Studies Directed toward the Total Synthesis of Cerorubenic Acid-III. 1. Expedient Construction of the Tetracyclic Core by Oxyanionic Sigmatropy

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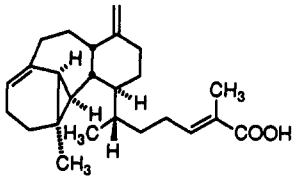
A synthesis of the ABCD ring framework of cerorubenic acid-III is described. Diketone **5** was first prepared by intramolecular oxidative coupling of the dienolate **10** and then suitably desymmetrized to deliver **15b**. Anionic oxy-Cope rearrangement of this intermediate resulted in construction of **18**, a ketone not only having all three contiguous stereogenic centers properly established but also equipped with adequate functionality for the further elaboration of ring D. In the present effort, this thrust took the form of homologation to **21**, conversion to the activated diene **22**, and Diels–Alder cycloaddition to methyl acrylate at high pressure. Once it became obvious that first-formed ketone **26** greatly preferred adoption of trans stereochemistry at the ring juncture, attempts to skirt this issue were made by preparing both **29** and **32**. However, these advanced intermediates proved unresponsive to conjugate reduction, and attention was therefore redirected to alternative possible means for elaboration of the eastern sector.

In the late 1940's, Yasumatsu and Tachikawa not only identified the presence in Kyushu of the encyrtid wasp *Anicetus beneficus* but recognized a direct relationship between its distribution and that of the scale insect *Ceroplastes rubens* Maskell.[2] In fact, the release of *A. beneficus* in orchards densely populated with *C. rubens* proved to control the scale insect remarkably well.[3] Ensuing entomological studies by Ohgushi[4] and by Noda et al.[5] established the existence of an especially high specificity between the two species, with *C. rubens* serving as the natural host. Further, this parasitic behavior manifests itself in appropriate control of the ovipositional behavior and host feeding traits peculiar to *A. beneficus*.

More recently, Naya's group in Osaka succeeded in isolating five most unusual sesterterpenes from the secretions of *C. rubens*.[6] All have been shown by Takahashi to act as the kairomones responsible for the contact chemoreception and distinctive recognition behavior.[7] A principal component of the secretion, cerorubenic acid-III (**1**), is the first natural substance recognized to possess



1

a tetracyclo[8.4.1.0.0]pentadecane framework. The novel molecular architecture of **1** easily qualifies it as the structurally most complex substance currently recognized to play an important role in insect communication. For this reason and because cerorubenic acid-III and closely related analogues appear worthy of broad pharmacological evaluation, we have undertaken studies directed toward their *de novo* synthesis.

Results and Discussion

Development of a Synthetic Plan. One of the more provocative features of **1** is the vinylcyclopropane subunit so intricately positioned within its ABC ring network that the associated double bond occupies a bridgehead site. In a retrosynthetic sense, one might consider attempting to establish such a bond connectivity first (see **2**, Scheme I), with a view to annealing ring D and the carboxyl-substituted side chain later in the synthesis. While this option is not without important stereochemical nuances,[8,9] it does hold considerable attraction because the very rapid assembly of ketone **2** in a *single* step by anionic oxy-Cope rearrangement[10] of **3** was considered to be eminently feasible. This concise stratagem rested, of course, on the ready availability of dienol **3**. In the addition of vinylmagnesium bromide to **4** were appropriately stereoselective, the requirements would be reduced to a direct synthesis of 2-methyltricyclo[3.2.1.0^{2,7}]octane-6,8-dione (**5**).[11] The C_s symmetry of this β-diketone could well lend itself to monoolefination without concern for the regioselectivity of the Wittig (or equivalent) process since the two carbonyl groups are related by the intrinsic mirror plane. Herein we describe the pursuit of this tactical concept which was actually arrived at by prosynthetic logic.[12]

(1) NSERCC Postdoctoral Fellow, 1985–1987.
(2) Yasumatsu, K.; Tachikawa, T. *J. Fac. Agri., Kyushu Univ.* **1949**, *9*, 99.
(3) Ishii, T.; Yasumatsu, K. *Mushi* (Fukuoka) **1954**, *27*, 69.
(4) (a) Ohgushi, R. *Mem. Coll. Sci. Univ. Kyoto (B)* **1956**, *23*, 55. (b) Ohgushi, R. *Mem. Coll. Sci. Univ. Kyoto (B)* **1958**, *25*, 31.
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(10) (a) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 609. (b) Paquette, L. A. *Synlett* **1990**, 67.
(11) Poupart, M.-A.; Lassalle, G.; Paquette, L. A. *Org. Synth.* **1990**, *69*, 173.
(12) Preliminary communications: (a) Paquette, L. A.; Poupart, M.-A. *Tetrahedron Lett.* **1988**, *29*, 269. (b) Poupart, M.-A.; Paquette, L. A. *Tetrahedron Lett.* **1988**, *29*, 273.

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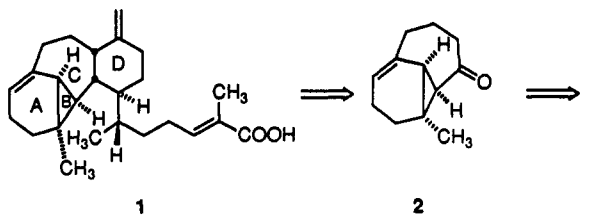
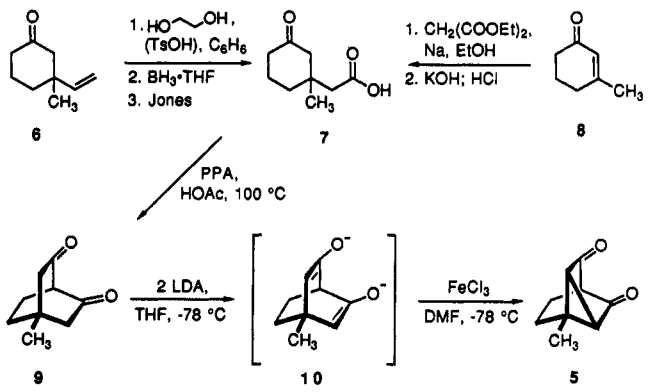
Scheme I



Scheme II



Synthesis and Desymmetrization of 2-Methyltricyclo[3.2.1.0^{2,7}]octane-6,8-dione. Although the $TiCl_4$-catalyzed 1,4-addition of allyltrimethylsilane to α,β-unsaturated ketones can be applied to many systems,[13] 3-methylcyclohexenone proved to be very sluggish in its reactivity toward this reagent combination. Alternate recourse to the use of a vinyl magnesiocuprate[14] did, however, provide **6** readily (Scheme II). When the latter was converted to its ethylene ketal, hydroborated, and oxidized with Jones reagent, keto acid **7** was produced in 64% overall yield. Since larger quantities of **7** were ultimately to be required, we came to favor the less cumbersome route wherein diethyl malonate is added in conjugate fashion to **8**[15] and the Michael adduct is subsequently saponified and decarboxylated.[11,16]

The acid-catalyzed cyclization of **7** to **9** was adapted from earlier studies aimed at producing the parent system[17] and more highly substituted analogues.[18] Installation of the cyclopropane ring in **9** was realized by intramolecular oxidative coupling.[19] For stereoelectronic reasons, the bridgehead α-carbonyl proton in **9** is nonenolizable. As a consequence, the dienolate **10** can be generated directly at −78 °C in THF and added *inversely* to a solution of anhydrous $FeCl_3$ in DMF at the same temperature. Although three-membered rings have not heretofore been constructed in this manner, the associated strain energy did not surface as a deterrent and **5** could reproducibly be obtained in 46–55% yield. Other oxidants such as $CuCl_2$[20,21] and $Cu(OTf)_2$[22] were found to accomplish this enolate coupling, although somewhat less effectively. The plane-symmetric nature of **5** is evident from its simplified high-field ^1H (four sets of signals) and ^{13}C (seven lines) NMR spectra.

Following the successful acquisition of **5**, attention was directed to those structural changes that accompany introduction of the cyclopropane bond. There was no doubt that the two conjoined carbon atoms are brought into substantially closer proximity. However, the carbonyl groups do not follow suit. Rather, as MODEL calculations[23] reveal (Figure 1), the pair of sp^2-hybridized centers in **5** are outwardly splayed to a degree considerably more exaggerated than in **9**. The advantages of this change in geometry are obvious. In particular, **5** should exhibit a significantly greater propensity for nucleophilic capture from that direction illustrated by the arrows.

