Realization of Complete Regiochemical Control during the Conversion of Squarate Esters into Complex Linear and Angular Polyquinanes. The Consequences of Incorporating a Leaving Group into One of the Alkenyllithium Reactants

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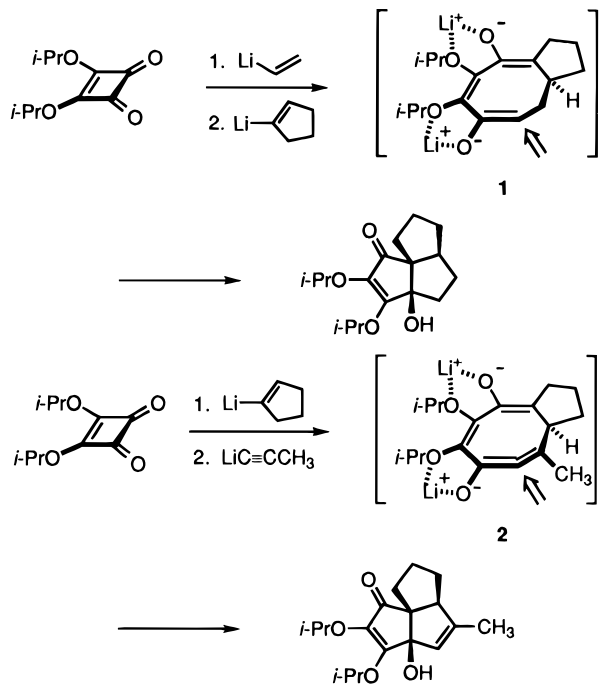
A useful method is presented for controlling whether linear or angular triquinanes are formed during a reaction cascade initiated by the 2-fold addition of alkenyl anions to diisopropyl squarate. The key feature of the process involves the incorporation of a leaving group into one of the original nucleophilic reagents. Placement of the nucleofuge within a cyclic anion leads ultimately to formation of a linear product. Extracyclic and intracyclic options are possible, with preference given to the better leaving group when a competitive situation exists. When the leaving group is incorporated into an acyclic component, angular triquinanes result instead. Several other aspects of this impressive scaffolding scheme are detailed.

Of the several cascade reactions available for dramatically increasing molecular complexity, that initiated by trans 1,2-addition of two alkenyl anions to a squarate ester is particularly impressive.[1−3] As detailed elsewhere,[4] spontaneous conrotatory 4π and 8π electrocyclic reactions culminate in the formation of an eight-membered bisenolate (Scheme 1). When the reactive anionic centers differ meaningfully in their level of substitution as in **1**, ensuing monoprotonation occurs regioselectively at the lesser substituted site and leads unidirectionally to a single polyquinane product. Sequential condensation with an alkenyl anion and a lithium acetylide initiates a related series of transformations that eventuates in formation of the highly strained ring system **2**.[4,5] The constitutional features of **2** are such that protonation is initially directed to the more reactive cumulenic sector. As before, this site selectivity has the utilitarian effect of producing a unique end product.

Described herein is an important variant of this "power reaction" [6] which proceeds with highly predictable regioselectivity to establish the precise course of the transannular aldolization. As a consequence, the tactic allows for the directed synthesis of an angular or linear polyquinane[7] on demand. The strategy is based on the proper positioning of a prospective leaving group adjacent to the carbanionic site in one of the alkenyl anions.[8]

The three generic examples presented in Scheme 2 were considered to be worthy of examination. The key feature of the first example, **3**, is the placement of the leaving group X on the cyclic nucleophile. Once this intermediate is formed, β-elimination can operate and the

Scheme 1



stage is set for transannular aldolization well in advance of any quenching. The laterally unsaturated linear triquinane shown then necessarily materializes.

If the X group is translocated as in **4**, its ultimate loss so positions the developing double bond that it ultimately resides at an intracyclic site. Accordingly, two modes of elimination should be capable of operation to deliver isomerically related polycyclic end products.

The simple expedient of incorporating the potential leaving group within the acylic component as in **5** was expected to constitute an advantageous means for accessing angular triquinanes instead. Thus, the proper incorporation of the leaving group into one or the other of the nucleophiles could provide a flexible and highly effective means for regulating the production of tri- and tetraquinanes, frameworks present in many biologically active natural products.[7]

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

(1) Negri, J. T.; Morwick, T.; Doyon, J.; Wilson, P. D.; Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 12189.
(2) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1995**, *117*, 1451.
(3) Wilson, P. D.; Friedrich, D.; Paquette, L. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1351.
(4) Paquette, L. A.; Morwick, T. M. *J. Am. Chem.Soc.* **1997**, *119*, 1230.
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(7) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: New York, 1987.
(8) Preliminary report: Paquette, L. A.; Doyon, J. *J. Am. Chem. Soc.* **1995**, *117*, 6799.

