Studies Directed toward the Total Synthesis of Trixikingolide. Analysis of the Capacity for Transannular Carbon-Carbon Bond Formation in Various Bicyclic and Tricyclic Intermediates

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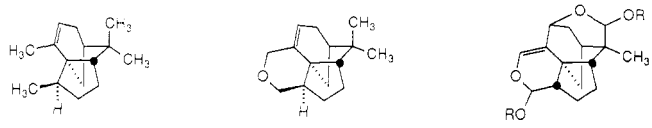
Several polyfunctional di- and triquinanes have been synthesized for the purpose of realizing intramolecular alkylation and generation of the isocedrane ring system. Following an improved preparation of diketone **15**, the tricyclic ketone **14** was rapidly assembled and transformed into **31**. Stereocontrolled cyclopentannulation of this intermediate was best achieved by thermal vinylcyclopropane rearrangement of **42**. Once tetracyclic ketone **40** was in hand, it proved an easy matter to gain access to intermediates **46**, **52**, **56**, **63**, and **71**. However, their subsequent exposure to appropriate reagents and reaction conditions did in no instance result in cyclization with formation of the five-membered ring central to the isocedrane nucleus. These negative results have been attributed to an inability of these systems to attain conformations conducive to operation of the internal S_N2 displacement.

Extensive phytochemical study by Bohlmann and coworkers of the tribe *Mutisieae* (including the species *Jungia*, *Moscharia*, *Perezia*, *Pleocarpus*, *Proustia*, and *Trixis*) during the past decade has resulted in the isolation and characterization of a large number of sesquiterpenes (ca. 80) whose carbon frameworks are of the unusual isocedrane type.[1] The interesting structural and stereochemical features of this class of molecules range from those residing in the parent tricyclic system **1** through **2** to those found in the novel pentacyclic oxygenated network **3** common to the trixikingolides.[1b] Although the biosynthesis of these substances remains to be elucidated, their origin is no doubt related to that of α-cedrene (**6**) and closely related molecules, which arise via cationic rearrangement of farnesyl pyrophosphate (**4**, Scheme I).[2] The pathway to the isocedrenes, however, must be distinctive in providing adequate means for migration of the C(3) methyl group to C(5) as in **5** → **7**.[1a]

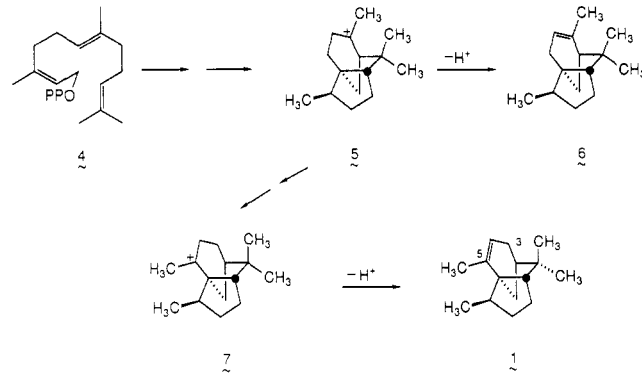


1 **2** **3**

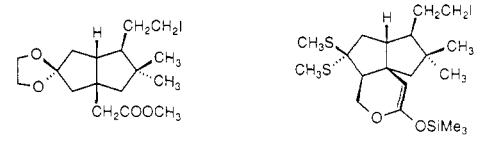
Our interest in the more highly oxygenated pentacyclic isocedrenes (**3**) stems from their highly condensed nature, their distant structural relationship to known pharmacologically active lactones, and the challenge offered in developing a practical synthesis of these relatively complex natural products.

In the latter connection, we were cognizant of two closely related, yet contrasting, literature observations. In Danishefsky's successful assault on quadrone,[3] the pivotal step consisted of the intramolecular cyclization of **8** by means of lithium diisopropylamide in tetrahydrofuran. The efficiency of this ring closure, which required 1,3-spanning across a *cis*-bicyclo[3.3.0]octane template was approximately 55%. In contrast, the Annis-Schostarez approach to the same target that was based on **9** and its derived enolate anion gave no positive indication of undergoing the same bond-forming process.[4]

Scheme I



4 **5** **6** **7** **1**



8 **9**

In order to gain greater *quantitative* appreciation of these differing reactivities, this pair of structures was subjected to energy minimization within the MODEL KS 2.93 program by suitable adoption of Allinger's MM2 force field. The respective global minima were found by making use of multiconformer generation in MODEL followed by batch minimization using BAKMDL. The resulting lowest energy conformations were then submitted to MMX88 for the calculation of strain energies. No attempt was made to force alignment on the C-I bond. The relevant findings are compiled in Figure 1.

From among the several geometries that can be adopted by **8**, the illustrated conformation is the least strained option that projects the β-iodoethyl substituent into the necessary quasi-axial orientation. Otherwise, the enolate center is clearly too remote from the electrophilic site to resemble the transition state for cyclization. Relative to other molecules we shall consider, the MM2 and strain energies relevant to **8** are seen to be rather elevated. Also, the distance between reaction sites in the ground state (4.88 Å) must be viewed as substantial. Notwithstanding,

(1) (a) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1979**, *112*, 427. (b) Bohlmann, F.; Zdero C. *Ibid.* **1979**, *112*, 435. (c) Bohlmann, F.; Suirta, A.; Jakupovic, J.; King, R. M.; Robinson, H. *Phytochemistry* **1981**, *20*, 1649. (d) Bohlmann, F.; King, R. M.; Robinson, H. *Ibid.* **1983**, *22*, 1201. (e) Singh, P.; Jakupovic, J.; Bohlmann, F. *Ibid.* **1985**, *24*, 1525. (f) Zdero, C.; Bohlmann, F.; King, R. M.; Robinson, H. *Ibid.* **1986**, *25*, 2873. (g) Zdero, C.; Bohlmann, F.; Solomon, J.; Dominguez, X. A. *Ibid.* **1988**, *27*, 849.

(2) (a) Ohta, Y.; Hirose, Y. *Chem. Lett.* **1972**, 263. (b) Gutsche, J. R.; Maycock, E. T. *Tetrahedron* **1968**, *24*, 43, 859.

(3) Danishefsky, S.; Vaughn, K.; Gadwood, R.; Tsuzuki, K. *J. Am. Chem. Soc.* **1981**, *103*, 4136.

(4) Paquette, L. A.; Annis, G. D.; Schostarez, H. *J. Am. Chem. Soc.* **1982**, *104*, 6646.

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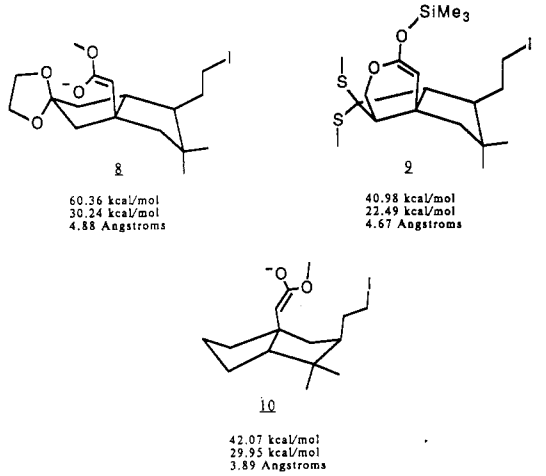


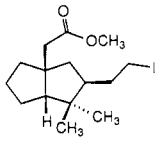
Figure 1. Low-energy conformations of **8–10** as determined by computer calculation (see text). The three numbers below each structure relate in order to the global MM2 energy, the strain energy, and the nonbonded internuclear distance between nucleophilic and electrophilic centers.

bond formation operates smoothly in this case.

For **9**, the distance associated with the intended S_N2 reaction is marginally shorter (4.67 Å). The system is inherently less strained, but the structural network is somewhat more rigid as a result of the added annulation. Thus, we see that while the ground-state strain energy decreases for **9** relative to **8** and the gap between its reaction centers is decreased slightly, transannular cyclization cannot be implemented.

Are the strain energy costs of less importance, as the limited experimental results appear to indicate, and conformational flexibility the major controlling factor for successful bimolecular displacement? Experimental tests are possible. According to the above criteria, reaction centers that find themselves initially far apart in the ground state might well engage in bonding after modest conformational realignment to gain added proximity.

This reasoning has led us to examine the possible synthesis of complex isocedrenes via variants of the theme exemplified by **10** and elaborated upon in the sequel. As



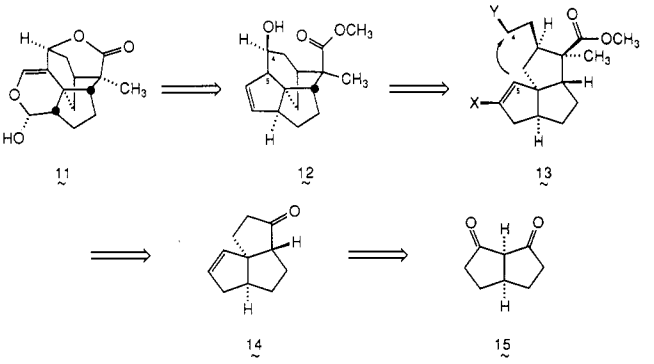
10

seen in Figure 1, **10** incorporates a strain energy not dissimilar from that of **8**. However, the transannular distance of consequence at 3.89 Å is the most advantageous within the triad, probably as a direct result of the alternative positioning of the functional groups on the bicyclooctane core. At issue, then, is whether these facets of **10** and related intermediates are of adequate significance to permit kinetically favorable cyclization.

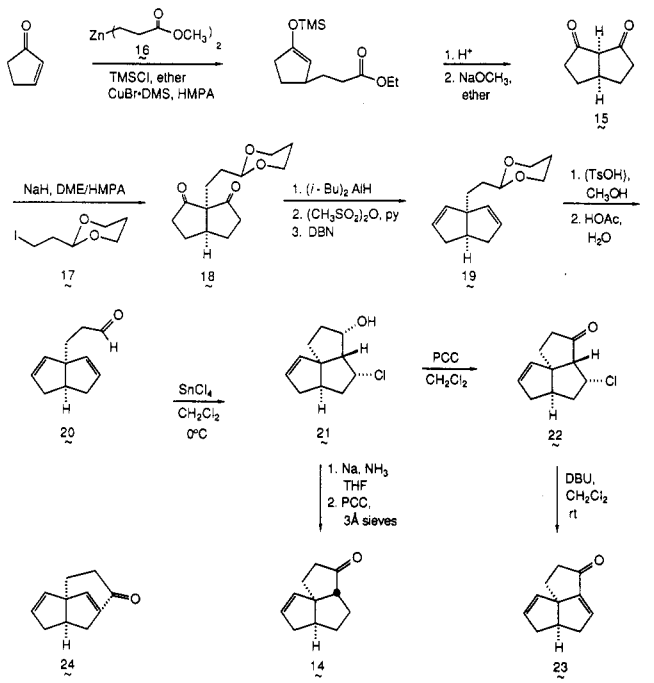
Synthesis of the Angular Triquinane Ketone 14

Our retrosynthetic planning was designed with a long-range view toward the preparation of lactol lactone **11**, regarded to be one of the simplest members of the trixikingolide family (Scheme II). The hypothetical ester **12** is related to **11** by lactonization, oxidative cleavage of the double bond to deliver the dialdehyde, and acid-catalyzed cyclization concomitant with epimerization at C(7). The overall scheme was obviously designed to incorporate the unique bond-forming process outlined above, viz, instal-

Scheme II



Scheme III



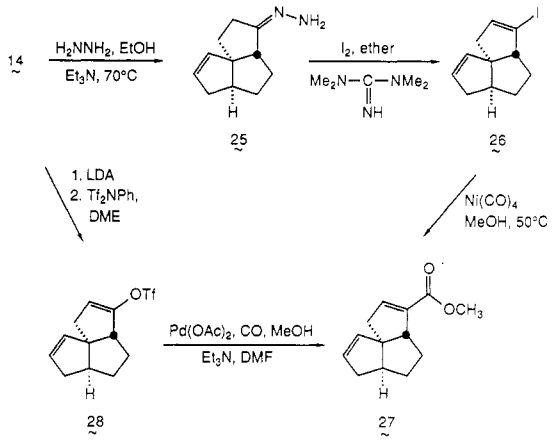
lation of the pivotal (C(4)–C(5) linkage within **13**. The protocol was required further to be adequately flexible to allow substantive variation in X and Y, a precondition seemingly well accommodated by tricyclic ketone **14**. Additional simplification led us to the symmetric diketone **15**.

Stetter and co-workers first synthesized **15** in 1961 from 2-cyclopentenone in eight steps and 17% overall yield.[5] Since then, somewhat improved syntheses have appeared.[6,7] However, all continue to suffer from modest overall yields, long reaction times, and at least one difficultly available starting material. The more expedient approach developed here (Scheme III) takes advantage of the efficacy with which Kuwajima's zinc homoenolate **16**[8] adds to 2-cyclopentenone. The second step is accomplished according to Eaton.[6]

Condensation of the sodium enolate of **15** with iodo acetal **17** in DME (HMPA) eventuates in exclusive C-alkylation. With **18** in hand, its carbonyl groups were reduced with diisobutylaluminum hydride. The predominant diol was the β,β-isomer as determined on the basis

(5) Stetter, H.; Krüger-Hansen, I.; Riza, M. *Chem. Ber.* **1961**, *94*, 2702.
(6) Eaton, P. E.; Mueller, R. H.; Carlson, G. R.; Cullison, D. A.; Cooper, G. F.; Chou, T.; Krebs, E. *J. Am. Chem. Soc.* **1977**, *99*, 2751.
(7) Duthaler, R. O.; Maienfisch, P. *Helv. Chim. Acta* **1984**, *67*, 856.
(8) Nakamura, E.; Kuwajima, J. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) *Ibid.* **1983**, *105*, 651. (c) *Ibid.* **1984**, *106*, 3368.

Scheme IV



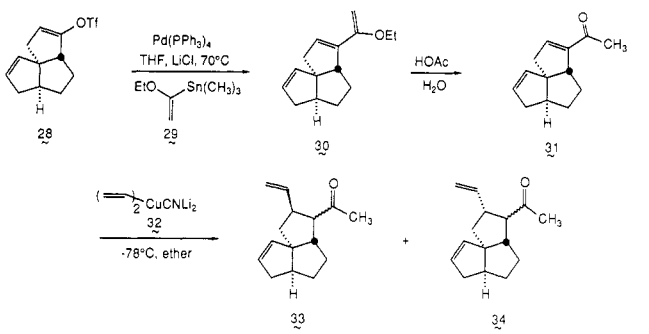
of its symmetry characteristics (^{13}C NMR) and its low polarity (TLC). On preparative scale, the diol isomers were not separated but directly converted to their dimesylates with methanesulfonic anhydride[9] and subjected to 2-fold E_2 elimination in the presence of hot diazabicyclononene (DBN).

Having secured **19**, we quickly recognized that direct hydrolysis to aldehyde **20** could not be smoothly accomplished. Consequently, transacetalization to the more reactive dimethyl acetal was performed in advance of hydrolysis. The C_s symmetry of **20** is revealed by its eight-line ^{13}C NMR spectrum.

