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FREE RADICAL CYCLIZATION APPROACH TO A FUNCTIONALIZED [3]PERISTYLANE

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Abstract: A nine-step synthesis, starting from the readily available bicyclo[2.2.2]oct-7-ene-2,5-dione (**19a**), has provided access to a hydroxyl-substituted [3]peristylane. Furthermore, the disubstituted nature of peristylane **24** causes it to be the first chiral member of this compound class to be synthesized. The featured ring closure step that leads to **24** provides an especially stringent test of cyclohexanol ring construction via addition of a carbon-centered radical onto a carbonyl group. The precursor to **24** already contains a cyclopropane ring in its structure and the cyclization actually sets a rim bond in place. The three-membered ring was elaborated efficiently through deployment of the oxa-di-π-methane rearrangement. It is expected that this particular approach to hemispherical molecular construction will have application in numerous other related synthetic undertakings.

When first synthesized,[1] hydrocarbon **1** was viewed predominantly as a chemical curiosity. The molecule was initially called "triaxane" in an effort to capture the C_{3v} symmetry of its tetracyclic framework and to depict that the cyclopropane ring rests on three axial pillars fixed to a cyclohexane chair.[2] Somewhat later, however, Eaton and Mueller successfully prepared **3** and called this compound "peristylane", a word of Greek origin that alludes to the similarity of **3** to "a group of columns arranged about an open space in a manner designed to support a roof". Several years later, Garratt and White noted that **1**-**3** constitute a series of compounds characterized by the interconnection of a smaller n-membered ring to one twice the original size at alternate carbon atoms of the latter.[4] They chose to generalize the Eaton nomenclature proposal and to refer to **1** as [3]peristylane and to **3** as [5]-peristylane. With the subsequent acquisition of **2** by Paquette and co-workers,[5] the terminology was sufficiently well ingrained that this $C_{12}H_{16}$ pentacycle was called [4]peristylane without additional modification.

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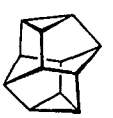

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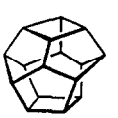

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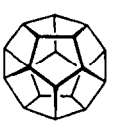

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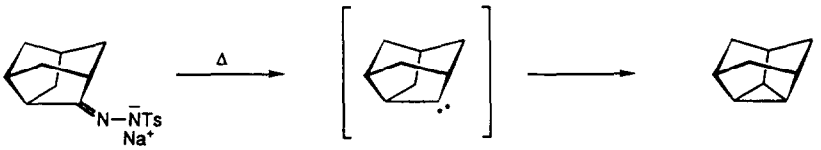
Increased relative importance was placed on these compounds following their promulgation as a subset of the polycyclic saturated $(CH)_{2n}$ systems represented by 4-6.[4] Here the central *n*-membered alicycle is linked to a pair of *n*/2-membered rings by alternate carbon atoms. For reasons of symmetry, *n* is required to be an even integer. The "capping" of 1,[6] 2,[5b,7] and 3[8] (as functionalized derivatives) to arrive at 4-6 is not a straightforward feat and indeed has not yet been realized.[9] While dodecahedrane (6)[10,11] and a dimethyl derivative of 4[12] are known, these successes were realized by application of entirely different tactics.

Herein we highlight a new, free radical-based approach to the synthesis of a functionalized [3]peristylane. At present, routes to this class of compounds are quite limited in number. The Nickon-Pandit approach to the parent system took advantage of the propensity of carbene 8 for intramolecular C-H insertion.[1] However, this protocol gives no evidence of lending itself to modification as required for the preparation of specifically substituted derivatives.



