Mapping the Chemical Reactivity of Polyquinanes Produced by 2-fold Addition of Vinyl Anions to Squarate Esters. A Bicyclic Case Study

Tina M. Morwick[1] and Leo A. Paquette*

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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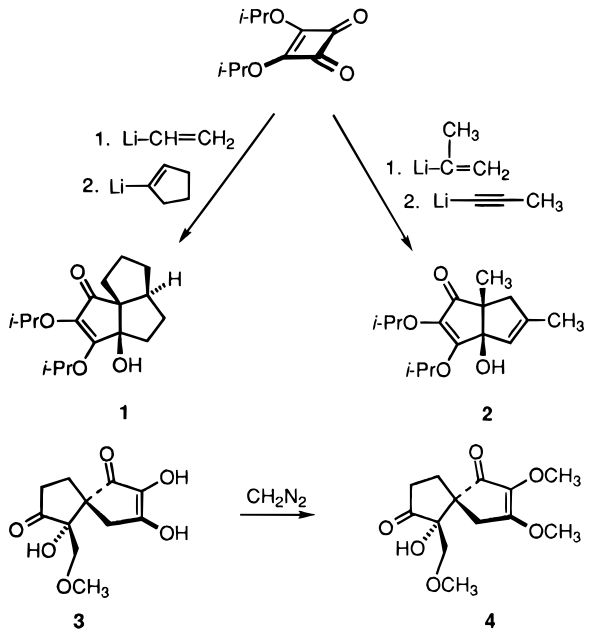
A highly oxygenated diquinane representative of the product class obtained from the condensation of squarate esters with a pair of vinyl anions has been subjected to a battery of chemical reactions for the purpose of achieving utilitarian functional group transformations. Reduction with lithium aluminum hydride proceeds predominantly, but not exclusively, by 1,4-reduction. Dehydration of the γ-hydroxy-α,β-(bisalkoxy)cyclopentenone to extend conjugation into the B ring was achieved via chlorination and subsequent removal of HCl. Access to dienone **12** in this manner has opened the door to reductive removal of the γ-hydroxyl substituent, to angular methylation, and to allied chemical changes. The global results disclose that the previously unknown functional group array present in **5** and its congeners is amenable to convenient modification, thereby providing the backdrop for more advanced annulation and structural elaboration. The prospects for utilization of the several new compound types as serviceable building blocks are considered to be numerous.

The polyquinanes formed directly upon reaction of squarate esters with vinyl or acetylenic anions[2−6] offer the prospect of serving as useful starting materials for the synthesis of a wide variety of cyclic compounds. The remarkable scaffolding which accompanies the rapid conversion of these achiral reactants into structural assemblies that possess several stereogenic centers is illustrated for **1** and **2**. A noteworthy feature of these products is the resident γ-hydroxy-α,β-bis(alkoxy)cyclopentenone functional array. To our knowledge, this oxygenation pattern has not been described elsewhere. A close analogy is found in the dimethyl ether **4**, produced by treatment of gloiosiphone A (**3**) with diazomethane in order to facilitate its isolation.[7a] Additional relatives have been produced from chemical modification of squarates by others.[7b] As a consequence, a working knowledge of the chemical potential of this motif gains importance on its own merit.

For our present purposes, chemical manipulation has been selectively directed toward the acquisition of substrates which might prove amenable to more advanced annulation and structural modification. The diquinane **5**[8] was selected for this pilot investigation because its readily identifiable angular methyl and methine protons provide an especially time-efficient means for establishing carbon−carbon connectivity via semiselective DEPT experiments at 300 MHz.



Results and Discussion

The reduction of **5** with lithium aluminum hydride was examined first. Stirring of the two reactants in THF at 0−20 °C for a short time led to the isolation of **8** (56%) and **9** (16%) (Scheme 1). The identity of the major alcohol as the product of initial 1,4-addition was secured by oxidation to **10** with the Dess−Martin reagent[9] and NMR analysis of this ketone by means of semiselective DEPT studies.[10] In particular, irradiation of the singlet at δ 1.11 attributable to the angular methyl substituent gave rise to an intense response from the carbonyl carbon at 206.4 ppm in the ^{13}C subspectrum. This phenomenon,

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(5) Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799.

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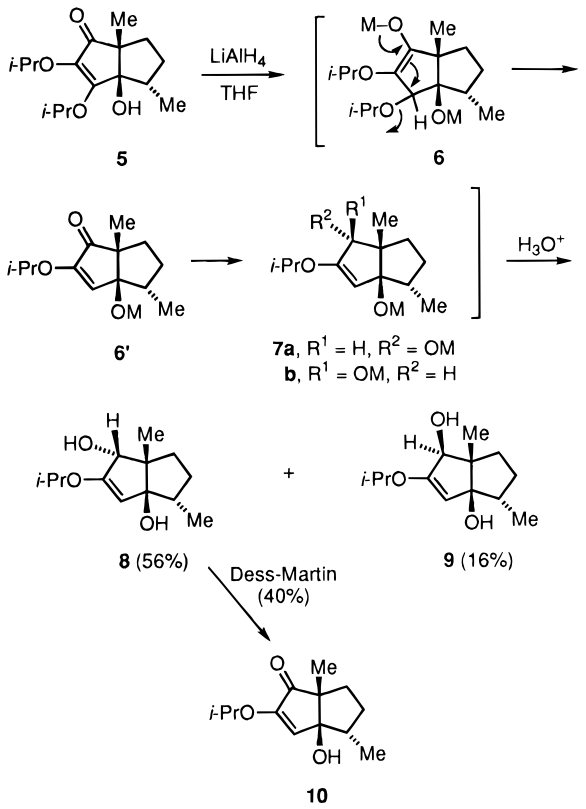
Scheme 1

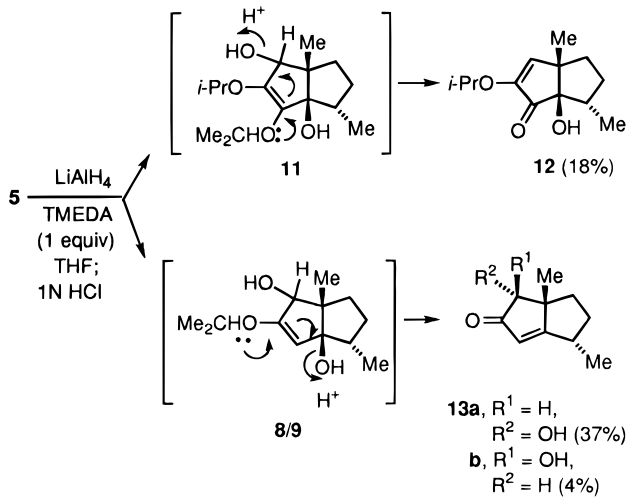


due to effective three-bond coupling, requires that the interacting groups be related by dihedral angles approaching 0° or 180°. Alcohol **9** was shown to be epimeric to **8** by related semiselective DEPT studies (see Experimental Section). The substitution pattern in **8** and **9** presumably reflects the fact that $LiAlH_4$ adds to **5** in kinetically-controlled 1,4-fashion perhaps via complexation to the angular hydroxyl and β-alkoxy substituents to deliver enolate anion **6**, which finds it possible to eject the allylic isopropoxy group by means of conventional β-elimination. Reduction of ketone **6′** proceeds in the 1,2-mode, with attack from the β-face predominating for obvious steric reasons. The salient feature of the two-step conversion of **5** to **10** is that removal of the β-alkoxy substituent can be readily achieved in a fully controlled manner.

