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A PHOTOCHEMICAL APPROACH TO 1,3-CYCLOHEXANEDIONE FORMATION

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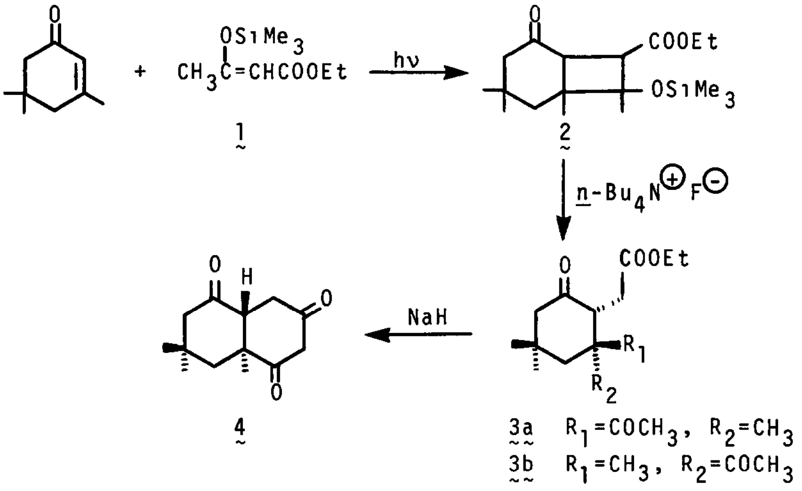
Summary A convenient procedure which accomplishes the overall addition of an 1,3-dioxobutane moiety regioselectively across the carbon-carbon double bond of a conjugated enone has been developed.

The application of photoannelation reactions to synthesis has drawn considerable attention in recent decades. By the use of these methods with or without subsequent modification of the resulting cyclobutane rings, a large number of relatively complex compounds have been synthesized in remarkably simple fashion[1,2] This communication describes a convenient photochemical approach[3] to the addition of a 1,3-dioxobutane moiety regioselectively across the carbon-carbon double bond of a conjugated enone

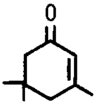
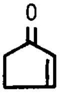
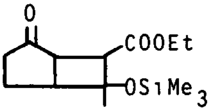
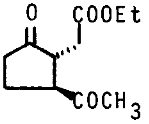
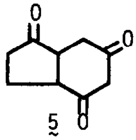
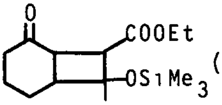
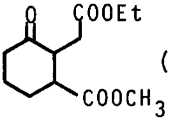
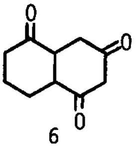
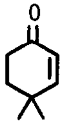
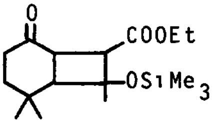
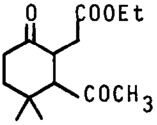
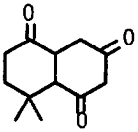
The 1,3-cyclohexanedione formation process, illustrated schematically with isophorone (Scheme 1), involves a three step general sequence initiated with the photocycloaddition of α,β-unsaturated ketones to ethyl β-trimethylsilyloxycrotonate **1**[4] Irradiation (450 W Hanovia high-pressure mercury-vapor lamp and Pyrex filter) of isophorone and a fifteen-fold excess of olefin **1** in benzene at room temperature for 24 hr resulted in the formation of a diastereomeric mixture of adducts **2**,[5] b p. 143-5°C/0 5 torr, in quantitative yield On brief treatment with tetrabutylammonium fluoride in tetrahydrofuran at ambient temperature, the photoadducts **2** underwent cyclobutane ring-opening giving two epimeric diketo esters **3a** and **3b**[6] (ca 3 2[7]) in 70% yield Claisen condensation of these isomeric diketo esters proceeded on treatment with sodium hydride (2.2 eq.) in refluxing tetrahydrofuran for 24 hr, and a single enolized trione **4**,[8] m p. 172°C, was isolated in greater than 85% yield regardless of whether the pure **3a** or **3b** or the mixture of two was used as the starting material. By the same reaction sequence, 2-cyclopentenone, 2-cyclohexenone and its 4,4-dimethyl derivative were subjected to the annelation and triones **5**-**7**[9] were isolated in synthetically useful yields These results are summarized in Table 1

Although the above enones underwent photocycloaddition with **1** with complete regioselectivity to give adducts possessing the expected orientation,[1] the reactions of 3,4-dimethyl-2-cyclohexenone and 4-cholesten-3-one took a different course and each produced a mixture of the two possible regioisomers, the former gave adducts **8** and **9** in 3 1 ratio in a combined yield of 75%[11] and the latter compound gave a quantitative yield of **10** and **11** in near-equal amounts. Treat-

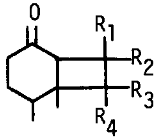


Scheme 1

Table 1. Preparation of triones from conjugated enones

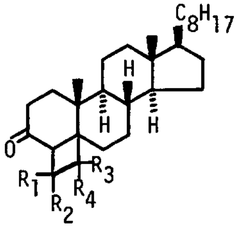
Enone	Photoadducts (% yield)	Fragmentation Products(s) (% yield)	Trione (% yield)
	2 (100)	3a + 3b (70) (3.2)	4 (>85)
	 (65)	 (90)	 5 (76)
	 (99)	 (71)[10] (trans cis=1:1)	 6 (45)
	 (90)	 (90)[10] (trans cis=1 3)	 7 (77)

ment of the inseparable mixture of 8 and 9 with tetrabutylammonium fluoride gave the desired diketo esters 12 (50% yield) along with 3,4-dimethyl-2-cyclohexenone (17% yield) and ethyl acetoacetate Similar treatment of 10 and 11 also produced ethyl acetoacetate in addition to ca 40% yield each of 4-cholesten-3-one and a single diketo ester **13**.[12] The two starting enones were apparently regenerated from the undesired photoadducts **9** and **11** respectively which could undergo a retro-aldol reaction in preference to a retro-Claisen type cleavage leading eventually to the observed products by further elimination of ethyl acetoacetate as depicted in Scheme 2 The general applicability of the method is improved considerably by this preferential mode of fragmentation It facilitates the separation of the undesired photoadduct when formed and makes the use of the starting enone more efficient



