Application of the de Mayo Reaction to the Preparation of Tricyclo[6.3.0.0^{2,6}]undecanes: A Photochemical Synthesis of (±)-Hirsutene[1,2]

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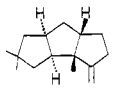
A sequence is described which allows the preparation of the tricyclo[6.3.0.0^{2,6}]undecane skeleton found in a number of physiologically active fungal metabolites. The sequence proceeds via generation of a bicyclo[6.3]-undecane-2,6-dione by photocycloaddition of a cyclohexane-1,3-dione to a cyclopentene, followed by intramolecular reductive coupling of the dione with a low-valence titanium compound. A formal route to the fungal metabolite hirsutene is described using this procedure. The route involves photochemical 2 + 2 addition of 5,5-dimethylcyclohexane-1,3-dione to 2-methyl-2-cyclopentenol followed by in situ silylation of the photoadducts with *tert*-butyldimethylsilyl chloride to give an 89% yield of isomeric silylated, hydroxy-substituted cyclooctane-1,5-diones; treatment of these silyl ethers with a low-valence titanium reagent (obtained by reduction of titanium trichloride with potassium metal) resulted in intramolecular reductive coupling of the dione function to give the hirsutene carbon skeleton with the desired regiochemistry in 57% yield. Desilylation with fluoride ion, followed by sequential catalytic hydrogenation and Jones' oxidation (36% overall yield) completed the formal synthesis by yielding the norketone obtained by ozonolysis of hirsutene. The norketone was produced in five steps in 6% overall yield.

Introduction

A large number of fungal metabolites possessing the *cis-anti-cis*-tricyclo[6.3.0.0^{2,6}]undecane ring system have been isolated in recent years,[3] and because of the interesting physiological activity of some of these compounds the development of routes for their preparation has received substantial attention. The simplest member of this family of compounds is hirsutene (**1**), and its synthesis by a number of pathways has been reported.[4] In this paper



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a route to the tricycloundecane ring system and to hirsutene itself is described which offers the benefits of brevity and ready availability of starting materials and which is potentially applicable to other members of this group of natural products.[5]

Results and Discussion

The approach originally conceived for the synthesis of hirsutene is shown in Scheme I. The first step involved the photochemical cycloaddition of the carbon–carbon double bond of an enolized cyclic 1,3-diketone, 5,5-dimethyl-1,3-cyclohexanedione (dimedone), to the alkenyl ketal **2a** (the de Mayo reaction[6]) to give, after spontaneous retro-aldol opening of the initially formed cyclobutanol **3**, the cyclooctanedione **4a**. In **4a** the ring fusion has the thermodynamically less stable[7] cis stereochemistry because of its origins in the cyclobutane–cyclopentane fused system in **3**. It has been shown that the cis stereochemistry is preserved during the retro-aldol opening.[8] Two regioisomeric modes of addition are possible in the photochemical cycloaddition reaction when a nonsymmetrical alkene is used, and in the reaction of dimedone with **2a** this would lead to a mixture of the regioisomers **4a** and **4b**. It has been shown that, in the absence of overriding steric constraints, the favored regiochemistry of the cycloaddition reaction can be predicted on the basis of the electrostatically more favorable alignment of the dipoles of the reacting alkene and the enone excited state.[6,9] It has also been shown that the regioselectivity is subject to a solvent effect;[10] in polar solvents the regioselectivity predicted by the more favorable alignment of the dipoles of the reactants is less pronounced, and a mixture of regioisomers is obtained. In the reaction of dimedone with **2a** the application of these findings suggests that the yield of the regioisomer **4a**, which is desired for the synthesis of the hirsutene system, should be maximized if a polar solvent is used.

In the second key step of the proposed synthetic route it was anticipated that treatment of **4a** with a low-valence titanium reagent, such as the McMurry reagent,[11] would result in intramolecular reductive cyclization of the diketone to yield, via an intermediate 1,2-diol, the alkene

(1) Contribution 375 from the Photochemistry Unit, the University of Western Ontario.

(2) Our thanks are due to the Natural Sciences and Engineering Research Council of Canada for a grant which defrayed the cost of this investigation.

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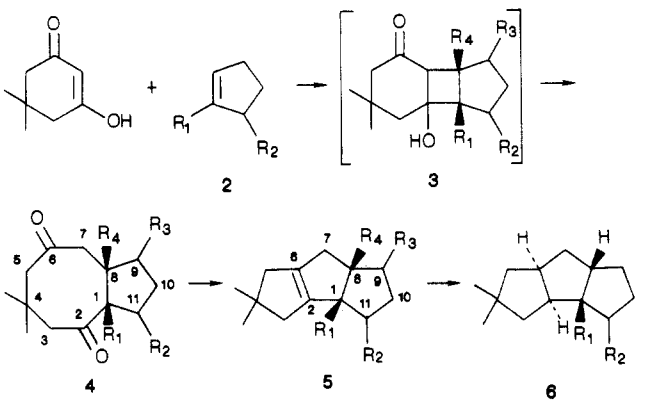
Scheme I



	R_1	R_2	R_3	R_4
4a	CH_3	OCH_2CH_2O	H	H
b	H	H	OCH_2CH_2O	CH_3
c	H	H	H	H
d	H	OH	H	H
e	H	H	OH	H
f	H	H	O	H
g	H	O	H	H
h	H	$OSiMe_2$-*t*-Bu	H	H
i	H	H	$OSiMe_2$-*t*-Bu	H
j	CH_3	$OSiMe_2$-*t*-Bu	H	H
k	H	H	$OSiMe_2$-*t*-Bu	CH_3

	R_1	R_2
2a	CH_3	OCH_2CH_2O
b	H	H
c	CH_3	OH
d	H	OH

	R_1	R_2
6a	CH_3	O
b	H	H
c	H	O

	R_1	R_2	R_3	R_4
5a	CH_3	OCH_2CH_2O	H	H
b	H	H	H	H
c	H	OH	H	H
d	H	H	OH	H
e	H	$-OSiMe_2$-*t*-Bu	H	H
f	H	H	$-OSiMe_2$-*t*-Bu	H
g	H	H	$-OSiMe_2$-*t*-Bu	H
h	CH_3	$OSiMe_2$-*t*-Bu	H	H
i	H	H	$OSiMe_2$-*t*-Bu	CH_3
j	CH_3	OH	H	H
k	H	H	OH	CH_3
l	CH_3	O	H	H
m	H	H	O	CH_3

