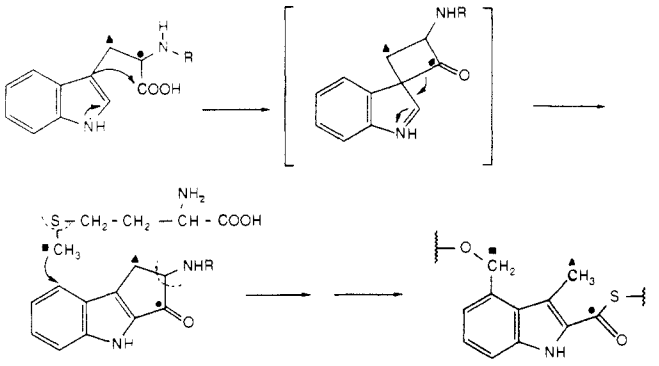


Figure 3. Formation of the indolic acid moiety of **1** from tryptophan.

and a C_1 fragment followed by assembly of the pyridine ring from these pieces.

The assembly of the indolic acid moiety from tryptophan represents a novel rearrangement of this amino acid, for which there seems to be no obvious biochemical or, for that matter, chemical precedent. The reaction presumably proceeds via a tricyclic intermediate (Figure 3), the formation of which can be easily rationalized (intramolecular acylation at indole C3 and rearrangement of the intermediate spiro indolenine by a 1,2-shift). The mechanism of ring opening of this tricyclic intermediate and of the extrusion of C2′ and the amino nitrogen is less obvious; future work will address this intriguing question. Methylation of the indole moiety of tryptophan is evidently not an early reaction step since labeled 4-methyltryptophan was not incorporated into **1**; the methyl group must therefore be introduced at some later stage in the biosynthesis. Finally, another interesting question is the mode of attachment of the tryptophan moiety to the rest of the molecule. All the other components of **1** can be arranged logically in a single polypeptide chain. However, the indolic acid moiety is not connected to this polypeptide by traditional amide bonds. Conceivably, the precursor tryptophan may be initially connected to this precursor polypeptide as an amide, and this bond is subsequently cleaved during the modification of the tryptophan to the indolic acid moiety. Again, this issue will be examined in future experiments.

Acknowledgment. We are indebted to Dr. J. Lunel of Rhône-Poulenc for providing samples of nosiheptide and to Dr. Edith W. Miles, National Institutes of Health, for the generous supply of tryptophan synthase. This work was supported by Merck Sharp and Dohme (salary support for D.R.H.), the National Institutes of Health (Research Grant AI20264) and the NIH (RR02231)-USDOE/OHER Stable Isotope Program at Los Alamos.

Registry No. 1, 56377-79-8; L-Cys, 52-90-4; L-Glu, 56-86-0; L-Thr, 72-19-5; L-serine, 56-45-1; L-tryptophan, 73-22-3.

A Convergent Synthesis of Triquinane Sesterterpenes. Enantioselective Synthesis of (−)-Retigeranic Acid A

Jonathan Wright, Gary J. Drtina, Richard A. Roberts,[1] and Leo A. Paquette*

Contribution from the Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210. *Received January 22, 1988*

Abstract: The total synthesis of enantiomerically pure (−)-retigeranic acid A has been achieved in a convergent manner from (*R*)-(+)-pulegone and (*S*)-(−)-limonene. In the pivotal coupling step, the Grignard reagent derived from optically pure bromide **46** was found to undergo exclusive 1,4-addition to α,β-unsaturated tricyclic ketone **10** (100% ee). The resulting two epimeric condensation products were separately carried forward through construction of the six-membered ring and introduction of the carboxyl functionality. Two diastereomers initially considered to be candidates for the structure of retigeranic acid B were thereby also prepared.

First isolated by Sheshadri in 1965 from the lichens of the *Lobaria retigera* group in the Western Himalayas,[2] retigeranic acid was initially believed to possess a tetracyclic skeleton.[3] Successful structural eludication was not completed, however, until 1972[4] when Shibata and co-workers established the correct skeletal arrangement and absolute configuration of this complex natural product by X-ray crystallography of the *p*-bromoanilide derivative.[5] At about this time, retigeranic acid was also isolated from *Lobaria isidiosa* and *Lobaria subretigera* in the Eastern Himalayas by Yoshimura.[6] Although the possible biological activity of **1** has not been determined, members of the genus *Lobaria* are considered to be important in perfumery and tanning and have been used as vegetable drugs for the cure of eczema and lung disorders.[2,6]

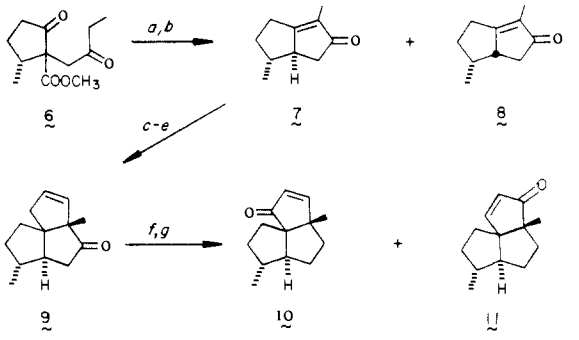
Retigeranic acid holds the distinction of being the first sesterterpene found to occur in lichens. This unusually structured pentacyclic carboxylic acid also bears no close correlation to any other existing sesterterpenes. Recently, Corey and his associates completed a total synthesis of racemic **1**[7] only to recognize that native retigeranic acid is composed of two isomeric substances of which **1** is the less prevalent constituent. This finding was subsequently confirmed in the Shibata laboratory. Evidently, recrystallization of the *p*-bromoanilides in preparation for the crystallographic analysis proceeded with fractionation in favor of the less soluble minor isomer. In light of these developments, the suggestion has been advanced to refer to **1** more accurately as retigeranic acid A.[8] In Corey's view, the major stereoisomer B was considered possibly to differ from **1** only at the methyl-bearing carbon in the E ring. This suggestion was later shown not to be tenable.[8]

Herein we describe the elaboration of carboxylic acids **1–3** in optically pure condition and show that retigeranic acid B is neither of the last two stereoisomers.[9] In planning this synthetic venture,

(1) Continental Oil Company Fellow, 1982.
(2) Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1965**, *34*, 9.
(3) Rao, P. S.; Sarma, K. G.; Seshadri, T. R. *Curr. Sci.* **1966**, *35*, 147.
(4) Kaneda, M.; Takahashi, R.; Iitaka, Y.; Shibata, S. *Tetrahedron Lett.* **1972**, 4609.
(5) Kaneda, M.; Iitaka, Y.; Shibata, S. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1974**, *B30*, 358.
(6) Yoshimura, I. *J. Hattori, Bot. Lab.* **1971**, *34*, 231.
(7) Corey, E. J.; Desai, M. C.; Engler, T. A. *J. Am. Chem. Soc.* **1985**, *107*, 4339.
(8) Shibata, S., private communication, September 24, 1986.
(9) Preliminary communication: Paquette, L. A.; Wright, J.; Drtina, G. J.; Roberts, R. A. *J. Org. Chem.* **1987**, *52*, 2960.

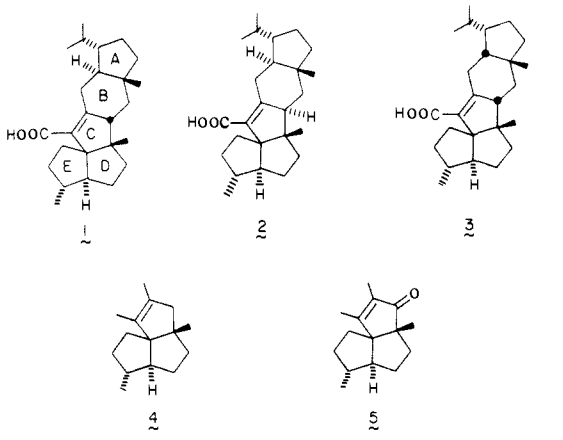
0002-7863/88/1510-5806$01.50/0 © 1988 American Chemical Society

Scheme I



[a] (a) NaH, toluene, reflux, 18 h; 10% HCl; (b) LiI·3H_2O, DMF; reflux, 18 h, 10% HCl; (c) $(C_4H_7O_2)CH_2CH_2MgBr$ ($C_4H_7O_2$ = 1,3-dioxan-2-yl), CuBr·Me_2S, THF, −78 °C (10 h) → 0 °C (2 h); NH_4Cl (H_2O); (d) HCl, aqueous THF, 20 °C, 72 h; (e) *p*-$CH_3C_6H_4OC(S)Cl$, py; 180 °C, 1 h; (f) K_2CO_3, $H_2NNH_2·H_2O$, diethylene glycol, 130–200 °C (7 h); 10% HCl; (g) Na_2CrO_4, HOAc, Ac_2O.

the close similarity of the southern sector of **1–3** to (−)-silphiperfol-6-ene (**4**),[10,11] and (−)-5-oxosilphiperfol-6-ene (**5**) was noted.[11,12] Attention was therefore first directed to generation of tricyclic enone **10** as a homogeneous, optically pure substance.



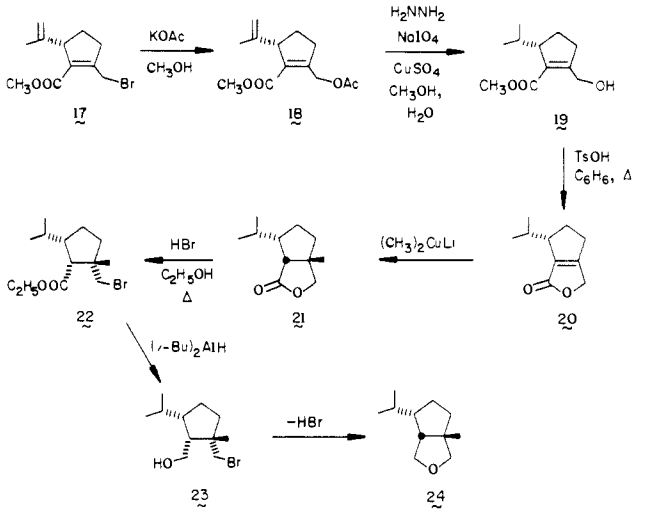
Synthesis of the Southern Triquinane Sector. β-Keto ester **6**, which is readily available from (*R*)-(+)-pulegone,[11a,13] has been transformed into **7** by a two-step cyclization–decarboxylation sequence (Scheme I). Because this transformation provides in 85% yield an approximately 66:34 mixture of the chromatographically separable isomers **7** and **8**, some concern arose about possible loss of optical activity during the formation of **7** via double-bond equilibration. The less than maximum $[\alpha]_D$ value for **4** realized in our synthesis of (−)-silphiperfol-3-ene[11a] provided additional motivation for direct *experimental* assessment of the situation. In this earlier investigation, **8** had been independently subjected to alkaline isomerization as a means of obtaining additional quantities of **7**.

Samples of **7** produced *directly* by decarboxylation exhibited $[\alpha]^{20}_D$ +90.55° and were shown to be homogeneous by capillary GC and optically pure by chiral lanthanide shift studies in the presence of Eu(tfc)$_3$. Following admixture of a *racemic* sample of **7** with 1 molar equiv of the shift reagent in $CDCl_3$, the vinyl methyl absorption was cleanly split ($\Delta\delta$ = 0.08) into two singlets in the δ 7.60 region of the spectrum. In contrast, the optically active sample exhibited only the more deshielded of these signals at δ 7.67, with no evidence for the second peak due to its enantiomer. Consequently, we consider samples of **7** exhibiting the rotation indicated above to possess 100% ee. Heating of this high quality material with aqueous potassium hydroxide in toluene under phase-transfer conditions for two sequential 48-h periods caused the $[\alpha]^{20}_D$ to drop to +88.16° and +85.59°, respectively. In contrast, no change in rotation was observed following the heating of **7** with LiI·3H_2O in DMF for 16 h.

Table I. Equilibration Studies Involving **8**

initial composition **7**:**8**	reaction conditions	final composition **7**:**8**	$[\alpha]^{20}_D$ of **7**
18:82	KOH, H_2O, $PhCH_3$, reflux, 16 h	59:41	+86.40
18:82	KOH, H_2O, $PhCH_3$, reflux, 48 h	82:18	+80.17
18:82	KOH, H_2O, $PhCH_3$, reflux, 72 h	77:23	

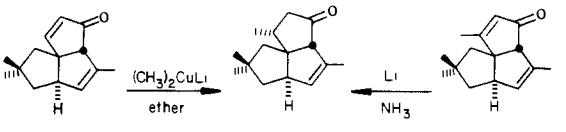
Scheme II



The studies to be described in the sequel were carried out exclusively with **11** of 100% ee. It was independently demonstrated to be imprudent to rely on the equilibration of **8** as a source of added amounts of **7** (see Table I). This isomer was therefore not utilized.

Although the allylic oxidation of desoxy **9** was best realized with sodium chromate in an acetic acid–acetic anhydride solvent system,[14] significant amounts (23–36%) of transposed enone (**11**) accompanied the formation of **10**. This pair of isomers could be chromatographed apart only inefficiently. However, low-temperature (−78 °C) diisobutylaluminum hydride (Dibal-H) reduction of the **10**/**11** mixture gave rise to two alcohols characterized by very different R_f values. Independent reoxidation of the purified major alcohol made substantive amounts of **10** conveniently available.