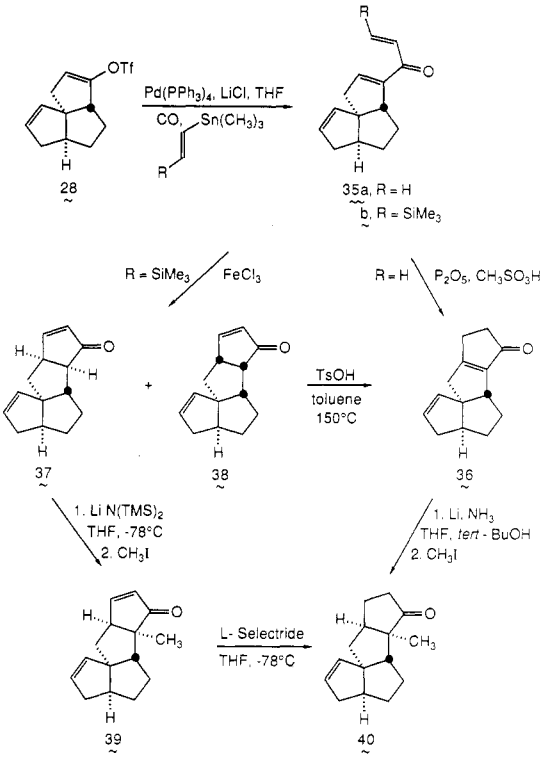
On exposure of **20** to various Lewis acids, the normal Prins reaction course[10] was not followed. Instead, chloro alcohol **21** was produced under most, though not all, circumstances.[11] This reaction pathway is believed to predominate because of the inability of the oxygen atom on the rigid tricyclic framework to abstract that proton necessary to introduce the site of unsaturation. In order to verify the triquinane nature of **21**, its oxidation and dehydrochlorination were effected. Both **22** and **23** were clearly five-ring ketones. The involvement of ii[11] is thereby precluded since **24** would be impossibly strained. The ease of elimination of chloride ion is considered to be strongly suggestive of the α-orientation of this halogen in **21**. Dissolving metal reduction of **21** followed by oxidation provided the tricyclic target **14** in high yield.

The carbonyl carbon in **14** can readily be transformed into a nucleophilic vinyl anion center (Scheme IV). Iodination of hydrazone **25** in the presence of tetramethylguanidine[12] afforded vinyl iodide **26** efficiently. Reaction of **26** with nickel carbonyl in hot methanol[13] proceeded to

Scheme V



Scheme VI



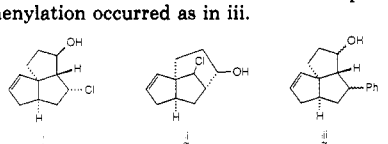
furnish the α,β-unsaturated ester **27**. An alternative route[14] to **27** mediated by enol triflate **28** was found to work equally well. However, **27** proved to be notably unreceptive to the 1,4-addition of cuprate reagents.[15,16]

In an effort to gain insight into the stereoselectivity of conjugate additions to tricyclic acceptors of this structural type, enol triflate **28** was converted instead into ketone **31**. Utilizing palladium(0)-based methodology developed earlier by Stille,[18] we found that condensation of **28** with the vinyl tin species **29** gave rise smoothly to diene enol ether **30**, direct hydrolysis of which generated **31** in 56% overall yield (Scheme V). As expected, **31** is a molecule

(9) Under the more classical mesylation conditions (CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C), extensive chlorinative displacement of methanesulfonate ion occurred. The chlorine atoms so incorporated were resistant to E_2 elimination.

(10) Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem.* **1982**, *47*, 4538.

(11) Exposure of **20** to 1.2 equiv of $SnCl_4$ in dichloromethane at −78 → 10 °C gave rise to 25% of **21**, 23% of the corresponding β-hydroxy epimer i, and 4.4% of isomer ii. When the reaction was performed instead in benzene, phenylation occurred as in iii.



(12) Barton, D. H. R.; Bushiandes, B.; Fourrey, J. L. *Tetrahedron Lett.* **1983**, *24*, 1605.

(13) (a) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 1233. (b) Corey, E. J.; Semmelhack, M. F.; Hegedus, L. S. *Ibid.* **1968**, *90*, 2416, 2417. (c) Corey, E. J.; Kirst, H. G.; Katzenellenbogen, J. A. *Ibid.* **1970**, *92*, 6314. (d) Paquette, L. A.; Annis, G. D.; Schostarez, H. *Ibid.* **1982**, *104*, 6646.

(14) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

(15) This lack of reactivity is precedented [for example: Oppolzer, W.; Löher, H. *Helv. Chim. Acta* **1981**, *64*, 2802] even when a Lewis acid such as boron trifluoride etherate is present [Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1981**, *47*, 3263] or HMPA is added [Magnus, P.; Quagliato, D. *J. Am. Chem. Soc.* **1985**, *50*, 1621].

(16) At the time that this work was performed, the studies of Corey,[17a] Johnson,[17b] and Kuwajima[17c] had not yet made their appearance. These reagent systems characteristically add to unsaturated esters in good yield.

(17) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015, 6019. (b) Johnson, C. R.; Marren, T. J. *Ibid.* **1987**, *28*, 27. (c) Horiguchi, Y.; Matsuawa, S.; Nakamura, E.; Kuwajima, I. *Ibid.* **1986**, *27*, 4025, 4029.

(18) (a) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4603. (b) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634. (c) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

that exhibits appreciable reactivity toward cuprate reagents. Its response to the higher order vinyl cuprate **32** is exemplary, reaction being complete in approximately 5 min at −78 °C. The level of facial selectivity encountered in such transformations proved, however, to be much lower than anticipated. The ratio of **33** to **34**, for example, was only 1.8:1. The relevant stereochemical assignments are based on the assumption that the major product results from attack on the convex face of **31**.

In view of our requirements for highly controlled β-orientation of a side chain at the site (consult **13** in Scheme II), attention was turned to securing an alternative pathway involving initial cyclopentannulation from the β-face, followed by appropriate cleavage of the newly introduced five-membered ring to set the necessary YCH_2CH_2 and carbomethoxy appendages as in **13**.

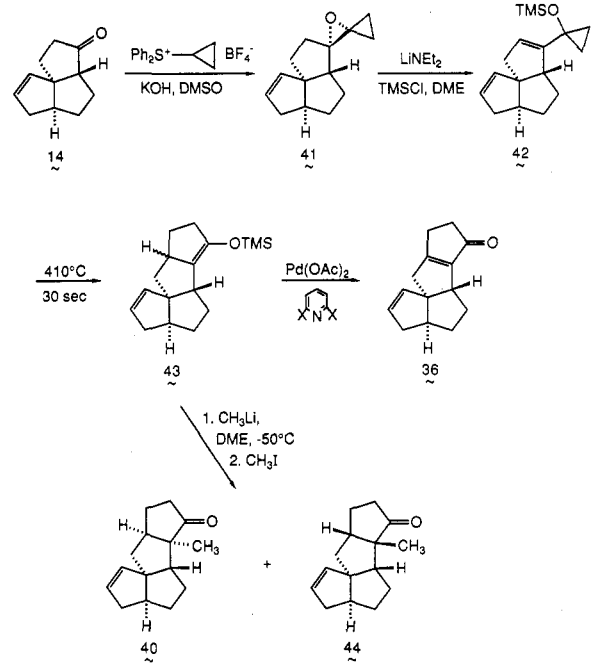
Stereocontrolled Cyclopentannulation of 14

The success of the scenario just outlined rested on our ability to construct **40** in a reasonably efficient manner. Since dissolving metal reduction of enone **36** and subsequent trapping with methyl iodide should deliver the desired cis-anti product,[19] our initial thrust centered about application of the Nazarov reaction.[20] Therefore, **28** was carbonylated in the presence of vinyltrimethyltin and $Pd(PPh_3)_4$[18] to accomplish the conversion of **35a** (Scheme VI). Rather unexpectedly, attempts to cyclize **35a** under a variety of conditions did not succeed in providing tetracyclic ketone **36** in a sufficiently efficient manner for the route to be viable. The two best reagent systems, $FeCl_3$ (0 °C → room temperature)[20] and P_2O_5/CH_3SO_3H[21] (0 °C, 5 min), afforded **36** in only 8 and 10–20% yield, respectively.

Silicon-assisted cyclization was next considered since the requisite conditions are often milder and the yields higher than for the unadorned Nazarov process.[22] Like the parent example, the silicon-mediated reaction is thought to proceed via a [2 + 2] conrotatory closure. The silicon atom plays the added role of stabilizing the intermediate β-carbocation. Nucleophilic attack on the silicon atom thus activated produces the double bond regioselectively in the position depicted in **37** and **38**.

Exposure of **35b** to boron trifluoride etherate in toluene at room temperature succeeded in producing the desired enone **37**, but only in 25% yield.[23] Ferric chloride was found to give cyclization product in higher yield but at the expense of stereoselectivity (**37**:**38** = 1.5:1). Stereochemical assignment to this inseparable product mixture was founded on the expectation that **37** would predominate

Scheme VII



because this isomer lacks the steric congestion present in the concave-shaped alternative. This conclusion was later corroborated by X-ray crystallographic analysis of an advanced intermediate synthesized from **40**. In addition to the lack of stereoselectivity, the ferric chloride induced cyclization exhibited the added complication of promoting the rapid dimerization of product enone.[25]

The inseparable **37**/**38** mixture was in turn equilibrated with *p*-toluenesulfonic acid in hot toluene, in anticipation of forming **36**, the presumed double-bond stabilomer. Curiously, only **38** responded to isomerization. The outcome was useful, since the unreacted **37** and newly formed **36** could now be cleanly separated by chromatographic means. Enone **37** was subsequently transformed into **39** by an established[26,27] alkylation–reduction sequence. The yield of the angular methylation step was consistently low and could not be optimized. No side products were isolated.

In order to realize the conversion of **36** to **40** in a satisfactory way, careful attention had to be paid to the reaction conditions. Use of 1 equiv of *tert*-butyl alcohol as proton source[28] resulted in little methylation. Omission of this co-reagent permitted isolation of modest amounts (30–55%) of **40**. Eventually, it was determined that 0.6

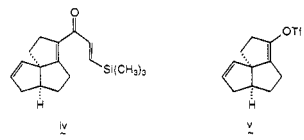
(19) Consult, for example: Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M. *J. Chem. Soc., Chem. Commun.* **1986**, 1049.

(20) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. S. *J. Org. Chem.* **1980**, *45*, 3017 and relevant references cited therein.

(21) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *23*, 4071.

(22) (a) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642. (b) Denmark, S. E.; Jones, T. K. *Helv. Chim. Acta* **1983**, *66*, 2378, 2397.

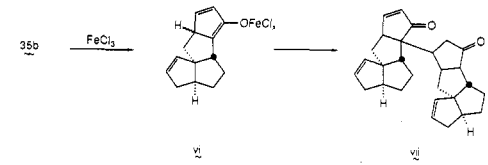
(23) In actuality, a 9:1 mixture of **36** and iv was produced. The presence of this minor product implicated the coformation of v in the O-triflation step. This is indeed the case (28:v = 9:1), a fact that had been earlier overlooked (see Scheme IV). The formation of v was expected to be disfavored kinetically because of its inherently more strained nature relative to **28**.[24]



iv v

(24) Agosta, W. C.; Wolff, S. J. *J. Org. Chem.* **1975**, *40*, 1699.

(25) Spectroscopic data suggests that a formal Michael addition has occurred, perhaps through the intermediacy of iron enolate vi. It is striking that bond formation occurs readily between such bulky molecules at 0 °C. This side reaction was often difficult to control since the rate of reaction was variable (1–8 h). This in turn may have been connected to the varying level of moisture in the particular reaction mixture, since Denmark has observed that under strictly anhydrous conditions ferric chloride alone will not induce reaction.[22]



vi vii

(26) Lee, R. A.; McAndrews, C.; Patel, K. M.; Reusch, W. *Tetrahedron Lett.* **1973**, 965.

(27) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.

(28) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R. V.; Tsuji, J. *J. Am. Chem. Soc.* **1965**, *87*, 275.

equiv of *tert*-butyl alcohol was optimal. As expected, only the cis-anti isomer was obtained (67%).

To this point, **40** has been synthesized from **14** in 14% overall yield. However, as the key intermediate in a linear synthesis, it was essential that this tetracyclic ketone be made available in a more efficient manner. A suitable solution to this problem, summarized in Scheme VII, takes advantage of a cyclopentannulation sequence developed by Trost,[29,30] but little used in natural products synthesis.[31]

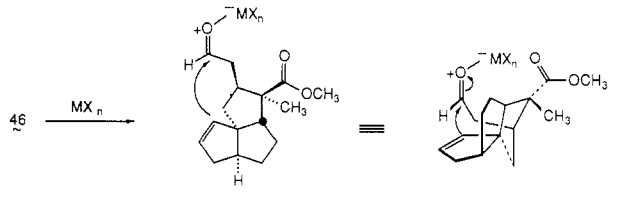
Formation of spiro epoxide **41** and its base-promoted cleavage to **42** permitted exploitation of the thermal vinylcyclopropane rearrangement. That the flash vacuum pyrolysis of **42** provided a mixture of the epimeric enol ethers **43** was spectroscopically apparent. Their separation was not attempted for lability reasons. Direct exposure of the isomers to methyllithium and methyl iodide gave rise to **40** (44%) and **44** (29%) after chromatographic purification. More favorable to our purposes, however, was the direct oxidation of **43** to **36** with palladium acetate.[32] The yield of this reaction (78%) was made reproducible by the addition of 2,6-di-*tert*-butylpyridine as proton sponge. Reductive methylation of **36** as reported above ultimately provided **40** in five steps and 45% overall yield from **14**, and was clearly the avenue of choice for producing quantities of this tetracyclic ketone.

D-Ring Cleavage and Attempts at Direct C(4)–C(5) Bond Construction

At this stage, the plan called for unveiling an array of functional groups typified by structure **13**. Originally, it was anticipated that oxidative cleavage of ring D might be accomplished by regioselective ozonolysis of the silyl enol ether derived from **40**.[33] However, the desired selectivity was never observed, even with very slow and controlled addition of ozone in the presence of a suitable indicator (sudan red) and reactivity modifier (pyridine).

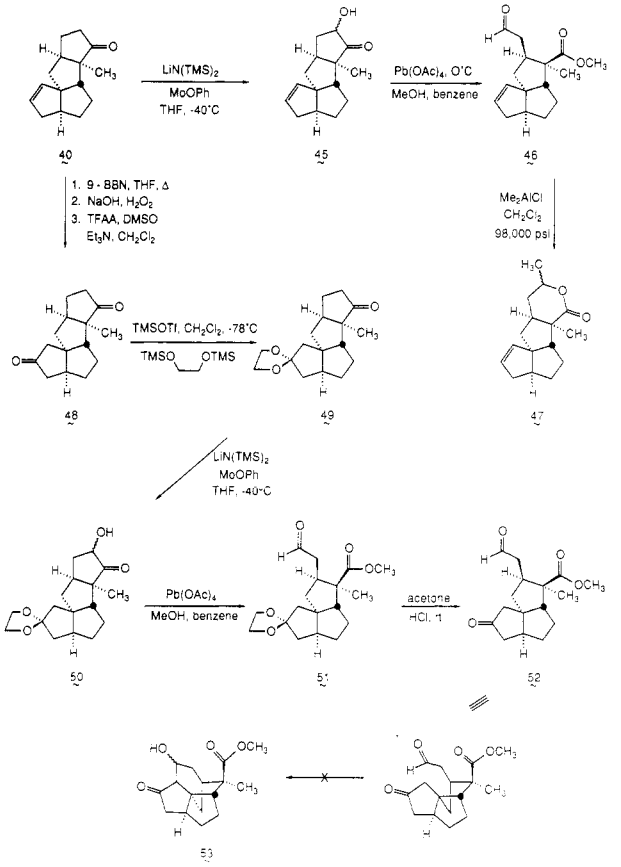
A much more satisfying result was obtained on making recourse to α-hydroxylation with MoOPh,[34] followed by lead tetraacetate oxidation in a 1:3 mixture of methanol and benzene (Scheme VIII). α-Diketone formation was initially observed to be a serious side reaction (up to 30% of product), but was suppressed by inverse addition of the enolate anion to a cold slurry of the molybdenum reagent. Also, the level of recovered **40** could be routinely reduced to 3–8% through use of an excess of base and oxidant.[35]

The Prins cyclization of **46** was expected to proceed via a chair transition state with the carbonyl group facing the exterior of the molecule for steric reasons (see **54**). Although the developing six-membered ring might be somewhat strained when formed, Dreiding models suggested that C(4) and C(5) could become positioned within adequate proximity to engage in bond formation. Notwithstanding, treatment of **46** with a variety of Lewis acids invariably returned unreacted starting material. Use of more forcing conditions such as extended reaction times, excess Lewis acid, or gentle heating produced only baseline material (TLC analysis).