5a, which on hydrolysis would produce ketone **5l** which has been characterized as a synthetic intermediate in published syntheses of hirsutene.[4c,d,i,j] It has been converted to hirsutene by stereoselective catalytic hydrogenation of the double bond followed by Wittig methylenation of the ketone.[4j] At the outset of this work the use of low-valence titanium reagents for the intermolecular reductive coupling of ketones had been shown to proceed;[11] it had also been demonstrated that alkanediones could undergo intramolecular coupling to give cycloalkenes.[11d,f] The reaction had not been exemplified for the conversion of cycloalkanediones to yield bicyclic alkenes in the manner required in the route for the synthesis of hirsutene shown in Scheme I.

In previous work in this laboratory the applicability of the route shown in Scheme I for the preparation of the tricyclo[6.3.0.$0^{2,6}$]undecane ring system has been demonstrated by using an underivatized cyclopentene[8] (i.e., dimedone + **2b** → **4c** → **5b**). The cyclooctane-1,5-dione **4c** was produced in over 90% yield and was reductively coupled with the McMurry's reagent to yield the tricyclo[6.3.0.$0^{2,6}$]undecane ring containing system **5b** as the only product. In our initial attempts to apply the sequence to the synthesis of hirsutene using the alkene **2a**, problems were encountered in purifying the ethylene ketal of 2-methyl-2-cyclopentenone, i.e., **2a**. The ketal **2a** was prepared by treatment of 2-methyl-2-cyclopentanone with ethylene glycol in benzene containing toluenesulfonic acid; however, it was found impossible to avoid completely the presence of the parent ketone, and this caused complications in the photochemical addition reaction because of competing cyclopentenone photochemistry. In consequence, it was decided to use the allylic alcohol **2c** as the alkene component in the photochemical cycloaddition. In addition to avoiding the problems associated with the use of **2a** this expedient removed the potential problem of instability of the ketal function in the reduction step; for example, it has been reported that ethylene and diethyl ketals undergo partial reduction in the presence of low-valent titanium compounds.[11d,e] The use of alcohol **2c** leads to the possibility of mixtures of stereoisomers in the desired regioisomers of the later intermediates (e.g., at position 11 in structures **4** and **5**); however, this is not important for the synthesis of hirsutene since the 11-hydroxy is oxidized to a ketone in the steps leading from **5** to **6a**.

Prior to the application of the scheme leading to the synthesis of hirsutene, a model study using 2-cyclopentanol (**2d**) as the alkene addend was conducted. In part this was because unambiguous spectral assignment of structures to the products of reaction of dimedone with **2c** required the corresponding normethyl adducts derived from reaction of dimedone and **2d**. In addition, the use of **2d** also leads to a formal synthesis of hirsutene since the conversion of compound **6c** to hirsutene has been described.

In methanolic solutions dimedone exists in equilibrium with the enolized form which absorbs strongly in the ultraviolet region; ultraviolet light (254 nm) irradiation of a 1% methanolic solution of dimedone containing alkene **2d** (fivefold excess) resulted in conversion to a mixture of adducts, which were separated by chromatography to yield regioisomers **4d** (38%) and **4e** (49%). The stereochemistries of the hydroxyl groups were not determined; however, only one epimer was isolated in each instance, although smaller amounts of the other diastereoisomers may have been present in the irradiation product mixture. The assigned structures are consistent with the mass spectral and IR data. The ^{13}C NMR spectra of both compounds exhibited the required number of carbon signals and with the expected multiplicities. A comparison of the chemical shifts of the ring-fusion methine carbons at positions 1 and 8 in compounds **4d** and **4e** with those of the non-hydroxyl-substituted analogue **4c** is shown in the first three entries in Table I. It can be seen that in each case the ring-fusion methine carbon α to the hydroxy-substituted methine carbon is shifted downfield, while the ring-fusion methine carbon β to the hydroxy-substituted methine is shifted upfield. This is in accord with the expected substituent effect.[12] The regiochemical assignment is confirmed by the ^1H NMR spectra of the adducts. The signals due to the hydroxymethine proton at position 11 in **4d** and position 9 in **4e** were readily identified from their low chemical shifts. Irradiation of these signals allowed identification of the signal due to the ring-fusion methine

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Table I. ^{13}C NMR Spectral Data for Ring-Fusion Methines of Photoadducts and Their Derivatives Recorded in $CDCl_3$[a]

compd	C(1)	C(8)	compd	C(1)	C(8)
4c[b]	58.8	38.4	**4k**[c]	60.3	47.5
4d	65.8	36.6	**5b**[b]	47.12[d]	46.55[d]
4e	56.1	46.8	**5e**	57.9	45.7
4f	56.7	49.7	**5f**	45.7	56.3
4h	65.9	37.4	**5g**	45.5	50.5
4i	55.9	47.3	**5h**	57.2[e]	52.6
4j	70.65	47.5	**5i**	53.2	59.2[e]
4k[c]	58.9	47.9			

[a] Chemical shifts are quoted in ppm from the tetramethylsilane signal. [b] From ref 8. [c] Two isomers were isolated possessing this structure. They differed in their configuration at position 9. [d] Assignments may be reversed. [e] These carbons are quaternary; all others in the table are methines.

proton at position 1 in **4d** and position 8 in **4e**; in the case of **4d** the proton at position 1 appeared as a triplet (J = 8 Hz) at 2.85 ppm while in **4e** the signal assigned to the proton at position 8 appeared as a multiplet (J = 1.5, 4, 6, and 10 Hz) at 2.95 ppm. In **4d**, therefore, the ring-fusion methine proton adjacent to the hydroxymethine is coupled to two neighboring hydrogens only, while in **4e** the expected coupling to four adjacent hydrogens is seen. Because of the flexibility of the ring systems in **4d** and **4e**, the stereochemistry of the hydroxyl substituents could not be deduced without ambiguity form the observed coupling constants.

