83375-47-7; **5f**, 83375-48-8; (±)-**6a**, 87568-27-2; (±)-**6b**, 87568-28-3; **6c**, 83375-49-9; **6d**, 83375-50-2; **6f**, 83375-52-4; (±)-**8a**, 87568-29-4; (±)-**8b**, 87568-30-7; (±)-**8c**, 87568-31-8; (±)-**8d**, 87568-32-9; (±)-**8e**, 87568-33-0; (±)-**8f**, 87568-34-1; (±)-**9c**, 87568-35-2; (±)-**9e**, 87568-36-3; **10**, 2210-24-4; (±)-**10** PhSCl adduct (isomer 1), 87568-37-4; (±)-**10** PhSCl adduct (isomer 2), 87568-38-5; (±)-**11**, 87568-39-6; (±)-**12**, 87568-40-9; **13**, 39692-63-2; **14**, 87568-41-0; **16**, 87568-42-1; **17**, 69193-56-2; **18**, 87568-43-2; **19**, 87568-44-3; (±)-**20**, 87568-45-4; (±)-**21**, 87568-46-5; (±)-**22**, 87637-98-7; (±)-**25**, 87568-47-6; (*R*)-**26**, 87568-48-7; **26** PhSCl adduct (isomer 1), 87568-49-8; **26** PhSCl adduct (isomer 2), 87568-50-1; **27**, 87568-51-2; **27** sulfoxide, 87568-52-3; (*R*)-**28**, 87568-53-4; (±)-**29**, 81264-11-1; **30** (isomer 1), 87568-54-5; **30** (isomer 2), 87568-55-6; **31** (isomer 1), 87568-56-7; **31** (isomer 2), 74373-19-6; (±)-**32**, 87568-57-8; **33** (isomer 1), 87568-58-9; **33** (isomer 2), 87568-59-0; (±)-**34**, 87568-60-3; (±)-**35**, 87568-61-4; (±)-**37**, 77447-98-4; (±)-**38**, 77447-99-5; (*E*)-(±)-**39**, 87568-62-5; **40** (isomer 1), 87585-86-2; **40** (isomer 2), 87568-63-6; **41** (isomer 1), 87568-64-7; **41** (isomer 2), 87568-65-8; (±)-**42**, 87568-66-9; (±)-**43**, 87568-67-0; (±)-**44a**, 87568-68-1; (±)-**44b**, 87638-51-5; PhSCl, 931-59-9; benzyl carbamate, 621-84-1; pyruvic acid, 127-17-3; *p*-anisidine, 104-94-9; methacrylic acid, 79-41-4; methyl D-((*p*-benzyloxy)phenyl)glycinate, 71336-83-9; triphenylphosphine (((*p*-nitrobenzyl)oxy)carbonyl)methylene, 63760-39-4; *p*-nitrobenzyl glyoxalate, 64370-35-0; (±)-1-(hydroxy-(((*p*-nitrobenzyl)oxy)carbonyl)-methyl)-4(*R**)-(2,2-dimethoxyethyl)-3(*R**)-(1(*S**)-((((*p*-nitrobenzyl)-oxy)carbonyl)oxy)ethyl)azetidin-2-one (isomer 1), 87568-69-2; (±)-1-(hydroxy-(((*p*-nitrobenzyl)oxy)carbonyl)methyl)-4(*R**)-(2,2-dimethoxyethyl)-3(*R**)-(1(*S**)-((((*p*-nitrobenzyl)oxy)carbonyl)oxy)ethyl)azetidin-2-one (isomer 2), 87637-99-8.

Triquinane Sesquiterpenes. An Iterative, Highly Stereocontrolled Synthesis of (±)-Silphinene

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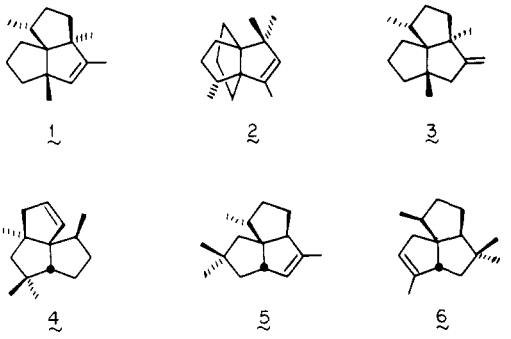
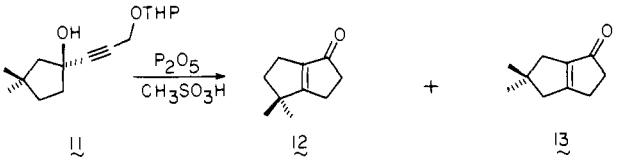
Abstract: A total synthesis of (±)-silphinene, a tricyclopentanoid sesquiterpene isolated from the roots of *Silphium perfoliatum* L., has been achieved. This structurally interesting triquinane was constructed in 15 steps and isolated in efficient overall yield. The key element of the synthesis was the implementation of an iterative cyclopentannulation scheme consisting of twofold conjugate addition of a functionalized organocopper reagent and subsequent aldol cyclization. This methodology is particularly serviceable for introducing vicinal quaternary carbon centers into polycyclic frameworks. A variety of other stereocontrolled chemical reactions were applied in the strategy that is outlined.