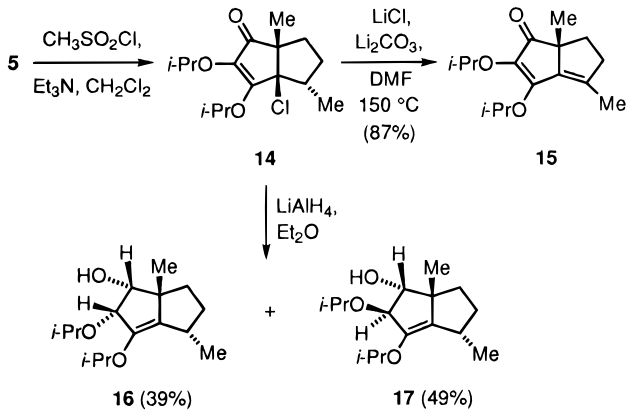
In an attempt to divert the regioselectivity of the initial reduction away from the 1,4-mode, chelating reagents were introduced in order to saturate the chelation sites on lithium (Scheme 2). With the inclusion of 1 equiv of tetramethylethylenediamine, 1,2-reduction was indeed accommodated as seen by the formation of **12**, but only to the 18% level. The predominant pathway continued to be that depicted in Scheme 1, producing **13a** and **13b** in 37% and 4% yield, respectively, after hydrolysis with 1 N hydrochloric acid.

Attention was next turned to the dehydration of **5** in order to extend conjugation into the adjacent ring. To this end, **5** was treated with methanesulfonyl chloride and triethylamine in CH_2Cl_2 as solvent (Scheme 3). It was anticipated that direct conversion to **15** would ensue. Instead, the corresponding chloride **14** resulted. The tertiary nature of this chloride and the retention of stereochemistry operative in this conversion would implicate the intervention of a carbocationic intermediate γ to the carbonyl of the enone. Indeed, the substitution pattern in this putative cation allows for stabilization to

Scheme 2



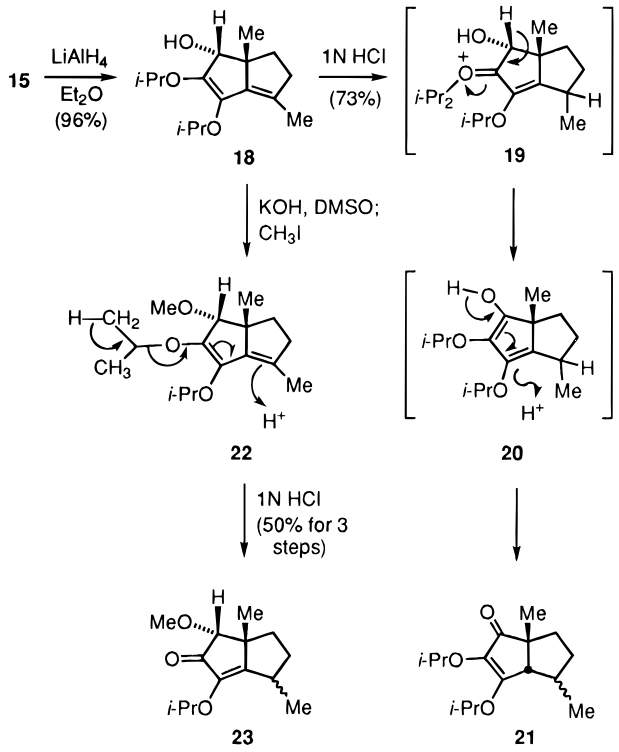
Scheme 3



materialize by electron donation through the double bond from the isopropoxy oxygen positioned α to the carbonyl. Chloride **14** was routinely converted without purification to **15** by heating with lithium chloride and lithium carbonate in DMF. The overall yield was 87%. Consequently, the introduction of added unsaturation does not appear to be problematic. The reduction of chloride **14** with $LiAlH_4$ in ether proceeds in an interesting manner. Evidently, chloride ion is first displaced by S_N' attack of hydride at the position α to the carbonyl to give a β,γ-unsaturated enone which experiences second-stage reduction from the β-face to deliver **16** (35%) and **17** (49%). Operation of the S_N' mechanism indicates that the site of nucleophilic attack is more electron deficient than usual, thereby lending credence to the concept advanced above that the carbocation precursor to **14** may well be stabilized by charge delocalization from the attached oxygen. The α-position is more distant from the site of the ring fusion and consequently hydride attack on the double bond is no longer stereoselective.

The next phase of the effort involved probing the chemistry associated with dienone **15**. This intermediate was treated with $LiAlH_4$ in ether, the logic being that arrival at carbinol **18** would constitute the first stage of producing the transposed α-alkoxy enone. While **18** was indeed produced in essentially quantitative yield, the subsequent acidic hydrolysis of this unstable product triggered a more deep-seated series of events than originally projected (Scheme 4). Instead of protonation at hydroxyl oxygen and ionization with loss of water, the conjugation afforded by the diene provides for kinetically

Scheme 4



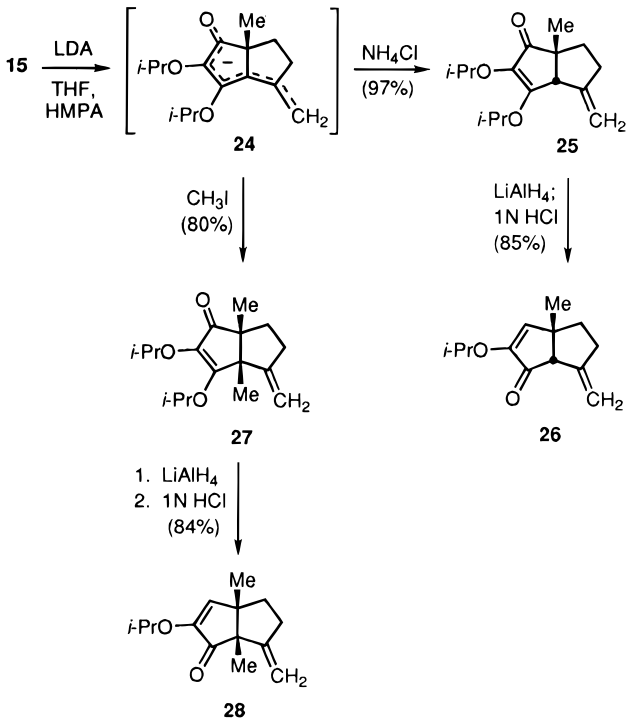
relevant protonation at the methyl-substituted terminus and generation of oxonium ion **19**. Once this has occurred, formation of dienol **20** can be envisioned by loss of a proton. The latter on reprotonation gives rise to **21** as an 8:1 mixture of epimers.

