Probe of the Stereochemically Determining Step in Squarate Ester Cascades. Proof that Helical Equilibration within the Octatetraene Intermediate Is Responsible and Definition of Steric Control Elements

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Abstract: The stereoselectivity associated with the coaddition of a chiral and an achiral cycloalkenyl anion to a squarate ester has been examined. The selective formation of polycyclic ketones is observed in all cases, although dual protonation at both of the available enolate sites in their penultimate cyclooctatrienyl dianion precursors was sometimes noted. Proof that the stereoselection was the result of interconversion between a pair of helical octatetraene intermediates, with resultant erosion of original stereogenicity, was established by isolation of diastereomeric monoadducts and separate submission of these hydroxy cyclobutenones to the original reaction conditions. The final stages of the cascade proceed via the lower energy transition state option where nonbonded steric effects are skirted as much as possible. These features are coordinated with subsequent stereocontrolled trans/annular aldol reactions during the quenching process. The adherence to these mechanistic guidelines is so all-encompassing that product stereochemistry can be reliably predicted from the outset.

The squarate ester cascade, the multicomponent mechanistic features of which are being systematically elucidated,[1−3] holds the prospect of evolving into a highly useful synthetic transformation in organic chemistry.[4−6] Its future development rests, however, on suitable elucidation of the particular step in the sequenced process which is controlling of product stereochemistry. In the examples studied heretofore, the extent and locus of substitution were insufficient to allow proper delineation of this more complex question. For the present purposes, it is necessary to fix one or more groups at positions within the reactants which ultimately force the developing polycyclic framework to respond in one stereochemical sense or the other. We now disclose informative examples which reveal the timing point where relative or absolute configuration is regulated in the product.[7]

The stages where stereoselection is amenable to operation are presented in Scheme 1. When a *chiral* alkenyl anion is added to **1**, the expectation is that the diastereomeric alkoxides **2** and **3** will arise via competing transition states. In light of the virtual planarity of the squarate electrophile, the two reaction trajectories would under normal circumstances not be very disparate in their energetic demands. In most examples, the **2:3** ratio should therefore be reasonably balanced. The distinctive stereochemical features inherent in **2** and **3** remain equivalently obvious as the reaction is carried through to the dialkoxides **4** and **5**. Adherence to orbital symmetry control during opening of the four-membered ring, with conrotation occurring so as to place the oxido anions to the exterior,[8] requires that **4** serve as the specific precursor to **6** and that **5** give rise to **7**. The diastereomeric distinction persists because the two octatetraenes are helical molecules possessing coils of opposite pitch. Octatetraene **6** is seen to be sterically disadvantaged relative to **7** because the R group finds itself intercalated inside the spiral rather than being positioned on its exterior. Should this structural feature prove to be a constraint on the rate of conrotatory 8π electrocyclization in **6**, the possibility is opened that uncoiling may occur with subsequent isomerization to **7**. No prior attention, either experimental or theoretical in nature, has been paid to this interesting possibility. Should equilibration operate, handedness would be eroded, and the distributions of **8** and **9** would then be determined not by the original proportions of **2** and **3** but by the relative rates of ring closure of **6** and **7**. Stated differently, the capability would exist for achieving complete chirality control simply by modulating the steric bulk of R such that passage to product via **9** becomes kinetically dominant or preferably exclusive.

Results

The Isopropyl Test. The relative ease with which enantiopure (*S*)-3-isopropylcyclopentenyl bromide can be prepared[9] prompted initial examination of its lithium derivative. Following addition of this cycloalkenyl anion to an equimolar amount of diisopropyl squarate at −78 °C in THF, small aliquots of the resulting solution were quenched. The ratio of α-hydroxy ketones corresponding to **2** and **3** was determined to be the 1:1 by 300 MHz ^{1}H NMR analysis. Subsequent addition to the

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(1) Paquette, L. A.; Morwick, T. M.; Negri, J. T.; Rogers, R. D. *Tetrahedron* **1996**, *52*, 3075.
(2) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 1230.
(3) Paquette, L. A.; Doyon, J. *J. Org. Chem.* **1997**, *62*, in press.
(4) Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1996**, *61*, 146.
(5) Paquette, L. A.; Kuo, L. H.; Doyon, J. *Tetrahedron* **1996**, *52*, 11625.
(6) Morwick, T. M. Ph.D. Thesis, The Ohio State University, 1996.
(7) Paquette, L. A.; Doyon, J.; Kuo, L. H. *Tetrahedron Lett.* **1996**, *37*, 3299.
(8) (a) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989. (b) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099. (c) Thomas, B. E., IV; Evansek, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165. (d) Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813.
(9) Paquette, L. A.; Dahnke, K.; Doyon, J.; He, W.; Wyant, K.; Friedrich, D. *J. Org. Chem.* **1991**, *56*, 6199.

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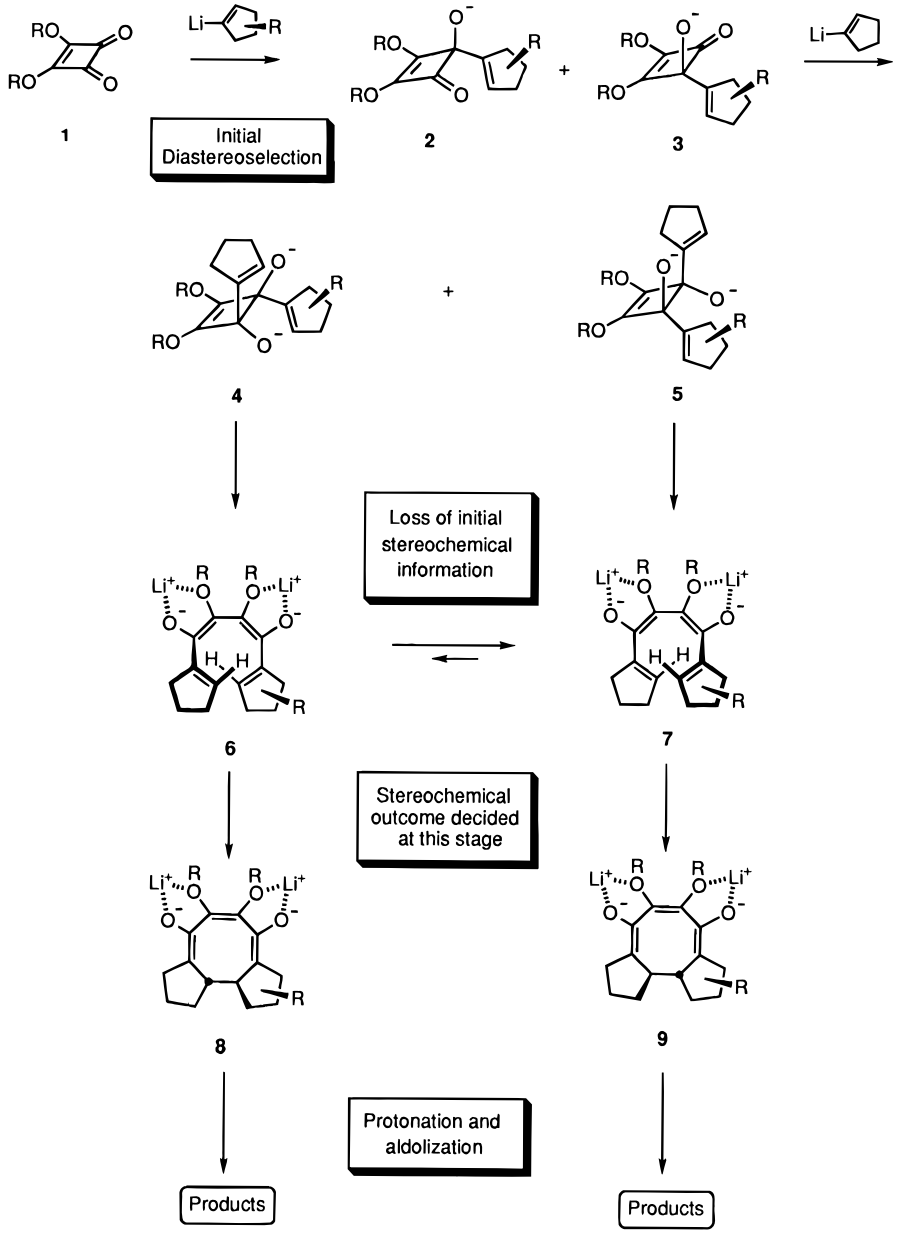
Scheme 1



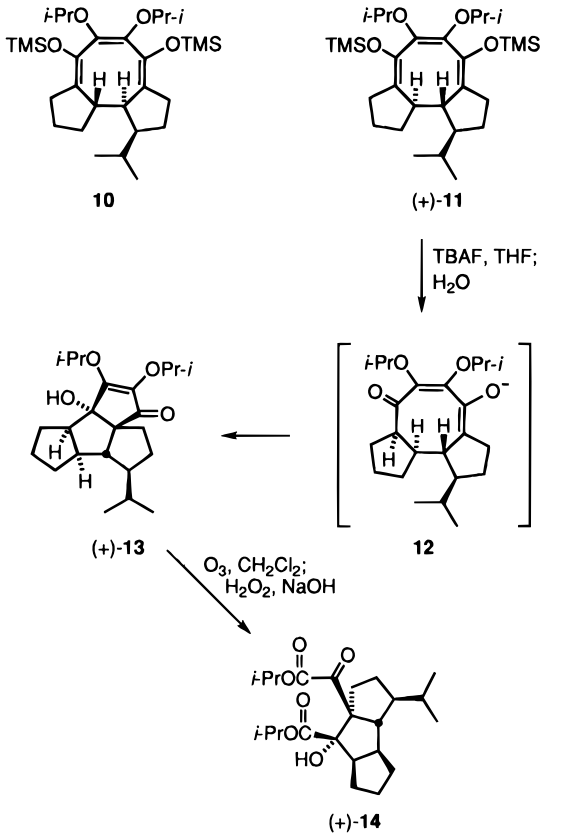
original reaction mixture of excess cyclopentenyllithium was followed by warming to room temperature and return to 0 °C prior to quenching with chlorotrimethylsilane and triethylamine. If stereochemistry is decided at step 1 and no "leakage" operates during passage through the two conrotatory steps, the electrocyclic model contemplates the formation of **10** and **11** in approximately equal amounts. However, careful chromatography resulted in the exclusive isolation of **11** in 64% yield (Scheme 2). Ensuing desilylation of **11** with tetra-*n*-butylammonium fluoride under aqueous workup conditions was met with more rapid protonation at the less sterically hindered enolate center to give **12**, transannular aldolization in which ultimately produced **13** (93%). Although we were initially unable to define unequivocally the interrelationship of the stereogenic centers in either **11** or **13**, ozonolytic cleavage of the tetracyclic product afforded diester **14** whose structure and relative (as well as absolute) stereochemistry was convincingly solved by a combination of COSY, HETCOR, and NOESY experiments at 300 and 500 MHz.

The sole production of **11** was the first indication that the initial condensation products **2** and **3** are both amenable to conversion to the advanced intermediate **9**. However, absolute proof of helical equilibration was not yet regarded as being in hand since the diastereomeric monoadducts were not separable and could not therefore be independently converted to **11**. This central issue will be discussed subsequently. It is important to point out here that, as a consequence of the several individual steps associated with the cascade, overall reaction efficiencies customarily peak at the 50−80% level.

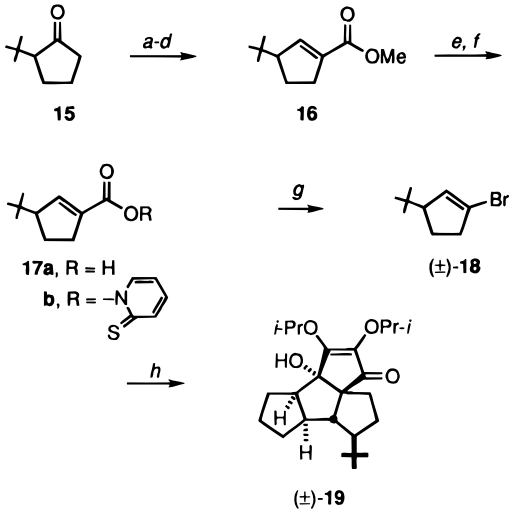
Increase of Substituent Bulk to the *tert*-Butyl Level. The unidirectional course of the cascade discussed above was attributed in large part to the specific position occupied by the isopropyl substituent in **6** and **7**. In effect, the alkyl group necessarily resides immediately adjacent to one of the two octatetraene reaction centers involved in the ring closure that generates the eight-membered ring. We reasoned that if the impact of isopropyl is very good, matters might be further improved in the *tert*-butyl analogue. Accordingly, 2-*tert*-butylcyclopentanone (**15**)[10] was carbomethoxylated, reduced with sodium borohydride, and dehydrated by conversion to its

(10) Chan, T. H.; Paterson, I.; Pinsonnault, J. *Tetrahedron Lett.* **1977**, 4183.

