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PHOTOCHEMICAL CYCLIZATION OF β-FARNESENE*

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Abstract—The naphthalene-sensitized and direct irradiation of β-farnesene (**9**) has been investigated. The sensitized reaction gives a mixture of stereoisomeric bicyclo[2.1.1]hexanes (**10** and **11**), which were separated via their tetrahydro derivatives (**13** and **14**). Direct irradiation of **9** affords a cyclobutene (**16**) as the major product, accompanied by small amounts of **10**, **11** and a fourth hydrocarbon assigned structure **19**. A mechanism is proposed for the formation of **10** and **11** in the sensitized process involving a complex of excited diene and ground-state olefin, which subsequently collapses to a biradical intermediate C.

ATTEMPTS to induce intermolecular cycloaddition of dienes to olefins by photosensitization methods have met with limited success, mainly as a result of competition from efficient dimerization of the diene unit.[1] With intramolecular addition, however, dimerization can be suppressed by dilution of the substrate, and the products in these cases have been shown to depend markedly on the nature of the excited diene.[2,3] For example, direct irradiation of myrcene, (**1**), is reported to lead to a complex mixture of products, among which β-pinene (**2**),[4] a cyclobutene (**3**),[5] and a bicyclo[2.1.1] hexane derivative (**4**),[6] have been identified. Sensitized irradiation of **1** on the other hand, leads exclusively to (**4**).[2] The latter process presumably involves addition of excited triplet diene to ground state olefin and suggests the intervention of a discrete biradical intermediate A. The stereochemical consequence of an intermediate such as A is, of course, not visible in the structure of the product derived from myrcene, but sensitized irradiation of *cis*- and *trans*-3-methylene-1,5-heptadienes (**5** and **6**) is found to produce the same mixture of stereoisomeric bicyclo[2.1.1] hexanes (**7** and **8**), suggesting a common intermediate B in which ring closure is slow relative to bond rotation.[2]

It was of interest to extend these photochemical studies to the case of *trans*-β-farnesene (**9**), where the diene component is presented with alternative alkene sites for addition within the molecule, and we now report results on the photochemistry of **9** which show that, in a sensitized reaction, this system undergoes a remarkably selective, intramolecular cycloaddition.

RESULTS

trans-β-Farnesene (**9**) was prepared by the method of Bhati[7] and was purified by passage through a column of silica gel impregnated with silver nitrate. Material obtained in this way was shown to be homogeneous by GLPC and was identified by its NMR spectrum[8] and by comparison with **9** prepared from π-geranyl-nickel bromide and 2-bromomethyl-1, 3-butadiene.[9] Irradiation of a 0·01M solution of **9** in n-pentane containing 1·5 mmoles of naphthalene through Pyrex for 24 hr afforded, after