The capacity of **5** for stereoselective 1,2-addition was initially probed by condensation with a modest excess of vinylmagnesium bromide in THF at −78 °C. Although a single alcohol was produced, its identity as **11** was not immediately established. Instead, **11** was directly subjected to Wittig olefination at rt (Scheme III). When the resulting carbinol exhibited no tendency to undergo anionic oxy-Cope rearrangement, the strong likelihood that the product of this two-step sequence was in fact **13b** could not be skirted. Although this result did occasion consternation, the computational model had not failed us.[24] Rather, **11** was soon recognized to lend itself notably well to rapid retro aldol cleavage (as in **12**) and reclosure in the opposite sense (see **13a**) when exposed to the basic medium containing the methylenetriphenylphosphorane reagent.[25]

This conclusion was substantiated in two ways. In the first, **11** was acetylated to provide **14**, subsequent olefination of which gave **15a** without comparable stereochemical inversion. When saponified, **15a** provided **15b** in which the two double bonds are now proximal. Alternatively, **16** was prepared by sequential reaction of **5** with (methoxymethylene)triphenylphosphorane[25] and then vinylmagnesium bromide. When photooxygenated,[26] this tertiary allylic alcohol also gave **11**.

The earlier complication was best avoided simply by reversing the original two steps. Once **17** was in hand, the

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(16) We thank Dr. Gilbert Lassalle for performing the conversion of **8** to **7**.

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(24) Comparable addition of vinylmagnesium bromide to **9** is nonstereoslective (2.6:1 *syn/anti*), although predominantly in the same direction. Compare: Martin, S. F.; White, J. B.; Wagner, R. *J. Org. Chem.* **1982**, *47*, 3192.

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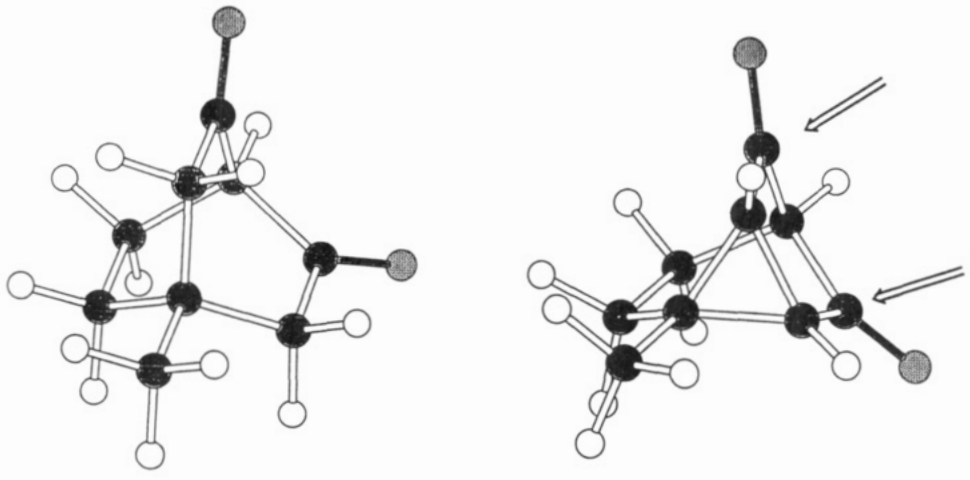
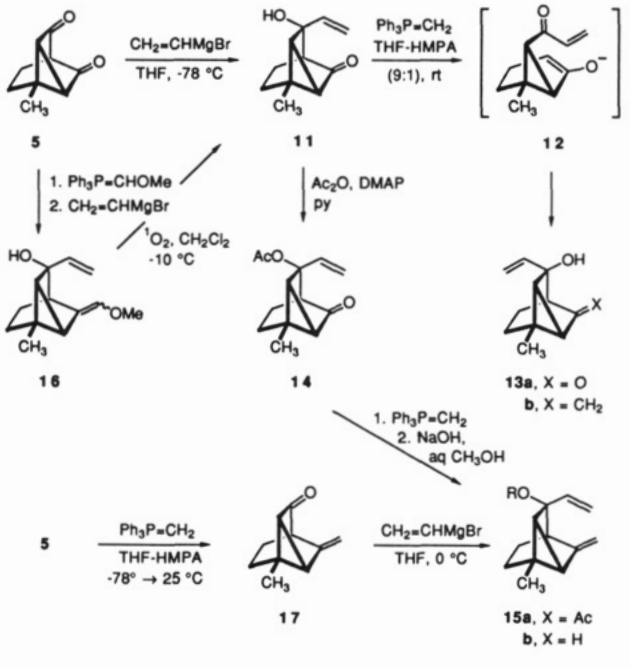
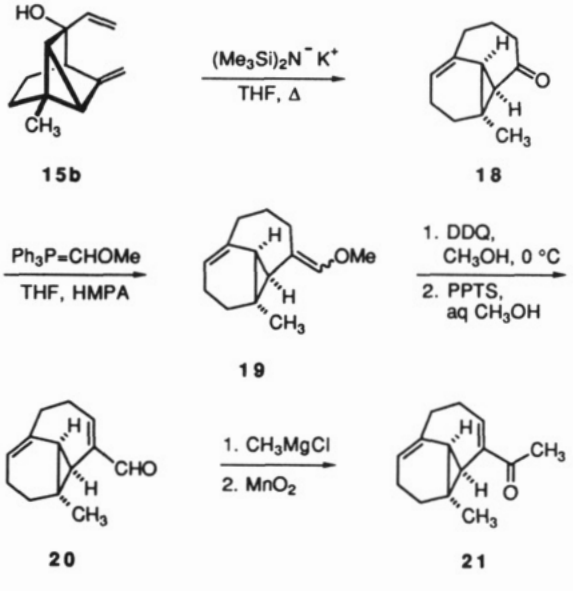


Figure 1. Global minimal energy conformations of **9** (left) and **5** (right) as determined by molecular mechanics calculations (Chem 3-D output).

Scheme III



Scheme IV



required transformation to **15b** was cleanly stereoselective and efficient.

Oxy-Cope Rearrangement and Functionalization of the Resulting Ketone. [3.3]Sigmatropic isomerization within **15b** was accomplished with potassium hexamethyldisilazide in refluxing THF. 18-Crown-6 was not a necessary additive to accelerate matters. After 20 h of heating, the colorless oily ketone **18** was obtained in 88% yield (Scheme IV). Decoupling studies at 300 MHz of the ^{1}H NMR spectrum of **18** clearly revealed that the three contiguous stereogenic centers located in the western sector of **1** had been properly established in a single step. The substitution plan about the three-membered ring serves to impart a reasonably buckled topography to **18**. The appearance of its infrared carbonyl absorption at 1680 cm^{-1} (in CH_2Cl_2) signals the likelihood of conjugation through the cyclopropane ring to the bridgehead double bond. As will be seen,[8,9,27] this most unusual structural feature impacts profoundly on the reactivity of these systems. One overriding consideration, for example, was the need to avoid exposure to strongly acidic reagents. A brief series of probe experiments indicated that pyridinium *p*-toluenesulfonate (PPTS) approached the maximum acidity that could be tolerated without the onset of extensive decomposition.

Armed with this information, we turned our attention to the annulation of ring D. Initially, it was intended to adopt the Traas modification[28] of the Shapiro reaction. However, exposure of **18** to tosylhydrazine under various conditions produced only multicomponent product mixtures. Once phosphorus ylides were discovered to react well with **18**, conversion to vinyl ether **19** was successfully undertaken by this means. Although attempts to transform **19** into α,β-unsaturated aldehyde **20** by tandem phenylselenenylation–oxidative elimination[29] were to no avail, the action of DDQ in methanol at 0 °C[30] proceeded satisfactorily. If the reaction mixture was first stirred briefly with PPTS in 9:1 methanol–water in order to

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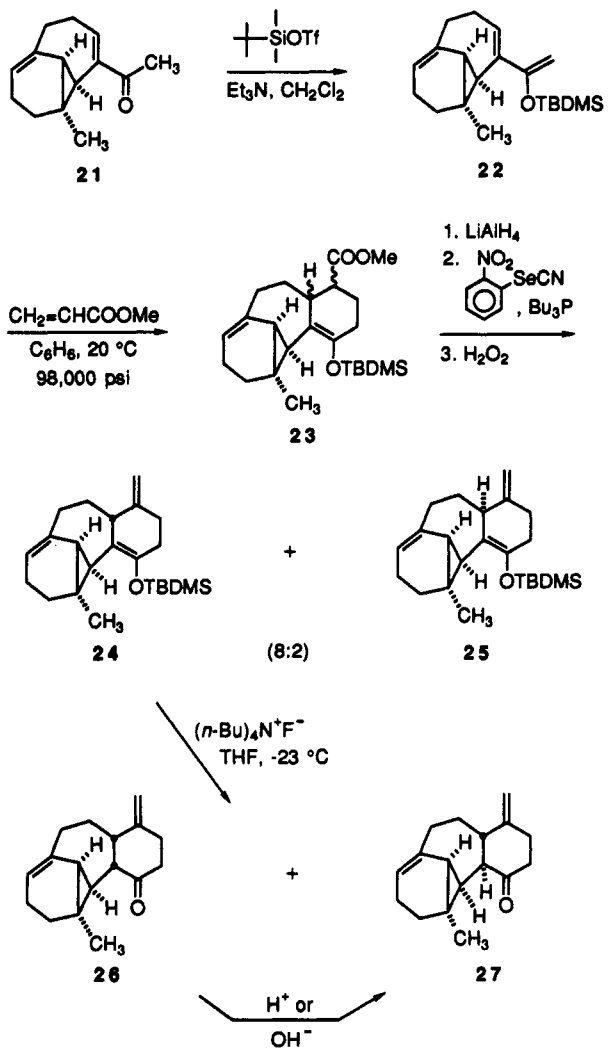
Scheme V



hydrolyze any dimethyl acetal that had formed, a 50% yield of **20** could be realized. The modest efficiency arises from the fact that one isomer of **19**, believed to carry its OMe syn to the cyclopropane ring,[31] is unreactive to these conditions and is recovered (39%).