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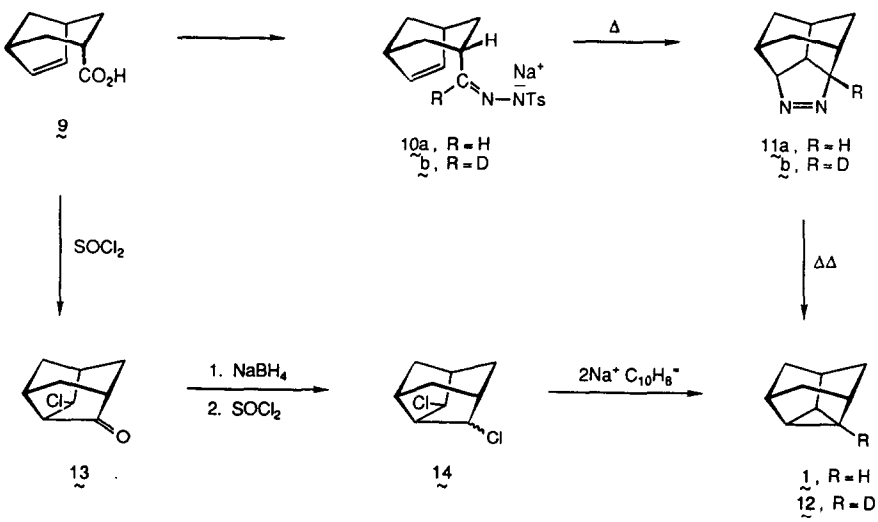
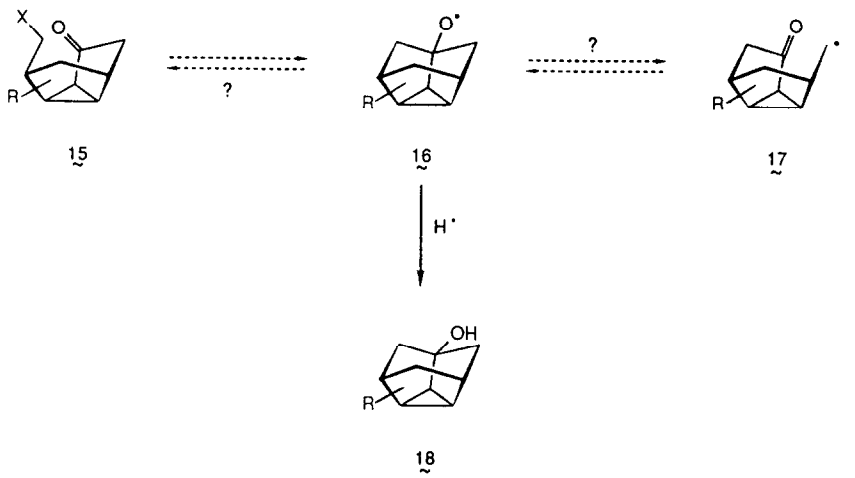
The other pair of preparative routes to [3]peristylane both originate from *endo*-bicyclo-[3.2.1]oct-6-ene-3-carboxylic acid (9).[4] Pyrolysis of the derived unlabeled tosylhydrazone salt (10a) or its monodeuterated counterpart 10b at 200-250 °C and low pressure effected conversion to the cyclic azo compounds 11a and 11b, respectively. Sublimation of these intermediates in turn into a hotter (500 °C) reaction chamber provided 1 and 12. Alter-



natively, 9 was reacted with thionyl chloride to provide 13, which gave rise to the target hydrocarbon in three additional steps.

The disconnection we envisioned for elaborating such molecules did not feature closure of a three-membered ring in the final step. Rather, formation of a "rim" carbon-carbon bond was now to complete the molecular construction. This tactic demanded, of course, that a cyclopropane unit be incorporated at an earlier stage and the oxa-di-π-methane rearrangement[13] was expected to serve well for this purpose.

Those factors that control the addition of free radicals to the carbonyl group of aldehydes and ketones are rapidly becoming understood.[14-17] Amptly demonstrated so far is the fact that intramolecular radical additions of this type can be performed in synthetically feasible fashion provided either the addition step is essentially irreversible or product formation is achieved in a sufficiently rapid trapping reaction. Thus, our plan was to study the possible cyclization of a representative ketone of general structure 15, where X is a group capable of being abstracted to generate a carbon-centered radical. Is 15 suitably constituted to undergo rapid closure to 16? Is this step adequately fast and exothermic to curtail β-fission and formation of 17 or an isomeric 2-cyclopropylethyl radical? Quenching of 17 would be most undesirable and form the basis of an abortive synthesis.