Scheme 2



Scheme 3

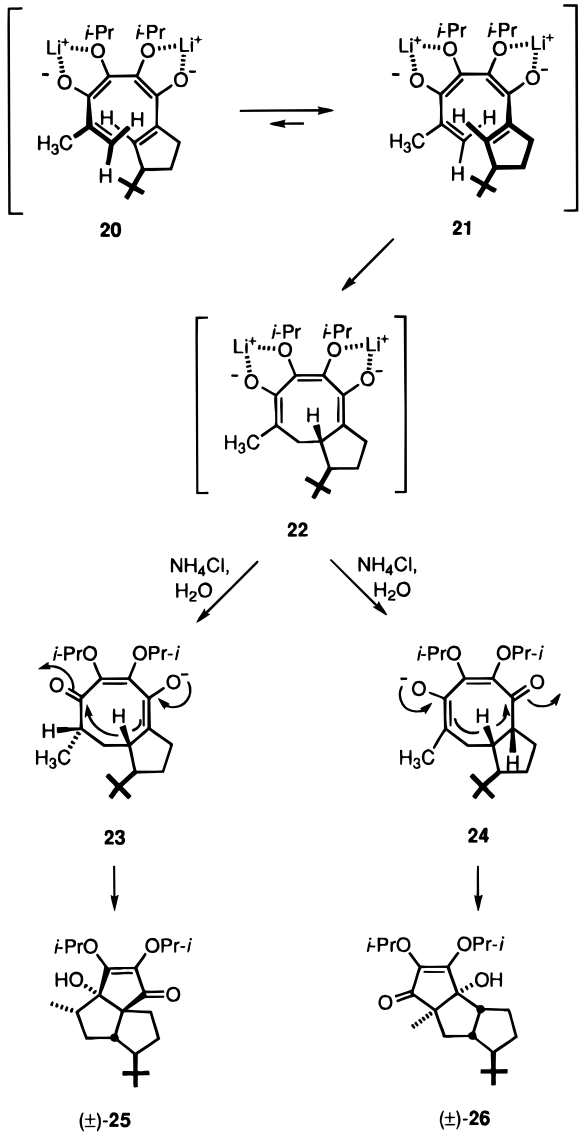


mesylate and subsequent elimination with DBU (Scheme 3). Saponification of **16**, formation of ester **17b,** and brominative decarboxylation under free radical conditions delivered **18**.

Subsequent to lithium−halogen exchange in **18**, cocondensation of this anion and 1-cyclopentenyllithium with diisopropyl squarate afforded uniquely **19** in 49% yield. The detailed structural features of this tetraquinane were ascertained by X-ray crystallographic analysis. The formation of **19** indicates that an entirely similar reaction profile had been followed, although the increased steric bulk of the *tert*-butyl substituent lowered reaction effficiency somewhat.

In a companion experiment, 2-propenyllithium was utilized as the coreagent with metalated **18**. This combination has as its consequence the omission of a five-membered ring at one terminus in each of the octatetraenes. As a result of this

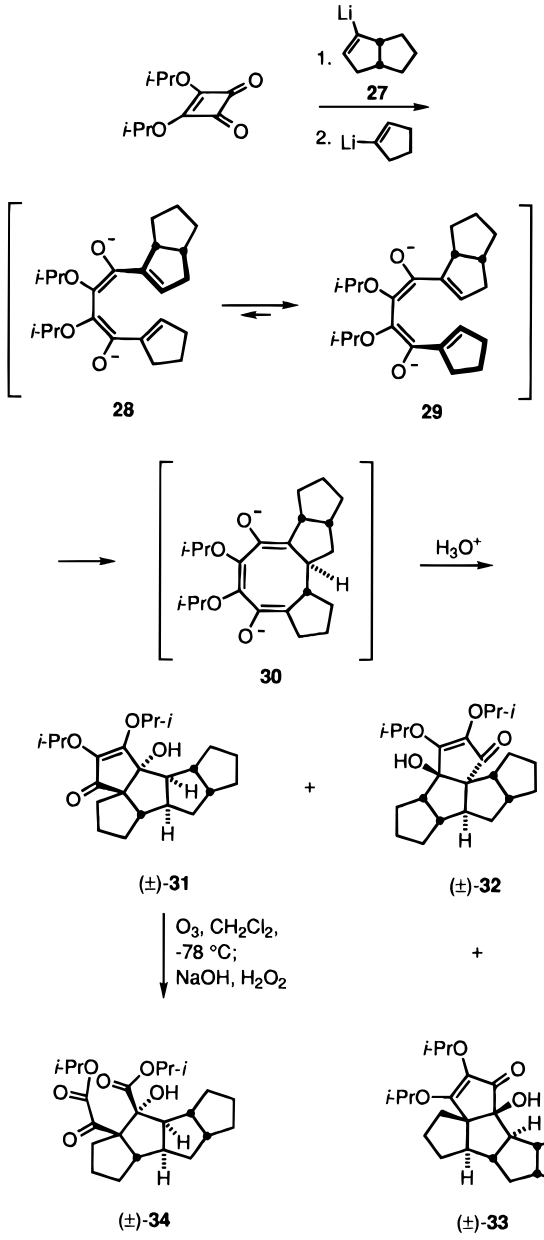
Scheme 4



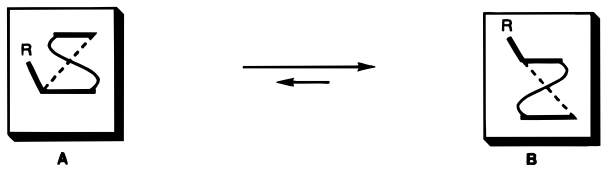
structural modification, the steric compression associated with the conrotatory cyclization of **20** and **21** has been reduced relative to that associated with the production of **19** (Scheme 4). Notwithstanding, the ring closure of **21** to **22** remained kinetically dominant, as revealed by the isolation of the angular triquinane **25** (23%) and its linear congener **26** (6%). Evidently, dianion **22** is preferentially protonated at the methyl-substituted carbon to provide **23** about four times more efficiently than at the cyclopentenyl site as in **24**. The relative stereochemistries of **25** and **26** were established by means of confirmatory NOE and COSY experiments. Particularly helpful in these studies was the appearance in $CDCl_3$ of the methyl substituent in **25** as a doublet ($J = 7$ Hz) at δ 1.17 and that in **26** as a singlet at δ 1.12.

Stereocontrolled Pentaquinane Construction. The consistency with which cyclooctatriene formation is kinetically biased in favor of **7** and **21** can be described pictorially as in **A** and **B**. The presence of a bulky R group such as isopropyl or *tert*-butyl on the interior of the coil as in **A** is sufficient to impede the cyclization of this helix diastereomer. Conrotation operates more rapidly when the R group is projected outwardly as in **B**. The profound consequence of still faster interconversion of **A** and **B** is that the configuration of the R substituted carbon would control the stereogenicity (either absolute as in

Scheme 5

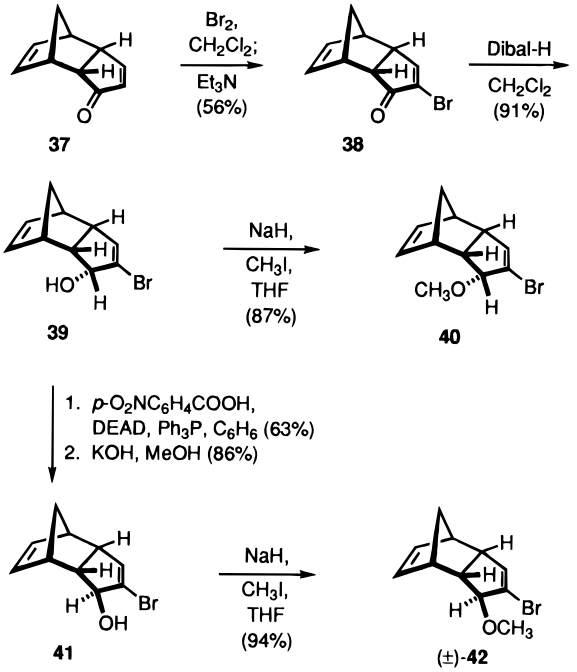


the case of **13** or relative as with **19**, **25**, and **26**) developing at the many additional chiral centers.



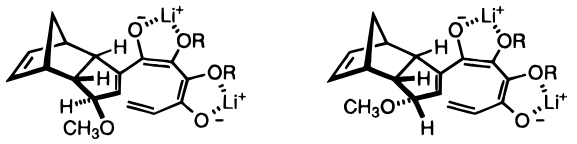
This mechanistic paradigm anticipates that the racemic bicyclo[3.3.0]octenyllithium reagent **27**[11] would for comparable reasons advance to the complex pentacyclic polyquinanes **31** and **32** via the cascade pathways involving **28** and **29** (Scheme 5). The diastereoselectivity for the monoaddition of **27** to diisopropyl squarate was 1.2:1. Submission of this mixture to the action of lithiocyclopentene under standard conditions resulted in the isolation of **31** (27%) and **32** (38%) in addition to 10% of the 1,4-addition[1] product **33**. As usual, pentaquinanes

Scheme 6



31 and **32** arise from competitive protonation at the two available sites in their common precursor **30**, which in turn is necessarily formed via **29** only. The three-dimensional structural features of **32** and **33** were unambiguously established by X-ray crystallography, while that of **31** was secured by detailed NMR analysis of the ozonolysis product of **34**.

More Insight on Steric Control Elements. In the examples presented above, isopropyl, *tert*-butyl, and bicyclo[3.3.0]octenyl subunits served to control the stereochemical course of the conrotatory electrocyclization of transiently generated 1,3,5,7-octatetraene intermediates. The biasing influence for exclusive bond formation from one face of each π terminus arises from the steric shielding provided by these pendant substituents. No counterbalancing forces are present to perhaps encourage ring closure in the opposite diastereofacial sense. This is not the case in **35**. Should the methoxyl group be controlling by overriding the steric compression prevailing on the endo surface, progression to product would occur anti to the oxygen atom. In **36**, the steric contributions are reinforcing, such that electrocyclization on the exo surface should be overwhelmingly favored. Were the norbornenyl framework to exert a greater steric barrier than methoxyl in **35**, then **35** and **36** would partake of identical stereocontrol during generation of the eight-membered ring.



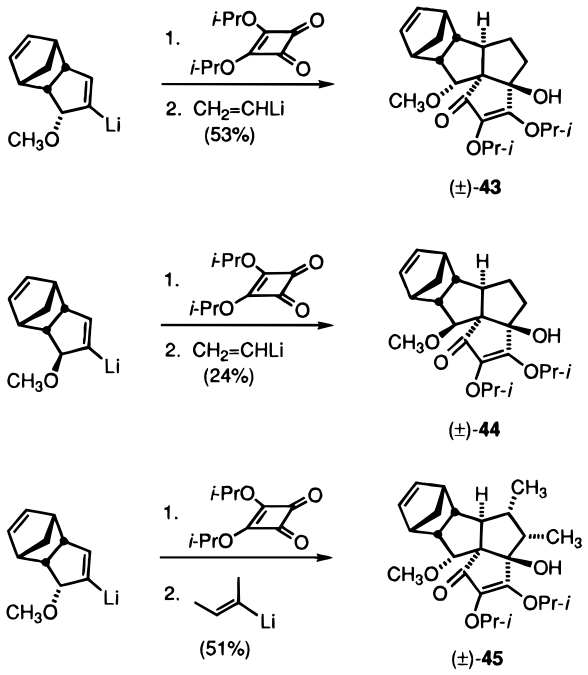
In keeping with established trends, dienone **37** underwent smooth bromination/ dehydrobromination to provide **38**[12] (Scheme 6). Sequential Dibal-H reduction and O-methylation of **38** proceeded via **39** to deliver **40**. Application of a variant of the Mitsunobu reaction[13] to **39** and hydrolysis of the resulting *exo*-*p*-nitrobenzoate furnished **41** from which **42** was produced.

(11) (a) Paquette, L. A.; Learn, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 7873. (b) Paquette, L. A.; Learn, K. S.; Romine, J. L.; Lin, H.-S. *J. Am. Chem. Soc.* **1988**, *110*, 879.

(12) Dols, P. P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1993**, *49*, 11373.

(13) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

Scheme 7

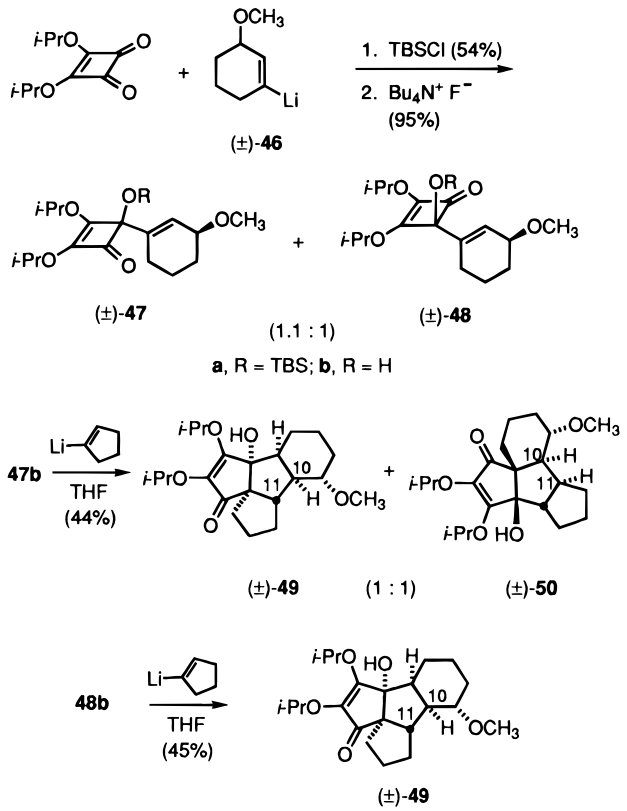


When the monoadducts formed from lithiated **40** and diisopropyl squarate were treated directly with vinyllithium, subsequently quenched with saturated NH_4Cl solution, and subjected to chromatography, the polycycle **43** was isolated as the only characterizable product in 53% yield (Scheme 7). The NMR coupling constants of the several methine protons in **43** provide an especially reliable means for establishing the relative configuration of its stereogenic centers. When **42** was similarly brought into reaction, stereoisomer **44** was produced in more modest yield (24%). The epimeric relationship between **43** and **44** at the methoxyl-substituted carbon atom was settled with certainty by noting in the ^{1}H NMR spectrum of **44** that the hydroxyl proton absorption appears at δ 4.74 (in C_6D_6) because of hydrogen bonding to the nearby exo methoxy substituent. In **43** where these functional groups are not proximate, the value of the corresponding chemical shift is in the usual range (δ 2.23 in C_6D_6).

