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Intramolecular [2+2]Photocycloaddition of the 3-(3-Butenyloxy)-2-cyclohexenone System

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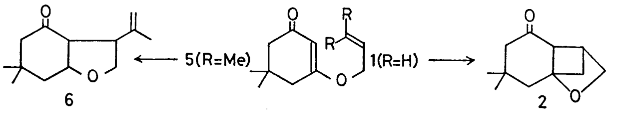
The irradiation of 5,5-dimethyl-3-(4-methyl-3-pentenyloxy)-2-cyclohexenone gave regioselectively, 6,6,10,10-tetramethyl-2-oxatricyclo[5.4.0.0^{1,5}]undecan-8-one, while, that of 5,5-dimethyl-3-[(3-methylcyclohexenyl)methoxy]-2-cyclohexenone afforded, regio- and stereoselectively, 1,5,5-trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{1,5}]tetradecan-3-one.

Since a successful synthesis of caryophyllene by Corey and his co-workers in 1963,[1] a number of [2+2]-photocycloaddition reactions have been reported as an important step[2] in the synthesis of natural products. Most of them were intermolecular reactions, for example, the addition of an α,β-unsaturated carbonyl moiety of one molecule to a double bond of a second one, but intramolecular approaches have limited to a few cases.[3–5] Nevertheless, the latter are very worthy of investigation because bond formation is expected to be prompted by the closer situation of reaction sites compared to the case of intermolecular reactions and becuase regio- and/or stereoselectivities will be enhanced by a specific and limited arrangement of reaction sites.

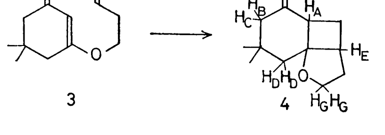
We will here report two intramolecular [2+2]-photocycloadditions of 3-(3-butenyloxy)-2-cyclohexenone derivatives, **7** and **10**. These cyclohexenones can be easily prepared from a β-diketone and a 3-butenyl alcohol derivative or a corresponding halide, as will be described below.

A simple system of 3-alkenyloxy-2-cyclohexenones had been investigated by Tamura and his co-workers.[6] In their work, 5,5-dimethyl-3-allyloxy-2-cyclohexenone-(**1**) changed into a tricyclic compound **2** upon irradiation with a Hg lamp, while 3-(3-butenyloxy)-2-cyclohexenone **3** was reversed in regioselectivity to give another tricyclic compound **4**. The reaction of the dimethyl compound **5** proceeded differently to afford a tetrahydrofuran derivative **6** as a result of a facile ene reaction. Therefore, we initially tried the photoreaction of 5,5-dimethyl-3-(4-methyl-3-pentenyloxy)-2-cyclohexenone(**7**), a dimethyl derivative of **3**, in order to clarify the influence of dimethyl groups on the reaction paths. The dimethyl compound **7** was prepared from dimedone and 5-chloro-2-methyl-2-pentene.[7]

The irradiation of a 1% hexane solution of **7** with an Ushio high-pressure mercury arc lamp gave a single photoadduct as a crystal in a 63% yield. The mass spectrum shows that the reaction was intramolecular, while the absorption at 1695 cm^{-1} in IR and the four methyl singlets at 0.94, 1.05, 1.05, and 1.08 ppm in NMR spectra clearly indicate that the reaction proceeded by means of [2+2]cycloaddition. Either structure, **8** or **8′**, is possible for the adduct; the NMR spectrum, a broad singlet at 2.35 (H_A), an AB center at 2.03 of J=18 Hz (H_B, H_C), a singlet at 1.90 ($2\times H_D$), and a complex multiplet between 3.60 and 4.20 (–CH$_2$–O–) are consistent with both structures, although, in **8′**, the coupling constant between H_A and H_E is nearly zero, as is to be anticipated from the dihedral angle (90°) of these two protons in the Dreiding models.