The one-carbon homologation found most serviceable in providing methyl ketone **21** involved the 1,2-addition of methylmagnesium bromide followed by oxidation with manganese dioxide.[32] Quite unexpectedly, both **20** and **21** proved to be strikingly poor Michael acceptors. For example, **21** was recovered intact following exposure to a functionalized vinyl copper reagent [LiC(=CH_2)CH_2OTBDMS, CuBr·SMe_2],[33] lithium divinylcuprate, and sodium phenylselenide. At the extreme, recourse to lithium dimethylcuprate, the simplest and least bulky reagent of this class, delivered the conjugate addition product in a maximum yield of 18% and only when Me_3SiCl[34] was present (THF, −45 °C).

Elaboration of the Tetracyclic Core. A more profitable thrust began by transforming **21** into its *tert*-butyldimethylsilyl enol ether **22** (Scheme V). The conjugated diene unit in this intermediate lends itself well to Diels–Alder cycloaddition with methyl acrylate in a high-pressure reactor (98 000 psi) at 20 °C. It was anticipated that electronic factors would guide the regioselectivity of this reaction, and indeed an 8:2 stereoisomeric mixture of tetracyclic esters **23**, each fraction of which consisted of two epimers, was obtained in 68% yield. As a direct consequence of the steric congestion resident on the "inner" face of the cycloheptenyl double bond in **22**, π-facial selectivity was expected to be kinetically biased in the exo direction. That the dienophile had indeed approached preferentially from the exterior of the molecular fold was established following transformation of the ester functionality into an exocyclic double bond.[35] This series of reactions provided a chromatographically separable mixture of **24** to **25** (ratio 8:2). Subsequent treatment of the major silyl enol ether with tetra-*n*-butylammonium fluoride in anhydrous THF at rt unmasked the carbonyl group. These conditions gave rise to a 7:3 mixture of **26** and the corresponding trans isomer **27**. The greater thermodynamic stability of the latter substance was ascertained by stirring **26** in acetonitrile containing silica gel or, more simply, by allowing the ketone to stand in chloroform or methanol at rt [$t_{1/2}$ (MeOH) = 260 min]. The trans stereochemical assignment to **27** was conclusively established by a combination of difference NOE and 2-D COSY NMR experiments.

In light of the above scenario, it was now clear that elaboration of the western sector by any pathway that would position an enolizable group immediately adjacent to ring C would not maintain the integrity of the requisite cis C/D stereorelationship. Therefore, the challenge became one of developing an alternative means for incorporating the carboxylic acid side chain while simultaneously preserving this central structural feature. One might consider attempts to introduce the lower ring juncture hydrogen by conjugate addition of reductive means. One aspect of this formalism was probed by reacting **27** with trimethylsilyl cyanide and a catalytic amount of 18-crown-6 at high pressure.[36] The resultant mixture of silylated cyanohydrins (94%) was refluxed with phosphorus oxychloride and DBU in pyridine[37] for 5 h in order to achieve elimination (Scheme VI). Overlooking for the moment the fact that **29** was not the major regioisomer formed, this α,β-unsaturated nitrile was treated in turn with magnesium in methanol[38] and with copper hydride.[39] In neither instance was reduction of the conjugated double bond observed. This lack of reactivity prompted the conversion of **29** via aldehyde **31** to the acetyl derivative **32**. When **32** likewise proved unresponsive to the same reducing agents, attention was redirected to intramolecular processes in an attempt to maximize convergency and gain better reaction control in this region of the tetracyclic framework.[8,9]

(31) This hypothesis is based on the working premise that the sterically less congested anti isomer is initially produced in larger amounts.

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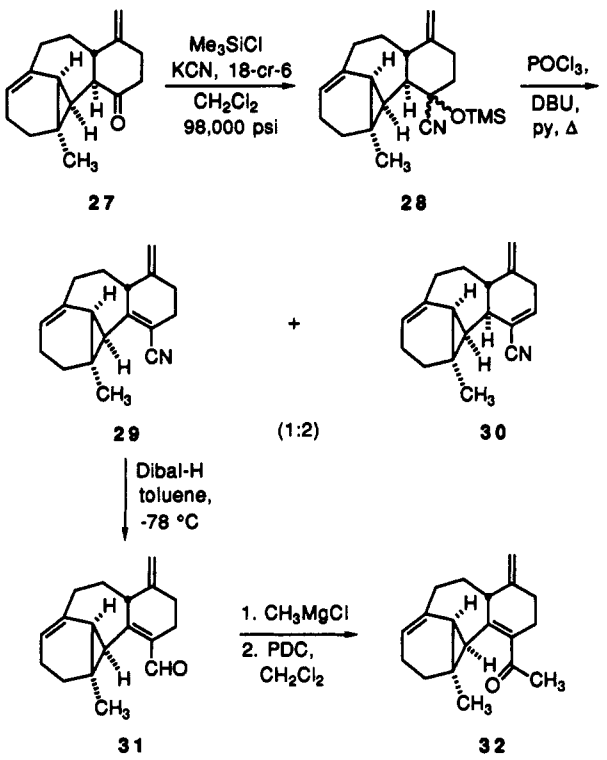
Scheme VI



Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 or 20 MHz. Mass spectra were reocrded on a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The chromatographic separations were carried out either under flash conditions on Fluka silica gel H or gravimetrically on Woelm silica gel 63-200. The organic extracts were dried over magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

3-Methyl-3-vinylcyclohexanone (6). To a mechanically stirred suspension of magnesium turnings (14.58 g, 600 mmol) in dry THF (1.1 L) containing a small crystal of iodine was added a few mL of a solution of vinyl bromide (70.6 g, 660 mmol) in dry THF (100 mL). The reaction mixture was heated until the yellow color of iodine had dissipated, at which point the remaining vinyl bromide solution was added dropwise at such a rate as to maintain gentle reflux. Upon completion of the addition, the mixture was stirred for 2 h while it cooled to rt. The resulting pink solution was cooled to −5 °C, and purified cuprous iodide (60.00 g, 315 mmol) was added in one portion. The jet-black solution was stirred for 3 min at this temperature, rapidly cooled to −78 °C, and treated sequentially with chlorotrimethylsilane (40.0 mL, 315 mmol) and with 3-methylcyclohexenone (31.0 mL, 273 mmol) dissolved in dry THF (50 mL) at such a rate as to maintain the temperature below −70 °C. After 30 min, methanol (20 mL) was added rapidly followed by 25% sulfuric acid in water (65 mL). The reaction mixture was allowed to warm to rt during 2 h, filtered through Celite, evaporated under reduced pressure, and diluted with ether (600 mL) and water (200 mL). After a second filtration, the separated organic layer was washed with water (4 × 100 mL), dried, and evaporated. Distillation of the residue afforded 26.61 g (71%) of **6** as a colorless liquid: bp 55 °C/0.5 Torr; IR (neat, cm^{-1}) 3080, 1710, 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (q, J = 10.8 Hz, 1 H), 4.99–4.90 (m, 2 H), 2.45–2.12 (m, 4 H), 1.86–1.77 (m, 2 H), 1.70–1.56 (m, 2 H), 1.03 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 211.1, 145.8, 112.7, 51.7, 41.5, 40.8, 36.5, 27.2, 22.1; MS m/z (M^+) calcd 138.1045, obsd 138.1050.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.27; H, 10.16.

Ethylenedioxy Ketal of 6. A solution containing **6** (53.2 g, 385 mmol), ethylene glycol (64.5 mL, 1.16 mol), p-toluenesulfonic acid (7.3 g, 38.5 mmol), and benzene (600 mL) was refluxed for 3 h under a Dean-Stark trap with azeotropic separation of water. The cooled reaction mixture was washed with saturated $NaHCO_3$ solution (4 × 50 mL), dried, and evaporated. Distillation of the residue afforded the ketal (66.8 g, 95%) as a colorless liquid, bp 65 °C/1.1 Torr; IR (neat, cm^{-1}) 3080, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (q, J = 10.8 Hz, 1 H), 4.94–4.86 (m, 2 H), 3.91 (ABq, J_{AB} = 1.6 Hz, $\Delta\nu$ = 1.8 Hz, 4 H), 1.70–1.25 (series of m, 8 H), 1.06 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 148.8, 109.4, 109.2, 64.1, 63.9, 45.1, 37.7, 36.4, 34.8, 26.1, 19.8; MS m/z (M^+) calcd 182.1307, found 182.1310.