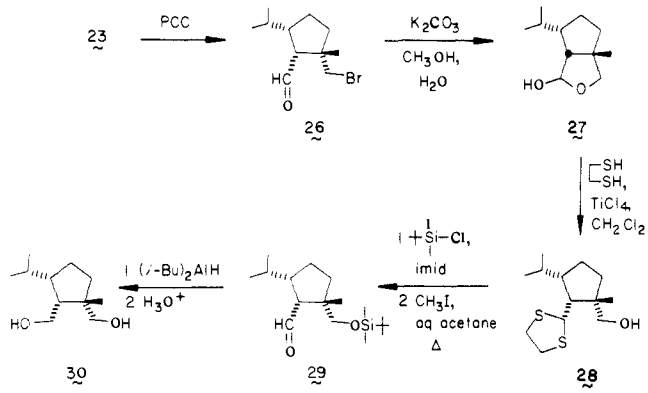
Neither of the two lowest energy conformations of **10**, as deduced by energy minimization first in Still's MODEL program and subsequently in MMP according to Allinger (Figure 1, supplementary material), provide convincing indication of any anticipated π-facial preference for nucleophilic capture by the conjugated ketone chromophore. The closest published precedent rests with **12** and **14**.[15] The first triquinane undergoes kinetically controlled



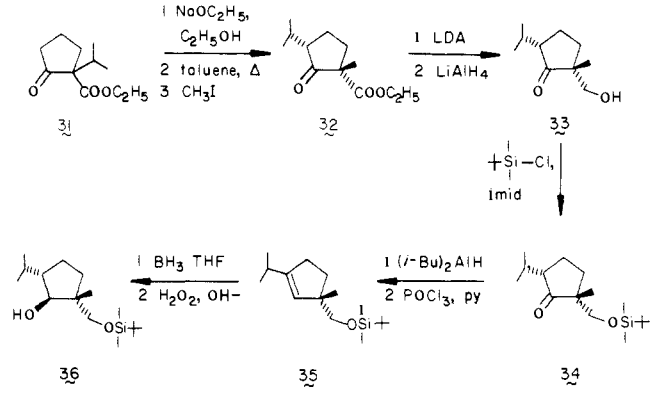
condensation with lithium dimethyl cuprate to provide **13** as the

(10) Isolation: Bohlmann, F.; Jakupovic, J. *Phytochemistry* **1980**, *19*, 259.
(11) Synthesis: (a) Paquette, L. A.; Roberts, R. A.; Drtina, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6690. (b) Wender, P. A.; Singh, S. K. *Tetrahedron Lett.* **1985**, *26*, 5987. (c) Curran, D. P.; Kuo, S. K. *J. Am. Chem. Soc.* **1986**, *108*, 1106.
(12) Isolation: Bohlmann, F.; Suding, H.; Cuatrecasas, J.; Robinson, H.; King, R. M. *Phytochemistry* **1980**, *19*, 2399.
(13) Marx, J. N.; Naman, L. R. *J. Org. Chem.* **1975**, *40*, 1602 and references cited therein.
(14) (a) Marshall, J. A.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 192. (b) Marshall, J. A.; Brady, S. F. *Ibid.* **1970**, *35*, 4068.
(15) Paquette, L. A.; Annis, G. D. *J. Am. Chem. Soc.* **1983**, *105*, 7358.

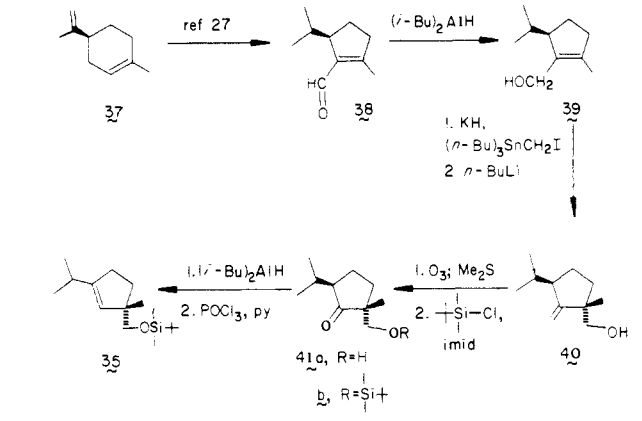
Scheme III



Scheme IV

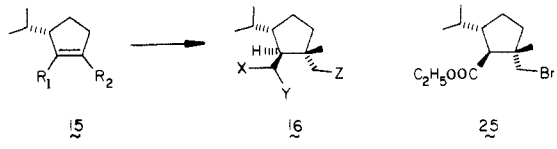


Scheme V



lone conjugate addition product. Dissolving metal reduction of **14** also delivers exclusively **13**, thereby unmistakably indicating that the relevant methyl group prefers to reside within the concave surface. The actual experimental response of **10** is detailed below.

Experiments Aimed at the Direct Stereochemical Elaboration of a Functionalized 1,1,2,3-Tetrasubstituted Cyclopentane. Our goal in this exploratory phase can be defined as the development of an expedient route to cyclopentanoid **16** from a chiral 1,2,3-trisubstituted cyclopentene precursor (**15**) already endowed with the stereochemically proper α-isopropyl side chain. To this end,



the readily available[16] bromo ester **17** was transformed quantitatively into **18** (Scheme II). Exposure of **18** to diimide[17] resulted in concurrent saturation of the isopropenyl group and hydrolysis of the acetoxyl substituent. Subsequent cyclization provided lactone **20** in approximately 75% overall yield from **17**.

Conjugate addition of lithium dimethylcuprate to **20** was successful without need for Lewis acid catalysis[18] and proceeded with complete stereocontrol. The structural assignment to **21** rests on the presumption that bonding occurred exclusively from the more sterically open π surface and is supported by the somewhat reduced magnitude of J for the α-carbonyl proton (4.7 Hz).[19,20]

Cleavage of the lactone ring within **21**, as exemplified by the conversion to **22**, provided intermediates where the stereochemical relationship between the quaternary carbon and isopropyl group has been properly delineated. To rule out the possibility that epimerization had materialized during lactone cleavage, **22** was reduced with Dibal-H to give the unstable bromo alcohol **23**, a molecule that spontaneously loses hydrogen bromide at room temperature to furnish tetrahydrofuran **24**. Arrival at a suitable coupling partner for **10** was now dependent upon epimerization α to the carbomethoxy group. Quite unexpectedly, all attempts to epimerize **22** proved unsuccessful. Treatment with a variety of bases at room temperature led to complete recovery of starting material. More elevated temperatures caused decomposition in some instances. When exposed to acidic conditions, **22** was efficiently returned to lactone **21**. Under no circumstances was **25** observed, despite the fact that MM2 calculations show it to be only 0.3 kcal mol^{-1} *less* stable than its epimer **22**.[21]

In an attempt to dismiss the complications contained within **22**, **23** was oxidized to bromo aldehyde **26**. That epimerization had not adventitiously materialized was confirmed by cyclization to lactol **27** (Scheme III). Titanium tetrachloride mediated dithioketalization[22] of **27** afforded **28** in 85% yield. The subsequent elaboration of **29** followed conventional methodology.[23] Since the hydride reductions of both **29** and lactone **21** furnished diol **30**, no stereochemical crossover had obviously occurred during masking and unmasking of the aldehyde functionality. In fact, the ability of **29** to tolerate a wide array of reagents[24] without change proved impressive.

Since there existed little doubt that the β face of the double bond in **35** (Scheme IV) is less sterically encumbered, the serviceability of this intermediate was examined next. Its hydroboration–oxidation proceeds exclusively syn to the methyl group to deliver **36** as established by Eu(fod)$_3$ shift studies on **36** (Figure 2, supplementary material).[25] Since **35** proved unreactive toward alkylboranes, however, direct introduction of a β-carboxaldehyde unit by a carbonylation sequence[26] could unfortunately not be implemented.

(16) Roberts, R. A.; Schull, V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 2076.

(17) (a) Hoffman, J. M.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1971**, 1245. (b) Corey, E. J.; Mock, W. L.; Pasto, D. J. *Tetrahedron Lett.* **1961**, 347. (c) Hünig, S.; Müller, H. R.; Thiel, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271. (d) Miller, C. E. *J. Chem. Educ.* **1965**, *42*, 254.

(18) (a) Yamamoto, Y.; Yamamoto, S.; Yatagi, H.; Ishihara, Y.; Maruyama, K. J. *J. Org. Chem.* **1982**, *47*, 119. (b) Pernet, A. G.; Nakamoto, H.; Ishizuka, N.; Aburatani, M.; Nakahashi, K.; Sakamoto, K.; Takeuchi, T. *Tetrahedron Lett.* **1979**, 3933.

(19) Compare: Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1982**, *104*, 3733.

(20) Paquette, L. A.; Ohkata, K.; Jelich, K.; Kitching, W. *J. Am. Chem. Soc.* **1983**, *105*, 2800 and relevant references cited therein.

(21) In the space-filling model of **22**, the α-carbonyl proton can be seen to be somewhat buried. This may explain its reluctance to epimerize, although the calculations indicate that at thermodynamic equilibrium the mixture may not strongly favor **25**.

(22) Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. *Tetrahedron Lett.* **1983**, *24*, 3555.

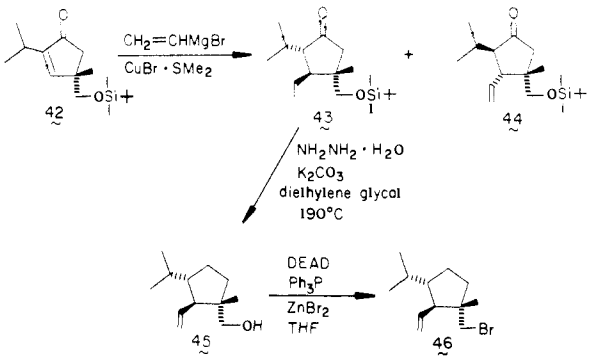
(23) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.

(24) Complications of a related type have surfaced previously [Paquette, L. A.; Crouse, G. D. *Tetrahedron* **1981**, *37*, 281]. In those circumstances, epimerization was most efficiently achieved with *p*-chloroaniline in a mixed solvent system of isopropyl alcohol and acetic acid (ca. 7:1). Compound **29** was stable to these conditions.

(25) The inability of the ether oxygen in β-*tert*-butyldimethylsiloxy aldehydes to coordinate to Lewis acids has been convincingly demonstrated [Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281] and is assumed for similar reasons to be non-operative in the **36** Eu(III) complex.

(26) Review: Brown, H. C.; Negishi, E. *Tetrahedron* **1977**, *33*, 2331.

Scheme VI



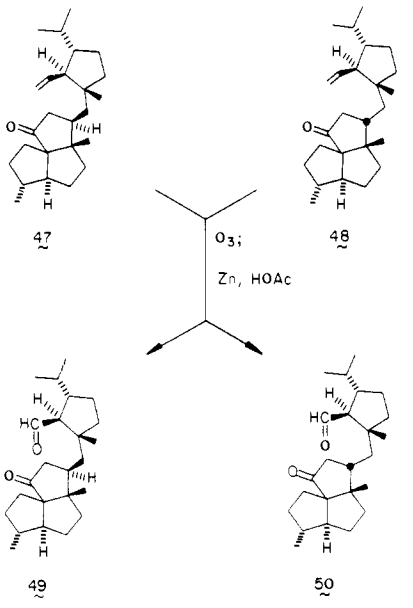
Construction of the Northern Sector by Chirality Transfer. The central element of our plan to bypass the need for epimerization yet maintain reliable stereocontrol over installation of three contiguous chiral centers was the assumption that an isopropyl group is well suited to the control of stereoselective carbon–carbon bond formation in its immediate vicinity. The synthetic transforms **20** → **21** and **31** → **32** described above exemplify the basis of our contention. Retrosynthetically, the homoallylic alcohol **40** led us back to (*S*)-(−)-limonene (**37**, Scheme V). It was recognized that setting of the proper absolute stereochemistry at the quaternary center in **40** required the isopropyl side chain to exist initially in the β configuration.

Intermediate aldehyde **38** was obtained by modification of an earlier procedure.[27] Following reduction to alcohol **39** and application of the Still rearrangement,[28] the resulting isomerically pure alcohol was confirmed as **40** by an independent (racemic) synthesis of its isomer via Wittig methylenation of **34** and removal of the silicon protecting group. The extent of chirality transfer in the **39** → **40** step was assayed as 100% by converting the product alcohol to its (+)-*O*-methylmandelic acid ester. Ozonolysis of **40** gave keto alcohol **41a**, which was efficiently transformed into optically active **35** in 19% overall yield from limonene. The conversion of optically pure **35** into bromide **46** was therefore next pursued.

In actual fact, the absolute stereodisposition of the quaternary carbon in **35** was now to serve as the cornerstone of more advanced molecular construction. Conversion to cyclopentanone **42** (Scheme VI) was best achieved through oxidation with the chromium trioxide–3,5-dimethylpyrazole complex.[29] The ensuing conjugate addition of lithium divinylcuprate[30] proceeded with a 77:23 bias for bonding from the β face as anticipated.[25,31] The stereochemical assignment to major epimer **43** was based principally on the ^1H and ^{13}C shifts of the quaternary-bound methyl group and confirmed at a later stage by an X-ray crystallographic analysis. The configurations of the isopropyl groups follow from the customary propensity of 1,4-additions to lead to 2,3-trans substitution patterns following protonation of the copper enolate.[30b,32]

Wolff–Kishner reduction[33] of **43** proceeded with concurrent deblocking of the siloxy functionality and without affecting the α stereodisposition of the isopropyl side chain (NOE studies). The ultimate conversion of neopentyl alcohol **45** to bromide **46** proved to be unexpectedly problematical. For example, exposure to such reagents as triphenylphosphine dibromide in dichloromethane or phosphorus tribromide in pyridine returned unreacted alcohol. The desired conversion could be accomplished in 91% yield, however, by making recourse to the combined action of triphenylphosphine, zinc bromide, and diethyl azodicarboxylate as recently developed by Ho and Davies.[34]

Scheme VII



The Convergent Coupling Step. The projected attachment of **45** to **10**, clearly the most crucial phase of the synthetic plan, holds interest from several aspects. One of these concerns the CH_2Br group in **46**, which much be transformed into a nucleophilic center and ultimately serve as the *interconnective link between two quaternary centers*. The potential steric complications had to be directly addressed. Also, as indicated earlier, the π-facial selectivity anticipated during nucleophilic capture by **10** could not convincingly be predicted on an a priori basis.

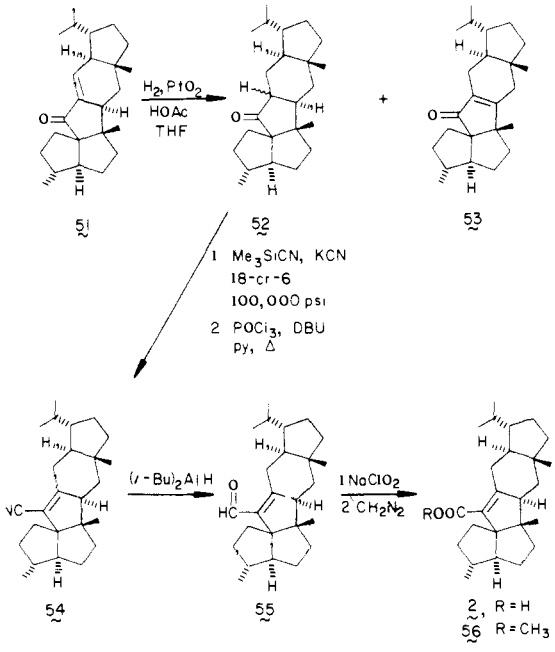
The efficient conversion of **46** to a magnesio bromide was not straightforward. The best conditions ultimately uncovered involved the use of activated magnesium turnings[35] with ethylene dibromide as entrainer.[36] In order to avoid the reduction of **10** by the excess magnesium reagent, the Grignard solution was syringed from the reaction mixture and added to the enone. Importantly, the Grignard solution had to be utilized when freshly prepared. Otherwise, storage for as little as 3 h resulted in complete dimerization. This behavior foreshadowed the relative ease with which this organometallic species can undergo electron-transfer reactions.