15 16 17

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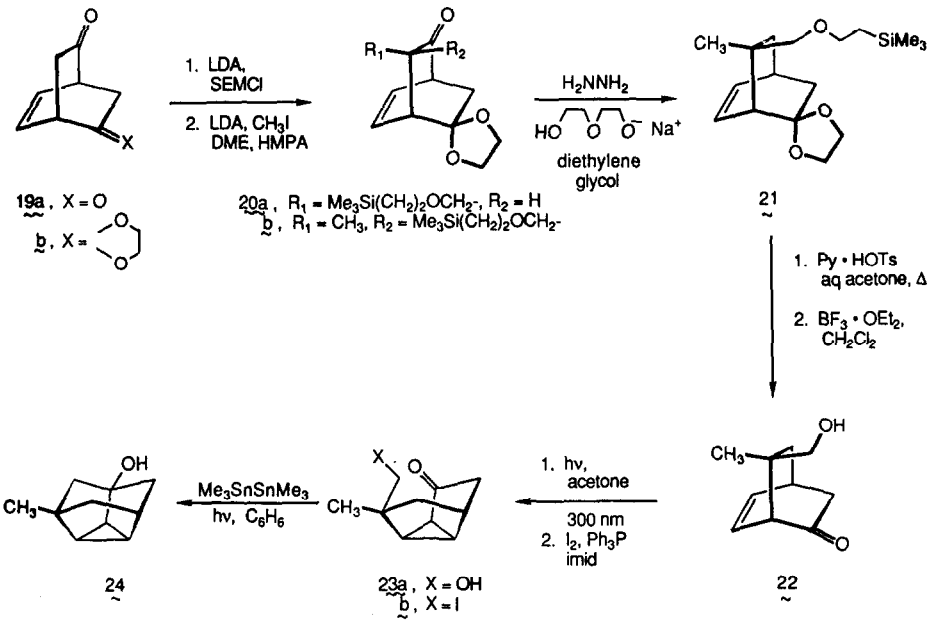
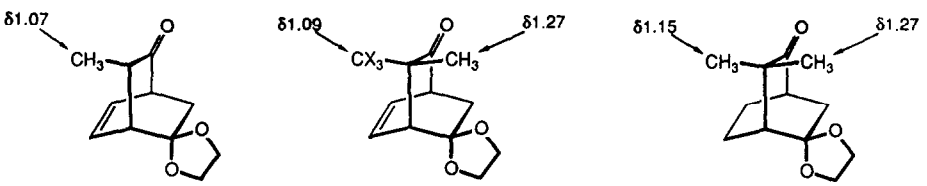
Results and Discussion

With these objectives in mind, the synthetic phase was initiated by selective monoketalization[18] of the well known enedione 19a.[19] Following purification of 19b by distillation, its enolate anion was treated with one equivalent of SEM chloride.[20] This alkylation was cleanly stereoselective, the newly introduced sidechain presumably entering from the less sterically hindered surface syn to the double bond as in 20a. Since it was necessary to position the β-(trimethylsilyl)ethoxymethyl group proximal to the ketal functionality, 20a was deprotonated and methylated to deliver 20b with excellent stereocontrol once again.

These consecutive S_N2 reactions play a pivotal role in setting the proper relative stereochemistry for ultimate radical cyclization. Added proof that the actual configura-



tional state of affairs at the newly formed stereogenic center in 20b is as claimed stems from the following ancillary experiments. Monomethylation of 19b was easily achieved and the doublet for the methyl substituent in 25 was seen to experience modest shielding (δ 1.07). Following dimethylation, the pair of well-separated methyl singlets in 26a made their appearance (in $CDCl_3$) at δ 1.27 and 1.09. Use of iodomethane-d_3 in the second stage (see 26b) resulted in disappearance of the more upfield absorption. Finally, hydrogenation of 26a led to 27 (δ 1.27, 1.15). Clearly, the more shielded methyl substituent in these doubly alkylated ketones is positioned above the double bond. Therefore, enolates derived from 19b, 20a, and 25 capture an electrophile with exceptionally good π-face selectivity from that surface occupied by the ethylene bridge.