If the timing of events in this mechanistic cascade has been accurately portrayed, then the possibility appeared open for redirecting events merely by O-alkylation of the hydroxyl group in **18**. The conversion to **22** could be implemented without difficulty. Since the ensuing protonation should position positive charge on one of the isopropoxy oxygens as reflected in **19** and proton loss from an enol is no longer possible, dealkylation could operate to provide a route to distinctively different enone **23**. Indeed, **23** was obtained in 50% overall yield from **15** as a 2:1 mixture of diastereomers.

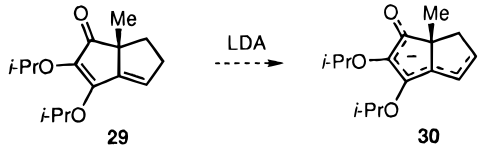
Notwithstanding the opportunities offered by the acquisition of **23**, a means for effecting 1,3-carbonyl transposition had not yet been secured. We came to favor a route wherein **15** would be deprotonated to generate the extended enolate **24**, protonation or alkylation of which should be directed to a site closer to the carbonyl. Once the structural change of this type had been accomplished (Scheme 5), the expectation was that the isolated α,β-dialkoxy enone chromophore should exhibit conventional reactivity.

At the experimental level, the deconjugative protonation to give **25** (97%) and methylation to afford **27** (80%) proved to be highly efficient and regioselective processes. When this pair of intermediates were subjected in turn to hydride reduction and workup with 1 N HCl, smooth conversion to **26** (85%) and **28** (84%) was noted. The practicality of this sequence is obviously high. Furthermore, the information gained from these studies may prove relevant to simpler analogs such as **29** that lack the secondary methyl substituent. In such examples, the relevant issue is whether deprotonation will occur as readily *within* the unsubstituted five-membered ring and

Scheme 5



permit equally convenient access to the delocalized anion **30**. These studies are in progress.



Conclusion

The inherent strength of the transformations outlined herein is that usefully substituted diquinanes are generatable from very simple starting materials. Coupling of the "squarate ester cascade" to no more than two additional synthetic steps leads effectively from the γ-hydroxy-α,β-bis(alkoxy)cyclopentenone part structure to a broad range of functionalized intermediates. The tactics lend themselves conveniently to advanced molecular construction, including the elaboration of natural products. We hope to be in a position to report on applications of this methodology in the near future.

Experimental Section[11]

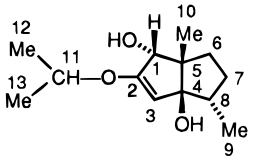
(1*R,3a*S**,4*S**,6a*S**)-1,5,6,6a-Tetrahydro-2-isopropoxy-4,6a-dimethyl-1,3a(4*H*)-pentalenediol (8) and (1*R**,3a*R**,4*R**,6a*R**)-1,5,6,6a-Tetrahydro-2-isopropoxy-4,6a-dimethyl-1,3a(4*H*)-pentalenediol (9).** A cold (0 °C), magnetically stirred suspension of $LiAlH_4$ (44 mg, 1.16 mmol) in 5 mL of dry THF was treated under argon via cannula with a solution of **5** (143 mg, 0.51 mmol) in THF (5 mL) also cooled to 0 °C. The reaction mixture was stirred at 0 °C for 45 min and at rt for 30 min before being returned to 0 °C and treated with methanol (3 drops) and 10% Rochelle's salt solution (10 mL). After 30 min of stirring, brine (25 mL) was added, and the products were extracted into ether (2 × 25 mL). The combined organic phases were washed with brine, dried, and concentrated. The residue was subjected to flash chromatography

(11) The general experimental protocols followed in this study parallel those described in a recent report: Paquette, L. A.; Ezquerra, J.; He, W. *J. Org. Chem.* **1995**, *60*, 1435.

on silica gel (elution with 30 → 50% ethyl acetate in hexanes) to give 65 mg (56%) of **8** and 19 mg (16%) of **9**.

For **8**: colorless solid, mp 82−84 °C; IR (film, cm^{-1}) 3410, 1650; ^1H NMR (300 MHz, C_6D_6) δ 4.34 (s, 1 H), 4.27 (s, 1 H), 3.93 (hept, J = 6 Hz, 1 H), 2.54−2.47 (m, 1 H), 2.36 (s, 1 H), 1.90 (qd, J = 13, 6.6 Hz, 1 H), 1.58−1.50 (m, 1 H), 1.24−1.09 (m, 2 H), 1.13 (s, 3 H), 1.07 (d, J = 6 Hz, 3 H), 1.06 (d, J = 7 Hz, 3 H), 1.02 (d, J = 6 Hz, 3 H) (OH signal not seen); ^{13}C NMR (75 MHz, C_6D_6) ppm 160.7, 97.4, 90.9, 81.4, 71.6, 50.6, 44.3, 31.9, 31.2, 24.2, 21.7, 21.2, 14.0; MS m/z (M^+) calcd 226.1569, obsd 226.1564.

For **9**: colorless solid, mp 118−120 °C; IR ($CHCl_3$, cm^{-1}) 3596, 1643; ^1H NMR (300 MHz, $CDCl_3$) δ 4.55 (s, 1 H), 4.24 (hept, J = 6 Hz, 1 H), 3.96 (s, 1 H), 1.93−1.85 (m, 2 H), 1.66−1.51 (m, 4 H), 1.29 (d, J = 6 Hz, 3 H), 1.28 (d, J = 6 Hz, 3 H), 1.02 (s, 3 H), 0.98 (d, J = 7 Hz, 3 H), 0.99−0.87 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 160.9, 99.3, 91.4, 82.6, 71.7, 50.8, 42.6, 38.9, 30.1, 21.5, 21.3, 17.9, 14.7; MS m/z (M^+) calcd 226.1569, obsd 226.1568.