A variety of structurally interesting substances are produced by the roots of *Silphium perfoliatum* L.[2] The nonpolar extracts comprise a source, for example, of the previously characterized sesquiterpenes isocomene (**1**),[3,4] modhephene (**2**),[5,6] and β-isocomene (**3**).[6d,7] Also isolated was a fourth highly condensed tricyclopentanoid hydrocarbon for which the name silphinene was proposed. On the basis of NMR studies involving several oxidation products, silphinene was formulated as **4**.[2] The molecular array embodied in **4** is common to an increasingly widespread class of natural products that includes **1**, pentalenene (**5**),[8,9] and senoxydene (**6**).[10] As part of a program directed toward the synthesis of these fundamental triquinane[11] systems and their more highly oxygenated representatives, the construction of silphinene was viewed as a desirable undertaking.



Scheme I



From the outset, our interest in **4** as a synthetic target was prompted by the unique arrangement of its methyl substituents and double bond, which differs so extensively from those in **1**, **5**, and **6** as to require a radically altered protocol. In fact, no common synthetic thread has yet been found by which these tricyclic frameworks may be interwoven. An additional point of attraction was the close similarity of the silphinene nucleus to three of the four rings that form part of Nature's only fenestrane molecule, laurenene (**7**).[12] We therefore hoped to gain information on

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(3) Isolation: (a) Zalkow, L. H.; Harris, R. N., III; Van Derveer, D.; Bertrand, J. A. *J. Chem. Soc., Chem. Commun.* **1977**, 456. (b) Zalkow, L. H.; Harris, R. N., III; Burke, N. I. *J. Nat. Prod.* **1979**, *42*, 96. (c) Bohlmann, F.; LeVan, N.; Pickhardt, J. *Chem. Ber.* **1977**, *110*, 3777.
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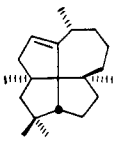
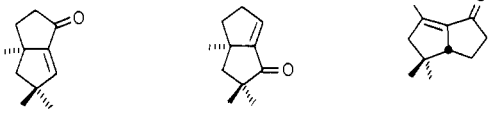


7

possible viable approaches to **7**. Our efforts have resulted in the first recorded synthesis of silphinene by means of a short, completely stereoselective process that is based on an efficient, iterative cyclopentannulation sequence.[13a]

From the retrosynthetic perspective, enones **8–10** each appeared



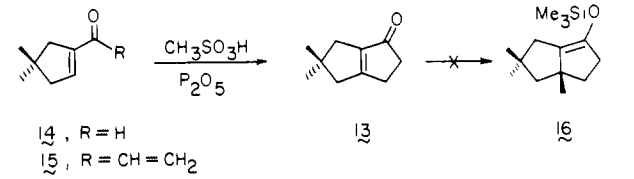
8 9 10

to be reasonable intermediates for the elaboration of **4**. Consequently, we shall first describe our attempts to secure these bicyclic compounds and subsequently detail the route adapted for conversion of **10** to racemic silphinene.

3,3,5-Trimethylbicyclo[3.3.0]oct-1-en-8-one (8). In planning the synthesis of this bicyclic enone, specific attention was initially paid to cyclopentannulation schemes wherein the starting five-membered ring already contained the *gem*-dimethyl pair. Consequently, the readily available and heavily utilized 4,4-dimethylcyclopentenone[14,15] was sequentially hydrogenated[16] and transformed into **11** by conventional means (Scheme I).[17] Concordant with the earlier findings of Dreiding,[18] Raphael,[19] and Nozaki,[20] **11** underwent smooth cyclization when treated with phosphorus pentoxide in methanesulfonic acid. Unfortunately, bicyclooctenone formation proved not to be regioselective. The isolation of ca. 1:1 mixtures of **12** and **13** was construed to mean that the geminal methyl groups were not playing as useful a steric role in deterring closure to **12** as we had hoped. The positional isomers proved not to be separable by chromatography.

A simple solution to this particular obstacle was arrived at by converting 3,3-dimethylcyclopentanone to α,β-unsaturated aldehyde **14** by the method of Wilson.[21,22] Following the addition of **14** to vinylmagnesium bromide[23] (Scheme II), the resulting dienol was oxidized with manganese dioxide on carbon.[24] Nazarov cyclization[25] of **15** afforded exclusively **13** in 40% isolated yield.