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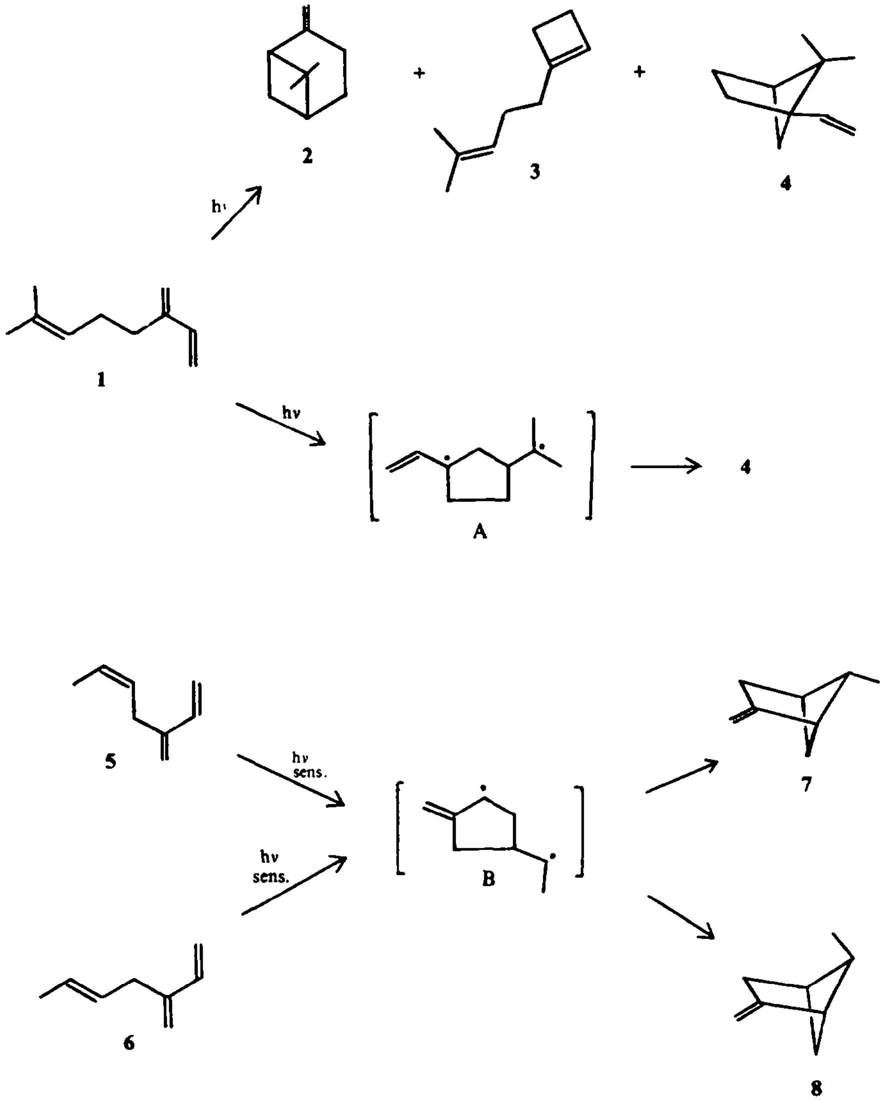
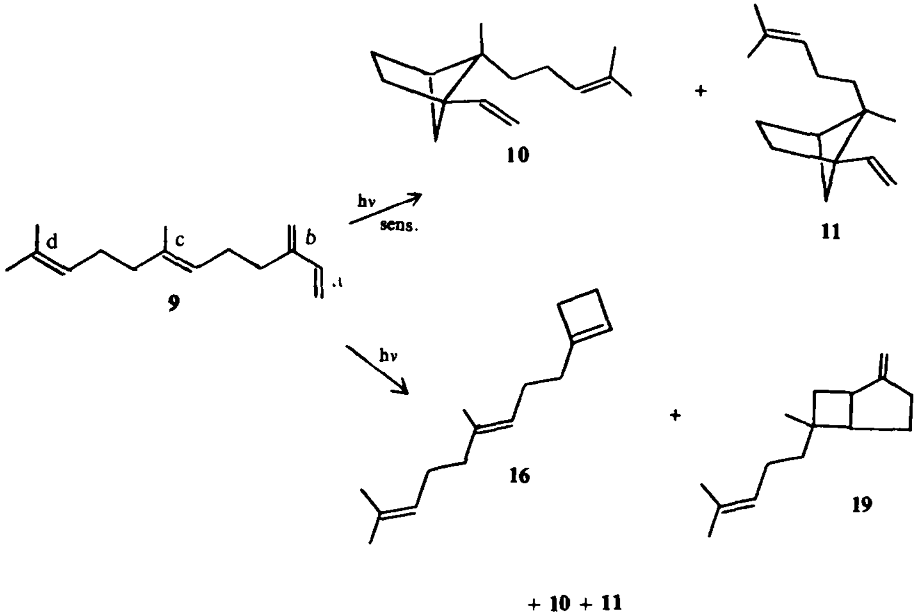
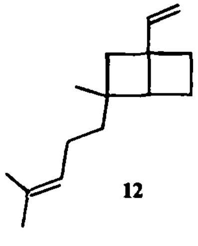
removal of the solvent and distillation of the oily residue, a small amount of unchanged **9** and 50% of two stereoisomeric bicyclo[2.1.1]hexane derivatives (**10** and **11**). The bicyclic products were poorly resolved under all GLPC conditions investigated and characterization of these substances was carried out on the mixture. It is apparent from the NMR spectrum of the mixture, which shows four vinylic Me groups in two sets (δ 1·59 and 1·65) and eight vinylic protons distributed between two groups of signals (6H and 2H), that each product is derived by internal addition of bonds b and c. The thermal stability of the mixture at temperatures up to 320° argues strongly for products (bicyclo[2.1.1]hexanes) derived from cross addition of b and c, rather than bicyclo[2.2.0]-hexanes (**12**) derived from parallel addition.[3,10] Two sharp singlets at δ