Irradiate	Observe	% NOE
H-3	H-11	13.4
	H-12,13	5.9
H-1	H-10	4.8
H-6	H-1	3.3
H-10	H-1	14.8
	H-8	4.3
H-8	H-10	0.6

Semiselective DEPT for **8**: irradiate H-8 (δ 1.89), observe C-3 (97.4 ppm, ^3J), C-4 (90.9 ppm, ^2J), C-7 (31.2 ppm, ^2J), and C-9 (14.0, ppm, ^2J); irradiate H-10 (δ 1.13), observe C-4 (90.6 ppm, ^3J), C-1 (81.4 ppm, ^3J), C-5 (50.3 ppm, ^2J), and C-6 (31.6, ppm, ^3J).

Semiselective DEPT for **9**: irradiate H-10 (δ 1.02), observe C-4 (91.4 ppm, ^3J), C-1 (82.6 ppm, ^3J), C-5 (50.8 ppm, ^2J), and C-6 (38.9, ppm, ^3J).

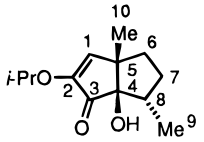
(3a*R,4*R**,6a*S**)-4,5,6,6a-Tetrahydro-3a-hydroxy-2-isopropoxy-4,6a-dimethyl-1(3a*H*)-pentalenone (10).** To a solution of **8** (10 mg, 0.044 mmol) in CH_2Cl_2 (3 mL, distilled from CaH_2) was added 75 mg (4 equiv) of the Dess−Martin reagent[9] in a single portion. The reaction mixture was stirred at rt for 3 h, diluted with ether (25 mL), washed with saturated $NaHCO_3$ (25 mL) and 10% $NaHSO_3$ solutions (25 mL) and brine (25 mL), and then dried and evaporated. Flash chromatography (elution with 10% ethyl acetate in dichloromethane) furnished 4 mg (40%) of **10** as a colorless oil: IR (neat, cm^{-1}) 3420, 1712, 1622; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 4.36 (hept, J = 6 Hz, 1 H), 2.01−1.93 (m, 2 H), 1.60 (ddd, J = 12, 6, 6 Hz, 1 H), 1.50−1.40 (m, 2 H), 1.35 (d, J = 6 Hz, 3 H), 1.33 (d, J = 6 Hz, 3 H), 1.11 (s, 3 H), 1.07 (d, J = 7 Hz, 3 H), 0.88−0.75 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.4, 155.8, 124.7, 85.3, 72.8, 55.7, 44.3, 35.9, 30.1, 21.5, 21.1, 19.3, 14.1; MS m/z (M^+) calcd 224.1412, obsd 224.1421.

Semiselective DEPT: irradiate angular methyl protons (δ 1.11): observe C=O (206.4 ppm, ^3J).

(3a*R,6*R**,6a*S**)-4,5,6,6a-Tetrahydro-6a-hydroxy-2-isopropoxy-3a,6-dimethyl-1(3a*H*)-pentalenone (12) and (1*R**/1*S**,4*S**,6a*R**)-4,5,6,6a-Tetrahydro-1-hydroxy-4,6a-dimethyl-2(1*H*)-pentalenone (13a and 13b).** A magnetically stirred slurry of $LiAlH_4$ (32 mg, 0.86 mmol) in dry THF (4 mL) was cooled to 0 °C and treated with TMEDA (0.15 mL, 1 mmol). After 30 min, a cold (0 °C) solution of **5** (105 mg, 0.38 mmol) in the same solvent (5 mL) was introduced via cannula, and the reaction mixture was stirred at 0 °C for 15 min and at rt for 30 min before being returned to 0 °C and carefully quenched with 1 N HCl (1 mL). After 2 h of agitation at rt, the mixture was diluted with brine (15 mL) and extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried, and evaporated to leave an oil which was purified by MPLC on silica gel. Elution with 25% ethyl acetate in hexanes afforded 15 mg (18%) of **12**, 23.5 mg (37%) of **13a**, and 2.5 mg (4%) of **13b**.

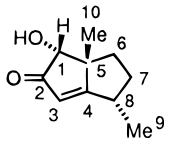
The preferable way to produce pure **13a** and **13b** is to hydrolyze **8** and **9** independently.

For **12**: colorless crystals, mp 127−128 °C; IR ($CHCl_3$, cm^{-1}) 3553, 1715, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 6.00 (s, 1 H), 4.32 (hept, J = 6 Hz, 1 H), 2.70 (s, 1 H), 2.02 (m, 1 H), 1.68−1.60 (m, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.29 (d, J = 6 Hz, 3 H), 1.15 (s, 3 H), 1.13−0.98 (m, 1 H), 0.91 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.1, 153.0, 135.7, 86.1, 71.9, 51.0, 46.9, 36.9, 30.4, 22.2, 21.3, 21.2, 14.9; MS m/z (M^+) calcd 224.1412, obsd 224.1414.



Semiselective DEPT: irradiate H-10 (δ 1.15), observe C-1 (135.7 ppm, ^3J), C-4 (86.1 ppm, ^3J), C-5 (51.0 ppm, ^2J), and C-6 (36.9, ppm, ^3J); irradiate H-8 (δ 2.04), observe C-3 (204.1 ppm, ^3J), C-4 (^2J), C-2 (30.4 ppm, ^2J), and C-9 (14.8, ppm, ^2J).

For **13a**: colorless solid, mp 72−73 °C; IR (film, cm^{-1}) 3413, 1709, 1623; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (d, J = 2 Hz, 1 H), 3.84 (s, 1 H), 3.18 (s, 1 H), 3.04−2.95 (m, 1 H), 2.47−2.33 (m, 1 H), 2.09−1.95 (m, 1 H), 1.53−1.40 (m, 2 H), 1.196 (s, 3 H), 1.193 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.5, 200.1, 118.8, 79.3, 53.5, 33.0, 31.5, 27.5, 26.2, 17.3; MS m/z (M^+) calcd 166.0994, obsd 166.0999.



Semiselective DEPT: irradiate H-1 (δ 3.84), observe C-4 (200.1 ppm, ^3J) and C-10 (26.2, ppm, ^3J); irradiate H-8 (δ 2.99), observe C-4 (^2J), C-3 (118.8 ppm, ^3J), C-6 or C-7 (31.5 ppm, ^2J or ^3J), and C-9 (17.3, ppm, ^2J); irradiate H-3 (δ 5.71), observe C-2 (210.5 ppm, ^2J), C-4 (^2J), C-1 (79.3 ppm, ^3J), and C-5 (53.5, ppm, ^3J).