6 2



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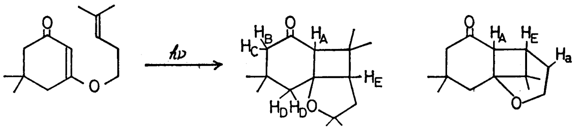


7 8 8′

The pseudo-contact shift with Eu-FOD was measured; the results are shown in Fig. 1 and in Table 1. The three protons (H_A, H_B, and H_C) adjacent to the carbonyl group are most deshielded, and the magnitudes of the shifts are very close to each other. This shows that the shift reagent nearly comes in contact with the carbonyl oxygen and on the same side with H_A (see **9**). On the other hand, the H_E proton shifts

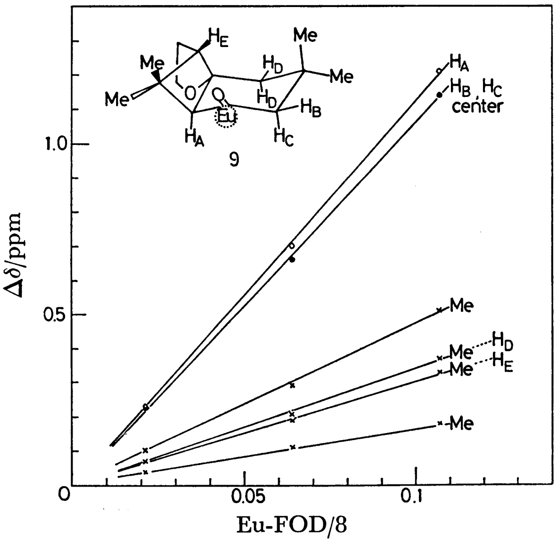


Fig. 1. Pseudocontact shifts of **8** with Eu-FOD in CCl$_4$.

TABLE 1. PSEUDOCONTACT SHIFTS OF **4**, **8**, AND **16** WITH THE ADDITION OF 0.1 mol EQUIVALENT OF Eu-FOD IN CCl$_4$

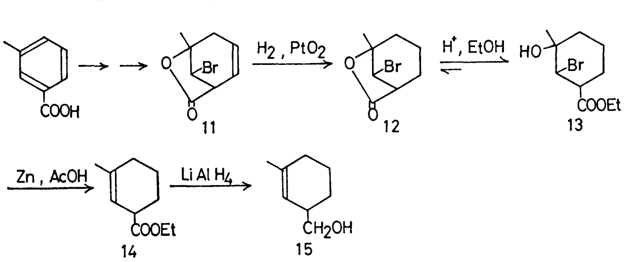
Proton	$\Delta\delta$ Values in ppm		
	4	**8**	**16**
H_A	1.18	1.12	1.18
H_B,H_C	1.08[a]	1.05[a]	1.14[a]
H_D	0.40	0.34	0.34
H_E		0.30	0.26
H_G	0.2_5[b]	0.3_7[b]	0.28
	0.2_0[b]	0.1_9[b]	0.19
CH$_3$	0.36	0.47	0.49
	0.31	0.34	0.32
		0.30	0.17
		0.17	

a) Shifts at AB-type center. b) Less precise because of complex multiplets.

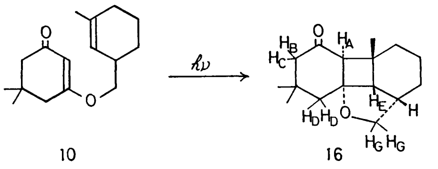
less than H_A and has a magnitude similar to that of H_D. These facts well accord with the structure **8**. In the alternate structure, **8′**, the H_E proton is situated closer to the carbonyl group than H_D; thus, it must have a larger $\Delta\delta$ value. Furthermore, H_E was found to be a double doublet with the coupling constants of 7 and 5 Hz upon the addition of the shift reagent. This is also inconsistent with the structure **8′**, in which the dihedral angle between H_E and the neighbouring axial proton (H_a) is very close to 90°.

