Diyl Trapping Reactions To Synthesize Taxol Analogs

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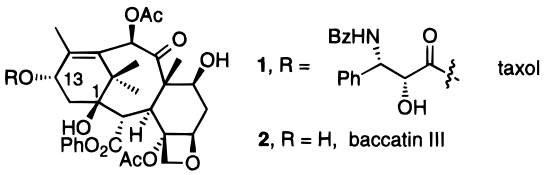
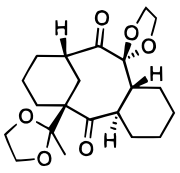
A new and efficient entry to the ABC-ring system common to taxol and related materials has been developed. Highlights include the use of a regioselective intramolecular diyl trapping reaction to synthesize tricyclic alkene **5**, the creation and oxidative cleavage of the tetrasubstituted olefin found in ketal **20a**,**b** to afford a highly functionalized eight-membered ring (**21a**), and cyclization of **22**, thereby providing the tricyclic core.

The importance of taxol (**1**) and related materials in the treatment of a variety of forms of cancer is exceptionally clear.[1] While many ingenious approaches to the skeleton have been developed, only three total syntheses have been published.[2] As indicated recently by Danishefsky and co-workers, the availability of a renewable source of baccatin III (**2**) reduces the impact new total synthesis might have upon the supply problem.[2h] The development of general strategies that will allow the construction of a wide range of analogs whose bioactivity might equal or exceed that of the naturally occurring materials clearly represents a laudable and noteworthy objective. In this paper, we report the results of our initial investigations dealing with the possible applicability of the intramolecular diyl trapping reaction to the assembly of the ABC ring system of the natural materials.[3] Our target structure was tricycle **3**, a system possessing much of the functionality found in the B-ring. We believe that the methodology described herein can readily be adapted to allow the incorporation of much of the functionality deemed necessary for bioactivity.





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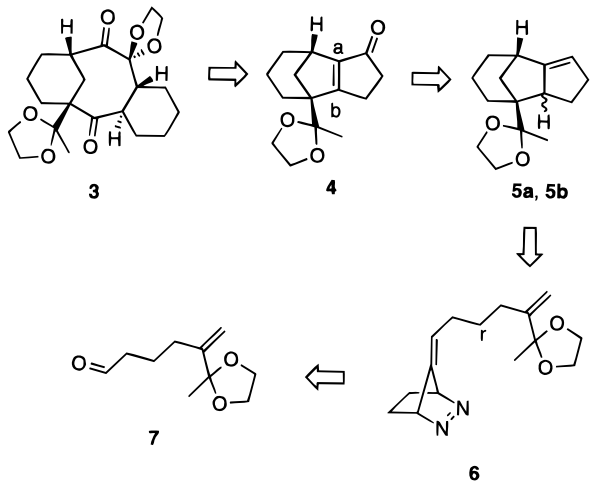
Key to the successful implementation of the plan was the construction of aldehyde **7** and its conversion to the bicyclic diazene **6** in a manner that would allow the subsequent diyl trapping reaction to be conducted on a multigram scale; see Scheme 1. Previous studies indicated that cycloaddition ought to preferentially afford the bridged adduct **5** rather than the linearly fused regioisomer.[3] The ketal, which is critical to guarantee formation of the bridged cycloadduct, is designed to serve as a synthon for the hydroxyl group appended to C_1 of the natural products. Conversion of **5** to the target structure

Scheme 1



3 was predicated upon being able to move the C−C π-bond from its original tri- to the tetrasubstituted position located between carbons C_a and C_b, as in **4**. Subsequent oxidative cleavage of that bond promised to afford the [5.3.1] ring system common to the natural materials.

THF served as an inexpensive, readily available starting material. Ring opening using sodium iodide and benzoyl chloride in acetone,[4] followed by alkylation of acetyl acetone, the addition of paraformaldehyde, and deacylative methylenation in DMSO, afforded vinyl ketone **10** (Scheme 2).[5] This material was most conveniently used without purification in a sequence consisting

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(1) *Taxane Anticancer Agents*; Georg, G. I., Chen, T. T., Ojima, I., Vyas, D. M., Eds.; American Chemical Society: San Diego, 1995; Vol. 583.

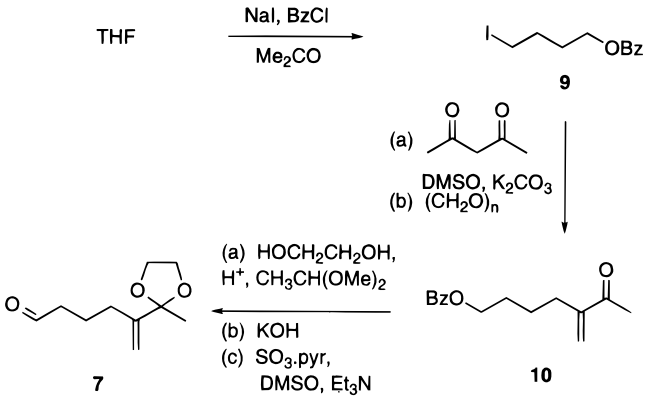
(2) (a) Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. S.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (c) Nicolaou, K. C.; Zang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *357*, 630. (d) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (e) Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. (f) Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. (g) Nicolaou, K. C.; Ueno, H.; Liu, J. J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (h) Masters, J. J.; Link, J. T.; Snyder, L. B.; Young, W. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1723.

(3) Little, R. D. *Chem. Rev.* **1996**, *96*, 93.

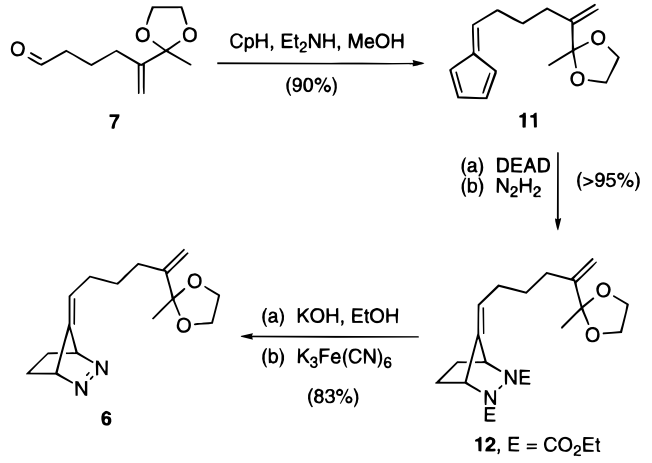
(4) Nyström, J. E.; McCanna, T. D.; Helquist, P.; Amouroux, R. *Synthesis* **1988**, 56.

S0022-3263(97)00042-X CCC: $14.00

Scheme 2



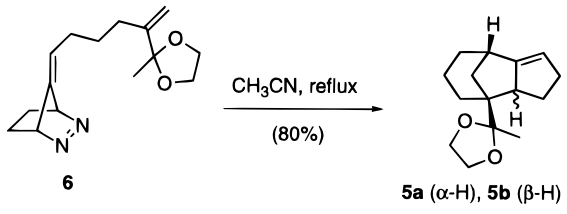
Scheme 3



of ketalization, removal of the benzoate, and Doering oxidation[6] to provide aldehyde **7** in a 60% yield overall.