For **13b**: colorless solid, mp 72−73 °C; IR ($CHCl_3$, cm^{-1}) 3540, 1710, 1620; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (d, J = 2 Hz, 1 H), 3.94 (s, 1 H), 2.99−2.96 (m, 1 H), 2.46−2.35 (m, 1 H), 1.90 (ddd, J = 13, 8, 4 Hz, 1 H), 1.67 (ddd, J = 13, 13, 8 Hz, 1 H), 1.53−1.42 (m, 1 H), 1.21 (d, J = 7 Hz, 3 H), 1.07 (s, 3 H) (OH signal not observed); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 196.5, 118.2, 84.6, 54.3, 34.9, 32.9, 32.3, 22.1, 17.7; MS m/z (M^+) calcd 166.0994, obsd 166.0994.

(3a*R,4*S**,6a*S**)-3a-Chloro-4,5,6,6a-tetrahydro-2,3-diisopropoxy-4,6a-dimethyl-1(3a*H*)-pentalenone (14).** An argon-blanketed solution of **5** (1.20 g, 4.25 mmol) and triethylamine (3.5 mL, 25.6 mmol) in CH_2Cl_2 (40 mL) was cooled to 0 °C and treated dropwise with 0.72 and 0.60 mL portions (2.4 equiv) of methanesulfonyl chloride at an interval of 30 min. The reaction mixture was stirred for an additional 30 min at 0 °C and then diluted with water (50 mL). The separated aqueous phase was extracted with CH_2Cl_2 (25 mL), and the combined organic layers were washed sequentially with water (25 mL), 1 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (25 mL) prior to drying and solvent evaporation. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) yielded **14** containing a small amount of **15**. This oily material was generally used directly. A pure sample of **14** could be acquired by flash chromatography on silica gel (elution with 3% ethyl acetate in CH_2Cl_2).

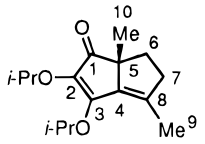
For **14**: IR (neat, cm^{-1}) 1703, 1619; ^1H NMR (300 MHz, C_6D_6) δ 5.34−5.22 (m, 2 H), 2.16 (qdd, J = 5.6, 1.2, 19.5 Hz, 1 H), 2.08 (dd, J = 12, 6 Hz, 1 H), 1.36 (s, 3 H), 1.32−1.21 (m, 1 H), 1.19−1.10 (m, 1 H), 1.15 (d, J = 6 Hz, 3 H), 1.13 (d, J = 6 Hz, 3 H), 1.10 (d, J = 7 Hz, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.05 (d, J = 6 Hz, 3 H), 0.92−0.78 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.8, 163.4, 133.8, 79.4, 73.9, 71.4, 56.9, 49.6, 35.3,

30.9, 22.6, 22.3 (2 C), 22.1, 14.8 (one methyl C masked); MS *m/z* (M^+) calcd 300.1492, obsd 300.1513.

Anal. Calcd for $C_{16}H_{25}ClO_3$: C, 63.97; H, 8.39. Found: C, 64.08; H, 8.43.

6,6a-Dihydro-2,3-diisopropoxy-4,6a-dimethyl-1(*H*)-pentalenone (15). Lithium chloride (1.09 g, 25.7 mmol, dried by heating at 140 °C and 5 Torr for 3 h) and lithium carbonate (2.10 g, 28.4 mmol) were added to DMF (50 mL, freshly distilled from CaH_2 at 70 Torr), and the mixture was heated to 120 °C. A solution of impure **14** from the previous experiment dissolved in dry DMF (15 mL) was introduced, and the stirred mixture was heated at 150 °C for 5 h, cooled to rt, diluted with ether (100 mL), and filtered through a pad of Celite. The filtrate was washed with brine (3 × 25 mL), dried, and evaporated to leave a solid which was purified by chromatography on silica gel (elution with 3% ethyl acetate in dichloromethane). There was isolated 978 mg (87% for two steps) of **15** as a colorless, crystalline solid, mp 90−91 °C (from ether/hexanes): IR ($CHCl_3$, cm^{-1}) 1682, 1568; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (hept, J = 6 Hz, 1 H), 4.91 (hept, J = 6 Hz, 1 H), 2.88−2.77 (m, 1 H), 2.22 (ddd, J = 8.2, 7.5, 0.7 Hz, 1 H), 1.91 (dd, J = 0.7, 1.8 Hz, 1 H), 1.84−1.73 (m, 1 H), 1.66 (dd, J = 12, 6 Hz, 1 H), 1.36 (d, J = 6 Hz, 3 H), 1.31 (d, J = 6 Hz, 3 H), 1.26 (d, J = 6 Hz, 3 H), 1.23 (s, 3 H), 1.20 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.5, 159.5, 136.8, 135.1, 132.2, 73.3, 71.9, 56.5, 39.6, 31.4, 23.2, 22.8, 22.4, 14.7 (two methyl C masked); MS *m/z* (M^+) calcd 264.1725, obsd 264.1712.

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.98; H, 9.33.

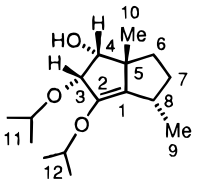


Semiselective DEPT: irradiate H-10 (δ 1.23), observe C-1 (203.5 ppm, ^3J), C-4 (136.8 ppm, ^3J), C-5 (56.5 ppm, ^2J), and C-6 (31.4, ppm, ^3J); irradiate H-9 (δ 1.91), observe C-3 (159.5 ppm, ^4J), C-4 (136.8 ppm, ^3J), C-8 (132.2 ppm, ^2J), and C-7 (39.6 ppm, ^3J).

(1*R,2*R**,4*S**,6a*R**)-1,2,4,5,6,6a-Hexahydro-2,3-diisopropoxy-4,6a-dimethyl-1-pentalenol (16) and (1*R**,2*S**,4*S**,6a*R**)-1,2,4,5,6,6a-Hexahydro-2,3-diisopropoxy-4,6a-dimethyl-1-pentalenol (17).** A magnetically stirred slurry of $LiAlH_4$ (4 mg, 0.1 mmol) in anhydrous ether (2 mL) was cooled to 0 °C, treated via cannula with a solution of **14** (17 mg, 0.057 mmol) in the same solvent (1 mL), stirred at 0 °C for 45 min, and treated sequentially with methanol (1 drop) and 10% Rochelle's salt solution (5 mL). After 30 min of additional stirring, the mixture was diluted with brine (5 mL) and ether (5 mL), and the separated aqueous phase was extracted with ether (10 mL). The combined organic layers were washed with brine (15 mL), dried, and evaporated. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) yielded 6.0 mg (39%) of **16** and 7.5 mg (49%) of **17**.