Direct addition to **10** in this manner resulted in formation of the 1,4-addition products **47** and **48** (Scheme VII). No alcohols arising from possible 1,2-addition were seen. The coaddition of various copper reagents, which was examined in an attempt to enhance the yield, served only to render the coupling less efficient. The crystallinity of major isomer **47** permitted its structure to be established by X-ray analysis (Figure 3, supplementary material). Since it proved difficult and inefficient to achieve separation of the epimers at this stage, ozonolysis was performed directly on the mixture to give aldehydes **49** and **50**. The separate isolation of these key intermediates could be achieved chromatographically with very acceptable effectiveness. That only **49** and **50** were produced suggested once again that equilibration α to the aldehyde group is not easily accomplished in molecules of this type.

The convergent intermolecular joining of **46** to **10** proved, therefore, to be a synthetically workable strategy. The exclusive 1,4-mode of Grignard addition is believed to be an indicator of facile electron transfer between the reaction partners, subsequent C–C bond formation arising by standard radical coupling. The

(27) Newhall, W. R. *J. Org. Chem.* **1958**, *23*, 1274.
(28) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1928.
(29) (a) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. (b) Kok, P.; DeClercq, P. J.; Vandewalle, M. E. *Ibid.* **1979**, *44*, 4553.
(30) (a) Gadwood, R. C.; Lett, R. M. *J. Org. Chem.* **1982**, *47*, 2268. (b) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. S. *Ibid.* **1975**, *40*, 1460.
(31) Conjugate addition to the *tert*-butyldiphenylsiloxy analogue was briefly examined in order to determine if the added steric bulk would lead to heightened formation of the β-vinyl product. No real improvement was noted.
(32) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1.
(33) Hansen, H. J.; Sliwa, H. R.; Hug, W. *Helv. Chim. Acta* **1979**, *62*, 1120.
(34) Ho, P. T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027.
(35) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749.
(36) (a) Pearson, D. E.; Cowan, D.; Beckler, J. D. *J. Org. Chem.* **1959**, *24*, 504. (b) Lai, Y. H. *Synthesis* **1981**, 585 and relevant references cited therein.

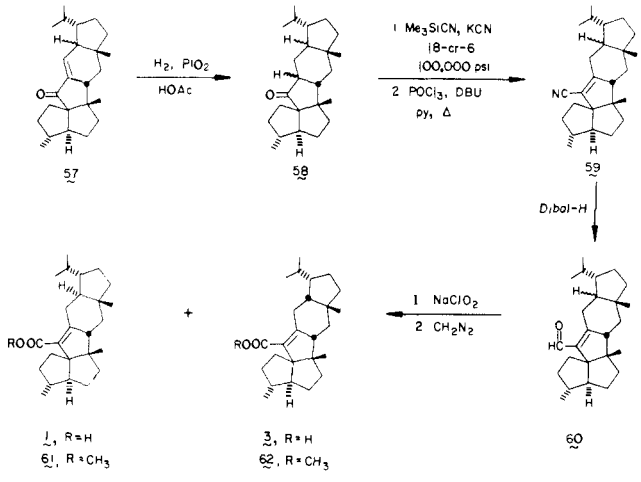
Scheme VIII



3:1 preference for linkage from the β face is taken as a reflection of the development of lesser steric constraints during bond formation from that surface syn to the angular methyl substituent.[37] The kinetic partitioning between **49** and **50** that operates during Grignard coupling is strikingly comparable to the product distribution realized upon dissolving metal reduction of the structurally related conjugated enone.[38] Thermodynamic control usually accompanies protonation of the β carbon in such reactions.

Elaboration of the Retigeranic Acids. With a viable route to keto aldehydes **49** and **50** secure, attention was next paid to their aldol cyclization and completion of the syntheses. To this end, the major intermediate **49** was treated with piperidine and acetic acid in refluxing toluene with provisions for water removal. After extensive periods of heating, **49** was recovered essentially unchanged.[39] When recourse was made instead to 4-Å molecular sieves and neutral alumina in dichloromethane,[7] a 95:5 ratio of **51** to **49** was realized, although the actual isolated yield was poor. However, the sought-after cyclization was satisfactorily effected with excess sodium hydride in hot toluene. These conditions provided the pentacyclic trans-locked ketone **51** in 82% yield and 99.5% purity (capillary GC analysis) after chromatography. Confirmation that the trans ring junction in **51** had not suffered equilibration was realized by heating the product with potassium carbonate in ethanol for 44 h. These conditions induced 84% conversion to the cis indane isomer.[40]

Scheme IX

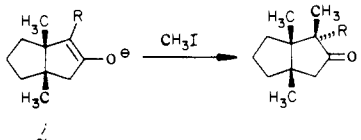


Saturation of the double bond in **51** proved to be a somewhat more difficult task than expected. Whereas diimide[17a] and copper hydride[41] were both totally ineffective, lithium in liquid ammonia reduction produced a *single* alcohol, the oxidation of which proved sluggish and is to be discussed subsequently. The substantial steric hindrance offered to reagents requiring bonding or coordination to ring C in **51** was revealed as well from another direction. Heating of the enone with rhodium trichloride trihydrate in ethanol–chloroform (1:1)[42] failed to cause isomerization to **53**. Despite such problems, success was realized through hydrogenation over Adams catalyst at 80 psi in tetrahydrofuran containing a small amount of acetic acid (Scheme VIII). The three resulting products were spectroscopically identified as the pair of epimeric ketones **52** (84% combined yield) and the isomerized enone **56** (16%).

We had now arrived at the stage where the carbonyl group in **52** had to be homologated. To achieve the addition of trimethylsilyl cyanide to this very hindered functional group, it was necessary to involve potassium cyanide and 18-crown-6 as coreagents and to apply 100 000 psi at room temperature for 5 days. These forcing conditions were adequate to bring both isomers into very efficient reaction. Conversion to unsaturated nitrile **54** was completed by refluxing the silylated cyanohydrins with phosphorus oxychloride and DBU in pyridine.[43]

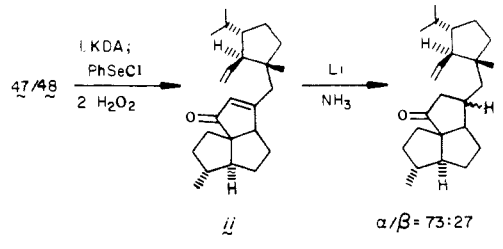
As anticipated, **54** was smoothly reduced to aldehyde **55** with diisobutylaluminum hydride. Subsequent oxidation with sodium

(37) The structurally less intricate enolate anion i has been reported [Paquette, L. A.; Han, Y.-K. *J. Am. Chem. Soc.* **1981**, *103*, 1831] to experience methylation exclusively syn to the angular methyl group. This has been interpreted in terms of a smaller steric volume for two freely rotating methyl groups relative to a fused cyclopentane ring.



i

(38) The dienone ii, obtained by selenenylation/oxidation of the **47**/**48** mixture, was reduced with lithium in liquid ammonia. This treatment returned **47** and **48** in a 73:27 ratio (capillary GC analysis).



ii

(39) A very minor amount of a UV-active substance (perhaps **51**) was formed under these conditions, but was neither isolated nor characterized.

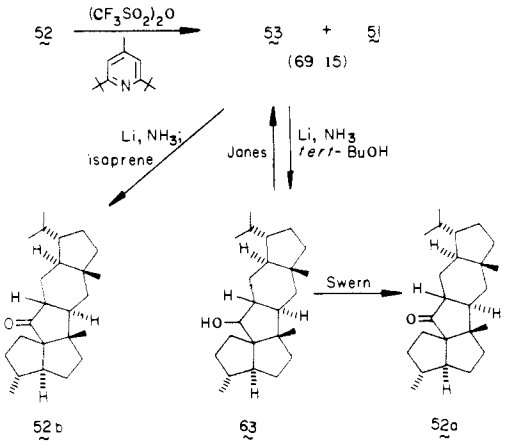
(40) For other methods leading to the successful elaboration of trans hydrindane systems, consult (inter alia): (a) Stork, G.; Atwal, K. S. *Tetrahedron Lett.* **1983**, *24*, 3819. (b) Stork, G.; Winkler, J. D.; Saccomano, N. A. *Ibid.* **1983**, *24*, 465. (c) Hart, D.; Chuang, C. *J. Org. Chem.* **1983**, *48*, 1782. (d) Stork, G.; Shiner, C. S.; Winkler, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 310. (e) Stork, G.; Atwal, K. *Tetrahedron Lett.* **1982**, *23*, 2073. (f) Snider, B. B.; Kirk, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 2364. (g) Snider, B. B.; Deutsch, E. A. *J. Org. Chem.* **1983**, *48*, 1822. (h) Ziegler, F. E.; Mencel, J. *Tetrahedron Lett.* **1983**, *24*, 1859. (i) Rousch, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (j) Corey, E. J.; Engler, T. A. *Tetrahedron Lett.* **1984**, *25*, 149. (k) Yamamoto, K.; Iijima, M.; Ogimura, Y.; Tsuji, J. *Ibid.* **1984**, *25*, 2813. (l) Hutchinson, J. H.; Money, T.; Piper, S. E. *J. Chem. Soc., Chem. Commun.* **1984**, 455. (m) Boeckman, R. K., Jr.; Napier, J. J.; Thomas, E. J.; Sato, R. *J. Org. Chem.* **1983**, *48*, 4152. (n) Kurth, M. J.; Burns, D. H.; O'Brien, M. J. *Ibid.* **1984**, *49*, 731. (o) Paquette, L. A.; Romine, J. L.; Lin, H.-S. *Tetrahedron Lett.* **1987**, *28*, 31.

(41) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180.

(42) (a) Andrieuz, J.; Barton, D. H. R.; Patin, H. *J. Chem. Soc. Perkin Trans. 1* **1977**, 359. (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

(43) Sugihara, Y.; Wakabayashi, S.; Saito, N.; Murata, I. *J. Am. Chem. Soc.* **1986**, *108*, 2773.

Scheme X



chlorite in *tert*-butyl alcohol–aqueous sodium dihydrogen phosphate[44] at room temperature delivered 11-epiretigeranic acid (**2**), which was esterified for direct comparison with natural retigeranic acid B methyl ester. The two compounds were seen by high-field ^{1}H NMR spectroscopy to be closely related in structure, though clearly nonidentical.

To our surprise, aldehyde **50** proved virtually inert to sodium hydride in refluxing toluene. In contrast, heating with piperidine and acetic acid in toluene gave enone **57** in 41% yield (Scheme IX). Significantly, however, this reagent combination delivered a product that consistently proved to be a 75:25 mixture of β (epimerized) and α isomers. For the sake of convenience, these enones were transformed together into the nitriles **59** as before. Sequential Dibal-H reduction and sodium chlorite oxidation gave the pair of retigeranic acids **1** and **3**, which were treated with diazomethane and separated under reverse-phase HPLC conditions. The synthetic ester **61** proved identical in all respects with the methyl ester of retigeranic acid A obtained from natural sources.

The ^{1}H NMR spectrum of **62** again did not match with that of methyl retigeranate B, although a number of characteristic peaks in common were discerned. Consequently, it was clear that the B series was not epimeric with A at either C-4 or C-11. At about this time, word was received from Professor Shibata[8] that he and his associates had undertaken the isolation of a pure sample of retigeranic acid B. Through X-ray crystallographic analysis, the substance was demonstrated to differ from **1** only in the β-isopropyl configuration of ring A.

Studies Directed at Inverting the C-11 Center. Although a synthesis of (−)-retigeranic acid A had been successfully realized, a higher level of convergency would be at hand if C-11 in nitrile **54** or methyl ester **56** would prove capable of configurational inversion. The likelihood of this process was first assessed computationally (via MACROMODEL and MM2) in terms of the relative energies of esters **56** and **61** (Figure 4, supplementary material). A direct consequence of this analysis was the finding that methyl retigeranate A (**61**) is 2.4 kcal mol^{-1} more stable than its α epimer **56**. We were therefore striving to advance in the thermodynamically acceptable direction.

Despite this advantage, no conditions were found to achieve the desired stereochemical crossover in either **54** or **56**. The apparent lack of kinetic acidity may have its origin in the less than ideal alignment of the proton attached to C-11 in this series. As concerns **56**, this C–H bond is seen to be tilted 40° out of plane relative to the π cloud of the α,β-unsaturated ester moiety. Whatever the cause, the epimerization ploy is not tactically feasible from this direction.

In the course of certain ancillary experiments, we uncovered the fact that attempted conversion of ketones **52** to the enol triflate led instead to enones **53** and **51** (Scheme X). Evidently, steric crowding about the carbonyl group forces triflation of the enolate anion to occur on carbon, to be followed by the elimination of triflinic acid.[45]

This straightforward elimination of two chiral centers bears an obvious direct relationship to the C-11 stereoinversion question and prompted a detailed examination of the reduction of **53**. The ensuing developments were to cast an ironic light on the unforeseen difficulties we encountered in controlling to our advantage the stereodisposition of C-11. Addition of **53** to lithium in liquid ammonia followed by destruction of the excess reducing agent with isoprene and an ammonium chloride quench gave rise to a single epimer of **52**, referred to in Scheme X as **52b**. While we did not pursue elucidation of the precise orientation of the α-carbonyl proton, the ^{1}H NMR spectrum and capillary GC response[46] of this pure product clearly indicated it to carry an α-proton at C-11.

Comparable dissolving metal reduction but with *tert*-butyl alcohol present gave the stereochemically *homogeneous* alcohol **63**. Whereas Jones oxidation of this product surprisingly resulted in overoxidation to return **53**, the milder Swern conditions furnished **52a** as a pure product. This substance proved without question to be epimeric with **52b** only at the α-carbonyl site. Thus, these experiments make irrefutably clear the fact that the reduced form of **53** experiences α-proton capture exclusively from the α surface of the pentacyclic nucleus. The circuit was a closed one!

Summary

Coupling of the enantiomerically pure intermediates **46** and **10** leads *directly* to a 75:25 mixture of **47** and **48**, which were separately transformed into the unsaturated nitriles **54** and **59**. The optically pure 11-epi- and 4-epiretigeranic acids (**2** and **3**, respectively) were subsequently elaborated and shown not to be identical with retigeranic acid B. The same methodology also provided enantiomerically homogeneous "natural" (−)-retigeranic acid A (**1**).[47]

Experimental Section

(−)-(3aβ,5aα,6α,8aα)-4,5,6,6a,7,8-Hexahydro-3a,6-dimethylcyclopenta[*c*]pentalen-1(3a*H*)-one (10). Ketone **7**, $[\alpha]^{20}_D$ +90.55° (*c* 0.22, $CHCl_3$), was transformed into **10** and **11** with minor improvements according to the predescribed report.[11a] The separation of these isomeric enones was achieved in a practical way as follows.