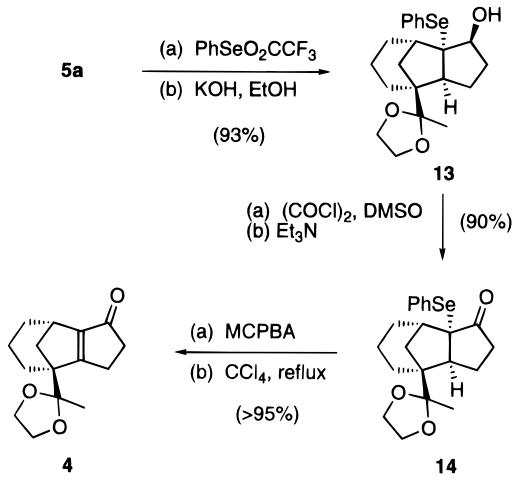
Treatment of **7** with cyclopentadiene and diethylamine in methanol afforded fulvene **11** in a 90% yield.[7] A subsequent Diels−Alder reaction with diethyl azodicarboxylate, followed by reduction of the Δ-5,6 π bond of the adduct using diimide generated *in situ*, led efficiently (>95%) to the biscarbamate **12** (Scheme 3). The diazene linkage was unveiled in a customary fashion, to provide 20 g of diazene **6** in an overall yield, *from THF*, of 35%.

We were delighted to discover that the intramolecular diyl trapping reaction could conveniently be carried out on this scale, a point that is of obvious practical significance. This was achieved simply by adding a solution of **6** in acetonitrile to the solvent at reflux *via* addition funnel over 48 h.[8] An 80% isolated yield of a 1:1 mixture of stereoisomeric bridged cycloadducts **5a** and **5b** was obtained consistently.



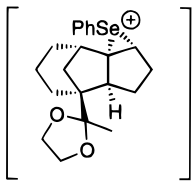
(5) The sequence leading from **9** to **10** was originally explored and developed by Mr. Scott Meehan of UCSB. The use of DMSO allowed the chemistry to be conducted at room temperature, made the process very convenient to conduct, and led to significantly improved yields. Details concerning the general procedure will be published elsewhere.

Scheme 4



Our next objective was to move the double bond in preparation for oxidative cleavage leading to the eight-membered ring.[9] In principle, both stereoisomers **5a** and **5b** can be converted to the same enone **4**. Despite considerable effort, only **5a** has proven useful. Corrective measures continue to be explored. As shown in Scheme 4, the operation could conveniently be carried out *via* the addition of phenylselenyl trifluoroacetate (93%),[10] Swern oxidation of the hydroxyl group in **13** (90%), and elimination of the selenoxide derived from **14** (>95%), in the usual manner, to afford enone **4**.

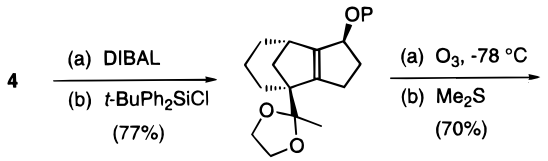
The regiochemical outcome of the oxyselenation step is of interest as it led exclusively to the adduct wherein selenium was appended to the more highly substituted carbon of the alkene. Presumably this is a consequence of the need to form a cis, rather than a highly strained trans-fused bicyclo[3.3.0] subunit.[11] Once the presumed selenonium ion intermediate **15** is formed, ring opening occurs by nucleophilic attack at the less substituted carbon to afford the cis-fused adduct. An alternative pathway involving the development of a partial positive charge at the quaternary bridgehead carbon is unlikely given the increase in strain that would accompany rehybridization.



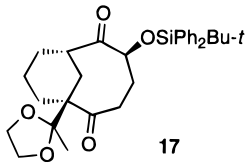
A first indication of the viability of the proposed route to the eight-membered ring was obtained after selective 1,2-reduction and protection of enone **4** to obtain the allylic silyl ether **16b** in a 77% yield as a separable 4:1 mixture of diastereomers. Ozonolytic cleavage of the

(6) Parikh, J. R.; Doering, W. E. *J. Am.Chem. Soc.* **1967**, *89*, 5505.
(7) Stone, K. J.; Little, R. D. *J. Org. Chem.* **1984**, *41*, 1849.
(8) The dimethyl ketal analog of diazene **6** proved too labile toward conversion to the corresponding ketone and was not useful.
(9) (a) Blechert, S.; Müller, R.; Beitzel, M. *Tetrahedron* **1992**, *48*, 6953. (b) Galatsis, P.; Manwell, J. J. *Tetrahedron* **1995**, *51*, 665. (c) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757.
(10) (a) Reich, H. J.; *J. Org. Chem.* **1974**, *39*, 428. (b) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697.
(11) Van Hijfte, L.; Little, R. D.; Petersen, J. L.; Moeller, K. D. *J. Org. Chem.* **1987**, *52*, 4647.

major isomer afforded diketone **17** (70%), a material that displays two carbonyl absorptions in the infrared (1702 and 1698 cm^{-1}) and in the ^{13}C NMR spectrum (215.7 and 213.4).[9a,b]



16a, P = H
16b, P = $SiPh_2Bu$-*t*



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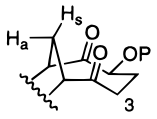
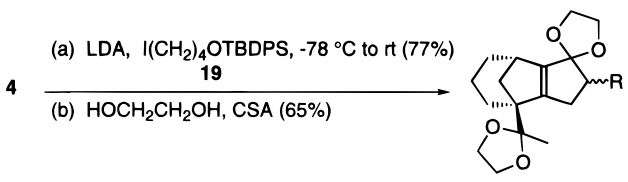
Verification of structure was obtained by NMR using HMQC TOCSY. A particularly remarkable observation was that the chemical shift difference between the methylene protons, H_s and H_a, of the one-carbon bridge was 1.9 ppm! This suggests that the material exists in a conformation wherein the carbonyl units are oriented as shown in **18**, with syn proton, H_s, resonating at 3.76, and the anti, H_a, at 1.89 ppm. A similar difference was observed for the methylene protons located at C_3 (taxol numbering), one appearing at 1.89, the other deshielded considerably, appearing at 3.83 ppm. This helps to define the conformation of the eight-membered ring and suggests that one of the protons is aligned properly to allow removal in subsequent acid−base chemistry.



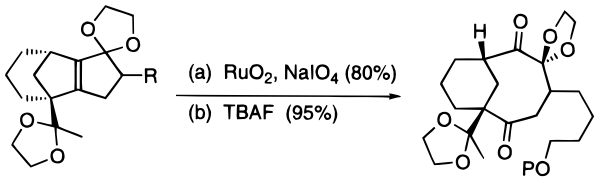
18

The formation of a highly functionalized central ring and the annulation of ring C was achieved in the following manner. The enolate of enone **4** was regioselectively alkylated using iodo ether **19** to afford a 2.5:1 mixture of diastereoisomers that were separated by column chromatography and fully characterized. Decoupling and NOE experiments were used to determine that the α-alkylated material was the major product. Molecular mechanics calculations (SYBYL) strengthened this notion, consistently placing it at a slightly lower energy than its stereoisomer. It proved advantageous to use the mixture in the ketalization step, since the use of either of the pure forms met with epimerization. In fact, each isomer independently afforded the same 2.5:1 ratio of isomeric ketals, suggesting that the initial alkylation ratio reflected a thermodynamic product distribution.