Although the formation of **43** and **44** confirmed that **35** and **36** both entered into structural reorganization by bonding from the exterior of the cyclopentene, the vinyl group is insufficiently substituted to prove that the electrocyclization pathway was actually operative. For this reason, recourse was also made to (*Z*)-2-butenyllithium. Coreaction of the squarate ester with this organometallic and **40**-Li afforded **45**, the cis-α disposition of the two secondary methyl groups in which was elucidated by single-crystal X-ray crystallography. Consequently, the formation of all three pentacyclic stereoisomers **43**−**45** correlates well with operation of the general pathway shown in Scheme 1, with the norbornenyl part-structure contributing overwhelmingly to steric control of the conrotatory closure of the exo helix. This finding occasioned no surprise.

Proof of Helical Equilibration. The provocative results detailed above suggest that equilibration between pairs of helical octatetraenyl bisoxy anions might well be operative but do not demand this conclusion. To prove conformational interconversion at this key stage in the cascade requires either very high yields of the "correct" product or proper demonstration that the "wrong" helix is in fact generated, does not lead to decomposition and actually gives rise to the crossover cyclization product. On the basis of the latter working premise, success would be realized if it were possible to isolate the initial diastereomeric *monoadducts* in pure condition and to subject each of these intermediates independently to the action of a second common alkenyl anion.

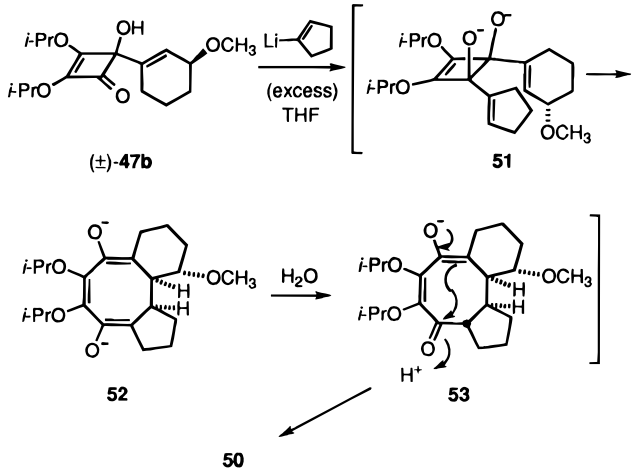
Scheme 8



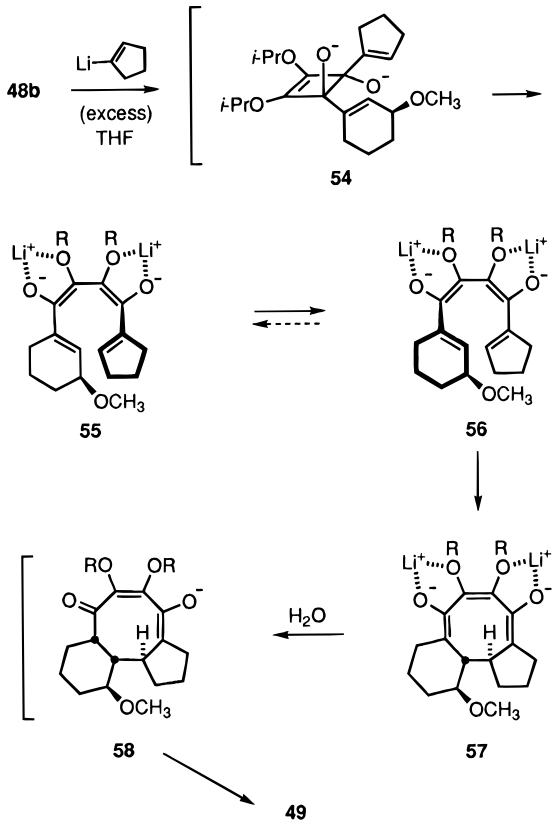
The central element of this plan is outlined in Scheme 8. Treatment of diisopropyl squarate with somewhat less than 1 equiv of 3-methoxycyclohexenyllithium (**46**) was followed by direct conversion to the O-silylated adducts **47a** and **48a**. The lowered polarity of these protected monoketones relative to the free alcohols was properly conducive to their chromatographic separation. Based on the weights of the purified fractions and ^{1}H NMR analysis of original product mixtures, **47** and **48** were seen to be formed in approximately equal amounts (ratio 1.1:1). Individual unmasking of the tertiary hydroxyl group proceeded very efficiently in both cases to return diastereomerically pure **47b** and **48b** in yields of 95% or better. Moreover, the high crystallinity of **47b** allowed for its structural definition by X-ray diffraction. As a consequence, the three-dimensional stereochemical features of **48** were also made known.

At this stage, **47b** was treated with cyclopentenyllithium in order to initiate the squarate ester cascade. An equimolar mixture of **49** and **50** was obtained in 44% isolated yield. Once again, reliance was placed on X-ray crystallographic analysis for the purpose of corroborating product stereochemistry. The cis relationship of the hydrogen atoms bonded to C-10 and C-11 clearly identifies this product to be the result of cis addition to **47b**, with ensuing rearrangement occurring via a dianionic oxy-Cope pathway as depicted in Scheme 9. Arrival at **51** and subsequent adherence to an energetically favorable boatlike transition state leads to **52**, which undergoes subsequent protonation preferably at the more strained cyclopentenyl site to deliver **53**. Transannular aldol cyclization within **53** gives rise to **50**. It will be recognized that this particular reaction channel reliably transcribes the stereochemistry originally present in **47b** into that resident in **50**.

Scheme 9



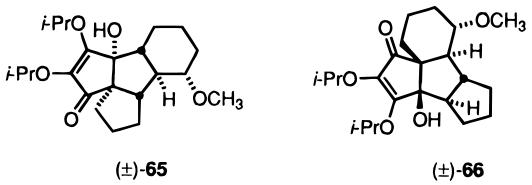
Scheme 10



The second cascade product was identified as **49** on the strength of convincing long-range DEPT and NOE measurements. In this instance, the trans relationship of the hydrogen atoms across the C(10)−C(11) linkage requires that this tetracyclic ketone arise via the electrocyclic mechanistic scheme. The important issue here is that **49** was also generated from **48b**! In this example, **49** was the only polycyclic compound observed. In light of this development, the stereochemical features that cause **47b** to be diastereomeric with **48b** are seen to have been lost during progression through the electrocyclic cascade. This can be so only if helical equilibration operates, necessitating the interconversion of **55** with **56**, and ultimate cyclization via the latter tetraene because of the reduced nonbonded steric interaction as bonding materializes (Scheme 10). Cyclobutenone **47b** enters the manifold at **56** and shares intermediates **56**−**58** in common with **48b** during conversion into **49** (see Discussion).

It is noteworthy that **48b** exhibits no detectable tendency for entering into cis addition in a manner parallel to **47b**. Obviously, the relative orientation of the methoxyl substituent has a direct bearing on the π-facial stereoselectivity of nucleophilic capture by the cyclobutenone carbonyl group in these systems. Although this phenomenon has since been examined more globally,[14] a companion study involving **59** was presently undertaken. The objective was to elucidate the impact of an ether oxygen having significantly reduced basicity. To this end, diisopropyl squarate was treated sequentially with **59** and cyclopentenyllithium without intermediate isolation of the monoadducts (Scheme 11). Careful chromatography of the reaction mixture allowed for the isolation of three isomeric tetracyclic ketones in a ratio of 2.7:1.2:1 (63% combined yield). The structural assignments were elucidated via a combination of COSY, HETCOR, long-range DEPT, and NOE experiments at high field. Added corroboration was achieved in the case of **61** following its conversion to **63** and analysis of this alcohol by X-ray diffraction. The availability of **63** led to the formation of methyl ether **64**, whose linear triquinane substructure stereochemistry proved to be distinctively different from that present in **50**.

It will be recognized that **60**, **61**, and **62** are the end-products of an electrocyclic cascade. The distinction between **61** and **62** arises from initial regioselective protonation of the cyclooctatriene dienolate from opposite surfaces. Isomer **60** originates from quenching at the alternative anionic site subsequent to ring closure. For purposes of structural corroboration, **60** and **62** were desilylated and O-methylated to give **65** and **66**, respectively, neither of which had surfaced in the earlier studies involving **46**.



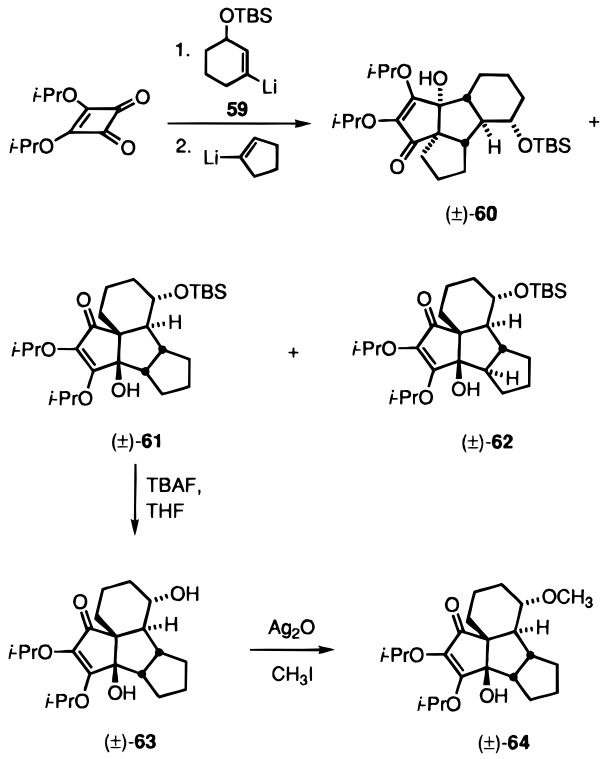
As anticipated, the significantly reduced capacity of the *tert*-butyldimethylsilyl oxygen in **59** for coordination to lithium is accompanied by an inability on the part of either diastereomeric monoadduct to enter into cis addition with cyclopentenyllithium. The absence of products arising from the dianionic oxy-Cope route is customary.[2,3,5−7] Accordingly, **47b** deserves consideration as a harbinger of previously unappreciated substituent-induced stereocontrol in these remarkable sequenced reactions.[14]

Discussion

Previous studies of the squarate ester cascade lacked the benefit of adequate stereochemical labeling for gaining insight into the possible operation of helical interconversion prior to conrotatory cyclization of the octatetraene intermediates. What has now become clear is that the chirality inherent in the helix component of these intermediates can be completely eroded if steric control elements are properly deployed. This is not to say that high stereoselectivity will cease to be observed. Rather, ring closure is guided specifically into that reaction channel which is characterized by the lower transition state energy, irrespective of the precise point at which the preequilibrium manifold is entered. The clear-cut criterion is that *the steric bulk of a properly positioned substituent will skirt nonbonded steric compression and thereby exert complete chirality control on the overall process in a highly predictable direction.*

(14) Paquette, L. A.; Kuo, L. H.; Doyon, J. Submitted for publication.

Scheme 11



Closer inspection of the manner in which the *trans*-dialkoxides rearrange provides useful clarification. These early intermediates are relegated for reasons of orbital symmetry constraints and the electronic character of the oxido anions to undergo conrotatory ring opening in a *single direction. The oxy anions must move to the molecular exterior*.[8] In so doing, the two stereogenic centers resident in the cyclobutene ring are transmuted into components of the cisoid double bonds of the octatetraene and, more particularly, into a very specific helical pitch (see, for example, **55** and **56**). While the cyclopentene terminus finds itself positioned above the cyclohexene subunit in **56** on the surface opposite to that occupied by the methoxyl group, a more congested syn arrangement prevails in **55**. As a direct consequence, **55** is unable to cyclize readily. Instead, the more enthalpically attractive route involving conversion to the octatetraene of opposite helicity, *viz.* **56**, and 8π conrotation to generate **57** is followed. The net effect of this crossover is to compromise the stereogenicity of the oxido-substituted ring carbons in the cyclobutene adducts and to surrender full control of the stereochemical outcome of the cascade to the methoxyl substituted carbon.

Experimental Section

The general experimental protocols followed in this study parallel those described earlier in ref 1.

