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Toward the Synthesis of the Taxol C,D Ring System: Photolysis of α-Methoxy Ketones

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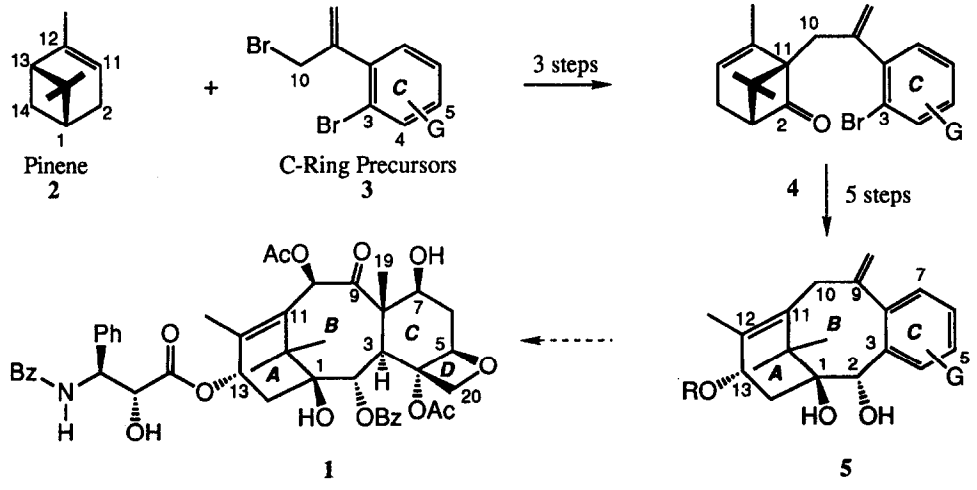
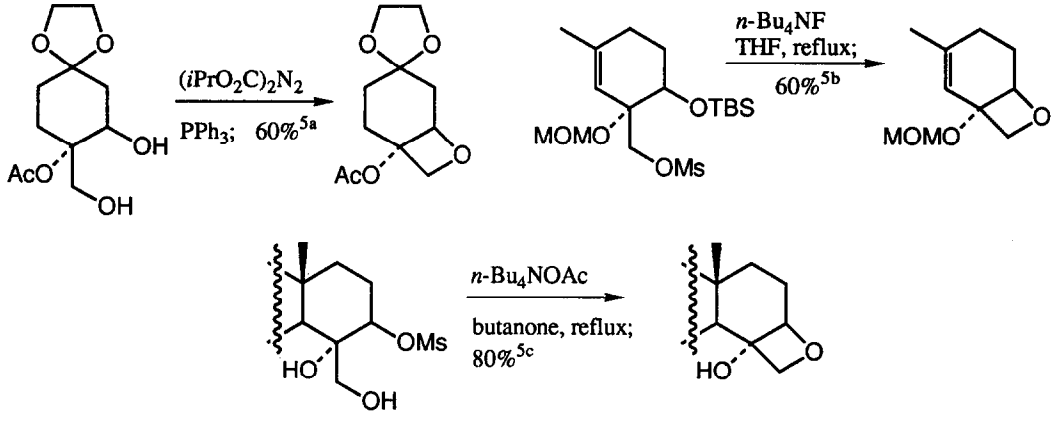
Abstract: Model systems for the synthesis of the C and D rings of taxol are described, involving photolyses of α-methoxy ketones. *Cis*-fused oxetanols common to taxol are formed along with novel *trans*-fused oxetanols. Experiments bearing on the selectivity of this process as well as a mechanistic hypothesis are also described.

Currently in phase III clinical trials in the U.S., the natural product taxol (**1**) holds remarkable promise for the treatment of breast and ovarian cancer.[1] As a consequence of its novel mode of action involving the facilitated assembly and stabilization of microtubules, taxol additionally represents an exciting new lead in cancer chemotherapy.[2] In an effort to address issues related to taxol supply, the basis for its molecular mode of action, and the development of improved but structurally simpler agents, we have focused attention over the past several years on the development of a practical route to taxol and its analogues.[3] In the first report of these studies, we described a process (Scheme 1, **2** - **5**) in which pinene (**2**), a chiral and inexpensive component of the industrial

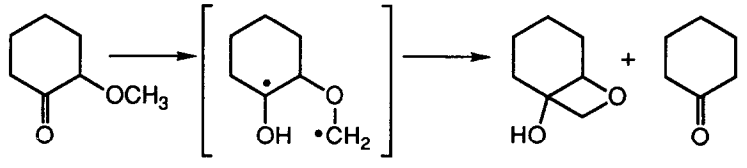


Scheme 1. Structure of taxol **1** and synthesis of ABC tricarbocyclic core.

solvent turpentine, is converted into 10 of the 20 carbons of the ABC tricarbocyclic core of taxol in five stereocontrolled steps.[4] This process allows for the convergent union of pinene with variable aromatic (*e.g.* **3**) and non-aromatic C-ring precursors, providing access to varied analogues as needed to elucidate systematically the structural basis for taxol's unique biological activity. For several applications of this strategy, it was expected that the D-ring oxetanol of taxol could be obtained from a C5-methoxy-C4-ketone functionality derived either from an aromatic or non-aromatic C-ring progenitor. We now describe model studies undertaken to explore the factors governing the viability of this conversion.



Scheme 2. Reported methods for the synthesis of the D-ring of taxol.



Scheme 3. Formation of an oxetanol from the photolysis of an α-methoxy ketone.

Several impressive methods have been reported for synthesizing the D ring of taxol (Scheme 2).[5] Common to all of these procedures is a requirement for the preparation of a selectively functionalized triol and ring closure through the displacement of an activated oxygen. In principle, formation of the oxetanol ring of

taxol could also be achieved through *carbon-carbon bond formation*. Noteworthy in this regard is the Norrish type II reaction (Scheme 3), allowing for the conversion of an α-methoxy ketone directly to an oxetanol.