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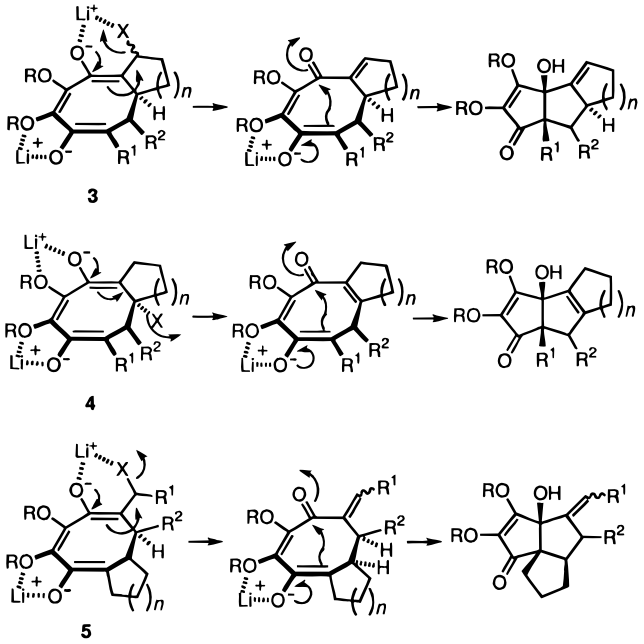
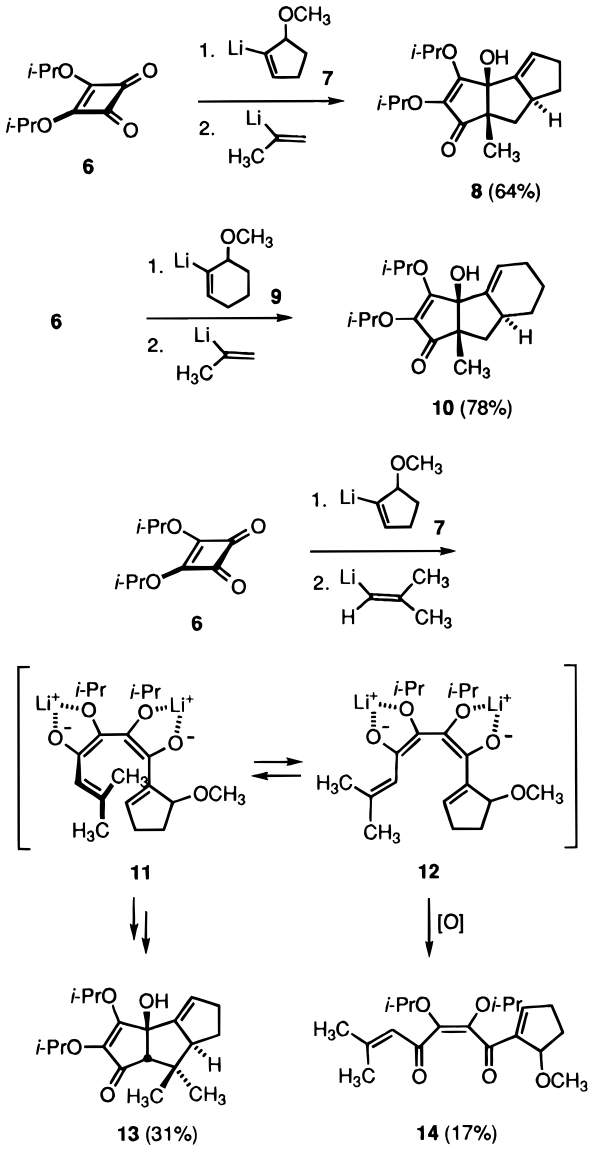
Scheme 2



Scheme 3



Results and Discussion

The Exocyclic Option. The relative ease with which methoxide ion can be eliminated in the course of selected reactions[9] prompted the initial consideration of examples in which X = OCH_3. To this end, 1.3 equiv of 1-bromo-5-methoxycyclopentene[10] was subjected to halogen−metal exchange with *tert*-butyllithium to give **7**, which was directly added to 0.5 equiv of diisopropyl squarate (**6**). Subsequent treatment of the resulting monoadduct with 2 equiv of 2-propenyllithium resulted in the isolation of **8** (64%) as the only product (Scheme 3). On some occasions, 2 equiv of **7** were required to consume all of the squarate in the first maneuver. Since no bis-addition was observed under these circumstances, chelation to lithium counterions may already be important at this early stage. In our experience, this behavior is common to all bromoolefins that carry one or more alkoxy groups. Consequently, this stoichiometry was adopted where relevant throughout this study.

Spectroscopically, the vinyl proton of **8** was observed in C_6D_6 solution to be a distinct doublet with $J = 6$ Hz at δ 5.31, while the angular methyl group appeared as a sharp singlet at δ 1.38. Although the 300 MHz NMR spectrum was well resolved, signals such as that for the methine proton consisted of complex multiplets as a consequence of extensive coupling. Since this phenomenon precluded the definitive assignment of relative stereochemistry, reliance was placed on X-ray diffraction to corroborate the anti-1,3-relationship of the latter two substituents.

The cyclohexenyl analog **9**[10] proved to be an equally suitable reactant. Under similar conditions, **10** was in fact produced with even greater efficiency (78%). Once again, advantage was taken of the highly crystalline nature of this product to corroborate its stereochemistry by crystallographic means.

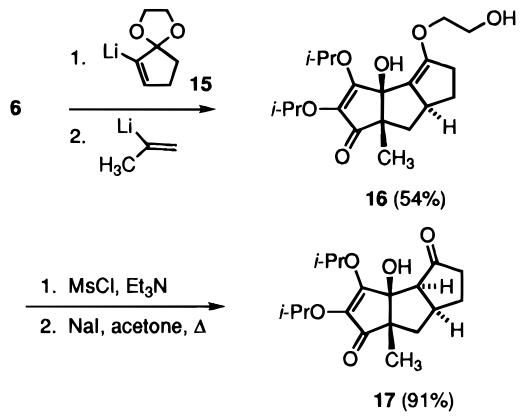
A central element of the reaction cascade leading to **8** and **10** is the conrotatory cyclization of a doubly-charged octatetraene intermediate.[2,4] This 8π ring closure becomes sterically disadvantaged simply upon placement of cis substituents on the terminal reaction centers.[4,11] In this context, it can be envisioned that the replacement of 2-propenyllithium by 1-lithio-2-methylpropene in either of the above reactions would be met with the stereocontrolled generation of a helical intermediate whose further progress toward a polycyclic product would be kinetically impeded to some unknown degree. The example illustrated in Scheme 3 involves **7** as the initial reactant. Our concern over the ability of **11** to be eventually converted to **13** was alleviated when the discovery was made that this triquinane was formed with reduced efficiency (31%) rather than not at all. Accordingly, quaternary centers can be set in this manner. Conjecture had been based upon the notion that prevailing nonbonded interactions within **11** would promote equilibration with **12** and related rotamers without necessarily incurring the loss of chelation to lithium ion. Although the terminal olefinic carbons in **12** are too distal

(9) (a) Paquette, L. A.; Shi, Y.-J. *J. Org. Chem.* **1989**, *54*, 5205. (b) Paquette, L. A.; Reagan, J.; Schreiber, S. L.; Teleha, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 2331. (c) Paquette, L. A.; Shi, Y.-J. *J. Am. Chem. Soc.* **1990**, *112*, 8478.

(10) (a) Johnson, C. R.; Sakaguchi, H. *Synlett* **1992**, 813. (b) Johnson, C. R.; Adams, P. A.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917.

(11) Huisgen, R.; Dahmen, A.; Huber, H. *J. Am. Chem. Soc.* **1967**, *89*, 7130.