54

Scheme VIII



Since the intramolecular ene reaction has a small negative volume of activation, the application of pressure should enhance reaction rate.[36] The tendency of **46** to polymerize under these conditions was demonstrated when it was reacted with stannic chloride at 98000 psi. An exception to this trend was noted with dimethylaluminum chloride. Under identical conditions, **47** was formed in 57% isolated yield. Evidently, the added methyl group is introduced by 1,2-alkyl shift from aluminum to carbon within the Lewis acid–aldehyde complex, with ensuing intramolecular lactonization.

Although the precise factors that inhibit the Prins process are not known, we assumed that some insight into this matter might be gained by examination of the aldol variant **52** → **53**. The working premise was made that the conformational demands and steric constraints attending this cyclization are not materially different from those placed upon the earlier system.

When initial efforts to functionalize the double bond in **46** or its dimethyl acetal proved troublesome, **40** was found to undergo totally regioselective hydroboration with 9-BBN in refluxing tetrahydrofuran.[37] Following oxidation to the diketone level,[38] the less hindered carbonyl group of **48** was

(29) (a) Trost, B. M.; Bogdanowicz, M. *J. Am. Chem. Soc.* **1973**, *95*, 289. (b) Trost, B. M.; Schudder, P. H. *J. Org. Chem.* **1981**, *46*, 506.
(30) See also: (a) Salaün, J. R.; Conia, J. M. *Tetrahedron Lett.* **1972**, 2849. (b) Denis, J. M.; Conia, J. M. *Ibid.* **1972**, 4593.
(31) Trost, B. M.; Nishimura, Y.; Yamamoto, K. *J. Org. Chem.* **1978**, *43*, 1012.
(32) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(33) See, for example: Heathcock, C.; Clark, R. D. *Tetrahedron Lett.* **1974**, 2027.
(34) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
(35) Niwa, H.; Wakamatsu, K.; Hida, T.; Niiyamu, K.; Kigoshi, H.; Yamada, M.; Nagase, H.; Suzuki, M.; Yamada, K. *J. Am. Chem. Soc.* **1984**, *105*, 4547.
(36) Matsumoto, K.; Sera, A. *Synthesis* **1985**, 1000.
(37) Scouten, C. G.; Brown, H. C. *J. Org. Chem.* **1973**, *38*, 4092.
(38) Omura, K. O.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957.

Scheme IX

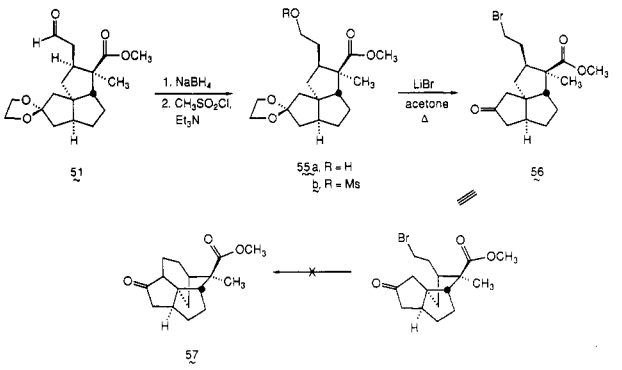


Table I. Crystallographic Details for 56

formula wt, amu	343.26
space group	$P2_12_12_1$
a, Å	7.865 (1)
b, Å	8.102 (1)
c, Å	25.175 (19)
volume, Å^3	1604
Z	4
density (calcd), g/cm^3	1.42
crystal size	0.20 mm × 0.35 mm × 0.40 mm
radiation	Mo Kα with graphite monochromator
linear abs coeff, cm^{-1}	27.2
temperature	ambient
2θ limits	$4° \leq 2\theta \leq 50°$
scan range	$[0.75 + 0.35(\tan\theta)]°$ in ω
data collected	$+h,+k,+l$
unique data	1663
unique data, with $F_o^2 > 2\sigma(F_o^3)$	925
final number of variables	111
$R(F)^a$	0.091
$R_w(F)^b$	0.057
error in observation of unit weight, e	5.20

$^a R(F) = \sum||F_o| - |F_c||/\sum|F_o|$. $^b R_w(F) = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$ with $w = 1/\sigma^2(F_o)$.

selectively ketalized[39] and the cleavage of ring D was accomplished in the predescribed manner. The α-hydroxylation of **49** was routinely 10–15% more efficient than that of **40**, implicating the double bond in the latter as a site of possible secondary reaction.[40] Overall, the six-step conversion of **40** to **52** proceeded with an efficiency of 42%.

Submission of **52** to various acidic and basic conditions provided no positive indication that **53** had formed. It is, of course, possible that ring closure had materialized, but that the higher latent strain energy of the product shifts the equilibrium far on the side of **52**. Consequently, efforts were directed to removal of this reversibility component by making recourse instead to intramolecular S_N2 alkylation.

An initial probe of this question necessitated the synthesis of **56** (Scheme IX). The reduction of **51** with sodium borohydride afforded **55a** quantitatively without competitive lactonization. Whereas direct brominative substitution of this alcohol by reagents such as PPh_3/CBr_4[41] and PPh_3/NBS[42] fared poorly, stepwise mesylation and displacement with bromide ion worked very well, especially since the last step also effected removal of the ketal protecting group in situ.[43] With the structural subunit contained within **56** now available, extensive study was made of its base-promoted ring closure to **57**. Disappointingly, the isocedrane framework was not observed to form under any of the conditions studied, unreacted **56** being returned under all circumstances.

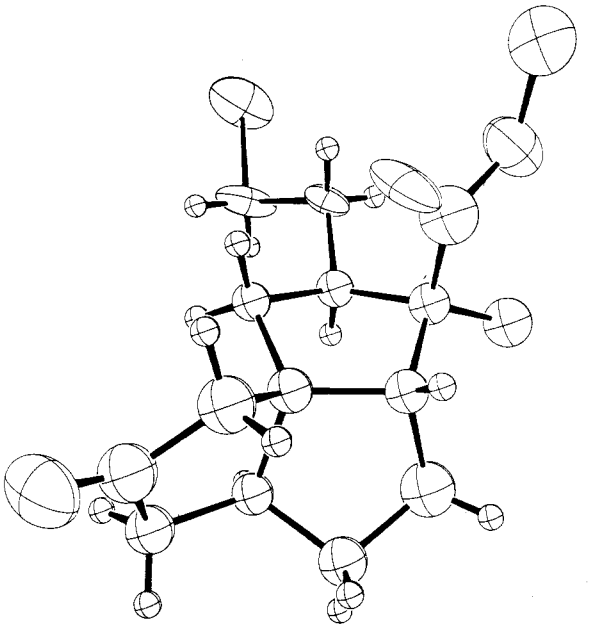


Figure 2. Computer-generated perspective drawing of **56** as determined by X-ray crystallography.

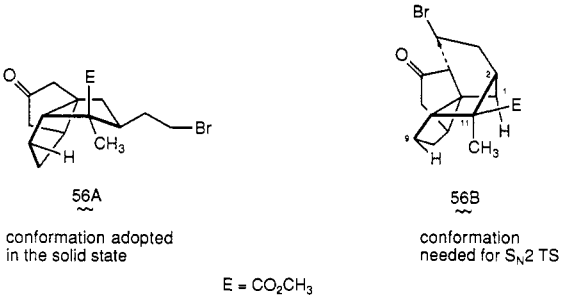


Figure 3. Selected conformations of **56**.

The singular unreactivity of **56** led to investigation of its ground-state conformation by X-ray crystallographic analysis (Table I). As shown in Figure 2, C(2) is puckered in a downward direction, thereby projecting both the β-bromoethyl substituent and C(11) methyl group equatorially. A possible underlying cause of this geometric preference is the relief of 1,3-diaxial interactions between the C(11) methyl and the endo protons at positions 1 and 9. Two conformations of **56** are shown in Figure 3. Since **56B** represents the overall topography required for intramolecular alkylation to operate, this may account for the failure to achieve ring closure in this instance.

Chemical Modification of Ring A

Ultimate acquisition of the trixiginkgolides requires that the cyclopentene ring in **13** and its analogues be oxidatively

(39) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(40) (a) Mimoun, H.; Serce de Roch, L.; Sajus, L. *Tetrahedron* **1970**, *26*, 37. (b) Tolstikov, G. A.; Dzhemilev, U. M.; Yut'ev, V. P. *Zh. Org. Khim.* **1972**, *8*, 2204. (c) Sharpless, K. B.; Townsens, J. M.; Williams, D. R. *J. Am. Chem. Soc.* **1972**, *94*, 295. (d) Arakawa, H.; Morooka, Y.; Ozuki, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2958. (e) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem.* Soc. **1973**, *95*, 136.

(41) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

(42) Bose, A. K.; Bansi, L. *Tetrahedron Lett.* **1973**, *23*, 3937.

(43) Extensive chlorination occurred in the mesylation step with methylene chloride as solvent and it was later found that this could be minimized by performing the reaction in ether in which the triethylammonium chloride is less soluble. Notwithstanding, bromide **56** prepared according to Scheme IX was invariably contaminated with about 8% of the corresponding chloro compound from which it could not be separated.

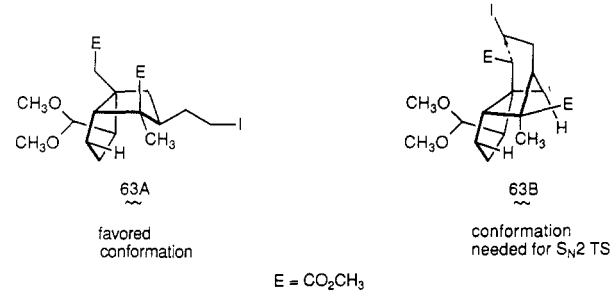
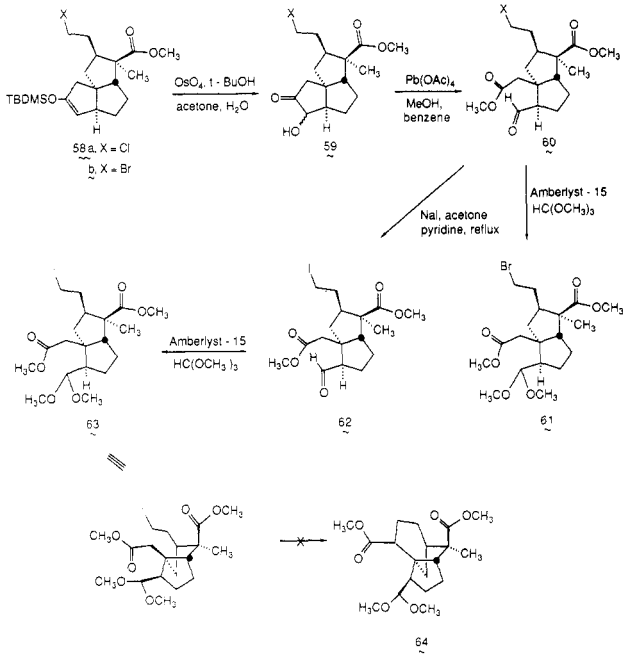


Figure 4. Selected conformations of **63**.

Scheme X



cleaved. Consequently, efforts were also undertaken to open the A ring in several intermediates with the intent of giving these molecules the additional flexibility they might need to achieve the required transition-state conformation. This pathway is precisely that scrutinized in advance from the theoretical vantage point. Hydroxy ester **55a** was therefore treated with the triphenylphosphine–carbon tetrachloride reagent, deketalized, and converted to silyl enol ether **58a** by kinetic deprotonation with lithium diphenyltetramethyldisilazide as base[44] (Scheme X). Excellent regioselectivity was seen only with this very bulky base. The selection of **58a** was based on the expectation that its carbon–chlorine bond would be stable to all interim transformations, yet be susceptible to eventual halide exchange for arrival at potentially serviceable intermediates. Bromide **58b** could be prepared analogously. Osmium tetraoxide oxidation of the activated double bond in either substrate provided **59a** and **59b** in satisfactory yield,[45] thereby setting the stage for oxidative cleavage to the respective aldehydo diesters **60a,b**.

At the experimental level, iodide displacement of chloride ion in **60a** proceeded only very slowly, and therefore **60b** proved to be the utilitarian precursor to **62**. Conversion to acetals **61** and **63** was then achieved conventionally. These products were exposed in turn to a large

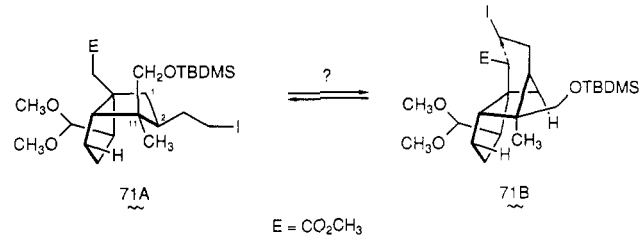
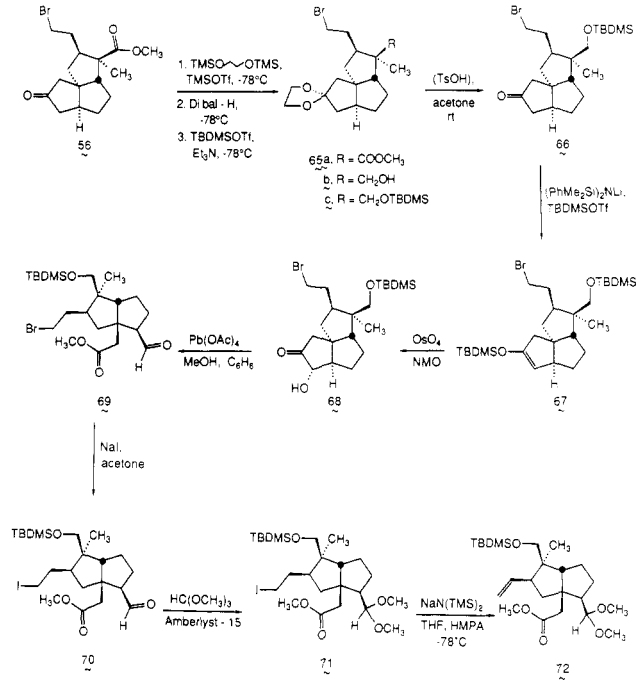


Figure 5. Selected conformations of **71**.