Dibal-H (25 mL of 1.0 M in hexanes, 0.025 mol) was added dropwise over 1 h to a magnetically stirred, nitrogen blanketed solution of the **10/11** mixture (70:30, 3.51 g, 0.018 mol) in dry ether (150 mL) at −78 °C. After 1 h at this temperature, 1 N hydrochloric acid (50 mL) was introduced over 20 min. The mixture was vigorously stirred as it warmed to room temperature where an additional 50 mL of the HCl was added. The separated aqueous phase was extracted with ether (3 × 75 mL), and the combined ethereal layers were washed with 1 N hydrochloric acid (400 mL), saturated sodium bicarbonate solution (400 mL), and brine (400 mL) prior to drying. The solution was filtered through silica gel and evaporated to leave 3.66 g of a pale yellow oily solid. HPLC of this material on silica gel (elution with 10% ethyl acetate in petroleum ether) resulted in clean separation of the major alcohol (2.49 g) from the minor one (540 mg, 85% combined yield).

The major isomer was stirred in cold (0 °C) glacial acetic acid (25 mL) and acetic anhydride (20 mL) as sodium chromate tetrahydrate (4.28 g, 0.018 mmol) was added in portions during 30 min. The mixture was stirred overnight at 23 °C and added to cracked ice (ca. 200 mL). After neutralization with solid sodium carbonate, the mixture was extracted with ether (4 × 100 mL), and the combined extracts were washed with saturated sodium bicarbonate solution (500 mL) and brine (500 mL) before drying and solvent evaporation. The residual yellow oil (2.54 g) was purified by HPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) to give pure **10** (2.37 g, 96%) as a colorless solid, mp 40–41 °C: $[\alpha]^{23}_D$ −48.63° (*c* 2.0, $CHCl_3$); IR (CCl_4, cm^{-1}) 1692; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 5.7 Hz, 1 H), 6.04 (d, J = 5.7

(44) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(45) Hendrickson, J. B.; Bair, K. W.; Burgeon, R.; Giga, A.; Skipper, P. L.; Sternbach, D. D.; Wareing, J. A. *Org. Prep. Proced. Int.* **1977**, *9*, 173.

(46) The several epimers of **52** and **58** possess distinctively different retention times that have proven to be well defined and characteristics of the particular stereoisomer in question.

(47) The reported $[\alpha]^{23}_D$ for **1** is −86.5° (C_2H_5OH). Professor Shibata has also informed us that retigeranic acid B is levorotatory, $[\alpha]^{23}_D$ −30.4° (C_2H_5OH).

Hz, 1 H), 1.95–1.30 (m, 12 H), 1.09 (s, 3 H), 0.96 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.20, 169.96, 130.72, 67.46, 59.45, 55.68, 39.75, 36.03, 35.09, 28.51, 25.83, 21.90, 18.09; MS, m/z (M^+) calcd 190.1308, obsd 190.1303.

Entirely comparable oxidation of the minor isomer gave pure **11** as a colorless oil: $[\alpha]^{24}_D$ −86.77° (c 1.7, $CHCl_3$); IR (neat, cm^{-1}) 1708, 1591, 1462, 837; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, J = 5.6 Hz, 1 H), 5.95 (d, J = 5.6 Hz, 1 H), 2.00–1.05 (series of m, 10 H), 1.02 (s, 3 H), 0.99 (d, J = 6.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.60, 170.64, 128.72, 66.46, 58.62, 57.48, 39.40, 36.00, 35.42, 30.52, 26.21, 20.38, 19.26; MS, m/z (M^+) calcd 190.1358, obsd 190.1331.

1-(Acetoxymethyl)-2-carbomethoxy-3-isopropenylcyclopentene (18). A solution of **17** (500 mg, 1.93 mmol) and potassium acetate (4.5 g, 20.4 mmol) in methanol (25 mL) was stirred at room temperature for 24 h, during which time potassium bromide precipitated. The methanol was removed in vacuo, and the residue was partitioned between water and ether. The organic layer was removed, and the aqueous phase was extracted with ether. The combined ethereal solution was washed with water and brine, dried, and evaporated. MPLC purification of the residue (silica gel; elution with 12% ethyl acetate in petroleum ether) afforded 440 mg (96%) of **18** as a colorless oil: IR (neat, cm^{-1}) 1750, 1720, 1650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (m, 2 H), 4.50 (m, 2 H), 3.60 (s, 3 H), 3.6–3.4 (m, 1 H), 2.8–2.0 (series of m, 4 H), 2.00 (s, 3 H), 1.80 (s, 3 H); MS, m/z (M^+) calcd 238.1205, obsd 238.1212.

1-(Hydroxymethyl)-2-carbomethoxy-3-isopropylcyclopentane (19). To a solution of **18** (440 mg, 1.85 mmol) in methanol (75 mL) under a nitrogen atmosphere was added hydrazine hydrate (9 mL), acetic acid (9 drops), and saturated copper sulfate solution (10 drops). This stirred mixture was maintained at 25 °C while a solution of sodium periodate (7.9 g, 20 equiv) in water (60 mL) was added dropwise during 1 h. Upon completion of the addition, stirring was maintained for 36 h before removal of most of the methanol under reduced pressure. The product was taken up in ether, washed with water and brine, dried, and concentrated in vacuo. There was obtained 330 mg (90%) of **19** as a colorless oil, which was not further purified: ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.4 (m, 2 H), 3.70 (s, 3 H), 3.1–1.4 (series of m, 7 H), 0.95 (d, J = 6 Hz, 3 H), 0.70 (d, J = 6 Hz, 3 H); MS, m/z (M^+) calcd 198.1256, obsd 198.1262.

3,4,5,6-Tetrahydro-6-(1-methylethyl)-1-oxocyclopenta[*c*]furan (20). A solution of **19** (550 mg, 2.52 mmol) in benzene (50 mL) containing p-toluenesulfonic acid (50 mg) was heated at reflux under a Dean–Stark trap for 18 h. The cooled reaction mixture was washed with saturated sodium bicarbonate solution, dried, and evaporated. MPLC purification of the residue (silica gel, elution with 10% ethyl acetate in petroleum ether) afforded 340 mg (81%) of **20** as a colorless, homogeneous oil: IR (neat, cm^{-1}) 1765, 1650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80–4.71 (m, 2 H), 2.91–2.83 (m, 1 H), 2.65–2.44 (m, 3 H), 2.26–2.15 (m, 1 H), 2.03–1.92 (m, 1 H), 0.94 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H); MS, m/z (M^+) calcd 166.0994, obsd 166.0997. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.18; H, 8.46.

Hexahydro-3a-methyl-6-(1-methylethyl)-1-oxocyclopenta[*c*]furan (21). A solution of dimethylcopperlithium was prepared by addition of ethereal methyllithium (1.3 M) to a slurry of copper iodide (2.3 g, 12.1 mmol) in dry ether (40 mL) at 0 °C until the mixture became homogeneous and almost colorless. Approximately 18.6 mL of reagent was required. The resulting solution was cooled to −78 °C, and **20** (400 mg, 2.41 mmol) in ether (4 mL) was slowly added via syringe pump over a 4-h period. The dark solution was stirred at −78 °C for an additional 4 h, warmed to 0 °C, and quenched with basic ammonium chloride solution. The mixture was extracted with ether, and the combined ether extracts were washed with ammonium chloride solution and brine before drying. Evaporation of the solvent and purification by MPLC (silica gel; elution with 10% ethyl acetate in petroleum ether) gave **21** as a clear colorless oil (310 mg, 71%): IR (neat, cm^{-1}) 1780, 1030; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 and 3.93 (AB q, J = 9 Hz, 2 H), 2.28 (d, J = 4.7 Hz, 1 H), 2.05–1.95 (m, 1 H), 1.89–1.82 (m, 1 H), 1.69–1.49 (m, 4 H), 1.19 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 77.2, 54.8, 51.8, 47.6, 38.6, 33.1, 30.2, 23.7, 21.4, 20.4; MS, m/z (M^+) calcd 182.1307, obsd 182.1314. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.25; H, 9.86.

Ethyl (1α,2α,5α)-2-(Bromomethyl)-2-methyl-5-(1-methylethyl)cyclopentanecarboxylate (22). Into a solution of **21** (3.0 g, 16.5 mmol) in absolute ethanol (50 mL) at 0 °C was bubbled anhydrous hydrogen bromide over a period of 5 h. The mixture was heated at reflux for 8 h, cooled, added to water (20 mL), and extracted with ether. The combined ether extracts were washed with water and brine, dried, evaporated, and purified by HPLC (silica gel; elution with 2% ethyl acetate in petroleum ether) to give recovered lactone **21** (0.6 g, 20%) and bromo ester **22**, a colorless oil (2.6 g, 54%): IR (neat, cm^{-1}) 1730; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.15 (q, J = 6 Hz, 2 H), 3.45, 3.30 (AB q, J = 9 Hz, 2 H), 2.40 (d, J = 9 Hz, 1 H), 2.35–1.40 (m, 6 H), 1.28 (t, J = 6 Hz, 3 H), 1.25 (s, 3 H), 0.87 (d, J = 6 Hz, 3 H), 0.84 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 60.4, 58.3, 49.6, 47.3, 42.5, 38.4, 33.0, 27.2, 26.3, 20.9, 20.2, 14.3; MS, m/z (M^+) calcd 290.0882, obsd 290.0891.

(3aβ,6α,6aβ)-Hexahydro-3a-methyl-6-(1-methylethyl)-1*H*-cyclopenta[*c*]furan (24). To a solution of **22** (0.34 g, 1.18 mmol) in ether (30 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 3.5 mL, 3.5 mmol). The solution was stirred at −78 °C for 1.5 h before the addition of 10% hydrochloric acid solution. The mixture was allowed to warm to room temperature and stirred for 15 min. The product was extracted into ether, washed with 10% hydrochloric acid solution and brine, dried, evaporated, and purified by MPLC (silica gel; elution with 7% ethyl acetate in petroleum ether) to give unstable oily hydroxy bromide **23** (0.15 g, 51%); IR (neat, cm^{-1}) 3400; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.90 (s, 1 H), 3.70 (d, J = 5 Hz, 2 H), 3.49 (s, 2 H), 1.90–1.20 (m, 7 H), 1.15 (s, 3 H), 0.90–0.70 (m, 6 H).

A solution of hydroxy bromide **23** in $CDCl_3$ was monitored by ^{1}H NMR spectroscopy. The formation of ether **24** was seen to occur within a few hours. After 2 days, no starting material remained giving only **24**, which could be isolated by vapor-phase chromatography (5% SE-30, 6 ft × 0.25 in., 150 °C) as a homogeneous, colorless oil: IR (neat, cm^{-1}) 1120; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80–3.50 (m, 3 H), 3.30–3.20 (m, 1 H), 1.80–1.20 (m, 7 H), 1.10 (s, 3 H), 0.90 (d, J = 6 Hz, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8/.7, 79.8, 57.2, 56.2, 52.0, 39.4, 33.4, 31.7, 25.1, 21.7, 21.2; MS, m/z ($M^+ - C_3H_7$) calcd 125.1000, obsd 125.1003.

(1α,2α,5α)-2-(Bromomethyl)-2-methyl-5-(1-methylethyl)cyclopentanecarboxaldehyde (26). To a solution of **22** (200 mg, 0.687 mmol) in ether (20 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 1.7 mL, 1.7 mmol). The solution was stirred for 1.5 h at −78 °C before the addition of 10% hydrochloric acid. The mixture was allowed to warm to room temperature and stirred for 15 min. After extraction of the product into ether, the combined organic layers were washed with 10% hydrochloric acid solution and brine, dried, and evaporated. Crude alcohol **27** so obtained was immediately dissolved in dichloromethane (5 mL) and added to a well-stirred mixture of pyridinium chlorochromate (32.5 mg, 1.51 mmol) in dichloromethane (10 mL) at room temperature. After 4 h, 5% sodium hydroxide solution was added, and the mixture was stirred until all solids dissolved. The solution was extracted with dichloromethane, and the combined extracts were washed with 10% hydrochloric acid and brine, dried, evaporated, and purified by MPLC (silica gel; elution with 2% ethyl acetate in petroleum ether) to give **26** as a clear oil (0.12 g, 70%): IR (neat, cm^{-1}) 1720; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (d, J = 3 Hz, 1 H), 3.40 (br s, 2 H), 2.50–1.40 (m, 7 H), 1.28 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 0.85 (d, J = 6 Hz, 3 H); MS, m/z ($M^+ - CH_3$) calcd 231.0385, obsd 231.0392.

Hexahydro-3a-methyl-6-(1-methylethyl)-1*H*-cyclopenta[*c*]furan-1-ol (27). A. Reduction of 27. To a solution of lactone **27** (0.9 g, 4.95 mmol) in ether (30 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 10 mL, 10 mmol). The mixture was stirred for 2 h at −78 °C, treated with 10g hydrochloric acid, allowed to warm to room temperature, and stirred for 30 min before extraction with ether. The combined organic layers were washed with 10% hydrochloric acid and brine, dried, and evaporated to give lactol **27** (0.8 g, 88%), which was used without purification: IR (neat, cm^{-1}) 3400; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.10 (s, 1 H), 3.65–3.50 (m, 3 H), 1.90–1.10 (m, 7 H), 1.08 (s, 3 H), 0.90 (d, J = 6 Hz, 3 H), 0.85 (d, J = 6 Hz, 3 H); MS, m/z ($M^+ - H_2O$) calcd 166.1358, obsd 166.1361.

B. Solvolysis of 26. To a solution of potassium carbonate (0.5 g) in methanol (10 mL) containing water (5 mL) was added aldehyde **26** (0.1 g). The mixture was stirred at room temperature for 1 h before extraction with ether. The combined extracts were washed with water, dried, and concentrated. The residue (0.06 g) so obtained was found to be lactol **27**. No aldehyde was present.

Titanium(IV)-Mediated Dithioketalization of 27. To a solution of **27** (300 mg, 1.63 mmol) in dichloromethane (10 mL) was added 1,2-ethanedithiol (0.18 mL, 2.22 mmol). The solution was cooled to −78 °C before addition of titanium tetrachloride (0.1 mL, 0.91 mmol). The mixture was allowed to stir at −78 °C for 1 h, warmed to 0 °C, treated with 5% sodium hydroxide solution at 0 °C, and extracted with ether. The organic layer was washed with 5% sodium hydroxide solution and brine, dried, freed of solvent, and purified by MPLC (silica gel; elution with 10% ethyl acetate in petroleum ether) to give **28** as a colorless oil (360 mg, 85%): IR (CCl_4, cm^{-1}) 3650, 3480; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.81 (d, J = 5 Hz, 1 H), 3.64, 3.52 (AB q, J = 11.2 Hz, 2 H), 3.30–3.05 (m, 4 H), 2.10–1.90 (m, 2 H), 1.70–1.55 (m, 3 H), 1.45–1.30 (m, 1 H), 1.25–1.20 (m, 2 H), 1.10 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H); MS, m/z (M^+) calcd 260.1283, obsd 260.1285.