Scheme 4



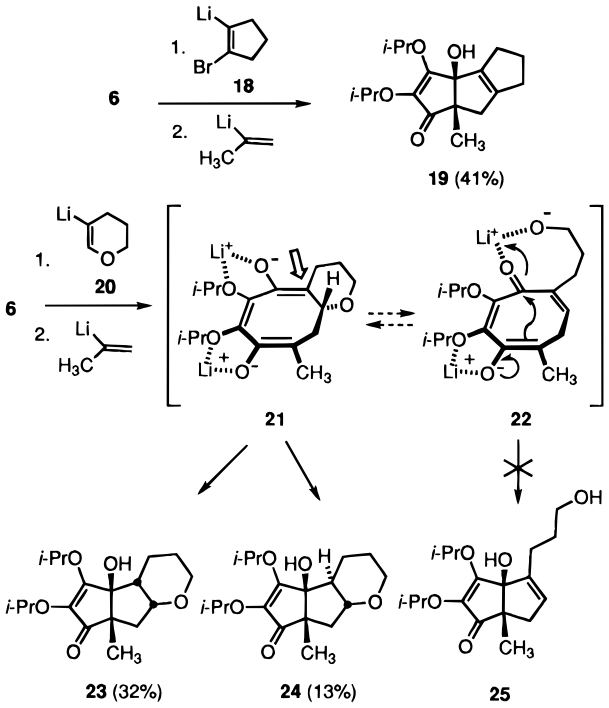
to engage in mutual bonding, this particular conformer seemingly has no alternative low-energy reaction pathway available by which to reduce its high level of unsaturation. The viability of its return to **11** for advancement to **13** presumably constitutes a reasonable option. This is not overly favorable, however, since **14** was isolated in 17% yield alongside **13**. This trienedione results from air oxidation of the protonation product of **12**. Although the geometry about the central double bond in **14** would be expected to be as shown on mechanistic grounds, this feature has not been unequivocally established.

The capacity for generating the site of β-elimination at a higher oxidation level was next probed. Metalation of the ethylene acetal of 2-bromo-2-cyclopenten-1-one[12] produced **15**, which was added to **6**. The subsequent introduction of 2-lithiopropene resulted in the isolation of **16** in 54% yield (Scheme 4). The 2-hydroxyethyl side chain in **16** was most efficiently removed by conversion to the mesylate and heating of this sulfonate ester with sodium iodide in acetone.

The Intracyclic Alternative. As noted earlier, examination of the cyclooctatriene dianions generated prior to β-elimination suggested that the arrangement present in **3** was not uniquely suited to the construction of linear polycyclic systems. Should the leaving group be positioned at a bond-forming site, an endocyclic elimination mode would be made available as in **4** and deliver products having a double bond central to two rings. The pursuit of this objective as a means for expanding the scope of this methodology held mechanistic interest as well. In order to arrive at a system such as **4**, it is necessary that the group X be projected into the interior of the octatetraene helix much as the cis methyl group in **11** and be similarly subject to steric compression as the transition state for ring closure is approached. The successful formation of **13** was cause for optimism.

1,2-Dibromocyclopentene, although commercially available, can be prepared in two steps by the bromination of chlorocyclopentene followed by treatment with potassium *tert*-butoxide. Following the monometalation of this dihalide to give **18**,[13] the functionalized cycloalkenyllithium was brought into reaction with **6** in advance of 2-propenyllithium (Scheme 5). The exclusive formation

Scheme 5



of **19** (41%) is noteworthy for at least two reasons. The first is that electrocyclization proceeds quite well despite the rather larger size of the bromine atom. In addition, a tetrasubstituted intraannular double bond is amenable to direct installation.

This finding prompted investigation of a variant of the theme in the form of lithiated dihydropyran **20**.[14] In order to skirt the very facile ring opening of **20** to an acetylenic alkoxide, the halogen−lithium exchange must be performed at −110 °C and the reagent not allowed to warm above −80 to −90 °C. This instability dictates the order of addition of the anions to **6**. Thus, while first-stage reactions leading to monoadducts are generally rapid and complete at −78 °C, second-stage additions do not normally occur until somewhat more elevated temperatures are reached. For this reason, **20** was admixed with **6** in advance of 2-propenyllithium. The conversion to products materialized very slowly in this case. After a reaction time of 48 h at rt, the tricyclic epimers **23** and **24** were isolated in a 2.5:1 ratio and 45% combined yield.

The major constituent was demonstrated to be the β isomer on the basis of its X-ray crystallographic analysis. No product resulting from potential β-elimination was found.

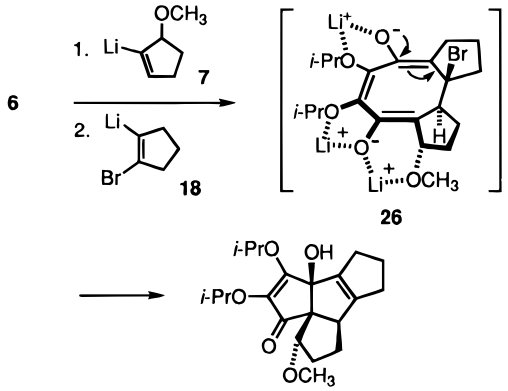
The extended length of time required to arrive at **21** could be a reflection of the change in the electronic nature of its very electron-rich octatetraene precursor. Once formed, **21** exhibits no obvious tendency to undergo β-elimination with generation of **22**. This interconversion could, of course, be reversible. Notwithstanding, arrival at **22** should be met with irreversible intramolecular aldolization and conversion to **23** even if the concentration gradient of the ring-opened tautomer **22** is low at equilbrium. Consequently, no evidence has been uncovered for cleavage of the tetrahydropyran ring in this example. As will be discussed below, this unreactivity may be due to the fact that the pyranyl oxygen is not

(12) (a) Shih, C.; Fritzen, E. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 4462. (b) Smith, A. B., III; Branca, S. J.; Piller, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (c) Smith, A. B., III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 271.

(13) Okano, Y.; Sawa, H.; Aonuma, S.; Kato, R. *Chem. Lett.* **1993**, 1851.

(14) Ficini, J.; Kahn, P.; Falou, S.; Touzin, A. M. *Tetrahedron Lett.* **1979**, 67.

Scheme 6



properly positioned to profit from coordination to Li^+ (nonassisted elimination).

The regioselectivity with which **21** is protonated holds interest in that only the enolate anion proximal to the heterocyclic ring is involved. This notable discrimination may arise because of the greater ring strain at this site. Also, cis protonation leading predominantly to **23** is seen to be kinetically advantaged.