[[(1*S*,10a*R*,10b*R*)-1,2,3,8,9,10,10a,10b-Octahydro-5,6-diiso-ropoxy-1-isopropyldicyclopenta[*a,c*]cyclooctene-4,7-ylene]dioxy]bis[trimethylsilane] (11). The general procedure for lithium−halogen exchange and coupling to the squarate ester was the same as that detailed elsewhere.[3] Reaction of 227 mg (1.2 mmol) of (3*R*)-(+)-1-bromo-3-isopropylcyclopentene with 200 mg (1.0 mmol) of diisopropyl squarate (reaction time, 1 h) and 582 mg (3.0 mmol) of cyclopentenyl iodide was followed by overnight warming to room temperature, cooling to 0 °C, treatment with 1.087 g (10 mmol) of trimethylsilyl chloride and 300 mg of triethylamine, and pouring directly onto a short silica gel column (elution with 50% ethyl acetate-hexanes). After concentration, the residue was purified by flash chromatography (silica gel, elution with 3% ethyl acetate in hexanes containing 0.5% triethylamine) to give 333 mg (64%) of **11** as a colorless oil ^{1}H NMR (300 MHz, C_6D_6) δ 4.34 (heptet, J = 6 Hz, 1 H), 4.28 (heptet, J = 6 Hz, 1 H), 2.86 (ddd, J = 16, 10, 3 Hz, 1 H), 2.70 (d, J = 11 Hz, 1 H), 2.64 (dd, J = 8, 6 Hz, 1 H), 2.19 (dt, J = 12, 5 Hz, 1 H), 2.20−2.01 (m, 2 H), 1.78−1.51 (series of m, 4 H), 1.50−1.34 (series of m, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.27 (d, J = 6 Hz, 3 H), 1.25 (d, J = 6 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H), 0.91 (d, J = 6 Hz, 3 H), 0.85 (d, J = 6 Hz, 3 H), 1.21−1.05 (m, 1 H), 0.28 (br s, 9 H), 0.27 (br s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 139.2, 138.2, 136.3, 135.7, 134.5, 130.90, 70.8, 70.6, 51.4, 51.1, 46.0, 31.48, 31.45, 28.6, 27.5, 26.5, 23.9, 23.5, 23.3, 23.0, 22.0, 21.5, 20.4, 1.05 (3 C), 0.90 (3 C); MS *m/z* (M^+) calcd 520.3404, obsd 520.3414; [α]S(21,D) = +14.6 (*c* 1.05, $CHCl_3$).

Anal. Calcd for $C_{29}H_{52}O_4Si_2$: C, 66.87; H, 10.06. Found: C, 66.85; H, 9.96.

(1*S*,3a*S*,6a*S*,6b*R*,9a*R*,9b*R*)-1,2,3,6a,6b,7,8,9,9a,9b-Decahydro-6a-hydroxy-5,6-diisopropoxy-1-isopropyl-4*H*-dicyclopenta[*a,b*]pentalen-4-one (13). The general procedure for lithium−halogen exchange and coupling to the squarate ester was the same as that detailed elsewhere.[3] Reaction of 227 mg (1.2 mmol) of (3*R*)-(+)-isopropyl-1-bromocyclopentene with 200 mg of diisopropyl squarate (reaction time, 1 h) and 582 mg of cyclopentenyl iodide (3.0 mmol), overnight stirring at room temperature, and quenching with saturated $NaHCO_3$ solution, followed by usual workup and flash chromatography (silica gel, elution with 5−20% ethyl acetate in hexanes) gave 132 mg (35%) of **13** as a pale yellow oil: IR (neat, cm^{-1}) 1618, 1250, 1212, 1175, 1108, 1060, 1032, 879, 843; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (heptet, J = 6 Hz, 1 H), 5.27 (heptet, J = 6 Hz, 1 H), 2.40−2.26 (m, 3 H), 2.21 (t, J = 6 Hz, 1 H), 2.09 (br s, 1 H), 1.89−1.56 (series of m, 7 H), 1.48−1.35 (series of m, 4 H), 1.16 (d, J = 6 Hz, 3 H), 1.11−1.09 (d, J = 6 Hz, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.3, 165.9, 130.1, 84.8, 73.9, 71.7, 69.1, 57.4, 56.4, 55.3, 52.5, 32.5, 30.6, 29.9, 28.4, 25.4, 23.0, 22.8, 22.7, 22.3, 22.2, 20.5; MS *m/z* (M^+) calcd 376.2614, obsd 376.2619; [α]$^{22}_D$ = +16.7 (*c* 0.93, $CHCl_3$).

The same compound was obtained by hydrolysis of **11**. This bissilyl enol ether (40 mg, 77 μmol) was dissolved in THF (2 mL), treated dropwise with tetrabutylammonium fluoride solution (1 mL of 1 M in THF (1.0 mmol) (containing 5% wt of water), and quenched with 1 mL of saturated NH_4Cl solution prior to extraction with ether. The combined organic extracts were dried, concentrated, and purified chromatographically (silica gel, elution with 10% ethyl acetate in hexanes) to give 27 mg of **11** as a colorless oil identical in all respects to the material generated earlier.

(3a*R*,3b*R*,4*S*,6a*S*,7*S*,7a*R*)-7-Carboxydecahydro-7-hydroxy-4-isopropyl-6a*H*-cyclopenta[*a*]pentalene-6a-glyoxylic Acid Diisopropyl Ester (14). Tetraquinane **13** (55 mg, 0.146 mmol) was dissolved in 30 mL of dry CH_2Cl_2, cooled to −78 °C, and ozonolyzed for 15 min. Subsequently, 5 mL each of 30% hydrogen peroxide and 10% sodium hydroxide were added, and the temperature was allowed to reach 25 °C. Neutralization with 10% HCl, extraction with CH_2Cl_2, washing with $NaHCO_3$ solution, drying, concentration, and filtration over silica gel (elution with 10% ethyl acetate in hexanes) gave 50 mg (84%) of **14** as a colorless oil: IR (film, cm^{-1}) 3456, 1732, 1718; ^{1}H NMR (300 MHz, C_6D_6) δ 4.94 (heptet, J = 6 Hz, 1 H), 4.84 (d, J = 6 Hz, 1 H), 3.36 (s, 1 H), 3.03 (ddd, J = 10, 9, 6 Hz, 1 H), 2.96 (t, J = 5 Hz, 1 H), 2.32 (dt, J = 14, 6.5 Hz, 1 H), 2.05−1.90 (m, 2 H), 1.85−1.50 (series of m, 7 H), 1.45−1.30 (m, 2 H), 1.20−1.00 (m, 1), 1.06 (d, J = 6 Hz, 3 H), 1.04 (d, J = 6 Hz, 3 H), 0.99 (d, J = 6.5 Hz, 3 H), 0.96 (d, J = 6 Hz, 3 H), 0.95 (d, J = 6 Hz, 3 H), 0.82 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 192.8, 174.9, 163.1, 88.0, 76.4, 70.6, 69.7, 59.0, 56.7, 55.4, 52.7, 33.2, 33.1, 32.4, 30.5, 27.8, 27.0, 22.7, 21.55, 21.51, 21.4, 21.3, 21.2; MS *m/z* (M^+) calcd 408.2479, obsd 408.2453; [α]$^{22}_D$ = +14.5 (*c* 1.02, $CHCl_3$).

Methyl 3-*tert*-Butyl-2-oxocyclopentanecarboxylate. A 500 mL flask was charged with potassium hydride (15.30 g of 35% in mineral oil, 0.13 mmol) and dry THF (250 mL). 2-*tert*-Butylcyclopentanone (6.25 g, 44.6 mmol) in dry THF (50 mL) was added slowly at 0 °C, and the reaction mixture was stirred at 22 °C for 3 h. Dimethyl carbonate (5.6 mL, 67.0 mmol) was introduced at 0 °C, and the reaction mixture was stirred at 22 °C for another 12 h. After the addition of water (250 mL) at 0 °C, the reaction mixture was extracted with ether (2 × 250 mL), and the combined organic layers were washed with water (250 mL) and brine (250 mL) prior to drying and concentration.

Purification of the residue by vacuum distillation (bp 102−104 °C, 0.3 Torr) gave the β-keto ester as a clear liquid consisting of a 2:1 mixture of diastereomers (6.18 g, 70%): IR (film, cm^{-1}) 1753, 1726, 1366, 1241; ^1H NMR (300 MHz, $CDCl_3$) δ [3.59 (s, major) and 3.55 (s, minor, 3 H combined)], [3.13−3.09 (m, minor), 2.93 (dd, J = 12.1, 8.0 Hz, major, total 1 H)], 2.18−1.81 (m, 4 H), 1.61−1.49 (m, 1 H), [0.85 (s, major), 0.83 (s, minor), total 9 H]; ^{13}C NMR (75 MHz, $CDCl_3$) ppm (major isomer) 211.8, 169.7, 57.8, 56.5, 51.9, 32.3, 27.2, 24.0, 23.6; (minor isomer) 212.0, 168.9, 57.9, 54.8, 51.9, 32.3, 27.4, 24.7, 24.0; MS *m/z* (M^+) calcd 198.1291, obsd 198.1273.

Methyl 3-*tert*-Butyl-1-cyclopentenecarboxylate (16). A solution of the preceding keto ester (2.42 g, 12.2 mmol) in methanol (60 mL) was treated slowly at 0 °C with sodium borohydride (0.46 g, 12.1 mmol). After the reaction mixture had stirred at 0 °C for 3 h, water (50 mL) was added, and the product was extracted into ether (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), then dried, concentrated, and used directly without further purification.

The crude β-hydroxy ester was dissolved in THF (120 mL) and treated successively with methanesulfonyl chloride (1.4 mL, 18 mmol) and triethylamine (5.1 mL, 36.7 mmol) at 0 °C. After the reaction mixture had stirred at 22 °C for 15 h, water (100 mL) was added, and the product was extracted into ether (2 × 100 mL), dried, and concentrated to provide the crude mesylate which was dissolved in benzene (30 mL), treated with DBU (2.7 mL, 18.1 mmol), and heated at 80 °C for 5 h. Water (20 mL) was added, and the mixture was extracted with ether (2 × 30 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried, and concentrated to leave a yellow liquid, distillation of which at 97−99 °C and 0.3 Torr gave **16** as a clear liquid (1.02 g, 46% for three steps): IR (film, cm^{-1}) 1720, 1633, 1365, 1097; ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (d, J = 1.9 Hz, 1H), 3.62 (s, 3 H), 2.58−2.50 (m, 1 H), 2.47−2.37 (m, 2 H), 1.92−1.57 (m, 1 H), 1.54−1.51 (m, 1 H), 0.78 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 165.5, 145.4, 136.3, 57.5, 51.0, 33.1, 31.1, 27.3, 25.1; MS *m/z* (M^+) calcd 182.1264, obsd 182.1290.

3-*tert*-Butyl-1-cyclopentenecarboxylic Acid (17a). A solution of **16** (0.89 g, 4.89 mmol) in methanol (20 mL) containing potassium hydroxide (0.89 g, 15.9 mmol) was heated at 65 °C for 13 h, cooled, acidified with 2 N aqueous hydrochloric acid, and diluted with ether (50 mL). The resulting mixture was washed with water (25 mL) and brine (25 mL), dried, and concentrated to leave a residue which was purified by flash chromatography (elution with 20% ethyl acetate in hexanes) to give **17a** as a pale yellow solid (0.75 g, 91%), mp 64−66 °C: IR (film, cm^{-1}) 1688, 1427, 1292, 932; ^1H NMR (300 MHz, $CDCl_3$) δ 11.52 (br s, 1 H), 6.90 (m, 1 H), 2.90−2.63 (m, 1 H), 2.57−2.45 (m, 2 H), 2.04-1.92 (m, 1 H), 1.79−1.05 (m, 1 H), 0.88 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 171.1, 148.7, 136.3, 58.0, 33.3, 30.9, 27.5, 25.3; MS *m/z* (M^+) calcd 167.1148, obsd 182.1149.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.54; H, 9.57.

1-Bromo-3-*tert*-butylcyclopentene (18). A mixture of **17a** (1.23 g, 7.32 mmol) and thionyl chloride (1.7 mL, 36.3 mmol) was stirred at 22 °C for 24 h and freed of excess reagent in vacuo to provide the acid chloride as a yellow liquid, which was dissolved in bromotrichloromethane (35 mL) containing a catalytic quantity of AIBN. This solution was introduced via syringe pump into a hot (100 °C) mixture of the sodium salt of 1-hydroxypyridine-2-thione (1.20 g, 8.05 mmol) and bromotrichloromethane during 30 min. The reaction mixture was heated at 100 °C for another 10 min, cooled, filtered through Celite (hexane rinse), and concentrated under reduced pressure to provide a brown liquid, purification of which by flash chromatography on silica gel (hexane elution) gave **18** as a yellow liquid (0.99 g, 67% overall): IR (film, cm^{-1}) 1622, 1365, 1185, 797; ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 2.58−2.44 (m, 2 H), 2.16−1.90 (m, 1 H), 1.78−1.66 (m, 1 H), 1.35-1.15 (m, 1 H), 0.85 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 133.1, 121.3, 56.8, 39.7, 32.2, 30.4, 27.2; MS *m/z* (M^+) calcd 202.0110, obsd 202.0145.

