Tetrahedron Vol 49, No 4, pp 947-964, 1993
Printed in Great Britain

0040-4020/93 $6 00 + 00
Pergamon Press Ltd

Steric Effects in Intramolecular [2+2] Photocycloaddition of C=C Double Bonds to Cyclohexenones.

D. Becker* and N. Haddad.

Department of Chemistry, Technion-Israel Institute of Technology, Haifa 32000, Israel

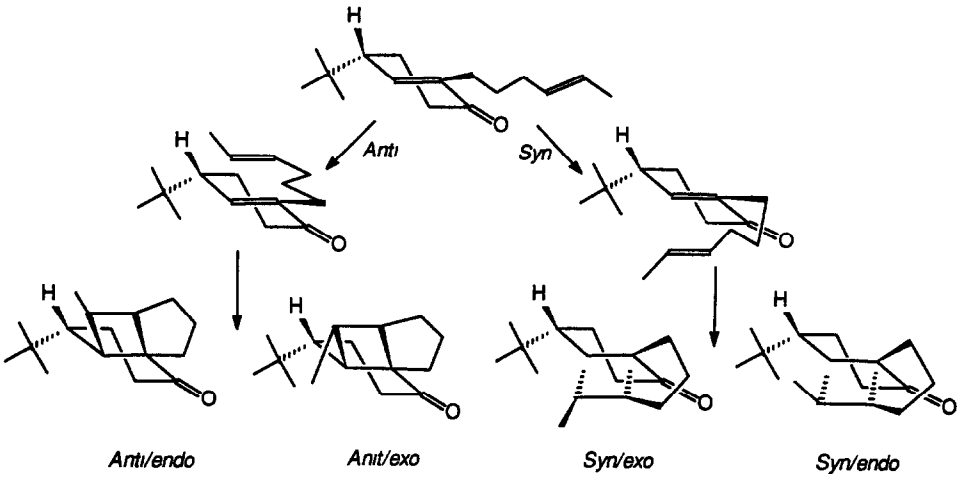
(*Received in UK 29 September* 1992)

Abstract The effect of substituents on the mode of approach and the *endo/exo* ratio in intramolecular [2+2] photocycloaddition reactions were studied

Introduction

Controlling the stereochemistry of [2+2] photocycloaddition of olefins to cycloalkenones is difficult, and often a stereoisomer mixture is obtained This is the main reason preventing this type of reaction from becoming a much more useful tool in synthesis of complex organic compounds Although it has been studied for more than thirty years its mechanism is not yet fully understood[1] Among photochemists it is agreed that an excited triplet state is involved in the first stage of the reaction It has been proposed[2] that a twisted $\pi\rightarrow\pi^*$ state is the reactive intermediate and not the polarized $n\rightarrow\pi^*$. Whether this is generally the case is not very certain since the energy gap between the two states in cyclohexenones is small Also it is not yet clear whether the enone in the triplet state is reacting with the olefin or whether that triplet is a precursor for another reactive intermediate There are some recent results that have been explained by assuming that the olefin reacts with a vibrationally excited enone in its ground state[3] The formation of an exciplex as intermediate in the [2+2] photocycloaddition has been proposed by Corey[4] and latter by de-Mayo[5] as a result of careful kinetic studies Schuster and Turro[6] have lately questioned this, arguing lack of experimental evidence to justify its existence The dearth of knowledge of intermediates involved in [2+2] photocycloaddition, and particularly their charge distribution and conformation, is the main reason for poor predictability A high degree of selectivity has been achieved in some examples[7] of intramolecular [2+2] photocycloaddition where a steric effect was apparent These include studies towards

a specific target such as the total synthesis of longifolene[8] Our intention was to study systematically to what extent a substituent on a cyclohexenone can control the *anti* to *syn* isomer ratio by a steric effect. If we find that the olefin approach can be controlled then we shall examine whether the *endo* to *exo* ratio of the two stereoisomer products can be influenced by the mode of approach of the reacting functions (see Scheme 1).

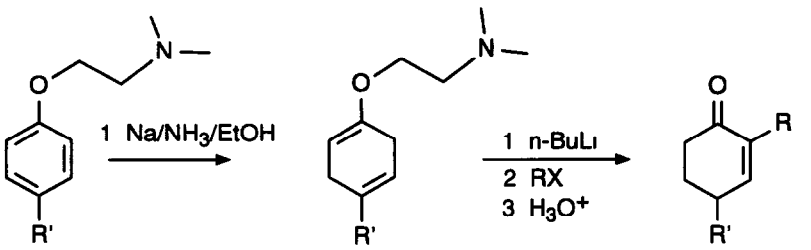


Scheme 1

Results

In order to obtain information about approach and its effect on the stereoisomer ratio we have synthesized cyclohexenones having a substituent on carbon γ (C^4) of the six membered ring and an olefin chain linked to the α-carbon The substituted cyclohexenones were prepared as in Scheme 2, from the corresponding protected phenols and halo-olefins, following Sutherland's[9] procedure The corresponding halo-olefins were prepared either by known or modified procedures as described in the experimental part

Irradiation of compound **9** dissolved in cyclohexane, *via* a Uranium glass filter, gave two main photoadducts in a ratio of 2 3 1, and in over 95% yield All efforts to separate the adducts by liquid chromatography failed, and pure samples for structure determination were obtained by preparative gas-chromatography (PGC). The major product was assigned unequivocally as **11** and the minor one as **12**, by spectroscopic methods, as described in the following chapter. We can therefore conclude that in this instance the steric effect does control the olefin approach, and that the *anti*-isomer is the major photoadduct as expected. Replacement of the bulky t-butyl substituent by a methyl group (**10**), led on irradiation to a mixture of two photoadducts (**13** and **14**) in a ratio of 1 4 1 These were separated by PGC and their structures were determined unequivocally by NMR The results indicate clearly that the size of



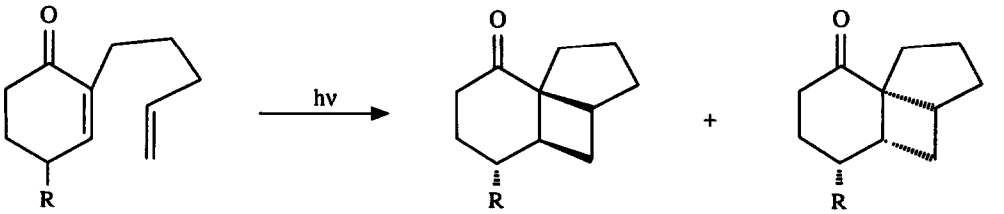
R' = Bu^t or Me

Halo-olefins used for alkylation

1 Br-$(CH_2)_3$CH=CH_2
2 Br-CHMe$(CH_2)_2$CH=CH_2
3 Br-CH_2CHMeCH_2CH=CH_2
4 Br-$(CH_2)_3$CMe=CH_2
5 Br-$(CH_2)_3$C=CMe_2
6 Br-$(CH_2)_3$CH$\overset{E}{=}$CHMe
7 Br-$(CH_2)_3$CH$\overset{Z}{=}$CHMe
8 I-$(CH_2)_3$CD$\overset{E}{=}$CDH