Inspection of the ^{13}C NMR spectrum of the mixture of adducts **4d** and **4e** prior to chromatographic separation and purification indicated that they were formed in approximately equal amounts and that therefore some loss of the regioisomer **4d** had occurred during the separation process since its isolated yield was less than that of **4e**. This may reflect the ability of **4d** to undergo retro-aldol cleavage of the β-hydroxy ketone system present, resulting in opening of the five-membered ring. This has been observed in related 11-hydroxy-substituted bicyclo[6.3]undecane-2,6-diones.[13] Similar reasoning can be used to explain the outcome of Jones' oxidation of the mixture of adducts **4d** and **4e**; this reaction was performed to confirm the structures of **4d** and **4e**, but in the event only a single product was obtained which was identified as the triketone **4f**. None of the regiosomeric systems **4g** was isolated. The failure to observe any of the latter may result from retro-aldol opening of the β-hydroxy ketone function of **4d** under the oxidizing reaction conditions, or it may result from hydrolytic opening of the β-diketone system of **4g**, if it is formed. The structure of **4f** followed from comparison of its ^{13}C NMR spectrum with those of **4c–e** (see Table I); the ring-fusion methine carbon at position 1 of **4f** experiences a β-effect and is shifted upfield by the new carbonyl function, while that at position 8 experiences an α-effect and is shifted downfield by the adjacent carbonyl. The ^1H NMR spectrum supports this assignment; the ring-fusion methine proton at position 8 appeared at 2.87 ppm as a double triplet (J = 3, 12 Hz) while that at position 1 was seen at 2.5 ppm as a multiplet (J = 12, 10, 7.5 Hz).

Treatment of a mixture of the cycloadducts **4d** and **4e** with McMurry's reagent[11] was expected to produce a mixture of the corresponding alkenes **5c** and **5d**. In the event, only **5d** was obtained, and this is also attributable to the ability of the β-hydroxy ketone function of **4d** to undergo retro-aldol opening.[13]

In order to circumvent the problems associated with the lability of the β-hydroxy ketone function in **4d**, the hydroxy group containing cycloadducts **4d** and **4e** were treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole;[14] this allowed the isolation of the silylated adducts **4h** and **4i** in 39% and 43% yields, respectively. As previously for **4d** and **4e**, the stereochemistry of the silylated hydroxyl was not determined, but in each case a single epimer was isolated. The structures of **4h** and **4i** were assigned by comparison of the chemical shifts of the ring-fusion methine carbons with those in compounds **4c–f** (Table I), allowing for the expected changes in chemical shifts induced by the α- and β-effects of the siloxy substituent in the 11-position of **4h** and the 9-position in **4i**.

When the crude mixture of silylated photoadducts was treated with McMurry's reagent three products were isolated. They were assigned structures **5e**, **5f**, and **5g**, and they were obtained in yields of 21%, 28%, and 10%, respectively. The stereoisomers **5f** and **5g** are presumably derived from the siloxy derivatives represented by structure **4i**, which in turn were derived from diketones represented by structure **4e**, although only one epimer of each of **4e** and **4i** were isolated from their respective reaction mixtures. Presumably **4i** is formed as a mixture of diastereoisomers of which only one was isolated; it is unlikely that the isolation of two diastereoisomers, **5f** and **5g**, is due to epimerization during the silylation procedure.

The structures of **5e–g** were determined from their NMR spectra. The ^{13}C NMR spectrum of the nonoxygenated analogue **5b** indicates that the ring-fusion methine carbons have similar chemical shifts[8] (see Table I); thus chemical shift changes induced for positions 1 and 8 of compounds **5e–g** by the presence of the siloxy group in positions 9 or 11 could not be used to assign their structures. However, the ^1H NMR spectra of the products were more informative; in each isomer, the siloxymethine proton was readily identified by virtue of its having the lowest chemical shift in the molecule, and irradiation of this signal allowed identification of the adjacent ring-fusion methine proton at either position 1 in **5e** or position 8 in **5f** and **5g**. Irradiation of the latter protons then allowed identification of the adjacent second ring-fusion methine protons. Analysis of the splitting patterns and measurement of the coupling constants for the ring-fusion methine protons in each isomer then confirmed that in the regioisomer **5e** the proton at position 1 was coupled to two other protons only, while in the regiosomeric stereoisomers **5f** and **5g** the proton at position 8 was coupled to four other protons as the assigned structures require. The magnitude of the coupling constant between the siloxymethine proton at position 11 in **5e** and position 9 in **5f** and **5g** with the ring-fusion methine proton at position 1 in **5e** and position 8 in **5f** and **5g** then allowed deduction of the stereochemistry of the siloxy substituent; thus a trans relationship of these protons in **5e** was indicated by a coupling constant of 2 Hz, while in **5f** the trans relationship was reflected by a coupling constant of 3 Hz, and in **5g** the cis relationship resulted in an observed coupling constant of 8 Hz. With the regiochemistries of the products **5e–g** established, it was possible to assign the ring-fusion methine carbon signals in their ^{13}C NMR spectra, assuming the expected α- and β-effects of the siloxy function upon the chemical shifts. The assignments are shown in Table I.

The results of the sequence dimedone + **2d** → **4d** + **4e** → **5e–g** indicated that the proposed synthetic route to

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(14) Corey, E. J.; Venkateswarlu *J. Am. Chem. Soc.* **1972**, *94*, 6190.

hirsutene was viable in that the desired regioisomer could be obtained in the photochemical step in equal amounts with the undesired isomer and that the reductive cyclization step could be performed in the presence of the oxygen function if it is silylated. In addition, the synthetic intermediates provided models for spectral assignment of the regiochemistry of the products isolated in the actual synthesis of hirsutene described below. Desilylation of the product **5e** followed by hydrogenation and Jones' oxidation would yield a formal synthesis since the product **6c** has been reported as a synthetic intermediate in a published route to hirsutene.[4i] However, it was chosen not to do this since the conversion of **6c** to hirsutene requires several more steps than the are needed in the sequence described below.