(1*S,3a*S**,6a*S**,6b*R**,9a*R**,9b*R**)-1,2,3,6a,6b,9,9a,9b-Decahydro-6a-hydroxy-5,6-diisopropoxy-1-*tert*-butyl-4(*H*)-dicyclopenta[*a,b*]pentalen-4-one (19).** *tert*-Butyllithium (1.6 mL of 1.7 M in pentane, 2.6 mmol) was added dropwise at −78 °C to a solution of **18** (0.24 g, 1.18 mmol) in anhydrous THF (6 mL), stirred at −78 °C for 1 h, and transferred to a cold (−78 °C) solution of diisopropyl squarate (0.19 g, 0.95 mmol) in dry THF (5 mL). After 2.5 h, 1-lithiocyclopentene [as generated from 1-iodocyclopentene (0.23 g, 1.2 mmol) in THF (6 mL) and *tert*-butyllithium (1.8 mL of 1.7 M in pentane, 2.6 mmol) at −78 °C for 1 h] was transferred via cannula to the above solution at −78 °C. After the mixture had stirred at 22 °C for 24 h, deoxygenated saturated NH_4Cl solution (10 mL) was added at 0 °C. After being stirred at 22 °C for another 10 min, the mixture was diluted with ether (20 mL), washed with water (10 mL) and brine (10 mL), dried, and concentrated. Purification of the residue by flash column chromatography on silica gel (elution with 7% ethyl acetate in hexanes) followed by recrystallization from pentane gave **19** as a white solid, mp 79−81 °C: IR (film, cm^{-1}) 3459, 1689, 1613, 1302; ^1H NMR (300 MHz, $CDCl_3$) δ 5.27 (heptet, J = 6.1 Hz, 1 H), 4.88 (heptet, J = 6.1 Hz, 1 H), 2.50−2.40 (m, 3 H), 2.34−2.07 (m, 1 H), 2.04−1.94 (m, 1 H), 1.89−1.55 (m, 7 H), 1.48−1.33 (m, 3 H), 1.29 (t, J = 6.1 Hz, 6 H), 1.16 (dd, J = 13.2, 6.1 Hz, 6 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 204.0, 165.8, 129.9, 84.2, 73.8, 71.6, 70.2, 60.2, 57.8, 54.0, 52.9, 32.9, 32.5, 31.5, 30.2, 28.8, 18.5, 26.2, 22.9, 22.8, 22.7, 22.3; MS *m/z* (M^+) calcd 390.2778, obsd 390.2774.

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.79; H, 9.81. Found: C, 74.05; H, 9.73.

(3a*R,4*R**,5a*R**,6*S*,8a*R**)-6-*tert*-Butyl-4,5,5a,6,7,8-hexahydro-3a-hydroxy-2,3-diisopropoxy-4-methylcyclopenta[*c*]pentalen-1(3a*H*)-one (25) and (3a*R**,3b*R**,6*R**,6a*S**,7a*R**)-6-*tert*-Butyl-3a,3b,4,5,6,-6a,7,7a-octahydro-3a-hydroxy-2,3-diisopropoxy-7a-methyl-1*H*-cyclopenta[*a*]-pentalen-1-one (26).** *tert*-Butyllithium (1.8 mL of 1.7 M in pentane, 3.0 mmol) was added dropwise at −78 °C to a solution of **18** (0.28 g, 1.38 mmol) in dry THF (7 mL). After 1 h at −78 °C, followed 2.5 h later by vinyllithium [generated from 2-bromopropene (0.19 g, 1.6 mmol) in THF (8 mL) and *tert*-butyllithium (2.0 mL of 1.7 M in pentane, 3.4 mmol) at −78 °C for 1 h]. The mixture was stirred at 22 °C for 24 h and worked up in the predescribed manner. Purification by flash chromatography on silica gel (elution with 7% ethyl acetate in hexanes) gave the less polar **26** (22 mg, 6%) followed by **25** (85 mg, 23%), both as yellowish oils.

For **25**: IR (film, cm^{-1}) 3453, 1691, 1611, 1099; ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (heptet, J = 6.1 Hz, 1 H), 4.94 (heptet, J = 6.1 Hz, 1 H), 2.16−2.08 (m, 3 H), 1.78−1.71 (m, 3 H), 1.69−1.58 (m, 1 H), 1.51−1.46 (m, 1 H), 1.38−1.29 (m, 2 H), 1.32 (d, J = 6.1 Hz, 3 H), 1.28 (d, J = 6.1 Hz, 3 H), 1.20 (d, J = 6.1 Hz, 6 H), 1.17 (d, J = 7.0 Hz, 3 H), 0.86 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.2, 165.4, 132.0, 83.1, 73.8, 71.5, 66.9, 56.9, 48.4, 42.9, 38.0, 33.1, 29.8 (2 C), 28.1, 23.0, 22.7, 22.6, 14.9; MS *m/z* (M^+) calcd 364.2626, obsd 364.2620.

For **26**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (heptet, J = 6.1 Hz, 1 H), 4.91 (heptet, J = 6.1 Hz, 1 H), 2.56 (m, 1 H), 2.33−2.24 (m, 1 H), 2.09 (dd, J = 12.8, 7.2 Hz, 1 H), 1.87−1.75 (m, 2 H), 1.72−1.55 (m, 3 H), 1.40−1.26 (m, 2 H), 1.31 (d, J = 6.1 Hz, 3 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.23 (d, J = 6.1 Hz, 3 H), 1.18 (d, J = 6.1 Hz, 3 H), 1.12 (s, 3 H), 0.77 (s, 9 H); MS *m/z* (M^+) calcd 364.2626, obsd 364.2620.

(3a*R,6a*R**,6b*S**,6c*R**,9a*R**,10a*S**,10b*S**)-2,3,6b,6c,7,8,9,9a,-10, 10a,10b-Dodecahydro-6a-hydroxy-5,6-diisopropoxytricyclopenta[*a,b,e*]pentalen-4(1*H*)-one (31), (3a*R**,3b*S**,6a*S**,6b*S**,7a*R**,-10b*R**,10b*R**)-3b,4,5,6,6a,6b,7,7a,8,9,10,10a-Dodecahydro-3a-hydroxy-2,3-diisopropoxytricyclopenta[*a,c,e*]pentalen-4(3a*H*)-one (32), and (3a*R**,6a*R**,6b*R**,6c*S**,9a*S**,10a*S**,10b*S**)-2,3,6a,6b,6c,7,8,9,9a,10,-10a, 10b-Dodecahydro-6a-hydroxy-5,6-diisopropoxytricyclopenta-[*a,b,e*]pentalen-6(1*H*)-one (33).** The general procedure for lithium−halogen exchange and coupling to the squarate ester was the same as that detailed elsewhere.[3] Reaction of 224 mg (1.2 mmol) of 2-bromo-[3.3.0]bicyclooct-2-ene, 200 mg (1.0 mmol) of diisopropyl squarate (reaction time, 1.25 h), and 582 mg (3.0 mmol) of cyclopentenyl iodide with overnight stirring at 25 °C and NH_4Cl quench followed by flash chromatography (silica gel, elution with 20−30% ethyl acetate in hexanes) led to the isolation of: **32** (144 mg, 38%) as a colorless solid, mp 106−107 °C (pentane): IR (KBr, cm^{-1}) 3600−3300, 1674, 1605, 1148, 1106, 1061; ^1H NMR (300 MHz, C_6D_6) δ 5.26 (heptet, J = 6.4 Hz, 1 H), 5.25 (d, J = 6.4 Hz, 1 H), 2.97 (dt, J = 9, 9.5 Hz, 1 H), 2.72 (dtt, J = 5, 9, 9 Hz, 1 H), 2.53 (dt, J = 7, 6 Hz, 1 H), 2.38 (ddt, J = 8, 3.5, 8 Hz, 1 H), 2.27 (dt, J = 9, 9 Hz, 1 H), 2.18−1.90 (m, 2 H), 1.90−1.85 (m, 1 H), 1.85−1.25 (series of m, 13 H), 1.19 (d, J = 6.4

Hz, 3 H), 1.17 (d, $J = 6.4$ Hz, 3 H), 1.13 (d, $J = 6.4$ Hz, 3 H), 1.07 (d, $J = 6.4$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.8, 164.2, 131.8, 86.3, 73.5, 71.5, 71.2, 57.4, 52.8, 52.3, 50.1, 44.8, 39.7, 31.8, 31.1, 28.9, 28.5, 27.3, 25.8, 23.2, 23.1, 22.7, 22.1; MS *m/z* (M^+) calcd 374.2457, obsd 374.2456.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.77; H, 9.19.

31 (100 mg, 27%) as a pale yellow oil: IR (neat, cm^{-1}) 3600−3100, 1685, 1610; ^{1}H NMR (300 MHz, C_6D_6) δ 5.32 (heptet, $J = 6$ Hz, 1 H), 5.28 (heptet, $J = 6$ Hz, 1 H), 2.50−2.30 (m, 4 H), 2.25−2.08 (m, 1 H), 2.05 (br s, 1 H, OH), 1.90−1.65 (m, 7 H), 1.19 (d, $J = 6$ Hz, 3 H), 1.19 (d, $J = 6$ Hz, 3 H), 1.19 (d, $J = 6$ Hz, 3 H), 1.12 (d, $J = 6$ Hz, 3 H), 1.08 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.7, 165.1, 130.8, 86.1, 73.5, 71.4, 69.0, 65.0, 55.2, 51.2, 46.2, 42.8, 38.3, 34.8, 34.0 (2 C), 33.2, 26.9, 25.8, 23.1 (2 C), 22.7, 22.4; MS *m/z* (M^+) calcd 374.2457, obsd 374.2453.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.69; H, 9.20.

33 was obtained pure after further purification by MPLC (silica gel, elution with 3−15% ethyl acetate in hexanes): colorless crystals, mp 136−138 °C (from methanol−pentane); IR (film, cm^{-1}) 3600−3400, 1688, 1600; ^{1}H NMR (300 MHz, C_6D_6) δ 5.33 (heptet, $J = 6$ Hz, 1 H), 5.26 (heptet, $J = 6$ Hz, 1 H), 3.27 (s, 1 H), 2.80−2.55 (m, 1H), 2.55−2.33 (m, 2 H), 2.33−1.95 (series of m, 5 H), 1.95−0.85 (series of m, 9 H), 1.10 (d, $J = 6$ Hz, 3 H), 1.03 (d, $J = 6$ Hz, 3 H), 1.03 (d, $J = 6$ Hz, 3 H), 0.99 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 200.9, 172.4, 127.0, 79.8, 73.3, 71.6, 71.1, 65.7, 56.4, 49.1, 38.4, 35.7, 33.3, 31.7, 31.6 (2 C), 27.1, 25.9, 22.8, 22.6 (2 C), 22.5; MS *m/z* (M^+) calcd 374.2457, obsd 374.2463.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.55; H, 9.15.

(3a*R,3b*S**,4*R**,4a*R**,7a*S**,7b*S**,8a*R**)-4-Carboxydodecahydro-4-hydroxydicyclopenta[*a,e*]pentalene-4a(1*H*)-glyoxylic Acid Diisopropyl Ester (34).** A CH_2Cl_2 (5 mL) solution of **31** (23 mg, 0.061 mmol) was cooled to −78 °C, and ozone was bubbled through until appearance of a blue color (almost instantaneous). The flow of ozone was stopped, stirring was continued for 20 min, and 2 mL each of 30% hydrogen peroxide and 10% sodium hydroxide were added. The temperature was allowed to rise to 20 °C over 15 min. Acidification with 10% HCl, extraction with CH_2Cl_2 (5 × 5 mL) followed by flash chromatography (silica gel, and elution with 30−50% ethyl acetate in hexanes) gave 25 mg (99%) of **34** as a colorless oil: IR (neat, cm^{-1}) 3500, 1728, 1714; ^{1}H NMR (300 MHz, C_6D_6) δ 4.95 (heptet, $J = 6$ Hz, 1 H), 4.88 (heptet, $J = 6$ Hz, 1 H), 4.22 (s, 1 H), 3.19 (br t, $J = 6$ Hz, 1 H), 2.72−2.59 (m, 1 H), 2.53−2.42 (m, 1 H), 2.44 (dd, $J = 9$, 4.5 Hz, 1 H), 2.15 (tt, $J = 8$, 7 Hz, 1 H), 1.95−1.71 (m, 2 H), 1.70−0.80 (series of m, 11 H), 1.08 (d, $J = 6$ Hz, 3 H), 1.07 (d, $J = 6$ Hz, 3 H), 1.70−0.80 (series of m, 11 H), 1.08 (d, $J = 6$ Hz, 3 H), 1.07 (d, $J = 6$ Hz, 3 H), 0.99 (d, $J = 6$ Hz, 3 H), 0.97 (d, $J = 6$ Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 193.0, 174.7, 162.9, 87.8, 74.1, 70.4, 70.1, 66.5, 52.4, 50.1, 45.5, 44.6, 39.4 35.6, 34.5, 33.7, 33.1, 26.6, 25.2, 21.5, 21.4, 21.35, 21.29; MS *m/z* ($M^+ - OH$) calcd 389.2328, obsd 389.2341; FAB ($M^+ + 1$) 407, (M^+) 406.

