Table II. Radioactivity in Rat Tissues at Different Survival Times following Intravenous Administration of 10 μCi/100 g bw of [^{14}C]Malathion Assayed by Liquid Scintillation Counting (Results Expressed as Micrograms of Malathion Equivalents/Gram of Tissue and Represent Values Obtained from Two Parallel Samples of 10 mg of the Tissues)

time after admin	liver	kidney	brain	small intestine	large intestine
1 min	3.38	12.35	0.05	0.00	0.11
3 min	4.05	2.51	0.25	0.73	0.01
10 min	1.21	8.98	0.11	1.31	0.01
1 h	1.19	0.98	0.13	4.19	0.07
2 h	0.30	0.73	0.00	0.12	0.29
6 h	0.00	0.34	0.00	0.00	0.38
12 h	0.00	0.00	0.00	0.00	0.29
24 h	0.00	0.07	0.00	0.00	0.02

DISCUSSION

Whole-body autoradiography gives a picture of the distribution of the total radioactivity administered and does not differentiate between the labeled compound and its metabolites. The results of the present study show that malathion is rapidly distributed to different organs in the rat, with the highest concentration found in the kidney. Peak levels of radioactivity in the liver and the kidney are reached within a few minutes following administration. After 1 h, the level in the kidney is reduced to about 5% of the maximum amount in that organ. After 24 h, the values of radioactivity are low in all organs. This indicates that the excretion of malathion is rapid. This is in agreement with the results published by Bourke et al. (1968). He found that after administration of 25 mg of [^{14}C]malathion to rats, activity appeared in the urine within 2 h and 91.7% was eliminated within 24 h, while an additional 7.75% remained in the gastrointestinal contents. Gupta and Paul (1976) have shown that over 90% of a single oral dose of malathion was excreted within 24 h in the hen. They found the highest concentration of malathion in the liver followed by the kidney and other organs. In a study on malathion used as an ectoparasitic agent on cattle, a rapid decline was demonstrated in the levels of malathion in blood and milk following an intravenous injection of the compound to lactating cows (Muan et al., 1985).

The presence of relatively high levels of radioactivity in the intestinal content may be due to bile excretion, mucosal secretion, or both. Eating of evacuation may be the explanation for the radioactivity detected in the esophagus and stomach. With the exception of the liver, the kidney, and the intestines, whole-body autoradiography revealed no particular accumulation organ for malathion.

Registry No. Malathion, 121-75-5.

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1-(4-Ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octanes: A New Order of Potency for Insecticides Acting at the GABA-Gated Chloride Channel

Christopher J. Palmer* and John E. Casida

1-(4-Ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octanes were prepared as candidate insecticides via palladium-catalyzed coupling of (trimethylsilyl)acetylene with the corresponding 1-(4-iodophenyl) compound or by dehydrobromination of the 1-[4-(1,2-dibromoethyl)phenyl] derivative. The 4-*tert*-butyl-1-(4-ethynylphenyl)trioxabicyclooctane has a topical LD_{50} for adult female houseflies (*Musca domestica* L.) of 0.06–0.09 μg/g alone or 0.01 μg/g on synergism with piperonyl butoxide at 25 or 35 °C. It is 20- to 40-fold more potent than previously reported 1,4-disubstituted trioxabicyclooctanes and is equal in potency to (1*R*,*cis*)-permethrin at 25 °C and (1*R*, *cis*,α*S*)-cypermethrin at 35 °C. This *tert*-butyl compound and its *n*-propyl and cyclohexyl analogues alone or with synergist are also much more potent than dieldrin, DDT, (1*R*,*trans*,α*S*)-allethrin, parathion, and propoxur. It therefore appears that suitable trioxabicyclooctanes acting at the GABA-gated chloride channel approach or reach the potency of the most effective established insecticides acting on sodium channels and the cholinergic system.

The 1,4-disubstituted 2,6,7-trioxabicyclo[2.2.2]octanes are a new class of insecticides that probably act as $GABA_A$ receptor antagonists and thereby inhibit GABAergic synaptic transmission (Palmer and Casida, 1985, 1987; Casida and Palmer, 1988). The compounds reported to date are very effective against houseflies and American cockroaches but only in the presence of piperonyl butoxide (PB), indicating that their toxicity is limited by oxidative detoxification.