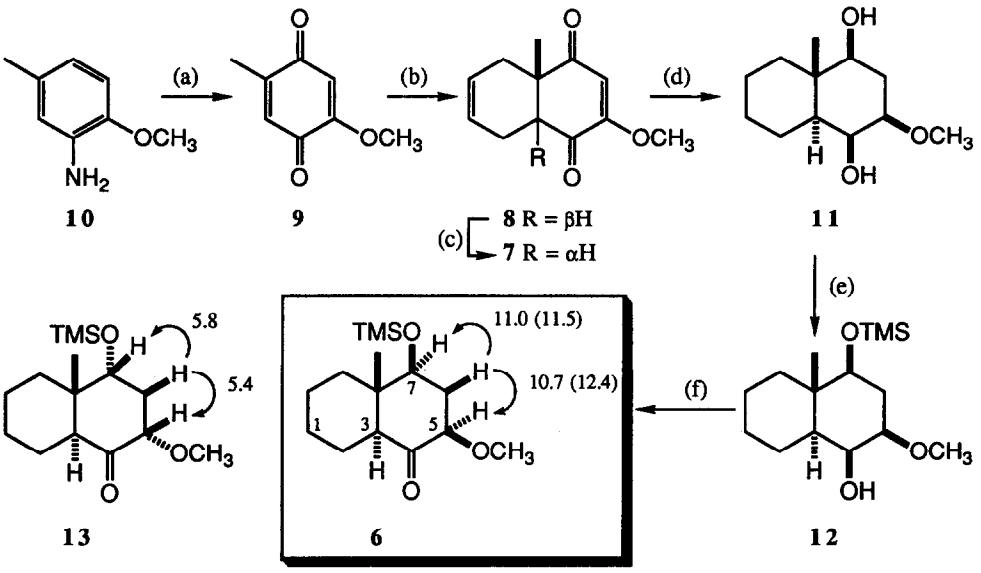
The Norrish type II reaction has been well studied and much is known about its mechanism.[6] It has been found that the mode selectivity (fragmentation versus cyclization), efficiency, and stereochemistry of this process are influenced by a number of factors including the conformation of the substrate, the steric environment of the ketone,[7,8] and the nature of the solvent.[9] For aryl alkyl ketones or dialkyl ketones, this process provides a rather efficient route to cyclobutanols.[9,10] Of direct relevance to the present study, heteroatoms are tolerated in the tether between the carbonyl group and the abstractable hydrogen. The photolysis of α-methoxy ketones, for example, has been used to remove methoxy groups from ketosugars,[11] presumably through the intermediacy of a diradical. Closure of the diradical to an oxetanol has also been observed; while the yields are good in the case of aryl alkoxyalkyl ketones, poorer yields are obtained with alkyl alkoxyalkyl ketones.[12] Oxetanols have also been observed as side products in the photolysis of 2-alkoxyquinones with alkynes[13] and alkenes[14] and in the photolysis of 2-alkoxy-2,5-cyclohexadien-1-ones with alkenes.[15] Remarkably even more highly strained rings can be made using this methodology as evidenced by the synthesis of alkylideneoxetanols in the photolysis of 2-methoxy-2-ene-1-ones.[16] While studies directly pertinent to the taxol problem have not been addressed, it is known that the photolysis of 2-methoxycyclohexanone gives a 3-oxetanol but in only 3% yield.[12b,17] The appearance in this reaction of substantial amounts of cyclohexanone arising from fragmentation of a putative diradical intermediate suggests that this process could be equally useful for oxetanol formation if fragmentation of the diradical could be suppressed. In view of the potential of this process for simplifying access to taxol and novel taxol analogues, we undertook the following investigation of the effect of conformation and solvent on the photocyclization of conformationally defined α-methoxy ketones.

RESULTS

Crucial to the implementation of this process in the synthesis of complex molecules is an understanding of how the conformation of the methoxy ketone influences the mode (fragmentation versus closure) and selectivity of the reaction. Since our projected synthesis of taxol would allow for the introduction of α-methoxy

ketones with different preferred conformations, we elected first to examine a model system with well-defined conformational features. The *trans*-decalone ring system **6** (Scheme 4) served well in this respect, incorporating an α-methoxycyclohexanone subunit, restricted in a chair conformation, with peripheral functionality (angular methyl, C7 oxygen) analogous to taxol progenitors. This system was additionally attractive because of the potential availability of **6** from *trans*-tetrahydronaphthoquinone **7**, an early intermediate in the Woodward steroid synthesis.[18]

For the synthesis of **7**, benzoquinone **9** was prepared in 40% yield by oxidizing readily available 2-methoxy-5-methylaniline (**10**) following the procedure of Anslow, Ashley, and Raistrick (Scheme 4, step a).[19] Diels-Alder cycloaddition (step b) with Lewis acid catalysis as reported by Hayakawa[20] produced **8**, which was readily isomerized to the *trans*-adduct **7** in 69% yield. A noteworthy by-product in this isomerization is the isolable enol of **8**.[18,20]



(a) $Na_2Cr_2O_7 \cdot 2H_2O$ / H_2O / H_2SO_4, 40%; (b) 1,3-butadiene / $BF_3 \cdot Et_2O$ / CH_2Cl_2, -15 °C, 12 h, 95%; (c) 1 *N* NaOH / *p*-dioxane; 1 *N* HCl, 82% (d) H_2 / PtO_2, EtOAc, 66%; (e) $(COCl)_2$ / DMSO / CH_2Cl_2, -78 °C; Et_3N, 69% (f) 1:1 $TMSNEt_2$ / acetone, CH_2Cl_2, reflux, 8 h, 83%; (g) $(COCl)_2$ / DMSO / CH_2Cl_2, -78 °C; Et_3N, 56%

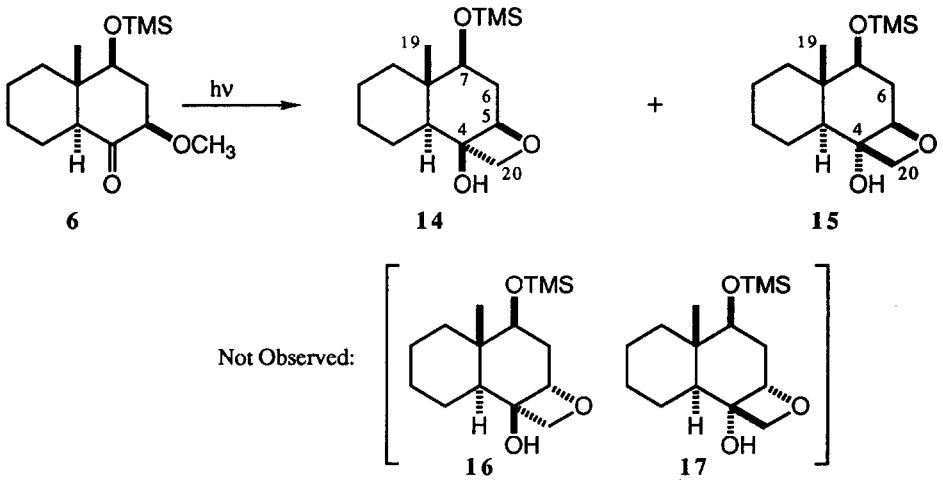
Scheme 4. Synthesis of a model C,D-ring precursor. Predicted coupling constants for the C6 βH are shown for **6** and **13**. Observed constants are given in parentheses.

Attempts to reduce the conjugated alkene in **7** without reduction of the isolated olefin met with only limited success so **7** was exhaustively hydrogenated over platinum oxide catalyst (step d) to form the diol **11**. Selective protection of **11** with *N,N*-diethyltrimethylsilylamine, reported to silylate equatorial hydroxyl groups selectively in the presence of axial hydroxyl groups,[21] gave monosilyl compound **12** (step e). Oxidation of this alcohol by using Swern conditions yielded *trans*-decahydronaphthalenone **6** (step f).