0·78 and 1·12 of approximately equal area account for Me groups attached to the cyclobutane ring, the lower field signal being assigned to isomer **11** with *endo* Me substituent (i.e. quasi-axial with respect to the cyclobutane ring).[11]



Catalytic hydrogenation of the mixture of **10** and **11** resulted in the uptake of two molar equivalents of hydrogen and quantitative formation of tetrahydro derivatives **13** and **14**. These could now be separated readily by preparative GLPC and their quantitative estimation indicated that the original mixture from photolysis of **9** had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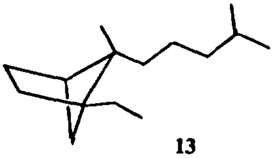
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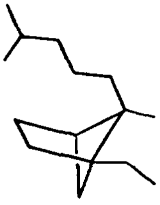
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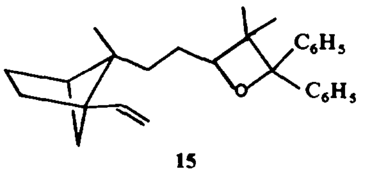
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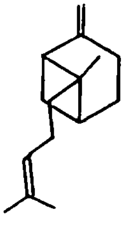
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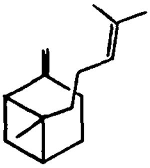
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consisted of 47% of **10** and 53% of **11**. Me singlets at δ 0·72 and 1·10 were again used to assign *exo* (**13**) and *endo* (**14**) stereochemistry respectively.[11]

Photolysis of **9** through Pyrex with benzophenone as sensitizer also led to **10** and **11**, but it became evident after several hours of irradiation that the sensitizer had been partially consumed. Cursory examination of the reaction products suggested that benzophenone had reacted with the trisubstituted double bonds of **10** and **11** to form oxetanes (e.g. **15**).

In contrast to the sensitized reaction, direct irradiation of **9** in n-pentane through a Vycor filter resulted, after distillation, in a mixture consisting of four principal components. Two of these, obtained in a combined yield of 5%, were identified as the same bicyclo[2.1.1]hexanes **10** and **11** (ratio 1 : 1) as were produced in the sensitized process. The major component of the photolysis mixture (56%) retained, according to the NMR spectrum, the three vinylic Me groups and possessed three olefinic protons, one of which (δ 5·67) could be assigned to a cyclobutene ring.[12] These features, together with the absence of infrared absorption due to a vinyl group, indicated structure **16**, and this was confirmed by pyrolysis at 240° with smooth regeneration of **9**.[3, 13] The fourth product (5%) from the photolysis of **9** was again isomeric with starting material and its IR spectrum which showed strong bands at 1645 and 875 cm^{-1}, but no absorption characteristic of a vinyl group, suggested a structure containing an *exo* methylene function. The NMR spectrum of this substance revealed two vinylic Me groups and a third attached to a saturated and fully substituted C atom. There were three olefinic protons, two of which appeared as a multiplet at δ 4·6 and are assigned to the *exo* methylene group. This product must, therefore, derive from addition of bonds a and c. Cross addition, in analogy to the formation of β-pinene from myrcene,[4] would yield **17** (assuming retention of stereo-

TABLE 1. IR BANDS AND PROTON CHEMICAL SHIFTS OF β-FARNESENE PHOTOPRODUCTS

		Chemical Shifts (δ)	
Cpd	$-\nu_{max}$(cm^{-1})	Olefinic	Methyl
9	1600, 990, 905, 890	6·1–6·7 (1 H)	1·69 (3 H)
		4·9–5·4 (6 H)	1·61 (6 H)
10 + **11**	1635, 990, 910, 830	5·6–6·2 (1 H)	1·65 (3 H)
		4·7–5·4 (3 H)	1·59 (3 H)
			$\left.\begin{array}{l}1\cdot12\\0\cdot78\end{array}\right\}$(3 H)
13	—	—	0·89* (6 H)
			0·72 (3 H)
14	—	—	0·88* (6 H)
			1·10 (3 H)
16	1640, 855	5·67 (1 H)	1·69 (3 H)
		4·9–5·3 (2 H)	1·62 (6 H)
19	1645, 875, 830	4·9–5·3 (1 H)	1·70 (3 H)
		4·6 (2 H)	1·62 (3 H)
			0·72 (3 H)