The present study attempts to improve the insecticidal activity of trioxabicyclooctanes and minimize the need for a synergist by appropriate modifications of substituents in the 1- and 4-positions. Houseflies are used for the primary bioassays because of the available structure–activity data with this species. A more general goal is to

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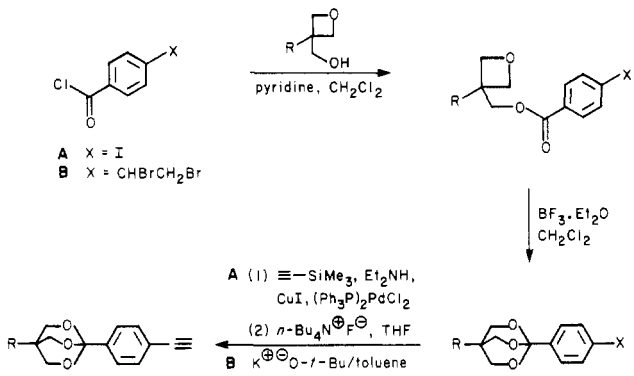

Figure 1. Two methods for synthesis of 1-(4-ethynylphenyl)-4-substituted-2,6,7-trioxabicyclo[2.2.2]octanes. Detailed syntheses are given in the text for the 4-*tert*-butyl analogue (compound 1) by method A and for the 4-*n*-propyl analogue (compound 2) by method B.

evaluate whether compounds presumed to act at the GABA-gated chloride channel can achieve a potency as high as that of established insecticides acting on sodium channels and the cholinergic system.

MATERIALS AND METHODS

Spectroscopy. Proton nuclear magnetic resonance (NMR) spectra were obtained at 300 MHz with a Bruker WM-300 spectrometer for samples dissolved in deuteriochloroform. Mass spectrometry (MS) utilized the Hewlett-Packard 5985 system with chemical ionization (230 eV with methane at 0.8 Torr) or electron impact (70 eV).

Syntheses. The 1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octanes were prepared by coupling 4-iodo- or 4-(1,2-dibromoethyl)benzoyl chloride with the appropriate 3-substituted 3-(hydroxymethyl)oxetane (Palmer and Casida, 1985; Casida et al., 1985) to give the benzoyl ester followed by rearrangement in the presence of boron trifluoride etherate to form the (4-iodophenyl)- or [4-(1,2-dibromoethyl)phenyl]trioxabicyclooctane, respectively. The 4-ethynylphenyl compounds were obtained from the 4-iodophenyl analogues by palladium-catalyzed coupling with (trimethylsilyl)acetylene (Takahashi et al., 1980) followed by removal of the trimethylsilyl protecting group (Figure 1A). Alternatively, the 4-(1,2-dibromoethyl)phenyl analogues were dehydrobrominated to the ethynylphenyl derivatives with potassium *tert*-butoxide (Stetter and Uerdingen, 1973) (or sodium in liquid ammonia as an alternative) (Figure 1B). Each compound gave the appropriate NMR and MS characteristics.