The stereochemistry of **6** was established by extensive NMR experiments. The ^{13}C NMR chemical shifts for **6** are in accord with standard shift assignments for related *trans*-fused systems. In *cis*-fused rings, the chemical shift of the angular methyl is δ 28.2 on average, while in *trans*-fused rings it is typically near δ 15.7.[22] An APT (Attached Proton Test) experiment indicated that the angular methyl in **6** appears at 11.1 ppm, in accord with the assigned *trans*-fused ring system. Molecular modeling experiments using the MM2 force field were also performed on the four possible isomers of **6** that contain the *trans*-fused ring. The coupling constants were determined from the energy-minimized structures and compared to the observed coupling constants (see Scheme 4, observed constants are given in parentheses). The observed values were consistent with two isomers, **6** and **13**, which could be further differentiated by NOE experiments. Irradiation of the angular methyl group gave a positive enhancement (5%) to the β hydrogen on C6,[23] which in turn was found to be coupled to hydrogens at C5 and C7 with constants of 12.4 and 11.5 Hz, a relationship consistent with only isomer **6**.

Compound **6** was photolyzed in benzene through borosilicate glass for 2.5 hours ($\approx$ 40% conversion). Examination of the crude photolysate by NMR indicated that there were two different oxetanol-containing molecules produced, as well as a compound arising from the loss of the methoxy group (presumably as formaldehyde). Photolysis of **6** for 5 hours (88% conversion) yielded the same mixture, allowing for chromatographic purification of the oxetanol-containing compounds. The major oxetanol **14** was isolated in 28% yield and the minor oxetanol **15** in 9% yield (32% and 11% respectively based on conversion). When the photolysis was done under identical conditions using cyclohexane instead of benzene as the solvent, the same two oxetanes were observed in a 2.5:1 (**14**:**15**) ratio, and were isolated in 26% and 15%, respectively.

It was originally thought that the two oxetanols were both *cis*-fused, with one arising from photoepimerization of the methoxy group through a Norrish type I mechanism. However, NMR data were not entirely consistent with this assumption. An APT experiment indicated that the angular methyl group appeared at

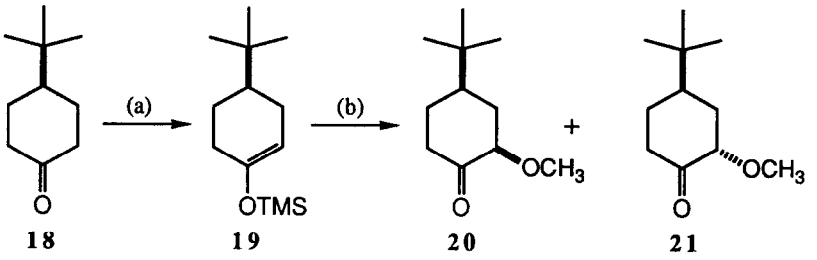


Scheme 5. Structures of oxetanols produced by photolysis of **6**.

15.6 ppm in the major oxetanol **14** and at 10.0 ppm in the minor oxetanol **15**, again in accord with the *trans*-fusion of the decalin ring. Molecular modeling was performed on the four possible oxetanol stereoisomers and the predicted coupling constants were compared to the observed values. The coupling constants in the major product were consistent with either the *trans*-fused oxetanol **14** or the *cis*-fused oxetanol **16** arising from the photoepimerization of the methoxy group. NOE enhancements were observed between the angular methyl group (C19) and the β-hydrogen on C6 (11%) as well as to the hydroxyl hydrogen on C4 (3%). Since these enhancements were consistent with both isomers, a second experiment was done by irradiating the hydrogen on C5. This gave a 16% enhancement of the C7 methine signal. This result is only consistent with the *trans*-fused oxetanol **14**. The stereochemistry of the minor oxetane was determined in a similar manner. The observed coupling constants are only consistent with the predicted constants for the *cis*-fused oxetane compound **15**. NOE experiments further corroborated this assignment by showing a 13% enhancement of one of the hydrogens from the methylene group (C20) of the oxetanol when the angular methyl group was irradiated.

If the oxetanols **14** and **15** arise from conformationally unequilibrated intermediates, their ratio should be influenced by a change in the photolysis conditions from solution to solid phase. Recently Wagner reported that the efficiency of a Norrish type II route to cyclopentanols could be improved when the compounds were

photolyzed as solids.[24] This effect was also encountered *when 6 was photolyzed in the solid state, oxetanol 14 was obtained as the only oxetanol containing compound.* The complete lack of the *cis*-fused oxetanol demonstrates not only that the selectivity of these reactions can be dramatically effected by environment and conformational mobility but also how drastically the product ratio can be changed by variations in reaction conditions.

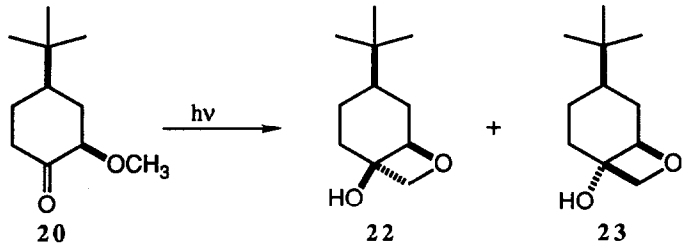


(a) TMSCl, Et_3N, DMF, reflux, 78%; (b) PhIO, BF_3•Et_2O, MeOH, -78 °C-rt, 55%

Scheme 6. Synthesis of 4-*t*-butyl-2-methoxycyclohexanone for photolysis studies.

Having established a reference point for oxetanol formation in the photolysis of **6**, we next sought to examine the steric role, if any, of the angular methyl group in this process. For this purpose, the photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (**20**) was investigated. While still conformationally constrained, **20** lacks the axial methyl group found in **6**. The trimethylsilyl enol ether **19** of 4-*t*-butylcyclohexanone[25] was oxidized by hypervalent iodine [26] to give **20** directly as well as *trans*-4-*t*-butyl-2-methoxycyclohexanone (**21**).

Ketone **20** was photolyzed in benzene through borosilicate glass and two oxetanols (**22** and **23**; 3:1, respectively) were isolated in 31% yield and identified by NMR. Some epimerization of the methoxy group was also noticed in this photolysis. When **20** was photolyzed in cyclohexane, a 2.5:1 ratio of the same two oxetanes was obtained without evidence for epimerization. Several studies were done to determine if the ratio of *trans*:*cis* products could be altered by changing the electronic state, temperature, or solvent involved in the reaction. These results are summarized in Table 1. When **20** was photolyzed in the presence of 1,3-pentadiene, a known triplet quencher, a slight decrease in the *trans*:*cis* ratio was seen. Photolysis in acetone proved ineffective and only starting material was present after extended photolysis. While it is known that the presence of heavy atoms



Scheme 7. Oxetanols formed from the photolysis of cyclohexanone **20**.

can favor the formation of the triplet state, photolysis of **20** in carbon tetrachloride caused only decomposition of the starting material. Sensitization with acetophenone had little effect on the ratio, and photolysis in the presence of xanthone gave only starting material. Photolysis in refluxing cyclohexane, or in *t*-butanol both increased the relative amount of *cis*-fused product, but the *trans*-fused oxetanol was still favored.

Table 1. Attempts to Alter the *Trans*:*Cis* Ratio of Oxetanols.