(1*R*,3a*S*,4*R*,7*S*,7a*R*)-2-Bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-ol (39). A cold (−78 °C), magnetically stirred solution of **38** (9.89 g, 43.9 mmol) in CH_2Cl_2 (350 mL) was treated dropwise with a solution of diisobutylaluminum hydride in hexanes (50.0 mL, 50.0 mmol) during 30 min. After 5 h at this temperature, the reaction mixture was quenched with saturated sodium potassium tartrate solution, stirred for 12 h, and extracted with CH_2Cl_2. The combined organic layers were dried and concentrated, and the residue was recrystallized from hexanes to give **39** as colorless crystals, mp 78.5−79.5 °C (9.64 g, 91%): IR ($CHCl_3$, cm^{-1}) 3588, 1618, 1343, 1309, 1237, 1096, 1054; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.17 (dd, $J = 5.6$, 2.4 Hz, 1 H), 5.81 (dd, $J = 5.6$, 3.1 Hz, 1 H), 5.78−5.75 (m, 1 H), 4.51 (td, $J = 7.7$, 0.9 Hz, 1 H), 3.22−3.15 (m, 1 H), 3.02−2.91 (m, 3 H), 1.60−1.55 (m, 2 H), 1.41−1.36 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 135.1, 134.12, 134.05, 125.5, 77.3, 51.6, 51.1, 46.6, 45.8, 44.6; MS *m/z* (M^+) calcd 225.9993, obsd 225.9991.

Anal. Calcd for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88. Found: C, 52.76; H, 4.86.

(1*R*,3a*S*,4*R*,7*S*,7a*R*)-2-Bromo-3a,4,7,7a-tetrahydro-1-methoxy-4,7-methanoindene (40). A cold (0 °C) solution of **39** (652 mg, 2.87 mmol) in dry THF (25 mL) was treated with sodium hydride (141 mg, 5.88 mmol) and stirred for 3 h prior to the introduction of methyl iodide (0.54 mL, 8.6 mmol). After 2 h of stirring, the reaction mixture was diluted with ether and quenched with water. The organic phase was washed with saturated $NaHCO_3$ solution and brine, dried, and concentrated. The residue was purified by chromatography on silica gel (elution with 5% ethyl acetate in hexanes) to provide **40** as a colorless oil (600 mg, 87%): IR ($CHCl_3$, cm^{-1}) 1354, 1120, 1025; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (dd, $J = 5.5$, 2.7 Hz, 1 H), 5.72 (t, $J = 2.0$ Hz, 1 H), 5.67 (dd, $J = 5.5$, 3.1 Hz, 1 H), 4.04 (dt, $J = 8.2$, 1.3 Hz, 1 H), 3.48 (s, 3 H), 3.14−3.10 (m, 1 H), 2.98−2.82 (m, 3 H), 1.50 (dt, $J = 8.3$, 1.7 Hz, 1 H), 1.32 (d, $J = 8.5$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 235.3, 135.0, 131.7, 123.5, 86.0, 59.0, 51.4, 50.2, 46.0, 44.6, 44.4; MS *m/z* (M^+) calcd 240.0150, obsd 240.0156.

Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.90; H, 5.48.

(1*S*,3a*S*,4*R*,7*S*,7a*R*)-2-Bromo-3a,4,7,7a-tetrahydro-4,7-methanoinden-1-ol (41). A solution of **39** (277 mg, 1.22 mmol), triphenylphosphine (650 mg, 2.48 mmol), and *p*-nitrobenzoic acid (390 mg, 2.33 mmol) in benzene (35 mL) was treated via syringe with diethyl azodicarboxylate (431 mg, 2.48 mmol) during 5 min. After 12 h of stirring at room temperature, the reaction mixture was freed of solvent in vacuo, and the residue was subjected to chromatography on silica gel (elution with 15% ethyl acetate in hexanes). There was isolated 291 mg (63%) of the inverted *p*-nitrobenzoate as a colorless solid, mp 154−155 °C (from hexanes): IR ($CHCl_3$, cm^{-1}) 1722, 1530, 1348, 1272, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32−8.20 (m, 4 H), 6.20 (dd, $J = 5.7$, 3.0 Hz, 1 H), 6.16−6.13 (m, 1 H), 6.03 (dd, $J = 5.7$, 3.0 Hz, 1 H), 5.21−5.17 (m, 1 H), 3.35−3.24 (m, 2 H), 2.95−2.89 (m, 1 H), 2.80−2.73 (m, 1 H), 1.67 (dt, $J = 8.6$, 1.8 Hz, 1 H), 1.40 (d, $J = 8.6$ Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 164.5, 150.6, 141.0, 135.9, 135.5, 133.0, 130.8, 123.5, 119.2, 84.9, 53.7, 50.7, 50.6, 44.9, 44.6; MS *m/z* (M^+) calcd 375.0106, obsd 375.0100.

A suspension of the *p*-nitrobenzoate (8.21 g, 21.8 mmol) in methanol (900 mL) was treated dropwise during 10 min with a solution of potassium hydroxide (31.1 g, 554 mmol) in methanol (450 mL). After 2 h, the solvent was removed under reduced pressure, and the residue was partitioned between ether (500 mL) and water (300 mL). The aqueous phase was twice extracted with ether and the combined organic phases were washed with saturated $NaHCO_3$ and brine, dried, and evaporated to leave a brown oil that was purified by chromatography on silica gel (elution with 15% ethyl acetate in hexanes). There was obtained 4.24 g (86%) of **41** as colorless crystals, mp 64.5−65 °C (from hexanes): IR ($CHCl_3$, cm^{-1}) 3587, 3423, 1616, 1341, 1322, 1239, 1063, 1038, 990, 968; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (dd, $J = 5.7$, 2.9 Hz, 1 H), 5.94 (dd, $J = 5.7$, 2.9 Hz, 1 H), 5.92−5.89 (m, 1 H), 3.97−3.93 (m, 1 H), 3.26−3.19 (m, 1 H), 3.11−3.06 (m, 1 H), 2.85−2.80 (m, 1 H), 2.70−2.64 (m, 1 H), 2.10 (s, 1 H), 1.59 (dt, $J = 8.4$, 1.8 Hz, 1 H), 1.38−1.33 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 137.4, 135.8, 132.7, 127.7, 81.3, 53.2, 51.4, 50.3, 44.6, 44.4; MS *m/z* (M^+) calcd 225.9993, obsd 225.9987.

Anal. Calcd for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88. Found: C, 52.80; H, 4.91.

(1*S*,3a*S*,4*R*,7*S*,7a*R*)-2-Bromo-3a,4,7,7a-tetrahydro-1-methoxy-4,7-methanoindene (42). A solution of **41** (3.13 g, 13.8 mmol) in dry THF (125 mL) was cooled to 0 °C, treated with sodium hydride (622 mg, 27.6 mmol), and stirred for 1 h at room temperature. Methyl iodide (5.93 g, 41.8 mmol, passed through basic alumina prior to use) was added dropwise, and the reaction mixture was stirred for 2 h prior to the addition of brine (70 mL). The aqueous phase was extracted twice with ether, and the combined organic phases were washed with brine, dried, and evaporated. The residue was chromatographed on silica gel (elution with 8% ethyl acetate in hexanes) to give 3.12 g (94%) of **42** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 1617, 1456, 1342, 1297, 1238, 1188, 1096, 1056, 1024, 984; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (dd, $J = 5.7$, 2.9 Hz, 1 H), 5.95−5.91 (m, 2 H), 3.66−3.62 (m, 1 H), 3.35 (s, 3 H), 3.23−3.15 (m, 1 H), 3.03−2.98 (m, 1 H), 2.85−2.79 (m, 1 H), 2.70−2.63 (m, 1 H), 1.58 (dt, $J = 8.4$, 1.8 Hz, 1 H), 1.39−1.34 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.5, 135.7, 132.4, 122.1,

89.3, 55.5, 53.2, 50.3, 48.2, 45.0, 44.4; MS *m/z* (M^+) calcd 240.0150, obsd 240.0154.

Anal. Calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 54.61; H, 5.34.

General Procedure for Squarate Additions Involving 40 and 42. All manipulations were carried out under an argon atmosphere. The vinyl bromide was dissolved in anhydrous THF (20 mL per mmol of bromide), cooled to −78 °C, and treated slowly via syringe with *tert*-butyllithium (2.1 equiv). After 2 h at −78 °C, a solution of diisopropyl squarate (1.0 equiv) in dry THF (10 mL per mmol) was introduced dropwise, and after 2 h at −78 °C, the reaction mixture was allowed to rise slowly to −20 °C during 2 h, recooled to −78 °C, and admixed via cannula with the second alkenyllithium (3.0 equiv). After being stirred at room temperature for 15 h, the mixture was cooled to 0 °C, quenched with deoxygenated saturated NH_4Cl solution (20 mL per mmol), and stirred for 24 h. The separated aqueous phase was extracted with ether, and the combined organic layers were washed with brine, dried, and evaporated prior to purification by chromatography on silica gel (elution with 25% ethyl acetate in hexanes).

A. (3a*R*,5a*R*,5b*R*,6*R*,9*S*,9a*R*,10*R*,10a*S*)-4,5,5a,5b,6,9,9a,10-Octahydro-3a-hydroxy-2,3-hydroxy-2,3-diisopropoxy-10-methoxy-6,9-methanopentaleno[1,6a-*a*]inden-1(3a*H*)-one (43): Obtained in 53% yield as a colorless solid of mp 134.5−135.5 °C; IR ($CHCl_3$, cm^{-1}) 3590, 1699, 1626, 1306, 1105; ^1H NMR (300 MHz, C_6D_6) δ 6.60 (dd, J = 5.6, 2.9 Hz, 1 H), 6.20 (dd, J = 5.6, 3.0 Hz, 1 H), 5.36−5.22 (m, 2 H), 4.06 (d, J = 7.7 Hz, 1 H), 3.13 (s, 3 H), 3.12−3.03 (m, 1 H), 2.95−2.90 (m, 1 H), 2.68−2.62 (m, 1 H), 2.54 (t, J = 6.8 Hz, 1 H), 2.38−2.29 (m, 1 H), 2.23 (s, 1 H), 2.15−2.06 (m, 1 H), 1.80−1.65 (m, 2 H), 1.46−1.04 (series of m, 15 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 194.9, 162.9, 139.0, 133.0, 131.8, 85.3, 82.7, 75.6, 73.3, 71.1, 58.7, 56.3, 54.2, 53.3, 48.0, 46.2, 45.1, 37.5, 27.7, 23.0, 22.7, 22.6, 22.2; MS *m/z* (M^+) calcd 388.2250, obsd 388.2251.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.94; H, 8.35.

B. (3a*R*,5a*R*,5b*R*,6*R*,9*S*,9a*R*,10*S*,10a*S*)-4,5,5a,5b,6,9,9a,10-Octahydro-3a-hydroxy-2,3-hydroxy-2,3-diisopropoxy-10-methoxy-6,9-methanopentaleno[1,6a-*a*]inden-1(3a*H*)-one (44): Obtained in 24% yield as a colorless oil that slowly crystallized; recrystallization from hexanes afforded colorless crystals, mp 97−97.5 °C; IR ($CHCl_3$, cm^{-1}) 3436, 1691, 1610, 1382, 1303, 1193, 1100; ^1H NMR (300 MHz, C_6D_6) δ 6.21 (dd, J = 5.7, 3.0 Hz, 1 H), 6.16 (dd, J = 5.7, 2.9 Hz, 1 H), 5.41 (heptet, J = 6.1 Hz, 1 H), 5.31 (heptet, J = 6.2 Hz, 1 H), 4.74 (s, 1 H), 3.98 (d, J = 8.0 Hz, 1 H), 2.91 (s, 3 H), 2.86−2.77 (m, 1 H), 2.60−2.55 (m, 1 H), 2.50−2.19 (m, 4 H), 1.88 (dd, J = 7.0, 5.6 Hz, 1 H), 1.58 (dt, J = 8.1, 1.8 Hz, 1 H), 1.40−1.10 (series of m, 15 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 198.1, 168.8, 136.50, 136.45, 133.1, 89.3, 84.3, 73.3, 72.3, 71.4, 58.0, 54.5, 53.1, 52.0, 47.8, 46.3, 45.5, 35.7, 28.2, 22.71, 22.69, 22.5; MS *m/z* (M^+) calcd 388.2250, obsd 388.2245.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 71.18; H, 8.32.