Different from the case of **1** *vs.* **5**, the dimethyl group did not exert any influence on the reaction path and regioselectivity in the case of 3-(3-butenyloxy)-2-cyclohexenone **3** *vs.* **7**. This remarkable regioselectivity to give the bicyclo[3.*m*.0]-system has been observed in other cases.[3b,4,8]

The successful conversion of **7** into **8** led us to investigate the photochemical reaction of 5,5-dimethyl-3-[(3-methyl-2-cyclohexenyl)methoxy]-2-cyclohexenone (**10**), which has a less flexible olefinic side chain containing one asymmetric carbon atom.



The bromo lactone **11**, prepared[9] from *m*-toluic acid, was hydrogenated over the Adams catalyst to give a saturated lactone **12**. As the direct reduction of **12** with zinc in acetic acid gave a mixture of an olefinic acid and a debromo lactone, probably produced during the isolation procedure, **12** was initially changed into an ethyl ester **13** and then reduced with Zn–AcOH to afford an unsaturated ester **14**. The ester group in **14** was reduced with lithium aluminum hydride to give an alcohol **15**. The reaction of dimedone with **15** in the presence of *p*-toluenesulfonic acid afforded the enol ketone **10** as an oil.



A similar irradiation of **10** gave a photoadduct in a 47% yield. Its spectroscopic properties well accord with the structure **16**: the carbonyl absorption at 1690 cm^{-1} in the IR spectrum and the three methyl singlets at 0.92, 1.00, and 1.01, the one broad proton singlet at 2.68, an AB-type quartet at 1.98 of J=18 Hz, a two proton singlet at 1.88, and the two triplets at 3.64 (J=9 Hz) and 3.94 (J=9 Hz) in the NMR spectrum. The *cis*-anti-*cis* stereochemical assignment was deduced from the fact that **16** was unchanged upon treatment with lithium diisopropylamide. The predominant formation of one diastereoisomer seems to be characteristic of the intramolecular reaction and is largely due to the steric requirement in the transition state.

Experimental

All the melting points are uncorrected. The IR spectra were taken on a Hitachi 215 grating spectrophotometer. The NMR spectra were obtained with Hitachi H-60 and JEOL MH-100 spectrophotometers, using TMS as the internal standard. The mass spectra were obtained with a Hitachi RMU-6MG mass analyzer. The flash chromatographies were performed using the Wakogel C-300 as the adsorbent.

Irradiation Procedure. A test solution of 170 mg of 5,5-dimethyl-3-(3-butenyloxy)-2-cyclohexenone (**3**) [ν(CHCl$_3$): 1640 and 1605 s cm^{-1}], prepared from dimedone and 4-bromo-1-butene in the presence of potassium methoxide, in 20 ml of hexane was irradiated in a Pyrex test tube with an Ushio 450 W high-pressure mercury arc lamp under nitrogen for 30 min. The solvent was then evaporated, and the residue was chromatographed with hexane–ethyl acetate (4:1) to give the known adduct, **4**[6a] (120 mg, 72%). *m/e*: 194 (M$^+$) and 124 (base); ν(CCl$_4$): 1700, 1065, and 1040 cm^{-1}; δ (CCl$_4$, 100 MHz): 1.00 (s, 3H), 1.06 (s, 3H), 1.71 (AB center, 2H, J=15 Hz), 2.15 (AB center, 2H), 2.62 (dd, 1H, J=11 and 6 Hz), 1.5—2.0 (m, 2H), 2.0—2.4 (m, 4H), 2.5—2.8 (m, 1H), and 3.7—4.2 (m, 2H).