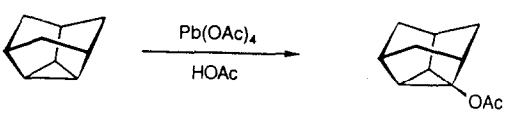


25 26a, X = H b, X = D 27

Following Wolff-Kishner reduction[21] of 20b to furnish 21, deketalization was implemented and the (hydroxymethyl) group was unmasked by reaction with 3 equiv of boron trifluoride etherate in dichloromethane at room temperature for 4 h. At this point, the β,γ-unsaturated keto alcohol (22) was directly subjected to acetone-sensitized photorearrangement. Satisfyingly, this excited-state isomerization proceeded to give 23a in 91% isolated yield without need of a hydroxyl blocking group.

The stage was now set for introduction of the substituent destined to serve as the seat of the homolytic transfer. An iodo atom was selected to play this role and the triphenylphosphine-based scheme[22] for implementing this transformation proceeded without event. With all reaction centers properly in place, it remained only to achieve free radical closure. Irradiation of a benzene solution of 23b and hexamethyldistannane in a quartz tube at 350 mm[23] proved adequate to deliver 24 efficiently (75%). The structural assignment to 24 rests entirely on spectroscopic grounds. Characteristic of the 300 MHz ^{1}H NMR spectrum (in $CDCl_3$) is the appearance of its only bridgehead proton as a multiplet at δ 2.52, the triad of cyclopropyl protons as a closely spaced multiplet centered at δ 2.06, the three equatorial hydrogens as an apparent triplet (J = 7.0 Hz) of area 1 at δ 1.87 and overlapping triplets (2 H) at δ 1.67, the axial hydrogens as two multiplets at δ 1.48 (2 H) and 1.15 (1 H), and the methyl singlet at δ 1.23. The ^{13}C NMR spectrum features ten lines when proton decoupled, intense hydroxyl absorption is seen in the infrared, and high resolution mass spectrometry clearly indicates formation of the correct molecular ion.

According to the IUPAC rules of organic nomenclature and current Chemical Abstracts practice, 24 should preferably be named hexahydro-3-methyl-2,3-methanocyclopropa[*cd*]pentalen-2(1*H*)-ol.[24] We prefer the less formal, more descriptive label 3-methyl[3]peristylan-2-ol. In any event, 24 is only the second known oxygenated [3]peristylane. The first reported example is acetate 28, obtained in 72% yield by lead tetraacetate oxidation of 1.[25] Whereas the disubstituted 24 is chiral, 28 is not. In view of the facility with which bicyclo[2.2.2]octenyl compounds 19 can be resolved,[18,19c] the acquisition of 24 in optically active condition could, in principle, be easily realized.



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In conclusion, the methodology employed herein demonstrates that radical cyclizations onto ketone carbonyl groups can be effectively utilized to generate cyclohexanols when geometrical parameters are conducive to ring formation. This protocol appears particularly well suited to the construction of hemispherical molecules and offers the advantage that alcohols are the end-products. Subsequent laboratory operations can be expected to enable acquisition of a variety of other functionalized derivatives. Alternatively, reduction could make available the hydrocarbon framework.

Experimental Section[26]

5-Dioxolanylbicyclo[2.2.2]oct-7-en-2-one (19b). A solution of **19a** (17.0 g, 125 mmol), ethylene glycol (7.75 g, 125 mmol), and *p*-toluenesulfonic acid monohydrate (1.2 g, 6.25 mmol) in toluene (300 mL) was refluxed for 6 h under a Dean-Stark trap to remove liberated water. The dark brown solution was diluted with dichloromethane (150 mL) and washed with saturated sodium bicarbonate (2 x 50 mL) and sodium chloride solutions (2 x 50 mL). GC analysis of this solution showed the three-component mixture to include **19b** (74%), unreacted **19a** (10%), and diketal (16%). MPLC purification gave **19b** as a colorless oil, bp 85 °C at 0.1 Torr. An analytical sample was obtained by preparative GC; IR (neat, cm^{-1})