Entry	Solvent[a]	Conditions[b]	*trans*:*cis*[c]
1	benzene	borosilicate, rt	3.0:1
2	cyclohexane	borosilicate, rt	2.5:1
3	cyclohexane	borosilicate, rt 1,3-pentadiene	2.0:1
4	acetone	borosilicate, rt	—
5	CCl_4	borosilicate, rt	—
6	cyclohexane	borosilicate, rt 10% acetophenone	2.7:1
7	cyclohexane	uranium, rt 16% xanthone	—
8	cyclohexane	pyrex, 81 °C	1.7:1
9	*t*-butanol	borosilicate, rt	2.0:1

[a]All solvents were degassed with argon prior to photolysis.
[b]All photolyses were carried out using a 450 W Hanovia lamp.
[c]Ratios determined by NMR.

DISCUSSION

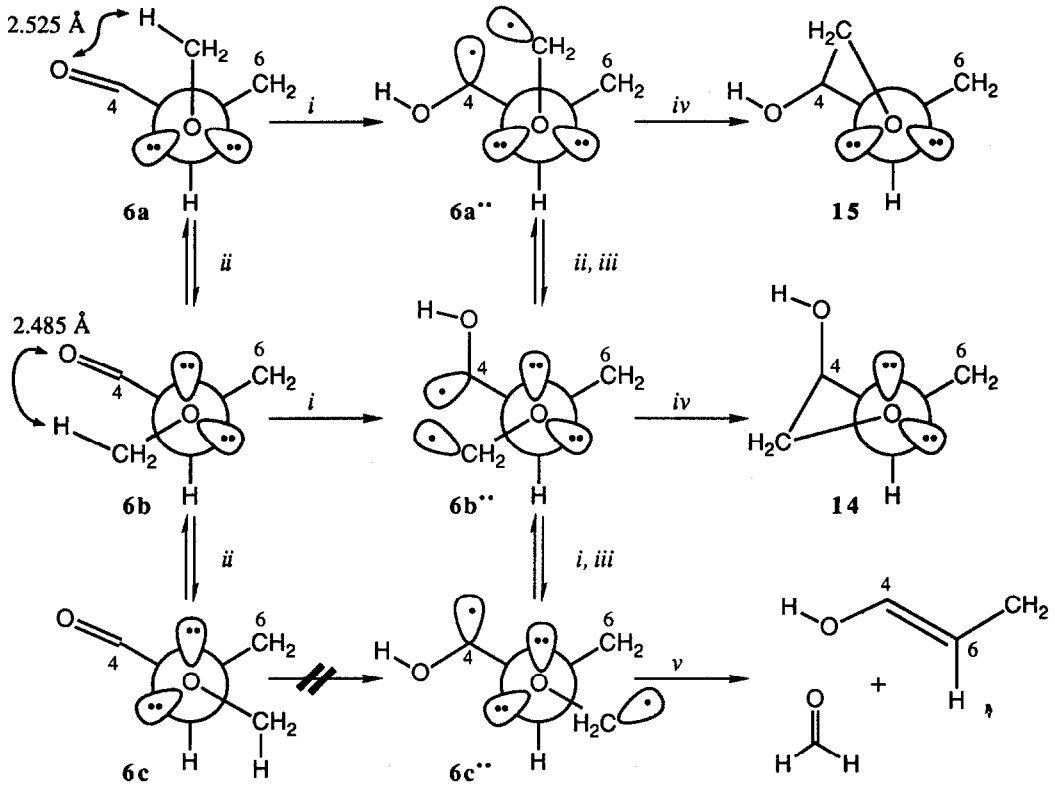
The above results show that oxetanols relevant to taxol and taxol analogues can indeed be formed through the photolysis of α-methoxy ketones. The formation of the *trans*-fused four-membered ring represents an interesting route to novel taxol analogues, but not a chemically unusual result. Paquette, for example, has

reported the synthesis of a *trans*-fused cyclobutane upon photolysis of a 2-(2-methylpropyl)cyclohexanone derivative.[27] One possible reason for the favored formation of the *trans*-fused isomer in this as well as the present study on oxetanol formation could be attributed to steric hindrance (*e.g.* from the angular methyl group in **6**). However, this steric effect would not be present in **20** and the similar ratios of oxetanols suggests that this is not a significant determinant of selectivity.

Another explanation that receives support from previous photochemical studies is that the ratios are biased by conformational factors. Lewis and coworkers have shown a dramatic example of ground-state conformational control in a Norrish type II photoreaction when they demonstrated that the photochemical reaction of cyclohexyl phenyl ketone was faster than inversion of the cyclohexane ring.[28] In addition, Wagner has found that the rate of hydrogen abstraction and product formation in conformationally mobile systems is faster than conformational equilibration.[29] Wagner has also presented evidence that further supports the idea that bond rotations and chemical reactions are competitive in the diradicals formed in related type II processes.[30] Any factors impeding rotation would be expected to bias the reaction further.

Examination of the energy-minimized decalone core of **6** indicates the methoxy appendage can exist in three energy minima as a result of rotation about the C4-O bond (Scheme 8: **6a-6c**; only partial structures in Newman projection form are shown for clarity). In conformer **6c**, the methyl is pointed away from the carbonyl at such a distance that hydrogen abstraction would not occur. In conformer **6a**, on the other hand, the methyl group is near the carbonyl and on the same side of the carbonyl plane as the angular methyl, while in conformer **6b** the methyl group is on the opposite side. The difference in energy between conformers **6b** and **6a** is calculated (MM2) to be 1.75 kcal which would give a ground state conformational bias of 19:1 in favor of **6b**. Similar conformers were found in the energy-minimized structures of **20**, with a 1.74 kcal difference existing between the corresponding two reactive conformers. These calculations indicate that hydrogen abstraction would be expected to occur preferentially from conformer **6b** and the corresponding conformer of **20**.

After hydrogen abstraction has occurred in conformer **6b**, oxetanol **14** would be expected to form readily with a minimum of nuclear movement (least motion path *iv*) from the kinetically produced diradical **6b**••. To form oxetanol **15** (*i.e.* the *cis*-fused oxetanol), both C4-O bond rotation and C4 inversion must occur to position the methyl radical and C4 radical for closure. The required rotation (clockwise for the direct path to **6a**••) is



i hν; *ii* C5-O bond rotation; *iii* C4 inversion; *iv* C4-C5 bond formation; *v* fragmentation.

Scheme 8. Conformations of methoxy ketone **6** leading to *trans*-oxetanol **14** and *cis*-oxetanol **15**. Only partial structures are shown in Newman projection form. View is down the O-C5 bond.

expected to be less favorable than counterclockwise rotation to give the other staggered diradical conformer (**6c**••), an intermediate which can lead to fragmentation. In accord with this analysis it is noted that a large amount of fragmentation accompanies the photolysis of **6**. The observation that the solid state photolysis of **6** gives only the *trans*-fused oxetane suggests that in the solid state, where bond rotations are severely limited, abstraction occurs from conformation **6b** and is followed by closure arising from the pathway of least motion. Excitation of conformer **6a** in solution would give the *cis*-fused oxetanol again following the least-motion pathway. It follows that systems designed to favor conformer **6a** would preferentially produce the *cis*-oxetanol product. This is further supported by the observed increase in *cis*-oxetanol **23** when the photolysis of **20** is

conducted at higher temperature.[31] In addition, photolysis of **20** in *t*-butanol, which would be expected to perturb the above equilibria through hydrogen bond formation to the C4 oxygen, again increased the relative amount of **23**.