5,5-Dimethyl-3-(4-methyl-3-pentenyloxy)-2-cyclohexenone (**7**). A solution of dimedone (2.48 g) in 15 ml of dry HMPA was added, drop by drop, to a solution of potassium methoxide, prepared from 1.02 g of potassium, 5 ml of dry methanol, and 10 ml of HMPA. 5-Chloro-2-methyl-2-pentene[7] (2.14 g) was added to the mixture, and the whole was heated at 100 °C overnight. Water was added, and the products were taken up in hexane. The solvent was evaporated, and the residue was chromatographed with hexane–ethyl acetate (9:2) to give **7** (741 mg, 19%) as an oil. An analytical sample was prepared by Kugelrohr distillation [bath temp: 70 °C/2 mmHg(1 mmHg=133.322 Pa)]. *m/e*: 222 (M$^+$) and 83 (base); ν (CCl$_4$): 1660, 1615, and 1220 cm^{-1}; δ (CCl$_4$): 1.08 (s, 6H), 1.65 (br. s, 3H), 1.73 (br. s, 3H), 2.08 (s, 2H), 2.23 (s, 2H), 2.37 (q, 2H, J=7 Hz), 3.78 (t, 2H, J=7 Hz), 5.1 (br. t, 1H, J=7 Hz), and 5.18 (s, 1H). Found: C, 75.35; H, 9.96%. Calcd for C$_{14}$H$_{22}$O$_2$: C, 75.63; H, 9.97%.

6,6,10,10-Tetramethyl-2-oxatricyclo[$5.4.0.0^{1,5}$]*undecan-8-one* (**8**).

A solution of 573 mg of **7** in 86 ml of hexane was divided into four Pyrex test tubes. The solution was then irradiated under nitrogen for 30 min. The solvent was evaporated, and the residual oil was chromatographed with hexane–ethyl acetate (5:1) to give colorless **8** (361 mg, 63%). Bath temp: 92 °C/2 mmHg; mp 48—49 °C (from pentane); *m/e*: 222 (M^+) and 83 (base); ν (CCl_4): 1695, 1180, and 1050 cm^{-1}; δ (CCl_4, 100 MHz): 0.94 (s, 3H), 1.00 (s, 3H), 1.05 (s, 3H), 1.08 (s, 3H), 1.90 (s, 2H), 2.02 (AB center, 2H, J=18 Hz), 1.7—2.4 (m, 3H), 2.34 (s, 1H), and 3.6—4.2 (m, 2H); δ (CCl_4, 100 MHz, with the addition of a 0.11 equivalent of Eu-FOD): 1.20 (s, 3H), 1.27 (s, 3H), 1.45 (s, 3H), 1.56 (s, 3H), 1.9—2.2 (m, 2H), 2.27 (s, 2H), 2.48 (dd, 1H, J=7 and 5 Hz), 3.17 (AB center, 2H, J=18 Hz), 3.56 (s, 1H), and 3.9—4.4 (m, 2H). Found: C, 75.57; H 10.06%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

*8-Bromo-*cis*-5-methyl-6-oxabicyclo[3.2.1]octan-7-one (**12**).* The known bromo lactone **11**[9] (1.02 g) in 20 ml of ethyl acetate was hydrogenated over the Adams catalyst (109 mg) at a pressure of 1 atm for 80 min. The catalyst was then removed by filtration, and the filtrate was evaporated to give crystals. Recrystallization from pentane gave **12** (0.59 g, 93%); mp 59—60 °C. ν (CCl_4): 1790s and 1105 cm^{-1}; δ (CCl_4): 1.45 (s, 3H), 1.0—2.5 (m, 6H), 2.75 (m, 1H), and 4.37 (d, 1H, J=6 Hz). Found: C, 43.97; H, 4.99%. Calcd for $C_8H_{11}O_2Br$: C, 43.86; H, 5.06%.

*3-Methyl-2-cyclohexenylmethanol (**15**).* A solution of **12** (13.4 g) in 60 ml of ethanol was refluxed in the presence of a catalytic amount of hydrochloric acid for 2 d. The mixture was passed through a sodium carbonate layer and then evaporated. The residue, after having been made free from a carboxylic acid produced, weighed 12.9 g. The IR spectrum of the residue showed that it was a mixture of **12** ($\nu_{C=O}$ 1790 cm^{-1}) and **14** ($\nu_{C=O}$ 1735 cm^{-1}) in the ratio of 1:3. The mixture was refluxed in 10 ml of acetic acid with 12.8 g of freshly activated (HCl) zinc powder. The solids were removed by filtration and washed with 20 ml of hexane. The filtrate and the washing were combined and then evaporated to give an oil (5.6 g). The oil was dispersed in a 5% sodium hydroxide solution and extracted with ethyl acetate. The extracts were washed with water, dried over Na_2SO_4, and then evaporated to give an ethyl ester **14** (4.4 g) as an oil; ν(CCl_4): 1730 and 1175 cm^{-1}.