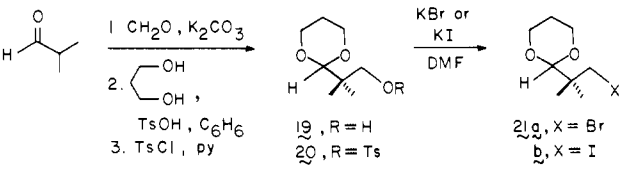
Scheme II



14, R = H
15, R = CH=CH2

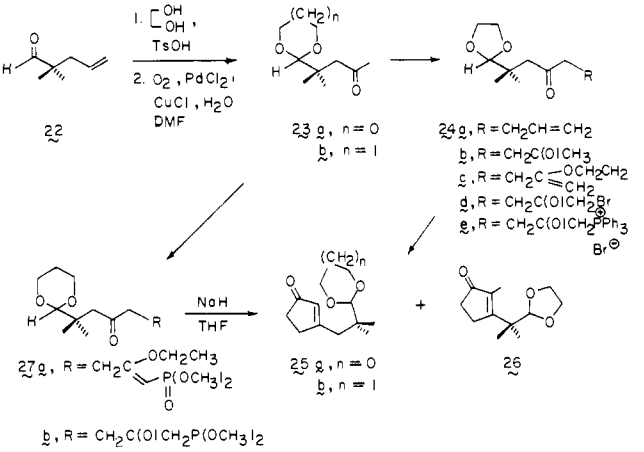
13 16

Scheme III



19, R = H
20, R = Ts
21 a, X = Br
b, X = I

Scheme IV



22

23 a, n = 0
b, n = 1

24 a, R = CH2CH=CH2
b, R = CH2C(OICH3
c, R = CH2C=CH2 OCH2CH2
d, R = CH2C(OICH2Br
e, R = CH2C(OICH2PPh3 Br⊖

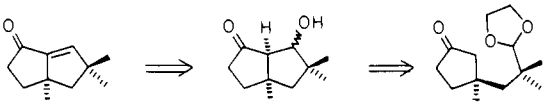
27 a, R = CH2C(OCH2CH3)P(OCH3)2=O
b, R = CH2C(OICH2P(OCH3)2

25 a, n = 0
b, n = 1

26

With **13** in hand, it remained to effect conjugate addition of lithium dimethylcuprate and trapping of the regiospecifically generated enolate with chlorotrimethylsilane in order to arrive at **16**. The acquisition of **8** was then to materialize by subsequent condensation of **16** with phenylselenyl chloride or bromde followed by oxidative elimination.[6d,26] However, these expectations were frustrated by our inability to transform **13** cleanly into **16** under conditions known to be otherwise favorable in related systems.[27]

In an alternative attempt to secure **8**, a protocol based upon the retrosynthetic plan **8** → **17** → **18** was examined. The primary



8 17 18

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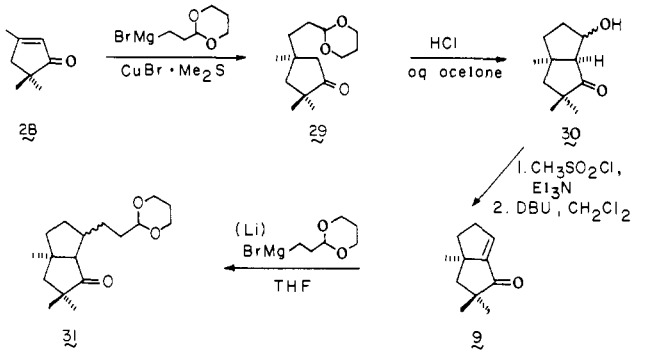
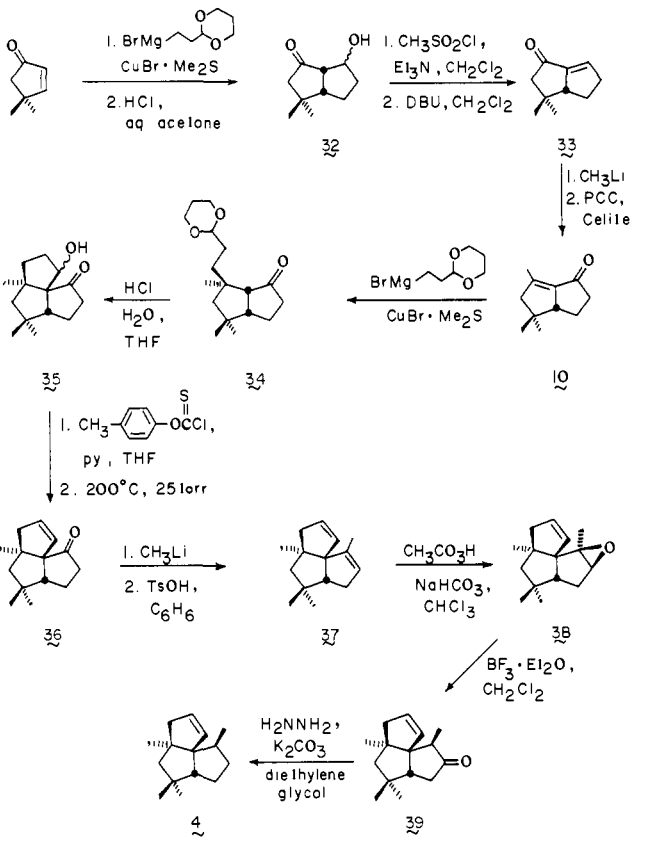
Scheme V



Scheme VI



halo acetals **21a** and **21b** were prepared from isobutyraldehyde by base-promoted condensation with formaldehyde (Scheme III).[28] Following protection of the carbonyl group and tosylation, S_N2 displacements at the neopentyl center were performed in dimethylformamide solution. Quite unexpectedly, neither **21a** nor **21b** could be induced to undergo conversion to their Grignard or lithium reagents. Evidently, the combination of steric congestion and flanking acetal oxygen atoms was adequate cause to preclude generation of the organometallic reagents.

Consequently, readily available aldehyde **22**[14] was transformed under standard conditions[29] to **23a**, the primary enolate of which could be formed regiospecifically and condensed efficiently with allyl bromide (Scheme IV). A second Wacker oxidation furnished the highly functionalized intermediate **24b** whose subsequent base-promoted cyclization proved heavily to favor the unwanted **26** rather than **25a**. The emergence of **26** as dominant product could be deterred by condensing the anion of **23b** with Piers reagent.[30] From a reactivity standpoint, **27b**, the acid hydrolysis product of **27a**, can only cyclize to **25**. Unfortunately, the yields of **25b** from this intramolecular Wadsworth–Emmons reaction proved to be highly variable and difficult to optimize.