3060, 2970, 2880, 1730, 1360, 1340, 1120, 1020, 1000, 955, 945, 900, 890, 715, ^{1}H NMR (300 MHz, C_6D_6) δ 6.11 (m, 1 H), 5.90 (m, 1 H), 3.40-3.26 (m, 4 H), 2.91 (m, 1 H), 2.44 (m, 2 H), 1.96 (dd, J = 2.4, 14 Hz, 1 H), 1.79 (m, 1 H), 1.74 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.4, 135.0, 129.4, 112.2, 64.3, 64.2, 50.0, 41.5, 38.1, 35.3; MS *m/z* (M^+) calcd 180.0786, obsd 180.0792.

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.47; H, 6.86.

3-[2-(Trimethylsilyl)ethoxymethyl]-5-dioxolanylbicyclo[2.2.2]oct-7-en-2-one (20a). Lithium diisopropylamide was generated at 0 °C in 50 mL of anhydrous tetrahydrofuran by addition of *n*-butyllithium (18.8 mL of 1.60 M in hexanes, 30.0 mmol) to diisopropylamine (3.29 g, 32.5 mmol). This solution was cooled to -50 °C, stirred for 20 min, and treated via syringe during 10 min with a solution of **19b** (4.5 g, 25.0 mmol) in the same solvent (50 mL). After being stirred for 1 h at -50 °C, 2-(trimethylsilyl)ethoxymethyl chloride (6.2 mL, 37.5 mmol) was introduced during 3 min. The reaction mixture was stirred in the cold for 2 h, allowed to warm slowly to room temperature, and treated with water (30 mL). The product was extracted into ether (3 x 150 mL) and the combined ether layers were dried and concentrated. MPLC purification of the residual oil (silica gel, elution with 25% ethyl acetate in petroleum ether) gave **20a** (6.76 g, 87%) as a colorless solid, mp 33-35 °C; IR (neat, cm^{-1}) 3035, 1725, 1100, 860, 840; ^{1}H NMR (300 MHz, C_6D_6) δ 6.27 (m, 1 H), 5.90 (m, 1 H), 3.83 (m, 1 H), 3.44-3.21 (m, 8 H), 3.07 (m, 1 H), 2.94 (m, 1 H), 2.03 (dd, J = 2.1, 14.2 Hz, 1 H), 1.82 (dd, J = 3.3, 14.2 Hz, 1 H), 0.86 (m, 2 H), -0.03 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.7, 134.4, 128.1, 112.2, 70.5, 68.2, 64.3. 64.2, 50.0, 45.4, 43.8, 37.9, 18.3, -1.2; MS *m/z* (M^+) calcd 310.1600, obsd 310.1621.

Anal. Calcd for $C_{16}H_{26}O_4Si$: C, 61.90; H, 8.44. Found: C, 62.02; H, 8.39.

3-Methyl-3-[2-(trimethylsilyl)ethoxymethyl]-5-dioxolanylbicyclo[2.2.2]oct-7-en-2-one (20b). A solution of lithium diisopropylamide (0.45 mmol) in anhydrous 1,2-dimethoxyethane (1 mL) was prepared at 0 °C in the predescribed manner. After 15 min, the reaction mixture was cooled to -45 °C whereupon a solution of **20a** (100 mg, 0.32 mmol) and HMPA (1.03 g, 5.75 mmol) in 1,2-dimethoxyethane (10 mL) was introduced dropwise during 10 min. At this point, neat methyl iodide (686 mg, 4.83 mmol) was slowly added. After 45 min at -45 °C, the solution was allowed to warm to room temperature, quenched with water (5 mL), and extracted several times with ether. The combined organic phases were dried and evaporated. The residual oil was purified by MPLC on silica gel (elution with 25% ethyl acetate in petroleum ether) to give 53 mg (51%) of **20b** as a colorless oil and 23 mg (23%) of unreacted **20a**.