Method A (Figure 1A). For example, synthesis of compound 1 was initiated by the addition of a solution of 4-iodobenzoyl chloride (3.1 g, 11 mmol) in dry dichloromethane (10 mL) to 3-*tert*-butyl-3-(hydroxymethyl)oxetane (1.4 g, 10 mmol) and dry pyridine (2 mL) in dry dichloromethane (20 mL) at 0 °C under a nitrogen atmosphere. The solution was stirred overnight, then extracted with water, dried (Na_2SO_4), filtered and evaporated to leave 3-*tert*-butyl-3-[[(4-iodobenzoyl)oxy]methyl]oxetane (3.7 g, 99%) as a solid residue: NMR, δ 1.05 (9 H, s, Me_3C), 4.40 (2 H, s, CH_2OCO), 4.60 (4 H, dd, CH_2OCH_2), 7.80 (4 H, s, aromatic). This residue was dissolved in dry dichloromethane (30 mL) and cooled to −70 °C under a nitrogen atmosphere, and boron trifluoride etherate (0.35 mL) was added. The mixture was allowed to warm to room temperature and after being stirred overnight was quenched with triethylamine, evaporated to dryness, and partitioned between dichloromethane and water. The organic layer was separated, dried (K_2CO_3), and evaporated to leave a solid residue. Purification on a basic alumina column and elution with hexane/dichloromethane (9:1, v/v) gave 4-*tert*-butyl-1-(4-iodophenyl)-2,6,7-trioxabicyclo[2.2.2]octane as white crystals: 2.5 g (60%); mp 202–204 °C; MS, $[M + 1]^+$ 375; NMR, δ 0.90 (9 H, s, Me_3C), 4.15 (6 H, s, $(CH_2O)_3$), 7.30 (2 H, d, aromatic), 7.65 (2 H, d, aromatic). A solution of this (iodophenyl)trioxabicyclooctane (1.12 g, 3 mmol), (trimethylsilyl)acetylene (0.5 g, 5 mmol), bis(triphenylphosphine)palladium(II) chloride (50 mg), and cuprous iodide (10 mg) in dry diethylamine (30 mL) under a nitrogen atmosphere was stirred for 4 h. The solution was evaporated and the residue partitioned between ether and water. The organic layer was dried ($MgSO_4$) and evaporated to leave 4-*tert*-butyl-1-[4-[(trimethylsilyl)ethynyl]phenyl]-2,6,7-trioxabicyclo[2.2.2]octane as brown flakes: 1.0 g (97%); mp 251–252 °C; MS, $[M + 1]^+$ 345; NMR, δ 0.20 (9 H, s, Me_3Si), 0.90 (9 H, s, Me_3C), 4.15 (6 H, s, $(CH_2O)_3$), 7.40 (2 H, d, aromatic), 7.50 (2 H, d, aromatic). To a stirred solution of this (trimethylsilyl)ethynyl intermediate (1.36 g, 3.9 mmol) in dry tetrahydrofuran (50 mL) under a nitrogen atmosphere was added tetrabutylammonium fluoride (4 mL of 1 M solution in tetrahydrofuran). The mixture was stirred for 1 h and evaporated to dryness, and the residue was partitioned between water and dichloromethane. The organic layer was separated, dried (K_2CO_3), and evaporated to leave a solid residue. Purification on a basic alumina column, eluting with hexane/dichloromethane (9:1, v/v), gave 4-*tert*-butyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]-octane (1) as white crystals: 0.7 g (65%); mp 167–168 °C; MS, M^+ 272; NMR, δ 0.90 (9 H, s, Me_3C), 3.05 (1 H, s, C≡CH), 4.15 (6 H, s, $(CH_2O)_3$), 7.45 (2 H, d, aromatic), 7.55 (2 H, d, aromatic).

Method B (Figure 1B). For example, compound 2 was prepared by the addition of 4-(1,2-dibromoethyl)benzoyl chloride (prepared from 4-vinylbenzoic acid, bromine, and thionyl chloride) (3.28 g, 10 mmol) to 3-(hydroxymethyl)-3-*n*-propyloxetane (1.30 g, 10 mmol) using the method described above to afford the 3-[[[4-(1,2-dibromoethyl)benzoyl]oxy]methyl]-3-*n*-propyloxetane: 4.20 g (100%); NMR, δ 0.95 (3 H, t, CH_3), 1.35 (2 H, m, CH_3CH_2), 1.75 (2 H, m, CH_2CH_2), 4.05 (2 H, m, CH_2Br), 4.45 (2 H, s, CH_2OCO), 4.55 (4 H, dd, CH_2OCH_2), 5.15 (1 H, dd, ArCHBr), 7.45 (2 H, d, aromatic), 8.05 (2 H, d, aromatic). Rearrangement of this ester with boron trifluoride etherate as above gave 1-[4-(1,2-dibromoethyl)-phenyl]-4-*n*-propyl-2,6,7-trioxabicyclo[2.2.2]octane (3.7 g, 88%) as a brown gum: NMR, δ 0.90 (3 H, t, CH_3), 1.15–1.30 (4 H, m, CH_2CH_2), 3.90–4.10 (2 H, m, CH_2Br), 4.10 (6 H, s, $(CH_2O)_3$), 5.10 (1 H, dd, ArCHBr), 7.35 (2 H, d, aromatic), 7.60 (2 H, d, aromatic). A mixture of this [(dibromoethyl)phenyl]trioxabicyclooctane (3.55 g, 8.5 mmol) and potassium *tert*-butoxide (5.6 g, 50 mmol) in dry toluene (50 mL) under a nitrogen atmosphere was heated to reflux overnight. The cooled mixture was poured into ice/water and extracted with ether. The organic extracts were dried (K_2CO_3) and evaporated to leave a white solid. Recrystallization from hexane/chloroform afforded 1-(4-ethynylphenyl)-4-*n*-propyl-2,6,7-trioxabicyclo[2.2.2]octane: 1.1 g (51%); mp 135–137°C; MS, $[M + 1]^+$ 259; NMR, δ 0.90 (3 H, t, CH_3), 1.15–1.30 (4 H, m, CH_2CH_2), 3.05 (1 H, s, C≡CH), 4.10 (6 H, s, $(CH_2O)_3$), 7.45 (2 H, d, aromatic), 7.55 (2 H, d, aromatic).