Scheme XI



variety of alkylation conditions, but cyclized material in the form of **64** was again not observed. This behavior contrasts most notably with the successful process developed by Danishefsky in his quadrone synthesis.[3]

The preferred conformational bias in **61** and **63** is, of course, not likely to differ significantly from that found in **56** (Figure 4). However, it seemed plausible that chemical modification of the C(11) ester group so as to increase substantively its relative bulkiness might force adoption of the alternative spatial arrangement (see **71B** in Figure 5). The *tert*-butyldimethylsilyl ether of the reduced carbinol was consequently prepared as summarized in Scheme XI.

Ketalization of **56** permitted controlled reduction of the ester functionality and protection of the hydroxyl group as in **65c**. Ketone **66** was next transformed into **69** by methodology developed earlier, as was the subsequent acquisition of **71**. Lithium hexamethyldisilazide proved insufficiently reactive for **71** and returned the iodo ester mostly unchanged. On the other hand, the related sodium base quickly eliminated hydrogen iodide, as did other strong bases (NMR analysis), to deliver **72**. Therefore, successful ring formation was once again not achieved in this instance. Evidently, the $CH_2OTBDMS$ group is insufficiently bulky to drive the equilibrium in Figure 5 to the right.

Conclusions

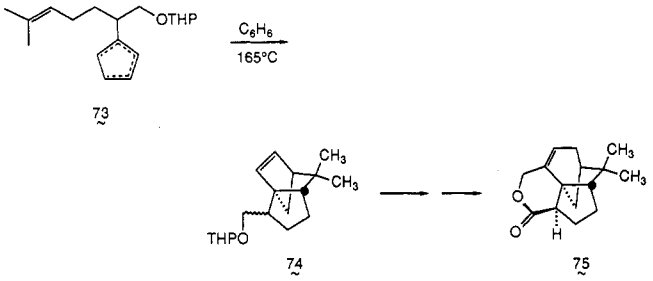
It can be stated with a high degree of assurance that the geometries of intermediates **56**, **63**, and **71** are not conducive to intramolecular S_N2 displacement. Neither are

(44) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
(45) (a) Kenny, M. J.; Mander, L. N.; Sehti, M. P. *Tetrahedron Lett.* **1986**, *27*, 3927. (b) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Ibid.* **1981**, *22*, 607.

46 and 52 structurally well suited to Prins and aldol chemistry, respectively. Were conformational alignment as in 10 (Figure 1) attainable, proximity effects and reaction trajectories appear adequate to allow the desired bonding process to proceed. The situation is particularly exacerbated in triquinanes 52 and 56 (see 54) because of the inhibition of internal rotations brought on by incorporation of one reaction center into a ring. What distinguishes the ability of 8 to advance into the desired reaction manifold from the latent unreactivity of 10 and its analogues can best be gauged by visual examination of Figures 3–5. The apparent inability to flex into the respective "B" conformations effectively deters ring closure.

Despite these disappointments, several potentially useful synthetic observations have emanated from this venture. First, an efficient two-step preparation of 15, an important starting material for polyquinane synthesis,[46] was developed. Secondly, the conversion of 14 to 31 represents a particularly expedient way in which to transform a saturated ketone regioselectively into a homologated α,β-unsaturated carbonyl system. A stereoselective application of the Trost cyclopentannulation sequence followed. In addition, the stannic chloride promoted cyclization of 20 to chloro alcohol 21 represents an aspect of the Prins reaction that merits more detailed scrutiny.

Finally, following completion of our study, Steinmeyer, Schwede, and Bohlmann reported that intramolecular Diels–Alder cycloaddition within 73 proceeds to give 74 (94%).[47] This tricyclic intermediate has subsequently been crafted by them into isocedrenes such as 75.



Experimental Section[48]

Lewis Acid Promoted Cyclization of 20. To an anhydrous solution of 20 (1.0 g, 6.17 mmol) in 50 mL of methylene chloride under argon and at −78 °C was added tin tetrachloride (1.93 g, 7.40 mmol). The mixture was allowed to warm to −30 °C over 1 h during which time a burgundy color appeared. After an additional h, more tin tetrachloride was added and the reaction mixture was stirred at −10 °C for 1 h. The mixture was cooled to −78 °C, quenched with saturated sodium bicarbonate solution, and extracted with methylene chloride. The combined extracts were washed with brine, dried, and passed through a short Florisil column. MPLC purification (silica gel, elution with 25% ethyl acetate in petroleum ether) provided 21, i, and ii as colorless oils in quantities of 290 mg (24%), 313 mg (27%), and 57 mg (5%), respectively. The first and second chloro alcohols were shown to be stereoisomers by conversion to 22.

For 21: IR (neat, cm^{-1}) 3600–3200, 3070, 2950, 2880, 2860, 1460, 995, 730; ^1H NMR (300 MHz, C_6D_6) δ 5.55 (br s, 2 H), 4.38–4.31 (m, 2 H), 2.67–2.61 (m, 1 H), 2.33–2.31 (m, 1 H), 2.25–2.21 (t, J = 6.5 Hz, 1 H), 2.08–1.59 (series of m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 137.34, 128.69, 75.21, 67.12, 63.10, 60.67, 46.54, 43.03, 39.60, 35.98, 35.29; MS m/z (M^+) calcd for $C_{11}H_{15}ClO$ 198.0812, obsd 198.0822.

For i: IR (neat, cm^{-1}) 3340, 3040, 2920, 2850, 1450, 1260, 1100, 930, 895, 820; ^1H NMR (300 MHz, C_6D_6) δ 5.48 (s, 2 H), 4.29–4.21 (m, 1 H), 3.62–3.53 (m, 1 H), 2.57–2.48 (dd, J = 13.3, 6.3 Hz, 1 H), 2.32–1.48 (series of m, 9 H), 1.40–1.30 (dd, J = 13.0, 6.2 Hz, 1 H); MS m/z (M^+) calcd for $C_{11}H_{15}ClO$ 198.0812, obsd 198.0798.

For ii: ^1H NMR (300 MHz, C_6D_6) δ 5.65–5.62 (m, 1 H), 4.25–4.24 (d, J = 3.6 Hz, 1 H), 3.56–3.47 (m, 1 H), 2.34–2.20 (m, 1 H), 2.14–1.49 (series of m, 11 H); MS m/z (M^+ − H) calcd for $C_{11}H_{14}ClO$ 197.0733, obsd 197.0714.

Tricyclic Chloro Ketone 22. To a slurry of pyridinium chlorochromate (94 mg, 0.44 mmol) and sodium acetate (7.5 mg, 0.093 mmol) in 3 mL of dry methylene chloride under argon was added 21 (51 mg, 0.26 mmol) in 3 mL of the same solvent. After 40 min, the reaction mixture was diluted with ether and passed through a short column of Florisil. Purification by MPLC (silica gel, elution with 12% ethyl acetate/petroleum ether) provided 44 mg (87%) of 22 as a colorless oil: IR (neat, cm^{-1}) 3040, 2960, 2925, 2850, 1730, 1450, 1400, 1350, 1160; ^1H NMR (300 MHz, C_6D_6) δ 5.69–5.60 (br s, 2 H), 4.58–4.53 (m, H), 2.89–1.81 (series of m, 10 H); MS m/z (M^+) calcd for $C_{11}H_{13}ClO$ 196.0655, obsd 196.0630.

Tricyclic Dienone 23. Chloro ketone 22 (43 mg, 0.22 mmol) was dissolved in 2 mL of dry methylene chloride. 1,8-Diazabicyclo[5.4.0]undec-7-ene (51 mg, 0.321 mmol) was added, and the reaction mixture was stirred overnight at room temperature under an argon atmosphere. The yellow-green mixture was diluted with methylene chloride and passed through a short Florisil column. The concentrated eluate was purified by MPLC (silica gel, elution with 13% ethyl acetate in petroleum ether) to give 31 mg (88%) of 23 as a colorless oil: IR (neat, cm^{-1}) 3040, 2920, 2845, 1730, 1630, 1445, 1405; ^1H NMR (300 MHz, C_6D_6) δ 6.42–6.40 (m, 1 H), 5.82–5.79 (m, 1 H), 5.71–5.67 (m, 1 H), 3.13–3.12 (ddd, J = 18.4, 9.1, 3.7 Hz, 1 H), 2.89–2.80 (dd, J = 15.9, 9.0 Hz, 1 H), 2.64–2.43 (m, 4 H), 2.25–2.19 (complex d, J = 18.0 Hz, 1 H), 1.98–190 (m, 2 H); MS m/z (M^+) calcd for $C_{11}H_{12}O$ 160.0874, obsd 160.0881.

Reductive Dechlorination of 21. Ammonia (9 mL, previously dried over sodium) was distilled into a flask equipped with a dry ice condenser, argon inlet, and bubbler and containing sodium metal (89 mg, 3.85 mmol). A mixture of 21 and its epimer (176 mg, 0.883 mmol) and ethanol (14 mg, 0.3 mmol) in 1.2 mL of tetrahydrofuran were added dropwise to the above mixture at −78 °C. After 30 min, isoprene was introduced slowly until the blue color of the reaction mixture was dissipated. Saturated ammonium chloride solution (0.5 mL) was added, and the ammonia was evaporated off. The residue was extracted with ether and dried. The product was purified by MPLC (silica gel, elution with 33% ethyl acetate in petroleum ether) to provide 139 mg (96%) of tricyclic alcohol as a colorless oil: IR (neat, cm^{-1}) 3600–3100, 3040, 2930, 2850, 1605, 1440, 1350, 1070, 990; ^1H NMR (300 MHz, C_6D_6) δ 5.60–5.57 (m, 1 H), 5.48–5.45 (m, 1 H), 3.97 (br s, 1 H), 2.57–2.48 (ddt, J = 16.7, 7.9, 2.2 Hz, 2 H), 2.16–1.15 (series of m, 11 H); MS m/z (M^+) calcd for $C_{11}H_{16}O$ 164.1121, obsd 164.1193.

Tricyclic Ketone 14. A slurry of powdered 3-Å molecular sieves (30 mg), sodium acetate (19 mg, 0.23 mmol), and pyridinium chlorochromate was prepared in dry methylene chloride (5 mL) under an argon atmosphere. A solution of the preceding alcohol (125 mg, 0.726 mmol) in methylene chloride (2 mL) was introduced via a double-ended needle. After 1 h, the reaction mixture was diluted with ether (25 mL) and poured over Florisil. The eluate was concentrated to give 116 mg (94%) of 14 as a colorless oil which required no further purification: IR (neat, cm^{-1}) 3040, 2940, 2865, 2840, 1730, 1450, 1440, 1400, 1360; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68–5.65 (m, 1 H), 5.52–5.49 (m, 1 H), 2.84–2.73 (ddt,

(46) (a) Paquette, L. A.; Doherty, A. M. *Polyquinane Chemistry*; Springer-Verlag: Heidelberg, 1987. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Paquette, L. A. *Ibid.* **1979**, *79*, 41.

(47) Steinmeyer, A.; Schwede, W.; Bohlmann, F. *Justus Liebigs Ann. Chem.* **1988**, 925.

(48) The purity of all title compounds was judged to be ≥95% by TLC analysis and 300-MHz ^1H NMR spectral determination in each instance.

(49) TEXSAN, TEXRAY Structure Analysis Package, version 2.1, Molecular Structure Corporation, College Station, TX, 1987.

(50) Beurskens, P. T. DIRDIF: Direct Methods for Difference Structures—An Automatic Procedure for Phase Extension and Refinement of Difference Structure Factors. Technical report 1984/1. Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

(51) Scattering factors for the bromine, oxygen, and carbon atoms and anomalous dispersion terms are from the *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, pp 71 and 148. The scattering factor for the hydrogen atom is from: Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175.

J = 17.2, 9.8, 2.3 Hz, 1 H), 2.49–1.64 (series of m, 10 H), 1.50–1.42 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 222.60, 136.14, 130.17, 65.89, 57.91, 48.19, 41.01, 38.44, 34.93, 32.10, 29.40; MS m/z (M^+) calcd for $C_{11}H_{14}O$ 162.1044, obsd 162.1036.

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.13; H, 8.62.

Carbonylation Routes to 27. A. Nickel Carbonyl and 26. Into a dry, two-necked flask equipped with a water condenser and argon gas inlet was placed sodium methoxide (119 mg, 2.20 mmol), 2 mL of dry methanol, and nickel tetracarbonyl (0.765 g, 4.50 mmol). After 10 min of stirring, **26** (94 mg, 0.36 mmol) was added as a solution in methanol and ether. The reaction mixture was then heated to 48 °C for 2 h, whereupon the excess nickel(0) was destroyed with a methanol/iodine solution. The mixture was poured into ether, washed with 3 × 35 mL of sodium thiosulfite solution, and dried. Purification by MPLC (silica gel, elution with 20% ethyl acetate in petroleum ether) gave 41 mg (55%) of **27** as a colorless oil: IR (neat, cm^{-1}) 3040, 2930, 1715, 1620, 1440, 1240, 1210, 1040; ^{1}H NMR (300 MHz, C_6D_6) δ 6.66–6.64 (m, 1 H), 5.54–5.28 (m, 2 H), 3.71 (s, 3 H), 3.05 (m, 1 H), 2.67–2.45 (m, 3 H), 2.33 (m, 1 H), 1.97–1.65 (m, 4 H), 1.39–1.34 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 165.46, 142.17, 137.90, 137.02, 128.75, 66.69, 56.16, 51.58, 51.16, 45.49, 39.65, 33.24, 30.41; MS m/z (M^+) calcd for $C_{13}H_{16}O_2$ 204.1140, obsd 204.1146.

B. Palladium-Catalyzed Conversion of 28. A solution of **28** (119 mg, 0.405 mmol), anhydrous triethylamine (82 mg, 0.81 mmol), triphenylphosphine (14 mg, 0.02 mmol), palladium(II) acetate (4.5 mg, 0.02 mmol), and dry methanol (152 mg, 4.76 mmol) in 1 mL of dimethylformamide was prepared under argon and at room temperature. The system was purged with carbon monoxide for 5 min and then maintained under 1 atm of carbon monoxide gas for 1.5 h. The reaction mixture was poured into water and extracted with ether. The extracts were dried and separated as above to yield 60 mg (60%) of **27**.

Coupling of 28 to 29. Anhydrous lithium chloride (54 mg, 1.3 mmol) and tetrakis(triphenylphosphine)palladium (26 mg, 0.022 mmol) were transferred under argon to a 25-mL flask equipped with a water condenser. A solution of (1-ethoxyvinyl)trimethyltin (109 mg, 0.463 mmol) and **28** (132 mg, 0.449 mmol) in 8 mL of dry tetrahydrofuran (degassed at −78 °C under vacuum) was added. The slurry was heated to 70 °C and stirred for 12 h. The mixture was cooled to room temperature, diluted with pentane, and poured into 10% ammonium hydroxide solution. The aqueous layer was removed, and the organic extract was washed with ammonium hydroxide solution (2 × 10 mL) and passed over a short Florisil column to yield 117 mg of **30** as a colorless oil, which was used without further purification: IR (neat, cm^{-1}) 3040, 2970, 2920, 1640, 1570, 1440, 1370, 1345, 1260, 1125, 975, 795, 735; ^{1}H NMR (300 MHz, C_6D_6) δ 6.12 (br s, 1 H), 5.53–5.50 (m, 1 H), 5.44–5.41 (m, 1 H), 4.23 (s, 1 H), 4.08 (s, 1 H), 3.51 (q, J = 7.0 Hz, 2 H), 3.06 (m, 1 H), 2.55–1.25 (series of m, 9 H), 1.11 (t, J = 7.0 Hz, 3 H); MS m/z (M^+) calcd for $C_{15}H_{20}O$ 218.1620, obsd 218.1586.

