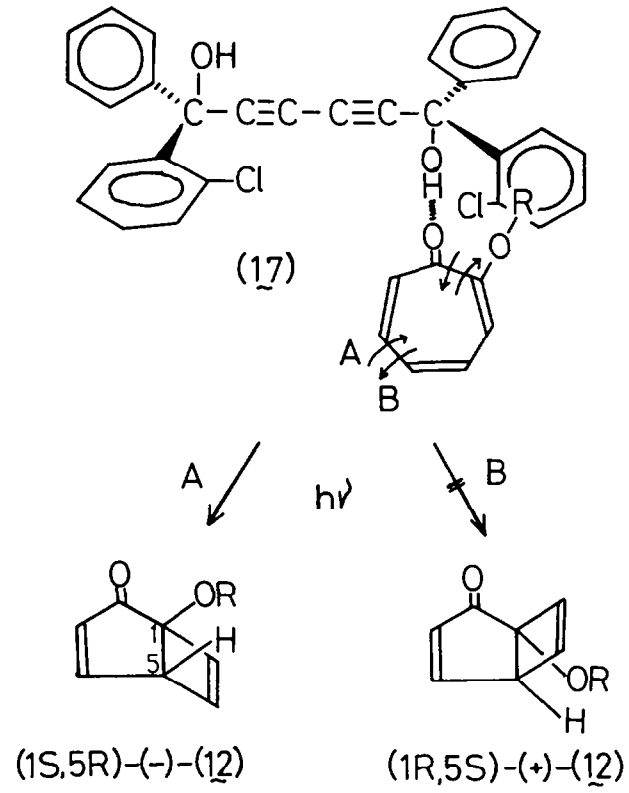


Figure 1. An imaginary depiction of the enantioselective photoreaction of 11 in a crystalline inclusion complex with 10

17a and 17b. It is not clear, however, whether the difference is due to the ratio of components or not.

The photochemical inertness of 11a in the complex with 18 is interesting. In the complex, disrotatory photocyclization of 11a is probably prevented in both the directions due to a steric hindrance. X-Ray crystal structural study of the complex of 11a and 18 is in progress. Nevertheless, this phenomenon can be used for a storage of photosensitive tropone derivatives.

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