20a, R = α-[$(CH_2)_4$OTBDPS]
20b, R = β-[$(CH_2)_4$OTBDPS]

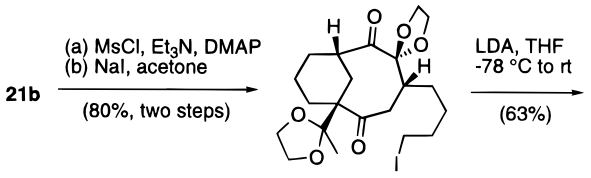
With **20** in hand, the stage was set to produce the eight-membered ring. Oxidative cleavage of the double bond was accomplished to afford an 80% yield of diketone **21a** by using ruthenium tetraoxide, generated *in situ* from sodium periodate (3 equiv) and 10 mol % ruthenium dioxide at 0 °C.[12] It was important to carefully monitor the course of this reaction, and in particular, to avoid prolonged reaction times; in this instance, 20 min proved optimal.



20a, R = α-[$(CH_2)_4$OTBDPS]
20b, R = β-[$(CH_2)_4$OTBDPS]

21a, P = TBDPS
21b, P = H

Completion of the sequence was initiated by removing the silyl ether, separating the major diastereomer, and converting the resulting alcohol **21b** to the corresponding iodide **22**. Closure to afford the C-ring was accomplished by treating **22** with a fivefold excess of LDA at −78 °C (0.5 h) and allowing the reaction mixture to gradually warm to room temperature. Workup, isolation, and characterization indicated, much to our delight, that the desired product **3** had been produced in a 63% yield. To ensure that the thermodynamically preferred trans ring fusion had been obtained, the product was treated for 8 h at room temperature with KOBu-*t*/*t*-BuOH. The starting material was recovered unchanged; isomerization did not occur.[13]



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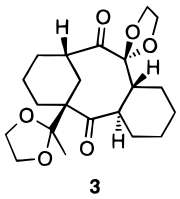

3

In closing, we note the ample opportunity to add key functionality to our second generation efforts, those designed to provide bioactive materials. For example, incorporation of a protected hydroxyl group at the central carbon of the tether that links diazene to diylophile (C_r in **6**, Scheme 1), would provide the important functionality at C_{13} of the taxol framework, and the use of a functionally more elaborate alkylating unit in conjunction with the addition of the C-ring would allow the incorporation of the oxetane. Other options exist, and several

(12) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Mehta, G.; Krishnamurthy, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1319.

(13) (a) Blechert, S.; Kleine-Klausing, A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 412. (b) Magnus, P.; Ujjainwalla, F.; Westwood, N.; Lynch, V. *Tetrahedron Lett.* **1996**, *37*, 6639. (c) SYBYL calculations consistently placed the trans-fused isomer at a substantially lower energy than the cis (>2 kcal/mol).

are under investigation. The results will be reported in due course.

Experimental Section

4-Iodo-1-(benzoyloxy)butane (9). To a stirring solution of benzoyl chloride (105.4 g, 0.75 mol) and THF (175.1 g, 2.74 mol) in acetone (1.5 L) was added sodium iodide (224.8 g, 1.5 mol). The orange reaction mixture was stirred at room temperature for 10 h and then turned clear after being quenched with saturated $NaHSO_3$ (500 mL). The water layer was extracted with ether (3 × 250 mL), and the combined organic layers were washed with saturated $NaHCO_3$ (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was filtered through silica gel (ether) to yield 207 g (0.69 mol) of pure alkyl iodide **9** (93%). TLC (SiO_2, 100% ether, UV, vanillin) $R_f = 0.50$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.55 (app dd, $J = 7.4$, 1.6 Hz, 1H), 7.43 (m, 2 H), 4.34 (t, $J = 6.2$ Hz, 2H), 3.24 (t, $J = 6.8$ Hz, 2H), 1.98 (tt, 2H), 1.89 (tt, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 132.8, 130.1, 129.4, 128.3, 63.6, 30.0, 29.6, 5.9; FTIR (neat/NaCl) 3064, 2952, 2895, 2854, 1717, 1595, 1452, 1273, 1110 cm^{-1}; HRMS (CI/CH_4) calcd for $C_{11}H_{13}O_2I$ [M − 57(C_4H_9)]: 305.0039, found: 305.0040.

1-(Benzoyloxy)-5-methylideneheptan-6-one (10). A 3 L round-bottom flask equipped with an overhead stirrer was charged with 2,4-pentanedione (75 g, 0.75 mol) and potassium carbonate (207.3 g, 1.5 mol) in DMSO (1.5 L). To the mixture was added 4-iodo-1-(benzoyloxy)butane (**9**) (222 g, 0.75 mol). After stirring for 10 h at room temperature, paraformaldehyde (100 g, 7.5 mol) was added in one portion. The reaction mixture was stirred for 3 h and quenched with saturated $NaHCO_3$ (300 mL). The aqueous layer was extracted with ether (5 × 250 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude oil was filtered through silica gel (ether) to yield 156.8 g (0.63 mol) of enone **10** (85%). TLC (SiO_2, 30% ether/pentane, UV, vanillin) $R_f = 0.57$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.50 (app tt, $J = 7.4$, 1.2, 2.0 Hz, 1H), 7.43 (m, 2 H), 5.99 (s, 1H), 5.75 (bt, $J = 1.2$ Hz, 1H), 4.28 (t, $J = 6.4$ Hz, 2H), 2.31 (s, 3H), 1.74 (m, 2H), 1.54 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 199.4, 166.4, 132.7, 130.2, 128.3, 128.2, 125.1, 64.6, 30.0, 28.3, 25.7, 24.8; FTIR (neat/NaCl) 3063, 2952, 2867, 1718, 1677, 1274, 1115 cm^{-1}.

5-(2-Methyl-1,3-dioxolan-2-yl)hex-5-enal (7). A 3 L round-bottom flask equipped with an overhead stirrer was charged with enone **10** (156.8 g, 637.5 mmol), ethylene glycol (1000 mL), and trimethyl orthoformate (500 mL). *p*-Toluenesulfonic acid (12 g, 63 mmol) was then added to this biphasic mixture. The solution immediately became clear and slowly became dark red upon stirring for 10 h at room temperature. A 26.5 M solution of KOH/H_2O (200 mL) was then added over 1 h. The dark red solution initially turned cloudy orange and then clear orange. After stirring for 2 h, the aqueous layer was extracted with methylene chloride (7 × 300 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation under reduced pressure (120−125 °C/0.1 Torr) afforded 89.2 g (471.7 mmol) of 5-(2-methyl-1,3-dioxolan-2-yl)hex-5-en-1-ol (74%). TLC (SiO_2, 70% ether/pentane, vanillin) $R_f = 0.20$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (d, $J = 1.0$ Hz, 1H), 4.89 (dd, $J = 1.0$, 2.5 Hz, 1H), 3.95 (m, 2H), 3.83 (m, 2H), 3.67 (bt, $J = 5.5$ Hz, 2H), 2.09 (t, $J = 7.5$ Hz, 2H), 1.56 (m, 4H), 1.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.5, 109.6, 109.0, 63.8, 61.7, 32.1, 29.9, 23.9, 23.8; FTIR (neat/NaCl) 3428, 3090, 2988, 2937, 2909, 1652, 1646, 1041 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{10}H_{18}O_3$ [M + H]$^+$: 187.1334, found: 187.1337.