Scheme 2

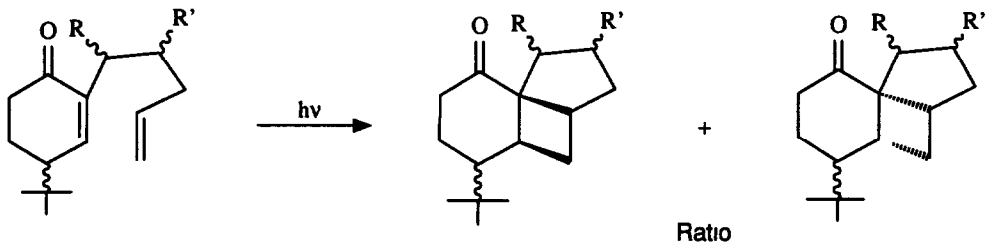
the substituent on C^4 of the cyclohexenone could play an important role in controlling the stereochemistry of this intramolecular [2+2] photocycloaddition reaction



		Ratio	
9 R = Bu^t	11	2 3/1	12
10 R = Me	13	1 4/1	14

Scheme 3

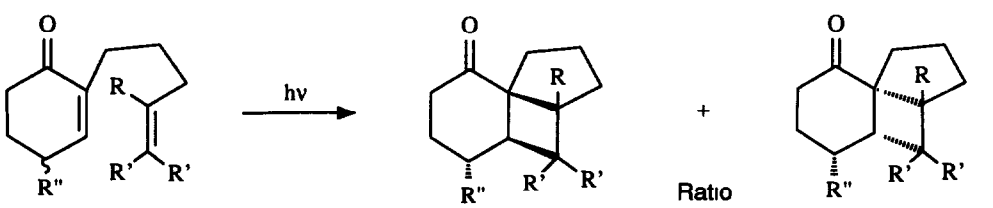
It was of interest to investigate whether substituents on the chain can improve the stereoselectivity of the photoaddition process Compound **15** was synthesized (as a 1·1 diastereomer mixture) having a methyl group on $C^{1'}$ of the chain linking the olefin to the cyclohexenone This mixture was irradiated, and the expected photocycloaddition reaction took place in good yield Four products were formed in a 2 2 1 1 ratio, showing that no improvement in the stereoselectivity had been achieved as compared with the unsubstituted chain model **9** Similar results were obtained for compound **16** having a methyl group on $C^{2'}$ It appears that in this system substituents on $C^{1'}$ and $C^{2'}$ have no significant influence on the selectivity of the cycloaddition process



15 R = Me, R' = H
16 R = H, R' = Me

Scheme 4

The next step was to study whether a substituent on the double bond could control the stereochemistry of the photoaddition To that end three compounds **17, 20,** and **21** were prepared Irradiation of **17** led to two photoadducts (*anti/syn*) in a 2 7 1 ratio, and in over 95% yield These were separated by PGC and determined by NMR to be *cis*, parallel, [2+2] photoadducts The major photoadduct **18** is the result of olefin approach to the enone face from the *anti* side, whereas the minor photoisomer **19** is formed by a *syn* approach The fact that substituents on the olefin can control the stereochemistry was reinforced by comparing the photoadduct ratio obtained from **20** to those obtained from **17** From the former we obtained one single photoadduct in nearly quantitative yield having structure **22** Irradiation of **21** gave two photoadducts in a 3 1 ratio, these were identified as **23** (*anti*) and **24** (*syn*) respectively This gave further weight to our conclusion that replacing the bulky t-butyl substituent on the ring by a methyl group led to reduced selectivity It is apparent that stereoselectivity of photocycloaddition could conceivably be controlled by fine tuning of the bulkiness of substituents on the ring and on the reactive centers of the olefin

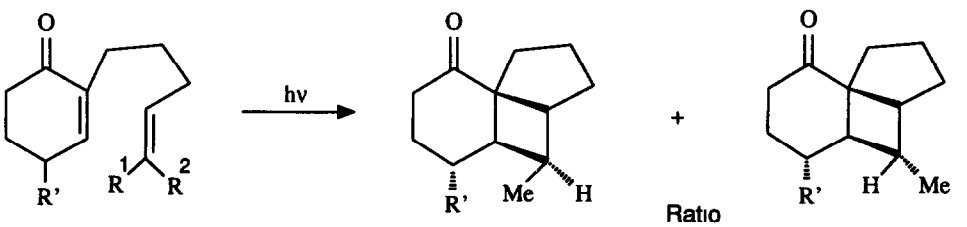


17 R = Me, R' = H, R" = Bu^t	18	2 7/1	19
20 R = H, R' = Me, R" = Bu^t	22		-
21 R = H, R' = Me, R" = Me	23	3/1	24

Scheme 5

In starting materials (**25-28**) where $R^1 \neq R^2$ (Scheme 6) two stereoisomer products (*endo* and *exo*) can be expected At this stage we were ready to explore whether the *endo exo* ratio depends on the direction of approach of the olefin to the enone face Compound **25** (E isomer) having R^1= Me, R^2= H was prepared here GC ascertained that the amount of the Z isomer, **26**, was <1% Its irradiation was followed by GC and

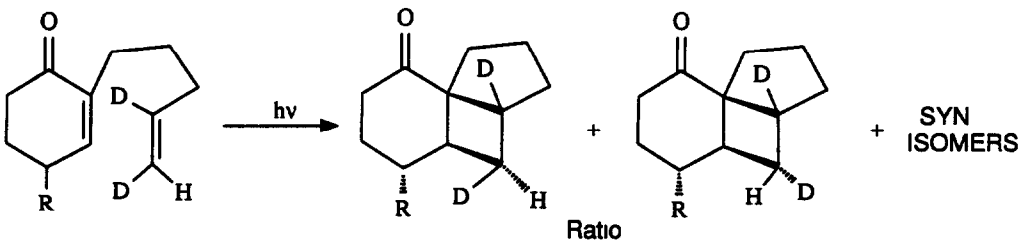
it appeared that photoisomerisation to geometrical isomer **26** accounted for less than 8% of the total amount of the reaction mixture We can therefore argue, that in this system as in previously studied ones[10], the rate of cyclization is faster than the E ⇆ Z interconversion Apparently, in the irradiation of **25**, the olefin function is forced by the t-butyl group to approach the enone face from the *anti* side, leading to *anti* photoadducts in 94% yield It is important to note that these are a mixture of *endo* and *exo* stereoisomers We can conclude that the approach was indeed controlled, but that selectivity in the formation of *endo* and *exo* stereoisomers was diminished, from 35 1 in the unsubstituted cyclohexenone **27**[10] to 4 1 for **25** The photoadducts of **25** were separated by PGC and found to be [2+2] parallel photoadducts, having a *cis*-junction between the four and the six-membered rings According to NMR analysis the methyl group is *endo* to the six-membered ring in the major stereoisomer **29** and *exo* in the minor stereoisomer **30** The same trend, of rapid formation of photoadducts relative to photoisomerization Z ⇆ E, was evidence when the Z isomer **26** was irradiated It was found that 86% of the products resulted from *anti* approach of the olefin to the enone However, the stereoselectivity in the photoadducts formed by anti approach was reduced to a 1 8 1 *endo* to *exo*-ratio, which is much lower than that observed in the unsubstituted compound **28** (5 8 1)[10]



		Ratio	
25 R^1 = Me, R^2 = H, R' = Bu^t	29	4/1	30
26 R^1 = H, R^2 = Me, R' = Bu^t		1 8/1	
27 R^1 = Me, R^2 = H, R' = H	31	35/1	32
28 R^1 = H, R^2 = Me, R' = H		5 8/1	