*Doublet (J = 6 cs)

chemistry at bond c during addition), a structure assigned to the sesquiterpene β-bergamotene.[14] However, comparison of our compound with natural β-bergamotene[*] showed that they differed in several respects, particularly in regard to the chemical shift of the Me group attached to saturated carbon.[†] Moreover, the properties of the photoproduct also differed from those reported for *cis*-β-bergamotene (**18**),[‡] recently synthesized by Gibson and Erman.[14] The structure of this compound is accordingly formulated as the bicyclo[3.2.0]heptane derivative **19**, derived from parallel addition of a and c, with stereochemistry undefined. Despite careful analysis of the mixture of photoproducts from **9**, no β-bergamotene could be detected. Direct irradiation of **9** in ether solution gave results virtually identical with those obtained with n-pentane as solvent, and addition of cuprous chloride to the ethereal solution produced no noticeable change in product distribution after photolysis.

DISCUSSION

The formation of stereoisomeric products **10** and **11** in the sensitized cyclization of **9** is consonant with a biradical intermediate C, and the ratio of the two products indicates that, within the limits of detection, complete stereochemical randomization has occurred.[‖] According to the Wigner hypothesis,[17] C would inherit triplet character from excited sensitizer and, as previously noted,[2] bond closure to form the bicyclo[2.1.1]hexane skeleton might be delayed relative to bond rotation either by the requirement for spin inversion or by thermodynamic effects involving development of ring strain.

The clear preference for formation of intermediates having a 5-membered ring is more striking and in the present case, as in other instances of photochemical cyclization of dienes,[18] is not explicable simply in terms of the relative stabilization through inductive or resonance effects of biradical intermediates. Liu and Hammond have suggested that this selectivity is associated with kinetic control of the first addition step and that "the preference for formation of 5-membered rings may merely reflect the fact that the C atoms that become bonded are, on the average, closer together than those that would have to interact to form a 6-membered ring."[2] A purely statistical argument of this type would necessitate a highly oriented ground state of the substrate to account for the observed specificity, a premise which seems unlikely for the hydrocarbon systems exhibiting this behavior. On the other hand, experimental evidence points strongly towards a mechanism in which the mode of intramolecular addition is determined in a step prior to formation of the intermediate biradical, and we have,

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[*] We are indebted to Professor R. B. Bates, University of Arizona, for a sample of natural α- and β-bergamotene.

[†] The signal for this Me group appears at δ 0·95 in the published spectrum of β-bergamotene and at δ 1·22 in synthetic **18**.[14]

[‡] The *cis* formulation **18** for β-bergamotene was preferred by Bhattacharyya *et al.*[15] but is disproved by synthesis.[14] The stereochemical designation **17** is in accord with that assigned to α-bergamotene by Kovats.[16]

[‖] Recovery of unreacted β-farnesene at the end of the sensitized reaction, and examination by GLPC under conditions (12 ft column of 5% Carbowax 20M on base-washed Chromosorb P at 150°) shown to resolve *cis* and *trans* isomers, indicated that no detectable isomerization of **9** to the *cis* isomer had occurred.

therefore, been prompted to consider an oriented complex of excited diene and ground state olefin as the reactive species controlling the first step of cycloaddition.* A consideration of MO interactions between partners in a photochemical reaction leads to the general conclusion that a stabilizing situation will develop when the orbital which loses an electron in the excited component can interact with an orbital of *lower* energy in the ground state component and when the orbital containing the promoted electron can interact with an orbital of *higher* energy in the ground state molecule.† Both of these conditions can be met by a complex of excited diene and ground state olefin, and Figure 1 shows the redistribution of energy levels in such a complex resulting from mixing of ψ_2 and ψ_3 orbitals of the diene (triplet) with ψ_1 and ψ_2 of the olefin respectively.‡ Although the precise geometry of this complex is not specified in the above treatment,§ the most favorable orientation on steric grounds would seem to be that involving coordination of bonds b and c (which leads to a complex, e.g. D