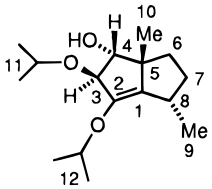
For **16**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3508, 1685, 1455; ^1H NMR (300 MHz, C_6D_6) δ 4.52 (dd, J = 4, 3.4 Hz, 1 H), 4.10 (hept, J = 6 Hz, 1 H), 3.87 (dd, J = 4, 2.7 Hz, 1 H), 3.47 (hept, J = 6 Hz, 1 H), 3.06 (d, J = 2.7 Hz, 1 H), 2.49−2.41 (m, 2 H), 2.20−2.07 (m, 1 H), 1.50−1.40 (m, 1 H), 1.27 (d, J = 7 Hz, 3 H), 1.26−1.13 (m, 1 H), 1.14 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H), 1.03 (d, J = 6 Hz, 3 H), 0.99 (d, J = 6 Hz, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 142.4, 134.8, 84.2, 76.5, 72.2, 71.1, 55.1, 35.5, 31.0, 29.2, 24.7, 23.0, 22.8, 22.5, 22.3, 19.0; MS *m/z* (M^+) calcd 268.2038, obsd 268.2036.

For **17**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3612, 1696, 1454; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (s, 1 H), 4.15 (hept, J = 6 Hz, 1 H), 3.74 (hept, J = 6 Hz, 1 H), 3.65 (s, 1 H), 2.63−2.52 (m, 1 H), 2.37−2.23 (m, 1 H), 1.79−1.72 (m, 1 H), 1.60 (s, 1 H), 1.52−1.43 (m, 1 H), 1.24 (d, J = 6 Hz, 3 H), 1.27−1.09 (m, 1 H), 1.18 (d, J = 6 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.16 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.13 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.4, 137.3, 90.3, 77.8, 71.2, 70.6, 56.2, 36.2, 29.7, 28.7, 26.2, 23.3, 22.7, 22.4, 22.1, 18.4; MS *m/z* (M^+) calcd 268.2038, obsd 268.2028.



Irradiate	Observe	% NOE
H-10	H-3	5.6
	H-4	10.2
	H-7β	3.5
H-9	H-7α	3.6
H-7α	H-9	2.0
H-4	H-10	3.5
H-3	H-4	6.5
	H-10	2.1

The semiselective DEPT for **16** is very similar to that for **17**.

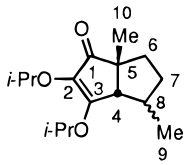


Semiselective DEPT for **17**: irradiate H-4 (δ 3.65), observe C-2 (143.4 ppm, ^3J), C-1 (137.3 ppm, ^3J), and C-10 (26.2 ppm, ^3J); irradiate H-3 (δ 4.18), observe C-2 (^2J), C-1 (^3J), C-4 (77.8 ppm, ^2J), C-11 (71.2 ppm, ^3J), and C-5 (56.2 ppm, ^3J); irradiate H-8 (δ 2.58), observe C-2 (^3J), C-1 (^2J), and C-9 (18.4 ppm, ^2J); irradiate H-6 (δ 1.74), observe C-4 (^3J), C-5 (56.2 ppm, ^2J), C-7 (36.2 ppm, ^2J), C-8 (29.7 ppm, ^3J), and C-10 (26.2 ppm, ^3J); irradiate H-7α (δ 1.47), observe C-1 (^3J), C-5 (^3J), C-6 (28.7 ppm, ^2J), C-8 (^2J), and C-9 (18.4 ppm, ^3J).

(1*R,6a*R**)-1,5,6,6a-Tetrahydro-2,3-diisopropoxy-4,6a-dimethyl-1-pentalenol (18).** A 16 mg (0.033 mmol) sample of **15** in anhydrous ether (3 mL) was reduced with $LiAlH_4$ (1.25 mg, 0.033 mmol) in the manner described above. Flash chromatography of the crude product on silica gel (elution with 10% ethyl acetate in hexanes) afforded 15.5 mg (96%) of **18** as a colorless oil: IR (neat, cm^{-1}) 3486, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (hept, J = 6 Hz, 1 H), 4.30 (s, 1 H), 4.28 (hept, J = 6 Hz, 1 H), 2.73−2.61 (m, 1 H), 2.18 (ddd, J = 16, 8, 0.7 Hz, 1 H), 1.88 (s, 1 H), 1.76 (dd, J = 0.8, 0.8 Hz, 3 H), 1.78−1.60 (m, 2 H), 1.28 (d, J = 6 Hz, 3 H), 1.25 (d, J = 6 Hz, 6 H), 1.19 (d, J = 6 Hz, 3 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.5, 140.1, 133.1, 121.0, 79.6, 72.1, 71.8, 56.0, 40.1, 37.1, 22.9, 22.8, 22.6, 22.0, 17.8, 14.5; MS *m/z* (M^+) calcd 266.1882, obsd 266.1881.

(3a*R,6a*S**)-4,5,6,6a-Tetrahydro-2,3-diisopropoxy-4,6a-dimethyl-1(3a*H*)-pentalenone (21).** An 82 mg (0.31 mmol) sample of **15** was reduced with $LiAlH_4$ (6.4 mg, 0.17 mmol) in anhydrous ether (6 mL) as before. The unpurified product was taken up in 4 mL of 1 N HCl, stirred overnight at rt, and diluted with brine (15 mL) and ether (15 mL). The separated aqueous layer was extracted with ether (25 mL), and the combined organic phases were dried and concentrated to leave 58 mg (70%) of **21** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1690, 1606; ^1H NMR (300 MHz, C_6D_6) δ 5.30 (hept, J = 6 Hz, 1 H), 5.29 (hept, J = 6 Hz, 1 H), 2.03 (d, J = 1.4 Hz, 1 H), 2.03−1.94 (m, 1 H), 1.60−1.49 (m, 1 H), 1.46−1.36 (m, 1 H), 1.21 (s, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.14 (d, J = 6 Hz, 3 H), 1.13 (d, J = 6 Hz, 3 H), 1.125 (d, J = 6 Hz, 3 H), 1.09 (d, J = 6 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 204.1, 169.1, 130.9, 72.8, 71.0, 57.6, 52.1, 37.2, 34.3, 32.4, 24.2, 22.8, 22.73, 22.67, 22.59, 20.6; MS *m/z* (M^+) calcd 266.1882, obsd 266.1882.

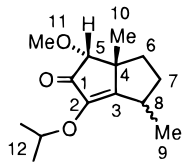
Semiselective DEPT: irradiate H-10 (δ 1.19), observe C-1 (205.5 ppm, ^3J), C-4 (57.2 ppm, ^3J), C-5 (51.8 ppm, ^2J), and C-6 (33.8 ppm, ^3J); irradiate H-8 (δ 2.03), observe C-3 (170.9 ppm, ^3J), C-5 (^3J), C-6 (^3J), and C-9 (20.5 ppm, ^2J); irradiate H-4 (δ 2.10), observe C-1 (^3J), C-3 (^2J), C-2 (130.6 ppm, ^3J),



C-5 (^2J), C-8 (36.6 ppm, ^2J), C-7 (32.1 ppm, ^3J), C-10 (23.8 ppm, ^3J), and C-9 (^3J).