C. (3a*R*,4*S*,5*S*,5a*R*,5b*R*,6*R*,9*S*,9a*R*,10*R*,10a*S*)-4,5,5a,5b,6,9,9a,10-Octahydro-3a-hydroxy-2,3-hydroxy-2,3-diisopropoxy-10-methoxy-4,5-dimethyl-6,9-methanopentaleno[1,6a-*a*]inden-1(3a*H*)-one (45): Obtained in 51% yield as a colorless solid, mp 161.5−162 °C (from hexanes); IR ($CHCl_3$, cm^{-1}) 3589, 1704, 1630, 1379, 1305, 1107; ^1H NMR (300 MHz, $CDCl_3$) δ 6.25−6.17 (m, 2 H), 5.25 (heptet, J = 6.1 Hz, 1 H), 4.88 (heptet, J = 6.2 Hz, 1 H),4.18 (d, J = 8.3 Hz, 1 H), 3.25 (s, 3 H), 3.14−3.06 (m, 1 H), 2.93−2.88 (m, 1 H), 2.81−2.76 (m, 1 H), 5.25 (quintet, J = 4.7 Hz, 1 H), 2.40 (s, 1 H), 2.18−1.95 (m, 3 H), 1.47 (dt, J = 7.9, 1.8 Hz, 1 H), 1.34−1.29 (m, 7 H), 1.22 (d, J = 6.2 Hz, 3 H), 1.12 (d, J = 6.1 Hz, 3 H), 0.79 (d, J = 6.8 Hz, 3 H), 0.70 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.7, 161.0, 137.7, 132.5, 132.4, 85.7, 84.8, 75.3, 73.5, 71.2, 58.6, 55.1, 54.8, 52.8, 51.5, 48.8, 46.3, 45.7, 44.3, 23.1, 22.9, 22.7, 21.6, 14.9, 11.4; MS *m/z* (M^+) calcd 416.2563, obsd 416.2562.

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.99; H, 8.66.

1-Bromo-3-methoxycyclohexene. Sodium hydride (370 mg, 15.3 mmol) was added in portions to a cold (0 °C), magnetically stirred solution of 1-bromocyclohexen-3-ol[15] (2.25 g, 12.7 mmol) and methyl iodide (0.95 mL, 15.3 mmol) in dry THF (15 mL). The reaction mixture was kept at 20 °C for 1 h, quenched with saturated NH_4Cl solution, and extracted with ether (3 × 50 mL). The combined ethereal phases were washed with brine (75 mL), dried, and concentrated. Chromatography of the residue on silica gel (elution with 9:1 petroleum ether/ether) gave rise to the methyl ether as a colorless liquid (2.17 g, 89%): IR ($CHCl_3$, cm^{-1}) 1646, 1451, 1432, 1354, 1325, 1245, 1190; ^1H NMR (300 MHz, $CDCl_3$) δ 6.18 (ddd, J = 3.7, 1.5, 1.5 Hz, 1 H), 3.74 (ddd, J = 3.7, 3.4, 3.4 Hz, 1 H), 3.33 (s, 3 H), 2.51−2.31 (m, 2 H), 1.90−1.69 (m, 2 H), 1.68−1.59 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 128.9, 127.2, 75.4, 55.9, 35.3, 26.7, 20.6; MS *m/z* (M^+-1) calcd 188.9915, obsd 188.9911.

Anal. Calcd for $C_7H_{11}BrO$: C, 44.00; H, 5.80. Found: C, 44.11; H, 5.80.

(*R)-4-(*tert*-Butyldimethylsiloxy)-2,3-diisopropoxy-4-[(*S**)-3-methoxy-1-cyclohexen-1-yl]-2-cyclobuten-1-one (47a) and (*R**)-4-(*tert*-Butyldimethylsiloxy)-2,3-diisopropoxy-4-[(*R**)-3-methoxy-1-cyclohexen-1-yl]-2-cyclobuten-1-one (48a).** A cold (−78 °C), magnetically stirred solution of 1-bromo-3-methoxycyclohexene (4.91 g, 25.7 mmol) in dry THF (50 mL) was treated dropwise with *tert*-butyllithium (31.3 mL of 1.7 M in pentane, 53.2 mmol) via syringe. After 1 h, the flask was charged with diisopropyl squarate (5.60 g, 28.3 mmol) in dry THF (60 mL), precooled to −78 °C, and introduced rapidly. Stirring was maintained for 2.5 h prior to the dropwise addition of a solution of *tert*-butyldimethylsilyl chloride (7.75 g, 51.4 mmol) in THF (70 mL). The reaction mixture was allowed to warm to room temperature, stirred overnight, diluted with water (100 mL), and extracted with ether (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried, and concentrated. The residue was chromatographed on silica gel (elution with 3% ethyl acetate in CH_2Cl_2) to give 3.06 g (28%) of **47a** and 2.78 g (26%) of **48a**.

For **47a**: colorless oil; IR (neat, cm^{-1}) 1773, 1629, 1464, 1384; ^1H NMR (300 MHz, C_6D_6) δ 6.38 (ddd, J = 2.9, 1.5, 1.5 Hz, 1 H), 4.98 (heptet, J = 6.1 Hz, 1 H), 4.74 (heptet, J = 6.2 Hz, 1 H), 3.69−3.64 (m, 1 H), 3.16 (s, 3 H), 2.35−2.21 (m, 2 H), 1.78−1.52 (m, 3 H), 1.51−1.35 (m, 1 H), 1.16−1.14 (d, J = 6.1 Hz, 3 H), 1.10−1.06 (m, 9 H), 1.03 (s, 9 H), 0.37 (s, 3 H), 0.30 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 184.5, 166.2, 139.4, 133.2, 125.4, 90.3, 76.4, 74.9, 73.4, 55.4, 28.2, 26.1, 25.8, 22.9, 22.8, 22.5, 22.3, 22.2 (3 C), 20.2, 18.6, −3.15, −3.23; MS *m/z* (M^+) calcd 424.2645, obsd 424.2649.

Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.01; H, 9.54.

For **48a**: colorless oil; IR (neat, cm^{-1}) 1773, 1630, 1464, 1384; ^1H NMR (300 MHz, C_6D_6) δ 6.47 (ddd, J = 3.1, 1.6, 1.6 Hz, 1 H), 4.97 (heptet, J = 6.1 Hz, 1 H), 4.76 (heptet, J = 6.2 Hz, 1 H), 3.72−3.69 (m, 1 H), 3.16 (s, 3 H), 2.28−2.19 (m, 2 H), 1.78−1.51 (m, 2 H), 1.50−1.33 (m, 1 H), 1.15 (d, J = 6.1 Hz, 3 H), 1.12−1.04 (m, 19 H), 0.39 (s, 3 H), 0.32 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 184.4, 166.4, 139.1, 133.4, 125.5, 90.5, 76.5, 74.7, 73.4, 55.5, 28.1, 26.1 (3 C), 25.8, 22.9, 22.8, 22.5, 22.3, 19.7, 18.6, −3.16, −3.24; MS *m/z* (M^+) calcd 424.2645, obsd 424.2633.

(*R)-4-Hydroxy-2,3-diisopropoxy-4-[(*S**)-3-methoxy-1-cyclohexen-1-yl]-2-cyclobuten-1-one (47b).** A cold (0 °C) solution of **47a** (307 mg, 0.73 mmol) in THF (10 mL) was treated with tetra-*n*-butylammonium fluoride (1.10 mL of 1.0 M in THF), allowed to warm to room temperature, stirred for 1 h, and diluted with water. The reaction mixture was extracted with ether (3 × 20 mL), and the combined organic layers were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with 1:1 petroleum ether/ethyl acetate) afforded 225 mg (97%) of **47b** as a white solid, mp 67−68°C: IR (neat, cm^{-1}) 3396, 1766, 1614, 1382, 1325, 1098; ^1H NMR (300 MHz, C_6D_6) δ 6.37−6.35 (m, 1 H), 4.96 (heptet, J = 6.1 Hz, 1 H), 4.73 (heptet, J = 6.2 Hz, 1 H), 3.67−3.61 (m, 1 H), 3.30−3.25 (br s, 1 H), 3.16 (s, 3 H), 2.29−2.16 (m, 2 H), 1.74−1.51 (m, 1 H), 1.43−1.28 (m, 1 H), 1.15−1.02 (series of m, 14 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 183.9, 165.1, 137.8, 124.6, 87.8, 75.7, 73.9, 72.4, 54.5, 27.0, 24.9, 24.6, 21.7, 21.4, 21.2, 18.9; MS *m/z* (M^+) calcd 310.1780, obsd 310.1774.

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.61; H 8.52.

(*R)-4-Hydroxy-2,3-diisopropoxy-4-[(*R**)-3-methoxy-1-cyclohexen-1-yl]-2-cyclobuten-1-one (48b).** Comparable treatment of **48a** (1.306 g, 3.07 mmol) furnished 901 mg (95%) of **48b** as a colorless oil: IR (neat, cm^{-1}) 3396, 1765, 1614, 1458, 1382, 1325; ^1H NMR (300 MHz,

C_6D_6) δ 6.45−6.43 (m, 1 H), 4.93 (heptet, J = 6.1 Hz, 1 H), 4.73 (heptet, J = 6.2 Hz, 1 H), 3.68−3.64 (m, 1 H), 3.45−3.35 (br s, 1 H), 1.15−1.05 (series of m, 14 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 184.7, 166.3, 138.0, 133.1, 133.0, 125.5, 88.6, 76.5, 74.3, 73.2, 55.4, 27.7, 25.50, 22.47, 22.45, 22.2, 19.4; MS *m/z* (M^+) calcd 310.1780, obsd 310.1794.

(3a*R,6a*S**,6b*S**,7*S**,10a*S**)-5,6,6a,6b,7,8,9,10,10a,10b-Decahydro-10b-hydroxy-1,2-diisopropoxy-7-methoxydicyclopent[*a,b*]inden-3(4*H*)-one (49) and (3a*R**,6a*S**,6b*S**,7*S**,10a*R**)-5,6,7,7a,7b,8,9,10,10a,10b-Decahydro-10b-hydroxy-1,2-diisopropoxy-7-methoxydicyclopent[*a,b*]inden-3(4*H*)-one (50).** A cold (−78 °C), magnetically stirred solution of 1-iodocyclopentene (580 mg, 2.99 mmol) in dry THF (5 mL) was treated with *tert*-butyllithium (3.61 mL of 1.7 M in pentane, 6.1 mmol) via syringe, stirred for 1 h, and admixed dropwise with a solution of **47b** (309 mg, 1.0 mmol) in 5 mL of the same solvent precooled to −78 °C. The reaction mixture was allowed to warm slowly to room temperature and to stir overnight prior to being quenched with saturated $NaHCO_3$ solution. After extraction with ether (3 × 40 mL), the combined organic layers were washed with brine, dried, and evaporated. The residue, shown to consist of two products in a 1:1 ratio by GC, was subjected to chromatography on silica gel (elution with 4:1 petroleum ether/ethyl acetate). There was isolated 82 mg (22%) of **49** and 83 mg (22%) of **50**.

For **49**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3586, 1685, 1616, 1448, 1373, 1303; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (heptet, J = 6.1 Hz, 1 H), 4.91 (heptet, J = 6.1 Hz, 1 H), 3.29 (s, 3 H), 2.41−2.35 (m, 1 H), 2.23−2.18 (m, 1 H), 2.13−2.00 (m, 3 H), 1.78−1.63 (m, 4H), 1.60 (s, 1 H), 1.54−1.37 (m, 4 H), 1.34−1.31 (m, 7 H), 1.25 (d, J = 6.2 Hz, 3 H), 1.17 (d, J = 6.2 Hz, 3 H), 1.17 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.8, 165.0, 130.7, 85.4, 74.0, 71.8, 66.0, 55.9, 48.1, 47.5, 45.5, 33.9, 31.9, 26.4, 24.4, 24.2, 23.1, 22.9, 22.7, 22.2, 19.1; MS *m/z* (M^+) calcd 378.2406, obsd 378.2406.

For **50**: colorless crystals, mp 98−100 °C; IR ($CHCl_3$, cm^{-1}) 3586, 1692, 1616, 1448, 1379; ^{1}H NMR (300 MHz, C_6D_6) δ 5.35 (heptet, J = 6.1 Hz, 1 H), 5.29 (heptet, J = 6.1 Hz, 1 H), 3.11 (s, 3 H), 3.08−3.00 (m, 1 H), 2.50 (dd, J = 10, 5.3 Hz, 1 H), 2.18−2.01 (m, 2 H), 1.84−1.54 (m, 9 H), 1.33−1.06 (series of m, 16 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.6, 163.6, 132.1, 79.2, 76.8, 73.3, 71.0, 67.5, 58.6, 54.3, 48.9, 44.1, 29.7, 28.7, 26.9, 23.0, 22.8, 22.7, 22.4, 22.3, 22.2, 22.0; MS *m/z* (M^+) calcd 378.2406, obsd 378.2386.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.70; H, 9.03.

Conversion of 48b into 49. Treatment of a 157 mg (0.51 mmol) sample of **48b** with 1-lithiocyclopentene [from 298 mg (1.54 mmol) of the iodide and 1.85 mL of *tert*-butyllithium (1.7 M in pentane) in dry THF (5 mL)] in an entirely analogous manner afforded 861 mg (45%) of **49**, identical in all respects to the sample obtained earlier.