Scheme 6

In order to check the hyphothesis that steric interactions between the substituent on the olefin and the bulky group on the six-membered ring affect the stereoisomer formation, a hydrogen atom was stereospecifically replaced by deuterium and the *endo*/*exo* ratio was determined by ^2H NMR analysis Hence compound **33** was synthesized and irradiated and two photoadducts were formed in high yield (>95%) The ratio of the *anti* to *syn* isomer was 2 3 1 as expected The main *anti* isomer **35** was separated and the *endo*/*exo* ratio was determined by integration of the relevant signals in the ^2H NMR spectrum to be 2 1 respectively



33 R = Bu^t 35 2/1 36

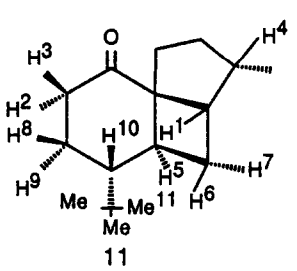
34 R = H 2/1

Ratio

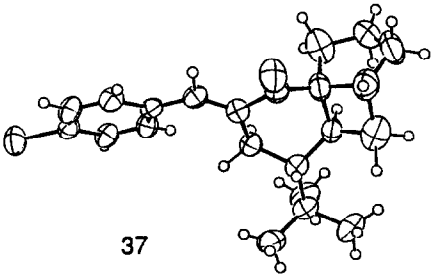
Scheme 7

Structure determination

As indicated above, this was based on measurment of ^1H, and ^{13}C NMR spectra, and on application of COSY, C-H heterocosy, NOE, and ^2H spectra In some cases protons adjacent to a ketone group were determined by exchange with deuterium by mild basic conditions In order to reinforce our conclusion that the structure of the major photoadduct of **9** is **11**, a crystalline derivative **37** was prepared by aldol condensation of **11** with p-bromobenzaldehyde, and its structure determined by X-ray crystallography As can seen in Figure 1 the structure is in full agreement with the NMR analysis The key protons in the photoproducts were assigned as shown Table 1



11



37

Figure 1

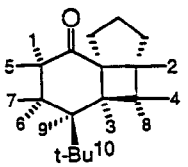
The assignment of H^2 and H^3 as protons α-to carbonyl was established by exchange with deuterium in basic CH_3OD Protons H^1, H^5 and H^{10} were assigned as methynes using C-H heterocosy and DEPT Analysis of the COSY and NOE spectra coupled with the information about the methyne protons, enabled assigning the structure of **11** unequivocally The same type of analysis was applied to the other photoadducts and the results are summarized in Table 2

Table 1 ^{1}H NMR of photoadduct **11**

	δ (ppm)[a]	COSY	NOE (%)
H^1	2 82	H^6, H^7, H^4	H^4 (0.5); H^6 (1 5)
H^2	2.31	H^3, H^8, H^9	H^3 (3 2), H^8 (0 4), H^9 (0 4)
H^3	2 07	H^2, H^8, H^9	H^2 (3.2)
H^4	1 78	H^1,	
H^5	1 71	H^6, H^7, H^{10}	H^7 (2.5)
H^6	1 62	H^1, H^5, H^7	H^1 (1.5), H^7 (3.5), H^{10} (1)
H^7	1 45	H^1, H^5, H^6	H^6 (3 2)
H^8	1 41	H^9, H^{10}, H^2, H^3	
H^9	0.98	H^8, H^2, H^3	H^8 (3)
H^{10}	0 95	H^5, H^8	
H^{11}	0 77		H^5 (1 5), H^7 (0.5); H^9 (1 1), H^{10} (1 5)

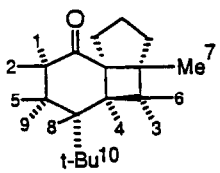
a) $CDCl_3$

Table 2 ^{1}NMR of photoadducts in $CDCl_3$.



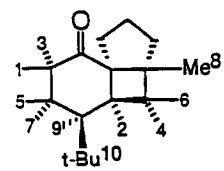
12

H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8	H^9	t-Bu^{10}
2 52	2 4	2 3	2 02	1.98	1.57	1.44	1.21	0.97	0 73



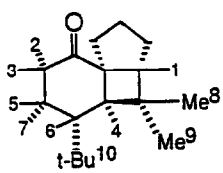
18

H^1	H^2	H^3	H^4	H^5	H^6	Me^7	H^8	H^9	t-Bu^{10}
2 37	1 9	1 79	1.75	1 41	1 36	1 11	1 06	0 91	0 72



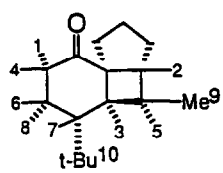
19

H^1	H^2	H^3	H^4	H^5	H^6	H^7	Me^8	H^9	t-Bu^{10}
2 47	2.25	1 91	1 78	1 58	1 49	1.43	0 98	0.94	0 76



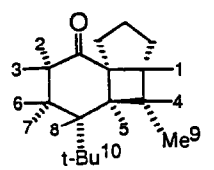
22

H^1	H^2	H^3	H^4	H^5	H^6	H^7	Me^8	Me^9	t-Bu^{10}
2 41	2 3	2 05	1.78	1 45	1.26	1 11	0 9	0.9	0 84



29

H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8	Me^9	t-Bu^{10}
2 3	2 28	2 08	2.02	1 62	1 42	1 29	1 05	0 82	0 7

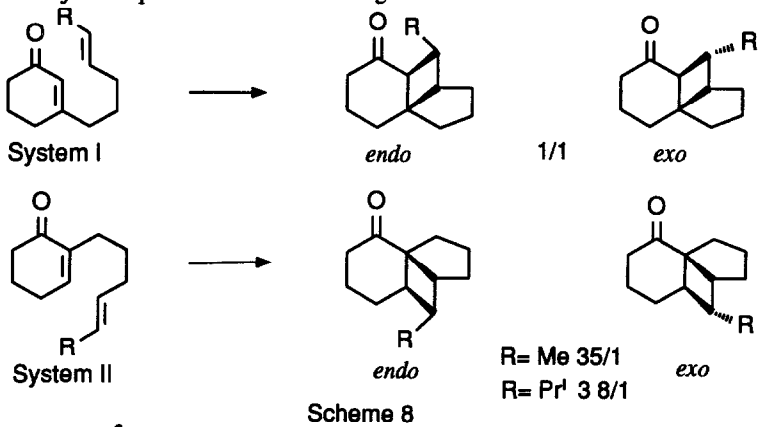


30

H^1	H^2	H^3	H^4	H^5	H^6	H^7	H^8	Me^9	t-Bu^{10}
2 85	2.38	2.18	1 9	1 63	1 52	1 12	1 02	0 82	0 78

Discussion

Photocycloaddition of double bonds to conjugated cycloalkenones is one of the most synthetically useful reactions for preparation of four-membered ring compounds The main drawback of the process arises from the fact that control of stereochemistry is as yet rather unpredictable It is known[7] that in some intramolecular [2+2] photocycloadditions steric effects can play an important role in controlling the stereochemistry of the reaction Our previous work[10] on system I has established that on irradiation two stereoisomers (*endo/exo*) are formed in a 1 1 ratio, independently of the configuration (E or Z) of the olefin in the starting material No steric effect appeared to influence this ratio, since on irradiation in cyclohexane at room temperature using deuterium, methyl, isopropyl or t-butyl as substituents, practically the same 1.1 ratio of *endo* to *exo* isomers was observed On the other hand, if the chain is attached to the cyclohexenone α-carbon (system II) the ratio of the *endo/exo* stereoisomers formed in the photoaddition was found to be dependent on the size of the substituent and on the configuration (E or Z) of the olefin used. The fact that the stereoselectivity in system II was found to be decreasing with increasing size of the substituent encouraged us to subject the process to further investigation