(1α,2α,3α)-2-[(*tert*-Butyldimethylsiloxy)methyl]-5-isopropyl-2-methylcyclopentanecarboxaldehyde (29). To a solution of **29** (0.044 g,

0.169 mmol) in dimethylformamide (5 mL) was added imidazole (30 mg) followed by *tert*-butyldimethylsilyl chloride (30 mg, 0.20 mmol). The resulting solution was allowed to stir at room temperature for 24 h, treated with 5% sodium bicarbonate solution, and extracted with ether. The organic layer was washed with water and brine, dried, and freed of solvent. Purification by MPLC (silica gel; elution with 1% ethyl acetate in petroleum ether) gave the silylated product as a colorless oil (54 mg, 85%): IR (CCl_4, cm^{-1}) 2970, 1420, 1270, 1210; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (d, J = 6 Hz, 1 H), 3.49 (s, 2 H), 3.21–3.05 (m, 4 H), 2.10–2.00 (m, 2 H), 1.91–1.86 (m, 1 H), 1.69–1.50 (m, 2 H), 1.45–1.40 (m, 1 H), 1.14–1.10 (m, 1 H), 1.04 (s, 3 H), 0.89 (d, J = 7 Hz, 3 H), 0.88 (s, 9 H), 0.81 (d, J = 7 Hz, 3 H), 0.02 (s, 6 H); MS, m/z (M^+) calcd 374.2133, obsd 374.2132.

To a solution of this material (70 mg, 0.187 mmol) in acetone (5 mL) was added water (1 mL), methyl iodide (2 mL), and solid sodium carbonate (50 mg). The mixture was heated at reflux for 12 h, cooled, and concentrated in vacuo. The residue was taken up in ether, washed with water and brine, dried, and freed of solvent. Purifiction by MPLC (silica gel; elution with 1% ethyl acetate in petroleum ether) gave **29** as a clear oil (40 mg, 72%): IR (CCl_4, cm^{-1}) 1720; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, J = 4 Hz, 1 H), 3.43, 3.33 (AB q, J = 10 Hz, 2 H), 2.26–2.17 (m, 1 H), 2.08–2.04 (m, 1 H), 1.90–1.80 (m, 1 H), 1.66–1.29 (m, 4 H), 1.07 (s, 3 H), 0.86 (s, 9 H), 0.85 (d, J = 7 Hz, 3 H), 0.81 (d, J = 7 Hz, 3 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 67.8, 64.8, 51.0, 48.0, 36.4, 32.5, 28.0, 25.9, 21.7, 20.2, 18.2, −5.6; MS, m/z (M^+ − H) calcd 297.2237, obsd 297.2235.

(1α,2α,3α)-1-Methyl-3-(1-methylethyl)-1,2-cyclopentanedimethanol (30). A. From Lactone 21. To a suspension of lithium aluminum hydride (100 mg, 2.63 mmol) in ether (15 mL) at −78 °C was added a solution of **21** (0.2 g, 1.10 mmol) in ether (2 mL). The mixture was stirred at −78 °C for 2 h before being quenched with 10% hydrochloric acid, extracted with ether, washed with 10% hydrochloric acid solution and brine, dried, and freed of solvent. The residue was purified by MPLC (silica gel; elution with 34% ethyl acetate in petroleum ether) to give **30** as a colorless oil (0.16 g, 78%): IR (CCl_4, cm^{-1}) 3400; ^1H NMR (300 MHz, $CDCl_3$) δ 3.70, 3.36 (AB q, J = 11.3 Hz, 2 H), 3.64 (d, J = 5.4 Hz, 2 H), 3.14 (s, 2 H), 1.66–1.18 (m, 7 H), 1.07 (s, 3 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 3 H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.4, 63.1, 52.9, 48.1, 45.9, 36.4, 31.1, 25.7, 25.0, 22.1, 18.5; MS, m/z ($M^+ = H_2O$) calcd 168.1540, obsd 168.1543.

B. From Aldehyde 29. To a solution of **29** (0.2 g, 0.67 mmol) in tetrahydrofuran (15 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 1.0 mL, 1.0 mmol). The mixture was stirred at −78 °C for 2 h before addition of saturated ammonium chloride solution. The resultant two-phase mixture was stirred at room temperature for 16 h, extracted with ether, washed with saturated ammonium chloride solution and brine, and dried. Removal of the solvent and purification by MPLC (silica gel; elution with 34% ethyl acetate in petroleum ether) gave **30** (62 mg, 50%), identical in all respects with the material obtained above.

2-Isopropyl-2-carbethoxycyclopentanone (31). To dry toluene (1500 mL) contained in a 3-L three-necked flask equipped with a mechanical stirrer, addition funnel, and condenser was added sodium (28 g, 1.2 mmol) in small pieces. The mixture was stirred and heated at reflux for 1 h to disperse the sodium. Diethyl adipate (202 g, 1 mol) was added dropwise over a 1-h period. The sluggish mixture was heated at reflux for 2 h. A mixture of ethanol and toluene (400 mL) was then removed by distillation. The reaction mixture was cooled, and isopropyl iodide (150 mL, 1.5 mol) was added. The mixture was heated at reflux for 5 days, cooled, poured onto ice (400 g), and extracted with ether. The combined organic phases were washed with 10% hydrochloric acid and brine, dried, and concentrated. Distillation of the residue gave **31** as a colorless liquid (140.2 g, 71%): bp 75–85 °C (0.3 Torr) (lit.[48] bp 112 °C (11 Torr); IR (neat, cm^{-1}) 1750, 1725; ^1H NMR (200 MHz, $CDCl_3$) δ 4.2 (q, J = 6 Hz, 2 H), 2.80–1.60 (m, 7 H), 1.30 (t, J = 6 Hz, 3 H), 0.90 (d, J = 6 Hz, 3 H), 0.80 (d, J = 6 Hz, 3 H).

2-Methyl-2-carbethoxy-5-isopropylcyclopentanone (32). To a sodium ethoxide solution prepared from absolute ethanol (150 mL) and sodium (10.5 g, 0.46 mol) was added **31** (90 g, 0.46 mol) at room temperature. The solution was heated at reflux for 8 h, and about half of the ethanol was removed by distillation. Upon addition of toluene (250 mL), the remainder of the ethanol was removed by azeotropic distillation; more toluene was added as necessary. The residue was cooled to 0 °C, methyl iodide (68 g, 30 mL, 0.48 mol) was added, and the resulting mixture was stirred at room temperature overnight, treated with 10% hydrochloric acid, and extracted with ether. The combined organic layers were washed with 5% sodium bicarbonate solution and brine, dried, and concentrated. Distillation of the residue gave **32** as a colorless liquid (79.5 g, 82%): bp 70–75 °C (0.5 Torr); IR (neat, cm^{-1}) 1750, 1730; ^1H NMR (200 MHz, $CDCl_3$) δ 4.10–4.00 (m, 2 H), 2.50–1.50 (m, 6 H), 1.15 (s, 3 H), 1.10–1.05 (m, 3 H), 0.95 (d, J = 6 Hz, 3 H), 0.85 (d, J = 6 Hz, 3 H); MS, m/z (M^+) calcd 212.1412, obsd 212.1422.

2-(Hydroxymethyl)-2-methyl-5-isopropylcyclopentanone (33). To a solution of lithium diisopropylamide prepared from *n*-butyllithium (1.6 M in hexane, 100 mL, 160 mmol) and diisopropylamine (23.4 mL, 167 mmol) in tetrahydrofuran (300 mL) at −78 °C was added **32** (23.0 g, 109 mmol) in tetrahydrofuran (20 mL). The mixture was stirred at −78 °C for 16 h before addition of lithium aluminum hydride (3.5 g, 92 mmol), allowed to warm to −40 °C, and stirred at that temperature for 3 h prior to careful addition of 10% hydrochloric acid. Extraction with ether was followed by washing with saturated ammonium chloride solution and brine, drying, and removal of solvent. Purification by HPLC (silica gel; elution with 27% ethyl acetate in petroleum ether) gave **33** as a clear oil (12.0 g, 65%); IR (CCl_4, cm^{-1}) 3620, 3460, 1735; ^1H NMR (300 MHz, $CDCl_3$) δ 3.55, 3.45 (AB q, J = 11 Hz, 2 H), 2.50–2.40 (m, 1 H), 2.20–1.80 (m, 4 H), 1.80–1.50 (m, 2 H), 0.98 (d, J = 6 Hz, 3 H), 0.97 (s, 3 H), 0.80 (d, J = 6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 224.3, 67.3, 56.5, 50.9, 30.4, 27.1, 20.8, 20.5, 18.4; MS, m/z calcd 170.1307, obsd 170.1308.

2-[(*tert*-Butyldimethylsiloxy)methyl]-5-isopropylcyclopentanone (34). To a solution of **33** (6.32 g, 37.2 mmol) in dry dimethylformamide (75 mL) containing imidazole (10 g) was added *tert*-butyldimethylsilyl chloride (6.1 g, 40.7 mmol). The mixture was stirred at room temperature for 16 h, treated with sodium bicarbonate solution, and extracted with ether. The combined organic phases were washed with water and brine, dried, and evaporated. Purification by HPLC (silica gel; elution with 1% ethyl acetate in petroleum ether) gave **34** as a clear oil (9.3 g, 88%): IR (CCl_4, cm^{-1}) 1740, 1470, 1260, 1100; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68, 3.31 (AB q, J = 11 Hz, 2 H), 2.20–1.80 (m, 4 H), 0.99 (d, J = 6 Hz, 3 H), 0.89 (s, 9 H), 0.85 (s, 3 H), 0.81 (d, J = 6 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.4, 67.8, 56.9, 51.3, 30.3, 27.0, 25.9, 21.1, 20.7, 18.7, 18.5, 18.3, 5.6; MS, m/z ($M^+ - C_4H_9$) calcd 227.1467, obsd 227.1499.

3-[(*tert*-Butyldimethylsiloxy)methyl]-1-isopropyl-3-methylcyclopentane (35). To a solution of **34** (2.07 g, 7.29 mmol) in ether (50 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 10.9 mL, 10.9 mmol). The mixture was allowed to stir at −78 °C for 2 h before the addition of 10% hydrochloric acid, extraction with ether, washing with 10% hydrochloric acid and brine, drying, and evaporation of solvent. The resulting hydroxy ether was immediately taken up in pyridine (30 mL). To this pyridine solution was added phosphorus oxychloride (1.6 mL, 17.2 mmol) at room temperature. The mixture was heated at 40–45 °C for 12 h (higher temperatures caused extensive decomposition). After cooling, the mixture was poured onto ice water and extracted with ether. The combined ether extracts were washed with 10% hydrochloric acid and brine, dried, and evaporated. Purification by MPLC (silica gel; elution with 0.5% ethyl acetate in petroleum ether) gave **35** as a colorless liquid (1.35 g, 69%): IR (CCl_4, cm^{-1}) 3040, 1640, 1480, 1380, 1360, 1260, 1080; ^1H NMR (200 MHz, $CDCl_3$) δ 5.20 (s, 1 H), 3.20 (s, 2 H), 2.30–2.10 (m, 3 H), 1.80–1.50 (m, 2 H), 1.05 (d, J = 6 Hz, 6 H), 1.01 (s, 3 H), 0.90 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 128.4, 70.9, 50.6, 34.3, 32.3, 29.9, 26.0, 23.8, 21.61, 21.59, 2.19, 2.15; MS, m/z ($M^+ - C_4H_9$) calcd 211.1487, obsd 211.1532. Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.54; H, 12.01.

(1α,2α,5α)-2-[(*tert*-Butyldimethylsiloxy)methyl]-2-methyl-5-(1-methylethyl)cyclopentanol (36). To a solution of **35** (0.20 g, 0.75 mmol) in tetrahydrofuran (1.0 mL) was added borane–tetrahydrofuran complex (1 M in tetrahydrofuran, 1.0 mL, 1.0 mmol). The resulting mixture was heated at reflux for 3 h, cooled to 0 °C, and treated with 5% sodium hydroxide solution (5 mL) and 30% hydrogen peroxide (2 mL). The mixture was stirred at room temperature for 2 h before extraction with ether. The combined ethereal extracts were washed with water and brine, dried, and evaporated. Purification by MPLC (silica gel; elution with 3% ethyl acetate in petroleum ether) gave **36** as a colorless oil (85 mg, 40%): IR (CCl_4, cm^{-1}) 3400, 1420, 1390, 1370, 1260, 1080; ^1H NMR (300 MHz, $CDCl_3$) δ 3.62 (d, J = 8.2 Hz, 1 H), 3.48, 3.38 (AB q, J = 9 Hz, 2 H), 2.31 (br s, 1 H), 1.70–1.50 (m, 3 H), 1.30–1.20 (m, 3 H), 0.96 (d, J = 6 Hz, 3 H), 0.94 (s, 3 H), 0.88 (s, 9 H), 0.85 (d, J = 6 Hz, 3 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.7, 72.9, 50.2, 45.7, 31.9, 30.8, 25.9, 23.0, 21.3, 19.5, 18.2, 17.5, 5.6; MS, m/z ($M^+ - C_4H_9$) calcd 229.1592, obsd 229.1595.

(+)-(*R*)-1-Methyl-3-isopropylcyclopentene-2-carboxaldehyde (38). In a Parr hydrogenation vessel was placed (*S*)-(−)-limonene (50 g, 0.37 mol) and platinum oxide (0.1 g). The mixture was hydrogenated at a pressure not exceeding 30 psi until approximately 1 equiv of hydrogen had been consumed. The progress of this highly exothermic reaction was moni-

(48) (a) Guha, P. C.; Krishnamurthy, S. *Ber. Dtsch. Chem. Ges. A* **1937**, *70*, 2112. (b) Ruegg, R.; Jeger, O. *Helv. Chim. Acta* **1948**, *31*, 1753. (c) Kotz, A.; Schuler, P. *Justus Liebigs Ann. Chem.* **1906**, *350*, 217.

tored by ^{1}H NMR spectroscopy. After all of the limonene had been consumed, the mixture was filtered through Celite to give *p*-menth-1-ene (48 g, 94%), $[\alpha]^{20}_D$ −99.38° (*c* 16.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.42–5.39 (m, 1 H), 2.06–1.70 (m, 5 H), 1.67 (s, 3 H), 1.53–1.44 (m, 1 H), 1.31–1.20 (m, 2 H), 0.93 (d, *J* = 6 Hz, 3 H), 0.91 (d, *J* = 6 Hz, 3 H). Without further purification, the olefin was dissolved in chloroform (500 mL) containing sodium bicarbonate (37 g). The mixture was cooled to 0 °C, and a 40% aqueous solution of peracetic acid (85 mL, 0.45 mol) was added dropwise over a 2-h period. The resultant mixture was allowed to stir for 18 h. Excess oxidant was destroyed by the addition of 10% sodium bisulfite solution. After separation of the layers, the organic phase was washed with saturated sodium bicarbonate solution and brine prior to drying. Removal of the solvent gave the epoxide: $[\alpha]^{20}_D$ −46.78° (*c* 16.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10–2.90 (m, 1 H), 2.20–1.40 (m, 8 H), 1.35 (s, 3 H), 0.92, (d, *J* = 6 Hz, 6 H). To the epoxide was added 1% aqueous sulfuric acid solution (300 mL). The mixture was vigorously stirred for 12 h before extraction with ether. The combined ether extracts were washed with saturated sodium bicarbonate solution and brine before drying. After concentration, the crude diol so obtained was dissolved in tetrahydrofuran (150 mL). To the solution at 0 °C was added an aqueous solution of sodium periodate (103 g in 400 mL), and the mixture was stirred vigorously at 0 °C for 4 days. After filtration, the mixture was extracted with ether, and the ether layers were washed with water and brine, dried, and concentrated. The resulting keto aldehyde, $[\alpha]^{20}_D$ +15.1° (*c* 10, $CHCl_3$), was taken up in benzene (300 mL) and treated with piperidine (3 mL) and acetic acid (3 mL). This mixture was heated at reflux for 1 h with concomitant removal of water by means of a Dean–Stark trap. After cooling, the benzene solution was washed with 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine. Vacuum distillation of the oil obtained following drying and solvent evaporation gave aldehyde **38** as a colorless oil (33 g, 62% overall from *p*-menth-1-ene): $[\alpha]^{20}_D$ +7.31° (*c* 12.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.1 (s, 1 H), 3.00–2.35 (m, 3 H), 2.25 (s, 3 H), 2.00–1.60 (m, 3 H), 0.95 (d, *J* = 6 Hz, 3 H), 0.75 (d, *J* = 6 Hz, 3 H).