Acid Hydrolysis of 30. The unpurified enol ether **30** (120 mg) was dissolved in acetic acid/water (1:1) and stirred for 2 h. The mixture was neutralized with sodium bicarbonate solution and extracted with ether. Purification by MPLC (elution with 20% ethyl acetate in petroleum ether) gave 47 mg (56% for two steps) of **31** as a colorless oil: IR (neat, cm^{-1}) 3065, 3000, 2945, 2940, 2900, 2860, 2840, 2830, 1735, 1660, 1610, 1460, 1440, 1425, 1370, 1340, 1320, 1285, 1235, 1090; ^{1}H NMR (300 MHz, C_6D_6) δ 6.58 (dd, J = 9.27, 3.15 Hz, 1 H), 5.51 (m, 2 H), 3.05 (m, 1 H), 2.65–2.56 (m, 2 H), 2.34–2.26 (m, 1 H), 2.27 (s, 3 H), 2.02–1.95 (m, 2 H), 1.91–1.85 (m, 1 H), 1.77–1.73 (m, 1 H), 1.66–1.54 (m, 1 H), 1.38–1.30 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 196.56, 147.30, 142.49, 136.99, 128.53, 66.45, 55.63, 51.56, 45.80, 39.49, 33.49, 30.58, 26.87; MS m/z calcd for $C_{13}H_{16}O$ 188.1201, obsd 188.1203.

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.56. Found: C, 82.72; H, 8.51.

Vinylcuprate Addition to 31. A slurry of copper cyanide (31 mg, 0.348 mmol) was prepared under argon in 0.5 mL of dry ether and cooled to −78 °C. Vinyllithium (0.75 mmol) in 1 mL of ether was added. The mixture was warmed to 0 °C and then cooled again to −78 °C, whereupon **31** (40 mg, 0.213 mmol) in 0.75 mL of ether was added dropwise over 2 min. The previously green mixture became deep yellow. After 1 h at −78 °C, the reaction mixture was quenched with saturated ammonium chloride/ammonium hydroxide solution (1:1) and extracted with ether. The combined extracts were poured over a short Florisil column, and the product was purified by MPLC (silica gel, elution with 6% ethyl acetate in petroleum ether) to yield 32 mg (70%) of a colorless oil, containing all four possible isomers of **33** and **34** as an inseparable mixture: IR (neat, cm^{-1}) 3400, 3080, 3040, 2430, 2850, 1700, 1635, 1440, 1350, 1270, 990, 915; ^{1}H NMR (300 MHz, C_6D_6) δ 6.07–4.90 (series of m, 3 H), 3.50–1.12 (series of m, 14 H), four singlets at 2.12, 2.11, 2.10, 2.09 in a 2:2:4:1 ratio (3 H); MS m/z (M^+) calcd for $C_{15}H_{20}O$ 216.1512, obsd 216.1490.

Trienone 35a. To a flask under an argon atmosphere and containing anhydrous lithium chloride (324 mg, 9.00 mmol) and tetrakis (triphenylphosphine)palladium (144 mg, 0.12 mmol) was added a solution of **28** (610 mg, 2.07 mmol) and trimethylvinyltin (603 mg, 2.2 mmol) in 21 mL of dry tetrahydrofuran via syringe. The system was purged with carbon monoxide for 15 min before being sealed under a static pressure of carbon monoxide maintained by a Fisher gas bag. The reaction mixture was heated to 55 °C and maintained there for 48 h, after which time the mixture was diluted with pentane, washed with water and brine, and passed over a short Florisil column. Separation by MPLC (silica gel, elution with 7% ethyl acetate in petroleum ether) provided 207 mg (50%) of a colorless oil identified as the desired product **35a** and 48 mg (12%) of that isomer resulting from the enol triflate isomer v.

For **35a**: IR (neat, cm^{-1}) 3040, 2925, 2890, 2840, 1655, 1600, 1405, 1215, 980; ^{1}H NMR (300 MHz, C_6D_6) δ 6.61 (dd, J = 8.4, 17.0 Hz, 1 H), 6.27 (dd, J = 2.2, 17.1 Hz, 1 H), 6.11 (dd, J = 4.2, 2.7 Hz, 1 H), 5.43–5.33 (m, 2 H), 5.28 (dd, J = 2.1, 8.2 Hz, 1 H), 3.24 (m, 1 H), 2.52–0.81 (series of m, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 187.02, 147.64, 141.70, 137.28, 133.08, 128.83, 126.69, 66.42, 56.47, 51.85, 46.14, 40.01, 33.73, 30.68; MS m/z (M^+) calcd for $C_{14}H_{16}O$ 200.1201, obsd 200.1196.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.53; H, 7.94.

For the isomer: ^{1}H NMR (300 MHz, C_6D_6) δ 6.61 (dd, J = 17.0, 10.3 Hz, 1 H), 6.33 (dd, J = 17.1, 2.2 Hz, 1 H), 5.5–5.4 (complex d, 2 H), 5.27 (dd, J = 10.3, 2.6 Hz, 1 H), 3.01 (dd, J = 8.7, 15.6 Hz, 1 H), 2.86–1.38 (series of m, 10 H); MS m/z (M^+) calcd for $C_{14}H_{16}O$ 200.1201, obsd 200.1182.

Nazarov Cyclization of 35a. A mixture of phosphorus pentoxide and methanesulfonic acid (1:9 by weight, 20 g) was added to **25a** (95 mg, 0.48 mmol). After 5 min, the carmel-colored reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with methylene chloride. The combined organic layers were dried and evaporated to leave an oil that was purified by MPLC (elution with 20% ethyl acetate in petroleum ether) to yield 19 mg (20%) of **36** as a crystalline solid: mp 68–69 °C; IR (neat, cm^{-1}) 3040, 2930, 2900, 2840, 1680, 1625, 1380, 1225, 740, 725; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60–5.57 (m, 1 H), 5.48–5.45 (m, 1 H), 3.97 (br s, 1 H), 2.57–2.48 (ddt, J = 16.7, 7.9, 2.2 Hz, 1 H), 2.16–1.15 (series of m, 12 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 201.23, 182.11, 149.45, 136.88, 129.24, 73.49, 51.58, 50.91, 44.61, 40.38, 33.38, 28.20, 25.29; MS m/z (M^+) calcd for $C_{14}H_{16}O$ 200.1201, obsd 200.1208.

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.83; H, 8.10.

Conversion of 28 to 35b. To a flask containing anhydrous lithium chloride (360 mg, 8.78 mmol) and tetrakis(triphenylphosphine) palladium (140 mg, 0.12 mmol) under argon was added a solution of (2-(trimethylsilyl)vinyl)trimethyltin (878 mg, 2.53 mmol) and **28** (706 mg, 2.41 mmol) in 25 mL of dry tetrahydrofuran. The system was purged with carbon monoxide for 15 min and maintained under a static pressure of 1 atm while being heated to 70 °C. After 48 h, the mixture was diluted with pentane and washed with water and brine prior to being passed over a short Florisil column. Purification by MPLC (silica gel, elution with 1.5% ethyl acetate in petroleum ether) provided 522 mg (80%) of **35b** as a colorless oil and 54 mg (8%) of its isomer iv.

For **35b**: IR (neat, cm^{-1}) 3050, 2960, 2900, 2865, 2845, 1640, 1600, 1420, 1335, 1245, 1225, 990; ^{1}H NMR (300 MHz, C_6D_6) δ 7.43 (d, J = 18.6 Hz, 1 H), 7.06 (d, J = 18.3 Hz, 1 H), 6.24 (dd, J = 4.3, 2.5 Hz, 1 H), 5.46–5.37 (m, 2 H), 3.37–3.35 (m, 1 H), 2.55–2.45 (ddt, J = 18.8, 16.8, 2.1 Hz, 1 H), 2.39–2.29 (m, 1 H), 2.23–1.55 (series of m, 6 H), 1.32–1.23 (m, 1 H), 0.14 (s, 9 H); ^{13}C

NMR (75 MHz, C_6D_6) ppm 186.08, 147.77, 145.01, 141.46, 139.01, 137.36, 128.85, 66.42, 56.70, 51.90, 46.2, 40.07, 33.81, 30.74, -1.72; MS m/z (M^+) calcd for $C_{17}H_{24}OSi$ 272.1597, obsd 272.1576.

Anal. Calcd for $C_{17}H_{24}OSi$: C, 83.96; H, 8.05. Found: C, 83.62; H, 8.04.

For iv: IR (neat, cm^{-1}) 3040, 2945, 2890, 2850, 1638, 1581, 1450, 1438, 1352, 1335, 1248, 1199, 995, 840, 784, 725; ^1H NMR (300 MHz, C_6D_6) δ 7.39 (d, J = 18.6 Hz, 1 H), 7.03 (d, J = 18.6 Hz, 1 H), 5.46 (s, 2 H), 3.18–1.42 (series of m, 11 H), 0.02 (s, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 187.05, 167.40, 144.63, 141.47, 134.17, 132.92, 130.10, 76.83, 43.42, 41.94, 37.47, 36.97, 35.50, 27.06, -1.72; MS m/z (M^+) calcd for $C_{17}H_{24}OSi$ 272.1597, obsd 272.1595.

Nazarov Cyclization of 35b. A solution of **35b** (32 mg, 0.12 mmol) in dry methylene chloride (2 mL) was prepared under argon and cooled to -17 °C. Ferric chloride was added (21 mg, 0.13 mmol), and the reaction mixture was warmed to 0 °C and stirred there for 14 h, whereupon it was poured into an equal volume of water and extracted with ether. The combined extracts were washed with water, sodium bicarbonate solution, and brine prior to drying. MPLC on silica gel (elution with 17% ethyl acetate in petroleum ether) gave 17 mg (72%) of a colorless, UV-active oil, consisting of **37** and **38** as an inseperable mixture in the ratio of 1.6:1 by NMR (300 MHz). Separation of these isomers was accomplished by preparative TLC.

For **37**: IR (neat, cm^{-1}) 3400, 3060, 2960, 2880, 1710, 1590, 1455, 1355; ^1H NMR (300 MHz, C_6D_6) δ 6.76 (dd, J = 2.6, 6.0 Hz, 1 H), 5.80 (dd, J = 2.2, 5.8 Hz, 1 H), 5.45–5.42 (m, 1 H), 5.18–5.12 (m, 1 H), 3.76–3.70 (m, 1 H), 2.82–0.91 (series of m, 11 H); MS m/z (M^+) calcd for $C_{14}H_{16}O$ 200.1201, obsd 200.1225.

For **38**: IR (neat, cm^{-1}) 3050, 3040, 3020, 1725, 1680, 1580, 1460, 1445, 1345, 1200, 730; ^1H NMR (300 MHz, C_6D_6) δ 6.88–6.82 (dd, J = 5.6, 1.6 Hz, 1 H), 5.78 (dd, J = 5.5, 1.6 Hz, 1 H), 5.36–5.16 (m, 2 H), 2.78–2.70 (m, 1 H), 2.57–2.44 (ddt, J = 17.2, 9.2, 2.2 Hz, 1 H), 2.32 (d, J = 4.7 Hz, 1 H), 2.17 (dd, J = 6.6, 4.4 Hz, 1 H), 2.19–1.43 (m, 6 H), 1.24 (dd, J = 13.1, 7.1 Hz, 1 H), 1.20–1.11 (m, 1 H); MS m/z (M^+) calcd for $C_{14}H_{16}O$ 200.1201, obsd 200.1201.

Methylation of 37. To a solution of diisopropylamine (19 mg, 0.19 mmol) in 1 mL of tetrahydrofuran was added *n*-butyllithium (0.18 mmol, 1.5 M in hexane) at 0 °C. After 5 min, the reaction mixture was cooled to -78 °C, and **37** (29 mg, 0.145 mmol) was added in 1 mL of tetrahydrofuran over 20 min. After 1 h, methyl iodide (123 mg, 0.87 mmol) was introduced. The reaction mixture was allowed to warm and stir at room temperature before being quenched with saturated ammonium chloride solution. The solution was extracted with ether and dried. Purification of the residue by MPLC gave 7.8 mg (25%) of **39** as a colorless oil: IR (neat, cm^{-1}) 3060, 3045, 2870, 1735, 1700, 1595, 1460, 1380; ^1H NMR (300 MHz, C_6D_6) δ 6.80 (dd, J = 5.5, 4 Hz, 1 H) 5.89 (dd, J = 1.7, 5.7 Hz, 1 H), 5.51–5.25 (m, 2 H), 2.55–1.14 (series of m, 11 H), 1.03 (s, 3 H); MS m/z (M^+) calcd for $C_{15}H_{18}O$ 214.1357, obsd 214.1357.

Reductive Alkylation of 36. To a three-necked round-bottomed flask equipped with a dry ice condenser, argon inlet, and bubbler was placed low-sodium lithium wire (20 mg, 2.90 mmol). Ammonia (15 mL, previously dried over sodium) was distilled into the reaction vessel. After 15 min of stirring at -78 °C, a solution of **36** (204 mg, 1.02 mmol) and dry *tert*-butyl alcohol (38 mg, 0.51 mmol) in 5 mL of tetrahydrofuran was added over 25 min. After 40 min, 0.75 mL of methyl iodide (1.4 g, 12 mmol, previously passed through a short basic alumina column) was added over 1 min. After the first 4–5 drops, the blue color dissipated. A larger volume bubbler was attached, and the mixture was allowed to warm to room temperature slowly. After 3 h, most of the ammonia had evaporated, and saturated ammonium chloride solution was added (2 mL). The reaction mixture was extracted with ether, and the combined extracts were dried over magnesium sulfate. Concentration and chromatography as above gave 146 mg (66%) of **40** as a colorless solid, mp 40–42 °C; IR (neat, cm^{-1}) 3055, 2930, 2860, 1730, 1460, 1445, 1405, 1368, 1072, 1028, 749, 732; ^1H NMR (300 MHz, C_6D_6) δ 5.40–5.37 (br s, 2 H), 2.85–2.61 (m, 1 H), 2.54–2.45 (m, 1 H), 2.08–1.20 (m, 12 H), 1.13–1.05 (dd, J = 11.3, 13.6 Hz, 1 H), 0.71 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 221.26, 138.61, 128.61, 68.70, 59.30, 54.78, 50.23, 47.37, 43.26, 39.71, 35.40, 32.85, 29.22, 21.60, 16.55; MS m/z (M^+) calcd for $C_{15}H_{20}O$ 216.1514, obsd 216.1507.

Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.05; H, 9.35.

Conjugate Reduction of 39. To a cold (-78 °C) solution of enone **39** (7 mg, 0.032 mmol) in 2 mL of dry methylene chloride under argon was added L-Selectride (Aldrich; 0.032 mmol, 1 M in tetrahydrofuran). After 20 min, the cooling bath was removed, and the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether. The combined extracts were dried and poured over a short Florisil column. Purification by MPLC (silica gel, elution with 10% ethyl acetate in petroleum ether) gave 6.8 mg (98%) of product that proved spectroscopically identical with **40**.