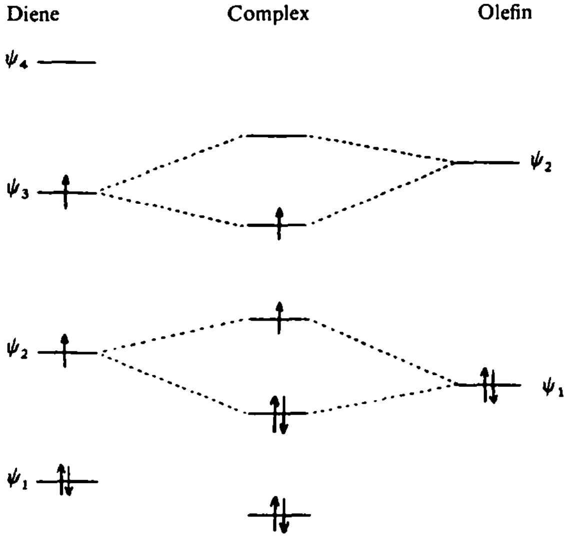

FIG. 1 Redistribution of energy levels in a complex of excited (triplet) diene and ground-state olefin.

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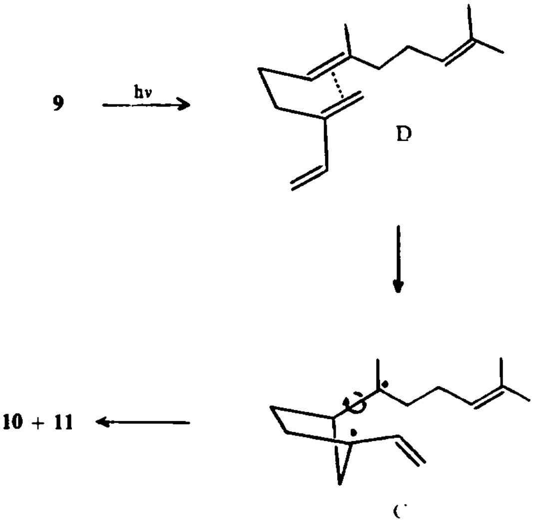
*An oriented π-complex has been postulated to explain selectivity in the mode of photochemical cycloaddition of enones to olefins.[19]

†This principle has been developed in detail by Salem.[20]

‡ A referee has suggested the possibility "that naphthalene was not acting as a triplet sensitizer, but that its singlet state and the 'ene' acceptor were forming a reactive complex with the diene." We had considered this alternative but rejected it on the following counts: (i) other sensitizers (benzophenone, xanthone) also lead to **10** and **11** as primary photoproducts; (ii) in the demonstrated absence of isomerization of **9** to *cis*-β-farnesene, a singlet mechanism does not readily account for formation of stereoisomeric bicyclo[2.1.1]hexanes; (iii) the sensitized reaction is quenched by piperylene.

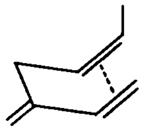
§ However, if the configuration of the complex is determined primarily by $\psi_2^{\text{diene}}\psi_1^{\text{olefin}}$, as seems reasonable, the symmetries of the interacting states would require that the olefin coordinate in a 1,2 sense with the diene (ψ_3^{diene} ψ_2^{olefin} would lead to a 1,2 or 1,3 interaction).

containing a pseudo 6-membered ring). All other combinations (except a and b) lead to complexes with rings containing more than six members and should, therefore, be disfavored by the attendant non-bonded interactions. Subsequent bond formation from the complex may be determined by radical stabilities, at least where such bond formation proceeds stepwise or unsymmetrically so that collapse of D would lead to C.*



Formation of cyclobutene **16** as the major product from direct irradiation of **9** parallels the photochemical behavior of myrcene (**1**), and is presumed to occur via an excited singlet state of **9**. The small amount of **10** and **11** formed in the direct photolysis may represent leakage of this excited singlet into the triplet manifold and reaffirms the inefficiency of intersystem crossing for dienes. In the formation of **19** and the absence of a bicyclo[3.1.1]heptane cycloaddition product, the photochemistry of **9** diverges from that of **1**. Conceivably, this could be due to small differences in ground- or excited-state conformations of the mono- and sesquiterpenes.

