Efficient Monoacetal Formation, Unprecedented β-Cleavage in Caged Cyclobutyl Ketones and Dual Epimerization of 1,4-Diones in the Photochemistry of Hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3,10-dione and Related Systems in Alcoholic Solvents†

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Irradiation of the title compound and related caged cyclobutyl diones in alcoholic solvents at 300 nm furnishes good yields of monoacetals and leads to products arising from β-cleavage and dual epimerization.

As part of a programme for the stereocontrolled synthesis of a cyclic 12-membered ring (**1**), the locked 12-membered ring (**2**) is envisaged as an intermediate, offering considerable opportunity for stereochemical manipulation.[1,2] Recently we[2] and Coxon *et al.*[3] have shown that (**2**) can react exclusively with various kinds of dienophiles from either the cyclobutane or the ketone face, depending on the nature of the dienophile.[4] For successful unlocking of (**2**), the cleavage of a cyclobutyl–carbonyl bond is necessary.

Using Baeyer–Villiger oxidation, we have introduced oxygen regioselectively into the cyclobutyl–carbonyl bond in

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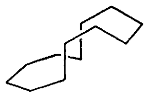
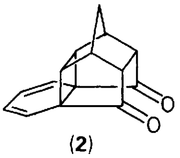
† N.C.L. communication no. 4675.



(**1**)



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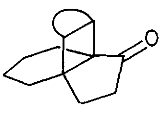

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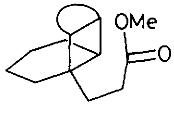

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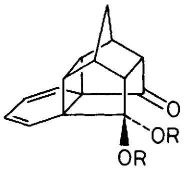


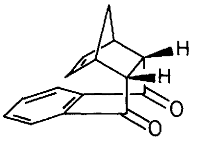
(**5**)

a; R = Me

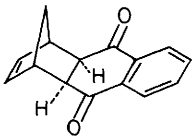
b; R = Et

c; R = Pr^i

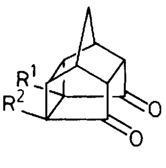
d; R-R = CH_2—CH_2



(**6**)



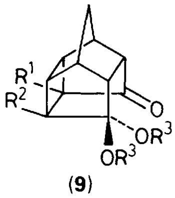
(**7**)



(**8**)

a; R^1- R^2 = $\begin{array}{l}-CH_2-CH_2\\ \qquad\quad\ \vert\\ -CH_2-CH_2\end{array}$

b; R^1- R^2 = H



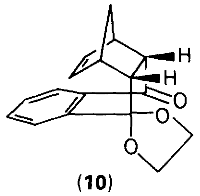
(**9**)

a; R^1-R^2 = $\begin{array}{l}-CH_2-CH_2\\ \qquad\quad\ \vert\\ -CH_2-CH_2\end{array}$

R^3= Et

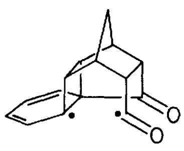
b; R^1 = R^2= H, R^3 = Me

c; R^1 =R^2= H, R^3 = Et

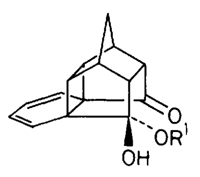


(**10**)

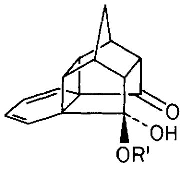
systems related to (**2**).[1,5] However carbonyl photochemistry offers a direct method to achieve these goals *via* α-cleavage. In fact, in a closely related system, *e.g.* (**3**), Tobe *et al.*[6] have reported exclusive and quantitative formation of (**4**) *via* α-cleavage. Thus, with a view to unlocking (**2**) *via* α-cleavage, the photochemistry of (**2**) and related systems was examined. However, contrary to our expectations, we report that



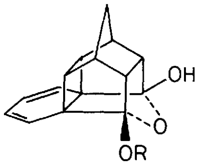
(**11**)



(**12**)



(**13**)



(**14**)

photolysis in alcoholic solvents led to products arising from monoacetal formation, β-cleavage, and subsequent dual epimerization.