This observation caused us to pursue the preparation of phosphonium salt **24e**. For unknown reasons, the alkylation step leading to **24c** and its ensuing reaction with *N*-bromosuccinimide[31] were low-yielding processes. The generation of **24e** proved to be equally inefficient. When all attempts to convert **24e** to **25a** failed, the decision was made to consider alternative routes to silphinene that were not based upon **8**.

5,7,7-Trimethylbicyclo[3.3.0]oct-1-en-8-one (9). In this phase of our study, advantage was taken of an earlier report by Hayashi and co-workers[32] that described a method for arriving quickly at trisubstituted cyclopentenone **28**. The ready availability of the Grignard reagent derived from 2-(2-bromoethyl)-1,3-dioxane[33] and the efficiency with which this reactive intermediate undergoes $CuBr{\cdot}Me_3S$-promoted conjugate addition to **28** (Scheme V) were a further attraction.[34] Following the logic of the hypothetical **18** → **17** conversion, acid hydrolysis of **29** was accompanied by aldolization. Indeed, **30** was isolated in 48% overall yield. Since spontaneous dehydration is not encountered in β-hydroxy ketones of this type, arrival at **9** required conversion to the mesylate and elimination with DBU in dichloromethane.

It was necessary to effect 1,2 addition to the carbonyl group of **9**. From the outset, we recognized the level of steric congestion present in ring A of this molecule to be quite high. In this connection, conditions were not found to attain the necessary objective, Grignard and organolithium reagents showing a very strong kinetic preference for 1,4 addition (cf. **31**) as a means of avoiding the neighboring geminal methyl substituents. For this reason, **9** was clearly not a serviceable intermediate.

2,4,4-Trimethylbicyclo[3.3.0]oct-1-en-8-one (10). In practice, diquinane **10** proved to be the most readily accessible of the three enone candidates (Scheme VI). The combination of 4,4-dimethylcyclopentenone as starting material and the cyclopentannulation sequence developed in Scheme V was unquestionably a winning one. With the isolation of **33**, our hope was that pyridinium chlorochromate oxidation of its tertiary methylated alcohol would result in rearrangement to **10**.[35] However, no precedence for inter-ring 1,3-chromate ester migration could be found. Rather than experience conversion to transposed enones, such allylic alcohols are known most frequently to deliver isomerized epoxy ketones.[36] In the present instance, however, **10** was obtained in 70% overall yield.[37]

Following this highly successful installation of ring B, the stage was set for elaboration of the third five-membered ring in an iterative manner. Thus, conjugate addition to **10** of the dioxanyl Grignard reagent followed by acid hydrolysis resulted in highly stereocontrolled formation of two new carbon–carbon bonds from the β face to give **35** exclusively. As expected, dehydration of

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(37) The presence of Celite has a notably advantageous effect on yield: Boeckmann, R. K., Jr., personal communication.

35 could not be implemented under ordinary conditions because of ready retroaldolization. Accordingly, 35 was condensed with 4-methylphenyl thiochloroformate to give the thiocarbonate ester (100%), which was pyrolyzed at 200 °C and 45 torr.[38] Tricyclic enone 36 was thereby secured in 84% yield.

Arrival at silphinene was thus reduced to stereocontrolled introduction of a secondary β-methyl group at the carbonyl site in 36. Any scheme that would rely on catalytic hydrogenation had to be avoided as it would serve not only to generate predominantly the unwanted α isomer[4] but also to saturate the lesser substituted double bond. However, when 36 was treated with methyllithium and the resulting tertiary alcohol was dehydrated under acidic conditions, diene 37 was formed in high yield without evidence of skeletal rearrangement.[4c] Furthermore, on the basis of their differing levels of alkyl substitution, the two sites of unsaturation in 37 were expected to be chemically distinguishable. In actual fact, buffered peracetic acid (1 equiv) in chloroform at 0 °C was adequate to transform the diene quantitatively into β-epoxide 38. As expected, the reactivity of the trisubstituted double bond in 37 is sufficiently heightened to be the sole detectable site of electrophilic attack.[39]

Stereospecific rearrangement of 38, with the secondary methyl group now occupying the thermodynamically more stable quasi-equatorial position, was achieved by overnight treatment with boron trifluoride etherate in benzene at room temperature.[6C,40] Given the α orientation of the oxiranyl hydrogen which must undergo the 1,2 shift and the in-plane nature of this migration, the methyl-substituted carbon necessarily experiences inversion of configuration. The ensuing Wolff–Kishner reduction of 39 with potassium carbonate and hydrazine hydrate in hot diethylene glycol[41] was similarly found not to cause epimerization. Following isolation of the resulting hydrocarbon by VPC, its high-field ^{1}H NMR spectrum proved identical with that of natural silphinene (4).[42]

In summary, a fully stereocontrolled synthesis of (±)-silphinene has been achieved. The synthetic route from 4,4-dimethylcyclopentenone (Scheme VI) is both relatively short (15 steps) and exceptionally efficient (10% overall yield). These characteristics manifest themselves as a direct consequence of the iterative approach which is followed, the carbocyclic framework of 4 arising from twofold conjugate addition of a functionalized organocopper reagent and subsequent aldol cyclization. In addition to highlighting the utility and efficiency of this methodology for polyquinane construction, the present protocol also provides a practical solution to the ready introduction of vicinal quaternary carbon centers into polycyclic frameworks and affords at least one intermediate, viz., 35, that should prove serviceable for ultimate arrival at laurenene (7).