For **20b**: IR (neat, cm^{-1}) 3060, 2960, 2890, 1725, 1360, 1250, 1100, 1035, 1020, 860, 840; ^{1}H NMR (300 MHz, C_6D_6) δ 6.23 (m, 1 H), 5.81 (m, 1 H), 3.88 (d, J = 8.5 Hz, 1 H), 3.66-3.33 (m, 7 H), 3.03 (d, J = 2.1 Hz, 1 H), 2.91 (m, 1 H), 1.99 (m, 2 H), 1.35 (s, 3 H), 0.91 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 211.6, 137.2, 127.1, 112.4, 74.6, 68.2, 64.4, 63.3, 49.6, 47.5, 46.7, 37.4, 24.7, 18.5, -1.2; MS *m/z* (M^+-$C_6H_{15}OSi$) calcd 193.0864, obsd 193.0885.

Anal. Calcd for $C_{17}H_{28}O_4Si$: C, 62.93; H, 8.70. Found: C, 62.72; H, 8.55.

3-Methyl-3-[2-(trimethylsilyl)ethoxymethyl]-5-dioxolanylbicyclo[2.2.2]oct-7-ene (21). Freshly cut sodium metal (20 mg, 0.87 mmol) was placed in diethylene glycol (1 mL) and heated at 180-190 °C until dissolution was complete. Ketone **20b** (47 mg, 0.15 mmol) and anhydrous hydrazine (101 mg, 3.16 mmol) were added and the mixture was heated at 180-190 °C for 10 h. After cooling, water (3 mL) was introduced and the product was extracted into ether (3 x 10 mL). The dried organic layers were concentrated and the residue was subjected to MPLC purification (silica gel, elution with 10% ethyl acetate in petroleum ether) to give **21** as a colorless solid (33 mg, 71%); IR (neat, cm^{-1}) 3050, 2935, 1370, 1252, 1103, 845; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.23 (m, 2 H), 4.00-3.42 (m, 8 H), 3.27 (d, J = 8.5 Hz, 1 H), 2.61 (m, 1 H), 1.74 (m, 2 H), 1.27 (m, 1 H), 1.13 (m, 1 h), 0.94 (m, 2 H), 0.43 (s, 3 H), 0.02 (s, 9 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 133.5, 132.6, 113.8, 79.5, 68.0, 64.3, 63.0, 44.6, 40.1, 38.8, 37.7, 31.8, 27.6, 18.5, -1.13; MS *m/z* calcd 310.1964, obsd 310.1987.

Deketalization of 21. A solution of 21 (250 mg, 0.805 mmol) and pyridinium tosylate (101 mg, 0.403 mmol) in 10% aqueous acetone (5 mL) was refluxed for 5 h. The usual workup followed by MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether) gave the ketone as a colorless oil (203 mg, 90%); IR (neat, cm^{-1}) 3250, 2950, 2860, 1712, 1250, 1100, 830, 820, 700; ^{1}H NMR (300 MHz, C_6D_6) δ 6.05 (m, 1 H), 5.88 (m, 1 h), 3.37 (m, 2 H), 2.97 (dd, J = 9.0, 12.5 Hz, 2 H), 2.87 (dd, J = 6.6, 1.0 Hz, 1 H), 2.40 (m, 1 H), 1.85 (m, 2 H), 1.51 (dd, J = 12.8, 2.6 Hz, 1 H), 1.00 (dt, J = 12.7, 2.8 Hz, 1 H), 0.90 (m, 2 H), 0.81 (s, 3 H), -0.01 (s, 9 H); ^{13}C NMR (20 MHz, C_6D_6) ppm 208.6, 136.9, 128.8, 79.2, 68.8, 58.5, 40.0, 39.1, 36.9, 33.1, 25.0, 18.2, -1.2; MS *m/z* (M^+) calcd 266.1702, obsd 266.1658.

7-(Hydroxymethyl)-7-methylbicyclo[2.2.2]oct-5-en-2-one (22). To a solution of the preceding ketone (203 mg, 0.724 mmol) in dichloromethane (2 mL) cooled to 0 °C was added boron trifluoride etherate (308 mg, 2.20 mmol). The reaction mixture was stirred for 4.5 h with slow warming to room temperature. Following a saturated sodium bicarbonate quench (1 mL), the product was extracted into ether (3 x 25 mL), and the combined organic phases were dried and concentrated. MPLC purification (silica gel, elution with 40% ethyl acetate in petroleum ether) furnished 97 mg (81%) of **22** as a sticky, colorless oil. A considerable amount (as high as 1:1) of the hemiacetal tautomer was spectroscopically evident and the material was therefore directly irradiated.