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.58; H, 9.90.

3-Methylcyclohexanone-3-acetic Acid (7). A. Hydroboration–Oxidation–Hydrolysis of the Ketal of 6. A solution of the above ketal (66.8 g, 366 mmol) in dry THF (1 L) was cooled to 0 °C and treated with a solution of the borane-THF complex in THF (366 mL of 1 M, 366 mmol) over a period of 1 h. The reaction mixture was stirred for 1 h at this temperature and treated dropwise with water (40 mL) to destroy excess reagent. While still at 0 °C, the mixture was treated dropwise with Jones reagent (prepared from 85.5 g (855 mmol) of CrO_3 dissolved in 128 mL of a 1:1 mixture of water and H_2SO_4 and diluting to 320 mL with water) at such a rate as to maintain the temperature below 10 °C. The cooling bath was removed, stirring was maintained for 3 h, and water (500 mL) and ether (500 mL) were added. The separated organic phase was washed with water until the aqueous phases were colorless (8 × 200 mL) and with 1 M NaOH (5 × 200 mL). The combined aqueous extracts were cooled to 0 °C, acidified to pH 3 with HCl, and extracted with CH_2Cl_2 (5 × 150 mL). These extracts were dried, evaporated, and placed under high vacuum overnight to give 43.2 g (69%) of **7** as a colorless oil; IR (cm^{-1}) 1730, 1705; ^1H NMR (300 MHz, $CDCl_3$) δ 9.2 (br s, 1 H), 2.44–2.14 (m, 5 H), 1.97–1.77 (m, 3 H), 1.74–1.61 (m, 2 H), 1.07 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 179.7, 176.9, 53.0, 45.4, 40.7, 38.0, 35.7, 25.3, 21.8; MS m/z (M^+) calcd 170.0943, obsd 170.0944.

B. Malonate Addition to 3-Methylcyclohexenone, Hydrolysis, and Decarboxylation. A solution of sodium ethoxide was prepared by adding sodium metal (20.87 g, 908 mmol) portionwise to ethanol (1 L). Once the sodium had reacted completely, the solution was cooled to 0 °C, diethyl malonate (137.8 mL, 908 mmol) was added slowly followed by 3-methylcyclohexenone (100.0 g, 908 mmol), and stirring was maintained for 9 days at rt. The mixture was poured into ice–water, neutralized with concentrated HCl, and extracted with ether (600 mL; 4 × 300 mL). The combined organic layers were washed with brine (3 × 250 mL), dried, filtered, and concentrated. The Michael adduct (191.7 g, 78%) was purified by vacuum distillation, bp 155–185 °C/2–3 Torr.

For the major diester: IR (neat, cm^{-1}) 1740, 1730; ^1H NMR (300 MHz, $CDCl_3$) δ 4.14–3.86 (m, 4 H), 2.33–2.03 (m, 3 H), 2.13 (s, 2 H), 1.80–1.00 (series of m, 4 H), 1.10 (t, J = 7.1 Hz, 6 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.3, 171.3 (2 C), 59.6 (2 C), 52.9, 42.6, 39.0, 34.9, 34.3, 24.6, 19.0, 13.9 (2 C); MS m/z (M^+) calcd 270.1467, obsd 270.1448.

The diester mixture (162.9 g, 602 mmol) was placed into 1 M KOH solution (1235 mL, 1.23 mol), stirred overnight, and heated at reflux for 1 h. The mixture was cooled, acidified with concentrated HCl (165 mL), and heated at reflux for 20 min. The cooled solution was extracted with CH_2Cl_2 (6 × 200 mL), washed with brine (200 mL), dried, filtered, and concentrated. The residue was purified by Kugelrohr distillation (155–175 °C/1 Torr) to give 79.9 g (78%) of **7**.

4-Methylbicyclo[2.2.2]octane-2,6-dione (9). To a mechanically stirred solution of 27.1 g (157 mmol) of **7** in 430 mL of acetic acid was added 247 g of polyphosphoric acid, and the solution was heated at 100 °C for 7 h, cooled, diluted with brine (1 L), and continuously extracted with toluene for 3 days. The cooled solution was washed with saturated $NaHCO_3$ solution (3 × 100 mL) and with brine (2 × 100 mL), dried, filtered, and concentrated. The residue was purified by sequential Kugelrohr distillation (100 °C, 0.1 Torr) and silica gel chromatography to afford 19.3 g (80%) of **9** as a pale yellowish solid: mp 75–76 °C; IR (neat, cm^{-1}) 1735, 1710; ^1H NMR (300 MHz, $CDCl_3$) δ 3.16 (t, J = 2.9 Hz, 1 H), 2.22 (ABq, J_{AB} = 8.0 Hz, $\Delta\nu_{AB}$ = 35.1 Hz, 4 H),

2.13–2.07 (m, 2 H), 1.73–1.67 (m, 2 H), 1.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.6 (2 C), 63.4, 50.4 (2 C), 33.9, 31.0, 25.7, 22.7; MS m/z (M^+) 152.0837, obsd 152.0823.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.97; H, 8.09.

(1*R,7*S**)-2-Methyltricyclo[3.2.1.0^{2,7}]octane-6,8-dione (5).** To a cold (−78 °C) solution of LDA (223 mmol) in THF (170 mL) (prepared from 148.6 mL of 1.5 M of *n*-butyllithium and 31.24 mL of diisopropylamine) was added 15.42 g (101 mmol) of **9** in THF (32 mL), and the solution was stirred for 30 min, added rapidly via cannula to a mechanically stirred solution of 284 mL (304 mmol) of a 1.07 M solution of $FeCl_3$ in 40 mL of DMF at −78 °C, and stirred for 2 h. The reaction mixture was quenched with 24 mL of methanol, diluted with brine (300 mL), and filtered through Celite. The filtrate was extracted with ether (4 × 250 mL), washed with brine (3 × 150 mL), dried, filtered, and concentrated on a rotary evaporator. The residue was purified by flash chromatography (elution with 1:6 ethyl acetate–petroleum ether) to afford 6.06 g (40%) of **5**: IR (neat, cm^{-1}) 1760, 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (d, J = 1.3 Hz, 2 H), 2.68–2.46 (m, 1 H), 2.30–2.27 (m, 2 H), 2.06–2.00 (m, 2 H), 1.26 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.5 (2 C), 52.6, 48.9 (2 C), 47.1, 30.9, 26.6, 23.3; MS m/z (M^+) calcd 150.0681, obsd 150.0699.

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.90; H, 6.81.

(1*R,2*R**,5*S**,7*S**,8*S*)-8-Hydroxy-2-methyl-8-vinyltricyclo[3.2.1.0^{2,7}]octan-6-one (11).** To a solution of **5** (280 mg, 1.86 mmol) in dry toluene (28 mL) was added dropwise at −78 °C a 0.75 M solution of vinylmagnesium bromide in dry THF (3.73 mL, 2.80 mmol). After 15 min, methanol (1 mL) was introduced followed by saturated NH_4Cl solution (15 mL). The separated aqueous phase was extracted with ether (5 × 10 mL), and the combined organic solutions were dried and evaporated. The residue was purified by MPLC on silica gel (elution with 50% ethyl acetate in petroleum ether) to give **11** as a colorless oil (290 mg, 87%): IR (CH_2Cl_2, cm^{-1}) 3570, 1710; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.63 (m, 3 H), 2.28–1.99 (m, 4 H), 1.92–1.81 (m, 4 H), 1.16 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 210.6, 141.7, 113.6, 74.6, 50.5, 41.6, 41.5, 37.1, 24.0 (2 C), 22.8; MS m/z (M^+) calcd 178.0994, obsd 178.0995.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.17; H, 7.91.

(1*R,2*S**,5*R**,6*S**,7*R**)-2-Methyl-8-methylene-6-vinyltricyclo[3.2.1.0^{2,7}]octan-6-ol (13b).** A solution of methyltriphenylphosphonium bromide (267 mg, 0.747 mmol) in dry THF (5 mL) was treated with *n*-butyllithium (0.50 mL of 1.49 M in hexanes, 0.747 mmol), stirred for 10 min, and exposed dropwise to **11** (61 mg, 0.340 mmol) dissolved in THF (1 mL). After 15 min, the reaction mixture was quenched by the addition of saturated NH_4Cl solution, and the separated aqueous phase was extracted with petroleum ether (5 × 5 mL). The combined organic solutions were dried and evaporated, and the residue was subjected to MPLC on silica gel (elution with 23% ethyl acetate in petroleum ether) to give **13b** as a colorless oil (21 mg, 35%): IR (neat, cm^{-1}) 3600–3200, 1650; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (m, 3 H), 4.89 (s, 1 H), 4.79 (s, 1 H), 2.13 (br s, 1 H), 1.81–1.49 (m, 7 H), 1.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 153.6, 139.2, 115.6, 103.3, 80.5, 50.3, 39.8, 32.6, 30.0, 26.1, 23.9, 22.9; MS m/z (M^+) calcd 176.1201, obsd 176.1193.