(−)-1-Methyl-2-(hydroxymethyl)-3(*R*)-isopropylcyclopentene (39). To a solution of **38** (14.1 g, 93 mmol) in ether (200 mL) at −78 °C was added diisobutylaluminum hydride (1 M in hexane, 105 mL, 105 mmol). The mixture was stirred at −78 °C for 2 h before quenching with 10% hydrochloric acid (200 mL), stirred at room temperature for 15 min, and extracted with ether. The combined ethereal extracts were washed with 10% hydrochloric acid and brine prior to drying. Concentration and purification by HPLC (silica gel, elution with 12% ethyl acetate in petroleum ether) gave **38** as a colorless oil (14.4 g, 100%): $[\alpha]^{20}_D$ −16.57° (*c* 9.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 and 4.01 (AB q, *J* = 12 Hz, 2 H), 2.80–2.75 (m, 1 H), 2.35–1.70 (m, 4 H), 1.68 (s, 3 H), 1.60–1.50 (m, 2 H), 0.90 (d, *J* = 6 Hz, 3 H), 0.65 (d, *J* = 6 Hz, 3 H).

(+)-1(*S*)-(Hydroxymethyl)-3(*R*)-isopropyl-1-methyl-2-methylenecyclopentane (40). A solution of **39** (53.92 g, 0.35 mol) in dry tetrahydrofuran (325 mL) was added dropwise to a suspension of potassium hydride (25.6% dispersion in oil, 77.42 g, 1.4 equiv) in the same solvent (900 mL) at 0 °C. Upon completion of the addition, the mixture was stirred at room temperature for 3 h. A solution of (iodomethyl)tri-*n*-butyltin (150.9 g, 0.35 mol) in dry tetrahydrofuran (250 mL) was added to the mixture at 0 °C during 1 h, and stirring was maintained at room temperature for 40 h. Following cooling to −78 °C, *n*-butyllithium (1.6 M in hexanes, 325 mL, 0.52 mol) was added dropwise and stirring was continued at −78 °C for 2 h. Saturated ammonium chloride solution (500 mL) was carefully introduced, and the mixture was left to warm to room temperature overnight, poured into water (1 L), and extracted with ether (3 × 1 L). The combined organic layers were washed with water (1 L) and brine (1 L), dried, filtered, and evaporated. The resulting yellow oil (240 g) was distilled at 51–54 °C (0.25 Torr) to give **40** as a colorless oil (44.2 g, 75%): $[\alpha]^{20}_D$ +63.18° (*c* 4.4, $CHCl_3$); IR (CCl_4, cm^{-1}) 3400, 1650; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.88–4.83 (m, 2 H), 3.42 and 3.31 (AB q, *J* = 10.8 Hz, 2 H), 2.40–2.35 (m, 1 H), 2.00–1.36 (m, 6 H), 0.95 (s, 3 H), 0.94 (d, *J* = 6 Hz, 3 H), 0.75 (d, *J* = 6 Hz, 3 H); MS, *m/z* (M^+) calcd 168.1474, obsd 168.1470. Anal. Calcd for $C_{11}H_{20}C$: C, 78.51; H, 11.98. Found: C, 78.10; H, 11.87.

(+)-2(*R*)-(Hydroxymethyl)-3(*R*)-isopropyl-2-methylcyclopentanone (41a). A mixture of **40** (6.65 g, 39.76 mmol) in methanol (700 mL) was exhaustively ozonolyzed at −78 °C. The solution was flushed with nitrogen for 30 min before addition of dimethyl sulfide (15 mL). The solution was stirred at −78 °C for 2 h and at room temperature overnight. After concentration in vacuo, the residue was taken up in ether (700 mL), and the organic phase was washed with water (2 × 150 mL) and brine (150 mL) prior to drying. Removal of the solvent and purification by HPLC (silica gel; elution with 28% ethyl acetate in petroleum ether) gave **41a** as a colorless oil (4.76 g, 70%): $[\alpha]^{20}_D$ +97.49° (*c* 8.3, $CHCl_3$); IR (CCl_4, cm^{-1}) 3400, 1735; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.62 and 3.40 (AB q, *J* = 8 Hz, 2 H), 2.70–2.55 (m, 1 H), 2.40–1.40 (m, 6 H), 0.99 (d, *J* = 6 Hz, 3 H), 0.85 (s, 3 H), 0.78 (d, *J* = 6 Hz, 3 H); MS, *m/z* (M^+) calcd 170.1307, obsd 170.1308.

2(*R*)-[(*tert*-Butyldimethylsiloxy)methyl]-3(*R*)-isopropyl-2-methylcyclopentanone (41b). Solid *tert*-butyldimethylsilyl chloride (4.64 g, 30.8 mmol) was added to a solution of **41a** (4.76 g, 28.0 mmol) and imidazole (7.53 g, 0.11 mol) in anhydrous dimethylformamide (80 mL). After 16 h at room temperature, the reaction mixture was poured into saturated sodium bicarbonate solution (600 mL) and extracted with ether (4 × 150 mL). The combined organic layers were washed with water and brine, dried, and concentrated. The residual oil (7.77 g) was purified by HPLC (elution with 1% ethyl acetate in petroleum ether) to give 6.75 g (85%) of **41b** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (d, *J* = 9.4 Hz, 1 H), 3.31 (d, *J* = 9.4 Hz, 1 H), 2.16–1.25 (series of m, 6 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.84 (s, 9 H), 0.82 (s, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.01 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 222.2, 67.8, 56.9, 51.2, 30.3, 27.0, 25.9, 21.1, 20.7, 18.7, 18.5, −5.6. Anal. Calcd for $C_{16}H_{32}O_2Si$: C, 67.54; H, 11.34. Found: C, 67.54; H, 11.43.

(−)-3(*S*)-[(*tert*-Butyldimethylsiloxy)methyl]-3-methyl-1-isopropylcyclopentane (35). A solution of **41b** (78.8 g, 0.28 mol) in anhydrous ether (1 L) was cooled to −78 °C, and then Dibal-H (1 M in hexanes, 350 mL, 0.35 mol) was added. After 3 h at −78 °C, the reaction mixture was treated with 1 N hydrochloric acid (750 mL) and allowed to warm to room temperature. Extraction with ether furnished a solution that was washed with 1 N hydrochloric acid and brine prior to drying. Concentration in vacuo gave 78.8 g of diastereomeric alcohols as an oil.

Without further purification, the oil was dissolved in anhydrous pyridine (1 L). Freshly distilled phosphorus oxychloride (55 mL, 0.59 mol) was added, and the resulting mixture was heated at 40–45 °C for 14 h, allowed to cool to room temperature, and poured into ice water (4 L). The resulting mixture was diluted with water (5 L) and extracted with ether (4 × 1 L). The combined ethereal extracts were washed with 1 N hydrochloric acid (4 × 1 L), water (1 L), saturated sodium bicarbonate solution (1 L), and brine (1 L) prior to drying. Concentration in vacuo gave an oil that was purified by column chromatography (silica gel, hexane elution) to give **35** as a colorless oil (55.9 g, 75%): $[\alpha]^{23}_D$ −18.09° (*c* 2.9, $CHCl_3$); the spectra are identical with those reported above for the racemic material.

(−)-4(*S*)-[(*tert*-Butyldimethylsiloxy)methyl]-4-methyl-2-isopropylcyclopentenone (42). A stirred suspension of chromium trioxide (1.50 g, 15.0 mmol) in anhydrous dichloromethane (10 mL) was cooled to −15 °C, and 3,5-dimethylpyrazole (1.44 g, 15.0 mmol) was added in one portion. After 20 min, a solution of (−)-**35** (240 mg, 0.90 mmol) in 1 mL of the same solvent was introduced, and the reaction mixture was stirred at −10 °C for 5 h prior to the addition of 5 N sodium hydroxide solution (7 mL). After 30 min at 0 °C, the mixture was extracted with ether, and the combined organic layers were washed with 10% hydrochloric acid, water, and brine. Drying and solvent evaporation left an oil, which was purified by MPLC (silica gel, elution with 4% ethyl acetate in petroleum ether) to give 123 mg (49%) of **42** as a colorless oil: $[\alpha]^{20}_D$ −35.81° (*c* 3.6, $CHCl_3$); IR (CCl_4, cm^{-1}) 2970, 2960, 2860, 1715, 1470, 1310, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 1 H), 3.46 (d, *J* = 9.5 Hz, 1 H), 3.44 (d, *J* = 9.5 Hz, 1 H), 2.59 (br d, *J* = 6.8 Hz, 1 H), 2.41 (d, *J* = 18.3 Hz, 1 H), 2.07 (d, *J* = 18.3 Hz, 1 H), 1.15 (s, 3 H), 1.08 (d, *J* = 6.8 Hz, 6 H), 0.86 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 160.8, 151.4, 69.6, 46.3, 44.2, 25.8, 25.75, 24.5, 22.8, 21.33, 21.30, 18.2, −5.5, −5.6; MS, *m/z* ($M^+ - C_4H_9$) calcd 225.1310, obsd 225.1283.

(+)-2α-Isopropyl-3β-vinyl-4β-methyl-5β-[(*tert*-butyldimethylsiloxy)-methyl]cyclopentanone (43). Freshly recrystallized copper bromide–dimethyl sulfide complex (0.36 g, 1.75 mmol) was dissolved in anhydrous dimethyl sulfide (5 mL), and the resulting pale yellow solution was cooled to −78 °C. Vinylmagnesium bromide (0.78 M in tetrahydrofuran, 13 mL, 10.3 mmol) was added to the cold suspension, which became dark green. After 15 min, the mixture was diluted with anhydrous tetrahydrofuran (5 mL), and a solution of **42** (0.70 g, 2.48 mmol) in tetrahydrofuran (5 mL) was introduced over a 3-h period. Upon completion of the addition, the mixture was allowed to warm to −25 °C and was stirred an additional hour prior to treatment with saturated ammonium chloride solution. After being stirred overnight at room temperature, the reddish mixture was extracted with ether. The combined extracts were washed with saturated ammonium chloride solution, ammonium hydroxide, and brine prior to drying. Concentration in vacuo afforded an oil that was purified by MPLC (silica gel, elution with 3% ethyl acetate in petroleum ether) to give 383 mg (50%) of pure ketones **43** and **44** in a 77:23 ratio.

For **43**: colorless oil; $[\alpha]^{20}_D$ + 76.81° (*c* 7.8, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2970, 2870, 1735, 1470, 1260, 1100; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.61 (m, 1 H), 5.15–5.04 (m, 2 H), 3.44 (d, *J* = 9.8 Hz, 1 H),

3.26 (d, J = 9.8 Hz, 1 H), 2.92 (dd, J = 9.1, 11.4 Hz, 1 H), 2.50 (d, J = 17.6 Hz, 1 H), 2.18–2.09 (m, 2 H), 1.91 (dd, J = 1.7, 17.5, Hz, 1 H), 0.95 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 7.2 Hz, 3 H), 0.90 (s, 9 H), 0.79 (s, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.3, 138.3, 117.6, 65.7, 56.9, 49.9, 45.8, 42.9, 28.0, 25.9, 19.6, 19.5, 1891, 18.0, -5.7, -5.8; MS, m/z ($M^+ - C_4H_9$) calcd 253.1624, obsd 253.1616. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.44; H, 11.05.

For **44**: colorless oil; $[\alpha]^{20}_D$ -53.42° (c 2.8, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 2980, 2880, 1740, 1470, 1260, 1090; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.86–5.74 (m, 1 H), 5.15–5.04 (m, 2 H), 3.53 (d, J = 9.8 Hz, 1 H), 3.21 (d, J = 9.8 Hz, 1 H), 2.43–1.1 (series of m, 5 H), 0.98 (s, 3 H), 0.91 (d, J = 7.4 Hz, 3 H), 0.88 (d, J = 7.3 Hz, 3 H), 0.85 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 218.3, 138.4, 117.3, 69.0, 58.9, 53.7, 51.4, 42.0, 28.4, 25.7, 22.5, 19.6, 19.5, 18.1, -5.8, -5.9; MS, m/z ($M^+ - C_4H_9$) calcd 253.1624, obsd 253.1625. Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.44; H, 11.05.

Wolff–Kishner Reduction of 43. Ketone **43** (1.18 g, 3.80 mmol) in diethylene glycol (2 mL) was treated with potassium carbonate (0.95 g, 6.87 mmol) and hydrazine hydrate (760 μL, 15.67 mmol). The resulting mixture was slowly heated to 150 °C. After 1 h, the condenser was replaced with a distillation head, and the pot temperature was raised to 190 °C. The distillate was collected over 1 h. After 2.5 h at 190 °C, the mixture was allowed to cool to room temperature and diluted with water. Extraction with ether furnished an organic solution that was washed with 1 N hydrochloric acid and brine. Drying and concentration in vacuo gave 1.32 g of brown oil that was purified by MPLC (silica gel, elution with 8% ethyl acetate in petroleum ether) to give 507 mg (73%) of **45** as a colorless oil: $[\alpha]^{23}_D$ -37.47° (c 0.53, $CHCl_3$); IR ($CDCl_3$, cm^{-1}) 3630, 1450, 1110; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79–5.64 (m, 1 H), 5.07–4.96 (m, 2 H), 3.49–3.34 (m, 2 H), 2.06–1.01 (m, 7 H), 1.03 (s, 1 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.88 (s, 3 H), 0.81 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 115.8, 71.1, 53.7, 49.4, 47.3, 35.2, 29.5, 24.4, 22.0, 19.1, 17.8; MS, m/z ($M^+ - H_2O$) calcd 164.1565, obsd 164.1551. Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.87; H, 12.17.