Bioassays. LD_{50} values were determined for adult female houseflies (*Musca domestica* L., SCR strain, ~20 mg each) held 24 h at 25 or 35 °C after application of the test compound to the ventrum of the abdomen (Palmer and Casida, 1985). Synergized toxicity was evaluated for flies pretreated topically with PB at 250 μg/g 2 h before ad-

Table I. Topical Toxicity to Houseflies of Several 2,6,7-Trioxabicyclo[2.2.2]octanes and Established Insecticides at 25 °C

	$RC(CH_2O)_3CC_6H_4$-4-X		LD_{50},[a] μg/g		factor of
no.	R	X	alone	with PB	synergism
1	*tert*-butyl	ethynyl	0.087	0.011	8
2	*n*-propyl	ethynyl	0.68	0.023	30
3	cyclohexyl	ethynyl	0.53	0.030	18
4	*tert*-butyl	cyano	4.8	0.23	21
5	cyclohexyl	bromo	6.5	0.25	26
6	cyclohexyl	cyano	115	0.65	177
7	*tert*-butyl	bromo	3.5	0.83	4

		LD_{50},[a] μg/g		factor of
no.	established compound	alone	with PB	synergism
8	dieldrin	0.65	0.83	0.8
9	DDT	14	12	1.2
10	allethrin (1*R*,*trans*,α*S*)	14	0.32	44
11	permethrin (1*R*,*cis*)	0.21	0.012	18
12	cypermethrin (1*R*,*cis*,α*S*)	0.029	0.0012	24
13	parathion	1.3	0.43	3
14	propoxur	23	1.4	16

[a] Data for compounds 4–10 and 13 are from Palmer and Casida (1985).

ministering the toxicant. Adult male American cockroaches (*Periplaneta americana* L.) were used for LD_{50} determinations alone and with PB (200 μg/g, 2-h pretreatment) at 25 °C (Palmer and Casida, 1985). The carrier vehicle for each application was 0.5 μL of acetone for houseflies and 1.0 μL of acetone for cockroaches. The experiments were repeated until the reproducibility of the results was verified.

RESULTS AND DISCUSSION

Insecticidal Activity of 1-(4-Ethynylphenyl)trioxabicyclooctanes. The most potent trioxabicyclooctanes to houseflies previously reported are **4**, **5**, and **7** alone and **4**–**7** with PB (Table I) (Palmer and Casida, 1985). Because of the high intrinsic or synergized potency of **4** and **6**, it was of interest to replace the cyano group with an ethynyl substituent. Surprisingly, this structural change giving compounds with *tert*-butyl (**1**), *n*-propyl (**2**), and cyclohexyl (**3**) substituents increases the potency to houseflies over the best earlier compounds (Palmer and Casida, 1985) by up to 40-fold without synergist and 21-fold with PB. The factor of synergism is less within the same series for the ethynyl and bromo compounds than for the cyano derivatives and for the *tert*-butyl analogues compared with the *n*-propyl and cyclohexyl compounds.

The topical LD_{50}s of **1**–**3** for American cockroaches are 0.6, 6, and 0.6 μg/g, respectively, alone (and 0.4, 2, and 0.5 μg/g, respectively, with PB), making them 3- to 30-fold more potent without synergist than any trioxabicyclooctane previously reported (Palmer and Casida, 1985).

Mode of Action and Mammalian Toxicity. Compounds **1**–**3** (this study) and **4**–**7** (Casida et al., 1985) act at nanomolar levels to inhibit the binding site of [^{35}S]-*tert*-butylbicyclophosphorothionate in mouse brain membranes, an assay correlated with blocking the GABA-gated chloride channel (Obata et al., 1988). Trioxabicyclooctanes **1**–**3** are also highly toxic to mice with intraperitoneal LD_{50} values of less than 1 mg/kg.