In summary, we have shown that the photolysis of α-methoxy ketones does allow for the formation of *trans*- and *cis*-fused oxetanols, the latter directly corresponding to the D-ring of taxol. While the *trans*-fused oxetanol is preferred in our model systems, these results provide a more general basis for understanding how one can influence the selectivity of the closure reaction. Since the conformation of an actual synthetic precursor to taxol could be effected by the substituents on the A and B rings it is proposed that those synthetic intermediates that preferentially assume a conformation similar to **6a** will provide the *cis*-oxetanol product. Studies on this point will be reported in due course.

EXPERIMENTAL

General Methods

All commercially available reagents were used without further purification unless otherwise noted. Butadiene, BF_3•Et_2O, $(COCl)_2$, anhydrous DMSO, $TMSNEt_2$, TMSCl, DMF, 2-methoxy-5-methylaniline, and iodobenzene diacetate were purchased from Aldrich Chemical Co. Ethyl acetate and $Na_2Cr_2O_7$•$2H_2O$ were obtained from J. T. Baker and absolute methanol was purchased from Fisher. CH_2Cl_2, Et_3N, TMSCl, and DMF were distilled from CaH_2 prior to use. Flash chromatography refers to column chromatography following the procedure of Still[32] using Merck Silica Gel 60 (40-60 μm) as stationary phase. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. IR spectra were measured on a Perkin Elmer model 1605 FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were measured as dilute solutions in $CDCl_3$ with TMS as an internal reference using a Varian GEM-300 spectrometer or a Varian XL-400 spectrometer as noted. High resolution mass spectroscopy (HRMS) was performed by the Mass Spectrometry Facility, University of California-San Francisco supported by the NIH Division of Research Resources. Elemental analysis was obtained from Desert Analytics, Tucson, Arizona.

2-Methoxy-5-methyl-1,4-benzoquinone (9):

Compound **9** was prepared following the procedure of Anslow, Ashley, and Raistrick.[19] A stirred solution of concentrated H_2SO_4 (98.0 mL) in distilled water (280.0 mL) was cooled to 0 °C and 2-methoxy-5-methylaniline (15.0 g, 109.3 mmol) was added in one portion. A solution of $Na_2Cr_2O_7$•$2H_2O$ (14.0 g, 47.0 mmol) in water (80.0 mL) was added dropwise over 1 hour and the resulting solution was stirred at 0 °C for 18 hours. A second aliquot of $Na_2Cr_2O_7$•$2H_2O$ (28.0 g, 94.0 mmol) in water (160.0 mL) was added gradually and a precipitate began to form. The reaction was maintained at 0 °C for 4 hours, and was then extracted with CH_2Cl_2. The combined organic layers were then stirred over 200 g of Florisil (60-100 mesh) until the solution turned a lemon yellow color and then filtered. Concentration gave **9** as a dark yellow solid (6.1 g). The Florisil was washed with fresh CH_2Cl_2 until the eluant was colorless and concentration gave additional amounts of **9** as a light yellow solid (1.1 g; total yield 7.2 g, 43%). An analytical sample was obtained by crystallization from $CHCl_3$/methanol yielding benzoquinone **9** as brilliant yellow plates, m.p. 175.5-177 °C (lit[18] 174-175.5 °C). ^{1}H-NMR (300 MHz): δ = 2.07 (d, *J* = 1.6 Hz, 3H), 3.83 (s, 3H), 5.94 (s, 1H), 6.56 (d, *J* = 1.6 Hz, 1H).

***cis*-2-Methoxy-4a-methyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (8):**

Compound **8** was prepared following the procedure of Hayakawa.[20] To a stirred solution of benzoquinone **9** (4.5 g, 29.6 mmol) in $CHCl_3$ (50 mL), BF_3•Et_2O (3.6 mL, 29.6 mmol) was added over 5 minutes. After 45 minutes, the mixture was cooled to -10 °C and 1,3-butadiene (2 mL, 36 mmol) was added. The resulting solution was stirred at -10 °C for 15 hours and then was warmed to 15 °C for an additional 7

hours. The reaction was quenched with water (50 mL), and the aqueous layer was extracted with $CHCl_3$ (2 x 50 mL). The combined organic layers were washed with water and brine, and then dried over Na_2SO_4. The solution was filtered and concentrated giving **8** as a light yellow powder (5.8 g, 95%). Analytical samples were obtained by recrystallizing twice from ethanol giving a fine white crystalline solid, m.p. 93-94 °C (lit[18] 94.5-95.5 °C). ^{1}H-NMR (300 MHz): δ = 1.34 (s, 3H), 1.82-1.88 (m, 1H), 2.14-2.24 (m, 1H), 2.45-2.53 (m, 1H), 2.66-2.74 (m, 1H), 2.92 (m, 1H), 3.79 (s, 3H), 5.60-5.73 (m, 2H), 5.84 (s, 1H).

***trans*-2-Methoxy-4a-methyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (7):**

Isomerization of **8** was accomplished using Woodward's procedure.[18] Compound **8** (1.0 g, 4.8 mmol) was dissolved in *p*-dioxane (1.3 mL) under nitrogen by warming the solution to 40 °C. This solution was then cooled to room temperature, and 1 *N* NaOH (5 mL) was added slowly over 10 minutes. After addition was complete, water (10 mL) was added followed by pure *trans* adduct **7** (50 mg) to seed the crystallization. To this mixture, 1 *N* HCl was added dropwise until the solution turned to a bright yellow color. A precipitate formed during the addition and was isolated by filtration and washed with water. The solid was dried to give **7** as a light yellow powder (856 mg, 82%). The aqueous filtrate was extracted with ether (3 x 50 mL) and the organic layers were dried over $MgSO_4$. Concentration gave 143 mg of a mixture of the *cis*- and *trans*-adducts, as well as the stable enol of **8** which could all be resubmitted to the above reaction conditions. An analytical sample of **7** was obtained by recrystallization from ethanol yielding a white powder, m.p. 127-128 °C (lit[18] 130-131 °C). ^{1}H-NMR (300 MHz): δ = 1.16 (s, 3H), 2.19-2.50 (m, 4H), 2.96 (dd, J_1 = 5.8 Hz, J_2 = 10.2 Hz, 1H), 3.80 (s, 3H), 5.70 (bs, 2H), 5.87 (s, 1H).