Ultraviolet light irradiation of a solution of dimedone and the 2-methyl-2-cyclopentenol (**2c**), which was obtained by reduction of 2-methyl-2-cyclopentenone,[15] gave a mixture of products. Analysis by coupled gas chromatography–mass spectrometry (GC–MS) indicated that the mixture contained species whose molecular weights were consistent with their being the photoadducts derived from reaction of dimedone with **2c**. However, attempts to separate the adducts were unsuccessful because of apparent decomposition. This may have been due to retroaldol opening of the β-hydroxy ketone function of one of the pairs of regioisomers. As noted above, the same instability was also observed for the adducts from **2d**, although to a lesser extent; the greater lability of the products derived from **2c** presumably reflects the presence of the angular methyl substituent. In order to circumvent this problem, the crude mixture of photoadducts was treated with *tert*-butyldimethylsilyl chloride, and the products were then successfully separated by column chromatography. Three cycloadducts were isolated, and they were obtained in approximately equal amounts in a combined yield of 89%; from comparison of their ^{13}C NMR spectra with those of the products from addition of **2d** to dimedone (i.e., compounds **4d** and **4e** and their silylated derivatives **4h** and **4i**) the structure of one of the products was assigned as **4j**, and the other two adducts were both assigned structure **4k** and are epimeric at the 9-position. Thus in the adduct assigned structure **4j** the quaternary ring-fusion carbon at position 1 appeared at 70.65 ppm, which is slightly downfield of the signals for the corresponding carbons in **4d** and **4h**, presumably because of the methyl substituent. The ring-fusion methine at position 8 of **4i** occurs at 47.5 ppm, which is comparable with the positions of the signals for the corresponding carbons in **4d** and **4h** (see Table I). The other two silylated adducts are both assigned structure **4k**, also because of the similarity of the chemical shifts of the ring-fusion methines at positions 1 and 8 with those in the analogues **4e** and **4i**. These adducts differ in the stereochemistry at the siloxy methine at position 9 and are thus diastereoisomeric adducts with the regiochemistry opposite to that required for the synthesis of the hirsutene molecule.

Treatment of the crude mixture of silylated adducts obtained from photoaddition of dimedone with **2c** (i.e., the mixture containing **4j** and **4k**) with McMurry's reagent gave a mixture from which two compounds were isolated by chromatography in 17% and 38% yields. These were assigned the structures **5h** and **5i**, respectively. As was the case with the non-methyl-substituted analogues **5f** and **5g** it was not possible to assign the structures unambiguously from the chemical shifts of the ring-fusion methines in the ^{13}C NMR spectrum (the values for **5h** and **5i** are shown in Table I). In addition, because of the presence of the methyl group in **5h** and **5i** it was not possible to use the coupling data for the ring-fusion methine proton at position 1 in **5h** and position 8 in **5i** to assign the regiochemistry. The ring-fusion methine proton at position 8 in **5h** and position 1 in **5i** could however be seen; in the case of **5h** this proton was split by three others with coupling constants of 9, 3.5, and 1 Hz, while in **5i** it was split by four others with coupling constants of 3, 3, 2.7, and 1.5 Hz. This coupling pattern is consistent with the structures assigned if it is assumed that the third coupling in **5h** arises from a long-range interaction through the double bond; however, it does not prove the assignments, since both compounds might be stereoisomers of **5i** with one of the coupling constants close to 0. In order to disprove this possibility, the major of the two products was treated with ozone. This resulted in generation of the precursor ketone **4k** as determined by comparison of their ^1H NMR and ^{13}C NMR spectra and confirmed the assignment of the structure **5i** to this product. It was then assumed that the second product was one of the stereoisomers of the desired regioisomer **5h**, and this compound was carried through the remaining steps of the synthesis to **6a**. The correctness of the assignment was confirmed by the identity of the spectra of the sample of **6a**, prepared as described below, with those reported in the literature.[16]

Desilylation of a mixture of **5h** and **5i** with tetrabutylammonium fluoride gave the alcohols **5j** and **5k** in 76% yield and these were then oxidised with Jones' reagent. However, only ketone **5m** could be isolated and none of **5l**. It was surmised that the β,γ-unsaturated carbonyl function of **5l** was responsible for its instability, and so it was decided to reduce the double bond of the alcohol **5j** prior to oxidation to the ketone. Hydrogenation of the alcohol **5j** should proceed with cis stereochemistry but can give two isomers depending upon which the face of the molecule reduction occurs. This will yield either the *cis-anti-cis*- or the *cis-syn-cis*-tricyclo[6.3.0.$0^{2,6}$]undecane ring systems, and it is the former that is required for the preparation of hirsutene. Normally the less hindered face of the alkene would be reduced during hydrogenation, and here this would lead to the wrong isomer. However, at the outset of the synthesis it was reasoned that the oxygen function at position 11 of **5l** would control the adsorption of the molecule onto the hydrogenation catalyst surface and promote reduction on the more hindered face. This has been supported by the report in another synthesis of hirsutene that the double bond of **5m** is reduced from the more hindered face to give the tricyclo[6.3.0.$0^{2,6}$]undecane ring system with the desired stereochemistry.[4c,d] In the event, catalytic hydrogenation of alcohol **5j** gave a single major product, which on oxidation with Jones' reagent gave the norketone **6a** (47% yield based on **5j**), so constituting a formal synthesis of the hirsutene molecule.[4c,d,i,j] Comparison of the spectral data of the sample prepared with those in the literature[16] confirmed the structure of **6a** and thus confirmed that the reduction had proceeded with the desired stereochemistry.

Conclusion

The photochemical cycloaddition/reductive coupling sequence for the preparation of the tricyclo[6.3.0.$0^{2,6}$]undecane ring system has been shown to be applicable in the presence of an oxygen functionality and has been applied

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(16) We thank Professor T. Hudlicky for supplying copies of the spectra of this compound.

to a short synthesis of hirsutene which gave norketone **6a** in five steps in 6% overall yield.