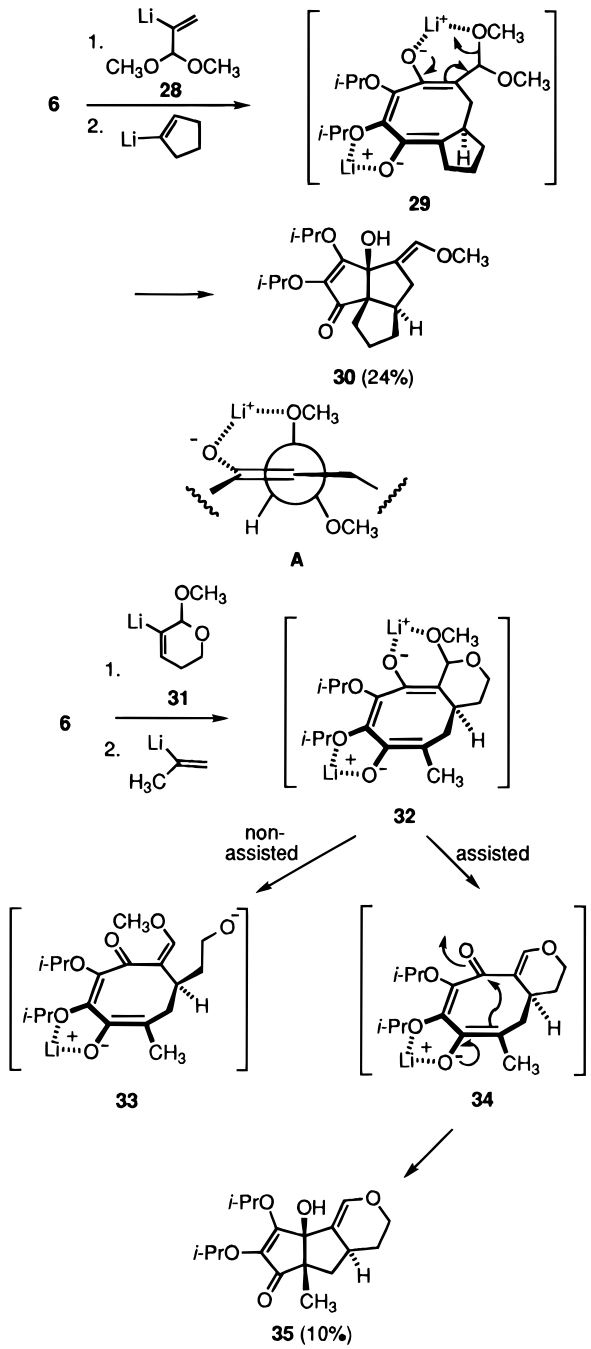
A competition experiment was undertaken in order to determine if adherence to established nucleofugal reactivities would be observed. In the event, sequential treatment of **6** with **7** and then **18** was projected to give rise to **26** (Scheme 6). The expectation was that loss of bromide would be the overwhelmingly favored pathway. Indeed, tetraquinane **27** resulted in an unoptimized yield of 28% and was the only polycyclic product formed.

The Case for Angular Triquinane Construction. Fundamental bond construction can be redirected by the simple expedient of incorporating an alkoxide leaving group within the acylic component as in **5**. Sequential addition of **28** and cyclopentenyllithium to **6** did indeed result in the formation of **30** (Scheme 7). In this instance, the modest yield of product could be traced to the sensitivity of its exocyclic enol ether functionality to chromatography. The *E* geometry about this double bond, elucidated convincingly by application of NOE techniques, requires that the structural arrangement depicted in **A** be involved in the elimination step if chelation to lithium ion facilitates the departure of methoxide ion (assisted elimination). Of course, alternative rotameric arrangements are possible if chelation is of little importance as a driving force.

As a further probe of this issue, recourse was made to the dihydropyranyl anion **31**.[15] In combination with 2-propenyllithium, arrival at bisenolate **32** is anticipated via initial trans addition to **6**. The increased conformational rigidity imposed by the tetrahydropyran ring effectively precludes intramolecular chelation to the ring oxygen while fostering coordination to the methoxyl substituent. As matters turned out, this condensation gave rise to a complex array of products from which only **35** proved characterizable. Although the isolation of **35** conforms to expectations based on chelate control, this finding cannot be construed to be confirmatory proof, particularly in light of the low yield of this heterocycle (10%) and the possibility that conversion to **33** could be met by subsequent wholesale destruction of this intermediate.

(15) (a) Roff, J. E.; Braun, R. K. *Can. J. Chem.* **1973**, *51*, 3354. (b) Braun, R. K. *Can. J. Chem.* **1968**, *46*, 2283.

Scheme 7



Conclusions

We have investigated the possibility of controlling the regioselectivity of the squarate ester−1,3,5,7-octatetraene−polyquinane cascade with considerable success. The locus of a leaving group resident in one of the alkenyllithium reactants can be selected to provide exclusively either a linear or angular product. Placement of the nucleofuge within a cyclic anion has the ultimate consequence of delivering linear frameworks. Two options are available depending on whether the key β-elimination occurs in an exocyclic or intracyclic mode. While the first of these positions the double bond along a lateral edge of the product framework, the second generates a tetrasubstituted olefinic center between two of the fused rings. The consequence of positioning a potential leaving group on an acyclic nucleophilic reagent is to control transannular aldol cyclization such that only angular polycyclics result.

Alkoxides are readily eliminated in the exocyclic mode, but not in the intracyclic variant. It has proven difficult to assess whether this behavior is dependent on the ability of the departing oxygen to engage in chelation to a lithium ion. This is chiefly because probes of this interesting question have not proceeded with high efficiency. Also, one has to deal with issues that surround reversible equilibration with ring-cleaved tautomers when an ether oxygen is incorporated into a heterocyclic ring.

In contrast, bromide ion is readily and selectively eliminated in the intracyclic mode. Both alkenyl bromides and enol ethers undergo spontaneous conrotatory electrocyclization once the helical 1,3,5,7-octatetraene intermediate is reached, but with notably reduced rates for the latter. Substitution at one of the bond-forming carbons by a *cis*-methyl group impedes electrocyclization to some degree. Comparable kinetic retardation is not observed when bromine occupies the same position, despite an anticipated increase in steric buttressing. It is possible that stereoelectronic effects gain importance at this kinetically sensitive stage of the cascade.