***trans*-1,4-Dihydroxy-2-methoxy-10-methyldecahydronaphthalene (11):**

Hydrogenation of **7** to form diol **11** was done as described by Woodward.[18] A suspension of platinum oxide (154 mg, 0.63 mmol) in ethyl acetate (5 mL) was prereduced with H_2 gas. To this suspension, compound **7** (0.50 g, 2.4 mmol) dissolved in ethyl acetate (10 mL) was added and the solution was stirred vigorously for 24 hours while the H_2 atmosphere was maintained. The reaction was diluted with CH_2Cl_2 (0.5 mL), filtered through celite, and concentrated yielding a pale yellow powder (495 mg). Flash chromatography (5% $CH_3OH/CHCl_3$) yielded **11** (347 mg, 66%) as a white powder, m.p. 144-145 °C (lit[18] 144-145 °C raised to 145-146 °C). ^{1}H-NMR (300 MHz): δ = 0.90-1.01 (m, 2H), 1.05 (s, 3H), 1.20-1.42 (m, 1H), 1.43-1.57 (m, 4H), 1.75-2.01 (m, 6H), 3.18-3.29 (m, 2H), 3.39 (s, 3H), 3.82 (bs, 1H); ^{13}C-NMR (75 MHz): δ = 12.7, 21.3, 24.9, 26.9, 31.0, 38.4, 38.9, 44.2, 55.9, 70.8, 77.8, 79.1; HRMS: Calc. for $C_{12}H_{22}O_3$: 214.1563. Found: 214.1569; IR (KBr): ν_{max} = 3414.7, 2929.4, 2863.5, 1441.8, 1377.5, 1293.5, 1103.1, 1080.6, 1059.1, 1028.0 cm^{-1}.

***trans*-1-hydroxy-2-methoxy-10-methyl-4-trimethylsiloxydecahydronaphthalene (12):**

To a solution of diol **11** (296 mg, 1.38 mmol) in CH_2Cl_2 (4 mL) was added acetone (2.9 mL) and *N,N*-diethyltrimethylsilylamine (2.9 mL, 15 mmol) and the mixture was heated at reflux (65-70 °C) for 8 hours. Concentration using a rotary evaporator gave a brown oil which was flash chromatographed twice (20% EtOAc/hexanes with 1% Et_3N) to give monosilylated compound **12** (328 mg, 83%) as an oil. ^{1}H-NMR (300 MHz): δ = 0.10 (s, 9H), 0.75-0.96 (m, 2H), 1.02 (s, 3H), 1.18-1.25 (m, 1H), 1.39-1.54 (m, 3H), 1.65-1.98 (m, 6H), 3.14-3.23 (m, 2H), 3.38 (s, 3H), 3.82 (bs, 1H); ^{13}C-NMR (75 MHz): δ = 0.1, 13.0, 21.5, 25.1, 27.0, 31.8, 38.6, 39.3, 44.2, 55.8, 70.4, 78.0, 79.3; HRMS: Calc. for $C_{15}H_{30}O_3Si$: 286.1972. Found: 286.1964; IR (KBr): ν_{max} = 3473.0, 2928.4, 2863.1, 1249.6, 1122.8, 1076.5, 890.0, 839.2 cm^{-1}.

***trans*-2-methoxy-10-methyl-4-trimethylsiloxydecahydro-1-naphthalenone (6):**

A stirred solution of oxalyl chloride (0.025 mL, 0.28 mmol) in dry CH_2Cl_2 (0.5 mL) was cooled to -78 °C under argon and after 5 minutes anhydrous DMSO (0.042 mL, 0.59 mmol) was added. After an additional 10 minutes monosilylated diol **12**, dissolved in dry CH_2Cl_2 (1.0 mL), was added. This solution was stirred for 15 minutes and then Et_3N (0.16 mL, 1.2 mmol) was added followed by warming to room temperature. After an additional 30 minutes of stirring, the reaction was quenched with water (1.5 mL), and the organic layer was separated. The aqueous layer was extracted once with CH_2Cl_2 (5 mL) and the organic layers were combined, washed with water, dried over $MgSO_4$ and concentrated. Flash chromatography (20% EtOAc/hexanes with 1% Et_3N) afforded a white powder (37.0 mg, 56%), m.p. 72.5-73.5 °C. ^{1}H-NMR (300 MHz): δ = 0.14 (s, 9H), 0.73 (s, 3H), 0.98-1.15 (m, 2H), 1.28-1.49 (m, 1H), 1.50-1.59 (m, 3H), 1.76-1.80 (m, 2H), 1.88 (ddd, J_1 = 12.5 Hz, J_2 = 12.4 Hz, J_3 = 11.6 Hz, 1H), 2.02 (dd, J_1 = 4.1 Hz, J_2 = 10.7 Hz, 1H), 2.31 (ddd, J_1 = 4.7 Hz, J_2 = 7.2 Hz, J_3 = 12.4 Hz, 1H), 3.46 (s, 3H), 3.75 (dd, J_1 = 4.7 Hz, J_2 = 11.5 Hz, 1H), 3.79 (dd, J_1 = 7.1 Hz, J_2 = 12.4 Hz, 1H); ^{13}C-NMR (75 MHz): δ = 0.45, 11.1, 20.0, 21.0, 25.3, 37.8, 38.5, 43.9, 52.2, 58.5, 76.6, 81.5, 209.9; HRMS: Calc. for $C_{15}H_{28}O_3Si$: 284.1808. Found: 284.1804; IR (KBr): ν_{max} = 2942.7,

2855.5, 1720.1, 1448.3, 1387.1, 1369.4, 1253.1, 1154.3, 1128.9, 1080.9, 1053.2, 997.1, 962.3, 950.8, 917.9, 887.0, 839.6, 747.7, 693.2 cm^{-1}; UV (CH_3OH) λ_{max} 202.6 (ε 395.1), 288.1 (29.0) nm.

4-*t*-Butyl-1-trimethylsiloxycyclohex-1-ene (19):

Silyl enol ether **19** was prepared using the House procedure.[25] To a stirred solution of freshly distilled TMSCl (9.9 mL, 78 mmol) and Et_3N (21.7 mL, 156 mmol) in dry DMF (20 mL) was added a solution of 4-*t*-butylcyclohexanone (10 g, 65 mmol) in DMF (5 mL). A pale yellow solid started to precipitate immediately. The reaction mixture was then heated at reflux for 20 hours and was cooled to room temperature, diluted with hexanes (50 mL), and washed three times with ice-cold saturated $NaHCO_3$. The hexane layer was dried over $MgSO_4$ and concentrated to give 15.2 g of crude material which was distilled under vacuum to give **19** as a colorless oil (11.5 g, 78%), b.p. 105-109 °C at 7 Torr (lit[25] 94-96 °C at 3.9 Torr). ^{1}H-NMR (300 MHz): δ = 0.14 (s, 9H), 0.83 (s, 9H), 1.10-1.30 (m, 2H), 1.69-1.83 (m, 2H), 1.91-2.08 (m, 3H), 4.78-4.85 (m, 1H).