Condensation of 14 with Cyclopropyldiphenylsulfonium Ylide. To a solution of **14** (1.5 g, 9.25 mmol) in dry dimethyl sulfoxide (20 mL) was added Trost reagent[29] (2.93 g, 9.33 mmol) and powdered potassium hydroxide (1.13 g, 20.2 mmol). The mixture turned orange-brown. After 8 h, hexane was added, and the layers were separated. The hexane layer was washed with 5% sodium bicarbonate solution and dried over sodium sulfate. The resulting binary mixture of **41** and diphenyl sulfide was carried on into the next step. For characterization, the oxirane can be removed selectively by Kugelrohr distillation at 40 °C and 0.01 Torr: IR (neat, cm^{-1}) 3035, 2930–2905, 1435, 1400; ^1H NMR (300 MHz, C_6D_6) δ 5.52–5.38 (m, 2 H), 2.60–2.50 (ddt, J = 17, 9.0, 2.2 Hz, 1 H), 2.24–1.37 (m, 11 H), 0.89 (br s, 2 H), 0.66–0.55 (m, 2 H); MS m/z (M^+) calcd for $C_{14}H_{18}O$ 202.1357, obsd 202.1364.

Base-Promoted Ring Opening of 41. The product mixture from the above reaction was dissolved under argon in 20 mL of dry hexane and diethylamine (1.22 g, 16.6 mmol). The solution was cooled to -75 °C and *n*-butyllithium (10.5 mL, 1.58 M in hexane, 16.6 mmol) was added. After 2–4 min, a white precipitate formed. After an additional 5–6 min, the dry ice bath was removed. The reaction mixture was warmed to room temperature and stirred for 15–20 min before freshly distilled trimethylsilyl chloride (2.74 g, 25.2 mmol) was introduced. The reaction mixture became clear, and dimethoxyethane (4 mL) was added. After 10 min, the mixture was diluted with 100 mL of dry hexane and the suspension was stored overnight at 5 °C before being filtered through 10 g of Florisil. Concentration and purification by MPLC (silica gel, elution with 15% dichloromethane in petroleum ether) gave 1.47 g (58% for two steps) of **42** as a clear oil: IR (neat, cm^{-1}) 3085, 3040, 3000, 2955, 2930, 2860, 2840, 1443, 1410, 1350, 1260, 1250, 1230, 1228, 1008, 905, 880, 843; ^1H NMR (300 MHz, C_6D_6) δ 5.62–5.59 (m, 1 H), 5.50–5.46 (m, 1 H), 5.23 (q, J = 2.1 Hz, 1 H), 3.05–3.01 (m, 1 H), 2.62–2.53 (qt, J = 8.9, 2.3 Hz, 1 H), 2.54–2.47 (dt, J = 16.8, 2.0 Hz, 1 H), 2.32–2.25 (dt, J = 17.1, 2.5 Hz, 1 H), 2.26–2.20 (m, 1 H), 1.97–1.70 (m, 4 H), 1.37–1.28 (m, 1 H), 1.02–0.89 (m, 2 H), 0.89–0.76 (m, 2 H), 0.59–0.49 (m, 9 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 147.88, 138.40, 132.45, 128.00, 67.84, 58.12, 55.36, 51.86, 45.23, 40.24, 34.22, 30.48, 15.54, 11.99, 1.29; MS m/z (M^+) calcd for $C_{17}H_{26}OSi$ 274.1753, obsd 274.1788.

Anal. Calcd for $C_{17}H_{26}OSi$: C, 74.39; H, 9.55. Found: C, 74.35; H, 9.55.

Thermal Isomerization of 42. A solution of **42** (5.36 mmol) in dry hexane (5 mL) was placed in a 10-mL addition funnel (alternatively a syringe pump may be used). Meanwhile, a 1.5 cm × 40 cm Pyrex glass column was packed with Pyrex glass helices for 20 cm of its height. The column was pretreated by washing it with 5% sodium bicarbonate solution, distilled water, acetone, hexane, and trimethylsilyl chloride. The column was dried under reduced pressure and washed with triethylamine and finally hexane. The column (set in a vertical position) was heated to 430 °C, and argon was passed through it at a rate of 15 mL/min. The addition funnel was attached at the top, and a pre-tared 250-mL flask (three-necked, equipped with septa and bubbler) was attached at the bottom. The flask was cooled in dry ice and acetone, and the solution of substrate was added dropwise into the column at a rate of 1–2 drops/min. After the addition was complete, the flask was removed and the yellow mixture was concentrated to give 1.43 g (97%) of a yellow oil. This product was not characterized, but carried directly into the next reaction.

A portion of the preceding silyl enol ether mixture (220 mg, 0.803 mmol) was dissolved in 4 mL of dry acetonitrile, 2,6-Di-*tert*-butylpyridine (170 mg, 0.892 mmol) was next added, followed by palladium acetate (222 mg, 0.993 mmol) in one portion. The solution soon turned brown, then nearly black. After 80 min, the

solvent was removed in vacuo and the black residue was washed with methylene chloride. The extract was filtered through Celite, and the filtrate was concentrated and chromatographed over preparative grade silica gel with 5–20% ethyl acetate in petroleum ether as eluant to give 125 mg (78%) of **36**.

Methylation of 43. A solution of **43** (1.43 g, 5.20 mmol) was cooled to −78 °C, and methyllithium (5.72 mmol, 1.5 M in ether, low halide content) was added dropwise during 5 min. After 20 min, the reaction mixture was warmed to 0 °C. After an additional 20 min, the mixture was recooled to −78 °C, and methyl iodide (25 mmol, 3.5 g, dried by passage through basic alumina) was added in one portion. After being stirred for 10 min, the mixture was warmed to room temperature, quenched with saturated ammonium chloride solution, and extracted with petroleum ether. The combined extracts were poured over Florisil and purified by MPLC (silica gel, 2% ethyl acetate in petroleum ether) to give 496 mg (44%) of **40** as a white crystalline material of mp 40–42 °C and 326 mg (29%) of its stereoisomer **44** as a colorless oil. The spectra of **40** were identical with those described above.

For **44**: IR (neat, cm^{-1}) 3025, 2930, 2845, 1725, 1445, 1400, 1135, 1100, 748, 728; ^1H NMR (300 MHz, C_6D_6) δ 5.60–5.57 (m, 1 H), 5.49–5.46 (m, 1 H), 2.58–2.48 (m, 1 H), 2.23–1.19 (m, 14 H), 1.16 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 220.61, 138.85, 126.65, 70.64, 62.98, 57.96, 52.36, 50.26, 43.44, 38.80, 38.19, 36.48, 30.56, 24.69, 24.48; MS m/z (M^+) calcd for $C_{15}H_{20}O$ 216.1514, obsd 216.1504.

α-Hydroxylation of 40. A solution of diisopropylamine (58 mg, 0.58 mmol) in 2 mL of dry tetrahydrofuran was cooled to −78 °C under argon and *n*-butyllithium was added (0.6 mmol, 1.55 M in hexanes). The mixture was warmed to −20 °C, stirred for 10 min, and then cooled again to −78 °C. A solution of **40** (52 mg, 0.24 mmol) in 2 mL of tetrahydrofuran was introduced over a 5-min period. After 30 min, the enolate solution was transferred via cannula to a stirred suspension of MoOPh (420 mg, 0.970 mmol) in 2 mL of tetrahydrofuran at −44 °C over 5 min. After 15 min, the suspension had disappeared and a dark orange color materialized. Saturated sodium sulfite solution was added, and the mixture was allowed to warm gradually to room temperature. The product was extracted into ether, and the extract was washed with 10% hydrochloric acid, sodium bicarbonate solution, and brine. The extracts were dried, and product purification was achieved by silica gel chromatography (elution with 20% ethyl acetate in petroleum ether) to give 39 mg (71%) of **45** as a colorless oil in addition to 4 mg (8%) of unreacted starting material. For the epimeric mixture: IR (neat, cm^{-1}) 3440, 2935, 2860, 1735, 1442, 1295, 1200, 988, 735; ^1H NMR (300 MHz, C_6D_6) δ 5.47–5.21 (m, 2 H), 5.01–3.95 (8 line pattern + dd, J = 1.5, 8.5 Hz, 1 H), 2.63–1.05 (series of m, 14 H), 0.84 and 0.68 (s, 3 H total); MS m/z (M^+) calcd for $C_{15}H_{20}O_2$ 232.1463, obsd 232.1453.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.69.

Lead Tetraacetate Cleavage of 45. A dry solution of acyloin **45** (10 mg, 0.043 mmol) in benzene (1.5 mL) and methanol (0.5 mL) was prepared and cooled to 5 °C. Lead tetraacetate (20 mg, 0.046 mmol) was added in one portion. After 5 min, 0.5 mL of saturated sodium bicarbonate solution was added, and the mixture was filtered through Celite and extracted with benzene. Drying and concentration gave 10.5 mg of **46** as a colorless oil (93%; larger scale reactions gave up to 100% yield): IR (neat, cm^{-1}) 3045, 2940, 2850, 2720, 1720, 1460, 1445, 1210, 1130; ^1H NMR (300 MHz, C_6D_6) δ 9.35 (m, 1 H), 5.97–5.94 (m, 1 H), 5.46–5.43 (m, 1 H), 3.26 (s, 3 H), 2.50–2.40 (m, 2 H), 2.30–2.24 (m, 1 H), 2.11–1.92 (m, 3 H), 1.77–1.68 (dd, J = 12.8, 13.7 Hz, 2 H), 1.52–1.43 (t, J = 12.6 Hz, 2 H), 1.13–0.99 (m, 3 H), 1.01 (s, 3 H); MS m/z (M^+) calcd for $C_{16}H_{22}O_3$ 262.1569, obsd 262.1535.

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25, H, 8.45. Found: C, 73.04; H, 8.46.

Attempted Prins Cyclization of 46. A solution of **46** (6 mg, 0.023 mmol) in dry methylene chloride (1 mL) and dimethylaluminum chloride (0.06 mmol, 1 M hexane) was subjected to 98 000 psi at room temperature for 9 h. The mixture was diluted with methylene chloride and washed with 1 N sodium hydroxide solution. The extract was dried, and the product was purified by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) to give 3.6 mg (57%) of **47** as a colorless oil. By TLC, it appeared that the other methyl isomer was present although in lesser amounts (10–20%); IR (neat, cm^{-1}) 3040, 3030, 2850, 1720, 1443, 1380, 1260, 1200, 1108, 640; ^1H NMR (300 MHz, C_6D_6) δ 5.63–5.60 (m, 1 H), 5.38–5.36 (m, 1 H), 4.11–3.85 (m, 1 H), 1.92–0.84 (series of m, 16 H), 1.02–0.96 (s, 3 H); MS m/z (M^+) calcd for $C_{16}H_{22}O_2$ 246.1620, obsd 246.1594.

Hydroboration–Oxidation of 40. A solution of **40** (38 mg, 0.18 mmol) in dry benzene was transferred to a dry flask, and the solvent was removed under reduced pressure. At this point, 1 mL of tetrahydrofuran and 9-BBN (65 mg, 0.53 mmol) were added. The mixture was heated to reflux for 4.5 h, cooled to 0 °C, and treated with 0.5 mL each of ethanol, 6 N sodium hydroxide, and 30% hydrogen peroxide. After overnight stirring at room temperature, this mixture was extracted with methylene chloride, and the combined extracts were passed through a magnesium sulfate/Florisil column. Purification by MPLC (silica gel, elution with 70% ethyl acetate in petroleum ether) gave 40 mg (94%) of diol as a colorless oil: IR (neat, cm^{-1}) 3370, 2940, 2870, 1560, 1270, 1075, 995, 745; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (m, 1 H), 3.98 and 3.73 (2 t, J = 8.2, 5.5 Hz, 1 H), 2.26–1.20 (series of m, 19 H), 0.90 and 0.85 (s, 3 H); MS m/z (M^+) calcd for $C_{15}H_{24}O_2$ 236.1777, obsd 236.1774.

A solution of dimethyl sulfoxide (53 mg, 0.68 mmol) in 3 mL of dry methylene chloride under argon at −78 °C was treated over 10 min with trifluoroacetic anhydride (107 mg, 0.51 mmol). After 10 min, a solution of the above diol (40 mg, 0.17 mmol) in 3 mL of methylene chloride was added dropwise over 10 min. The reaction mixture was warmed to room temperature over 30 min and stirred at this temperature for 0.5 h, after which time dry triethylamine (0.2 mL) was added. The mixture was diluted with methylene chloride, washed with water, and dried. Purification by MPLC (silica gel, elution with 25% ethyl acetate in petroleum ether) gave 28 mg (72%) of **48** as a crystalline solid, mp 79–81 °C; IR (KBr, cm^{-1}) 2945, 2910, 2880, 2855, 1745, 1730, 1475, 1405, 1180, 1095, 1085, 1040; ^1H NMR (300 MHz, C_6D_6) δ 2.41 (t, J = 7.1 Hz, 1 H), 2.20–2.02 (m, 2 H), 1.97 (dd, J = 2.8, 10.0 Hz, 1 H), 1.92–0.64 (series of m, 14 H), 0.618 (s, 3 H); MS m/z (M^+) calcd for $C_{15}H_{20}O_2$ 232.1463, obsd 232.1497.

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.29; H, 8.68.

Selective Ketalization of 48. Diketone **48** (54 mg, 0.23 mmol) was dissolved in 0.3 mL of dry methylene chloride. 1,2-Bis-[(trimethylsilyl)oxy]ethane (49.4 mg, 0.240 mmol) was added, and the solution was cooled under argon to −78 °C. Trimethylsilyl trifluoromethanesulfonate (0.007 mmol, 0.02 M in methylene chloride) was added, and the mixture was stirred for 6 h, after which time dry pyridine (8 mg, 0.01 mmol) was introduced. The mixture was diluted with methylene chloride and was washed with brine. The organic layer was dried and evaporated. MPLC purification (silica gel, elution with 10% ethyl acetate in petroleum ether) gave 54 mg (84%) of **49** as a crystalline solid: mp 71–72 °C; IR (neat, cm^{-1}) 2940, 2860, 1730, 1450, 1428, 1308, 1105, 1030; ^1H NMR (300 MHz, C_6D_6) δ 3.48 (s, 4 H), 3.46 (m, 1 H), 2.16–0.70 (series of m, 16 H), 0.71 (s, 3 H); MS m/z (M^+) calcd for $C_{17}H_{24}O_3$ 276.1361, obsd 276.1364.

α-Hydroxylation of 49. To a flask containing 2 mL of dry tetrahydrofuran was added *n*-butyllithium (0.165 mmol, 1.5 M in hexane) followed by diisopropylamine (0.17 mmol). The mixture was warmed to −20 °C and allowed to stir for 15 min before being cooled to −78 °C, at which point **49** (18 mg, 0.064 mmol) was added in tetrahydrofuran (1.5 mL) during 5 min. After 0.5 h of stirring, the clear enolate solution was added to a stirred suspension of MoOPh (120 mg, 0.271 mmol) in the same solvent (2 mL) at −44 °C over a 3-min period. Shortly thereafter, the suspension dissipated and the solution became yellow-green in color. The mixture was warmed over 15 min to −30 °C, quenched with a saturated solution of sodium sulfite, warmed to room temperature, and stirred there for 0.5 h. The product was extracted with ether, and the combined organic phases were washed with 1.5 M hydrochloric acid solution, sodium bicarbonate solution, and brine before being dried. Concentration and purification via silica gel chromatography (elution with 50% ethyl acetate in petroleum ether) gave 14 mg (74%) of **50** as a crystalline solid: mp 85–90 °C; IR (neat, cm^{-1}) 3440, 2950, 1730, 1460, 1445, 1425; ^1H NMR (300 MHz, C_6D_6) δ 4.05–3.91 (m, 2 H), 3.50–3.37 (m, 4 H), 2.73–2.69 (t, J = 7 Hz, 1 H), 2.39–2.35 (t, J = 6.5 Hz, 1 H), 2.16–1.12 (series of m, 13 H), 0.84–0.71 (2 s, 3 H); MS m/z (M^+)

calcd for $C_{17}H_{24}O_4$ 292.1674, obsd 292.1657.