Photoisomerization of 22. A solution of **21** (16.0 mg, 0.096 mmol) in acetone (3 mL) was deoxygenated by bubbling nitrogen through for 30 min and transferred to a quartz tube. This solution was irradiated through a Corex filter with a bank of eight 3000 Å lamps in a Rayonet reactor. After 6 h, the resulting pale yellow solution was concentrated and subjected to MPLC (silica gel, elution with 50% ethyl acetate in petroleum ether). There was isolated 14.6 mg (91%) of **23a** as a viscous colorless oil; IR ($CHCl_3$, cm^{-1}) 2950, 1715, 1601; ^1H NMR (300 MHz, $CDCl_3$) δ 3.45 (ABq, J = 11.0 Hz, $\Delta\nu$ = 22.0 Hz, 2 H), 3.00-2.90 (m, 2 H), 2.63-2.54 (m, 1 H), 2.20 (br s, 1 H), 2.02-1.88 (m, 3 H), 1.78-1.52 (m, 3 H), 1.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.5, 69.6, 49.8, 49.1, 47.6, 42.3, 38.4, 38.0, 37.5, 27.9; MS m/z (M^+) calcd 166.0993, obsd 166.1005.

endo-7-(Iodomethyl)-*exo*-7-methyltricyclo[3.3.0.$0^{2,8}$]octan-3-one (23b). A mixture of **23a** (74.5 mg, 0.448 mmol), iodine (341 mg, 1.34 mmol), imidazole (123 mg, 1.80 mmol), and triphenylphosphine (470 mg, 1.80 mmol) in benzene (8 mL) was heated at reflux for 5 h. The cooled reaction mixture was treated with saturated sodium bicarbonate solution (3 mL), stirred for 5 min, treated with elemental iodine until the organic layer was colored, and finally washed with 10% sodium thiosulfate solution. The separated aqueous phase was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine (2 x 10 mL), concentrated, and purified by TLC mesh column chromatography (elution with 10% ethyl acetate in petroleum ether). The iodo ketone was isolated as a colorless oil (98 mg, 79%); IR (neat, cm^{-1}) 2958, 1716, 1453, 1380, 1316, 1193; ^1H NMR (300 Hz, $CDCl_3$) δ 3.22 (ABq, J = 10.4 Hz, $\Delta\nu$ = 10,4 Hz, 2 H), 3.02 (m, 2 H), 2.65 (m, 1 H), 2.24 (m, 1 H), 2.00 (m, 2 H), 1.73 (m, 1 H), 1.64 (m, 1 H), 1.40 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.8, 50.9, 49.5, 46.5, 43.4, 38.9, 38.52, 38.48, 32.0, 20.1; MS m/z (M^+) calcd 275.9994, obsd 276.0003.

3-Methyl[3]peristylan-2-ol (24). A solution of **23b** (80 mg, 0.290 mmol), hexamethylditin (190 mg, 0.580 mmol), and undecane (1.5 mg, internal standard) in freshly deoxygenated benzene (4 mL) was placed a quartz tube and sealed with a rubber septum. The reaction mixture was irradiated with a bank of seven 3500 Å lamps in a Rayonet reactor. The progress of reaction, monitored at regular intervals by GC, was found to be complete after 16 h. The yield of **24** was 75%. The benzene solvent was carefully removed by distillation at atmospheric pressure to a volume of approximately 0.5 mL. Purification was achieved by elution with 20% ethyl ether in pentane through TLC mesh silica gel and finally preparative GC (4 mm x 10 ft 10% SE-30, 90 °C). There was isolated 25.7 mg (59%) of **24** as a colorless oil; IR ($CHCl_3$, cm^{-1}) 3605, 3400, 2951, 1458, 1320; ^1H NMR (300 MHz, $CDCl_3$) δ 2.52 (m, 1 H), 2.06 (m, 3 H), 1.87 (t, J = 7.0 Hz, 1 H), 1.73 (s, 1 H), 1.67 (m, 2 H), 1.48 (m, 2 H), 1.23 (s, 3 H), 1.15 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 84.5, 59.4, 51.83, 51.78, 45.7, 39.8, 39.7, 38.7, 32.6, 22.8; MS m/z (M^+) calcd 150.1037, obsd 150.1037.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.84; H, 9.59.