***trans*- and *cis*-4-*t*-Butyl-2-methoxycyclohexanone (20 and 21):**

Oxidation of silyl enol ether **19** was effected as described by Moriarty.[26] To a stirred suspension of iodosobenzene[33] (2.1 g, 9.7 mmol) in absolute methanol (20 mL) was added BF_3•Et_2O (2.2 mL, 17.7 mmol) in one portion. The solid dissolved quickly and the mixture was then cooled to -78 °C after which silyl enol ether **19** (2.0 g, 8.8 mmol) dissolved in methanol (20 mL) was added. The solution was allowed to stir for 3 hours at -78 °C and was then warmed to room temperature over 3 hours. The methanol was removed using a rotary evaporator, distilled water (40 mL) was added, and the solution was neutralized with saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (10% EtOAc/hexanes) gave *cis*-4-*t*-butyl-2-methoxycyclohexanone **20** (707.3 mg, 44%), and trans-4-*t*-butyl-2-methoxycyclohexanone **21** (173.0, 11%), both as colorless oils. Data for *cis*-4-*t*-butyl-2-methoxycyclohexanone **20**: ^{1}H-NMR (300 MHz): δ = 0.93 (s, 9H), 1.35-1.50 (m, 2H), 1.55-1.70 (m, 1H), 2.04-2.20 (m, 1H), 2.25-2.50 (m, 3H), 3.48 (s, 3H), 3.82 (dd, J_1 = 6.2 Hz, J_2 = 12.2 Hz, 1H); ^{13}C-NMR (75 MHz): δ = 27.4, 28.2, 32.2, 35.3, 39.7, 45.8, 57.9, 83.7, 210.1; HRMS: Calc. for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1465; IR (neat): ν_{max} = 2964.1, 1728.1, 1471.7, 1367.8, 1203.0, 1135.7 cm^{-1}; UV (CH_3OH) λ_{max} 205.7 (ε 256.2), 284.0 (15.6) nm; Calc. for $C_{11}H_{20}O_2$: C 71.70; H 10.94. Found: C 71.49; H 11.18. Data for *trans*-4-*t*-butyl-2-methoxycyclohexanone **21**: ^{1}H-NMR (300 MHz): δ = 0.90 (s, 9H), 1.38-1.56 (m, 2H), 1.82-1.91 (m, 1H), 2.04-2.11 (m, 1H), 2.20-2.27 (m, 2H), 2.75 (ddd, J_1 = 6.0 Hz, J_2 = 13.6 Hz, J_3 = 13.6 Hz, 1H), 3.30 (s, 3H), 3.50 (bs, 1H); HRMS: Calc. for $C_{11}H_{20}O_2$: 184.1463. Found: 184.1462.

Photolyses:

General Procedures. Irradiations were performed using a Hanovia 450 W high-pressure lamp in a water-cooled quartz well unless otherwise noted. All samples were placed in borosilicate tubes, hung 1.0 cm away from the photolysis well, deoxygenated prior to photolysis by bubbling with a stream of argon or nitrogen for at least 15 minutes, and maintained under inert atmosphere throughout the photolysis. Photograde benzene and acetone were obtained from Baker, HPLC grade cyclohexane was purchased from Aldrich Chemical, and spectrograde carbon tetrachloride was obtained from Burdick and Jackson Laboratories. All solvents were used without further purification.

Photolysis of *trans*-2-methoxy-10-methyl-4-trimethylsiloxydecahydro-1-naphthalenone (6): *Procedure A. Trans*-decalone **6** (79.8 mg, 0.281 mmol) was dissolved in benzene (55 mL), and irradiated for 5 hours after which the solution was concentrated to give 73.9 mg of a white solid. Flash chromatography (20% ethyl acetate/hexanes with 1% triethylamine) yielded *trans*-1-decalone **6** (9.7 mg), *trans*-oxetanol **14** (22.3 mg, 28%; 32% based on conversion), and *cis*-oxetanol **15** (7.4 mg, 9%; 11% based on conversion). All other isolated material did not contain signals in the NMR spectrum either for the methoxy group or for an oxetane and was not characterized further. Spectral data for ***trans,trans*-1,2-epoxymethano-1-hydroxy-10-methyl-4-trimethylsiloxy decahydronaphthalene (14)**: ^{1}H-NMR (300 MHz): δ = 0.10 (s, 9H), 0.88-1.04 (m, 1H), 1.08 (s, 3H), 1.12-1.77 (m, 8H), 1.89 (ddd, J_1 = 3.6 Hz, J_2 = 3.9 Hz, J_3 = 10.8 Hz, 1H), 2.34 (ddd, J_1 = 10.0 Hz, J_2 = 10.4 Hz, J_3 = 13.2 Hz, 1H), 2.56 (s, 1H), 3.35 (dd, J_1 = 3.9 Hz, J_2 = 9.9 Hz, 1H), 4.08 (d, J = 5.8 Hz, 1H), 4.37 (dd, J_1 = 3.5 Hz, J_2 = 13.1 Hz, 1H), 4.68 (d, J = 5.8 Hz, 1H); ^{13}C-NMR (75 MHz): δ = 0.07, 15.6, 21.3, 21.5, 26.1, 32.4, 40.5, 41.8, 47.7, 79.0, 80.0, 85.1, 88.8; HRMS: Calc. for $C_{15}H_{26}O_2Si$ ($M^+ - H_2O$): 266.1702. Found: 266.1699; IR (KBr): ν_{max} = 3327.9, 3000.2, 2932.7, 2864.0, 1465.9, 1413.8, 1381.7, 1251.4, 1228.4, 1152.4, 1100.6, 1027.9, 1014.4, 964.8, 949.8, 890.5, 753.6, 690.3 cm^{-1}; Calc. for $C_{15}H_{28}O_3Si$: C 63.34; H 9.92. Found: C 63.58; H 10.01. Spectral data for ***cis,trans*-1,2-epoxymethano-1-hydroxy-10-methyl-4-trimethylsiloxy decahydronaphthalene (15)**: ^{1}H-NMR (300 MHz): δ = 0.05 (s, 9H), 0.80-0.90 (m, 2H), 1.16 (s, 3H), 1.19-1.54 (m, 5H), 1.72-1.80 (m, 3H), 1.89

(ddd, J_1 = 2.5 Hz, J_2 = 10.9 Hz, J_3 = 15.0 Hz, 1H), 2.23 (ddd, J_1 = 7.1 Hz, J_2 = 9.2 Hz, J_3 = 15.0 Hz, 1H), 3.38 (dd, J_1 = 7.1 Hz, J_2 = 10.7 Hz, 1H), 4.24 (d, J = 7.7 Hz, 1H), 4.51 (d, J = 7.6 Hz, 1H), 4.76 (dd, J_1 = 2.2 Hz, J_2 = 9.2 Hz, 1H); ^{13}C-NMR (75 MHz): δ = 0.09, 9.9, 20.4, 21.2, 26.0, 37.3, 37.7, 38.7, 49.8, 74.4, 76.7, 77.7, 88.2; HRMS: Calc. for $C_{15}H_{26}O_2Si$ (M^+ - H_2O): 266.1702. Found: 266.1692; IR (KBr): ν_{max} = 3405.4, 2928.2, 2861.9, 1446.4, 1361.4, 1250.0, 1168.2, 1153.2, 1083.7, 1074.0, 978.3, 965.3, 943.2, 890.0, 839.0, 748.3.