Experimental Section

General Methods. Mass spectra were obtained on a Varian-MAT 311A instrument at 70 eV. All ^1H NMR spectra were recorded in $CDCl_3$ at either 200 or 300 MHz. Proton and carbon chemical shifts are reported in ppm downfield from tetramethylsilane internal standard (δ), and proton–proton coupling constants are reported in hertz. All ^{13}C NMR spectra were recorded in $CDCl_3$, and the multiplicities of the carbons were determined from the APT[17] and DEPT[18] spectra. The signals are indicated as 1°, 2°, 3°, or 4° according to whether they correspond to carbons attached to 3, 2, 1, or 0 protons, respectively. Gas chromatographic analysis was performed with flame ionization detectors on $^1/_4$ in. diameter, 6-ft glass columns packed with 5% SE30 on Chromosorb W; in all cases a linear temperature program was used, commencing at 130 °C and heating at 10 deg/min to 200 °C. Retention times refer to a flow rate of 30 mL/min. Preparative and analytical thin-layer chromatography was performed on silica gel plates containing a fluorescor (Kieselgel GF_{254}), and column chromatography was performed with silica gel (Baker, 60–200 mesh). Irradiations were performed on solutions contained in quartz tubes, which were placed in a jacketed, water-cooled immersion well suspended in a Rayonet reactor equipped with low-pressure mercury lamps emitting at 254 nm. The solutions were purged with nitrogen gas before irradiation and the progress of the irradiations was monitored by GC. Air-sensitive reactions were performed under a positive pressure of nitrogen with THF which had been distilled from a solution of sodium–benzophenone ketyl radicals. Following aqueous workup, organic extracts were dried with anhydrous K_2CO_3 in all cases. Samples of 2-cyclopentenol were prepared by $LiAlH_4$ reduction of 2-cyclopentenone in anhydrous ether.[19] Samples of 2-cyclopentenone were prepared by treatment of cyclopentene with singlet oxygen in the presence of pyridine using the method described by Mihelich and coworkers[20] except that tetratolylporphyrin was used as the sensitizer. Samples of 2-methyl-2-cyclopentenol were prepared by $LiAlH_4$ reduction of 2-methyl-2-cyclopentenone[15] in anhydrous ether.

Irradiation of 5,5-Dimethyl-1,3-cyclohexanedione with 2-Cyclopentenol: Preparation of 4d and 4e. A solution of dimedone (0.250 g, 1.78 mmol) and alkene **2d** (1.0 g, 12 mmol) was dissolved in methanol (40 mL) and irradiated until GC indicated none of the starting ketone remained (72 h). At the end of the reaction, GC indicated the presence of two major products with retention times of 7.5 and 8.0 min. The solvent was removed at room temperature under reduced pressure to yield a yellow oil; the ^{13}C NMR spectrum of this material confirmed the presence of two major products. A sample of the oil (235 mg) was purified by column chromatography on 50 g of silica gel (eluent hexane/diethyl ether/methanol) to yield **4d** (72 mg) and **4e** (92 mg) as white solids. For **4d**: mp (hexane) 91–94 °C; ^1H NMR 4.6 (1 H, q, J = 8, C(11)H), 3.1 (1 H, m, C(8)H), 2.85 (1 H, t, J = 8, C(1)H), 2.75 (1 H, d, J = 12, C(5)H or C(3)H), 2.45 (1 H, d, J = 12, C(5)H or C(3)H), 2.40 (1 H, d, J = 12, C(3)H or C(5)H), 2.60 (1 H, d, J = 12, C(3)H or C(5)H), 1.05 (3 H, s), 2.5 (2 H, m), 1.4–1.5 (4 H, m); IR (Nujol) 1680, 3550 cm^{-1}; ^{13}C NMR 71.4 (c(11)H), 65.8 (C(1)H), 53.0, 52.4, 49.9, 30.6, 30.1 (all 2°), 36.6 (C(8)H), 35.4 (4°), 32.5, 27.6 (both 1°), 211.5, 210.5 (both carbonyls); M^+, found 224.14101, $C_{13}H_{20}O_3$ requires 224.1412. For **4e**: mp (hexane) 100–103 °C; ^1H NMR 4.0 (1 H, dt, J = 1.6, 5.8, C(9)H, 3.45 (1 H, dt, J = 6, 8 C(1)H), 2.95 (1 H, m, J = 1.6, 4, 6, 10, C(3)H), 2.7 (1 H, d, J = 12, C(3)H or C(5)H), 2.6 (1 H, d, J = 12, C(3)H or C(5)H), 1.1 (6 H, s), 2.0–2.2 (4 H, m), 1.5–1.8 (4 H, m); IR (Nujol) u690, 3580 cm^{-1}; ^{13}C NMR 56.1 (C(1)H), 211.1, 210.2 (both carbonyl), 52.2, 52.6, 45.3, 32.0, 20.5 (all 2°) 35.3 (4°), 46.8 (C(8)H), 79.4 (C(9)H), 32.8, 27.3 (both 1°); M^+, found 224.14098, $C_{13}H_{20}O_3$ requires 224.1412.

Oxidation of 4d and 4e: Preparation of Triketone 4g. A mixture of the crude irradiation mixture containing **4d** and **4e** (350 mg) was dissolved in acetone (15 mL) and stirred in an ice bath while Jones' reagent (ca. 4 mL of a solution of CrO_3 (6.7 g) and H_2SO_4 (5.8 mL) in 15 mL of H_2O) was added dropwise until the reaction solution sustained the orange color of the Cr^{VI}. A few drops of 2-propanol were added to destroy excess oxidant, and the green solution was diluted with diethyl ether, filtered, and dried. GC analysis of the product solution indicated a single major component with a retention time of 6.7 min. The ether solution was evaporated under reduced pressure, and the residue (506 mg) was purified by column chromatography (eluent hexane/diethyl ether) to give **4g** as a white solid (58 mg). For **4g**: mp (hexane–diethyl ether) 130.5–131 °C; ^1H NMR 3.05 (1 H, dd, J = 16, 3, C(7)H), 2.76 (1 H, m, J = 12, 10, 7.5, C(1)H), 2.48 (1 H, d, J = 12, C(5)H), 2.39 (1 H, d, J = 12, C(4)H), 2.26 (1 H, dd, J = 12, 12 (?), C(7)H), 2.24 (1 H, dd, J = 12, 9.5 C(10)H), 2.129 (1 H, m C(10)H), 2.12 (1 H, d, J = 12, C(5)H), 2.06 (2 H, m $C(11)H_2$), 1.12 (3 H, s), 1.09 (3 H, s); IR (Nujol) 1690, 1730 cm^{-1}; ^{13}C NMR 214.07, 209.9, 209.29 (all carbonyl), 56.7 (C(1)H), 49.7 (C(8)H), 52.3, 50.47, 36.0, 22.6 (all 2°), 36.1 (4°), 30.7, 29.3 (both 1°).