*Naphthalene sensitization (E_t ~ 61 kcal/mole) probably leads initially to diene triplets with a *trans* configuration.[21] As complex formation proceeds, the barrier (~6 kcal/mole) separating *cisoid* and *transoid* triplets would presumably decrease—compensated in part by the stabilization energy of the complex. Thus, a planar excited diene system would not seem to be a requirement for complex formation, and an intermediate such as E preceding B (from 5) might be attainable, even though the π systems of the diene are virtually orthogonal.



E

Mass spectra were obtained with an A.E.I. MS–9 spectrometer at 70 eV. using direct insertion into the ion source. Analytical GLPC was carried out with an F & M Model 609 gas chromatograph equipped with flame ionization detector. For preparative GLPC a Wilkens Autoprep 700 was used with He as carrier. Irradiations were carried out using a 450 W high-press-Hg-vapor lamp (Hanovia. Type L) placed in a water-cooled quartz immersion well. The irradiation vessel was equipped with a gas inlet and the mixture was kept agitated during irradiation with a slow stream of N_2.

β-Farnesene (**9**). Crude material was prepared from 40 g farnesol by dehydration with 360 g powdered KOH.[7] The crude product was distilled and the fraction collected with b.p. 64–110° (1·5 mm). The distillate was chromatographed on silica gel impregnated with 10% $AgNO_3$. and the fractions eluted with 1 : 1 benzene-hexane were found to contain pure β-farnesene. In this way 3·0 g of **9** (>99·5%) was obtained. Later fractions gave a further 6·1 g of **9** containing a trace impurity which could be removed by a second passage through the column.

Sensitized irradiation of **9**. A soln of 2·94 g (14·4 mmoles) of **9** and 0·15 g (1·17 mmoles) naphthalene in 170 ml n-pentane was purged with a stream of N_2 and irradiated through a Corex filter for 20 hr. The soln was filtered (to remove a small quantity of precipitated. polymeric material) and the solvent was removed *in vacuo*. The residue was distilled under reduced press and a fraction having b.p. 50–64° (0·15 mm) was collected. The distillate was chromatographed on 90 g silica gel impregnated with 10% $AgNO_3$. and the fraction eluted with hexane–benzene (9 : 1) afforded 1·48 g (50%) of the mixture of **10** and **11**, as a colorless oil. *m/e* 204. Later fractions contained **10** and **11** admixed with small amounts of β-farnesene.

Hydrogenation of **10** and **11**. A soln of 0·88 g (4·3 mmoles) of the mixture of **10** and **11** in 30 ml of n-pentane containing 0·05 g 5% Pd–C was hydrogenated at atm press. H_2 uptake was rapid and stopped after 2 equivts had been consumed. The soln was filtered and the solvent was removed *in vacuo* to give 0·89 g (99%) of **13** and **14**. The saturated hydrocarbons were separated by preparative GPLC on an 8 ft column of 20% TCEP on Chromosorb W (column temp of 105°). The two fractions. eluted in order. were **14** (53%). *m/e* 208·2198 (calc. for $C_{15}H_{28}$: 208·2191) and **13** (47%). *m/e* 208·2189.

Direct irradiation of **9**. A soln of 0·660 g (3·23 mmoles) of **9** in 150 ml n-pentane was purged with a stream of N_2 and irradiated through a Vycor filter for 6 hr. After removal of the solvent. the residue was chromatographed on silca gel impregnated with 10% $AgNO_3$. Elution with hexane–benzene (3 : 1 – 1 : 1) afforded a mixture containing **9**. **10**. **11**. and **19**. Separation by preparative GLPC. using a 5½ ft column of 5% XE–60 on Chromosorb W at 125°. gave first a mixture of **10** and **11** (1 : 1 estimated from NMR). identical with the mixture obtained in the sensitized irradiation of **9**. followed by **19**. *m/e* 204·1885 (calc. for $C_{15}H_{24}$: 204·1878). Further elution of the silica–$AgNO_3$ column with benzene afforded 0·366 g (56%) of **16**. *m/e* 204·1863.

Pyrolysis of **16**. 136 mg (0·67 mmoles) of **19** was passed through a gas chromatograph with the inlet port at 240° and the column (XE–60 as above) at 125°. The eluant showed a single peak corresponding in retention time with β-farnesene. The product was identified as **9** by comparison of IR and NMR spectra with those of material prepared as described above.

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