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.91; H, 8.35.

Oxidative Cleavage of 50. To a dry solution of **50** (6 mg, 0.02 mmol) in benzene–methanol (2:1) at 5 °C was added lead tetraacetate (9.5 mg, 0.021 mmol) in one portion. After 3.5 min, the reaction mixture was quenched with sodium bicarbonate solution. The resulting suspension was filtered through Celite, and the filtrate was extracted with benzene. The combined extracts were dried and concentrated to give 6.2 mg (94%) of **51** as a colorless oil: IR (neat, cm^{-1}) 2930, 2860, 1720, 1380, 1330, 1205, 1110; ^1H NMR (300 MHz, C_6D_6) δ 9.3 (m, 1 H), 3.51 (s, 4 H), 3.24 (s, 3 H), 3.12–3.04 (m, 1 H), 2.95–2.87 (m, 1 H), 2.46–2.41 (t, $J \approx 7.6$ Hz, 1 H), 2.31–1.08 (series of m, 12 H), 1.07 (s, 3 H); MS m/z (M^+) calcd for $C_{18}H_{26}O_5$ 322.1780, obsd 322.1751.

Hydrolysis of 51. Ketal **51** (6 mg, 0.02 mmol) was dissolved in acetone (2 mL), and 0.3 mL of 5% hydrochloric acid solution was added. After 12 h, sodium bicarbonate solution was introduced, and all volatile materials were removed in vacuo. The residue was extracted with ether, and the extracts were dried. Chromatography over silica gel (elution with 20% ethyl acetate in petroleum ether) gave 5.5 mg (100%) of **52** as a colorless oil: IR (neat, cm^{-1}) 2960, 2850, 2720, 1730–1710, 1460, 1430, 1400, 1380, 1220; ^1H NMR (300 MHz, C_6D_6) δ 9.3 (m, 1 H), 3.21 (s, 3 H), 2.32 (d, J = 14.5 Hz, 1 H), 2.28 (d, J = 14.5 Hz, 1 H), 2.09–0.74 (series of m, 13 H), 0.92 (s, 3 H); MS m/z (M^+) calcd for $C_{16}H_{22}O_4$ 278.1518, obsd 278.1515.

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.55; H, 8.03.

Chemoselective Reduction of 51. To a cold (0 °C) solution of **51** (6 mg, 0.02 mmol) in 1 mL of dry methanol was added excess sodium borohydride (2.4 mg, 0.064 mmol). After 10 min, brine was added, the solvent was removed in vacuo, and the residue was extracted with methylene chloride. The extract was dried and concentrated to yield 6 mg (97%) of **55a** as a colorless oil: IR (neat, cm^{-1}) 3440, 2920, 2865, 1720, 1460, 1440, 1428, 1325, 1210, 1130, 1105, 1040; ^1H NMR (300 MHz, C_6D_6) δ 3.52 (s, 4 H), 3.30 (s, 3 H), 3.45–3.22 (m, 2 H), 2.49–2.44 (t, J = 7.6 Hz, 1 H), 2.42–1.08 (series of m, 15 H), 1.14 (s, 3 H); MS m/z (M^+) calcd for $C_{18}H_{28}O_5$ 324.2015, obsd 324.1953.

Mesylation of 55a. Hydroxy ester **55a** (145 mg, 0.448 mmol) was treated with dry triethylamine (181 mg, 1.82 mmol) and methanesulfonyl chloride (117 mg, 0.91 mmol) at −29 °C in dry ether (8 mL). After 2 h at 0 °C, the reaction mixture was diluted with ether, washed with water, and dried. Concentration gave 190 mg (100%) of **55b** as a colorless oil: IR (neat, cm^{-1}) 2940, 2870, 1718, 1460, 1448, 1430, 1350, 1330, 1210, 1170, 1125, 948; ^1H NMR (300 MHz, C_6D_6) δ 3.90–3.22 (m, 4 H), 3.50 (s, 2 H), 3.26 (s, 3 H), 2.15–2.14 (s, 3 H), 1.05 (s, 3 H), 2.43–0.84 (series of m, 15 H); MS m/z (M^+) calcd for $C_{19}H_{30}O_7S$ 402.1713, obsd 402.1711.

Bromo Ester 56. The above mesylate (190 mg, 0.47 mmol, crude) was refluxed in 8 mL of dry acetone containing lithium bromide (170 mg, 2.1 mmol) for 5 h. The mixture was concentrated, and the residue was extracted with ether and dried. Purification by silica gel chromatography (elution with 5–20% ethyl acetate in petroleum ether) yielded 130 mg (85%) of **56** as a crystalline solid, mp 79–80 °C. The product typically contained 5–8% of the corresponding chloride, as assayed by capillary gas chromatography: IR (neat, cm^{-1}) 2940, 2850, 1720, 1400, 1395, 1380; ^1H NMR (300 MHz, C_6D_6) δ 3.19 (s, 3 H), 3.09–3.02 (m, 1 H), 2.90–2.84 (m, 1 H), 2.36–2.34 (m, 1 H), 2.18–0.74 (series of m, 14 H), 1.00 (s, 3 H); MS m/z (M^+) calcd for $C_{16}H_{23}BrO_3$ 342.0830, obsd 342.0817.

Silyl Enol Ether 58a. A dry solution of **55a** (9.0 mg, 0.027 mmol) and triphenylphosphine (42 mg, 0.16 mmol) in carbon tetrachloride (1 mL) was refluxed for 14 h. The mixture was concentrated and chromatographically purified over silica gel (elution with 10% ethyl acetate in petroleum ether) to give 9.5 mg (100%) of the chloro ketal as a colorless oil: IR (neat, cm^{-1}) 2940, 2860, 1720, 1460, 1440, 1430, 1380, 1330, 1205, 1110; ^1H NMR (300 MHz, C_6D_6) δ 3.50 (s, 4 H), 3.23 (s, 3 H), 3.26–3.17 (m, 1 H), 3.11–3.03 (m, 1 H), 2.97–2.41 (t, J = 7.9 Hz, 1 H), 2.34–2.14 (m, 3 H), 1.94–0.85 (series of m, 11 H), 1.07 (s, 3 H); MS m/z (M^+) calcd for $C_{18}H_{27}ClO_4$ 342.1598, obsd 342.1559.

The chloro ketal (9.0 mg, 0.026 mmol) was dissolved in 1.5 mL of acetone. A drop of 10% hydrochloric acid solution was introduced, and the mixture was stirred for 10 h at room temperature. Sodium bicarbonate solution was added, and the mixture was concentrated. The residue was extracted with ether, the extract was dried and evaporated, and the residue was chromatographed over silica gel (elution with 10–20% ethyl acetate in petroleum ether) to yield 8.0 mg (98%) of a crystalline solid: mp 74–76 °C; IR (neat, cm^{-1}) 2940, 2860, 1730-1715, 1400, 1380, 1310, 1200, 1130, 1120; ^1H NMR (300 MHz, C_6D_6) δ 3.21 (s, 3 H), 3.28–3.16 (m, 1 H), 3.08–3.00 (m, 1 H), 2.42–2.27 (dd, J = 19.5, 6.4 Hz, 2 H), 1.60 (s, 3 H), 2.17–0.72 (series of m, 13 H); MS m/z (M^+) calcd for $C_{16}H_{23}ClO_3$ 298.1336, obsd 298.1316.

To a −78 °C solution of *n*-butyllithium (0.7 mmol, 1.5 M hexane) was added bis(dimethylphenylsilyl)amine (200 mg, 0.7 mmol). The clear reaction mixture was warmed to −10 °C and stirred for 15 min before being cooled to −78 °C. Meanwhile, a dry benzene solution containing the above chloro ketone (100 mg, 0.336 mmol) was transferred to a dry flask, and the benzene was removed in vacuo. Dry tetrahydrofuran (6 mL) was added, and the solution was introduced dropwise to the base over a 22-min period. After 0.5 h at −78 °C, neat *tert*-butyldimethylsilyl trifluoromethanesulfonate (185 mg, 0.70 mmol) was added in one portion followed 5 min later by 0.5 mL of triethylamine. The mixture was diluted with ether and washed with water. The organic layer was dried, and the product was purified by preparative TLC on silica gel (elution with 5% ethyl acetate in petroleum ether) to give 116 mg (83%) of **58a** as a colorless oil: IR (neat, cm^{-1}) 3060, 2955, 2860, 1725, 1640, 1460, 1440, 1390, 1380, 1330, 1250, 1220, 840, 780; ^1H NMR (300 MHz, C_6D_6) δ 4.59 (m, 1 H), 3.25 (s, 3 H), 3.24 (m, 1 H), 3.10 (m, 1 H), 2.81 (dt, J = 10.2, 2.0 Hz, 1 H), 2.58 (d, J = 17 Hz, 1 H), 1.91–1.19 (series of m, 11 H), 1.07 (s, 3 H), 0.98 (s, 9 H), 0.16 (s, 6 H); MS m/z (M^+) calcd for $C_{22}H_{37}ClO_3Si$ 412.2201, obsd 412.2154.

α-Hydroxylation of 58a. To a solution of **58a** (69 mg, 0.17 mmol) and *N*-methylmorpholine *N*-oxide (60 mg, 0.51 mmol) in 3.5 mL of acetone and 0.5 mL water was added osmium tetraoxide (0.0034 mmol, 0.026 M in *tert*-butyl alcohol). After 5 h of stirring, 300 mg of sodium hydrogen sulfite and 300 mg of magnesium silicate were introduced. After an additional 0.5 h, the suspension was filtered through Celite, the filtrate was adjusted to pH 7 with dilute hydrochloric acid, and the mixture was concentrated in vacuo. The residue was further acidified to pH 3 and extracted with ethyl acetate. The combined extracts were dried and evaporated, and the residue was chromatographed over silica gel (elution with 50% ethyl acetate in petroleum ether) to give 45 mg (84%) of **59a** as a colorless oil: IR (neat, cm^{-1}) 3430, 3080, 3030, 2940, 2860, 1740, 1720, 1480, 1460, 1450, 1430, 1380, 1315, 1210, 1120; ^1H NMR (300 MHz, C_6D_6) δ 3.55 (d, J = 5.5 Hz, 1 H), 3.18 (s, 3 H), 3.12–3.06 (m, 1 H), 2.97–2.91 (m, 1 H), 2.42 (d, J = 26 Hz, 1 H), 2.40 (d, J = 26 Hz, 1 H), 2.08 (t, J = 7.5 Hz, 1 H), 1.86 (q, J = 5 Hz, 1 H), 1.76–0.89 (series of m, 10 H), 0.97 (s, 3 H); MS m/z (M^+) calcd for $C_{16}H_{23}ClO_4$ 314.1285, obsd 314.1314.

Oxidative Cleavage of 59a. A solution of **59a** (7.5 mg, 0.026 mmol) in 1 mL of dry benzene and 0.5 mL of dry methanol was cooled to 0 °C, and lead tetraacetate (12 mg, 0.026 mmol) was added in one portion. After 5 min, the reaction mixture was quenched with sodium bicarbonate solution and poured over Celite. The organic layer was washed with brine and dried. Concentration gave 8.5 mg (100%) of **60a** as a pure colorless oil: IR (neat, cm^{-1}) 2965, 2880, 2740, 1720, 1465, 1450, 1435, 1360, 1270, 1260, 1225, 1200, 1180, 1115, 1050, 800, 750, 730; ^1H NMR (300 MHz, C_6D_6) δ 9.80 (m, 1 H), 3.45–2.99 (m, 2 H), 3.28 (s, 3 H), 3.20 (s, 3 H), 2.91 (d, J = 16.5 Hz, 1 H), 2.67 (d, J = 16.5 Hz, 1 H), 2.41–0.82 (series of m, 11 H), 1.11 (t, J = 7.0 Hz, 1 H), 0.94 (s, 3 H); MS m/z (M^+ − H) calcd for $C_{17}H_{24}ClO_5$ 343.1282, obsd 343.1255.

Silyl Enol Ether 58b. Bromo ketone **56** (133 mg, 0.388 mmol) in 4 mL of tetrahydrofuran was added to a solution of lithium tetramethyldiphenyldisilazide in 8 mL of the same solvent at −78 °C over 0.5 h. After 30 min, the reaction mixture was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (205 mg, 0.776 mmol). Following the predescribed workup, there was obtained 156 mg (88%) of **58b** as a colorless oil: IR (neat, cm^{-1}) 3060, 2950, 2930, 2900, 2860, 1725, 1640, 1460, 1388, 1380, 1330, 1250, 1225, 840, 785; ^1H NMR (300 MHz, C_6D_6) δ 4.62 (m, 1 H), 3.23 (s, 3 H), 3.20 (m, 1 H), 2.89 (m, 2 H), 2.58 (d, J = 17 Hz, 1

H), 1.91–1.19 (series of m, 11 H), 1.08 (s, 3 H), 0.98 (s, 9 H), 0.173 (s, 3 H), 0.167 (s, 3 H); MS m/z (M^+) calcd for $C_{22}H_{37}BrO_3Si$ 456.1695, obsd 456.1680.

α-Hydroxylation of 58b. Treatment of **58b** (32 mg, 0.070 mmol) with osmium tetraoxide as described above yielded 16 mg (66%) of **59b** as a colorless oil: IR (neat, cm^{-1}) 3460, 2940, 2860, 1740, 1460, 1445, 1430, 1380, 1310, 1230, 1110; ^1H NMR (300 MHz, C_6D_6) δ 3.57 (d, J = 5.3 Hz, 1 H), 3.29–2.72 (series of m, 4 H), 3.17 (s, 3 H), 2.46 (d, J = 18.5 Hz, 1 H), 2.37 (d, J = 18.5 Hz, 1 H), 2.09 (t, J = 7.5 Hz, 1 H), 1.91–0.94 (series of m, 12 H); MS m/z (M^+) calcd for $C_{16}H_{23}BrO_4$ 358.0779, obsd 358.0763.

Oxidative Cleavage of 59b. A 0.046-mmol sample of **59b** was subjected to a similar ratio of lead tetraacetate as described above. The identical workup provided 16.8 mg (94%) of **60b** as a crystalline solid: mp 82–84 °C; IR (neat, cm^{-1}) 3010, 2980, 2940, 2875, 1720, 1710, 1435, 1380, 1235, 1210, 1200, 1110; ^1H NMR (300 MHz, C_6D_6) δ 9.79 (m, 1 H), 3.29 (s, 3 H), 3.20 (s, 3 H), 3.22–2.86 (m, 2 H), 2.88 (d, J = 17 Hz, 1 H), 2.64 (d, J = 17 Hz, 1 H), 2.37 (t, J = 9 Hz, 1 H), 2.10–0.89 (series of m, 10 H), 0.94 (s, 3 H); MS m/z ($M^+ - CO_2CH_3$) calcd for $C_{15}H_{22}BrO_3$ 329.0757, obsd 329.0750.