Reduction of 4d and 4e: Preparation of 5d. A slurry of $TiCl_3$ (3.6 g) in dry THF (150 mL) was stirred under a positive pressure of dry nitrogen gas, and potassium metal (3.3 g) was added. The mixture was refluxed for 1 h, and the black reaction mixture was allowed to cool to room temperature. A sample of the crude irradiation mixture containing **4d** and **4e** (323 mg) in dry THF (5 mL) was added, and the resulting mixture was refluxed under nitrogen. Samples were periodically removed and worked up for GC analysis (see Discussion). After 4 days the reaction mixture was cooled in ice, and methanol (75 mL) was added to quench the reaction. The reaction mixture was filtered through Celite and concentrated under reduced pressure and the residue extracted with diethyl ether (3 × 50 mL). The combined extracts were evaporated under reduced pressure to yield a yellow oil (252 mg). GC indicated a single major product present with a retention time of 3.7 min. This was purified by column chromatography on 10 g of silica gel (10% diethyl ether in hexane as eluent) to give **5d** (87 mg) as an oil. For **5d**: ^1H NMR 3.95 (1 H, dt, J = 4, 2, C(9)H), 3.6 (1 H, dt, J = 8, 2, C(1)H), 2.85 (1 H, ddt, J = 8, 2, 4 C(8)H), 2.5 (1 H, dd, J = 16, 8, C(7)H), 1.95–1.85 (5 H, m), 1.55–1.3 (4 H, m), 1.1 (3 H, s), 1.05 (3 H, s); IR (film) 3610 cm^{-1}; ^{13}C NMR 146.0, 141.1 (both carbonyl), 81.3 (C(9)), 56.2 (C(1)), 46.4 (C(1)), 45.4 (4°), 45.8, 44.5, 35.6, 34.2, 27.1 (2°), 31.3, 31.1 (both 1°); M^+, found 192.1518, $C_{13}H_{20}O$ requires 192.1514.

Silylation of 4d and 4e: Preparation of 4h and 4i. *tert*-Butyldimethylsilyl chloride (1.6 g) and imidazole (1.5 g) were dissolved in DMF (1 mL), and the solution obtained was added to a stirred solution of the crude irradiation mixture containing **4d** and **4e** (244 mg) in CH_2Cl_2 (5 mL). The solution was cooled in ice during the addition and then stirred at room temperature for 12 h. The reaction mixture was diluted with diethyl ether (50 mL), washed with water (3 × 10 mL), dried, and evaporated under reduced pressure to give a yellow oil. GC analysis indicated that this contained two major components with retention times of 9.8 and 10.5 min. The oil was separated by column chromatography on 150 g of silica gel (50% diethyl ether in pentane as eluent) to give **4h** (140 mg, 39%) and **4i** (156 mg, 43%). For **4h**: ^1H NMR 4.55 (1 H, dt, J = 6.5, 6, C(11)H), 3.0 (1 H, m, C(8)H), 2.8 (1 H, dd, J = 6, 8, C(1)H), 2.85 (1 H, d, J = 12.5, CH_2 adjacent to carbonyl), 2.4 (1 H, d, J = 12.5, CH_2 adjacent to carbonyl), 2.35 (1 H, d, J = 12.5, CH_2 adjacent to carbonyl), 2.25 (1 H, d, J = 12.5, CH_2 adjacent to carbonyl), 2.1 (2 H, d, J = 12.5, $C(7)H_2$), 1.7–1.5 (4 H, m), 1.05 (6 H, s), 0.85 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 65.9 (C(1)), 215.9, 210.8 (both carbonyl), 51.7, 54.2, 50.4, 30.9, 31.4 (all 2°), 37.4 (C(8)H), 72.6 (C(11)), 27.5, 32.6, 25.7, -4.4, -4.6 (all 1°), 17.9, 35.6 (both 4°). For **4i**: ^1H NMR 3.9 (1 H, dt, J = 1.5, 4, C(9)H), 3.3 (1 H, dt, J = 8, 6, C(1)H), 2.9 (1 H, m, J = 9, 1.5, 6, 4, C(8)H), 2.6 (2 H, d, J = 12.5), 2.3–2.1 (4 H, CH_2 adjacent to carbonyl), 1.6–1.2 (4 H, m), 1.05 (6 H, s), 0.85 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 55.9 (C(1)H), 212.9, 211.7 (both carbonyl), 52.2, 52.6, 45.4, 32.3, 20.5 (all 2°), 35.1, 17.9 (both 4°), 47.3 (C(8)H), 79.9 (C(9)H), 27.5, 32.5, 25.7, -4.7, -4.8 (all 1°).