Compound **7** mimics the action of picrotoxinin in antagonizing GABA-mediated relaxation at a functional insect nerve–muscle synapse (Casida et al., 1985). Studies with insect synaptosomes and dissociated neuronal somata provide further evidence that the trioxabicyclooctanes perturb chloride channel function in the insect central nervous system (Nicholson et al., 1988).

Table II. Topical Toxicity to Houseflies of 4-*tert*-Butyl-1-(4-ethynylphenyl)-2,6,7-trioxabicyclo[2.2.2]octane and (1*R*,*cis*,α*S*)-Cypermethrin at 35 °C

		LD_{50}, μg/g	
no.	insecticide	alone	with PB
1	*t*-$BuC(CH_2O)_3CPhC{\equiv}CH$-4	0.064	0.009
12	(1*R*,*cis*,α*S*)-cypermethrin	0.14	0.015

Comparison with Established Insecticides (Tables I and II). The potencies of **1**–**3** alone or with PB to houseflies at 25 °C are much greater than those of dieldrin (**8**) (also a chloride channel antagonist), of DDT (**9**) and (1*R*, *trans*,α*S*)-allethrin (**10**) (which act at sodium channels), and of parathion (**13**) and propoxur (**14**) (which are anticholinergic insecticides). When assayed at 25 °C, **1** is equal in potency to (1*R*,*cis*)-permethrin (**11**) but much less active than the most effective isomer of cypermethrin (**12**) both alone and with PB. However, when the housefly assays are made at 35 °C, **1** is more potent than **12**. Clearly, trioxabicyclooctanes acting at the GABA-gated chloride channel can achieve an insecticidal potency as high as that of established neuroactive insecticides acting at other targets.

ACKNOWLEDGMENT

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Registry No. **1**, 108614-39-7; **1**·PB, 117439-70-0; **2**, 108614-26-2; **2**·PB, 117439-71-1; **3**, 108614-38-6; **3**·PB, 117470-44-7; **4**, 97720-14-4; **4**·PB, 117439-72-2; **5**, 97720-10-0; **5**·PB, 117439-73-3; **6**, 97720-15-5; **6**·PB, 117439-74-4; **7**, 97720-09-7; **7**·PB, 117439-75-5; **8**, 60-57-1; **8**·PB, 117439-76-6; **9**, 50-29-3; **9**·PB, 81341-27-7; **10**, 28434-00-6; **10**·PB, 117439-77-7; **11**, 54774-45-7; **11**·PB, 117439-78-8; **12**, 65731-84-2; **12**·PB, 117439-79-9; **13**, 56-38-2; **13**·PB, 117439-80-2; **14**, 114-26-1; **14**·PB, 8075-07-8; 4-iodobenzoyl chloride, 1711-02-0; 3-*tert*-butyl-3-(hydroxymethyl)oxetane, 99250-47-2; 3-*tert*-butyl-3-[[(4-iodobenzoyl)oxy]methyl]oxetane, 117439-66-4; boron trifluoride etherate, 109-63-7; 4-*tert*-butyl-1-(4-iodophenyl)-2,6,7-trioxabicyclo[2.2.2]octane, 117439-67-5; 1-[4-[(trimethylsilyl)ethynyl]phenyl]-4-*tert*-butyl-2,6,7-trioxabicyclo[2.2.2]octane, 117439-68-6; tetrabutylammonium fluoride, 429-41-4; 4-(1,2-dibromoethyl)benzoyl chloride, 108614-49-9; 3-(hydroxymethyl)-3-*n*-propyloxetane, 107829-94-7; 4-[[[(1,2-dibromoethyl)-benzoyl]oxy]methyl]-3-*n*-propyloxetane, 117439-69-7; 1-[4-(1,2-dibromoethyl)phenyl]-4-*n*-propyl-2,6,7-trioxabicyclo[2.2.2]octane, 108614-55-7.