Acetalization of 60b. Diester **60b** (16.8 mg, 0.043 mmol) was treated with 2 mL of trimethyl orthoformate and 20 mg of Amberlyst-15 for 2 h. The mixture was filtered, and all volatile materials were removed in vacuo to provide 18 mg (91%) of **61** as a colorless oil: IR (neat, cm^{-1}) 2950, 2870, 2820, 1720, 1460, 1445, 1430, 1380, 1360, 1225, 1190, 1120, 1065, 855, 900, 795; ^1H NMR (300 MHz, C_6D_6) δ 4.57 (d, J = 7 Hz, 1 H), 3.39 (s, 3 H), 3.36–2.91 (m, 2 H), 3.28 (s, 3 H), 3.22 (s, 3 H), 3.16 (s, 3 H), 2.82 (d, J = 15 Hz, 1 H), 2.73 (d, J = 15 Hz, 1 H), 2.08 (dd, J = 5.0, 12.0 Hz, 1 H), 1.90–0.96 (series of m, 10 H), 1.04 (s, 3 H); MS m/z ($M^+ - CO_2CH_3$) calcd for $C_{16}H_{28}BrO$ 403.1119, obsd 403.1145.

Finkelstein Reaction on 60b. A solution of **60b** (46 mg, 0.12 mmol) in acetone (2 mL) containing 1 drop of pyridine was treated with sodium iodide (91 mg, 0.61 mmol) at the reflux temperature for 12 h. The reaction mixture was concentrated in vacuo, and the residue was washed thoroughly with ether. The combined ethereal phases were washed with brine and dried. Concentration gave 46 mg (87%) of **62** as a colorless oil, which was used without purification: IR (neat, cm^{-1}) 2980, 2940, 1720, 1710, 1460, 1445, 1435, 1220, 1200, 1175; ^1H NMR (300 MHz, C_6D_6) δ 9.81 (m, 1 H), 3.28 (s, 3 H), 3.25 (s, 3 H), 3.35–2.78 (m, 2 H), 2.90 (d, J = 17.0 Hz, 1 H), 2.67 (d, J = 17.0 Hz, 1 H), 2.38 (t, J = 9.5 Hz, 1 H), 2.14–1.14 (series of m, 10 H), 0.95 (s, 3 H); MS m/z ($M^+ - CO_2CH_3$) calcd for $C_{15}H_{22}IO_3$ 309.1702, obsd 309.1706.

Acetalization of 62. Diester **62** (46 mg, 0.13 mmol) was treated with 1 mL of trimethyl orthoformate and 60 mg of Amberlyst-15. After 2 h, filtration and concentration gave 56 mg of crude product, which was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to yield 48 mg (89%) of a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 4.59 (d, J = 7.5 Hz, 1 H), 3.39 (s, 3 H), 3.27 (s, 3 H), 3.23 (s, 3 H), 3.18 (s, 3 H), 3.16–2.64 (m, 2 H), 2.83 (d, J = 15.0 Hz, 1 H), 2.73 (d, J = 15.0 Hz, 1 H), 2.11 (dd, J = 5.5, 12.0 Hz, 1 H), 1.90–0.84 (series of m, 10 H), 1.03 (s, 3 H); MS m/z ($M^+ - CH_4O$) calcd for $C_{18}H_{27}IO_5$ 450.0903, obsd 450.0874.

Ketalization of 56. To a cold (−78 °C) solution of **56** (195 mg, 0.570 mmol) and bis(trimethylsilyloxy)ethane (197 mg, 0.684 mmol) in methylene chloride (2 mL) was added trimethylsilyl trifluoromethanesulfonate (27 mg, 0.028 mmol). After 4 h of stirring, dry pyridine was added. The mixture was diluted with methylene chloride, washed with water, and dried. Purification by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) yielded 195 mg (89%) of **65a** as a colorless oil: IR (neat, cm^{-1}) 2940, 2860, 1720, 1460, 1440, 1425, 1325; ^1H NMR (300 MHz, C_6D_6) δ 3.51 (s, 4 H), 3.23 (s, 3 H), 3.23–3.04 (m, 1 H), 2.95–2.87 (m, 1 H), 2.44 (t, J = 7.9 Hz, 1 H), 2.29 (d, J = 14.0 Hz, 1 H), 2.21–1.14 (series of m, 13 H), 1.07 (s, 3 H); MS m/z (M^+) calcd for $C_{18}H_{27}BrO_4$ 388.1072, obsd 388.1007.

Reduction of 65a. A cold (−78 °C) solution of **65a** (30 mg, 0.078 mmol) in methylene chloride (2 mL) was treated with Dibal-H (0.125 mmol, 1 M in hexanes) for 20 min. Saturated potassium sodium tartrate solution (2 mL) was added, and after 1 h of stirring at room temperature, the product was extracted with methylene chloride and dried. Concentration gave 24 mg (86%) of **65b** as a colorless oil, which was carried into the next reaction without further purification: IR (neat, cm^{-1}) 3440, 2940, 2860, 1335, 1105, 1035; ^1H NMR (300 MHz, C_6D_6) δ 3.51 (s, 4 H), 3.09–2.86 (series of m, 4 H), 2.99 (d, J = 3.4 Hz, 1 H), 2.12–1.13 (series of m, 15 H), 0.76 (s, 3 H); MS m/z ($M^+ - C_2H_4O$) calcd for $C_{15}H_{23}BrO_2$ 314.0881, obsd 314.0864.

Silylation of 65b. To a cold (−78 °C) solution of **65b** (72 mg, 0.20 mmol) in methylene chloride (4 mL) was added dry triethylamine (101 mg, 1 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (211 mg, 0.8 mol). After 20 min of stirring, brine was added, and the mixture was extracted with methylene chloride. The combined extracts were dried and concentrated to give a cloudy residue. Purification by chromatography on neutral alumina (elution with ether) yielded 88 mg (95%) of **65c** as a colorless oil: IR (neat, cm^{-1}) 2945, 2920, 2840, 1415, 1410, 1335, 1250, 1095, 850, 835, 775; ^1H NMR (300 MHz, C_6D_6) δ 3.52 (s, 4 H), 3.30 (d, J = 9.6 Hz, 1 H), 3.21 (d, J = 9.6 Hz, 1 H), 3.17–3.09 (m, 1 H), 2.99–2.91 (m, 1 H), 2.20–1.11 (series of m, 15 H), 0.96 (s, 9 H), 0.87 (s, 3 H), 0.03 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{19}H_{32}BrO_3Si$ 415.1304, obsd 415.1372.

Deketalization of 65c. Ketal **65c** (101 mg, 0.217 mmol) was treated with *p*-toluenesulfonic acid (3 mg, 0.017 mmol) in acetone (10 mL) at room temperature for 24 h. Sodium bicarbonate solution was added, and the volatile materials were removed in vacuo. The residue was partitioned between methylene chloride and water, and the organic phase was dried and evaporated. Purification of the residue by silica gel chromatography (elution with 10% ethyl acetate in petroleum ether) provided 82 mg (90%) of **66** as a colorless oil: IR (neat, cm^{-1}) 2950, 2910, 2840, 1735, 1465, 1460, 1255, 1090, 835; ^1H NMR (300 MHz, C_6D_6) δ 3.29–3.02 (series of m, 4 H), 2.25 (d, J = 15.9 Hz, 1 H), 2.19–2.10 (m, 2 H), 2.08 (d, J = 15.5 Hz, 1 H), 1.92–0.88 (series of m, 11 H), 0.94 (s, 9 H), 0.80 (s, 3 H), 0.01 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{17}H_{28}BrO_2Si$ 371.1041, obsd 371.1105.

Silyl Enol Ether 67. Lithium bis(dimethylphenylsilyl)amide (0.145 mmol) was prepared as above in 1 mL of dry tetrahydrofuran under an argon atmosphere. The mixture was cooled to −78 °C, and a solution of ketone **66** (25 mg, 0.058 mmol) in 1 mL of tetrahydrofuran was added over a period of 15 min. After 30 min of stirring, *tert*-butyldimethylsilyl trifluoromethanesulfonate (46 mg, 0.18 mmol was added. After 5 min, the progress of reaction was arrested by adding triethylamine, diluting with pentane, and washing with water. The organic layer was dried and concentrated. Purification of the products by silica gel chromatography (elution with 2% ethyl acetate in petroleum ether) yielded 30 mg (95%) of two regioisomers (3.2:1, cap GC), the major of which was the desired **67**: IR (neat, cm^{-1}) 3060, 3040, 2950, 2920, 2850, 1640, 1465, 1455, 1250, 1090, 835, 775; ^1H NMR (300 MHz, C_6D_6) δ 4.71 and 4.62 (1:3.2) (m, 1 H), 3.31–1.18 (series of m, 17 H), 0.98 (s, 9 H), 0.96 (s, 9 H), 0.84 (s, 3 H), 0.17 (s, 6 H), 0.02 (s, 6 H); MS m/z (M^+) calcd for $C_{27}H_{51}BrO_2Si_2$ 542.2568, obsd 542.2608.

Osmylation of 67. A solution of **67** (30 mg, 0.058 mmol) in acetone (1.2 mL) and water (0.16 mL) was treated with osmium tetraoxide (0.0029 mmol, 0.026 M in *tert*-butyl alcohol) and 4-methylmorpholine *N*-oxide (20 mg, 0.17 mmol) at room temperature for 2 h. Magnesium silicate (60 mg) and sodium hydrogen sulfite (15 mg) were added, and the mixture was allowed to stir for 1 h before being filtered through Celite. One drop of 10% hydrochloric acid was added to the filtrate, and the latter was concentrated. The residue was dissolved in ethyl acetate and washed successively with 10% hydrochloric acid, 5% sodium bicarbonate solution, and brine. After being dried, the product was purified by silica gel chromatography (elution with 50% ethyl acetate in petroleum ether) to provide 18 mg (71%) of **68** as a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 3.55 (dd, J = 1.0, 6.0 Hz, 1 H), 3.11 (d, J = 19.3 Hz, 1 H), 3.01 (d, J = 19.4 Hz, 1 H), 3.04–2.95 (m, 1 H), 2.83–2.75 (m, 1 H), 2.32 (dd, J = 1.0, 17.9 Hz, 1 H), 2.10 (d, J = 17.8 Hz, 1 H), 1.91–0.99 (series of m, 12 H), 0.92 (s, 9 H), 0.74 (s, 3 H), −0.016 (s, 3 H), −0.02 (s, 3 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{17}H_{28}BrO_3Si$ 387.0991, obsd 387.0923.

Oxidative Cleavage of 68. To a solution of **68** (16 mg, 0.037 mmol) in benzene (1 mL) and methanol (0.5 mL) at 0 °C was introduced lead tetraacetate (20 mg, 0.045 mmol). After 3 min of stirring, 5% sodium bicarbonate solution was added. The mixture was filtered, and the filtrate was extracted with ethyl acetate. The combined extracts were dried and concentrated to give 15 mg (86%) of **69** as a colorless oil, which was used without further purification: IR (neat, cm^{-1}) 2950, 2920, 2850, 2715, 1730,

1710, 1405, 1250, 1195, 1085, 835, 875; ^{1}H NMR (300 MHz, C_6D_6) δ 9.81 (d, J = 2.0 Hz, 1 H), 3.28 (s, 3 H), 3.17 (d, J = 9.8 Hz, 1 H), 3.1 (d, J = 9.7 Hz, 1 H), 3.14–3.00 (m, 1 H), 2.95–2.87 (m, 1 H), 2.54 (d, J = 16.3 Hz, 1 H), 2.44 (d, J = 16.3 Hz, 1 H), 2.30–1.29 (series of m, 11 H), 0.93 (s, 9 H), 0.73 (s, 3 H), 0.00 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{18}H_{30}BrO_4Si$ 417.1097, obsd 417.1095.

Finkelstein Reaction and Acetalization of 69. Bromide **69** (11 mg, 0.023 mmol) was dissolved in 1 mL of acetone and treated with sodium iodide (35 mg, 0.23 mmol) at room temperature for 12 h. The mixture was diluted with pentane and filtered. The filtrate was concentrated, and the residual oil was redissolved in trimethyl orthoformate (1 mL). Amberlyst-15 ion exchange resin (20 mg) was introduced, and the mixture was stirred for 4 h. Filtration and concentration gave a cloudy oil, which was purified by silica gel chromatography (elution with 5% ethyl acetate in petroleum ether) to provide 10 mg (77%, overall yield) of **71** as a colorless oil: IR (neat, cm^{-1}) 2950, 2920, 2840, 1730, 1405, 1250, 1090, 830, 770; ^{1}H NMR (300 MHz, C_6D_6) δ 4.58 (d, J = 7.3 Hz, 1 H), 3.38 (s, 3 H), 3.31 (d, J = 9.6 Hz, 1 H), 3.22 (s, 3 H), 3.19 (d, J = 9.7 Hz, 1 H), 3.18 (s, 3 H), 2.94–2.89 (m, 1 H), 2.73–2.64 (m, 1 H), 2.50 (s, 2 H), 2.40 (t, J = 9.2 Hz, 1 H), 2.07 (dd, J = 6.1, 10.5 Hz, 1 H), 1.97–1.21 (series of m, 8 H), 0.97 (s, 9 H), 0.86 (s, 3 H), 0.04 (s, 6 H); MS m/z ($M^+ - C_4H_9$) calcd for $C_{20}H_{35}IO_5Si$ 511.1376, obsd 511.1346.

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Supplementary Material Available: Experimental procedures for the preparation of **15**, **17–20**, **25**, **26**, **28**, **29**, and the dimer of **35b**, as well as details of the X-ray analysis of **56**. Labeling scheme and tables of bond distances, bond angles, positional parameters, anisotropic thermal parameters, calculated positional parameters, and torsion angles for **56** (16 pages). Ordering information is given on any current masthead page.

Formal Synthesis of (–)-Calcimycin (A-23187) via the 3-Methyl-γ-butyrolactone Approach

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A synthesis of (+)-carboxylic acid **2a**, which has been previously converted into the ionophore (–)-calcimycin (A-23187) and analogues thereof, is described. The synthesis involves the use of (*S*)-3-methyl-γ-butyrolactone (**4**) and both enantiomers of allylic alcohol **3a** as the chiral entities.

The antibiotic calcimycin (A-23187, **1a**)[1] is representative of a structurally similar group of divalent ionophores that includes cezomycin (3-demethylaminocalcimycin, **1b**),[2] AC-7230 (3-demethylamino-3-hydroxycalcimycin, **1c**),[3] and X-14885A (3-demethylamino-15-demethyl-3-hydroxycalcimycin, **1d**).[4] The ionophore calcimycin forms a 2:1 monohydrated complex with calcium ion (X-ray)[5,6] that is believed to account for its ability to transport calcium ions across cell membranes[7] and unilaminar vesicles,[8] and through aqueous–organic phases.[9] The biological importance of calcimycin and its unique array of chelating heterocyclic rings and spiroketal nucleus have inspired successful routes to its synthesis.[10] Moreover, the degradation of calcimycin to the carboxylic acid **2a**[11] has expedited the synthesis of benzoxazole derivatives of the ionophore[11,12] as well as serving as an advanced intermediate in the synthesis of calcimycin itself.[10d,f]

We chose to examine the applicability of our 3-methyl-γ-butyrolactone strategy[13] for the synthesis of polypropionates to the carboxylic acid **2a**. The lactone *ent*-**7**[14] had been prepared previously[15] by this method. Accordingly, lactone **7** was available by linear iteration (Scheme I) of (*S*)-3-methyl-γ-butyrolactone (**4**) with

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