More elaborate multicyclic systems are expected to be available with equally striking selectivitiy. In addition, the extensive level of substitution in the products holds promise for varied chemical transformation[16] and serviceability in a variety of synthetic undertakings.[17]

Experimental Section

General. All reactions were carried out under an inert atmosphere of nitrogen. Glassware was invariably oven-dried or flame-dried in vacuo and purged with nitrogen. Tetrahydrofuran was distilled from sodium/benzophenone ketyl immediately prior to use. Reactions were monitored by thin-layer chromatography. Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230−400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high-field ^{1}H (300 MHz) and ^{13}C NMR (75 MHz). The high-resolution mass spectra were obtained at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Generic Procedure for Halogen−Metal Exchange. The vinyl halide, neat or dissolved in the indicated solvent, was placed in a dry three-necked flask and blanketed with dry N_2. The necessary quantity of dry THF was introduced so as to have a solution 0.1−0.2 M in alkenyl halide, and the contents were cooled to −78 °C or as indicated. Two equivalents of *tert*-butyllithium (1.7 M in pentane) were next introduced dropwise at such a rate as to keep the temperature below −70 °C (or below −100 °C where warranted), and the colorless or pale yellow solution was utilized directly after 15−30 min of stirring.

Generic Procedure for Coupling of Alkenyllithium Reagents to Diisopropyl Squarate. A 0.5−1.0 M solution of the squarate ester in THF was transferred rapidly via cannula to the cold (−78 °C unless otherwise indicated) alkenyllithium solution. The progress of the first addition, which was typically over after 30−45 min, was monitored by TLC. A reaction incomplete after 60 min was usually indicative that insufficient alkenyllithium was present. The second anion, generated in the same fashion, was transferred rapidly (to avoid warming of the anion during transfer) by cannula to the flask containing the monoadduct. The reaction mixture was kept at −78 °C for the indicated time, warmed to rt, stirred for the stated time at rt, quenched with saturated NH_4Cl or $NaHCO_3$ solution, and further stirred for the time shown. The reaction mixture was then diluted with water to dissolve the inorganic salts which usually precipitated and extracted three−four times with ether. The combined organic extracts were washed with small quantities of brine and water, dried, and concentrated by rotary evaporation. The residue was purified by chromatographic means.

(3a*R,6a*R**,7a*S**)-3a,5,6,6a,7,7a-Hexahydro-3a-hydroxy-2,3-diisopropoxy-7a-methyl-1*H*-cyclopenta[*a*]pentalen-1-one (8).** From 5-methoxy-1-bromocyclopentene (**7**) (230 mg, 1.3 mmol), 2.00 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 363 mg of 2-bromopropene (3.0 mmol), warmed up over 2 h, quenched with a saturated NH_4Cl solution, and stirred for 1 h followed by flash chromatography (silica gel, elution with 5% methanol/CH_2Cl_2), there was obtained 196 mg (64%) of **8** as a colorless solid, mp 111−112 °C (hexanes): IR (neat, cm^{-1}) 3326, 1694, 1614, 1380, 1311, 1218, 1183, 1105, 1066, 1010, 956, 907, 867, 814; ^{1}H NMR (300 MHz, C_6D_6) δ 5.56 (dd, J = 3, 4.5 Hz, 1 H), 5.32 (heptet, J = 6 Hz, 1 H), 5.31 (d, J = 6 Hz, 1 H), 2.75−2.55 (m, 1 H), 2.49 (dd, J = 12, 7 Hz, 1 H), 2.45−2.20 (m, 2 H), 2.00 (br s, 1H), 1.82 (ddt, J = 1, 7, 13 Hz, 1 H), 1.28 (s, 3 H), 1.30−1.10 (m, 1 H), 1.16 (d, J = 6 Hz, 3 H), 1.14 (d, J = 6 Hz, 3 H), 1.12 (d, J = 6 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H), 0.93 (t, J = 12 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.4, 164.7, 154.7, 132.8, 122.5, 78.0, 73.6, 71.6, 60.6, 46.3, 42.2, 37.1, 31.7, 22.8, 22.7, 22.6, 22.5, 19.7; MS m/z (M^+) calcd 306.1831, obsd 306.1827.

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.30; H, 8.55.

(3a*R,7a*R**,8a*R**)-5,6,7,7a,8,8a-Hexahydro-3a-hydroxy-2,3-diisopropoxy-8a-methylcyclopent[*a*]inden-1(3a*H*)-one (10).** From 354 mg (2.0 mmol) of 6-methoxy-1-bromocyclohexene (**9**), 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 242 mg (2.0 mmol) of 2-bromopropene, warmed up over 2 h, quenched with a saturated NH_4Cl solution, and stirred for 1 h followed by flash chromatography (silica gel, elution with 20% ethyl acetate in hexanes), there was obtained 250 mg (78%) of **10** as a colorless solid, mp 102−104 °C (hexanes): IR (film, cm^{-1}) 3426, 1693, 1610, 1215, 1101, 1045, 1008, 942, 916; ^{1}H NMR (300 MHz, C_6D_6) δ 5.82 (br d, J = 3 Hz, 1 H), 5.35−5.25 (br m, 2 H), 2.44 (dd, J = 7, 12 Hz, 1 H), 2.15 (br s, 1 H), 2.10−1.75 (series of m, 4 H), 1.74−1.60 (m, 1 H), 1.55−1.45 (m, 1 H), 1.29 (s, 3 H), 1.16 (d, J = 6 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.07 (d, J = 6 Hz, 3 H), 0.89 (t, J = 12 Hz, 1 H), 0.82 (q, J = 8 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.6, 165.5, 146.0, 132.2, 121.2, 81.4, 73.5, 71.6, 55.7, 41.6, 35.9, 28.9, 25.3, 22.9, 22.7, 22.5 (2 C), 22.3, 19.4; MS m/z (M^+) calcd 320.1988, obsd 320.1964.

Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.47; H, 8.85.