(1*R,2*R**,5*S**,7*S**,8*S**)-8-Acetoxy-2-methyl-8-vinyltricyclo[3.2.1.0^{2,7}]octan-6-one (14).** A solution of **11** (358 mg, 2.01 mmol) in pyridine (10 mL) was treated with 4-(dimethylamino)pyridine (25 mg, 0.201 mmol) followed by acetic anhydride (613 mg, 6.00 mmol), heated at 65 °C for 11 h, poured into ice-cold 1 M HCl (100 mL), and extracted with ether (4 × 20 mL). The combined ether extracts were washed with 1 M HCl (2 × 20 mL) and saturated brine (20 mL), dried, and evaporated. The residue was purified by MPLC on silica gel (elution with 30% ethyl acetate in petroleum ether) to furnish **14** as a colorless oil (384 mg, 87%): IR (CH_2Cl_2, cm^{-1}) 1740; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (dd, J = 11.0, 17.6 Hz, 1 H), 5.21 (dd, J = 11.0, 17.7 Hz, 2 H), 2.61 (d, J = 5.4 Hz, 1 H), 2.56 (br s, 1 H), 2.09 (s, 3 H), 2.06–1.81 (m, 4 H), 1.64 (br s, 1 H), 1.17 (s, 3 H); MS m/z (M^+) calcd 220.1099, obsd 220.1124.

(1*R,2*S**,5*R**,6*R**,7*R**)-2-Methyl-8-methylene-6-vinyltricyclo[3.2.1.0^{2,7}]octan-6-ol Acetate (15a).** To a suspension of methyltriphenylphosphonium bromide (280 mg, 0.785 mmol) in dry THF (2.5 mL) and dry HMPA (0.3 mL) was added at 0 °C a 0.90 M solution of potassium hexamethyldisilazide (0.81 mL, 0.725 mmol). After 15 min, the reaction mixture was cooled to −78 °C, and **14** (133 mg, 0.604 mmol) dissolved in THF (0.5 mL) was introduced dropwise over 5 min. After 1 h at rt, the usual extractive workup afforded an oil that was purified by MPLC (elution with 10% ethyl acetate in petroleum ether). There was isolated 10 mg (8%) of **15a** and 46 mg (35%) of unreacted **14**.

For **15a**: colorless oil: IR (CH_2Cl_2, cm^{-1}) 1760, 1665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.02 (dd, J = 10.9, 17.6 Hz, 1 H), 5.13 (dd, J = 18.1, 10.8 Hz, 2 H), 4.73 (s, 1 H), 4.66 (s, 1 H), 2.63 (br s, 1 H), 2.08 (s, 3 H), 1.99 (d, J = 5.8 Hz, 1 H), 1.82 (m, 4 H), 1.61–1.53 (m, 1 H), 1.03 (s, 3 H); MS m/z (M^+) calcd 218.1307, obsd 218.1293.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.56; H, 9.04.

(1*R,2*S**,5*R**,6*R**,7*R**)-2-Methyl-8-methylene-6-vinyltricyclo[3.2.1.0^{2,7}]octan-6-ol (15b).** A cold (0 °C) solution of **15a** (10 mg, 0.046 mmol) in methanol–water (9:1, 1 mL) was stirred for 3 h with 1 M NaOH (59.6 μL, 0.060 mmol) and allowed to stand overnight at rt. The reaction mixture was diluted with water (10 mL) and extracted with ether (3 × 3 mL). The combined ethereal layers were dried and evaporated to give 8 mg (95%) of **15b**: IR (CH_2Cl_2, cm^{-1}) 3590, 3540–3330, 1655; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (dd, J = 10.8, 17.3 Hz, 1 H), 5.27 (dd, J = 17.3, 1.3 Hz, 1 H), 5.05 (dd, J = 10.7, 1.4 Hz, 1 H), 4.71 (d, J = 1.0 Hz, 1 H), 4.63 (s, 1 H), 2.13–2.04 (m, 2 H), 1.95–1.83 (m, 2 H), 1.78 (d, J = 5.6 Hz, 1 H), 1.65 (s, 1 H), 1.58–1.47 (m, 2 H), 1.02 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 153.1, 142.8, 111.7, 101.4, 78.6, 47.5, 37.8, 35.1, 27.2, 24.5, 24.2, 23.6; MS m/z (M^+) calcd 176.1201, obsd 176.1204.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.56; H, 9.04.

(1*R,2*S**,5*R**,7*R**)-2-Methyl-8-methylenetricyclo[3.2.1.0^{2,7}]octan-6-one (17).** To 20.83 g (51.54 mmol) of methyltriphenylphosphonium iodide in THF (200 mL) and HMPA (20 mL) was added 94.5 mL (47.2 mmol) of 0.5 M potassium hexamethyldisilazide, and the solution was stirred for 15 min, cooled to −78 °C, and treated with **5** (6.45 g, 43.0 mmol) in THF (15 mL). The reaction mixture was allowed to warm to rt over 2 h and quenched with saturated NH_4Cl solution (20 mL) and H_2O (100 mL). The separated aqueous layer was extracted with petroleum ether (4 × 50 mL), and the combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography (elution with 4% ethyl acetate in petroleum ether) to afford 5.28 g (83%) of **17** as a colorless oil: IR (neat, cm^{-1}) 1735, 1665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.70 (s, 1 H), 4.55 (s, 1 H), 2.45 (d, J = 5.0 Hz, 1 H), 2.34 (s, 1 H), 1.88–1.70 (m, 5 H), 1.00 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 210.0, 146.3, 102.4, 48.9, 42.1, 41.4, 40.2, 31.2, 23.5, 23.2; MS m/z (M^+) calcd 148.0888, obsd 148.0879.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.05; H, 8.09.

Vinylation of 17. A 1.38-g (9.31 mmol) sample of **17** was treated in the predescribed manner with excess vinylmagnesium bromide at 0 °C. Following the usual workup, the residue was subjected to Kugelrohr distillation (90 °C, 1 Torr). There was isolated 1.43 g (86%) of **15b**, identical in all respects to the material prepared from **15a**.

(1*R,2*R**,5*S**,6*S**,7*S**)-8-(Methoxymethylene)-2-methyl-6-vinyltricyclo[3.2.1.0^{2,7}]octan-6-ol (16).** A cold (0 °C), magnetically stirred suspension of (methoxymethylene)triphenylphosphonium chloride (345 mg, 1.01 mmol) in dry THF (4 mL) and HMPA (0.5 mL) was treated with potassium hexamethyldisilazide (1.12 mL of 0.90 M in THF, 1.01 mmol). The solution was stirred for 15 min, cooled to −100 °C, and treated during 20 min with a solution of **5** (151 mg, 1.01 mmol) in THF (1 mL). Once the red color of the phosphorane had dissipated, the reaction mixture was quenched with methanol (100 μL) and saturated NH_4Cl solution. After the mixture was warmed to rt, water (15 mL) was introduced and the product was extracted into ether (4 × 5 mL). The combined organic layers were dried and evaporated to leave a residue that was chromatographed on silica gel (elution with

30% ethyl acetate in petroleum ether) to give the monoketone as a colorless oil (90 mg, 50%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (s, 0.8 H), 5.90 (s, 0.2 H), 3.60 (s, 0.8 H), 3.54 (s, 2.2 H), 2.88 (m, 1 H), 2.46 (d, J = 5.1 Hz, 0.8 H), 2.40 (br s, 0.2 H), 2.02–1.71 (m, 5 H), 1.15 and 1.13 (2s, total 3 H).

The above product (116 mg, 0.651 mmol) dissolved in THF (1 mL) was added to a cold (−23 °C) solution of vinylmagnesium bromide (8 equiv). The reaction mixture was stirred for 30 min at −23 °C, quenched with saturated NH_4Cl solution (2 mL) and water (10 mL), and extracted with ether (4 × 3 mL). The usual workup and MPLC purification (silica gel, elution with 15% ethyl acetate in petroleum ether) furnished **16** as a colorless oil (122 mg, 91%): IR (CH_2Cl_2, cm^{-1}) 3600–3400, 1700, 1630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.01–5.89 (m, 1.3 H), 5.82 (s, 0.7 H), 5.30–5.01 (m, 2 H), 3.56 (s, 0.9 H), 3.51 (s, 2.1 H), 2.49 (br s, 1 H), 2.08–1.36 (series of m, 8 H), 1.02 (s, 1 H), 0.98 (s, 1 H); MS m/z (M^+) calcd 206.1307, obsd 206.1322.