Experimental Section

3,3-Dimethylcyclopentanone. A mixture of 4,4-dimethylcyclopentenone (67 g, 0.61 mol), 51% palladium on carbon (1 g), and petroleum ether (50 mL) was hydrogenated at 55 psi and room temperature for 2.5 h. The resulting suspension was filtered and concentrated in vacuo to provide 62.1 g (91%) of the saturated ketone[16] as a pale yellow oil, which was used directly without further purification.

1-(((Tetrahydropyranyl)oxy)propargyl)-3,3-dimethylcyclopentan-1-ol (11). To a stirred solution of the tetrahydropyranyl ether of propargyl alcohol (10.0 g, 0.071 mol) in cold (−78 °C) anhydrous ether (150 mL) was added dropwise *n*-butyllithium in hexane (55 mL of 2.28 M, 0.126 mol). When the addition was complete, the reaction mixture was stirred at −78 °C for 1 h, the temperature was raised to 0 °C, and a solution of 3,3-dimethylcyclopentanone (8.0 g, 0.071 mol) in anhydrous ether (100 mL) was added dropwise. The golden solution was stirred overnight at room temperature and then treated with water until the precipitation of lithium hydroxide ceased. This mixture was filtered through Celite, and the filtrate was concentrated in vacuo to give 17.8 g of a golden oil, which was chromatographed in Florisil (elution with 5–10% ethyl acetate in petroleum ether). There was obtained 7.7 g (41%) of **11**: IR (cm^{-1}, neat) 3440, 2980, 2890, 2260; ^{1}H NMR ($CDCl_3$) δ 4.74 (br s, 1 H), 4.12 (s, 2 H), 3.9–3.3 (br m, 2 H), 2.40 (br s, 1 H), 2.2–1.3 (series of m, 12 H), 1.10 (s, 3 H), 1.04 (s, 3 H); *m/e* calcd ($M^+ - H_2O$) 234.1620, obsd 234.1626.

Cyclization of 11. Phosphorus pentoxide (2 g) was added to anhydrous methanesufonic acid (16 mL), and the reaction mixture was heated to 80 °C until a homogeneous solution resulted. This solution was cooled to room temperature and poured onto 1.13 g (4.5 mmol) of **11** at 0 °C. The ice bath was removed and the dark brown reaction mixture was stirred for 5 min, treated with ether (50 mL), and neutralized with saturated aqueous sodium bicarbonate solution. The organic layer was separated, washed with brine, dried, and concentrated. The resulting brown oil was chromatographed on Florisil (elution with 10% ethyl acetate in petroleum ether) to give a golden oil, which was determined to be an inseparable mixture of **12** and **13**: IR (cm^{-1}, neat) 2960, 2880, 1720, 1650, 1460, 1370; ^{1}H NMR ($CDCl_3$) δ 2.7–2.1 (series of m, 5 H), 1.7–1.2 (series of m, 6 H), 1.1 (s, 6 H), 1.0 (s, 6 H); *m/e* calcd (M^+) 150.1045, obsd 150.1047.

4,4-Dimethyl-1-cyclopentene-1-carboxaldehyde (14). Sodium hydride (2.5 g, 52 mmol) was added to 50 mL of anhydrous ether, and the mixture was cooled to 0 °C and treated dropwise while being stirred with ethyl formate (3.3 g, 45 mmol). 3,3-Dimethylcyclopentanone (5.0 g, 45 mmol) dissolved in the same solvent (50 mL) was introduced, and the reaction mixture was stirred overnight at room temperature. Water was carefully added until the tan solid dissolved. The layers were separated, and the organic phase was washed with 5% sodium hydroxide solution. The combined aqueous layers were acidified with hydrochloric acid and extracted with ether. The ethereal solution was washed with brine, dried, and evaporated to give 4.73 g (76%) of 4,4-dimethylcyclopentanone-2-carboxaldehyde as a crystalline solid, mp 100–104 °C (from dichloromethane–petroleum ether:[22] IR (cm^{-1}, $CHCl_3$) 1689 and 1580; ^{1}H NMR ($CDCl_3$) δ 7.05 (t, J = 1.5 Hz, 1 H), 3.65 (s, 1 H), 2.30 (d, J = 1.5 Hz, 2 H), 2.15 (s, 2 H), 1.15 (s, 6 H).

A solution of the formyl ketone (17.83 g, 0.127 mol) in benzene (1 L) was treated with *p*-toluenesulfonic acid (730 mg) and ethylene glycol (7.87 mL, 0.127 mol) and heated at reflux under a Dean–Stark trap overnight. The cooled reaction mixture was washed with saturated sodium bicarbonate solution, dried, and evaporated to give 18.3 g (78%) of the keto acetal, bp 90–95 °C (0.3 torr):[22] IR (cm^{-1}, neat) 1740; ^{1} NMR ($CDCl_3$) δ 5.05 (m, 1 H), 3.84 (m, 4 H), 2.73 (t of d, J = 9 and 2 Hz, 1 H), 2.02 (s, 2 H), 1.77 (d, J = 9 Hz, 2 H), 1.20 (s, 3 H), 1.04 (s, 3 H).