The substrates photolysed in alcoholic solvents included hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene-3,10-dione (**2**)[1—3] and its monoacetal (**5d**), hexacyclo-[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadecane-3,10-dione (**8a**), and pentacyclo[5.4.0.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]undecane-8,11-dione (**8b**)[7] (Table 1). The photolyses were carried out in alcoholic solvents, *e.g.* MeOH, EtOH, Pr^iOH, and ethylene glycol (1 mg ml^{-1}) in a pyrex vessel at 300 nm in a Rayonet–Srinivasan photoreactor for 2.5 h. As shown in Table 1, reasonable yields of acetals (40—84%, entries 1, 2, 4, 6, and 7)‡ and products of β-cleavage, *e.g.* (**6**) and (**10**), and subsequent dual epimerization to (**7**) (entries 1—4, 8, and 9) are obtained during photolysis. The synthetically useful cyclic acetal (**5d**) was formed most efficiently (84%, entry 4). Although a comparison of entries 2 and 5 implies that lower strain may be responsible for the lower yield (10%) of (**9a**) from (**8a**), presuming (**2**) is more strained than (**8a**) (from molecular model considerations), comparison of acetal formation from (**8a**) and (**8b**) does not support this hypothesis. Interestingly, only one of the keto groups could be acetalized in the cage diones (**2**) and (**8a, b**), perhaps for steric reasons. Even after exhaustive acetalization with toluene-*p*-sulphonic acid (PTSA)/ROH, refluxing in benzene, and azeotropic removal of water, only one keto group was acetalized. Aromatization, and consequent release of strain, appears to be the driving force for β-cleavage in alcoholic solvents (entries 1—4, 8, and 9) as no such products are obtained with Cookson's ketone (**8b**) and saturated dione (**8a**).[8]§ Subsequently, the solvent dependence of photocyclization of *endo*-(**6**) and its dual epimerization to *exo*-(**7**) in various solvents *e.g.* acetonitrile, cyclohexane, n-hexane, and ethyl acetate (entries 10—14) was examined. As indicated in Table 1, photocyclization was best accomplished in acetonitrile (98%, entry 10), and very inefficient dual epimerization was observed in acetonitrile and cyclohexane (entries 10 and 11).

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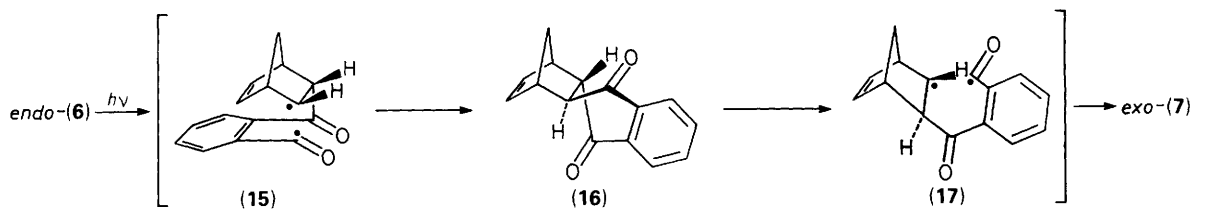
‡ In a blank experiment, in the absence of photolysis, no acetal formation was observed.

§ In ketone photochemistry β-cleavage processes are known to occur either with strained cyclopropyl[9a—c] and epoxy ketones[9d,e], or with ketones with a good leaving group, *e.g.* sulphonyloxy,[9f] acetoxy,[9g] bromine[9h] *etc.*



Scheme 1

Table 1.

Entry	Substrate	Solvent	Products^{a} (% yield) Acetal formation	β-Cleavage	Dual epimerization
1	**(2)**	MeOH	**(5a)** (40)	**(6)** (30)	**(7)** (30)
2	**(2)**	EtOH	**(5b)** (42)	**(6)** (30)	**(7)** (28)
3	**(2)**	Pr^{i}OH	**(5c)** (5)	**(6)** (40)	**(7)** (40)
4	**(2)**	(CH$_2$OH)$_2$	**(5d)** (84)	**(6)** (8)	**(7)** (8)
5	**(8a)**	EtOH	**(9a)** (10)		
6	**(8b)**	MeOH	**(9b)** (65)		
7	**(8b)**	EtOH	**(9c)** (64)		
8	**(5d)**	EtOH		**(10)** (40)	
9	**(5d)**	Pr^{i}OH		**(10)** (90)	
10	**(6)**	MeCN	**(2)** (98)		**(7)** (1)
11	**(6)**	Cyclohexane	**(2)** (88)		**(7)** (1)
12	**(6)**	n-Hexane	**(2)** (65)		
13	**(6)**	Ethyl acetate	**(2)** (52)		
14	**(6)**	Benzene^{b}	**(2)** (80)		

^{a} The remaining % is unreacted starting material. ^{b} A. S. Kushner, *Tetrahedron Lett.*, 1971, 3275.

The structures of acetals **(5a—d)**, **(9a—c)**, **(10)**, and *exo*-**(7)** were confirmed spectroscopically¶ and by comparison with authentic samples.[10] No product of α-cleavage and subsequent oxacarbene formation[11] was observed. α-Cleavage may occur in these systems to give **(11)** but, owing to the rigid frame, reclosure of biradicals becomes competitive. Efficient acetal formation is unusual in ketone photochemistry.[12] Normally an excited carbonyl abstracts hydrogen from C–H and not from the O–H bond of an alcohol.[13] However, Wagner *et al.*[14] have reported efficient quenching of triplet ketones by the alcoholic OH bond; such quenching might result in photochemical transformation of the ketone to a hemiacetal *e.g.* **(12)**. Caged diones in the excited state may behave as ionic species,[15] which could be trapped with alcohols to furnish hemiacetals.[16] We propose that the structure of the hemiacetal obtained during recrystallization of **(2)** in EtOH is **(12)** and not **(13)**. Hemiacetal **(13)** is likely to convert to **(14)** owing to the proximity of the OH and keto groups, which ultimately will lead to an acetal with no ketone functionality.