(3a*R,6a*S**,6b*S**,7*S**,10a*S**,10b*R**)-7-(*tert*-Butyldimethylsiloxy)-5,6,6a,6b,7,8,9,10,10a,10b-decahydro-10b-hydroxy-1,2-diisopropoxydicyclopent[*a,b*]inden-3(4*H*)-one (60), (3a*R**,7*S**,7a*S**,7b*S**,10a*S**,10b*R**)-7-(*tert*-Butyldimethylsiloxy)-5,6,7,7a,7b,8,9,10,10a,10b-decahydro-10b-hydroxy-1,2-diisopropoxydicyclopent[*a,b*]inden-3(4*H*)-one (61), and (3a*R**,6a*S**,6b*S**,7*S**,10a*R**,10b*R**)-7-(*tert*-Butyldimethyl-siloxy)-5,6,6a,6b,7,8,9,10,10a,10b-decahydro-10b-hydroxy-1,2-diisopropoxydicyclopent[*a,b*]inden-3(4*H*)-one (62).** A solution of 1-bromo-3-(*tert*-butyldimethylsiloxy)cyclohexene[16] (275 mg, 1.30 mmol) in dry THF (4 mL) was cooled to −78 °C, treated dropwise with *tert*-butyllithium (1.58 mL of 1.7 M in pentane, 2.7 mmol) via syringe, and stirred for 30 min. An equally cold solution of diisopropyl squarate (198 mg, 1.00 mmol) in THF (4 mL) was introduced via cannula. After 3 h, a solution of 1-lithiocyclopentene [from 507 mg (2.61 mmol) of the iodide and 3.15 mL of *tert*-butyllithium (1.7 M in pentane, 5.4 mmol) in THF (5 mL)] at −78 °C was added next and the reaction mixture was allowed to warm to room temperature and stirred overnight prior to quenching with deoxygenated saturated NH_4Cl solution (10 mL) and extraction with ether (3 × 40 mL). The combined organic solutions were washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 9:1 petroleum ether/ethyl acetate) to give 136 mg (35%) of **60**, 72 mg (15%) of **61**, and 63 mg (13%) of **62**.

For **60**: colorless crystals, mp 123 °C; IR ($CHCl_3$, cm^{-1}) 3590, 1693, 1617, 1594, 1461, 1374, 1304; ^{1}H NMR (300 MHz, C_6D_6) δ 5.39−5.21 (m, 2 H), 3.78−3.77 (m, 1 H), 2.58−2.52 (m, 1 H), 2.40−2.30 (m, 1 H), 2.28−2.20 (m, 1 H), 1.89−1.65 (m, 5 H), 1.59−1.29 (m, 2 H), 1.27−1.04 (series of m, 16 H), 0.97 (s, 9 H), 0.89−0.84 (m, 2 H), 0.06 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.9, 164.1, 131.3, 85.4, 73.6, 71.4, 68.3, 66.7, 52.3, 47.7, 46.2, 34.3, 32.5, 29.2, 26.8, 26.4, 26.1 (3 C), 25.0, 23.1, 22.6, 22.3, 19.4, 18.3, −4.7 (2 C); MS *m/z* (M^+) calcd 478.3115, obsd 478.3085.

Anal. Calcd for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.68. Found: C, 67.84; H, 9.63.

For **61**: colorless oil; IR ($CHCl_3$, cm^{-1}) 3389, 1698, 1622, 1463, 1380, 1307; ^{1}H NMR (300 MHz, C_6D_6) δ 5.28 (heptet, J = 6.1 Hz, 2 H), 3.70−3.66 (m, 1 H), 3.59−3.53 (m, 1 H), 2.77−2.67 (m, 1 H), 2.59−2.51 (m, 1 H), 2.44 (dd, J = 8.9, 2.9 Hz, 1 H), 2.07 (s, 1 H), 1.91−1.51 (m, 7 H), 1.49−1.27 (m, 4 H), 1.14 (t, J = 5.9 Hz, 6 H), 1.07 (d, J = 6.1 Hz, 6 H), 1.02 (s, 9 H), 0.10 (s, 6 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.6, 165.0, 130.5, 87.3, 74.2, 73.7, 71.1, 67.8, 63.0, 56.0, 51.6, 50.1, 33.5, 31.5, 30.8, −3.6, −4.5; MS *m/z* (M^+) calcd 478.3115, obsd 478.3120.

For **62**: colorless crystals, mp 139 °C; IR ($CHCl_3$, cm^{-1}) 3586, 1693, 1623, 1461, 1374; ^{1}H NMR (300 MHz, C_6D_6) δ 5.31 (heptet, J = 6.2 Hz, 2 H), 3.83−3.76 (m, 1 H), 2.42 (dd, J = 9.5, 5.3 Hz, 1 H), 2.24−2.13 (m, 2 H), 1.97−1.91 (m, 1 H), 1.86−1.33 (series of m, 11 H), 1.16−1.04 (series of m, 13 H), 0.99 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 202.0, 164.1, 132.3, 79.4, 73.6, 71.3, 70.0, 68.0, 58.9, 49.1, 46.6, 35.3, 29.9, 27.1, 26.3 (3 C), 26.1, 24.0, 13.0, 22.7, 22.6, 22.5 (3 C), 18.3, −2.2, -3.8; MS *m/z* (M^+) calcd 478.3115, obsd 478.3116.

Anal. Calcd for $C_{27}H_{46}O_5Si$: C, 67.74; H, 9.68. Found: C, 67.81; H, 9.61.

(3a*R,7*S**,7a*S**,7b*S**,10a*S**,10b*R**)-5,6,7,7a,7b,8,9,10,10a,10b-Decahydro-7,10b-dihydroxy-1,2-diisopropoxydicyclopent[*a,c*]inden-3(4*H*)-one (63).** A solution of **61** (72 mg, 0.15 mmol) in THF (1 mL) was cooled to 0 °C, treated with tetra-*n*-butylammonium fluoride (0.2 mL of 1.0 M in THF), allowed to warm to 20 °C, and stirred for 12 h. Following the addition of water, the product was extracted into ether (3 × 15 mL), the combined organic layers were dried and concentrated, and the residue was chromatographed on silica gel (elution with 1:1 petroleum ether/ethyl acetate). There was isolated 49 mg (90%) of **63** as colorless crystals, mp 52 °C; IR ($CHCl_3$, cm^{-1}) 3586, 3433, 1682, 1608, 1463, 1382, 1302; ^{1}H NMR (300 MHz, C_6D_6) δ 5.28 (heptet, J = 6.1 Hz, 1 H), 5.06 (heptet, J = 6.1 Hz, 1 H), 4.14 (br s, 1 H), 3.80 (s, 1 H), 2.48−2.24 (m, 3 H), 2.18−2.10 (m, 1 H), 1.97−1.71 (m, 4 H), 1.64−1.22 (series of m, 11 H), 1.13−1.00 (series of m, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.0, 167.6, 129.9, 85.1, 73.9, 71.7, 67.0, 58.4, 55.7, 51.9, 47.7, 29.6, 28.7, 26.2, 25.8, 22.9, 22.7, 22.6, 22.5, 17.7; MS *m/z* (M^+) calcd 364.2250, obsd 364.2255.

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.10, H, 8.92.

(3a*R,7*S**,7a*S**,7b*S**,10a*S**,10b*R**)-5,6,7,7a,7b,8,9,10,10a,10b-Decahydro-10b-hydroxy-1,2-diisopropoxy-7-methoxydicyclopent-[*a,c*]inden-3(4*H*)-one (64).** A solution of **63** (34 mg, 0.093 mmol) in methyl iodide (5 mL, 80 mmol) was treated with silver oxide (216 mg, 0.93 mmol), covered with foil, stirred overnight, and filtered through Celite. The filter cake was washed with ether (3 × 20 mL), and the filtrate was evaporated. Chromatography of the residue on silica gel (elution with 4:1 hexanes/ethyl acetate) afforded 31 mg (87%) of **64** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3414, 1679, 1606, 1463, 1381, 1300; ^{1}H NMR (300 MHz, C_6D_6) δ 5.30 (heptet, J = 6.1 Hz, 1 H), 5.22 (heptet, J = 6.1 Hz, 1 H), 4.19 (d, J = 11.3 Hz, 1 H), 3.83−3.79 (m, 1 H), 3.11 (s, 3 H), 2.49−2.38 (m, 3 H), 1.91−1.81 (m, 4 H), 1.78−1.66 (m, 1 H), 1.64−1.54 (m, 1 H), 1.52−1.22 (m, 5 H), 1.12−1.07 (m, 13 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 206.5, 165.3, 131.3, 90.9, 73.7, 71.4, 66.4, 57.8, 53.1, 52.8, 52.6, 46.7, 29.0, 28.4, 28.2, 26.4, 23.6, 22.8, 22.6, 22.4 (2 C), 17.1; MS *m/z* (M^+) calcd 378.2406, obsd 378.2413.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.94; H, 9.11.

O-Methylation of 60. Comparable treatment of **60** (64 mg, 0.134 mmol) with TBAF (0.2 mL of 1.0 M in THF) afforded 39 mg (80%) of the diol as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3600, 3377, 1693, 1616, 1457, 1382, 1308; ^{1}H NMR (300 MHz, C_6D_6) δ 5.33 (heptet, J = 6.1 Hz, 1 H), 5.24 (heptet, J = 6.1 Hz, 1 H), 3.57 (d, J = 2.5 Hz,

1 H), 2.54−2.49 (m, 1 H), 2.37−2.32 (m, 1 H), 2.15−2.02 (m, 2 H), 1.91 (s, 1 H), 1.86−1.50 (m, 4 H), 1.48−1.32 (m, 2 H), 1.28−1.05 (m, 16 H), 0.96−0.85 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.1, 164.9, 131.4, 85.5, 73.7, 71.5, 67.4, 66.6, 51.6, 47.2, 46.3, 34.4, 32.4, 28.8, 26.9, 24.9, 23.14, 23.11, 22.6, 22.3, 19.4; MS *m/z* (M^+) calcd 364.2250, obsd 364.2271.

A 63 mg (0.173 mmol) sample of the above diol was dissolved in methyl iodide (5 mL), treated with silver oxide (401 mg, 1.73 mmol), and allowed to react as described above. There was isolated 32 mg (48%) of **65** as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3611, 1689, 1613, 1450, 1380, 1308; ^{1}H NMR (300 MHz, C_6D_6) δ 5.39 (heptet, J = 6.1 Hz, 1 H), 5.25 (heptet, J = 6.1 Hz, 1 H), 3.52−3.48 (m, 2 H), 3.25 (s, 3 H), 2.73−2.68 (m, 1 H), 2.60−2.56 (m, 1 H), 2.20−2.16 (m, 1 H), 1.94−1.62 (m, 4 H), 1.60−1.21 (m, 6 H), 1.18−1.10 (m, 12 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 203.1, 164.0, 132.8, 89.8, 73.6, 71.4, 68.4, 66.3, 52.7, 52.1, 51.4, 48.2, 43.1, 33.0, 32.9, 30.5, 27.8, 24.1, 23.1, 23.0, 22.5, 20.4; MS *m/z* (M^+) calcd 378.2406, obsd 378.2412.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.68; H, 9.15.

O-Methylation of 62. Analogous desilylation of **62** (56 mg, 0.116 mmol) with TBAF (0.3 mL of 1.0 M in THF, 0.3 mmol) produced 38 mg (90%) of diol as a colorless oil: IR ($CHCl_3$, cm^{-1}) 3376, 1695, 1621, 1455, 1382, 1308; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (heptet, J = 6.1 Hz, 1 H), 4.95 (heptet, J = 6.1 Hz, 1 H), 3.64 (ddd, J = 6.0, 4.5, 4.5 Hz, 1 H), 2.50−2.44 (m, 1 H), 2.27−2.17 (m, 1 H), 1.99−1.80 (m, 4 H), 1.77−1.53 (m, 5 H), 1.52−1.38 (m, 4 H), 1.33 (d, J = 6.1 Hz, 3 H), 1.31 (d, J = 6.1 Hz, 3 H), 1.27−1.25 (m, 1 H), 1.21 (d, J = 6.1 Hz, 3 H), 1.18 (d, J = 6.1 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.6, 165.0, 131.8, 79.2, 74.1, 71.7, 68.3, 67.5, 58.4, 48.4, 46.2, 34.1, 29.4, 26.9, 23.1, 22.8, 22.7, 22.6, 22.3, 22.1, 20.7; MS *m/z* (M^+) calcd 364.2250, obsd 364.2256.

A solution of the above diol (37 mg, 0.103 mmol) in methyl iodide (5 mL) was allowed to react with silver oxide (239 mg, 1.03 mmol) in the predescribed manner. The same workup gave 25 mg (63%) of **66** as a white solid, mp 113−115 °C: IR ($CHCl_3$, cm^{-1}) 3695, 1728, 1603, 1375, 1252, 1109; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (heptet, J = 6.1 Hz, 1 H), 4.94 (heptet, J = 6.1 Hz, 1 H), 3.61 (ddd, J = 6.1, 4.7, 4.7 Hz, 1 H), 3.53 (s, 3 H), 2.26 (ddd, J = 6.5, 6.5, 5.8 Hz, 1 H), 1.99−1.89 (m, 3 H), 1.86−1.75 (m, 3 H), 1.70−1.48 (m, 5 H), 1.46−1.36 (m, 3 H), 1.33 (d, J = 6.1 Hz, 6 H), 1.22 (d, J = 6.1 Hz, 3 H), 1.18 (d, J = 6.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.5, 166.2, 132.4, 83.7, 74.0, 71.6, 68.3, 68.1, 54.7, 54.1, 48.5, 46.1, 34.2, 29.3, 26.9, 24.5, 23.2, 22.9 (2 C), 22.6, 21.9; MS *m/z* (M^+) calcd 378.2406, obsd 378.2406.

Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.90; H, 8.97.

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Supporting Information Available: Long-range DEPT and NOE data for several products (79 pages). See any current masthead page for ordering and Internet access instructions. The authors have deposited the atomic coordinates for the 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.

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