(1*R,6a*R**)-1,5,6,6a-Tetrahydro-2,3-diisopropoxy-1-methoxy-4,6a-dimethylpentalene (22).** A 40 mg (0.15 mmol) sample of **15** was reduced with $LiAlH_4$ in the predescribed manner. The resultant **18** was dissolved in DMSO (1 mL) and added to a slurry of finely ground KOH (34 mg, 4 equiv) in the same solvent (1 mL). After being stirred for 5 min at rt, this mixture was treated with methyl iodide (0.03 mL, 2 equiv), allowed to react for 30 min, poured into water (25 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL), dried, and evaporated to leave an oil, which was purified by chromatography on silica gel (elution with 10% ethyl acetate in hexanes). There was isolated 21 mg (50% for the two steps) of **22** as an unstable colorless oil: IR (neat, cm^{-1}) 1628; ^1H NMR (300 MHz, $CDCl_3$) δ 4.68 (hept, J = 6 Hz, 1 H), 4.33 (hept, J = 6 Hz, 1 H), 3.90 (s, 1 H), 3.34 (s, 3 H), 2.75−2.64 (m, 1 H), 2.27−2.15 (m, 1 H), 1.77 (s, 3 H), 1.77−1.67 (m, 2 H), 1.27 (d, J = 6 Hz, 3 H), 1.25 (d, J = 6 Hz, 3 H), 1.24 (d, J = 6 Hz, 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 144.0, 140.2, 134.6, 120.5, 89.1, 72.0, 71.8, 57.4, 55.3, 40.3, 38.1, 22.9, 22.8, 22.6, 22.1, 18.0, 14.3; MS *mz* (M^+) calcd 280.2038, obsd 280.2040.

(1*R,6a*R**)-4,5,6,6a-Tetrahydro-3-isopropoxy-1-methoxy-4,6a-dimethyl-2(1*H*)-pentalenone (23).** A solution of **22** (8 mg, .028 mmol) in THF (2 mL) was treated with 1 N HCl (1 mL), stirred at rt for 2 h, diluted with brine (5 mL), and extracted with ether (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried, and evaporated to leave a residue which was chromatographed on silica gel (elution with 10% ethyl acetate in hexanes) to give **23** (5 mg, 73%) as a 3:1 mixture of diastereomers: colorless oil; IR (neat, cm^{-1}) 1716, 1651; ^1H NMR (300 MHz, $CDCl_3$) δ (major isomer) 4.89−4.78 (m, 1 H), 3.51 (s, 3 H), 3.47 (s, 1 H), 2.96−2.86 (m, 1 H), 2.20 (ddd, J = 8, 8, 13 Hz, 1 H), 1.95 (dd, J = 6.7, 12 Hz, 1 H), 1.87−1.38 (m, 2 H), 1.28 (d, J = 7 Hz, 3 H), 1.21 (d, J = 6 Hz, 3 H), 1.14 (d, J = 6 Hz, 3 H), 1.08 (s, 3 H); (minor isomer) 4.89−4.78 (m, 1 H), 3.54 (s, 1 H), 3.51 (s, 3 H), 2.98−2.93 (m, 1 H), 2.41−2.34 (m, 1 H), 1.87−1.39 (m, 3 H), 1.25 (d, J = 6 Hz, 3 H), 1.23 (d, J = 7 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H), 1.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm (major isomer) 201.6, 167.2, 145.5, 91.0, 71.1, 58.7, 50.6, 38.4, 34.3, 32.5, 22.6 (2 C), 22.1, 20.4; (minor isomer) 202.0, 167.7, 145.1, 90.7, 71.3, 58.6, 51.3, 36.3, 33.7, 32.0, 22.7, 22.4, 22.0, 17.9; MS *m/z* (M^+) calcd 238.1569, obsd 238.1569.

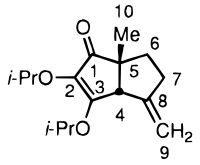


Semiselective DEPT for major isomer: irradiate H-8 (δ 2.90), observe C-3 (167.2 ppm, ^2J), and C-9 (20.4 ppm, ^2J); irradiate H-10 (δ 1.08), observe C-6 (38.4 ppm, ^3J), C-4 (50.6 ppm, ^2J), C-5 (91.1 ppm, ^3J), and C-3 (^3J).

Semiselective DEPT for minor isomer: irradiate H-10 (δ 1.02), observe C-6 (36.3 ppm, ^3J), C-4 (51.3 ppm, ^2J), C-5 (90.7 ppm, ^3J), and C-3 (167.7 ppm, ^3J); irradiate H-11 (δ 3.51), observe C-5 (^3J).

(3a*R,6a*S**)-4,5,6,6a-Tetrahydro-2,3-diisopropoxy-6a-methyl-4-methylene-1(3a*H*)-pentalenone (25).** Diisopropylamine (0.4 mL, 2.3 mmol) was dissolved in dry THF (16 mL), cooled to −15 °C, treated dropwise with *n*-butyllithium (1.4 mL of 1.6 M in hexane, 2.3 mmol), stirred for 15 min, and cooled to −78 °C before being treated dropwise via cannula with a solution of **15** (124 mg, 0.47 mmol) in dry THF (4 mL). After 30 min, HMPA (1 mL) was introduced and stirring was maintained for 15 min, at which point saturated NH_4Cl solution (6 mL) was added all at once. The reaction mixture was allowed to warm to rt, diluted with water (25 mL), and extracted with ether (2 × 25 mL). The combined organic phases were washed with 1 N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (25 mL) prior to solvent evaporation. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) furnished 120 mg (97%) of **25** as a colorless oil: IR (neat, cm^{-1}) 1699, 1617; ^1H NMR (300 MHz, $CDCl_3$) δ 5.29 (hept, J = 6 Hz, 1 H), 4.96 (dd, J = 1, 1 Hz, 1 H), 4.92 (dd, J = 1, 1 Hz, 1 H), 4.83 (hept, J = 6 Hz, 1 H), 2.83 (s, 1 H), 2.19−2.13 (m, 2 H), 2.03−1.96 (m, 1 H), 1.37−1.23 (m, 1 H), 1.30 (d, J = 6 Hz, 3 H), 1.19 (d, J = 6 Hz, 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H), 1.16 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 205.3, 168.9, 148.9, 130.9, 109.3, 73.3, 71.5, 54.5, 52.1, 34.7, 31.8, 23.0, 22.7, 22.5, 22.4, 22.3; MS *m/z* (M^+) calcd 264.1725, obsd 264.1737.

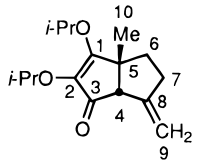
Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.67; H, 9.14.