A tentative mechanism for dual epimerization from *endo*-**(6)** to *exo*-**(7)** has been proposed *via* stepwise α-cleavage of **(6)** to biradical **(15)**, reclosure with epimerization to give highly strained **(16)**, repeat α-cleavage to **(17)**, and subsequent reclosure to *exo*-**(7)** (Scheme 1).‖

Simultaneous double α-cleavage of **(6)** and double reclosure with epimerization to **(7)** may be excluded, as it would result in splitting of both fragments, giving some norbornene in the product mixture, which is not observed. In support of a stepwise mechanism, the photolysis of monoacetal **(5d)** in alcoholic solvents stops at *endo*-**(10)** (entries 8 and 9, Table 1); the isolation of a monoacetal of *trans*-cyclohexenedione **(16)** might be energetically unfavourable. Highly strained and twisted cyclohexanones are known as transients,[17] and epimerization of the α-carbon in ketone photochemistry is an easy process.[18]

¶ *Selected physical and spectroscopic data* for **(5a)**: IR (Nujol) 1740 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 1.2—1.8 (m, 2H), 2.3—3.0 (m, 6H), 3.15 (s, 3H), 3.2 (s, 3H), 5.3—6.0 (m, 4H); ^{13}C NMR (90 MHz, CDCl$_3$) δ 36.00, 46.40, 49.98, 50.17, 51.41, 105.8, 120.8, 121.07, 123.69, 124.97, 211.87; *m/z* 270 (41%, M^+). **(5b)**: m.p. 100 °C; IR (CHCl$_3$) 1740 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 1.07 (t, 3H), 1.22 (t, 3H), 1.71 (s, 1H), 1.82 (s, 1H), 2.42—3.1 (m, 6H), 3.3—3.73 (m, 4H), 5.44—6.11 (m, 4H); ^{13}C NMR (90 MHz, CDCl$_3$) δ 15.01, 15.53, 36.13, 42.44, 44.39, 46.73, 50.37, 50.56, 52.06, 52.77, 56.22, 56.80, 58.69, 105.74, 121.21, 123.94, 125.56, 212.32; *m/z* 298 (22%, M^+). **(5c)**: IR (CHCl$_3$) 1740 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 1.0—1.3 (m, 12H), 1.75 (d, 2H), 2.2—3.2 (m, 6H), 4.0—4.3 (m, 2H), 5.5—6.0 (m, 6H). **(5d)**: m.p. 132 °C, IR (Nujol) 1740 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 1.35 (d, 1H), 1.75 (d, 1H), 2.35—3.1 (m, 6H), 3.85 (s, 4H), 5.38—5.62 (m, 2H), 5.73—6.09 (m, 2H); ^{13}C NMR (90 MHz, CDCl$_3$) δ 36.78, 42.698, 45.298, 47.37, 50.042, 50.952, 53.421, 54.591, 65.770, 65.960, 113.79, 121.141, 122.506, 123.741, 212.25; *m/z* 268 (36%, M^+). **(9a)**: IR (Nujol) 1740 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 1.0—1.3 (m, 6H), 1.3—3.0 (m, 6H), 3.4—3.8 (m, 4H); *m/z* 326 (10%, M^+). **(9b)** IR (Nujol) 1760 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 1.8 (d, 2H), 1.95 (d, 2H), 2.5—3.0 (m, 8H), 3.20 (s, 3H), 3.25 (s, 3H); *m/z* 220 (15%, M^+). **(9c)** m.p. 98 °C; IR (Nujol) 1750 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 1.07 (t, 3H), 1.20 (t, 3H), 1.64 (d, 1H), 1.84 (d, 2H), 2.3—3.0 (m, 8H), 4.44 (q, 2H), 4.66 (q, 2H); *m/z* 248 (30%, M^+). **(7)** m.p. 163 °C. IR (Nujol) 1640, 1600, 1590, 1460, 1380, 1330, 1300, 1150, 1120, 1055, 1025, 865 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 1.6 (s, 2H), 2.3—2.4 (m, 2H), 4.2—4.3 (m, 2H), 6.8—6.9 (m, 2H), 7.5—7.8 (m, 2H), 7.9—8.15 (m, 2H). The same compound has been obtained occasionally in the Diels–Alder reaction of cyclopentadiene and 1,4-naphthoquinone, as a side product. The similarity of the compounds was established on the basis of identical m.p.s, mixed m.p., TLC R_f values, and superimposable IR spectra. **(10)**: IR (Nujol) 1680, 1605, 1455, 1340, 1305, 1260, 1175, 1065 cm^{-1}; ^{1}H NMR (80 MHz, CDCl$_3$) δ 1.4 (s, 2H), 2.4—3.5 (m, 4H), 3.7—4.4 (m, 4H), 5.15—5.6 (m, 2H), 7.0—7.8 (m, 4H); *m/z* 268 (22%, M^+).

‖ A Referee has suggested the possibility of either a two photon process or photoenolization for dual epimerization.

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