Sulfur trioxide−pyridine complex (100 g, 500 mmol) was added at room temperature to a stirring solution of the alcohol (40 g, 215 mmol, obtained as described above) in triethylamine (536 mL) and DMSO (536 mL). After 20 min the reaction was complete. The solution was cooled to 0 °C, and water (500 mL) was added. Upon warming to room temperature, the aqueous layer was extracted with ether (5 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel (60% ether/pentane) afforded 35.38 g (189.2 mmol) of aldehyde **7** (88%). TLC (SiO_2, 60% ether/pentane, vanillin) $R_f = 0.54$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (t, $J = 1.5$ Hz, 1H), 5.30 (s, 1H), 4.89 (d, $J = 1.5$ Hz, 1H), 3.94 (m, 2H), 3.81 (m, 2H), 2.46 (td, $J = 7.3$, 1.5 Hz, 2H), 2.08 (t, $J = 7.8$ Hz, 2H), 1.82 (tt, $J = 7.7$, 7.3 Hz, 2H), 1.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.6, 148.0, 110.1, 108.7, 63.8, 43.0, 29.5, 23.8, 20.2; FTIR (neat/NaCl) 3096, 2989, 2952, 2884, 2721, 1726, 1651, 1444, 1041 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{10}H_{16}O_3$ [M + H]$^+$: 185.1177, found: 187.1171.

2-[1-(4-Cyclopenta-2,4-dienylidenebutyl)vinyl]-2-methyl-1,3-dioxolane (11). To a solution of aldehyde **7** (5.5 g, 30.2 mmol) and cyclopentadiene (5.0 g, 75.5 mmol) in MeOH (64 mL) at 0 °C was added diethylamine (3.31 g, 45.3 mmol) dropwise *via* syringe. The resulting homogeneous mixture was allowed to warm to room temperature. After 5 h, the reaction mixture was cooled to 0 °C, and glacial acetic acid (9.06 g, 151 mmol) was added in one portion. After 20 min the solution was diluted with water (50 mL), and the aqueous layer was extracted with ether (5 × 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Chromatography on silica gel (5% ether/pentane) afforded 6.09 g (26.3 mmol) of fulvene **11** as a bright yellow oil (87%). TLC (SiO_2, 5% ether/pentane, UV, vanillin) $R_f = 0.28$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (m, 2H), 6.44 (m, 2H), 6.21 (m, 1H), 5.30 (d, $J = 0.7$ Hz, 1H), 4.90 (bd, $J = 1.5$ Hz, 1H), 3.94 (m, 2H), 3.81 (m, 2H), 2.57 (dt, $J = 7.7$ Hz, 2H), 2.14 (t, $J = 8.0$ Hz, 2H), 1.74 (tt, $J = 8.0$, 7.7 Hz, 2H), 1.48 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.6, 146.1, 142.3, 132.9, 130.6, 125.4, 118.9, 110.2, 109.2, 64.2, 30.7, 30.2, 27.9, 24.2; FTIR (neat/NaCl) 3095, 3068, 2990, 2935, 2886, 1645, 1474, 1040 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_2$: 232.1463, found: 232.1452.

7-[5-(2-Methyl-1,3-dioxolan-2-yl)hex-5-enylidene]-2,3-diazabicyclo[2.2.1]hept-2-ene (6). To a solution of fulvene **11** (4.90 g, 21.1 mmol) in methylene chloride (84 mL) was added diethyl azodicarboxylate (3.83 g, 22 mmol) at room temperature. The solution was placed in the refrigerator (4 °C) for 8 h. To the solution of crude carbamate ($R_f = 0.74$ [100% ether], UV, vanillin) was added dipotassium azodicarboxylate (41 g, 211 mmol), and the mixture was stirred with an overhead stirrer. The reaction mixture was cooled to 0 °C, and glacial acetic acid (18.1 mL, 316 mmol) was added dropwise *via* addition funnel over 45 min. A vigorous gas evolution took place. After 4 h, the reaction mixture was filtered through a sintered glass funnel with ether and concentrated *in vacuo*. The crude reduced carbamate **12** ($R_f = 0.74$ [100% ether], UV, vanillin) was dissolved in ethanol (192 mL), the solution was degassed with argon for 20 min, and potassium hydroxide (21.3 g, 380 mmol) was added. The resulting mixture was refluxed for 2.5 h and then cooled to 0 °C. The reflux condenser was removed and replaced with an overhead stirrer. Potassium ferricyanide (21.53 g, 65.41 mmol) in water (172 mL) was added *via* addition funnel over 30 min.. After 2.5 h, the cloudy brown mixture was poured into a separatory funnel containing water (1 L) and ether (300 mL). The aqueous layer was extracted with ether (7 × 150 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica gel (50% ether/pentane) afforded 5.14 g (19.6 mmol) of diazene **6** (93%). TLC (SiO_2, 50% ether/pentane, vanillin) $R_f = 0.4$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (bs, 1H), 5.26 (d, $J = 1.0$, 1H), 5.12 (m, 2H), 4.83 (q, $J = 1.5$ Hz, 1H), 3.94 (m, 2H), 3.80 (m, 2H), 2.00 (m, 4H), 1.70−1.46 (m, 4H), 1.45 (s, 3H), 1.10 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 145.0, 117.2, 110.3, 109.4, 76.8, 72.6, 64.4, 30.1, 28.9, 28.0, 24.4, 21.5, 21.1; FTIR (neat/NaCl) 3092, 2984, 2941, 2888, 1645, 1455, 1039 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{15}H_{22}O_2N_2$ [M + H]$^+$: 263.1759, found: 263.1748.

Diyl Trapping Reaction: Diazene 6 in MeCN. A 2 L round-bottom flask was charged with acetonitrile (1000 mL) and degassed with argon for 30 min. A reflux condenser was then attached to the round-bottom flask. To the top of the reflux condenser was attached a 500 mL addition funnel, and the system was purged with argon. The addition funnel was charged with a solution of diazene **6** (15.30 g, 58.4 mmol) in

previously degassed acetonitrile (500 mL) *via* cannula. The addition funnel was wrapped in aluminum foil to prevent light-induced deazotization of the substrate, and the acetonitrile in the round-bottom flask was heated to reflux. The solution of diazene was slowly added dropwise (1 drop/4 s) through the condenser into the refluxing acetonitrile over 40 h. After 40 h, the empty addition funnel was rinsed with previously degassed acetonitrile (25 mL) which was allowed to drop into the reluxing reaction mixture over a period of 15 min. The solution was refluxed another 2 h and cooled to room temperature, and the solvent was removed *in vacuo*. The crude oil was purified by chromatography on silica gel (5% ether/pentane) to afford 11.1 g (47.3 mmol) of trapped products **5a** and **5b** (81%). The mixture contained *endo* and *exo* bridged products in a ratio of 1:1, as well as a trace amount of linearly fused tricyclopentanoid product. The ratio of bridged to linear products was 10:1. The spectral data were the following:

(3a*β*,4α,8α)-2-(3,3a,5,6,7,8-Hexahydro-2*H*-4,8-methanoazulen-4-yl)-2-methyl-1,3-dioxolane (5a). TLC (SiO_2, 10% ether/pentane, vanillin) $R_f = 0.42$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (t, $J = 4.0$ Hz, 1H), 3.97−3.75 (m, 4H), 2.64 (br t, $J = 2.5$ Hz, 1H), 2.59 (br t, $J = 8.0$ Hz, 1H), 2.36 (m, 1H), 2.15 (m, 1H), 1.94 (m, 2H), 1.79 (m, 1H), 1.68 (m, 1H), 1.58 (m, 5H), 1.44 (m, 1H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 120.7, 112.7, 65.1, 63.8, 53.7, 49.4, 40.3, 37.6, 35.1, 34.8, 34.0, 29.7, 20.7, 19.8; FTIR (neat/NaCl) 3045, 2936, 2871, 1451, 1375, 1154, 1080, 1040 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_2$: 234.1619, found: 234.1611.