A solution of the keto ketal (4.0 g, 0.0217 mol) in methanol (80 mL) was cooled to 0 °C, and sodium borohydride (3.3 g, 0.0858 mol) was added. The reaction mixture was stirred at room temperature overnight, diluted with water, and extracted with ether. The combined organic layers were dried and evaporated to leave an orange oil (4.0 g), which was taken up in ether (100 mL) and stirred vigorously with 3 N hydrochloric acid (100 mL). After 6 h, solid potassium carbonate was added portionwise as foaming would allow and the resulting slurry was filtered. The solids were washed with ether and the combined ethereal solutions were dried and evaporated. Distillation of the residue in a Kugelrohr apparatus at 40 °C and 0.5 torr afforded 1.45 g (54%) of **14** as a clear, colorless oil:[22] IR (cm^{-1}, $CHCl_3$) 1680; ^{1}H NMR ($CDCl_3$) δ 9.68 (s, 1 H), 6.64 (s, 1 H), 2.35 (s, 1 H), 2.35 (m, 4 H), 1.15 (s, 6 H).

3,3-Dimethyl-1-cyclopentenyl Vinyl Ketone (15). 1-(3,3-Dimethyl-1-cyclopentenyl)-1-hydroxy-2-propene was prepared by the method of Hudlicky et al.[23] To a magnetically stirred slurry of manganese dioxide on carbon[24] (40 g) in petroleum ether (200 mL) was added 4.0 g (0.026 mol) of this allylic alcohol. The black suspension was stirred vigorously at room temperature overnight and filtered through Celite. The solids were washed with dichloromethane–ethyl acetate (1:1, 500 mL), and the combined filtrates were concentrated to furnish 3.9 g (100%) of **15** as a pale yellow oil: IR (cm^{-1}, neat) 3040, 2940, 2870, 1740, 1650, 1600, 1460, 1400, 1350; ^{1}H NMR ($CDCl_3$) δ 6.95 (dd, J = 18 and 9 Hz, 1 H), 6.72 (m, 1 H), 6.21 (dd, J = 18 and 2.5 Hz, 1 H), 5.65 (dd, J = 9 and 2.5 Hz, 1 H), 2.38 (m, 4 H), 1.08 (s, 6 H); *m/e* calcd (M^+) 150.1045, obsd 150.1043.

7,7-Dimethylbicyclo[3.3.0]oct-1(5)-en-2-one (13). Phosphorus pentoxide (4 g) was added to 30 mL of anhydrous methanesulfonic acid, and the mixture was heated to 80 °C with magnetic stirring until a homogeneous solution resulted. After being cooled to 20 °C, this solution was poured onto **15** (750 mg, 5.0 mmol), which was being cooled in an ice bath. The cooling was removed and the dark brown mixture was stirred for 5 min before being diluted with ether (50 mL) and neutralized with saturated sodium bicarbonate solution. The organic phase was separated,

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washed with brine, dried, and concentrated. The dark residue was chromatographed on Florisil (elution with 25% ethyl acetate in petroleum ether) to give 300 mg (40%) of **13** as a pale yellow oil: IR (cm^{-1}, neat) 2960, 2860, 1695, 1640, 1440, 1380, 1230, 1160; ^1H NMR ($CDCl_3$) δ 2.7–2.0 (series of m, 8 H) and 1.15 (s, 6 H); *m/e* calcd (M^+) 150.1045, obsd 150.1047.

2,2-Dimethyl-3-hydroxypropionaldehyde Trimethylene Acetal (19). This substance was prepared in 81% yield by the method of Tsuzuki et al.[43] for the corresponding ethylene acetal and exhibited the following spectral characteristics: IR (cm^{-1}, neat) 3440, 2960, 2860, 1520, 1340, 1280, 1140, 1000; ^1H NMR ($CDCl_3$) δ 4.26 (s, 1 H), 4.1–3.5 (series of m, 4 H), 3.36 (s, 2 H), 3.22 (s, 1 H), 1.9 (m, 2 H), 0.9 (s, 6 H); *m/e* calcd (M^+) 159.1021, obsd 159.1026.

2,2-Dimethyl-3-(*p*-toluenesulfonyloxy)propionaldehyde Trimethylene Acetal (20). To a cold (0 °C) solution of *p*-toluenesulfonyl chloride (42.4 g, 0.22 mol) in pyridine (300 mL) was added 32 g (0.20 mol) of **19**. The reaction mixture was stirred at room temperature for 72 h, poured into water (1000 mL), and extracted with dichloromethane. The combined organic phases were washed with 10% sulfuric acid until neutral. After drying and concentration, there was obtained 61.74 g (98% of **20** as colorless crystals, mp 90–92 °C; ^1H NMR ($CDCl_3$) δ 7.62 (d, J = 8 Hz, 2 H), 7.18 (d, J = 8 Hz, 2 H), 4.18 (s, 1 H), 4.1–3.2 (series of m, 6 H), 2.40 (s, 3 H), 1.85 (m, 2 H), 0.90 (s, 6 H); *m/e* calcd (M^+) 314.1188, obsd 314.1180.