Photolysis of *trans*-2-methoxy-10-methyl-4-trimethylsiloxydecahydro-1-naphthalenone (6): *Procedure B. Trans*-decalone **6** (10.0 mg, 0.035 mmol) was dissolved in cyclohexane (3.5 mL) and irradiated for 6 hours after which the solution was concentrated. Flash chromatography (20% ethyl acetate/hexanes with 1% triethylamine) yielded *trans*-oxetanol **14** (2.6 mg, 26%), and *cis*-oxetanol **15** (1.5 mg, 15%).

Photolysis of *trans*-2-methoxy-10-methyl-4-trimethylsiloxydecahydro-1-naphthalenone (6): *Procedure C. Trans*-decalone **6** (25 mg, 0.089 mmol) was dissolved in 1 mL of CH_2Cl_2 and the solution was spread on the surface of a 1.5 x 15.5 cm plate of soda lime glass. The plate was dried by passing a stream of nitrogen over the surface followed by further drying under high vacuum leaving a thin film of solid on the glass. The plate was placed in a pyrex tube and irradiated for 10.1 hours. The solid was dissolved in $CDCl_3$ and examined by NMR. The only signals present between 4.0 and 5.0 ppm corresponded to *trans*-oxetanol **14**. Flash chromatography (20% ethyl acetate/hexanes with 1% Et_3N) yielded 14 mg of **6** and 5 mg (20%; 45% based on conversion) of oxetanol **14**.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20): *Procedure A.* Ketone **20** (110 mg, 0.60 mmol) was dissolved in benzene (120 mL) and irradiated for 6 hours after which the solution was concentrated to give a crude material (106 mg). Flash chromatography (30% ethyl acetate/hexanes) yielded ketone **20** (5.9 mg), and a mixture containing both the *trans*-oxetanol **22** and *cis*-oxetanol **23** in a 3:1 ratio (31.2 mg, 28%; 30% based on conversion). All other isolated material did not contain signals in the NMR spectrum either for the methoxy group or for an oxetane and was not characterized further.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20): *Procedure B.* Ketone **20** (212 mg, 1.15 mmol) was dissolved in cyclohexane (40 mL) and irradiated through pyrex for 6 hours after which the solution was concentrated to give a crude material (200 mg). The ratio of **22** to **23** was determined by NMR as 1.9:1. Flash chromatography (30% ethyl acetate/hexanes) yielded 108 mg of **20**, 30 mg (17%; 35% based on conversion) of cyclohexanone **18**, 13 mg (6%; 13% based on conversion) of *trans*-oxetanol **22**, and 6 mg (3%; 6% based on conversion) of *cis*-oxetanol **23**. Spectral data for ***trans*-4-*t*-butyl-1,2-epoxymethano-1-hydroxycyclohexane (22):** ^{1}H-NMR (400 MHz): δ = 0.89 (s, 9H), 1.52-1.90 (m, 7H), 2.82 (bs, 1H), 4.23 (d, J = 6.2 Hz, 1H), 4.46 (dd, J_1 = 4.9 Hz, J_2 = 11.6 Hz, 1H), 4.76 (d, J = 6.2 Hz, 1H); ^{13}C-NMR (100 MHz): δ = 21.5, 25.6, 27.8, 30.9, 33.0, 45.5, 77.4, 84.4, 90.9; IR (neat): ν_{max} = 3312.1, 2957.5, 2866.4, 1364.8, 1232.3, 1152.3, 980.9, 937.7, 888.2, 833.3 cm^{-1}. Spectral data for ***cis*-4-*t*-butyl-1,2-epoxymethano-1-hydroxycyclohexane (23):** ^{1}H-NMR (400 MHz): δ = 0.87 (s, 9H), 1.47-1.60 (m, 4H), 1.73-1.79 (m, 1H), 1.96-2.03 (m, 3H), 4.38 (d, J = 6.6 Hz, 1H), 4.49 (d, J = 6.7 Hz, 1H), 4.71 (dd, J_1 = 5.5 Hz, J_2 = 5.5 Hz, 1H); ^{13}C-NMR (100 MHz): δ = 20.4, 27.1, 28.9, 32.3, 32.8, 40.8, 72.7, 80.6, 89.6; IR (neat): ν_{max} = 3385.5, 2955.0, 2869.1, 1467.4, 1366.4, 1138.5, 961.8 cm^{-1}.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) with 1,3-pentadiene: Ketone **20** (30 mg, 0.16 mmol) was dissolved in cyclohexane (5 mL), and 1,3-pentadiene (1.5 mL) was added. Irradiation proceeded for 3 hours after which the solution was concentrated and the crude mixture was examined by NMR. The ratio of oxetanols was 2:1 (**22**:**23**).

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) with carbon tetrachloride: Ketone **20** (30 mg, 0.16 mmol) was dissolved in carbon tetrachloride (5 mL) and irradiated for 3 hours. The solution had become discolored but was concentrated and examined by NMR. No signals corresponding to an **22** or **23** were present.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) with 10% acetophenone: Ketone **20** (30 mg, 0.16 mmol) was dissolved in cyclohexane (5 mL) and acetophenone (2 μL) was added followed by irradiation for 3 hours after which the solution was concentrated, and the crude mixture was examined by NMR. The ratio of oxetanols was 2.7:1 (**22**:**23**).

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) in acetone: Ketone **20** (30 mg, 0.16 mmol) was dissolved in acetone (5 mL) and irradiated for 3 hours after which the solution was concentrated and the crude mixture was examined by NMR. No signals corresponding to **22** or **23** were evident.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) with 16% xanthone: Ketone **20** (30 mg, 0.16 mmol) was dissolved in cyclohexane (10 mL) and xanthone (5 mg) was added. A uranium glass filter was placed around the lamp and irradiation proceeded for 3 hours after which the solution was concentrated and the crude mixture was examined by NMR. Only starting material was present.

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) at elevated temperature: Ketone **20** (26.9 mg, 0.146 mmol) was dissolved in cyclohexane (5 mL) and the pyrex tube was fitted with a cold water condenser and placed in a hot water bath near the photolysis well. The solution was brought to reflux before irradiation for 3.1 hours. The solution was concentrated and the crude mixture was examined by NMR. The ratio of oxetanols was 1.7:1 (**22**:**23**). Flash chromatography (30% ethyl acetate/hexanes) yielded a mixture of both *trans*- and *cis*-fused oxetanes (2.5 mg, 9%; 12% based on conversion), 4-*t*-butylcyclohexanone **18** (2.8 mg), and ketone **20** (6.7 mg).

Photolysis of *cis*-4-*t*-butyl-2-methoxycyclohexanone (20) in *t*-butanol: Ketone **20** (30 mg, 0.16 mmol) was dissolved in *t*-butanol (5 mL) and irradiated for 3 hours after which the solution was concentrated to give a crude mixture (23.1 mg) that was examined by NMR. The ratio of oxetanols was 2:1 (**22**:**23**).

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