Semiselective DEPT (C_6D_6 solution): irradiate H-9 (δ 4.92), observe C-3 (168.9 ppm, ^4J), C-4 (54.5 ppm, ^3J), C-7 (31.8 ppm, ^3J); irradiate H-9 (δ 5.03), observe C-3 (^4J), C-8 (148.9 ppm, ^2J), C-4 (^3J), C-7 (^3J); irradiate H-4 (δ 2.83): observe C-1 (205.3 ppm, ^3J), C-3 (^2J), C-8 (^2J), C-2 (130.9 ppm, ^3J), C-5 (52.3 ppm, ^2J), C-7 (^3J), C-8 (^2J), C-9 (109.3 ppm, ^3J), C-10 (23.0 ppm, ^3J).

(3a*R,6a*R**)-4,5,6,6a-Tetrahydro-2-isopropoxy-3a-methyl-6-methylene-1(3a*H*)-pentalenone (26).** A cold (0 °C), magnetically stirred slurry of $LiAlH_4$ (6 mg, 0.16 mmol) in anhydrous ether (3 mL) was treated via cannula with a solution of **25** (69 mg, 0.26 mmol) in the same solvent (5 mL). After 30 min, the reaction mixture was carefully quenched with 1 N HCl (4 mL) and stirring was maintained at rt for 9 h. After dilution with water (25 mL), the product was extracted into ether (2 × 25 mL), and the combined organic phases were dried and evaporated. The residue was subjected to flash chromatography on silica gel (elution with 10% ethyl acetate in hexanes) to give 45.5 mg (85%) of **26** as a colorless oil: IR (neat, cm^{-1}) 1718, 1617; ^1H NMR (300 MHz, C_6D_6) δ 5.56 (s, 1 H), 5.31 (d, J = 1 Hz, 1 H), 4.92 (ddd, J = 1, 1, 2.4 Hz, 1 H), 3.98 (hept, J = 6 Hz, 1 H), 2.63 (dd, J = 1.6, 1.6 Hz, 1 H), 2.17−1.98 (m, 2 H), 1.40−1.23 (m, 2 H), 1.01 (d, J = 6 Hz, 3 H), 1.00 (d, J = 6 Hz, 3 H), 0.93 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 199.6, 153.8, 148.4, 134.3, 109.2, 71.7, 61.8, 46.9, 37.7, 32.8, 26.6, 21.4 (2 C); MS *m/z* (M^+) calcd 206.1307; obsd 206.1328.

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.58; H, 8.85.



Semiselective DEPT: irradiate H-10 (δ 0.93), observe C-1 (134.3 ppm, ^3J), C-4 (61.8 ppm, ^3J), C-5 (46.9 ppm, ^2J), C-6 (37.7 ppm, ^3J).

(3a*R,6a*S**)-4,5,6,6a-Tetrahydro-2,3-diisopropoxy-3a,6a-dimethyl-4-methylene-1(3a*H*)-pentalenone (27).** Diisopropylamine (0.085 mL, 0.65 mmol) was dissolved in dry THF (10 mL), cooled to −15 °C, treated dropwise with *n*-butyllithium (0.31 mL of 1.6 M in hexane, 0.5 mmol), stirred for 15 min, and cooled to −78 °C before being treated dropwise via

cannula with a solution of **15** (75 mg, 0.28 mmol) in dry THF (2 mL). After 30 min, HMPA (1 mL) was introduced and stirring was maintained for 15 min, at which point methyl iodide (6 mL) was added all at once. The reaction mixture was allowed to warm to rt, stirred for an additional 5 h, diluted with water (25 mL), and extracted with ether (2 × 25 mL). The combined organic phases were washed with 1N HCl (25 mL), saturated $NaHCO_3$ solution (25 mL), and brine (25 mL) prior to drying and solvent evaporation. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexanes) afforded 63 mg (80%) of **27** as a colorless oil: IR (neat, cm^{-1}) 1698, 1615; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (hept, J = 6 Hz, 1 H), 4.95 (s, 1 H), 4.92 (s, 1 H), 4.83 (hept, J = 6 Hz, 1 H), 2.17−2.10 (m, 2 H), 2.06−1.99 (m, 1 H), 1.31−1.22 (m, 1 H), 1.28 (d, J = 6 Hz, 3 H), 1.19 (d, J = 6 Hz, 6 H), 1.16 (d, J = 6 Hz, 3 H), 1.14 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 205.2, 171.8, 154.3, 130.4, 107.4, 73.2, 71.6, 55.0, 51.8, 34.2, 30.8, 22.59, 22.54, 22.3, 22.2, 19.9, 17.3; MS m/z (M^+) calcd 278.1882, obsd 278.1885.

Anal. Calcd for $C_{17}H_{26}O_3$: C, 73.35; H, 9.41. Found: C, 73.63; H, 9.42.

(3a*R,6a*R**)-4,5,6,6a-Tetrahydro-2-isopropoxy-3a,6a-dimethyl-4-methylene-1(3a*H*)-pentalenone (28).** A 50.5 mg (0.18 mmol) sample of **27** was reduced with $LiAlH_4$ (4 mg, 0.106 mmol) in the usual manner. The reaction mixture was carefully quenched with 1 N HCl (3 mL), stirred at 0 °C for 0.5 h and at rt for 2.5 h, diluted with water (20 mL), and extracted with ether (2 × 20 mL). The combined organic phases were washed with saturated $NaHCO_3$ solution (20 mL) and brine (25 mL), dried, and concentrated to leave a residue which was purified by flash chromatography on silica gel (elution with 10% ethyl acetate in hexanes). There was isolated 33.4 mg (84%) of **28** as a colorless oil: IR (neat, cm^{-1}) 1721, 1621; ^1H NMR (300 MHz, $CDCl_3$) δ 5.55 (s, 1 H) 5.19 (d, J = 2.5 Hz, 1 H), 4.91 (d, J = 2.2 Hz, 1 H), 4.03 (hept, J = 6 Hz, 1 H), 2.17−2.07 (m, 1 H), 2.03 (ddd, J = 15, 15, 7 Hz, 1 H), 1.38 (dd, J = 12, 7 Hz, 1 H), 1.25 (ddd, J = 12, 12, 7 Hz, 1 H), 1.13 (s, 3 H), 1.01 (d, J = 6 Hz, 3 H), 1.00 (d, J = 6 Hz, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.4, 154.1, 153.5, 133.6, 108.6, 71.2, 58.5, 50.2, 36.0, 30.8, 23.5, 21.2 (2 C), 17.3; MS m/z (M^+) calcd 220.1463, obsd 220.1456.

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 75.84; H, 9.18.

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Supporting Information Available: 300-MHz ^1H and 75-MHz ^{13}C spectra of new compounds lacking combustion data (24 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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