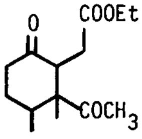
8 $R_1=H$, $R_2=COOEt$
$R_3=OSiMe_3$, $R_4=CH_3$

9 $R_1=OSiMe_3$; $R_2=CH_3$
$R_3=H$, $R_4=COOEt$

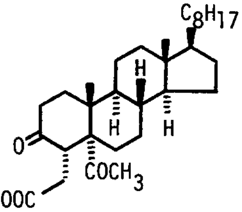


10 $R_1=H$, $R_2=COOEt$
$R_3=OSiMe_3$, $R_4=CH_3$

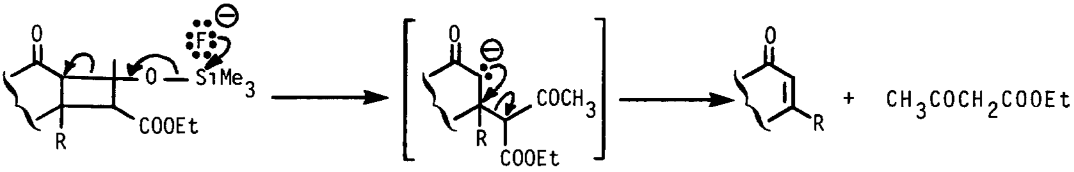
11 $R_1=OSiMe_3$, $R_2=CH_3$
$R_3=H$, $R_4=COOEt$



12



13



Scheme 2

The foregoing report describes a convenient procedure for the construction of polycyclic triketones with the carbonyl groups arranged in an orientation which cannot be readily achieved using conventional methods such as Diels-Alder reaction and Robinson annelation. Application of this procedure to the synthesis of highly oxygenated natural products is in progress.

Acknowledgment We wish to thank the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support and Alberta Heritage Foundation for Medical Research for a Studentship to T.D.A

REFERENCES AND NOTES

1 For reviews, see P.E Eaton, Accounts Chem Res , 1, 50 (1968), P.G. Bauslaugh, Synthesis, 287 (1970), P. de Mayo, Accounts Chem Res , 4, 41 (1971).

2. For some recent applications, see H.J. Liu and W.H. Chan, Can J Chem.,

57, 708 (1979), 58, 2196 (1980), B.A Pearlman, J. Am Chem. Soc., 101, 6398, 6404 (1979); R.B. Kelly, M.L Harley, and S.J. Alward, Can. J. Chem., 58, 755 (1980); M Van Audenhove, D De Keukeleire, and M. Vandewalle, Tetrahedron Lett. 1979 (1980), S.W. Baldwin, and J.M. Wilkinson, J. Am. Chem Soc., 102, 3634 (1980), A.J. Barker and G Pattenden, Tetrahedron Lett., 2599 (1981), and references therein.

3. This approach can be considered as a stretched-out version of the de Mayo reaction [P. de Mayo, H. Takeshita, and A.B.M.A. Sattar, Proc. Chem. Soc., 119 (1962), P. de Mayo and H. Takeshita, Can. J Chem., 41, 440 (1963)].
4. A. 2 1 mixture of (*E*)- and (*Z*)-isomers, b.p 56-7°C/0 75 torr, was prepared in 82% yield by treatment of ethyl acetoacetate with trimethylsilyl chloride (1.3 eq) in triethylamine at room temperature for 16 hr.
5. All new compounds were adequately characterized by spectroscopic methods and by exact mass measurement and/or elemental analysis.
6. In essence the two-step sequence effects the addition of the two fragments (acetyl and acetate) of acetoacetate to the enone C-C double bond with regiochemical control.
7. The ratio of these two diastereomers varies depending on the ratio of *cis* to *trans*-fused starting photoadduct **2** and the degree of epimerization during the reaction. When the pure *cis*-fused photoadducts (obtained by prolonged treatment of **2** with 10-camphorsulfonic acid in benzene) were used, **3b** and **3a** were obtained in a 2 1 ratio
8. Trione **4** exists completely in one enol form as evident from its sharp m.p. and spectral data, particularly ^{13}C nmr spectrum which consists of 13 lines The direction of enolization remains to be ascertained
9. Triones **5**-**7** which were also shown to be completely enolized were isolated in each case as a mixture of geometric and/or stereoisomers.

10 The diastereomeric mixture was used for the subsequent reaction.

11. This reaction was carried out in acetonitrile for three days. In benzene, the reaction was extremely slow and produced only traces of photoadducts after 24 hr.

12 The stereochemistry of **13** was tentatively assigned on the basis of the empirical rules governing the stereochemistry of the photocycloaddition of rigid α,β-unsaturated ketones to olefins [J F. Blount, G D. Gray, K S. Atwal, T Y R. Tsai, and K. Weisner, Tetrahedron Lett., 4413 (1980) and references cited therein]

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