Singlet Oxygenation of 16. A solution containing **16** (11 mg, 0.053 mmol) and 2% (w/w) Rose Bengal in 1:1 CH_2Cl_2/methanol (5 mL) was irradiated at −10 °C with a Sylvania 500-W tungsten halogen lamp while oxygen was constantly bubbled through the solution. After 25 min, the reaction mixture was diluted with ether (10 mL) and washed until the aqueous phases were colorless. The organic layer was dried and evaporated to leave 12 mg of dioxetane, which was kept at rt for 2 days to allow complete decomposition. MPLC purification (silica gel, elution with 35% ethyl acetate in petroleum ether) gave 8 mg (85%) of **11**, which proved identical in all respects to the earlier product of the same structure.

(1*R,2*R**,11*S**)-11-Methyltricyclo[5.4.0.0^{2,7}]undec-7-en-3-one (18).** A solution of **15b** (345 mg, 1.96 mmol) in dry THF (10 mL) was treated with a solution of potassium hexamethyldisilazide in THF (2.66 mL of 0.88 M, 2.35 mmol), refluxed for 20 h, cooled to 25 °C, and quenched by the addition of saturated NH_4Cl solution (1 mL) and water (20 mL). The separated aqueous phase was extracted with ether (4 × 5 mL), and the combined organic layers were dried and evaporated. The residue was subjected to Kugelrohr distillation (90 °C, 1 Torr) to give **18** as a colorless liquid (305 mg, 88%): IR (CH_2Cl_2, cm^{-1}) 1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (m, 1 H), 2.47–1.98 (series of m, 6 H), 1.83–1.58 (m, 4 H), 1.55–1.44 (m, 1 H), 1.28 (d, J = 9.0 Hz, 1 H), 1.19 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 209.7, 137.3, 127.9, 43.0, 40.6, 34.7, 27.6, 26.3, 23.8, 23.4, 22.7, 22.6; MS m/z (M^+) calcd 176.1201, obsd 176.1202.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.84; H, 9.14.

The stereochemistry of **18** was assigned on the basis of NOE experiments. Double irradiation of the methyl protons (δ 1.19) induced a 15% intensity enhancement of the adjacent cyclopropyl proton (δ 1.28) and a 3% intensity enhancement of the allylic cyclopropyl proton (δ 1.55–1.44). These effects were reciprocal, although more attenuated in the reverse direction.

(1*R,2*R**,11*S**)-3-(Methoxymethylene)-11-methyltricyclo[5.4.0.0^{2,11}]undec-7-ene (19).** To a suspension of (methoxymethyl)triphenylphosphonium chloride (890 mg, 2.60 mmol) in dry THF (8 mL) and dry HMPA (1 mL) was added at 0 °C a solution of potassium hexamethyldisilazide in THF (2.72 mL of 0.883 M, 2.40 mmol). After 15 min, a solution of **18** (353 mg, 2.0 mmol) in THF (2 mL) was introduced, stirring was maintained at 0 °C for 30 min, and quenching was accomplished with saturated NH_4Cl solution (1 mL) and water (5 mL). Ten drops of 30% hydrogen peroxide were also added to oxidize the small amounts of triphenylphine present. After 15 min, saturated Na_2SO_3 solution was added, and the aqueous phase was extracted with petroleum ether (5 × 5 mL). The combined organic solutions were washed with saturated Na_2SO_3 solution (2 × 5 mL) and brine (5 mL) prior to drying and solvent evaporation. The residue was subjected to Kugelrohr distillation (90 °C, 0.8 Torr) to give a colorless liquid that was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether). There was isolated 351 mg (86%) of **19**: IR (CH_2Cl_2, cm^{-1}) 1665; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87–5.58 (m, 2 H), 3.54 and 3.49 (2s, total 3 H), 2.55–1.51 (series of m, 8 H), 1.18 and 1.15 (2s, total 3 H), 1.48–0.98 (series of m, 4 H); MS m/z (M^+) calcd 204.1514, obsd 204.1515.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.85; H, 9.95.

(1*R,2*S**,11*S**)-11-Methyltricyclo[5.4.0.0^{2,11}]undeca-3,7-diene-3-carboxaldehyde (20).** To a solution of DDQ (2.75 g, 12.1 mmol) in dry THF (75 mL) was added at 0 °C during 10 min the neat vinyl ether **19** (2.48 g, 12.1 mmol). The transfer of **19** was completed by rinsing the container twice with 0.5 mL of dry methanol. The reaction mixture was stirred at 0 °C for 15 min and quenched with saturated $NaHSO_3$ solution. After an additional 10 min of stirring at 0 °C, the solution was transferred to a separatory funnel, diluted with water (100 mL) and brine (100 mL), and extracted with ether (6 × 40 mL). The combined ethereal extracts were washed with brine (5 × 50 mL), dried, and concentrated to leave a residue that was dissolved in methanol–water (9:1, 50 mL) and stirred at rt for 1 h in the presence of pyridinium p-toluenesulfonate (305 mg, 1.25 mmol). Following dilution with ether (200 mL), the solution was washed sequentially with water (2 × 30 mL), saturated $NaHCO_3$ solution (2 × 30 mL), and brine (2 × 30 mL). The organic phase was dried and evaporated to leave a residue that was chromatographed on silica gel (elution with 7% ethyl acetate in petroleum ether). There was obtained 958 mg (39%) of unreacted **19** and 1.144 g (50%) of **20**.

For **20**: colorless solid, mp 56–57 °C; IR (CH_2Cl_2, cm^{-1}) 1680, 1620; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.41 (s, 1 H), 6.71 (m, 1 H), 5.66 (m, 1 H), 2.98–2.85 (m, 1 H), 2.55 (m, 1 H), 2.40–2.30 (m, 1 H), 2.23–2.12 (m, 1 H), 1.92 (m, 1 H), 1.70–1.60 (m, 2 H), 1.27 (d, J = 8.3 Hz, 2 H), 1.25 (s, 3 H), 0.79 (dt, J = 13.5, 4.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 195.2, 155.4, 143.9, 137.6, 129.6, 31.1, 30.6, 27.8, 26.6, 26.3, 23.4, 22.9, 20.8; MS m/z (M^+) calcd 188.1201, obsd 188.1202.

Methyl (1*R,2*R**,11*S**)-11-Methyltricyclo[5.4.0.0^{2,11}]undeca-3,7-dien-3-yl Ketone (21).** A cold (−78 °C), magnetically stirred solution of **20** (1.14 g, 6.08 mmol) in dry THF (30 mL) was treated with methylmagnesium chloride (3.98 mL of 1.83 M in THF, 7.29 mmol), warmed to 0 °C over a 1-h period, quenched with 15% NH_4Cl solution (2 mL), diluted with brine, and extracted with ether (4 × 20 mL). The combined organic phases were dried and concentrated to give a residue that was chromatographed on silica gel (elution with 20% ethyl acetate in petroleum ether) to afford the carbinol (1.21 g, 97%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (m, 1 H), 5.61 (t, J = 6.3 Hz, 1 H), 4.17 (q, J = 6.4 Hz, 1 H), 2.69–2.61 (m, 1 H), 2.43 (m, 1 H), 2.25–1.93 (m, 3 H), 1.79–1.64 (m, 2 H), 1.51 (s, 1 H), 1.48 (s, 1 H), 1.28 (d, J = 6.4 Hz, 3 H), 1.22 (s, 3 H), 1.18–1.06 (m, 2 H); MS m/z (M^+) calcd 204.1514, obsd 204.1510.

The above carbinol (1.21 g, 5.92 mmol) was dissolved in dry CH_2Cl_2 (100 mL) and treated with freshly prepared manganese dioxide (11.1 g, 0.13 mol). The suspension was stirred for 3 h at rt, filtered through Celite, and washed with 20% methanol in ether (2 × 10 mL). The filtrate was evaporated, and the residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 1.11 g (93%) of **21** as a colorless oil; IR (CH_2Cl_2, cm^{-1}) 1660, 1600; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (t, J = 6.9 Hz, 1 H), 5.67 (d, J = 6.7 Hz, 1 H), 2.87–2.74 (m, 1 H), 2.52 (br t, J = 11.5 Hz, 1 H), 2.23 (s, 3 H), 2.27–2.08 (m, 2 H), 1.95 (br t, J = 14.0 Hz, 1 H), 1.73–1.62 (m, 2 H), 1.55 (d, J = 8.5 Hz, 1 H), 1.26 (s, 3 H), 1.12 (d, J = 8.6 Hz, 1 H), 0.80 (dt, J = 13.3, 3.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.8, 143.2, 141.1, 137.6, 129.3, 30.8, 30.6, 30.0, 26.2, 26.1, 25.2, 23.3, 22.8, 20.2; MS m/z (M^+) calcd 202.1358, obsd 202.1356.