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Photochemistry of Ethofenprox and Three Related Pyrethroids with Ether, Alkane, and Alkene Central Linkages

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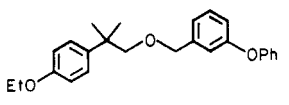
The pyrethroid insecticide ethofenprox (MTI-500) [2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether] undergoes two primary photochemical processes at the central $-C(CH_3)_2CH_2OCH_2-$ ether linkage, depending on the irradiation conditions. In oxygenated solutions or thin films the major process is benzylic oxidation to give the corresponding central $-C(CH_3)_2CH_2OC(O)-$ ester linkage. In deaerated solutions the loss of CH_2O predominates to form the central $-C(CH_3)_2CH_2-$ alkane linkage. These appear to be detoxification reactions. Seven other characterized photoproducts of ethofenprox are formed on cleavage of the central linkage without alteration of the ethoxy or phenoxy moiety. MTI-800 [1-(3-phenoxy-4-fluorophenyl)-4-(4-ethoxyphenyl)-4-methylpentane] with the central $-C(CH_3)_2(CH_2)_3-$ alkane linkage is generally more photostable than ethofenprox. Two tentatively identified photoproducts of MTI-800 are formed by elimination of the phenoxy group, giving the fluorophenyl analogue, and photocyclization, yielding the corresponding dibenzofuran. Structurally analogous alkenes with the $-(\overline{CCH_2CH_2})-CH{=}CHCH_2-$ central linkage are more photolabile than ethofenprox, undergoing isomerization and oxidation at both the *E* double bond and the cyclopropyl group.

Conventional pyrethroids have central ester groups, but high insecticidal activity is also observed in compounds with alternative central linkages such as suitable ether, alkane, and alkene substituents. Examples of these nonester pyrethroids are the ether ethofenprox (1) (also known as MTI-500 and Trebon) (Nakatani et al., 1982; Udagawa, 1986), the alkane MTI-800 (2) (Udagawa et al., 1985), and the alkenes NRDC 199 (3) and 200 (4) (Elliott, 1985). Compounds 1 and 2 have two useful properties relative to the ester pyrethroids, i.e., reduced toxicity to mammals and aquatic species and enhanced photochemical stability (Udagawa et al., 1985; Yano et al., 1986).



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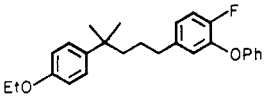

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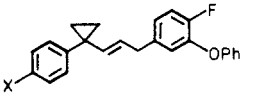

3 (X = Cl)
4 (X = OEt)

1: 2-(4-ethoxyphenyl)-2-methylpropyl 3-phenoxybenzyl ether
2: 1-(3-phenoxy-4-fluorophenyl)-4-(4-ethoxyphenyl)-4-methylpentane
3 (R = Cl) and 4 (R = OEt): 1-(4-chloro- or -ethoxyphenyl)-1-[(*E*)-(3-phenoxy-4-fluorophenyl)prop-1-enyl]cyclopropane

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This report examines the photodecomposition rates and products obtained on irradiation of 1–4 in various solvents and as thin films in the solid phase, focusing on the processes of ethofenprox, currently the most important of the nonester pyrethroids.

MATERIALS AND METHODS

Chromatography. Thin-layer chromatography (TLC) for monitoring reactions and isolation of photoproducts employed silica gel 60 F-254 precoated chromatoplates (E. Merck, Darmstadt, Germany; 0.25 or 0.5 mm) developed with hexane–acetone (20:1) or hexane–diethyl ether (20:1). Multiple developments were used for better resolution in preparative separations. Photoproducts were recovered by sonicating the gel in dichloromethane followed by centrifugation.

Liquid adsorption column chromatography (LC) for photoproduct isolation utilized 25 g of silica gel (Merck; 0.063–0.20 mm) and elution with *n*-hexane (100 mL), *n*-hexane–diethyl ether (30:1) (200 mL), and *n*-hexane–diethyl ether (10:1) (100 mL).

Gas–liquid chromatography (GC) for monitoring reaction rates as loss of the parent compound employed a Hewlett-Packard Model 5840A instrument equipped with a packed glass column (3% SP 2100 on Chromosorb, 2 m × 4 mm (i.d.), helium carrier gas 20 mL/min) and a flame ionization detector (FID). High-resolution gas chromatography (HRGC) for product analysis involved a fused silica capillary column (Supelco Inc., Bellefonte, PA; SE 54, 15 m × 0.25 mm (i.d.), 0.25-μm film; helium carrier gas 40 cm/s) with a 2:1 split ratio. Analyses were carried out isothermally with the packed column and by temperature program (90 °C for 3 min, 10 °C/min to 280 °C, and then 280 °C for 10 min) on the SE 54 capillary.

Spectroscopy. HRGC mass spectrometry (HRGC–MS) involved a Hewlett-Packard 5985B system operated under

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