(3aα,4α,8α)-2-(3,3a,5,6,7,8-Hexahydro-2*H*-4,8-methanoazulen-4-yl)-2-methyl-1,3-dioxolane (5b). TLC (SiO_2, 10% ether/pentane, vanillin) $R_f = 0.34$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (t, $J = 1.5$ Hz, 1H), 3.93−3.80 (m, 4H), 3.05 (br t, $J = 7.5$ Hz, 1H), 2.68 (br s, 1H), 2.63 (m, 1H), 2.50 (m, 1H), 2.11 (m, 1H), 1.85−1.58 (m, 5H), 1.52−1.36 (m, 4H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 115.4, 112.4, 65.0, 64.8, 56.5, 49.0, 43.9, 37.0, 33.7, 33.6, 27.2, 27.1, 20.7, 18.6; FTIR (neat/NaCl) 3045, 2947, 2874, 1440, 1352, 1210, 1151, 1046 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{22}O_2$: 234.1619, found: 234.1620.

(3a*β*,4α,8α)-4-(2-Methyl-1,3-dioxolan-2-yl)-8a-(phenylselenyl)decahydro-4,8-methanoazulen-1-ol (13). To a solution of bromine (1.36 g, 17.0 mmol) and propylene oxide (1.0 mL) in benzene (20 mL) was added diphenyl diselenide (7.95 g, 25.5 mmol) at room temperature. The mixture immediately turned black. After stirring 20 min, the mixture was transferred to a 100 mL round-bottom flask containing silver trifluoroacetate (7.5 g, 34.0 mmol). The resulting bright yellow reaction mixture was stirred for 20 min, and alkene **5a** (5.0 g, 21.5 mmol) dissolved in benzene (10.0 mL) was added dropwise *via* syringe. The mixture was allowed to stir for 3 h leading to the formation of the addition product ($R_f = 0.42$ [10% ether/pentane], UV, vanillin). Hydrolysis of the trifluoroacetate group was accomplished by the addition of potassium hydroxide (50 g, 890 mmol) in ethanol (117 mL). After stirring at room temperature for 5 min, the reaction was complete. Brine (100 mL) was added to the reaction mixture, the aqueous layer was extracted with ether (5 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (60% ether/pentane) to afford 8.07 g (20.0 mmol) of pure product **13** (93%). TLC (SiO_2, 60% ether/pentane, UV, vanillin) $R_f = 0.36$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, 2H, $J = 7.0$, 2.0 Hz), 7.29 (m, 3H), 4.63 (bt, $J = 7.0$ Hz, 1H), 3.97−3.73 (m, 4H), 2.57 (br d, $J = 3.1$ Hz, 1H), 2.15−1.99 (m, 5H), 1.90 (m, 1H), 1.78−1.56 (m, 7H), 1.30 (s, 3H), 1.14 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 129.9, 129.1, 127.8, 112.8, 84.0, 68.7, 65.4, 63.6, 56.4, 54.3, 38.0, 37.7, 35.4, 35.1, 31.4, 26.5, 20.9, 19.2; FTIR (neat/NaCl) 3461, 3437, 3045, 2949, 2873, 1477, 1376, 1055 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{28}O_3Se$: 408.1203, found: 408.1191.

(3a*β*,4α,8α)-4-(2-Methyl-1,3-dioxolan-2-yl)-8a-(phenylselenyl)octahydro-4,8-methanoazulen-1-one (14). To a stirring solution of DMSO (3.75 g, 48.0 mmol) in methylene chloride (100 mL) at −78 °C was added oxalyl chloride (2 M solution in methylene chloride, 12.0 mL, 24.0 mmol) *via* syringe. The reaction is slightly exothermic. The resulting pale yellow solution was stirred at −78 °C for 20 min. A solution of the alcohol **13** (8.07 g, 20.0 mmol) in methylene chloride (10 mL) was then slowly added *via* syringe. After stirring at −78 °C for 2 h, triethylamine (9.71 g, 96.0 mmol) was slowly added (again exotherm occurred), and the reaction mixture was allowed to warm to room temperature. After stirring at room temperature for 2 h, the reaction mixture was quenched with saturated NH_4Cl (100 mL). The aqueous layer was extracted with methylene chloride (5 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (60% ether/pentane) to afford 7.26 g (18.0 mmol) of pure ketone **14** (90%). TLC (SiO_2, 60% ether/pentane, UV, vanillin) $R_f = 0.50$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.35 (app tt, $J = 7.0$, 1.3 Hz, 1H), 7.43 (m, 2 H), 3.96−3.70 (m, 4H), 2.45 (d, $J = 9.0$ Hz, 1H), 2.41 (m, 1H), 2.23−2.15 (m, 3H), 2.0 (m, 2H), 1.66 (m, 4H), 1.53 (m, 1H), 1.47 (dd, $J = 11.5$, 5.5 Hz, 1H), 1.30 (s, 3H), 1.24 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.9, 137.0, 128.8, 128.7, 126.6, 111.7, 66.0, 65.2, 63.7, 55.4, 52.3, 40.2, 37.2, 36.3, 35.2, 28.2, 22.5, 20.9, 18.9; FTIR (neat/NaCl) 3063, 2950, 2875, 1719, 1469, 1438, 1375, 1044 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}O_3Se$: 406.1047, found: 406.1029.

(4α,8α)-4-(2-Methyl-1,3-dioxolan-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-4,8-methanoazulen-1-one (4). To a stirring solution of ketone **14** (7.26 g, 17.9 mmol) in methylene chloride (90 mL) was added *m*-CPBA (50%, 3.71 g, 21.5 mmol) at −78 °C. The homogeneous yellow solution turned to a heterogeneous orange mixture which was allowed to stir at −78 °C for 2 h. The reaction mixture was then transferred into a solution of refluxing triethylamine (6 mL) and carbon tetrachloride (200 mL). The dark orange solution was maintained at reflux for 8 h. The reaction mixture was then cooled to room temperature and quenched with saturated $NaHCO_3$ (100 mL). The aqueous layer was extracted with methylene chloride (5 × 100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel (70% ether/pentane) to afford 4.22 g (17.0 mmol) of pure enone **4** (95%). TLC (SiO_2, 70% ether/pentane, UV, vanillin) $R_f = 0.30$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04−3.95 (m, 4H), 2.87 (br s, 1H), 2.79−2.51 (m, 4H), 2.46 (m, 1H), 1.63 (m, 4H), 1.48 (m, 1H), 1.39 (app tdd, $J = 11.9$, 5.1, 1.8 Hz, 1H), 1.28 (s, 3H), 1.0 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 186.8, 149.3, 110.6, 64.5, 57.0, 48.0, 40.1, 33.6, 25.0, 24.6, 24.0, 20.2, 19.5; FTIR (neat/NaCl) 2942, 2872, 1686, 1613, 1445, 1380, 1146, 1103, 1041 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{20}O_2$: 248.1412, found: 248.1416.