***tert*-Butyldimethyl[[1-[(1*R**,2*R**,11*S**)-11-methyltricyclo[5.4.0.0^{2,11}]undeca-3,7-dien-3-yl]vinyl]oxy]silane (22).** A solution of **21** (1.10 g, 5.44 mmol) in dry CH_2Cl_2 (80 mL) was treated sequentially with triethylamine (1.52 mL, 10.9 mol) and *tert*-butyldimethylsilyl triflate (1.62 mL, 7.07 mmol), stirred for 2 h, diluted with ether (150 mL), and washed successively with water (2 × 20 mL), 0.1 M HCl (3 × 20 mL), and brine (25 mL). The organic phase was dried and evaporated to leave **22** as a pale yellow oil (1.9 g) that was used directly. A small sample was purified by silica gel chromatography (elution with petroleum ether); IR (CH_2Cl_2, cm^{-1}) 1620, 1585; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (t, J = 6.5 Hz, 1 H), 5.66 (d, J = 5.0 Hz, 1 H), 4.52 (s, 1 H), 4.21 (s, 1 H), 2.85–2.70 (m, 1 H), 2.52–2.46 (m, 1 H), 2.17–2.06 (m, 2 H), 1.99–1.89 (br m, 1 H), 1.73–1.54 (m, 2 H), 1.43 (d, J = 8.7 Hz, 1 H), 1.24 (s, 3 H), 1.27–1.02 (m, 2 H), 0.96 (s, 9 H), 0.16 (s, 3 H), 0.12 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 156.6,

138.5, 136.0, 128.8, 128.5, 91.9, 32.1, 30.9, 30.4, 26.5, 26.0, 25.7, 24.6, 23.7, 22.5, 19.9, 18.3, 18.1, -2.9, -4.5.

Methyl (1*R,1a*S**,8b*S**)-8-(*tert*-Butyldimethylsiloxy)-1a,3,4,4a,5,6,7,8b-octahydro-1-methyl-1*H*-1,2-[1]propan[3]-ylidenebenzo[*a*]cyclopropa[*c*]cycloheptene-5-carboxylate (23).** A solution of freshly prepared **21** (ca. 0.252 mmol) in dry benzene (1 mL) was treated with methyl acrylate (0.23 mL, 2.52 mmol), placed in a Teflon tube, and pressurized in a high-pressure reactor at 98 000 psi for 4.5 h. The resulting viscous material was triturated with CH_2Cl_2, and the extracts were evaporated. The residue was purified by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) to afford two epimers of **23**.

Epimer A: colorless oil; 55 mg (54%); IR (CH_2Cl_2, cm^{-1}) 1730, 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 9.5 Hz, 1 H), 3.65 and 3.63 (ratio 2:8, 2s, total 3 H), 2.60 (q, J = 4.0 Hz, 1 H), 2.45 (m, 1 H), 2.27–1.92 (series of m, 6 H), 1.84–1.71 (m, 2 H), 1.59–1.42 (m, 4 H), 1.20 (s, 3 H), 1.21–1.12 (m, 2 H), 0.92 (s, 9 H), 0.11 (s, 6 H).

Epimer B: colorless oil; 14 mg (14%); IR (CH_2Cl_2, cm^{-1}) 1725, 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, J = 6.4 Hz, 1 H), 3.71 and 3.68 (ratio 2:8, 2s, total 3 H), 2.47 (m, 1 H), 2.28–1.80 (series of m, 7 H), 1.79–1.57 (m, 3 H), 1.54–1.51 (m, 3 H), 1.20 (s, 3 H), 1.32–1.09 (m, 2 H), 0.93 (s, 9 H), 0.13 (s, 6 H); MS m/z (M^+) calcd 402.2590, obsd 402.2542.

Anal. Calcd for $C_{24}H_{38}O_3Si$: C, 71.59; H, 9.51. Found: C, 71.82; H, 9.56.

***tert*-Butyldimethyl[[(1*R**,1a*S**,8b*S**)-1a,3,4,4a,5,6,7,8b-octahydro-1-methyl-5-methylene-1*H*-1,2-[1]prop[3]-ylidenebenzo[*a*]cyclopropa[*c*]cyclohepten-8-yl]oxy]silane (24) and Epimer 25.** To a cold (0 °C), magnetically stirred suspension of lithium aluminum hydride (1.9 mg, 0.05 mmol) in dry THF (5 mL) was added during 5 min a solution of **23** (40 mg, 0.10 mmol) in ether (1 mL). After 90 min, the excess hydride was destroyed by the addition of a few drops of ethyl acetate followed by 0.1 M NaOH (10 mL). After further dilution with brine (20 mL), the product was extracted into ether (4 × 10 mL), and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel (elution with 30% ethyl acetate in petroleum ether) to give 38 mg (100%) of the alcohol mixture as a colorless oil which solidified on standing: IR (CH_2Cl_2, cm^{-1}) 3610–3500, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (d, J = 5.2 Hz, 1 H), 4.13 (d, J = 8.6 Hz, 1 H), 3.93 (dd, J = 8.6, 2.6 Hz, 1 H), 2.47–2.32 (m, 2 H), 2.12–2.02 (m, 2 H), 1.89–1.54 (series of m, 9 H), 1.30–0.85 (series of m, 4 H), 1.16 (s, 3 H), 0.84 (s, 9 H), 0.13 (s, 6 H); MS m/z (M^+) calcd 374.2641, obsd 374.2653.

A solution of the above alcohol (470 mg, 1.25 mmol) in dry THF (25 mL) was treated sequentially with solid *o*-nitrophenyl selenocyanate (855 mg, 3.76 mmol) and tri-*n*-butylphosphine (0.94 mL, 3.76 mmol). After 2 h, the solvent was evaporated, and the residue was taken up in ether (20 mL) and filtered. The filtrate was concentrated, and the residue was chromatographed on silica gel (elution with 5–15% ethyl acetate in petroleum ether) to give the diastereomeric selenides as a yellow foam (613 mg, 88%): IR (CH_2Cl_2, cm^{-1}) 1640, 1590, 1510, 1330; ^1H NMR (300 MHz, $CDCl_3$) δ 8.20–8.16 (m, 1 H), 7.47–7.38 (m, 2 H), 7.25–7.16 (m, 1 H), 5.53 (br s, 1 H), 2.95–2.81 (m, 1 H), 2.75 (t, J = 11.3 Hz, 1 H), 2.45 (br s, 1 H), 2.22 (br s, 1 H), 2.09–1.31 (series of m, 12 H), 1.13 and 1.09 (2s, total 4 H), 0.84 (s, 10 H), 0.04 (s, 6 H); MS m/z (M^+) calcd 557.2029, obsd 557.2016.

Hydrogen peroxide (12.1 mL of 30%, 120 mmol) in THF (5 mL) was added at 0 °C to a solution of the above selenides (672 mg, 1.20 mmol) in the same solvent (5 mL). After 20 min at 0 °C, the reaction mixture was diluted with water (30 mL) and extracted with ether (4 × 10 mL). The combined ethereal phases were washed with water (2 × 10 mL), saturated $NaHSO_3$ solution, and brine (10 mL) prior to drying and evaporation. The residue was dissolved in benzene (30 mL), triethylamine (0.50 mL) was added, and the mixture was refluxed for 2.5 h, washed with water (3 × 7 mL), and dried. After concentration, the residue was chromatographed on silica gel to give **24** (301 mg, 70%) and **25** (54 mg, 13%), both as colorless oils.

For **24**: IR (CH_2Cl_2, cm^{-1}) 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, J = 5.5 Hz, 1 H), 4.64 (s, 2 H), 2.64–2.54 (m, 2 H), 2.34–2.19 (m, 4 H), 2.10–1.99 (m, 2 H), 1.84–1.76 (m, 3 H), 1.56 (m, 3 H), 1.21 (s, 3 H), 0.98–0.83 (m, 1 H), 0.93 (s, 9 H), 0.12 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.1, 147.3, 138.6, 127.42, 127.38, 117.2, 103.9, 40.0, 36.0, 32.7, 32.6, 31.7, 29.7, 27.2, 26.9, 26.11, 26.07, 24.0, 23.4, 20.0, 18.2, -2.8, -3.1; MS m/z (M^+) calcd 356.2535, obsd 356.2548.

For **25**: IR (CH_2Cl_2, cm^{-1}) 1655; ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, J = 7.1 Hz, 1 H), 4.65 (s, 1 H), 4.55 (t, J = 1.6 Hz, 1 H), 2.64 (d, J = 11.5 Hz, 1 H), 2.42 (br d, J = 10.7 Hz, 1 H), 2.32 (dt, J = 3.6, 12.1 Hz, 1 H), 2.16–2.05 (m, 3 H), 2.00 (br t, J = 13.9 Hz, 2 H), 1.78–1.58 (m, 3 H), 1.34–1.22 (m, 3 H), 1.19 (s, 3 H), 0.93 (s, 9 H), 0.91 (br s, 1 H), 0.14 (s, 3 H), 0.11 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 151.6, 147.5, 141.3, 125.8, 115.2, 105.1, 49.1, 42.2, 36.4, 34.1, 32.6, 31.2, 28.3, 26.7, 26.22, 26.18, 26.14, 23.9, 23.8, 18.3, -2.2, -3.0 (1 C not observed).