Scheme 8

It has been proposed[2] that [2+2] photocycloaddition to cyclohexenones occurs *via* a twisted intermediate If a twisted form of the cyclohexenone is the active intermediate, the olefin can approach from two non-equivalent faces which will not necessarily lead to the same composition of stereoisomers In order to investigate whether the approaching mode is indeed an important factor in the reaction, we examined the possibility of directing the olefin preferentially to one face of the twisted cyclohexenone by blocking the alternative face with a bulky substituent

Indeed, in the first model studied (**9**), we found that steric effects can to some extent control olefin approach to the excited enone With a bulky group such as t-butyl addition of unsubstituted olefin led to a 2 3 1 *anti/syn* ratio Clearly, the effect is steric in origin, since replacing the t-butyl group with methyl, the

ratio was reduced to 1 4 1 The next step was to examine whether substituents on the chain could increase selectivity. There are some previously reported examples of high selectivity in substrates having substituents on the chain and the ring[11] We were disappointed to find that when methyl was used as the substituent on $C^{1'}$ (**15**) or on $C^{2'}$ (**16**) of the chain, the ratio of *anti* to *syn* photoadducts was only 2 1.

Some improvement in the selectivity apparent in the irradiation of **17**, having a methyl group connected to $C^{4'}$ of the chain and a t-butyl group to C^4 of the ring Here the *anti/syn* ratio was found to be 2 7 1. A dramatic improvement was then observed when at $C^{5'}$ two protons were replaced by methyl groups Irradiation of **20** gave only one photoadduct in practically qualitative yield, with *anti*-stereochemistry Here it appeared that steric effect could fully control olefin approach Clearly the effect is steric in nature, since on replacing the t-butyl by methyl (**21**) the *anti/syn* ratio decreased to 3 1 Encouraged by these findings we decided to proceed to the next step and investigate whether the approach has any influence on the *endo/exo* stereoisomer ratio

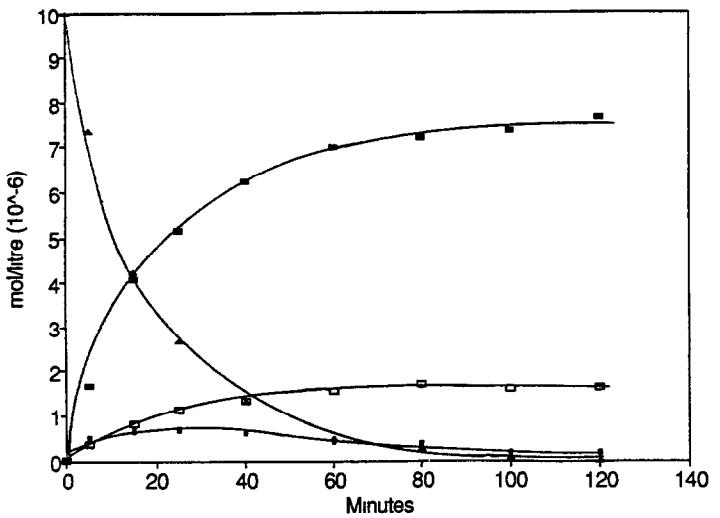
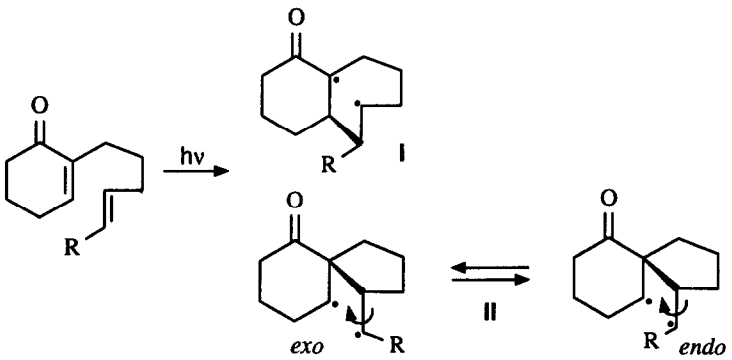


Fig 2 Irradiation of **25** in cyclohexane followed by gas chromatography.
Key. (▲) **25**, (▮) **26**, (■) **29**, (□) **30**

We reported[10] some years ago, that on irradiation of system II having an E (**27**) or Z (**28**) olefin side chain the ratio of *endo/exo* photoadducts (**31 32**) were 35 1 and 5 8 1 respectively, that during the irradiation the rate of photoisomerization of the E ⇆ Z is negligible relative to the rate of product formation, and that the major photoadduct was the *endo* stereoisomer The fact that the *endo/exo* ratio is dependent on the structure of the starting material suggested that in this system the major route to photoadducts does not occur *via* a common diradical intermediate These results were in sharp contrast to our previous observations on system I, where a common diradical intermediate had in fact been proposed

Hence, we now decided to ascertain to what extent the *endo/exo* ratio is dependent on the approaching mode In other words, could an approach from the *anti*-side lead to a different ratio than the one observed in the unsubstituted system? Irradiation of **25** (E) led to *anti*-addition in 94% yield, giving a 4 1 ratio mixture of *endo/exo* stereoisomers In the case of **26** (Z) the *anti*-isomer was formed in 86% yield, and *endo/exo* stereoselectivity was reduced to a 1 8 1 ratio This appears that product composition depends on whether an E or Z olefin is being used as starting material

The irradiation of **25** and of **26** was followed carefully by GC The results obtained for **25**, containing <1% of **26**, are represented in Figure 2 It is evident that in this system cyclization is faster than E⇆Z photoisomerization, and it is thus possible to correlate between starting material structure and products. Both, **25** and **26** have practically the same UV chromophore, and react at similar rates (1 1 1) The irradiation of **26** was followed in short intervals up to 10% conversion It can be concluded beyond any doubt that both stereoisomers **29** and **30** were formed directly from **26**, since the amount of **25** at 10% conversion was <2% of the total amount of enones in solution One can suggest at this point that the *endo/exo* ratio depends on two factors 1) the site of the first bonding (α or β carbon of the cyclohexenone) 2) the relative rates at which a 1,4-diradical intermediate **II** cyclizes to give either *endo* or *exo* The first



Scheme 9

factor is probably dependent on whether an E or a Z olefin approachs the enone If the first bonding is to the β-carbon of the enone, the structure of the stereoisomer is determined (intermediate **I**) If so, the E isomer will form an *endo* and the Z an *exo* adduct, (assuming that the double bonds of the olefin and the enone approach each other in parallel mode) On the other hand, if first bonding is to the α-carbon, then 1,4-diradical intermediate II is formed This can rotate and form two stereoisomers, *endo* and *exo* The second factor should lead to a mixture of *endo exo* photoadducts in a ratio that is not necessarily 1 1, as was found in our laboratory (to be published)

It has been demonstrated[12, 13] that olefins labelled with deuterium can provide information about the mechanism of [2+2] photocycloaddition, particularly on the site of the first bonding, uninfluenced by steric effects When we applied this approach to molecules lacking a substituent on the six membered ring a mixture of *endo/exo* (2 1) was formed With **33**, having a labelled olefin and a bulky t-butyl group, the photocycloaddition led to two *anti* and *syn* photoadducts in a 2 3 1 ratio (as we found in the unlabelled molecule **9**) Significantly, in the *anti* isomer (**35** + **36**) the ratio of *endo/exo* stereoisomers was also 2 1 The same ratio (within experimental error) was found in the case of the unsubstituted molecule **34** and the substituted **33** Our conclusion is that, if no steric effects influence the closure of the four membered ring, the stereoisomer ratio is 2 1 whether the approach is directed or not. Based on this ratio we can calculate that initial bonding to the α-carbon is twice as fast as to the β-carbon of the excited cyclohexenone in this system, assuming that bonding to α-carbon (having deuterium as substituent) leads to a 1 1 *endo/exo* ratio