(3a*R,4*S**,6a*R**)-4,5,6,6a-Tetrahydro-3a-hydroxy-2,3-diisopropoxy-4,6a-dimethyl-1(3a*H*)-pentalenone (13) and 2,3-Diisopropoxy-1-(5-methoxy-1-cyclopenten-1-yl)-6-methyl-2,5-heptadiene-1,4-dione (14).** A 213 mg (1.2 mmol) sample of 5-methoxy-2-bromocyclopentene (**7**), 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 270 mg (2.0 mmol) of 1-bromo-2-methylpropene was warmed up overnight, quenched with a saturated NH_4Cl solution, and stirred for 1 h. The product mixture was separated by flash chromatography (silica gel, elution with 5% methanol/CH_2Cl_2), and the order of elution of the two products was as follows:

Diketone **14** (60 mg, 17%) was obtained as a pale yellow oil. This compound is not stable and decomposes at rt after a few days to a dark tar: IR (neat, cm^{-1}) 3405, 1666, 1614, 1372, 1263, 1191, 1140, 1098, 1039, 999, 966, 908; ^{1}H NMR (200 MHz, C_6D_6) δ 6.80 (t, J = 2 Hz, 1 H), 6.72 (t, J = 1.5 Hz, 1 H), 4.82−4.52 (m, 1 H), 4.46 (heptet, J = 6 Hz, 1 H), 4.24 (heptet, J = 6 Hz, 1 H), 3.33 (s, 3 H), 2.35−2.20 (m, 1 H), 2.08 (d, J = 1 Hz, 3 H), 1.96−1.60 (series of m, 3H), 1.51 (d, J = 1 Hz, 3 H), 1.24 (d, J = 6 Hz, 3 H), 1.23 (d, J = 6 Hz, 3H), 1.15 (d, J = 6 Hz, 3 H), 1.12 (d, J = 6 Hz, 3 H); ^{13}C NMR (50 MHz, C_6D_6) ppm 189.3, 187.5, 155.9, 151.0, 147.8, 146.0, 140.8, 121.4, 83.9,

(16) Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 146.

(17) The authors have deposited the atomic coordinates for the three X-ray structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

74.7, 73.4, 57.4, 31.6, 30.3, 27.8, 23.0, 22.80, 22.78, 22.7, 20.9; MS *m*/*z* (M^+) calcd 350.2094, obsd 350.2091.

Triquinane **13** (100 mg, 31%) was obtained as a colorless solid, mp 87−88 °C (hexanes): IR (film, cm^{-1}) 3375, 1695, 1605, 1380, 1312, 1098; ^1H NMR (300 MHz, C_6D_6) δ 5.64 (dd, J = 2.5, 4.5 Hz, 1 H), 5.31 (heptet, J = 6 Hz, 1 H), 5.26 (heptet, J = 6 Hz, 1 H), 2.86−2.77 (m, 1 H), 2.50 (s, 1 H), 2.51−2.30 (m, 2 H), 1.80−1.40 (m, 2 H), 1.26 (s, 3 H), 1.16 (d, J = 6 Hz, 6 H), 1.10 (d, J = 6 Hz, 6 H), 1.20−1.05 (m, 1 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 197.7, 165.3, 151.6, 133.7, 122.7, 77.0, 73.6, 71.5, 69.6, 59.1, 40.0, 37.3, 24.8, 24.7, 23.1, 22.80, 22.75, 22.6, 22.5; MS *m*/*z* (M^+) calcd 320.1988, obsd 320.1989.

(3a*R,6a*R**,7a*R**)-3a,5,6,6a,7,7a-Hexahydro-3a-hydroxy-4-(2-hydroxyethoxy)-2,3-diisopropoxy-7a-methyl-1*H*-cyclopenta[*a*]pentalen-1-one (16).** From 458 mg (2.25 mmol) of the ethylene ketal of 2-bromo-2-cyclopenten-1-one (**15**), 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 145 mg (1.2 mmol) of 2-bromopropene, warmed up overnight, and quenched with saturated NH_4Cl solution followed by flash chromatography (silica gel, elution with 50% ethyl acetate in hexanes), **16** was obtained as a pale yellow oil (200 mg, 54%): IR (film, cm^{-1}) 3444, 1694, 1614, 1454, 1380, 1307, 1223, 1098, 909, 820, 771; ^1H NMR (300 MHz, C_6D_6) δ 5.39 (heptet, J = 6 Hz, 1 H), 5.29 (heptet, J = 6 Hz, 1 H), 4.00−3.75 (br s, 1 H), 3.83 (dt, J = 4.5, 11 Hz, 1 H), 3.72 (dt, J = 4.5, 11 Hz, 1 H), 3.52 (t, J = 6.5 Hz, 2 H), 3.10 (br s, 1 H), 2.66−2.60 (br m, 1 H), 2.49 (dd, J = 5, 12 Hz, 1 H), 2.40−2.30 (m, 1 H), 2.21 (ddt, J = 1.5, 10, 15.5 Hz, 1 H), 1.75−1.65 (m, 1 H), 1.37 (s, 3 H), 1.30−1.09 (m, 2 H), 1.23 (d, J = 6 Hz, 3 H), 1.21 (d, J = 6 Hz, 3 H), 1.16 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.5, 165.3, 151.6, 132.5, 122.4, 78.5, 74.0, 71.7, 71.3, 61.6, 61.3, 44.2, 43.2, 34.8, 28.5, 22.9, 22.7, 22.65, 22.5, 20.0; MS *m*/*z* (M^+) calcd 366.2061, obsd 366.2052.

(3aS*R,3b*R**,6a*R**,7a*R**)-3b,5,6,6a,7,7a-Hexahydro-3a-hydroxy-2,3-diisopropoxy-7a-methyl-1*H*-cyclopenta[*a*]pentalene-1,4-(3a*H*)-dione (17).** Triquinane **16** (140 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (5 mL), and triethylamine (116 mg, 1.16 mmol) and was treated with 64 mg (0.55 mmol) of methanesulfonyl chloride. After overnight stirring, the reaction mixture was diluted with CH_2Cl_2 and water. After extraction with CH_2Cl_2, washing (brine), drying, and concentration, the crude product was taken up in acetone containing an excess of NaI and refluxed overnight. The solvent was evaporated, and the residue was diluted with ether and water prior to extraction with ether. After drying and concentration of the organic extracts, 112 mg (91%) of **17** was obtained as a colorless oil, essentially pure by ^1H NMR: IR (film, cm^{-1}) 3450, 1723, 1698, 1621, 1381, 1300, 1251, 1234, 1213, 1177, 1148, 1109, 1046, 1017; ^1H NMR (300 MHz, C_6D_6) δ 5.33 (heptet, J = 6 Hz, 1 H), 5.27 (heptet, J = 6 Hz, 1 H), 5.12 (s, 1 H), 2.44 (d, J = 7.5 Hz, 1 H), 2.16 (ddd, J = 1.5, 7, 13 Hz, 1 H), 2.03 (dddd, J = 7, 14, 13, 14 Hz, 1 H), 1.85 (dq, J = 9, 19 Hz, 1 H), 1.72 (br dd, J = 9, 19 Hz, 1 H), 1.26 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.16 (d, J = 6 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.20−1.05 (m, 2 H), 0.90 (t, J = 12 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 221.8, 201.5, 165.7, 132.4, 84.4, 73.7, 71.7, 56.8, 56.6, 39.9, 38.2, 35.7, 22.9, 22.7, 22.6, 22.55, 22.4, 19.8; MS *m*/*z* (M^+) calcd 322.1780, obsd 322.1773.