2-[(4α,8α)-1-[(*tert*-Butyldiphenylsilyl)oxy]decahydro-4,8-methanoazulen-4-yl]-2-methyl-1,3-dioxolane (16b). To a solution of enone **4** (250 mg, 1.0 mmol) in CH_2Cl_2 (3 mL) at −78 °C was added DIBAL-H (1 M in hexanes, 1.5 mL, 1.5 mmol). After 15 min, saturated sodium potassium tartrate (10 mL) was added, and the mixture was allowed to warm to room temperature where it stirred for 30 min. Brine (3 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mixture of allylic alcohols **16a** were protected without further purification. TLC (SiO_2, 60% ether/pentane, UV, vanillin) $R_f = 0.40$ (major diastereomer), 0.55 (minor diastereomer).

To a stirring solution of allylic alcohols **16a** (250 mg, 1.0 mmol), DMAP (5 mg), and *tert*-butylchlorodiphenylsilane (302.3 mg, 1.1 mmol) in CH_2Cl_2 (3 mL) was added NEt_3 (0.417 mL, 3.0 mmol) at 0 °C. The cloudy mixture was allowed to warm to room temperature and stir for 8 h. The reaction was quenched with saturated NH_4Cl (3 mL), and the water layer was extracted with CH_2Cl_2 (5 × 6 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified by chromatography on silica gel (10% ether/pentane) to afford 376 mg (0.77 mmol) of diastereomers **16b** (77%) in a ratio of 4:1. TLC (SiO_2, 10% ether/pentane, UV, vanillin) $R_f = 0.30$ (major diastereomer), 0.40 (minor diastereomer). Major diastereomer **16b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.38 (m, 6H), 4.95 (app dt, $J = 6.5$, 2.0 Hz, 1H), 4.00−3.85 (m, 4H), 2.37 (m, 2H), 2.20 (m, 2H), 2.08 (ddt, $J = 16.3$, 8.0, 2.4 Hz, 1H), 1.99 (ddt, $J = 13.5$, 8.0, 2.4 Hz, 1H), 1.68−1.56 (m, 5H), 1.47−1.37 (m, 2H), 1.26

(m, 2H), 1.19 (s, 3H), 1.05 (s, 9H); FTIR (neat/NaCl) 3070, 3050, 2941, 2857, 1958, 1898, 1824, 1472, 1427, 1389, 1112, 1048 cm^{-1}.

(1α,5α,7α)-5-[(*tert*-Butyldiphenylsilyl)oxy]-1-(2-methyl-1,3-dioxolan-2-yl)bicyclo[5.3.1]undecane-2,6-dione (17). To a solution of silyl ether **16b** (100 mg, 0.2 mmol) in CH_2Cl_2/MeOH (2 mL, 3:1) at −78 °C was bubbled ozone until a pale blue color persisted (10 min). The excess ozone was removed by bubbling nitrogen through the solution until the reaction maintained a clear color (10 min). Excess methyl sulfide (124 mg, 2.0 mmol) was added at −78 °C, and the reaction was allowed to warm to room temperature where it stirred for 3 h. The solvents were removed *in vacuo*, and the crude product was purified by chromatography on silica gel (30% ether/pentane) to afford 72 mg (0.14 mmol) of pure dione (70%). TLC (SiO_2, 30% ether/pentane, UV, vanillin) $R_f = 0.50$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−6.78 (m, 10H), 4.54 (t, J = 3.5 Hz, 1H), 4.08−3.92 (m, 4H), 3.89 (m, 1H), 3.76 (dd, J = 14.7, 2.2 Hz, 1H), 2.39 (br s, 1H), 2.14 (m, 1H), 1,94 (m, 4H), 1.34−1.20 (m, 5H), 1.10 (s, 9H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.6, 213.5, 154.2, 135.1, 130.7, 130.4, 129.7, 129.6, 128.1, 122.1, 119.7, 119.5, 110.9, 80.2, 65.5, 64.6, 60.4, 43.0, 34.5, 33.9, 27.0, 25.8, 25.6, 25.1, 20.5, 18.9, 18.0; FTIR (neat/NaCl) 2979, 2955, 2933, 2890, 2859, 1702, 1698, 1596, 1492, 1251, 1112 cm^{-1}.

4-Iodo-1-(*tert*-butyldiphenylsiloxy)butane (19). To a stirring solution of *tert*-Butylchlorodiphenylsilane (105.4 g, 0.75 mol) and THF (175.1 g, 2.74 mol) in acetone (1.5 L) was added sodium iodide (224.8 g, 1.5 mol). The orange reaction mixture was stirred at room temperature for 10 h and then quenched with saturated $NaHSO_3$ (500 mL). The water layer was extracted with ether (3 × 250 mL), the combined organic layers were washed with saturated $NaHCO_3$ (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was filtered through silica gel (ether) to yield 207 g (0.70 mol) of pure alkyl iodide **19** (93%). TLC (SiO_2, 100% pentane, UV, vanillin) $R_f = 0.50$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (app dd, J = 8.0, 1.5 Hz, 4H), 7.44 (m, 6H), 3.72 (t, J = 6.0 Hz, 2H), 3.22 (t, J = 7.0 Hz, 2H), 1.99 (tt, J = 14.0, 7.0 Hz, 2H), 1.69 (tt, J = 14.0, 6.0 Hz, 2H), 1.10 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.5, 133.7, 129.6, 127.6, 62.6, 33.2, 30.1, 26.8, 19.2, 7.1; FTIR (neat/NaCl) 3069, 2949, 2857, 1958, 1896, 1824, 1472, 1427, 1224, 1112 cm^{-1}; exact mass [HRMS(CI/CH_4)] calcd for $C_{20}H_{26}OSiI$ [M − H]$^+$: 437.0798, found: 437.0792.

Synthesis of Alkylated Enones 20a and 20b. 2-[1,1-*O*-Ethylene-1,1-dihydroxy-2-[4-[(*tert*-butyldiphenylsilyl)-oxy]butyl]decahydro-4,8-methanoazulen-4-yl]-2-methyl-1,3-dioxolane (20a and 20b). To a stirring solution of *n*-BuLi (2.5 M solution in hexanes, 4.0 mL, 10.0 mmol) in THF (34 mL) was added diisopropylamine (1.40 mL, 10.0 mmol) at −78 °C. After 20 min the enone (2.0 g, 8.1 mmol) in THF (3 mL) was added dropwise *via* syringe and stirred at −78 °C for 1 h. The solution was warmed to 0 °C for 30 min and then cooled back to −78 °C for 30 min. Alkyl iodide **9** (6.0 g, 26.2 mmol) was added *via* syringe and the reaction was allowed to warm to room temperature. After stirring at room temperature for 3 h, the reaction was quenched with saturated NH_4Cl (20 mL). The aqueous layer was extracted with ether (5 × 100 mL), the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude products were purified and separated on silica gel (50% ether/pentane) to afford 3.49 g (6.24 mmol) of pure enones (77%) and recovered starting material (250 mg, 1.01 mmol, 89% based on recovered starting material). The product mixture contained the 2α,4α,8α and 2β,4α,8α-diastereomers in a ratio of 2.5:1; their spectral date follows.