To sum up, we have found that in the compounds studied the first bonding of the olefin does occur at both α and β-carbon of the excited enone This assumption must be made to explain the fact that the *endo/exo* ratio depends on starting material geometry A further necessary assumption is that steric factors control the *endo/exo* ratio of adducts that are formed from diradical intermediates possessing rotational freedom It seems that the mode of approach of the olefin to the excited cyclohexenone is thus not an important factor in controlling the *endo/exo* ratio

Experimental

General data. Nuclear magnetic resonance spectra were obtained on a Bruker AM-400 MHz NMR instrument equipped with an Aspect 3000 computer, or a Varian T-60 instrument, High resolution MS were measured on a Varian MAT-711 instrument, and GC-MS on an HP 5890 instrument using a Carbowax capillary column (25 m, 0 25 mm), a Perkin-Elmer 298 instrument was used for IR, GC analysis were carried out on an HP 5890 instrument using the following columns a Carbowax capillary column 40 m, 0 25 mm, b Preparative column, 15% CW-20M, Gas-Chromosorb Q, 72-100 mesh, 4 m, 5/32" ID Helium was used as carrier-gas 5-Bromo-1-pentene **1**, commercially available from Fluka, was used without further purification The halo-olefins (E)-6-bromo-2-hexene **6**, (Z)-6-bromo-2-hexene **7**, and (E)-1,2-dideuterio-5-iodo-1-pentene **8**, were prepared as described in ref 10

5-Bromo-1-hexene 2. Ethyl 2-(2-propene)-acetoacetate was prepared according to Valcavi[14] from ethyl acetoacetate (26 g, 0 2 Mol) and allyl bromide (39 g, 0 28 mol) to give 33 5 g of crude product in 98% yield IR ($CHCL_3$) 1720, 1745 cm^{-1}, ^1H NMR (60 MHz, CCl_4) δ 5 8 (m, 1H), 5 15 (m, 2H), 4 23 (q, 2H), 3 6 (t, 1H), 2 62 (t, 2H), 2 3 (s, 3H), 1 3 (t, 3H)

Crude ethyl 2-(2-propene)-acetoacetate (27 5 g, 0 16 mol) was dissolved 10% sodium hydroxide solution (700 mL) and refluxed for 20 h The reaction mixture was cooled to 0°C and acidified by conc hydrochloric acid to pH = 6 The reaction mixture was extracted with methylene chloride (3 x 30 mL), dried over $MgSO_4$, and solvent was removed under reduced pressure to give 10 3 g of crude 5-hexen-2-one in 65% yield IR ($CHCL_3$) 1720 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 5 8 (m, 1H), 5.15 (m, 2H), 2 18 (q, 2H)

To a slurry of LAH (4 g, 0 11 mol) in ether (50 mL) at 0°C was added dropwise crude 5-hexen-2-one (10 g, 0 11 mol) dissolved in ether (5 mL) and stirred at room temperature for 1 h The reaction was quenched with H_2O (4 mL) followed by aqueous NaOH (15%, 4 mL) and than H_2O (12 mL) was added The organic phase was separated from the solid by decantation, dried over $MgSO_4$ and the solvent was removed under reduced pressure The crude oil was chromatographed over silica-gel (eluant hexane-CH_2Cl_2, 1 2) to give 5 g of 5-hexen-2-ol in 50% yield IR ($CHCL_3$) 3620 cm^{-1}, ^1H NMR (60 MHz, CCl_4) δ 5 9 (m, 1H), 5 1 (m, 2H), 3 8 (m, 1H), 1 22 (d, 3H).

To a solution of 5-hexen-1-ol (0 7 g, 7 0 mmol) and triethylamine (1 2 mL) in THF (14 mL) at 0°C was added dropwise methanesulfonyl chloride (0 96 g, 8 4 mmol) The reaction was stirred for 30 min at 0°C and 30 min at room temperature Water (20 mL) was added and the solvent was removed under reduced pressure The reaction mixture was extracted with CH_2Cl_2 (3x20 mL), washed with H_2O (20 mL), dried over $MgSO_4$ and the solvent was removed to give crude 0 87 g of mesylate which was used without further purification ^1H NMR (60 MHz, CCl_4) δ 5 6 (m, 1H), 5 0 (m, 2H), 4 1 (m, 1H), 2 9 (s, 3H), 1 4 (d, 3H)

To a solution of 5-hexen-2-methansulfonate (0 87 g) in THF (20 mL) lithium bromide (anhydrous, 1 2 g, 14 mmol) was added and the reaction was refluxed for 4 h under N_2 The reaction mixture was cooled to room temperature and water (10 mL) was added and the solvent removed under reduced pressure The organic materials were extracted with CH_2Cl_2 (3x15 mL), washed with water (20 mL), dried over $MgSO_4$ and the solvent was removed to give crude oil The crude bromide was chromatographed over silica-gel (eluent hexane) to give 0 57 g of 5-bromo-1-hexene **2** in 50% yield ^1H NMR (60 MHz, CCl_4) δ 5 6 (m, 1H), 5 0 (m, 2H), 4 05 (m, 1H), 1 7 (d, 3H)

5-Bromo-4-methyl-1-pentene 3. Diethyl 2-propenyl malonate was prepared in 98% yield from diethyl malonate (12 3 g, 77 mmol) and allyl bromide (10 5 g 87 mmol) following the procedure described for **2** ^1H NMR (60 MHz, CCl_4) δ 5 6 (m, 1H), 5 1 (m, 2H), 4.23 (q, 4H), 3 3 (t, 1H), 2 6 (t, 2H), 1 36 (t, 6H)

Diethyl 2-propenyl malonate (15 g, 75 mmol) was alkylated with methyl iodide (11 3 g, 80 mmol) as described for **2** to give diethyl methyl (2-propenyl) malonate in 97% yield ^{1}H NMR (60 MHz, CCl_4) δ 5 5 (m, 1H), 5 1 (m, 2H), 4 1 (q, 2H), 2 6 (d, 2H), 1 35 (s, 3H), 1 3 (t, 6H)

Deethoxycarbonylation of diethyl methyl (2-propenyl) malonate (1 0 g, 4.67 mmol) was carried out according to Aneja[15] To a stirred slurry of NaH (0 14 g, 5 5 mmol) in THF (10 mL) at 0°C 1,2-propanediol (1 0 g, 13 mmol) was added and stirred for 30 min at 0°C and 1 h at room temperature A solution of the diester in THF (10 mL) was added and the reaction mixture was refluxed for 30 h The reaction was quenched at room temperature by buffer solution (pH=7, 20 mL) and the THF was removed under reduced pressure The reaction mixture was extracted by CH_2Cl_2 (3x10 mL), washed with brine (10 mL) and dried over $MgSO_4$ The solvent was removed under reduced pressure to give crude ethyl 2-methyl-4-pentenoate (0 58 g, 87%) which was used in the next step with out further purification ^{1}H NMR (60 MHz, CCl_4) δ 5 5 (m, 1H), 5 (m, 2H), 4 0 (q, 2H), 1 3 (3H), 1 22 (t, 3H)