(-)-1(S)-(Bromomethyl)-1-methyl-2β-vinyl-3α-isopropylcyclopentane (46). A solution of (-)-**45** (0.80 g, 4.4 mmol) and freshly recrystallized triphenylphosphine (3.45 g, 13.2 mmol) in anhydrous tetrahydrofuran (25 mL) was treated with a solution of zinc bromide (0.99 g, 4.4 mmol) in the same solvent (15 mL) followed by a solution of diethyl azodicarboxylate (2.1 mL, 13.3 mmol) in tetrahydrofuran (15 mL). After 15 min, the transparent orange solution became a slurry. The mixture was stirred at room temperature for 16 h and filtered. Concentration in vacuo of the filtrate gave an orange residue that was purified by chromatography on silica gel (hexane elution) to give 0.98 g (91%) of **46** as a colorless oil: $[\alpha]^{23}_D$ -13.98° (c 2.9, $CHCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.61 (ddd, J = 17.1, 10.3, 9.4 Hz, 1 H), 5.05 (dd, J = 10.3, 2.1 Hz, 1 H), 5.00 (dd, J = 17.2, 2.1 Hz, 1 H), 3.38 (d, J = 9.9 Hz, 1 H), 3.34 (d, J = 9.9 Hz, 1 H), 2.13 (dd, J = 9.6, 9.7 Hz, 1 H), 1.89–1.27 (series of m, 6 H), 0.96 (s, 3 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 116.6, 54.9, 48.8, 46.5, 45.8, 37.0, 30.0, 24.2, 21.9, 20.7, 18.0; MS, m/z (M^+ - Br) calcd 165.1643, obsd 165.1685.

Coupling of (-)-46 to (-)-10. The magnesium turnings recovered from a previous coupling were made up to ca. 1 g with fresh turnings in a 15-mL two-necked flask. The whole was reactivated by washing with saturated ammonium chloride solution (10 mL), water (5 × 10 mL), 100% ethanol (5 × 10 mL), and finally anhydrous ether (5 × 10 mL). The flask was fitted with a reflux condenser, septum, and stirrer bar, and the apparatus was dried under high vacuum (<0.05 mmHg) overnight, filled with argon, and evacuated/filled with argon 10 times. Freshly redistilled dry ether (2 mL) was added and brought to reflux while 1,2-dibromoethane (50 μL) was added. When vigorous gas evolution started, a mixture of (-)-**46** (136 mg, 0.56 mmol) and 1,2-dibromoethane (50 μL) in dry ether (1.5 mL) was introduced via syringe pump over 45 min and then washed in with dry ether (2 × 1 mL) over a 15-min period. After 30 min at reflux, the mixture was allowed to cool, and the solution of Grignard was removed from the excess magnesium via syringe and added to a mixture of (-)-**10** (91.0 mg, 0.46 mmol) in dry ether (2 mL) at reflux under argon over 30 min. The magnesium turnings were washed with ether (2 × 1 mL), and the washings were also added. After being heated at the reflux temperature for 16 h, the cooled (0 °C) reaction mixture was quenched with saturated ammonium chloride solution (5 mL) and stirred for 1 h at room temperature. The ether layer was separated, and the aqueous phase was extracted with ether (2 × 20 mL). The combined ether layers were washed with saturated ammonium chloride solution (50 mL) and brine (50 mL), dried, filtered, and evaporated to leave a yellow oil (219.6 mg). Prepurification was achieved via chromatography on silica gel (elution with 5% ethyl acetate in petroleum ether) to leave a pale yellow oil, which was further purified by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether). There was isolated 91.1 mg (53%) of a mixture of **47** and **48** as a colorless oil, which crystallized on cooling. The ratio of **47** to **48** was estimated (^{1}H NMR analysis) as being 74:26: IR ($CDCl_3$, cm^{-1}) 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70–5.55 (m, 1 H), 5.03 (d, J = 10.4 Hz, 1 H), 4.95 (d, J = 16.9 Hz, 1 H), 2.48–1.25 (series of m, 22 H), 1.00 (d, J = 5.6 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H), 0.83 (s, 3 H), 0.80 (d, J = 6.8 Hz, 3 H), 0.79 (s, 3 H); MS, m/z (M^+) calcd 356.3079, obsd 356.3116.

Ozonolysis of the 47/48 Mixture. A 150.3-mg (0.42-mmol) sample of **47/48** was stirred in 1:1 dichloromethane–methanol (15 mL) at -78 °C while ozone was bubbled through the solution until a blue tinge was apparent. The excess ozone was removed with a stream of nitrogen, and glacial acetic acid (2 mL) and zinc dust (100 mg) were added. The mixture was stirred during warming to room temperature, filtered through Celite, and evaporated to leave a white solid. This material was taken up in ether (20 mL) and water (20 mL). The ether layer was separated, washed with saturated sodium bicarbonate solution (2 × 20 mL) and brine (20 mL), dried, filtered, and evaporated to leave a colorless oily solid. This solid was filtered through silica gel with ether elution, and the evaporated residue was purified by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) to give **49** (87.4 mg, 58%) as a white crystalline solid and its isomer **50** (35.4 mg, 23%) as a colorless oily solid.

For **49**: mp 109–111 °C; $[\alpha]^{25}_D$ -87.93° (c 0.69, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1721, 1715; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (d, J = 4.3 Hz, 1 H), 2.6–1.0 (series of m, 22 H), 1.00 (d, J = 6.4 Hz, 3 H), 0.99 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.85 (s, 3 H), 0.82 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 223.56, 206.35, 71.26, 65.75, 58.37, 55.03, 48.03, 45.55, 44.65, 44.14, 43.39, 40.87, 36.13, 35.73, 34.83, 32.57, 31.57, 29.92, 27.50, 21.23, 21.07, 20.29, 19.00, 15.26; MS, m/z (M^+) calcd 358.2872, obsd 358.2906.

For **50**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J = 4.1 Hz, 1 H), 2.6–1.0 (series of m, 22 H), 1.07 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.97 (s, 3 H), 0.87 (d, J = 6.6 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H).

Aldol Cyclization–Dehydration of 49. A solution of **49** (30.0 mg, 0.084 mmol) in dry toluene (1 mL) was added to a suspension of sodium hydride (136.1 mg of 60% in oil, 3.4 mmol, prewashed twice with dry toluene) in dry toluene (1 mL) under argon and washed in with dry toluene (2 × 0.5 mL). The mixture was heated to reflux for 15 h, cooled, and treated dropwise with water (1 mL) at 0 °C. The mixture was stirred at room temperature for 30 min and added to ether (10 mL) and water (10 mL). The ether layer was washed with water (2 × 15 mL) and brine (15 mL), dried, filtered, and evaporated to leave a colorless oil, which began to crystallize on standing. This material was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **51** (23.5 mg, 82%) as a colorless crystalline solid, mp 106–108 °C: $[\alpha]^{26}_D$ -197.17° (c 2.4, cyclohexane); IR (cyclohexane, cm^{-1}) 1708, 1641; ^{1}H NMR (300 MHz, C_6D_6) δ 7.02 (dd, J = 3.7, 3.7 Hz, 1 H), 2.61 (ddd, J = 10.2, 8.4, 4.2 Hz, 1 H), 2.12 (ddd, J = 12.4, 6.0, 3.4 Hz, 1 H), 2.00–1.20 (m, 18 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.85 (d, J = 6.9 Hz, 3 H), 0.83 (d, J = 6.6 Hz, 3 H), 0.76 (s, 3 H), 0.51 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 207.78, 141.99, 135.28, 73.12, 58.54, 53.53, 52.82, 45.25, 45.02, 43.65, 41.47, 39.43, 37.52, 36.55, 34.69, 33.57, 31.32, 31.15, 27.77, 21.60, 20.54, 19.50, 18.19; MS, m/z (M^+) calcd 340.2766, obsd 340.2732. Anal. Calcd for $C_{24}H_{36}O$: C, 84.64; H, 10.66. Found: C, 84.28; H, 10.77.

Hydrogenation of 51. Enone **51** (103.3 mg, 0.30 mmol) was stirred in anhydrous tetrahydrofuran (3 mL) with glacial acetic acid (2 drops) and platinum oxide (5 mg) under hydrogen at 80 psi for 12 h. The mixture was filtered through Celite/silica gel and evaporated to leave a colorless oil (114.0 mg). This material was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **52** (87.7 mg, 84%) as a structure of diastereomers and **53** (16.1 mg, 16%) as a colorless solid.

For **52**: IR ($CHCl_3$, cm^{-1}) 1719; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (m, 1 H), 2.05–1.10 (series of m, 21 H), 1.02 (d, J = 5.9 Hz, 3 H), 0.93 (s, 3 H),0.89 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); MS, m/z (M^+) calcd 342.2922, obsd 342.2922.

For **53**: IR ($CHCl_3$, cm^{-1}) 1681, 1634; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (ddd, J = 17.1, 5.2, 1.9 Hz, 1 H), 2.27 (d,, J = 17.8, 1.5 Hz, 1 H), 2.00–1.20 (series of m, 16 H), 1.04 (s, 3 H), 0.97 (d, J = 5.9 Hz, 3 H), 0.91 (d, J = 6.7 Hz, 3 H), 0.83 (d, J = 6.5 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.74, 177.11, 137.03, 69.80, 59.60, 55.85, 47.25, 46.82, 42.05, 40.64, 38.54, 38.46, 36.64, 33.28, 30.32, 29.72, 29.16, 26.82, 25.09, 22.97, 21.76, 21.52, 18.75, 18.34; MS, m/z (M^+) calcd 340.2766, obsd 340.2763.

Cyanation of 52. Ketones **52** (42.1 mg, 0.12 mmol) were dissolved into trimethylsilyl cyanide (0.4 mL), following which 18-crown-6 (1 mg) and potassium cyanide (1 mg) were added. After a few minutes, the mixture

turned yellow and its was transferred to a teflon tube sealed at one end with a glass rod and washed with trimethylsilyl cyanide (2 × 0.4 mL). The other end of the tube was sealed with a second glass rod such that the minimum of air was trapped. The tube was pressurized at 100 000 psi for 5 days. The mixture was transferred to a flask with ether, and the excess trimethylsilyl cyanide and ether were evaporated under a stream of argon. The residue was dissolved in ether (2 mL), filtered through silica gel, and reevaporated to leave a brown oil. This oil was dissolved in 5% ethyl acetate in petroleum ether, again filtered through silica gel, and evaporated to leave a pale red oil (55.1 mg) free from trimethylsilyl cyanide. Purification of this oil by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) gave a mixture of the trimethylsilyl cyanohydrins as a colorless oil (49 mg, 90%; 97% based on recovered **52**) and some unreacted **52** (3.0 mg, 7%).

A mixture of the cyanohydrins (49.0 mg, 0.11 mmol), pyridine (2.5 mL), DBU (85 μL, 0.57 mmol), and phosphorus oxychloride (85 μL, 0.91 mmol) was heated at reflux overnight. The resulting black mixture was added to 1 M hydrochloric acid (10 mL) and ether (10 mL), and the separated ether layer was washed with water (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL). Drying and solvent evaporation delivered a colorless oil (25.4 mg), which was purified by chromatography on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **54** (14.6 mg, 37%) as a colorless solid: $[\alpha]^{24}_D$ −105.67° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2210; ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (m, 1 H), 2.59 (m, 1 H), 2.29 (m, 1 H), 1.95–1.15 (series of m, 19 H), 1.02 (d, *J* = 6.3 Hz, 3 H), 0.93 (s, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H), 0.70 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.97, 117.10, 115.43, 71.08, 59.35, 54.87, 50.98, 47.71, 45.54, 42.89, 42.36, 41.20, 40.22, 37.58, 36.14, 32.77, 31.06, 30.52, 29.22, 26.20, 21.63, 21.59, 19.39, 19.35, 18.09; GC/MS, *m/z* (M^+) calcd 3518 obsd 351.

Dibal-H Reduction of 54. Dibal-H (100 μL of 1.0 M in hexanes, 0.1 mmol) was added dropwise to a solution of **54** (6.4 mg, 0.02 mmol) in anhydrous ether (1 mL) at −20 °C under argon. The mixture was stirred for 3 h at −20 °C, treated dropwise with saturated ammonium chloride solution (1 mL), and allowed to warm to room temperature. Following dilution with ether (10 mL) and water (10 mL), the ether layer was washed with water (10 mL) and brine (10 mL), dried, filtered through alumina, and evaporated. The resulting yellow oil (8.4 mg) was purified by MPLC on silica gel (elution with 0.5% ethyl acetate in petroleum ether) to give **55** as an unstable yellow oil (1.4 mg, 22%) that was directly ozidized: ^1H NMR (300 MHz, C_6D_6) δ 9.99 (s, 1 H), 2.40–0.75 (series of m, 22 H), 1.22 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 3 H), 0.84 (d, *J* = 5.5 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.58 (s, 3 H); GC/MS, *m/z* (M^+) calcd 354, obsd 354.

Oxidation and Esterification of 55. Methyl 11-Epiretigeranate (56). Unsaturated aldehyde **55** (1.4 mg) was stirred into a solution of sodium chlorite (2.5 mg), monobasic sodium phosphate (2.5 mg), and 2-methyl-2-butene (2 μL) in a 20:1 *tert*-butyl alcohol–water mixture (1 mL) at room temperature. After 30 min, TLC analysis indicated that no aldehyde remained. The solvents were evaporated, and the residue was dissolved in 1 M hydrochloric acid (20 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with brine (50 mL), dried, filtered through silica gel, and evaporated. The yellow oily **2** was dissolved in ether (2 mL) and treated with an excess of diazomethane. The unconsumed diazomethane was removed with a stream of argon, and the reaction mixture was filtered through silica gel and evaporated. The yellow oil was purified by MPLC on silica gel (elution with 0.5% ethyl acetate in petroleum ether) to give somewhat less than 1 mg of **56**: ^1H NMR (300 MHz, C_6D_6) δ 3.72 (s, 3 H), 2.75 (m, 1 H), 2.55 (m, 1 H), 2.30 (m, 1 H), 1.9–1.1 (series of m, 19 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 0.94 (s, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.5 Hz, 3 H), 0.70 (s, 3 H); GC/MS, *m/z* (M^+) calcd 384, obsd 384.

Aldol Cyclization–Dehydration of 50. Keto aldehyde **50** (137.5 mg, 0.38 mmol) was admixed with dry toluene (15 mL), glacial acetic acid (2 drops), piperidine (2 drops), and 4-Å molecular sieves (2 g) and heated to reflux for 2 days. The mixture was filtered through Celite and evaporated. The resulting yellow oil (103.7 mg) was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **57** as a colorless oil (53.5 mg, 41%). Capillary GC analysis showed the oil to be a 79:21 mixture of diastereomers: ^1H NMR of major diastereomer (300 MHz, C_6D_6) δ 6.93 (br s, 1 H), 2.54 (m, 1 H), 2.23 (m, 1 H), 1.95–1.00 (series of m, 18 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 0.92 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.77 (s, 3 H), 0.74 (d, *J* = 6.6 Hz, 3 H); GC/MS, *m/z* (M^+) calcd 340, obsd 340.