A solution of **14**, without further purification, in 50 ml of dry THF was added, drop by drop, to a cooled solution of lithium aluminum hydride (1.06 g) in 50 ml of dry THF. The mixture was stirred at room temperature for 30 min and then treated successively with 1 ml of water, 1 ml of a 15% sodium hydroxide solution, and 3 ml of water. The granular precipitates were removed by filtration and washed with THF. The filtrate and the washing were combined and then evaporated to give an alcohol **15** (2.5 g, 33% from **12**). Bp 55—63 °C/1 mmHg; ν (CCl_4): 3400br, 1060, and 1030 cm^{-1}; δ (CCl_4): 1.65 (s, 3H), 1.1—2.4 (m, 8H), 2.83 (s, 1H, OH), 3.37 (d, 2H, J=6 Hz), and 5.30 (br.s, 1H).

Elemental analysis was performed on its *p*-nitrobenzoate derivative; mp 78—80 °C (from hexane); ν (KBr): 1715, 1520, 1345, 1285, 1270, and 815 cm^{-1}. Found: C, 65.60; H, 6.14; N, 4.71%. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08%.

*5,5-Dimethyl-3-[(3-methyl-2-cyclohexenyl)methoxy]-2-cyclohexenone (**10**).* A mixture of 200 mg of dimedone, 179 mg of **15**, and 25 mg of *p*-toluenesulfonic acid was heated under refluxing with 40 ml of toluene for 43.5 h, while the water was being removed continuously by means of a water-separator. The mixture was then washed with a 15% sodium hydroxide solution and water until the washing was neutral. After having been dried, the solvent was evaporated to give an oil. The oil was chromatographed with hexane–ethyl acetate (4:1) to give **10** (204 mg, 58%). Bath temp: 60—65 °C/2 mmHg; *m/e*: 248 (M^+) and 108 (base); ν (CCl_4): 1660, 1616, and 1220 cm^{-1}; δ (CCl_4): 1.08 (s, 6H), 1.66 (br.s, 3H), 2.08 (s, 2H), 2.25 (s, 2H), 1.0—2.8 (m, 10H), 3.65 (d, 2H, J=6.5 Hz), 5.22 (br.s, 1H), and 5.2—5.5 (m, 1H). Found: C, 77.08; H, 9.77%. Calcd for $C_{16}H_{24}O_2$: C, 77.37; 9.74%.

*1,5,5-Trimethyl-8-oxatetracyclo[8.3.1.0^{2,7}.0^{1,5}]tetradecan-3-one (**16**).* A solution of 200 mg of **10** in 22 ml of hexane was irradiated for 6 h. The solvent was then evaporated, and the residue was chromatographed with hexane–ethyl acetate (5:1) to give **16** (93 mg, 47%); mp 76—77 °C (from hexane); *m/e*: 248 (M^+) and 108 (base); ν (CCl_4): 1690, 1050, and 1045 cm^{-1}; δ (CCl_4, 100 MHz); 0.92 (s, 3H), 1.00 (s, 3H), 1.01 (s, 3H), 1.88 (s, 2H), 1.98 (AB center, 2H, J=18 Hz), 1.98 (d, 1H, J=10 Hz), 2.68 (br.s, 1H), 3.64 (t, 1H, J=9 Hz), and 3.94 (t, 1H, J=9 Hz). Found: C, 77.28; H, 9.74%. Calcd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%.

16 was unchanged even when it was treated with 5 equivalents of lithium diisopropylamide at room temperature overnight.

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