For (2α,4α,8α)-2-[4-[(*tert*-Butyldiphenylsilyl)oxy]butyl]-4-(2-methyl-1,3-dioxolan-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-4,8-methanoazulen-1-one: TLC (SiO_2, 50% Et_2O/pentane, UV, vanillin) $R_f = 0.30$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (app d, J = 6.5, 4H), 7.39 (m, 6H), 4.04−3.89 (m, 4H), 3.67 (t, J = 6 Hz, 2H), 2.86 (br s, 1H), 2.71 (dd, J = 19.0, 6.2 Hz, 1H), 2.63 (br s, 1H), 2.42 (m, 1H), 2.27 (d, J = 19.0 Hz, 1H), 1.84 (m, 1H), 1.60 (m, 6H), 1.44 (m, 6H), 1.27 (s, 3H), 1.0 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.8, 185.2, 148.6, 135.5, 135.4, 134.0, 133.9, 129.4, 129.3, 127.7, 127.5, 110.6, 64.6, 63.6, 57.0, 51.6, 47.8, 33.6, 32.5, 31.8, 31.2, 26.8, 24.8, 24.0, 23.5, 20.4, 19.5, 19.1; FTIR (neat/NaCl) 3061, 2940, 2864, 1686, 1615, 1460, 1381, 1104 cm^{-1}; exact mass [HRMS (CI/CH_4)] calcd for $C_{35}H_{46}O_4Si$ [M + H]$^+$: 559.3243, found: 559.3250.

For (2β,4α,8α)-2-[4-[(*tert*-Butyldiphenylsilyl)oxy]butyl]-4-(2-methyl-1,3-dioxolan-2-yl)-3,4,5,6,7,8-hexahydro-2*H*-4,8-methanoazulen-1-one: TLC (SiO_2, 50% Et_2O/pentane, UV, vanillin) $R_f = 0.28$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (app d, J = 6.5, 4H), 7.39 (m, 6H), 4.04−3.95 (m, 4H), 3.67 (t, J = 6.4 Hz, 2H), 2.86 (br s, 1H), 2.79−2.67 (m, 2H), 2.43 (m, 1H), 2.20 (d, J = 17.2 Hz, 1H), 1.86 (m, 1H), 1.60 (m, 6H), 1.49−1.26 (m, 6H), 1.27 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.8, 184.7, 148.7, 135.5, 134.0, 129.5, 127.6, 110.7, 64.6, 63.6, 57.0, 51.1, 47.9, 33.7, 32.5, 31.4, 26.8, 24.9, 24.0, 23.6, 20.3, 19.6, 19.2; FTIR (neat/NaCl) 3059, 2940, 2864, 1689, 1615, 1460, 1380, 1104 cm^{-1}; exact mass [HRMS (CI/CH_4)] calcd for $C_{35}H_{46}O_4Si$ [M + H]$^+$: 559.3243, found: 559.3224.

A 250 mL round-bottom flask was charged with a mixture of enones (2.20 g, 3.93 mmol; prepared as described above), camphorsulfonic acid (10 mg), ethylene glycol (100 mL), and benzene (100 mL). The biphasic mixture was heated to reflux, and water was azeotropically removed by using a Dean−Stark trap. After 12 h, the reaction mixture was cooled to room temperature and diluted with 200 mL of saturatated $NaHCO_3$, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on silica gel (30% ether/pentane) afforded 1.54 g (2.55 mmol, 65%) of inseparable ketals **20a** and **20b** (2.5:1) and recovered starting material (400 mg, 0.71 mmol, 83% based on recovered starting material). TLC (SiO_2, 50% Et_2O/pentane, UV, vanillin) $R_f = 0.55$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (app d, J = 6.5, 4H), 7.39 (m, 6H), 4.04−3.95 (m, 8H), 3.68 (t, J = 6.5 Hz, 2H, **20b**), 3.67 (t, J = 6.5 Hz, 2H, **20a**), 2.60 (br m, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 2.00 (dd, J = 15.5, 3.6 Hz, 1H, **20b**), 1.88 (dd, J = 16.5, 7.0 Hz, 1H, **20a**), 1.68−1.53 (m, 6H), 1.50−1.31 (m, 8H), 1.22 (s, 3H, **20a**), 1.21 (s, 3H, **20b**), 1.05 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) major diastereomer **20a** δ 152.0, 146.3, 135.5, 134.1, 129.4, 127.5, 117.3, 111.5, 65.6, 65.0, 64.9, 64.8, 64.0, 54.7, 50.7, 48.2, 36.2, 32.9, 31.8, 29.1, 26.8, 25.5, 24.4, 20.7, 19.8, 19.6, 19.2; minor diastereomer **20b** δ 152.0, 145.9, 135.5, 134.1, 129.4, 127.5, 116.7, 111.6, 65.4, 64.8, 64.4, 64.0, 54.5, 51.3, 48.7, 35.9, 32.8, 32.0, 30.0, 26.8, 25.2, 24.9, 24.3, 20.6, 19.8, 19.7, 19.2; FTIR (neat/NaCl) 3059, 2940, 2864, 1689, 1615, 1460, 1380, 1104 cm^{-1}; exact mass [HRMS (CI/CH_4)] calcd for $C_{37}H_{50}O_5Si$ [M + H]$^+$: 603.3505, found: 603.3495.

4-[4-[(*tert*-Butyldiphenylsilyl)oxy]butyl]-5,5-*O*-ethylene-5,5-dihydroxy-1-(2-methyl-1,3-dioxolan-2-yl)bicyclo[5.3.1]-undecane-2,6-dione (21a). To a stirring mixture of ketals **20a** and **20b** (256 mg, 0.40 mmol) and sodium periodate (263 mg, 1.23 mmol) in carbon tetrachloride (2 mL), acetonitrile (2 mL), and water (2 mL) was added ruthenium tetraoxide (10 mg) at 0 °C. The mixture turned black (with green overtones). After 20 min the reaction was complete by TLC. The mixture was transferred directly onto a premade column of silica gel and eluted with ether. The crude products were collected and concentrated *in vacuo*. Purification on silica gel (40% ether/pentane) afforded 205 mg (0.32 mmol, 80%) of inseparable diastereomers **21a** (2.5:1). TLC (SiO_2, 50% Et_2O/pentane, UV, vanillin) $R_f = 0.30$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (m, 4H), 7.39 (m, 6H), 4.11−3.87 (m, 7H,), 3.77−3.63 (m, 4H), 3.52−3.38 (m, 1H), 2.67 (br m, 1H), 2.22−2.05 (m, 4H), 2.01 (dd, J = 15.2, 5.5 Hz, 1H, minor diastereomer), 1.95 (dd, J = 14.8, 5.5 Hz, 1H, major diastereomer), 1.74−1.43 (m, 5H), 1.40−1.09 (m, 5H), 1.06 (s, 3H, minor diastereomer) and 1.05 (s, 3H, major diastereomer), 1.04 (s, 9H, major diastereomer) and 1.03 (s, 9H, minor diastereomer); ^{13}C NMR (50 MHz, $CDCl_3$) major diastereomer δ 214.2, 212.8, 135.5, 134.2, 129.5, 127.5, 112.2, 110.7, 66.4, 65.3, 65.0, 64.5, 63.7, 60.6, 45.6, 44.6, 39.7, 32.6, 27.6, 27.1, 26.8, 25.6, 23.5, 20.3, 19.2, 18.6, 17.6; minor diastereomer 212.8, 210.1, 135.5, 134.0, 129.3, 127.5, 111.1, 110.7, 65.6, 65.0, 64.0, 60.4, 45.2, 44.2, 35.9, 32.5, 27.4, 26.7, 25.4, 23.2, 20.0, 19.2, 18.6, 17.6; FTIR (neat/NaCl) 3067, 3047, 2950, 2932, 2880, 2856, 1732, 1707, 1690, 1460, 1424, 1377,

1136 cm^{-1}; exact mass [HRMS (CI/CH_4)] calcd for $C_{37}H_{50}O_7Si$ $[M + H]^+$: 635.3404, found: 635.3385.