Hydrogenation of 57. Enones **57** (46.1 mg, 0.13 mmol) were stirred vigorously in tetrahydrofuran (2 mL) with acetic acid (1 drop) and platinum oxide (5 mg) under hydrogen at 80 psi. After 16 h, the mixture was filtered through Celite and evaporated to leave a colorless oil (55.0 mg), which was purified by MPLC on silica gel (elution with 1.5% ethyl acetate in petroleum ether) to give a 58:17:5:20 mixture of isomeric ketones **58** (capillary GC analysis) as a colorless oil (399 mg, 86%): ^1H NMR of major diastereomer (300 MHz, $CDCl_3$) δ 2.68 (m, 1 H), 2.25–1.00 (series of m, 22 H), 1.16 (s, 3 H), 1.04 (d, *J* = 6.1 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.73 (s, 3 H); GC/MS, *m/z* (M^+) calcd 342, obsd 342.

Cyanation of 58. The ketones **58** (39.9 mg, 0.12 mmol) were treated exactly as described above for **52**. The same workup and MPLC purification provided the silylated cyanohydrins (47.3 mg, 92%) and unreacted **58** (1.7 mg, 4%).

The silylated cyanohydrins (47.3 mg, 0.11 mmol) were stirred in a mixture of pyridine (3 mL), DBU (85 μL, 0.57 mmol), and phosphorus oxychloride (85 μL, 0.91 mmol) at reflux overnight. The black mixture was poured into 1 M hydrochloric acid (10 mL) and ether (10 mL). The separated ether layer was washed with water (10 mL), saturated sodium bicarbonate solution (10 mL), and brine (10 mL) prior to drying, filtration, and evaporation. The resulting colorless oil was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **64** as a colorless oil, which solidified on cooling (11.6 mg, 31%). Capillary GC indicated the ratio of diastereomers to be 71:29: ^1H NMR of major diastereomer (300 MHz, C_6D_6) δ 2.55 (m, 2 H), 1.95–1.05 (series of m, 20 H), 0.92 (d, *J* = 5.9 Hz, 3 H), 0.80 (d, *J* = 9.8 Hz, 3 H), 0.78 (s, 3 H), 0.73 (s, 3 H), 0.70 (d, *J* = 6.6 Hz, 3 H); GC/MS, *m/z* (M^+) calcd 351, obsd 351.

Dibal-H Reduction and Oxidation of 59. A cold (0 °C), magnetically stirred solution of **59** (10.6 mg, 0.03 mmol) in anhydrous ether (1 mL) under argon was treated dropwise with Dibal-H (100 μL of 1.0 M in hexane, 0.1 mmol). After 1 h at 0 °C, saturated sodium potassium tartrate solution (1 mL) was added over 10 min, and the mixture was allowed to warm to room temperature with vigorous stirring. The mixture was partitioned between saturated sodium potassium tartrate solution (10 mL) and ether (10 mL), and the separated ether layer was washed with brine (10 mL), dried, filtered through basic alumina, and evaporated. The remaining yellow oil was stirred in a solution of sodium chlorite (2.5 mg), monobasic sodium phosphate (2.5 mg), and 2-methyl-2-butene (2 μL) in 20:1 *tert*-butyl alcohol–water for 40 min at 23 °C. The solvents were evaporated and the residue was partitioned between ether (10 mL) and 1 M hydrochloric acid (10 mL). The ether layer was washed with brine (10 mL), dried, filtered through silica gel, and evaporated. Column chromatography on silica gel of the yellow oil (elution with 2% then 10% ethyl acetate in petroleum ether) gave the unsaturated aldehyde **60** as a pale yellow oil (5.0 mg, 47%) and the unsaturated acids **1/3** as a pale yellow oil (1.4 mg, 13%). Capillary GC showed **60** to be an 81:19 mixture of diastereomers: ^1H NMR for the major diastereomer of **60** (300 MHz, C_6D_6) δ 10.08 (s, 1 H), 3.01 (dd, *J* = 4.8, 3.7 Hz, 1 H), 2.57 (dd, *J* = 12.7, 4.8, 1.1 Hz, 1 H), 2.40 (m, 1 H), 2.25–1.0 (series of m, 19 H), 1.18 (d, *J* = 6.6 Hz, 3 H), 0.84 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.73 (d, *J* = 6.6 Hz, 3 H), 0.70 (s, 3 H).

Oxidation of 60. The epimeric aldehydes **60** (5.0 mg, 0.01 mmol) were stirred into a solution of sodium chlorite (2.5 mg), monobasic sodium phosphate (2.5 mg), and 2-methyl-2-butene (2 μL) in 20:1 *tert*-butyl alcohol–water (1 mL). Further portions of sodium chlorite (10 mg) and monobasic sodium phosphate (10 mg) in water (100 μL) were added at 30-min intervals until TLC analysis indicated that no aldehyde remained. The solvents were evaporated, and the residue was dissolved in 1 M hydrochloric acid (20 mL) and extracted with ether (3 × 20 mL). The combined ethereal extracts were washed with brine (50 mL), dried, filtered through silica gel, and evaporated. The resulting yellow oil (15.2 mg) was purified by column chromatography on silica gel (elution with 5% and then 10% ethyl acetate in petroleum ether) to give **1/3** as a colorless oil (4.8 mg, 92%): ^1H NMR for the major idastereomer (300 MHz, $CDCl_3$) δ 3.33 (dd, *J* = 14.7, 6.3 Hz, 1 H), 2.61 (dd, *J* = 12.3, 5.3 Hz, 1 H), 2.12 (dd, *J* = 7.7, 7.6 Hz, 1 H), 1.90–1.00 (series of m, 19 H), 1.00 (d, *J* = 6.4 Hz, 3 H), 0.91 (s, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.86 (s, 3 H), 0.82 (d, *J* = 6.8 Hz, 3 H).

Methyl Retigeranate A (61) and Methyl 5-Epiretigeranate (62). Unsaturated acids **1/3** (4.8 mg, 0.01 mmol) in ether (2 mL) were treated with an excess of diazomethane. The excess diazomethane was removed with a stream of argon, and the solution was filtered through silica gel and evaporated. The remaining colorless oil (4.9 mg) was purified by MPLC on silica gel (elution with 0.5% ethyl acetate in petroleum ether) to give a mixture of the diastereomeric esters **61** and **62** as a colorless oil. The oil was separated into its components by reverse-phase HPLC (elution with methanol) to provide **61** (1.4 mg, 28%) and **62** (3.5 mg, 69%). The first ester was a colorless solid.

For **61**: $[\alpha]^{23}_D$ −36.3° (*c* 0.155, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 3.24 (dd, *J* = 15.9, 4.0 Hz, 1 H), 2.48 (dd, *J* = 11.38, 5.3 Hz, 1 H), 2.29 (ddd, *J* = 8.5, 6.8, 6.8 Hz, 1 H), 1.90–0.95 (series of m, 19 H), 1.02 (s, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.92 (d,

J = 6.7 Hz, 3 H), 0.86 (s, 3 H), 0.82 (d, J = 6.6 Hz, 3 H); GC/MS, m/z (M^+) calcd 384, obsd 384.

For **62**: $[\alpha]^{23}_D$ −14.67° (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (s, 3 H), 3.16 (dd, J = 14.5, 3.7 Hz, 1 H), 2.58 (dd, J = 12.8, 5.8 Hz, 1 H) 2.10 (dd, J = 7.5, 6.5 Hz, 1 H), 1.80–0.96 (series of m, 19 H), 1.00 (d, J = 6.1 Hz, 3 H), 0.92 (d, J = 6.8 Hz, 3 H), 0.90 (s, 3 H), 0.84 (s, 3 H), 0.82 (d, J = 6.8 Hz, 3 H); GC/MS, m/z (M^+) calcd 384, obsd 384.

Desaturation of 52. A solution of **52** (24.1 mg, 0.07 mmol) in a mixture of dichloromethane (4 mL), triflic anhydride (65 μL, 0.39 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (137.5 mg, 0.67 mmol) was heated overnight at the reflux temperature. After cooling, the reaction mixture was evaporated under a stream of argon and the residue was partitioned between 1 M hydrochloric acid (10 mL) and ether (10 mL). The ether layer was washed with water (10 mL) and brine (10 mL), filtered through silica gel, and evaporated to leave a yellow oil (38.9 mg). Capillary GC analysis revealed the mixture to consist of **53** (67%) and **51** (15%). The mixture was best not purified at this point but carried on directly to the next transformation.

Dissolving Metal Reduction of the 51/53 Mixture. A sample of unpurified **51/53** mixture (prepared from 8.6 mg of **52**) was dissolved in *tert*-butyl alcohol (210 μL of 0.14 M in tetrahydrofuran) and diluted with tetrahydrofuran (790 μL). This solution was added to lithium (23.4 mg) in ammonia (3 mL) at −78 °C under argon and washed in with additional tetrahydrofuran (2 × 0.5 mL). The mixture was allowed to reflux for 1 h, recooled to −78 °C, and treated with solid ammonium chloride (200 mg). The ammonia was allowed to evaporate, and the residue was partitionted between water (10 mL) and ether (10 mL). The ether layer was washed with water (10 mL) and brine (10 mL), dried, filtered through silica gel, and evaporated. The remaining colorless solid (16.1 mg) was purified by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) to give **63** as a colorless solid (7.9 mg, 91% from 52), mp 103–105 °C: IR ($CHCl_3$, cm^{-1}) 3615, 1590; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (d, J = 10.4 Hz, 1 H), 2.10–1.05 (series of m, 24 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.87 (s, 3 H), 0.81 (s, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 87.90, 65.95, 53.50, 52.45, 46.39, 45.12, 43.90, 42.88, 41.99, 40.72, 40.38, 40.17, 36.81, 35.66, 35.23, 31.27, 29.86, 25.18, 24.27, 23.09, 21.96, 20.58, 19.53, 18.28; GC/MS, m/z (M^+) calcd 344, obsd 344.

Jones Oxidation of 63. Alcohol **63** (7.9 mg) in acetone (1 mL) was stirred in 2 mL of Jones reagent (prepared from 27 g of chromium trioxide dissolved in 23 mL of sulfuric acid and diluted to 100 mL total volume with water) at room temperature for 1 h. Isopropyl alcohol (1 mL) was added, and after 5 min the solvent were evaporated. The residue was partitioned between ether (20 mL) and water (20 mL), and the ether layer was washed with water (20 mL) and brine (20 mL), dried, filtered through silica gel, and evaporated. The resulting oil (11.2 mg) was purified by MPLC on silica gel (elution with 1.5% ethyl acetate in petroleum ether) to give **53** as a colorless solid (4.7 mg, 60%), identical in all respects with the material described earlier.

Swern Oxidation of 63. Dimethyl sulfoxide (29 μL, 0.4 mmol) in dichloromethane (0.5 mL) was added over 5 min to oxalyl chloride (18 μL, 0.2 mmol) in the same solvent (1 mL) at −60 °C under argon. After 10 min of stirring at −60 °C, **63** (7.0 mg, 0.02 mmol) in dichloromethane (0.5 mL) was added over 5 min at −60 °C, and the mixture was stirred for 15 min. Diisopropylethylamine (139 μL, 0.8 mmol) was introduced over 5 min at −60 °C, and the mixture was allowed to warm to room temperature, diluted with ether (20 mL), washed with water (10 mL) and brine (15 mL), dried, and filtered through silica gel. Solvent evaporation left a yellow oil (9.3 mg), which was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **52a** as a white solid (6.4 mg, 92%), mp 84–86 °C: IR ($CHCl_3$, cm^{-1}) 1722; ^1H NMR (300 MHz, $CDCl_3$) δ 2.94 (ddd, J = 10.8, 8.1, 4.6 Hz, 1 H), 2.22 (ddd, J = 10.5, 10.5, 6.5 Hz, 1 H), 2.01–1.10 (m, 2 H), 1.01 (s, 3 H), 0.98 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.82 (d, J = 6.8 Hz, 3 H), 0.59 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 225.33, 68.02, 63.20, 51.72, 45.69, 45.49, 45.10, 43.66, 41.50, 40.83, 40.36, 39.67, 37.76, 36.29, 31.92, 30.55, 29.93, 24.28, 22.94, 21.91, 20.96, 20.34, 19.19, 18.37; GC/MS, m/z (M^+) calcd 342, obsd 342.

Aprotic Dissolving Metal Reduction of the 51/53 Mixture. A solution of the unpurified enones **51/53** (19.5 mg) in tetrahydrofuran (1 mL) was added dropwise to lithium (20.2 mg) in ammonia (2 mL) at −78 °C under argon and the mixture was stirred for 1 h. Isoprene (100 μL) was added dropwise at −78 °C to disperse the blue coloration followed by solid ammonium chloride (200 mg). After the mixture had warmed to room temperature and the ammonia had evaporated, water (10 mL) and ether (10 mL) were added and the mixture was stirred. The aqueous phase was discarded, and the ether layer was washed with water (10 mL) and brine (10 mL), dried, and filtered through silica gel. Solvent evaporation furnished a yellow oil, which was stirred in acetone (1 mL) with 1 M hydrochloric acid (5 drops) for 1 h and evaporated under high vacuum. The residual yellow oil (23.2 mg) was purified by MPLC on silica gel (elution with 1% ethyl acetate in petroleum ether) to give **52b** as a colorless solid (10.8 mg, 89%), mp 74–76 °C: IR ($CHCl_3$, cm^{-1}) 1719; ^1H NMR (300 MHz, $CDCl_3$) δ 2.50 (m, 1 H), 2.05–1.10 (series of m, 21 H), 1.02 (d, J = 5.9 Hz, 3 H), 0.93 (s, 3 H), 0.89 (s, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 224.02, 72.01, 59.27, 49.71, 47.36, 46.26, 44.46, 43.08, 42.92, 40.89, 39.77, 36.85, 36.64, 34.98, 32.84, 30.24, 28.41, 25.59, 24.12, 23.78, 21.86, 18.81, 18.73, 16.60; MS, m/z (M^+) calcd 342.2922, obsd 342.2922.

Acknowledgment. It is a pleasure to acknowledge the financial support of this investigation by the National Institutes of Health through Grant No. GM-28468. In addition, we thank Marc-André Poupart, George Maynard, and Richard Harper for the energy minimization calculations, and Professors E. J. Corey and S. Shibata for copies of relevant ^1H and ^{13}C NMR spectra.

Supplementary Material Available: Energy minimized conformations of **10**, **56**, and **61**, Eu(fod)$_3$ shift study of **36**, and crystallographic details for **47** (6 pages); observed and calculated structure factors for **47** (6 pages). Ordering information is given on any current masthead page.