(1*R,1a*R**,4a*R**,8a*S**,8b*S**)-Decahydro-1-methyl-5-methylene-8*H*-1,2-[1]prop[3]ylidenebenzo[*a*]cyclopropa[*c*]-cyclohepten-8-one (27).** To a solution of **24** (79 mg, 0.200 mmol) in dry THF (5 mL) was added at rt a solution of tetra-*n*-butylammonium fluoride (0.22 mL of 1 M, 0.22 mmol). After 15 min, the reaction mixture was poured into brine (20 mL), and the separated aqueous layer was extracted with ether (4 × 5 mL). The combined organic solutions were dried and evaporated, and the residue was chromatographed on silica gel to give 43 mg (89%) of a 71:29 mixture of **26** and **27** (^1H NMR analysis). The conversion of **26** to **27** was monitored by reversed-phase analytical HPLC (elution with 9:1 methanol–water) and **26** was found to have a half-life of 260 min. The major differences in the ^1H NMR spectra of **26** and **27** are found at the cyclopropyl methyl singlet (δ 1.24 vs 1.10) and the appearance of the exocyclic double bond [s at δ 5.30 vs d (J = 9.0 Hz) at δ 5.75].

For **27**: colorless liquid; IR (CH_2Cl_2, cm^{-1}) 1700, 1640; ^1H NMR (500 MHz, $CDCl_3$) δ 5.71 (d, J = 7.3 Hz, 1 H), 4.99 (s, 1 H), 4.94 (s, 1 H), 2.65–2.55 (m, 4 H), 2.51 (br m, 1 H), 2.45–2.37 (m, 2 H), 2.32–2.22 (m, 2 H), 2.00 (br m, 1 H), 1.87–1.81 (m, 1 H), 1.71–1.59 (m, 3 H), 1.10 (s, 3 H), 1.06 (s, 1 H), 0.87 (t, J = 12.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 213.6, 147.2, 138.6, 125.7, 109.4, 49.5, 43.4, 39.7, 33.6, 31.9, 28.6, 28.1, 27.6, 26.7, 24.7, 23.5, 21.0; MS m/z (M^+) calcd 242.1671, obsd 242.1667.

Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.21; H, 9.14.

(1*R,1a*R**,4a*R**,8a*S**,8b*S**)-Decahydro-1-methyl-5-methylene-8-(trimethylsiloxy)-1*H*-1,2-[1]propan[3]ylidenebenzo-[*a*]cyclopropa[*c*]cycloheptene-8-carbonitrile (28).** A solution of **27** (78 mg, 0.322 mmol), trimethylsilyl cyanide (86 μL, 0.644 mmol), and a catalytic amount of the potassium cyanide/18-crown-6 complex (2 mg) in CH_2Cl_2 (5 mL) was pressurized overnight at 98 000 psi. The solvent was evaporated and the residue was chromatographed on silica gel (elution with 3% ethyl acetate in petroleum ether) to give 104 mg (94%) of **28** as a mixture of two isomers; IR (CH_2Cl_2, cm^{-1}) 1635; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (br s, 1 H), 4.84 (t, J = 8.2 Hz, 2 H), 2.64 (br d, J = 4.7 Hz, 1 H), 2.47–1.77 (series of m, 15 H), 1.64–1.45 (m, 4 H), 1.26–0.85 (m, 1 H), 1.19 and 1.09 (2s, ratio 1:2.1, total 3 H), 0.53 (t, J = 9.4 Hz, 1 H), 0.25 and 0.22 (2s, ratio 1:1.9, total 3 H), MS m/z (M^+) calcd 341.2175, obsd 341.2170.

(1*R,1a*S**,4a*R**,8b*S**)-1a,3,4,4a,5,6,7,8b-Octahydro-1-methyl-5-methylene-1*H*-1,2-[1]prop[3]ylidenebenzo[*a*]cyclopropa-[*c*]cycloheptene-8-carbonitrile (29) and (1*R**,1a*R**,4a*R**,-8a*S**)-1a,3,4,4a,5,6,8a,8b-Octahydro-1-methyl-5-methylene-1*H*-1,2-[1]prop[3]ylidenebenzo[*a*]cyclopropa[*c*]cycloheptene-8-carbonitrile (30).** A solution of **28** (104 mg, 0.307 mmol) in dry pyridine (5 mL) was treated with DBU (0.14 mL, 0.911 mmol) and phosphorus oxychloride (0.28 mL, 3.04 mmol), refluxed for 5 h, and poured into 1 M HCl (20 mL). The separated aqueous layer was extracted with ether (4 × 6 mL), and the combined organic solutions were washed with 1 M HCl (5 mL) and saturated brine (5 mL) prior to drying and solvent evaporation. MPLC of the residue (silica gel, elution with 3% ethyl acetate in petroleum ether) gave 21 mg (28%) of **29** and 46 mg (60%) of **30**.

For **29**: IR (CH_2Cl_2, cm^{-1}) 2200, 1650, 1600; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (br d, J = 6.3 Hz, 1 H), 4.81 (s, 1 H), 4.73 (s, 1 H), 2.64 (br d, J = 8.7 Hz, 2 H), 2.66–2.31 (m, 4 H), 2.14–1.77 (series of m, 6 H), 1.33 (s, 3 H), 1.27–1.18 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 159.9, 147.1, 137.1, 128.2, 119.4, 111.7, 106.6, 43.0, 35.7, 34.7, 31.8, 29.0, 28.8, 26.7, 24.5, 23.0, 22.5 (one C not observed); MS m/z (M^+) calcd 251.1674, obsd 251.1682.

For **30**: IR (CH_2Cl_2, cm^{-1}) 2215, 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 6.55 (br s, 1 H), 5.78 (m, 1 H), 4.98 (s, 1 H), 4.92 (s, 1 H), 2.90 (t, J = 6.9 Hz, 2 H), 2.58 (br t, J = 6.6 Hz, 2 H), 2.44 (br m, 1 H), 2.29 (t, J = 10.3 Hz, 2 H), 2.07–1.61 (series of m, 6 H), 1.18 (s, 3 H), 1.14 (d, J = 13.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 143.4, 143.1, 138.2, 126.3, 118.9, 116.7, 109.0, 41.4, 37.2, 36.4, 31.6, 29.4, 29.3, 26.7, 25.7, 24.1, 23.7, 21.1; MS m/z (M^+) calcd 251.1674, obsd 251.1682.

Methyl (1*R,1a*S**,4a*R**,8b*S**)-1a,3,4,4a,5,6,7,8b-Octahydro-1-methyl-5-methylene-1*H*-1,2-[1]prop[3]ylidenebenzo[*a*]cyclopropa[*c*]cyclohepten-8-yl Ketone (32).** A cold (−78 °C) solution of **29** (18 mg, 0.072 mmol) in dry toluene (2 mL) was treated with diisobutylaluminum hydride (145 μL of 1 M in hexane, 0.145 mmol), stirred for 30 min at −78 °C, and quenched by addition of saturated NH_4Cl solution (1 mL). Following dilution with brine (20 mL), the mixture was extracted with ether (4 × 5 mL), and the combined organic layers were dried and evaporated. The resulting aldehyde was dissolved in THF (2 mL), cooled to 0 °C, and treated with methylmagnesium chloride (201 μL of 1.8 M in THF, 0.362 mmol). The reaction mixture was stirred overnight at 0 °C and quenched with saturated NH_4Cl solution (0.5 mL) and brine (10 mL). The product was extracted into ether (4 × 3 mL), and the combined organic layers were dried and evaporated. The residue was chromatographed on silica gel (elution with 5% ethyl acetate in petroleum ether) to return 48% of unreacted aldehyde and furnish 5 mg (24%) of the allylic alcohol: IR (CH_2Cl_2, cm^{-1}) 3590, 1630; MS m/z (M^+) calcd 270.1984, obsd 270.1973.

The above alcohol (5 mg) was dissolved in dry CH_2Cl_2 (2 mL), treated with pyridinium dichromate (10 mg, 0.026 mmol), stirred at rt for 24 h, diluted with 1:1 ether–petroleum ether, and filtered through Celite. The filtrate was chromatographed on silica gel (elution with 7% ethyl acetate in petroleum ether) to give **32** (1 mg, 21%) along with recovered alcohol (0.6 mg, 13%).

For **32**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.65 (d, J = 6.6 Hz, 1 H), 4.73 (br s, 2 H), 2.24 (s, 3 H), 2.60–1.99 (series of m, 8 H), 1.91–1.73 (m, 3 H), 1.24 (s, 3 H), 1.18–1.05 (m, 2 H), 0.90–0.86 (m, 1 H); MS m/z (M^+) calcd 268.1827, obsd 268.1824.

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Supplementary Material Available: 300-MHz ^1H and 75-MHz ^{13}C NMR spectra of those compounds lacking combustion data (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.