(3a*R,7a*R**)-3a,4,5,6,7,7a-Hexahydro-3a-hydroxy-2,3-diisopropoxy-7a-methyl-1*H*-cyclopenta[*a*]pentalen-1-one (19).** From 182 mg (1.5 mmol) of 2-bromopropene, 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 502 mg (2.0 mmol) of 1,2-dibromocyclopentene (**18**), kept 2 h at −78 °C, warmed to rt over 4 h, aged 3 h at rt, quenched with a saturated $NaHCO_3$ solution, and stirred overnight, followed by flash chromatography (silica gel, elution with 10−15% ethyl acetate in hexanes), there was isolated 125 mg (41%) of **19** as a thick oil: IR (neat, cm^{-1}) 3418, 1694, 1614, 1446, 1380, 1312, 1183, 1104, 1067, 1021, 994, 908, 858, 769; ^1H NMR (300 MHz, C_6D_6) δ 5.37 (heptet, J = 6 Hz, 1 H), 5.29 (heptet, J = 6 Hz, 1 H), 2.79 (br d, J = 17 Hz, 1 H), 2.40−2.30 (br m, 2 H), 2.20−2.05 (m, 2 H), 2.05−1.70 (series of m, 4 H), 1.51 (s, 3 H), 1.20 (d, J = 6 Hz, 3 H), 1.19 (d, J = 6 Hz, 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.14 (d, J = 6 Hz, 3 H); MS *m*/*z* (M^+) calcd 306.1831, obsd 306.1826.

(4a*R,4b*S**,7a*S**,8a*R**)-2,3,4,4a,4b,7a,8,8a-Octahydro-4b-hydroxy-5,6-diisopropoxy-7a-methyl-7*H*-pentaleno[2,3-*b*]pyran-7-one (23) and (4a*R**,4b*R**,7a*R**,8a*S**)-2,3,4,4a,4b,7a,8,8a-Octahydro-4b-hydroxy-5,6-diisopropoxy-7a-methyl-7*H*-pentaleno[2,3-*b*]pyran-7-one (24).** 3-Bromo-4,5-dihydropyran (**20**, 652 mg, 4.0 mmol) was dissolved in 5 mL of THF and 10 mL of ether and treated dropwise with 4.70 mL of *t*-BuLi (8.0 mmol, 1.7 M in hexanes), while maintaining the *internal* temperature below −100 °C through use of a liquid nitrogen/ether slurry as cooling bath. After 20 min, 400 mg (2.0 mmol) of diisopropyl squarate in 5 mL of THF was added slowly in order to maintain the temperature at approximately −100 °C. After 1 h, 2-lithiopropene generated from 2-bromopropene (850 mg, 7.0 mmol) in 20 mL of THF was added rapidly to the monoadduct solution at −78 °C. This solution was stirred at −78 °C for 1 h, allowed to warm up to 0 °C, and kept at this temperature for 2 h. Warming to rt, allowed to stir for 48 h, quenched with a saturated NH_4Cl solution, followed by the usual workup and flash chromatography (silica gel, elution with 10−20% ethyl acetate in hexanes), gave two products:

The less polar isomer was **24**: 83 mg (13%), a colorless oil; IR (film, cm^{-1}) 3456, 1685, 1601, 1106, 1080, 1029; ^1H NMR (300 MHz, C_6D_6) δ 5.30 (heptet, J = 6 Hz, 1 H), 5.26 (heptet, J = 6 Hz, 1 H), 3.78 (br d, J = 11.5 Hz, 1 H), 3.06 (td, J = 2.5, 12 Hz, 1 H), 2.86 (ddd, J = 5.5, 10.5, 10.5 Hz, 1 H), 2.61 (dd, J = 6, 11.5 Hz, 1 H), 2.09 (br s, 1 H), 2.05−1.95 (m, 1 H), 1.70−1.60 (m, 1 H), 1.62 (t, J = 11.5 Hz, 1 H), 1.50-.1.15 (series of m, 2 H), 1.25 (s, 3 H), 1.12 (d, J = 6 Hz, 3 H), 1.09 (d, J = 6 Hz, 3 H), 1.08 (d, J = 6 Hz, 3H), 1.07 (d, J = 6 Hz, 3 H), 1.15−0.95 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.2, 165.4, 132.3, 79.9, 78.0, 73.7, 71.5, 68.5, 53.3, 52.5, 40.5, 26.6, 26.2, 23.0, 22.9, 22.8, 22.6, 19.1; MS *m*/*z* (M^+) calcd 324.1936, obsd 324.1936.

The second product to elute was repurified by flash chromatoraphy (silica gel, elution with 10% ethyl acetate in hexanes) and gave 206 mg (32%) of **23** as a colorless solid, mp 138−140 °C: IR (film, cm^{-1}) 3408, 1682, 1605, 1104, 1079, 1034, 1010; ^1H NMR (300 MHz, C_6D_6) δ 5.49 (heptet, J = 6 Hz, 1 H), 5.27 (heptet, J = 6 Hz, 1 H), 3.66 (br d, J = 11 Hz, 1 H), 3.47 (dd, J = 4, 4 Hz, 1 H), 3.00 (td, J = 2, 11 Hz, 1 H), 2.55 (d, J = 14 Hz, 1 H), 2.29 (br s, 1 H), 2.20 (br d, J = 14 Hz, 1 H), 1.65−1.30 (m, 4 H), 1.26 (s, 3 H), 1.14 (d, J = 6 Hz, 3 H), 1.13 (d, J = 6 Hz, 6 H), 1.12 (d, J = 6 Hz, 3 H), 0.97 (d, J = 11 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.1, 165.3, 131.6, 81.9, 78.9, 73.7, 71.3, 66.6, 56.0, 49.0, 41.7, 22.90, 22.82, 22.79, 22.70, 21.7, 20.4; MS *m*/*z* (M^+) calcd 324.1936, obsd 324.1931.