Reduction of 4h and 4i: Preparation of 5e–g: The reduction was performed on a sample (872 mg) of the crude mixture of

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silylated adducts from above using the same procedure and quantities of reductant as described for the reduction of **4d** and **4e**. GC indicated that the reaction was complete after 48 h; two product components were resolved with retention times of 7.05 and 7.8 min. Aqueous workup of the methanol quenched reaction mixture as described above gave an oil (414 mg), which was separated by column chromatography on 40 g of silica gel (hexane as eluent) to give samples of **5e**, **5f**, and **5g** as oils in the ratio 21:28:10 (combined yield of 59%). For **5e**: ^{1}H NMR 4.05 (1 H, dt, J = 3, 2, C(11)H), 2.95 (1 H, dd, J = 2, 8), 3.25 (1 H, tq, J = 8, 3, C(8)H), 2.05–1.9 (6 H, m), 1.7–1.5 (4 H, m), 1.24–1.20 (6 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 144.4, 143.3 (both 4°), 76.0 (C(11)H), 57.9 (C(1)H), 45.4 (C(8)H), 44.1, 18.3 (both 4°), 45.2, 38.0, 34.5, 32.3, 26.6 (all 2°), 30.8, 30.6, 26.0, –4.3, –4.5 (all 1°). For **5f**: ^{1}H NMR 4.0 (1 H, q, J = 3, C(9)H), 2.9 (1 H, m, J = 3, 8, 3.5, C(8)H), 3.1 (1 H, m, C(1)H), 1.85–1.75 (5 H, m), 1.7–1.45 (4 H, m), 1.18, 1.1 (6 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 146.0, 141.1 (both 4°), 81.3 (C(9)H), 56.3 (C(8)H), 45.7 (C(1)H), 45.2, 18.3 (both 4°), 45.4, 43.7, 34.8, 34.0, 26.7 (all 2°), 30.9, 30.6, 26.0, –4.3, –4.4 (all 1°). For **5g**: ^{1}H NMR 4.1 (1 H, m, J = 5, 3, 8 C(9)H), 3.0 (1 H, m, C(1)H), 2.05–1.85 (6 H, m), 1.6–1.45 (4 H, m), 1.1 (6 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 144.8, 143.5 (both 4°), 75.5 (C(9)H), 50.5 (C(8)H), 45.5 (C(1)H), 45.3, 18.3 (both 4°), 44.5, 43.4, 32.9, 29.2, 27.3 (all 2°), 30.9, 30.6, 26.0, –4.5, –4.7 (all 1°).

Irradiation of 5,5-Dimethyl-1,3-cyclohexanedione with 2-Methyl-2-cyclopentenol (2c): Preparation of 4j and 4k. A solution of dimedone (250 mg) and alkene **2c** (1.0 g) in methanol (40 mL) was irradiated for 5 days. GC indicated 70% conversion of the dione to a mixture of products. Two major components were resolved and had retention times of 7.9 and 8.6 min. The reaction mixture was evaporated under reduced pressure and the residue treated with *tert*-butyldimethylsilyl chloride as described for the irradiation mixture containing **4d** and **4e**. GC of the product mixture indicated the presence of three major resolved components with retention times of 11.1, 12.2, and 12.9 min. These compounds were separated by column chromatography on silica gel (150 g) using 40% diethyl ether in hexanes as eluent to give **4j** and the two epimers of **4k** in equal amounts (total yield 89%). For **4j**: ^{1}H NMR 3.7 (1 H, dd, J = 6, 8.5, C(11)H), 2.95 (1 H, m, C(8)H), 2.35–2.25 (2 H, m, C(7)H$_2$), 2.15–1.77 (4 H, m), 1.8–1.55 (4 H, m), 1.15, 1.0 (9 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 211.0, 216.2 (both carbonyl), 81.1 (C(11)H), 70.65 (C(1)), 53.4 (C(8)H), 32.8 (C(4)), 55.2, 51.3, 33.9, 21.1 (all 2°), 31.6, 27.2, 25.7, 20.3 (all 1°), 18.0 (4°), –4.3, –4.9 (both 1°). For **4k** (first epimer): ^{1}H NMR 3.75 (1 H, dd, J = 6.5, 8.5, C(9)H), 3.05 (1 H, dd, J = 8.5, 6.5, C(1)H), 2.7–2.25 (6 H, m), 2.05–1.9 (4 H, m), 1.1, 1.0 (9 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 211.7, 212.7 (both carbonyl), 60.3 (C(1)H), 82.5 (C(9)H), 47.5 (C(8)), 54.5, 50.3, 45.6, 30.3, 21.1 (all 2°), 35.6 (C(4)), 31.2, 29.8, 25.8, 25.6, –4.39, –4.9 (all 1°). For **4k** (second epimer): ^{1}H NMR 3.7 (1 H, dd, J = 8, 6, C(9)H), 3.0 (1 H, dd, J = 9, 4.5, C(1)H), 2.77 (1 H, d, J = 13.5, C(3)H or C(5)H), 2.5 (2 H, s, C(7)H$_2$), 2.35 (1 H, d, J = 13.5, C(3)H, or C(5)H), 2.3–2.2 (2 H, d, J = 13.5, C(3)H and C(5)H), 1.85 (2 H, m), 1.5 (2 H, m), 1.1, 1.0 (9 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 210.7, 214.7 (both carbonyl), 80.6 (C(9)H), 58.9 (C(1)H), 47.9 (C(8)), 55.4, 55.2, 51.5, 30.7, 22.8 (all 2°), 34.4 (C(4)), 32.5, 28.7, 25.8, 21.1 (all 1°), 17.8 (4°), –4.3, –4.9 (1°).

Reduction of 4j and 4k: Preparation of 5h and 5i. The reduction was performed on 266 mg of the crude irradiation mixture containing **4j** and **4k** in the same manner as for **4d** and **4e**, except that only 24 h was required for complete conversion. GC analysis of the product mixture indicated the presence of two major resolved components with retention times of 7.0 and 7.9 min. These were separated by chromatography on silica gel (50 g, hexane as eluent) to give **5h** (17%) and **5i** (38%). For **5h**: ^{1}H NMR 3.7 (1 H, m, J = 5, 0.5, C(11)H), 2.6 (1 H, ddt, J = 2.75, 1.5, 3, C(8)H), 2.0–1.8 (6 H, m), 1.7–1.35 (4 H, m), 1.15, 1.1 (9 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 144.2, 142.6 (both 4°), 81.5 (C(11)H), 57.2 (C(1)), 52.6 (C(8)H), 43.6, 37.9, 33.3, 29.7, 27.8 (all 2°), 44.3 (C(4)), 30.8, 30.5, 25.9, 25.1 (1°), 18.2 (4°), –4.4, –4.8 (1°). For **5i**: ^{1}H NMR 3.69 (1 H, t, J = 4, C(9)H), 2.25 (1 H, m, J = 3.5, 9, 1, C(1)H), 1.95–1.9 (4 H, m), 1.85–1.75 (2 H, m, J = 16), 1.65–1.5 (4 H, m), 1.15, 1.1 (9 H, s), 0.9 (9 H, s), 0.05 (6 H, s); ^{13}C NMR 145.9, 139.7 (both 4°), 81.3 (C(9)H), 59.2 (C(8)), 53.2 (C(1)H), 44.4 (C(4)), 45.4, 44.1, 34.0, 26.4 (2°), 30.8, 30.5, 25.9, 23.3 (1°), 18.2 (4°), –4.4, –4.8 (1°).