Crude ethyl 2-methyl-4-pentenoate was reduced by LAH as described for **2** to give 2-methyl-4-pentenol in 90% yield IR ($CHCl_3$) 3640 cm^{-1}, ^{1}H NMR (60 MHz, CCl_4) δ 5 6 (m, 1H), 4 9 (m, 2H) 4 1 (s, 1H), 3 3 (d, 2H), 2 1 (m, 1H), 1 7 (m, 1H), 0 9 (d, 3H)

Crude 2-methyl-4-penten-1-ol (1 5 g, 15 mmol) was converted to 5-bromo-4-methyl-1-pentene **3** as described for **2** to give 1 47 g in 60% yield after chromatography over silica-gel using as eluant hexane (45% total yield from diethyl malonate) ^{1}H NMR (60 MHz, CCl_4) δ 5 6 (m, 1H), 5 0 (m, 2H), 3 3 (d, 2H) 1 1 (d, 3H)

5-Bromo-2-methyl-1-pentene 4. The bromo-olefin was prepared according to Pirrung's[11] procedure in 70% yield ^{1}H NMR (60 MHz, CCl_4) δ 4 6 (s, 2H), 3 3 (t, 2H), 1 65 (s, 3H)

6-Bromo-2-methyl-2-hexene 5. Diethyl (3-methyl-2-propenyl) malonate was prepared by alkylation of diethyl matonate and 4-bromo-2-methyl-2-butene as described for **2** in 97% yield ^{1}H NMR (60 MHz, CCl_4) δ 5 0 (t, 1H), 4 1 (q, 4H), 3 2 (t, 1H), 1 7 (d, 6H), 1 3 (t, 3H)

Deethoxycarbonylation was carried out according to Krapcho[16] Diethyl (3-methyl-2-propenyl) malonate (5 g, 22 mmol) was added to solution of DMSO (40 mL) H_2O (1 5 mL) and NaCl (2 g) and the whole heated under N_2 at 180 °C for 12 h The reaction mixture was cooled to room temperature, quenched by water (40 mL), extracted with ether (3x25 mL), washed with water (2x15 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure Ethyl 5-methyl-4-hexenoate (2 3 g, 70% yield) was used in the next step without further purification ^{1}H NMR (60 MHz, CCl_4) δ 5 0 (t, 1H), 4 1 (q, 2H), 2 3 (d, 2H), 1 7 (d, 6H), 1 3 (t, 3H)

Ethyl 5-methyl-4-hexenoate (4 0 g, 25 6 mmol) was reduced by LAH as described for **2**, to give 5-methyl-4-hexen-1-ol (2 5 g, 86% yield) IR ($CHCl_3$) 3615 cm^{-1}, ^1H NMR (60 MHz, CCl_4) δ 5 1 (t, 1H), 4 0 (s, 1H), 3 5 (t, 2H), 1 7 (d, 6H)

5-Methyl-4-hexen-1-ol was converted into the corresponding bromide **5** as described for **2** in 70% yield (41% total yield from diethyl malonate) ^1H NMR (60 MHz, CCl_4) δ 5 1 (t, 1H), 3 5 (t, 2H), 1 7 (d, 6H)

N,N-Dimethyl-2-[4-ter-butylphenoxy]-ethylamine. To a solution of sodium 4-t-butylphenoxide[17] (23 g, 0 133 mMol) in dry dimethylformamide (30 mL) at 50°C sodium hydride ~0 5 g was added till no evolution of hydrogen was observed The solution was cooled to 0°C and N,N-dimethylaminoethylchloride in toluene[18] [prepared from 24 6 g, (0 17 mMol) of N,N-dimethylaminoethylchloride hydrochloride, and 40 mL of toluene was added during 30 min The reaction was stirred for 4 h at 100°C, then cooled to 25°C, water (150 mL) was added and the organic phase was separated The aqueous layer was extracted with 1 1 diethyl ether hexane (3x30 mL) and the organic fractions were combined, washed with 20% NaOH solution, dried over K_2CO_3 and the solvent was removed by reduced pressure The crude oil was distilled (87°C/0 2 mmHg) to give 26 5 g of N,N-dimethyl-2-[4-t-butylphenoxy]-ethylamine in 90% yield ^1H (60 MHz, CCl_4) δ 7 2 (2H, d), 6 7 (2H, d), 4 0 (2H, t), 2 7 (2H,), 2 3 (6H, s), 1 4 (9H, s)

1-[2'-(N,N-Dimethylamino)ethoxy]-4-ter-butyl-1,4-cyclohexadiene . Sodium (4 35 g, 0 19 mMol) was added to ammonia (180 mL) at -33°C and the reaction was stirred for 30 min N,N-Dimethyl-2-[4-t-butylphenoxy]-ethylamine (8 1 g, 36 6 mMol) dissolved in diethyl ether (30 mL) and ethanol (10 mL) was added dropwise and the reaction was stirred at -33°C for 3 h Water ethanol (1 1) (40 mL) were added carefully to the reaction and the ammonia was removed The product was extracted with hexane (3x25 mL), washed with brine, dried over $MgSO_4$ and the solvent was removed under reduced pressure to give 7 36 g of colourless oil in 90% yield which was used in the next step without further purification ^1H (60 MHz, CCl_4) δ 5 4 (1H, t), 4 5 (1H, t), 3 7 (2H, t), 2 7 (2H, t), 2 2 (6H, s), 1 1 (9H, s)

2-[2'-(N,N-Dimethylamino)ethoxy]-5-ter-butyl-3-[4-pentenyl]-1,4- cyclohexadiene. 1-[2'-(N,N-dimethylamino)ethoxy]-4-t-butyl-1,4-cyclohexadiene (0 5 g, 2 24 mMol) was dissolved in dry THF ((5 mL) and the solution was cooled to -70°C n-Butyllithium 2 5M in hexane (1 1 mL, 2 75 mMol) was added *via* syringe, after 1 h hexamethylphosphamide (0 5 mL) was added and the reaction was stirred for 10 min at -70°C A solution of 5-bromopentene (0 33 g, 2 24 mMol) in THF (0 5 mL) was added and the reaction was stirred for 20 min at -70°C and for 3 h at room temperature Brine (5 mL) was added, the solvent was removed under reduced presure, the product was extracted with hexane (3x10 mL), washed with brine, dried over $MgSO_4$ and the solvent removed to give 0 54 g of yellow oil in 83% yield The

product was used in the next step without further purification ^{1}H (60 MHz, CCl_4) δ 5 7 (1H, t), 5 4 (1H, t), 5 0 (2H, m), 4.7 (1H, m), 3 8 (2H, t), 2 7 (2H, t), 2 3 (6H, s), 1 1 (9H, s)

4-ter-Butyl-2-[4-pentenyl]-2-cyclohexen-1-one 9. Hydrolysis of the crude 2-[N,N-dimethylaminoethylether]-5-t-butyl-3-[4-pentenyl]-1,4-cyclo hexadiene (0 5 g) was carried out in a mixture of acetone (20 mL) and 2N-hydrochloric acid (10 mL) under nitrogen at 50°C for 2 h Brine (20 mL) was added and the acetone removed under reduced pressure, the product was extracted with CH_2Cl_2 (3x10 mL), washed with 5% aqueous NaOH, 5% aqueous HCl solution, and brine, dried over $MgSO_4$ and the solvent removed The crude oil was chromatographed over silica gel (eluant hexane·methylene chloride 1 1) to give 0 25 g of 4-t-butyl-2-[4-pentenyl]-2-cyclohexen-1-one **9** in 67% yield IR ($CHCl_3$) 1670 cm^{-1}, ^{1}H (60 MHz, CCl_4) δ 6 6 (1H, d), 5 6 (1H, t), 5 0 (2H, d), 1 0 (9H, s); HRMS Calcd for $C_{15}H_{24}O$ 220 1890, found 220 1871