(3a*R,6a*S**,9b*R**)-1,2,3,6a,7,8,9,8b-Octahydro-6a-hydroxy-5,6-diisopropoxy-3-methoxy-4*H*-dicyclopenta[*a*,*b*]-pentalen-4-one (27).** From 354 mg (2.0 mmol) of 5-methoxy-1-bromocyclopentene (**7**), 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 452 mg (2.0 mmol) of 1,2-dibromocyclopentene (**18**), warmed to rt over 3 h, quenched with a saturated NH_4Cl solution, followed by flash chromatography (silica gel, elution with 20% ethyl acetate−hexanes), there was isolated 100 mg (28%) of **27** as a thick colorless oil: IR (film, cm^{-1}) 3418, 1694, 1614, 1182, 1106; ^1H NMR (300 MHz, C_6D_6) δ 5.45 (heptet, J = 6 Hz, 1 H), 5.31 (heptet, J = 6 Hz, 1 H), 4.24 (dd, J = 10, 6.5 Hz, 1 H), 3.23 (s, 3 H), 3.20−3.15 (m, 1 H), 2.46−2.20 (m, 3 H), 2.08-1.95 (m, 4 H), 1.95−1.75 (m, 2 H), 1.21−1.00 (m, 2 H), 1.19 (d, J = 6 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 198.3, 166.6, 152.0, 144.7, 133.0, 83.6, 80.5, 73.3, 73.0, 71.5, 57.7, 49.7, 33.2, 28.2, 27.3, 27.0, 26.8, 23.2, 22.9, 22.8, 22.2; MS *m*/*z* (M^+) calcd 362.2093, obsd 362.2092.

(3a*R,5a*S**,8a*R**)-4,5,5a,6,7,8-Hexahydro-3a-hydroxy-2,3-diisopropoxy-4-[(*E*)-methoxymethylene]cyclopenta-[*c*]pentalen-1(3a*H*)-one (30).** From 434 mg (2.4 mmol) of 2-bromoacrolein dimethyl acetal (**28**), 200 mg (1.0 mmol) of diisopropyl squarate (reaction time of 1 h), and 582 mg (3.0 mmol) of cyclopentenyl iodide, warmed up overnight, quenched with a saturated NH_4Cl solution, followed by flash chromatography (silica gel, elution wtih 20% ethyl acetate−hexanes), there was obtained 140 mg of **30** as pale yellow oil, which had partially decomposed. A second flash chromatography (silica

gel, elution with 40% ethyl acetate−hexanes plus 1% triethylamine) gave 80 mg (24%) of pure **30**, a pale yellow oil: IR (neat, cm^{-1}) 3440, 1698, 1622, 1454, 1381, 1306, 1100; ^1H NMR (300 MHz, C_6D_6) δ 6.35 (dd, J = 1.5, 2.5 Hz, 1 H), 5.33 (heptet, J = 6 Hz, 1 H), 5.32 (heptet, J = 6 Hz, 1 H), 3.19 (s, 3 H), 2.51 (ddd, J = 2, 12, 14.5 Hz, 1 H), 2.50 (s, 1 H), 2.26 (ddd, J = 2.5, 8, 16 Hz, 1 H), 2.10 (t, J = 7 Hz, 1 H), 2.09 (t, J = 7 Hz, 1 H), 1.94 (s, 1 H), 1.90−1.60 (series of m, 3 H), 1.30−1.15 (m, 1 H), 1.18 (d, J = 6 Hz, 3 H), 1.15 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H), 1.09 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.3, 165.2, 144.8, 132.3, 119.3, 81.9, 73.3, 71.4, 66.7, 59.4, 48.2, 34.8, 30.5, 29.9, 27.8, 22.80, 22.77, 22.6, 22.5; MS m/z ($M^+ + 1$) calcd 337.2025, obsd 337.2004.

(4a*R,5a*S**,8a*S**)-3,4,4a,5,5a,8a-Hexahydro-8a-hydroxy-7,8-diisopropoxy-5a-methyl-6*H*-pentaleno[1,2-*c*]pyran-6-one (35).** From 771 mg (4.0 mmol) of 2-methoxy-3-bromo-4,5-dihydropyran (**31**), 400 mg (2.0 mmol) of diisopropyl squarate (reaction time of 2 h), and 726 mg (3.0 mmol) of 2-bromopropene, warmed overnight to rt, quenched with a saturated NH_4Cl solution, and chromatographed (silica gel, 20% ethyl acetate−hexanes plus 1% triethylamine), there was obtained 65 mg (10%) of **35** as a colorless solid, mp 147−147.5 °C (hexanes−ether): IR (film, cm^{-1}) 3318, 1677, 1602, 1379, 1318, 1306, 1218, 1160, 1111, 1049, 928, 913; ^1H NMR (300 MHz, C_6D_6) δ 6.70 (d, J = 2 Hz, 1 H), 5.33 (heptet, J = 6 Hz, 1 H), 5.26 (heptet, J = 6 Hz, 1 H), 3.76 (ddd, J = 11, 2, 2 Hz, 1 H), 3.32 (ddd, J = 11, 11, 2 Hz, 1 H), 2.40 (dd, J = 12, 6.5 Hz, 1 H), 2.28 (br s, 1 H), 2.02−1.80 (m, 1 H), 1.47−1.30 (m, 1 H), 1.25 (s, 3 H), 1.18 (d, J = 6 Hz, 3 H), 1.16 (d, J = 6 Hz, 3 H), 1.11 (d, J = 6 Hz, 3 H), 1.10 (d, J = 6 Hz, 3 H), 1.20−0.95 (m, 1 H), 0.87 (dd, J = 12, 12 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.3, 165.6, 140.4, 131.6, 120.3, 81.4, 73.6, 71.7, 65.1, 57.3, 41.4, 32.2, 28.2, 22.9, 22.7, 22.4 (2 C), 19.4; MS m/z (M^+) calcd 322.1780, obsd 322.1758.

Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 66.81; H, 8.01.

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Supporting Information Available: High-field ^1H and ^{13}C NMR spectra of those compounds lacking combustion data (18 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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