3-Methyl-5-dioxolanylbicyclo[2.2.2]oct-7-en-2-one (25). To a cold (-55 °C), magnetically stirred solution of lithium diisopropylamide (0.64 mmol) in dry tetrahydrofuran (1 mL) was added via syringe a cold solution of **19b** (82.4 mg, 0.457 mmol) in the same solvent (1 mL). After 1 h, methyl iodide (65 mg, 0.46 mmol) was introduced and the reaction mixture was allowed to warm slowly to room temperature during 15 h. Saturated aqueous ammonium chloride solution (3 mL) was added, followed by the usual workup. MPLC purification (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 72 mg (81%) of **25** as a colorless oil; IR (neat, cm^{-1}) 2968, 2945, 2880, 1727, 1504, 1140; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (m, 1 H), 6.24 (m, 1 H), 3.94 (m, 4 H), 3.14 (m, 1 H), 2.74 (m, 1 H), 2.47 (m, 1 H), 2.05 (m, 2 H), 1.07 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 212.5, 134.0, 128.3, 112.2, 64.4, 49.6, 48.1, 38.7, 37.4, 16.7; MS m/z (M^+) calcd 194.0943, obsd 194.0933.

3,3-Dimethyl-5-dioxolanylbicyclo[2.2.2]oct-7-en-2-one (26a). To a cold (-45 °C), magnetically stirred solution of lithium diisopropylamide (0.79 mmol) in anhydrous 1,2-dimethoxyethane (2 mL) was added via syringe a cold solution of **25** (85.0 mg, 0.438 mmol) in the same solvent (1 mL). After 15 min, HMPA (392 mg, 2.20 mmol) was introduced followed by methyl iodide (326 mg, 2.20 mmol) one hour later. After a further 3 h at -45 °C, the reaction mixture was allowed to warm to room temperature overnight. Following the usual workup and MPLC on silica gel (elution with 20% ethyl acetate in petroleum ether), there was isolated 76 mg (84%) of **26a** as a colorless oil which slowly crystallized; IR (neat, cm^{-1}) 3032, 2964, 1722, 1472, 1115; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55-6.15 (m, 2 H), 4.04-3.80 (m, 4 H), 3.39-3.11 (m, 1 H), 2.64 (d, J = 6.4 Hz, 1 H), 2.14-1.20 (m, 2 H), 1.27 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 214.9, 137.4, 126.3, 112.3, 64.5, 63.1, 52.1, 48.8, 42.5, 36.9, 28.8, 25.5; MS m/z (M^+) calcd 208.1099, obsd 208.1106.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.26; H, 7.74.

When the identical reaction was performed with CD_3I, **26b** was obtained. This compound lacked the methyl singlet at δ 1.09, but was otherwise identical.

3,3-Dimethyl-5-dioxoanylbicyclo[2.2.2]octan-2-one (27). A solution of **26a** (35 mg, 0.168 mmol) in ethyl acetate (1 mL) was hydrogenated over platinum oxide (5 mg) at 40 psi for 4 h. Filtration and evaporation of the reaction mixture left 34 mg (96%) of **27** as a clear, colorless oil; IR (neat, cm^{-1}) 2992, 1722, 1453, 1360, 1113; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04-3.85 (m, 4), 2.37 (m, 1 H), 2.14 (m, 3 H), 1.82-1.68 (m, 4 H), 1.27 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 220.4, 109.8, 64.2, 63.1, 46.6, 44.9, 44.3, 38.6, 25.6, 24.9, 21.6, 18.1; MS m/z (M^+) calcd 210.1259, obsd 210.1285.

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(26) For those compounds lacking elemental analyses, homogeneity was established by TLC and GC in addition to the associated spectral properties.