4-(4-Hydroxylbutyl)-5,5-*O*-ethylene-5,5-dihydroxy-1-(2-methyl-1,3-dioxolan-2-yl)bicyclo[5.3.1]undecane-2,6-dione (21b). To neat mixed diones **21a** (200 mg, 0.31 mmol) was added TBAF (1 M solution in THF, 1 mL, 1 mmol) at room temperature. The reaction was complete by TLC after stirring for 3 h. Water (1 mL) was added, and the aqueous layer was extracted with methylene chloride (5 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on silica gel (20% ethyl acetate/pentane) afforded 117 mg (0.29 mmol, 95%) of separable alcohols (2.5:1). Major diastereomer **21b**: TLC (SiO_2, 20% ethyl acetate/pentane, vanillin) $R_f = 0.20$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12−3.88 (m, 7H), 3.75 (m, 1H), 3.63 (t, J = 6.5 Hz, 2H), 3.47 (dd, J = 14.7, 2.4 Hz, 1H), 3.41 (app t, J = 13 Hz, 1H), 2.68 (br s, 1H), 2.09 (m, 3H), 1.94 (dd, J = 14.7, 5.5 Hz, 1H), 1.75 (m, 2H), 1.55 (m, 4H), 1.42−1.23 (m, 4H), 1.15 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.3, 212.8, 112.2, 110.7, 66.5, 65.4, 65.0, 64.4, 62.8, 60.5, 44.5, 44.2, 39.8, 32.7, 27.4, 27.1, 26.7, 25.6, 23.2, 20.3, 17.6; FTIR (neat/NaCl) 3422, 2936, 2879, 1731, 1708, 1693, 1460, 1378, 1101 cm^{-1}; exact mass [HRMS (CI/NH_3)] calcd for $C_{21}H_{32}O_7$ $[M + H]^+$: 396.2226, found: 396.2227.

4-(4-Iodobutyl)-5,5-*O*-ethylene-5,5-dihydroxy-1-(2-methyl-1,3-dioxolan-2-yl)bicyclo[5.3.1]undecane-2,6-dione (22). To a stirring solution of alcohol **21b** (8 mg. 0.02 mmol), methanesulfonyl chloride (2.3 μL, 0.03 mmol), and DMAP (2 mg) in CH_2Cl_2 (0.5 mL) at 0 °C was added NEt_3 (4.3 μL, 0.03 mmol). After 1 h, saturated NH_4Cl (0.5 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (5 × 1 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude mesylate was carried on without further purification. TLC (SiO_2, 100% ether, vanillin) $R_f = 0.20$.

To a stirring solution of crude mesylate (9 mg, 0.02 mmol) in acetone (0.5 mL) at 0 °C was added sodium iodide (4.5 mg, 0.03 mmol). The reaction was allowed to warm to room temperature where it stirred for 8 h. Saturated $NaHCO_3$ (0.5 mL) was added, and the aqueous layer was extracted with ether (5 × 1 mL). The combined organic layers were washed with sodium bisulfite (3 mL), dried ($MgSO_4$), and concentrated *in vacuo*. Chromatography on silica gel (100% ether) afforded 8 mg (0.016 mmol) of pure iodide **22** (80%). TLC (SiO_2, 100% ether, vanillin) $R_f = 0.55$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10−3.88 (m, 7H), 3.75 (m, 1H), 3.44 (m, 2H), 3.16 (t, J = 7 Hz, 2H), 2.66 (br s, 1H), 2.14−2.01 (m, 4H), 1.94 (dd, J = 14.7, 5.3 Hz, 1H), 1.88−1.67 (m, 3H), 1.58−1.50 (m, 2H), 1.42−1.23 (m, 3H), 1.14 (m, 2H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.1, 212.7, 112.2, 110.7, 66.5, 65.4, 65.1, 64.5, 60.5, 44.3, 44.2, 39.9, 33.5, 27.9, 27.1, 26.7, 26.6, 25.6, 20.4, 17.6, 6.8; FTIR (neat/NaCl) 2945, 2890, 1702, 1698, 1596, 1485, 1230, 1150 cm^{-1}.

9,9-*O*-Ethylene-9,9-dihydroxy-1-(2-methyl-1,3-dioxolan-2-yl)tricyclo[9.3.1.0^{3,8}]pentadecane-2,10-dione (3). To a stirring solution of *n*-BuLi (1.6 M solution in hexanes, 18 μL, 0.03 mmol) in THF (0.5 mL) was added diisopropylamine (4.2 μL, 0.03 mmol) at −78 °C. After 20 min the dione **22** (4 mg, 0.008 mmol) in THF (0.25 mL) was added and stirred at −78 °C for 1 h. The solution was warmed to 0 °C for 5 min and then allowed to warm to room temperature for 5 min. The reaction was quenched with saturated NH_4Cl (1 mL), and the layers were separated. The aqueous layer was extracted with ether (5 × 1 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified on silica gel (100% ether/pentane) to afford 2 mg (0.005 mmol) of pure tricyclic dione **3** (63%). TLC (SiO_2, 100% ether, vanillin) $R_f = 0.7$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.22−3.88 (m, 7H), 3.70 (app q, J = 6.5 Hz, 1H,), 3.46 (m, 2H), 2.67 (br s, 1H), 2.09 (m, 2H), 2.00 (m, 1H), 1.92 (dd, J = 14.6, 5.5 Hz, 1H), 1.75−1.60 (m, 3H), 1.48−1.11 (m, 9H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5, 212.9, 112.0, 110.7, 66.8, 65.5, 64.9, 64.4, 60.3, 46.9, 46.6, 44.0, 30.6, 29.7, 27.5, 26.1, 25.5, 24.8, 24.0, 20.7, 17.4; FTIR (neat/NaCl) 3054, 2928, 2855, 1733, 1714, 1692, 1463, 1265, 1040 cm^{-1}; exact mass [HRMS (CI/CH_4)] calcd for $C_{21}H_{30}O_6$ $[M + H]^+$: 379.21206, found: 379.21169.

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Supporting Information Available: Spectral data for compounds **3**, **4**, **5a**, **5b**, **6**, **7**, **9**, **10**, **11**, **12**, **13**, **14**, **16a**, **16b**, **17**, **19**, **20**, **21a**, **21b**, and **22**, as well as HMQC TOCSY for **17** and decoupling and NOE data for the α-alkylated isomer of enone **4** [alkyl group = $(CH_2)_4$OTBDPS] (94 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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