N,N-Dimethyl-2-[4-methylphenoxy]-ethylamine. The procedure described for preparation of **9** was followed with sodium 4-methyl phenoxide to give N,N-dimethyl-2-[4-methylphenoxy]-ethylamine in 78% yield after distillation at 70°C/0 1 mmHg ^{1}H (60 MHz, CCl_4) δ 6 9 (2H, d), 3 9 (2H, t), 2 6 (2H, t), 2 3 (6H, s), 2 20 (3H, s)

1-[2'-(N,N-Dimethylamino)ethoxy]-4-methyl-1,4-cyclohexadiene. The procedure described for preparation of **9** was followed with N,N-dimethyl-2-[4-methylphenoxy]-ethylamine to give 1-[2'-(N,N-dimethylamino)ethoxy]-4-methyl-1,4-cyclohexadiene in 87% yield ^{1}H (60 MHz, CCl_4) δ 5 3 (1H, t), 4 5 (1H t), 3 7 (2H, t) 2 5 (2H,), 2 3 (6H, s), 1 7 (3H,)

2-[2'-(N,N-Dimethylamino)ethoxy]-5-methyl-3-[4-pentenyl]-1,4- cyclohexadiene. The procedure described for preparation of **9** was followed to give 2-[2'-(N,N-dimethylamino)ethoxy]-5-methyl-3-[4-pentenyl]-1,4- cyclohexadiene in 80% yield ^{1}H (60 MHz, CCl_4) δ 5 6 (1H, m), 4 9 (2H, m), 3 7 (2H, t), 2 6 (2H,), 2 2 (6H, s), 1 7 (3H,)

4-Methyl-2-[4-pentenyl]-2-cyclohexen-1-one 10. The procedure described for preparation of **9** was followed to give **10** in 60% yield after chromatography on silica gel (eluant hexane methylene chloride 1 1) ^{1}IR ($CHCl_3$) 1670 cm^{-1},H (60 MHz, CCl_4) δ 6 3 (1H, d), 5 6 (1H, t), 5 0 (2H, d), 4 7 (1H, t), 1 1 (3H, d)

4-ter-Butyl-2-[1-methyl-4-pentenyl]-2-cyclohexen-1-one 15. The procedure described for preparation of **9** was followed with 5-bromo-1-hexene (0 40 g, 2 47 mMol) and 1-[2'-(N,N-dimethylamino)ethoxy]-4-t-butyl-1,4-cyclohexadiene (0 55 g, 2 47 mMol) to give 0 53 g of crude product which was hydrolized without further purification ^{1}H (60 MHz, CCl_4) δ 3 9 (2H, t), 2 2 (6H, s), 1 3 (3H, d), 1 1 (9H, s)

The hydrolysis procedure for preparation of **9** was followed to give 0 2 g of **15** in 50% yield as a mixture of two diastereoisomers IR ($CHCl_3$) 1675 cm^{-1}, ^1H (400 MHz, $CDCl_3$) δ 6 6 (1H, m), 5.6 (1H, m), 5 0 (2H, d), 1 0 (3H, s), 0.996 (3H, d), 0.946 (9H, s), 0.941 (9H, s) HRMS Calcd for $C_{16}H_{26}O$: 234 2048 , found. 234.2028

4-ter-Butyl-2-[2-methyl-4-pentenyl]-2-cyclohexen-1-one 16. The procedure described for preparation of **9** was followed with 5-bromo-4-methyl-1-pentene (0 36g, 2.24 mMol) to give in 70% yield crude product, ^1H (60 MHz, CCl_4) δ 5 4-4 4 (5H, m), 3.9 (2H, t), 2.3 (3H, d), 2 2 (6H, s) 1 1 (9H, s) The hydrolysis of this was carried out as described for **9** to give **16** in 54% yield after chromatography, as a mixture of two diastereomers IR ($CHCl_3$) 1670 cm^{-1}, ^1H (400 MHz, $CDCl_3$) δ 6 45 (1H, d), 5 6 (1H, m), 5 0 (2H, d), 1.1 (3H, d), 1 0 (9H, s)

4-ter-Butyl-2-[4-methyl-4-pentenyl]-2-cyclohexen-1-one 17. The procedure described for preparation of **9** was modified in the following way. 1 2 eq of 5-bromo-4-methyl-1-pentene (0 44 g, 2 7 mMol) and the reaction was kept at -70°C for 3 h The crude product was isolated after work-up in 95% yield ^1H (60 MHz, CCl_4) δ 5 25 (5H, m), 4 45 (3H, m), 2 2 (6H, s), 1 7 (3H, d), 1 1 (9H, s) The hydrolysis of this (0 4 g, 1 31 mMol) was carried out in acetone (5 mL) and 1M hydrochloric acid (3 mL) at room temperature for 5 h Brine (20 mL) was added and the acetone was removed by reduced pressure, the reaction mixture was extracted by CH_2Cl_2 (3x15 mL), the organic phase was washed with water (10 mL) and the solvents removed According to NMR the crude product was a mixture of two isomers with double bond at 2 and 3, full rearrangement to conjugation was carried out dissolving the mixture in 2% NaOH in methanol (10 mL) and stirring for 10 h under nitrogen. Water (10 mL) was added, the methanol was removed by reduced pressure and the product was extracted by CH_2Cl_2 (3x15 mL) washed with brine and dried over $MgSO_4$, the solvent was removed The crude oil was chromatographed over silica-gel (eluant hexane methylene chloride 1 1) to give 0 16 g of **17** in 60% yield IR ($CHCl_3$) 1670 cm^{-1}, ^1H (400 MHz, $CDCl_3$) δ^1 6.5 (1H, s), 4 74 (1H, s), 4 68 (1H, s), 1 5 (3H, s), 1 0 (9H, s), ^{13}C (100 MHz, $CDCl_3$) δ 199 57 (C=O), 147 46 (=CH), 139 67, 130 02, 109 91 (=CH_2), 47 09, 38 27, 37 48, 32.99 ($C(CH_3)_3$), 29 56, 27 35 (CH_3), 26.83, 24 62, 22 34 HRMS Calcd for $C_{16}H_{26}O$. 234 2048, found 234 2021.