2,2-Dimethyl-3-bromopropionaldehyde Trimethylene Acetal (21a). A solution of potassium bromide (2.7 g, 0.023 mol) and **20** (5.8 g, 0.023 mol) in dimethylformamide was heated at 165 °C for 72 h, cooled, poured into water, and extracted with ether. The combined organic layers were dried and evaporated, and the residue was distilled to give 3.4 g (68%) of **21a** as a clear, colorless oil, bp 68–70 °C (3 torr); IR (cm^{-1} neat) 2980, 2870, 1730, 1680, 1470, 1380, 1150, 1110, 1010; ^1H NMR ($CDCl_3$) δ 4.28 (s, 1 H), 4.25–3.25 (series of m, 4 H), 3.35 (s, 2 H), 2.0 (m, 2 H), 0.95 (s, 6 H); *m/e* calcd (M^+ – 1) 221.0178, obsd 221.0180.

The iodo derivative **21b** was prepared analogously in 82% yield by substituting potassium iodide for bromide: IR (cm^{-1}, neat) 2980, 2875, 1730, 1680, 1470, 1380, 1150, 1100, 1010; ^1H NMR ($CDCl_3$) δ 4.22 (s, 2 H), 4.2–3.4 (series of m, 4 H), 3.17 (s, 2 H), 1.9 (m, 2 H), 1.0 (s, 6 H); *m/e* calcd (M^+ – 1) 269.0040, obsd 269.0047.

2,2-Dimethyl-4-pentenal Ethylene Acetal. A solution of **22**[14] (58.0 g, 0.52 mmol), *p*-toluenesulfonic acid (3.0 g, 0.016 mol), and ethylene glycol (37.2 g, 0.60 mol) in benzene (400 mL) was heated at reflux overnight under a Dean–Stark trap. The cooled reaction mixture was washed with saturated sodium bicarbonate solution, dried, and evaporated. There was isolated 80.8 g (100%) of the acetal as a pale yellow oil, which was used without further purification: IR (cm^{-1}, neat) 3080, 2975, 2880, 1640, 1475, 1395, 1360, 1220, 1110; ^1H NMR ($CDCl_3$) δ 5.8 (m, 1 H), 5.2 (m, 2 H), 4.6 (s, 1 H), 3.9 (br s, 4 H), 2.2 (d, J = 3.5 Hz, 2 H), 0.9 (s, 6 H); *m/e* calcd (M^+ – 1) 155.1072, obsd 155.1076.

2,2-Dimethyl-4-oxopentanal Ethylene Acetal (23a). This keto acetal was prepared in 80% yield according to the method of Magnus and Nobbs for 2,2-dimethyl-4-oxopentanal.[14] The colorless liquid exhibited bp 90–95 °C at 10 torr: IR (cm^{-1}, neat) 2975, 2880, 1720, 1470, 1395, 1210, 1100, 1040, 950; ^1H NMR ($CDCl_3$) δ 4.52 (s, 1 H), 3.80 (br s, 4 H), 2.39 (s, 2 H), 2.08 (s, 3 H), 1.03 (s, 6 H); *m/e* calcd (M^+ – 1) 171.1021, obsd 171.1027.

The trimethylene acetal **23b** was obtained analogously in 60% yield after distillation, bp 130–135 °C (30 torr): IR (cm^{-1}, neat) 3500, 2940, 2840, 1705, 1460, 1350; ^1H NMR ($DCCl_3$) δ 4.28 (s, 1 H), 4.25–3.4 (m, 4 H), 2.4 (s, 2 H), 2.12 (s, 3 H), 1.8 (m, 2 H), 1.0 (s, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 208.52, 106.20, 66.94, 49.64, 38.11, 32.22, 25.91, 22.70; *m/e* calcd (M^+ – 1) 185.1178, obsd 185.1185.

2,2-Dimethyl-4-oxo-7-octenal Ethylene Acetal (24a). To a solution of freshly distilled diisopropylamine (6.36 g, 0.063 mol) in 50 mL of cold (–78 °C), dry tetrahydrofuran was added dropwise a solution of *n*-butyllithium in hexane (38 mL of 1.6 M, 0.061 mol). The reaction mixture was stirred at –78 °C for 30 min, warmed to 0 °C for 15 min, and recooled to –78 °C before dropwise addition of a solution of **23a** (10.0 g, 0.058 mol) in dry tetrahydrofuran (5 mL). After 1 h of stirring at –78 °C, the mixture was warmed to 0 °C, and allyl bromide (7.0 g, 0.058 mol) was added. After 5 h at 0 °C, the reaction mixture was poured into water (200 mL) and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The residual golden oil (13.9 g) was fractionally distilled to return 7.0 g of unreacted **23a** and to give 3.3 g (96% based on recovered starting material) of **24a**, bp 95–100 °C (0.6 torr): IR (cm^{-1}, neat) 3075, 2960, 2880, 1715, 1640, 1470, 1390, 1350, 1100; ^1H NMR ($CDCl_3$) δ 5.7 (m, 1 H), 4.95 (m, 2 H), 4.58 (s, 1 H), 3.83 (m, 4 H), 2.7–2.1 (m, 6 H), 1.04 (s, 6 H); *m/e* calcd (M^+ – 1) 211.1334, obsd 211.1340.

2,2-Dimethyl-4,7-dioxooctanal Ethylene Acetal (24b). Following the procedure of Magnus and Hobbs,[14] **24a** was converted to **24b** in 80% yield after medium-pressure liquid chromatography on silica gel (elution with 50% ethyl acetate in petroleum ether): IR (cm^{-1}, neat 2975, 2880, 1715, 1470, 1395, 1360, 1100; ^1H NMR ($CDCl_3$) δ 4.55 (s, 1 H), 3.82 (br s, 4 H), 2.63 (s, 4 H), 2.42 (s, 2 H), 2.18 (s, 3 H), 1.05 (s, 6 H); *m/e* calcd (M^+ – 1) 227.6481, obsd 227.6485.