Ozonolysis of 5i. A sample of **5i** (20 mg) was dissolved in CH_2Cl_2, and the solution was cooled to –5 °C. Ozone was passed through the solution until a blue color was observed. Excess ozone was removed by passing ozone-free oxygen through the solution until the blue color disappeared. Zinc dust (0.5 g) and acetic acid (4 mL) were added to the solution, followed after 10 min by $CHCl_3$ (50 mL). The mixture was filtered, and the filtrate was washed with water, dried, and evaporated under reduced pressure to give a yellow oil (18 mg), which had the same retention time on GC as **4k**. The oil was passed through a column of silica gel (4 g, diethyl ether/hexane as eluent). The major fraction contained material whose ^{1}H NMR and ^{13}C NMR spectra were identical with those of **4k**.

Desilylation of 5h and 5i: Preparation of 5i and 5k. A sample of the mixture of **5h** and **5i** (57 mg) was dissolved in THF (2 mL). A 0.1 M solution of tetrabutylammonium fluoride in THF (1.5 mL) was added, and the mixture was stirred for 12 h. Workup consisted of dilution of the reaction mixture with CH_2Cl_2 (10 mL), washing with water (1 × 3 mL), drying, and concentration under reduced pressure to yield a mixture of **5j** and **5k**, which was separated by thick-layer chromatography (30% diethyl ether/hexane eluent) to give **5j** and **5k** (combined isolated yield 76%). For **5j**: ^{1}H NMR 3.95 (1 H, br dd, J = 5, 2.5, C(11)H), 2.6 (1 H, m, C(8)H), 2.05–1.30 (11 H, m, 1 H exchanged with D_2O), 1.15, 1.05 (9 H, s); ^{13}C NMR 145.3, 142.0 (both 4°), 81.5 (C(11)H), 57.3 (C(1), 53.2 (C(8)H), 44.3 (C(4)), 43.5, 37.5, 33.2, 29.3, 27.5 (2°), 30.8, 30.6, 25.2 (1°). For **5k**: ^{1}H NMR 3.9 (1 H, t, J = 4, C(9)H), 2.5 (1 H, m, J = 8.5, 2.5, 1 C(1)H), 2.0–1.4 (11 H, m, 1 H exchanged with D_2O), 1.15–1.05 (9 H, 3 s); ^{13}C NMR 145.6, 139.8 (both 4°), 81.1 (C(9)H), 58.7 (C(8)), 53.1 (C(1)H), 45.3, 44.2, 43.9, 33.5, 26.3 (all 2°), 44.1 (C(4)), 30.7, 30.5, 22.1 (all 1°).

Oxidation of 5j and 5k: Preparation of 5m. Alcohol **5k** (41 mg) was dissolved in acetone (5 mL), and the solution was cooled in an ice bath. Jones' reagent (ca. 1.5 mL of a solution of 6.7 g of CrO_3 in 15.5 mL of water containing 5.8 mL of H_2SO_4) was added dropwise until the solution remained orange in color. Excess oxidant was destroyed by addition of a few drops of 2-propanol, and the solution was diluted with acetone to precipitate inorganic salts. The solution was dried and evaporated and the residue taken up in CH_2Cl_2, filtered, and evaporated to yield a yellow oil, which was purified by thick-layer chromatography (35% diethyl ether in hexane as eluent) to give **5m** (29%). For **5m**: ^{1}H NMR 2.3–1.35 (11 H, m), 1.15–1.0 (9 H, 3 s); ^{13}C NMR 226.0 (carbonyl), 144.7, 143.7 (both 4°), 65.8 (C(8)), 51.6 (3°), 45.3, 41.9, 36.4, 21.9 (2°), 30.9, 30.3, 20.8 (1°).

Hydrogenation and Oxidation of 5j: Preparation of 6a. A sample of **5j** (52 mg) was dissolved in methanol (20 mL), and PtO_2 (12 mg) was added. The suspension was stirred for 10 h undr a positive pressure of hydrogen, filtered, and evaporated under reduced pressure to give an oil, which was oxidized with Jones' reagent by using the procedure described for the mixture of **5j** and **5k**. The product was purified by thick-layer chromatography to give **6a** (47% from **5j**), whose spectral data were identical with those previously reported for this compound.[16]

Registry No. (±)-**1**, 59433-37-3; (±)-**2c**, 108297-40-1; (±)-**2d**, 62894-08-0; (±)-**4d**, 108391-35-1; (±)-**4e** (isomer 1), 108391-36-2; (±)-**4e** (isomer 2), 108391-39-5; (±)-**4g**, 108297-34-3; (±)-**4h**, 108297-36-5; (±)-**4i** (isomer 1), 108297-37-6; (±)-**4i** (isomer 2), 108391-40-8; **4i**, 101213-89-2; (±)-**4k** (isomer 1), 101312-72-5; (±)-**4k** (isomer 2), 101213-83-6; **5d**, 108297-35-4; (±)-**5e**, 108297-38-7; (±)-**5f**, 108297-39-8; (±)**5g**, 108391-37-3; **5h**, 101213-86-9; **5i**, 101213-87-0; **5j**, 108297-41-2; **5k**, 108297-42-3; (±)-**5m**, 108297-43-4; (±)-**6a**, 59372-73-5; **6a** (R_2 = OH), 108391-38-4; dimedone, 3471-13-4.