4-ter-Butyl-2-[5-methyl-4-hexenyl]-2-cyclohexen-1-one 20. The procedure described for preparation of **9** was followed using 6-bromo-2-methyl-2-hexene (133 mg, 0 75 mMol) which yielded 155 mg of crude product ^1H (60 MHz, CCl_4) δ 5 4-4 9 (2H, m), 4 6 (1H, t), 4 1 (2H, t), 2 3 (6H, s), 1 75 (3H, s), 1 65 (3H, s), 1.0 (9H, s) The hydrolysis was carried out as described for **9** and the product was chromatographed over silica-gel (eluant hexane methylene chloride 1 1) to give 65 mg of **20** in 54% yield IR ($CHCl_3$) 1670 cm^{-1}, ^1H (60 MHz, CCl_4) δ 6 5 (1H, s), 5 1 (1H, t), 1 7 (3H, s), 1 6 (3H, s), 1 0 (9H, s)

HRMS Calcd for $C_{17}H_{28}O$· 248 2206; found 248 2179

4-Methyl-2-[5-methyl-4-hexenyl]-2-cyclohexen-1-one 21. The procedure described for preparation of **10** was followed using 6-bromo-2-methyl-2-hexene (133 mg, 0 75 mMol) which yielded 165 mg of crude product. ^1H (60 MHz, CCl_4) δ 5 4-4 8 (2H, m), 4 6 (1H, t), 4 1 (2h, t), 2 3 (6H, s), 1 6 (9H, bs), 1 1 (9H, s) Hydrolysis was carried out as described for **10** to give after chromatography 64 mg of **21** in 70% yield IR ($CHCl_3$) 1670 cm^{-1}, ^1H (60 MHz, CCl_4) δ 6 3 (1H, m), 5 1 (1H, t), 1 7 (3H, s), 1 6 (3H, s), 1 1 (3H, d)

4-ter-Butyl-2-[(E)-4-hexenyl]-2-cyclohexen-1-one 25. The procedure described for preparation of **9** was followed using (E)-6-bromo-2-hexene gave crude product in 90% yield ^1H (60 MHz, CCl_4) δ 5.3 (3H, m), 4 6 (1H, m), 3 7 (2H, t), 2 5 (2H, t), 1 6 (3H, d), 1 1 (9H, s) The hydrolysis was carried out as described for **9** to give after chromatography 63% yield pure **25** IR ($CHCl_3$) 1670 cm^{-1}, ^1H (400 MHz, $CDCl_3$) δ 6 6 (1H, d), 5 45 (2H, bs), 2 5 (2H, m), 1 6 (3H, d), 1 1 (9H, s) HRMS Calcd for $C_{16}H_{26}O$ 234 2048, found 234 2032

4-ter-Butyl-2-[(Z)-4-hexenyl]-2-cyclohexen-1-one 26. Alkylation was carried out with (Z)-6-bromo-2-hexene as described for **9** to give crude product in 90% yield ^1H (60 MHz, CCl_4) δ 5 1-5 5 (3H, m), 4 6 (1H, m), 3 7 (2H, t), 2 5 (2H, t), 1 6 (3H, d), 1 1 (9H, s). Hydrolysis was carried out as described for **9** to give in 70% yield after chromatography of pure **26** IR ($CHCl_3$) 1670 cm^{-1}, ^1H (400 MHz, $CDCl_3$) δ 6 6 (1H, d), 5 35 (2H, bs), 2 5 (2H, m), 1 6 (3H, d), 1 1 (9H, s) HRMS Calcd for $C_{16}H_{26}O$ 234 2048, found 234 1996

4-ter-Butyl-2-[(E)-4,5-dideuterio-4-pentyl]-2-cyclohexen-1-one 33. The procedure described for preparation of **9** was followed using (E)-1,2-dideuterio-5-iodo-1-pentene to give crude product that was hydrolized as described for **9** to give after chromatography **33** in 65% yield IR ($CHCl_3$) 1670 cm^{-1}; ^1H (400 MHz, $CDCl_3$) δ 6 6 (1H,s), 5 3 (1H, s), 2 5 (2H, m), 1 05 (1H, s).^2H (61 MHz, C_6D_6) δ 5 77 (1D, s), 4 97 (1D, s) HRMS Calcd for $C_{15}H_{22}D_2O$ 222 2014; found 222 1985

Irradiations: Irradiations were carried out in cyclohexane as solvent under nitrogen atmosphere The commercial cyclohexane was purified by shaking with concentrated sulfuric acid and then with 10% sodium carbonate Irradiation was carried out through quartz using a 450-W Hanovia lamp for 4 hours followed by distillation The photocyclizations were carried out in concentrations of < 0 05 mol using a 450-W Hanovia lamp or 80-W Hanau Mercury Vapor lamp (Q-81) with Uranium (λ >330 nm) or Pyrex (λ >295 nm) glass filters The photoreactions were followed by UV absorption of the starting material and/or GC analysis (columns a or b) Preparative GC was carried out by collecting the product in glass tubes ID= 2 mm using a gradient oven (200°C to -170 °C), for our compounds the efficiency achieved was >95%

All photoadducts have strong bend in IR at 1690 cm^{-1} The following retention times (column A', oven temp 120°C) and HRMS were recorded for the photoadducts **11**. 10 4 min, **12** 11 8 min; HRMS calc for $C_{15}H_{24}O$ 220.1827, found 220 1807 **13**. 5 6 min, **14** 6 4 min, HRMS calc for $C_{12}H_{18}O$ 178.1358, found 178.1334 **18** 9 0 min, **19** 10.3 min, HRMS calc for $C_{16}H_{26}O$ 234 1983, found 234 1941 **22**· 9 6 min, HRMS calc for $C_{17}H_{28}O$ 248 2140, found 248 2105. **23**. 6 6 min, **24** 7.6 min; HRMS calc for $C_{14}H_{22}O$ 206 1671, found 206 1687 **29** 10.4 min, **30**: 13 0 min, HRMS calc for $C_{16}H_{26}O$ 234.1984, found 234 2011 **35** 10 4 min, HRMS calc for $C_{15}H_{22}D_2O$ 222 1952, found 222 1907

Acknowledgment We thank Dr. M Kapon for X-ray analysis

References

1) a) Schuster, D. I., *The Chemistry of Enones*, Z Rappoport Ed ; Wiley, 1989, Part 2, 623-756 b) Crimmins, M. T. *Chem Rev* **1988**, *88*, 1453-1473

2) a) Kearns, D R., Marsh, G, Schaffner, K *J Amer Chem Soc* **1971**, *93*, 3129-3137 b) De Mayo, P *Acc Chem Res* **1971**, *4*, 41-47

3) Schuster, D I , Brown, P. B , Capponi, L. J , Rhodes, C. A., Scaiano, J C Tucker, P C. Weir, D *J Amer Chem Soc* **1987**,*109*, 2533-2534

4) Corey, E J., Bass, J D , LeMahieu, R , Mitra, R B *J Am Chem Soc* **1964**, *86*, 5570-5583

5) de Mayo, P , Loutfy, R O. *J Am Chem Soc* **1977**, *99*, 3559-3565

6) Schuster, D I , Heibel, G E , Brown, P B ; Turro, N J , Kumar, C V *J Am Chem Soc* **1988**, *110*, 8261-8263

7) Becker, D , Haddad, N *Org Photochemistry*, A Padwa Ed Dekker Inc New-York, 1989, *10*, 1-162

8) Oppolzer, W., Godel, T *Hel Chem Acta* **1984**, *67*, 1154-1167

9) Amupitan, J , Sutherland, J K *J Chem Soc , Chem Comm* **1978**, 852-853

10) Becker, D , Nagler, M , Sahali, Y , Haddad, N *J Org Chem* **1991**, *56*, 4537-4543

11) Pirrung, M C *J Amer Chem Soc* **1981**, *103*, 82-87

12) Schroder, C , Wolff, S., Agosta, W C *J Amer Chem Soc* **1987** *109* 5491-5497

13) Becker, D., Haddad, N *Israel J Chem* **1989**, *29*, 303-305

14) Valcavi, U , Farina, P , Innocenti, S *Synthesis* **1983**, 124-125

15) Aneja, R , Hollis, W M , Davis, A P , Eaton, G *Tetrahedron Lett* , **1983**, *24*, 4641-4644

16) Krapcho, A O , Lovely, A S *Synthesis* **1982**, 893-914

17) Boehme, W R. *Organic Synthesis*, Coll Vol IV, **1963**, 590-593

18) Hall, L A *Organic Synthesis*, Coll Vol IV, **1963**, 333-335