Cyclization of 24b. To a solution of lithium diisopropylamide (0.48 mmol) in tetrahydrofuran (1 mL) at –78 °C was added **24b** (100 mg, 0.44 mmol) in tetrahydrofuran (1 mL). After being stirred at room temperature overnight, the reaction mixture was poured into water and extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated to leave a yellow oil (92 mg), which was subjected to MPLC on silica gel (elution with 25% ethyl acetate in petroleum ether). There was isolated 12 mg (14%) of **25a** and 54 mg (55%) of **26**.

For **25a**: IR (cm^{-1}, neat) 2980, 2960, 2840, 1710, 1610, 1010; ^1H NMR ($CDCl_3$) δ 6.8 (s, 1 H), 4.1 (s, 1 H), 4.0 (s, 4 H), 2.7–2.0 (m, 6 H), 1.0 (s, 6 H); *m/e* calcd (M^+) 210.2143, obsd 210.2144.

For **26**: IR (cm^{-1}, neat) 2980, 2960, 2840, 1710, 1620, 1340, 1000; ^1H NMR ($CDCl_3$) δ 5.2 (s, 1 H), 3.8 (s, 4 H), 2.5–2.3 (m, 4 H), 2.1 (s, 3 H), 1.3 (s, 6 H); *m/e* calcd (M^+) 210.2143, obsd 210.2144.

Condensation of 23b with the Piers Reagent. To a cold (–78 °C) solution of lithium diisopropylamide (1. mmol) in tetrahydrofuran–hexane (prepared as described earlier) was added 200 mg (1.1 mmol) of **23b** in dry tetrahydrofuran (4 mL) during 4 h. Following dropwise addition of hexamethylphosphoramide (2 mL), the Piers reagent (290 mg, 1.1 mmol) was introduced as a tetrahydrofuran solution (2 mL). The dark brown reaction mixture was stirred at –78 °C for 30 min and at 0 °C for an identical period prior to quenching with saturated ammonium chloride solution. Additional ether and water were added prior to separation of the organic phase. The aqueous phase was extracted twice with ether and the combined ethereal solutions were washed with brine, dried, and concentrated to leave a brown oil (270 mg). MPLC purification on silica gel (elution with 100% ethyl acetate) gave **27a** as an unstable pale yellow oil (120 mg, 50%); IR (cm^{-1}, neat) 3450, 2960, 2840, 1710, 1580, 1450, 1360; ^1H NMR ($CDCl_3$) δ 4.30 (s, 1 H), 4.2–3.5 (m, 7 H), 3.85 (s, 3 H), 3.68 (s, 3 H), 3.2–2.0 (series of m, 4 H), 2.42 (s, 2 H), 1.5–1.2 (m, 2 H), 1.35 (t, J = 6.5 Hz, 3 H), 1.0 (s, 6 H).

Hydrolysis–Cyclization of 27a. To a cold (0 °C) solution of 0.5 M hydrogen chloride in acetone (1.5 mL) dissolved in added acetone (3 mL) was introduced 100 mg (0.27 mmol) in **27a**. The reaction mixture was stirred at this temperature for 30 min, poured into saturated brine, and extracted with ether. The combined ethereal layers were dried and evaporated to afford crude **27b** as a yellowish oil, which was directly dissolved in dry tetrahydrofuran (7 mL). Sodium hydride (14 mg of 50% dispersion in oil, 0.26 mmol) was added, and the mixture was heated at reflux for 12 h, cooled, filtered through Celite, diluted with ether, and washed with water. Following drying and evaporation of the organic layer, the golden oil so obtained (67 mg) was subjected to MPLC on silica gel (elution with 50% ethyl acetate in petroleum ether). There was isolated 49 mg (43%) of **25b**: IR (cm^{-1}, CCl_4) 3010, 2960, 2920, 2840, 1710, 1620, 1110; ^1H NMR ($CDCl_3$) δ 6.8 (s, 1 H), 4.1 (s, 1 H), 4.0–3.2 (m, 5 H), 2.7–2.0 (series of m, 7 H), 1.0 (s, 6 H); *m/e* calcd (M^+) 224.1412, obsd 224.1419.

2-Ethoxy-3-((methylsulfonyl)oxy)propene. Methanesulfonyl chloride (1.26 g, 0.011 mol) was added dropwise to a solution of 2-ethoxy-3-hydroxy-1-propene[31c] (500 mg, 0.005 mol) and triethylamine (1.31 g, 0.013 mol) in dichloromethane (15 mL) at 0 °C. After 30 min of stirring at 0 °C, the usual workup was carried out to give a yellow oil (800 mg, 91%), which decomposed rapidly on standing and was determined to be the desired mesylate on the basis of the ^1H NMR spectrum: ^1H NMR ($CDCl_3$) δ 4.5 (s, 2 H), 4.3 (q, J = 2 Hz, 2 H), 3.7 (s, 2 H), 3.0 (s, 3 H), 1.3 (t, J= 2 Hz, 2). This material was used immediately without further purification.

2,2-Dimethyl-4-oxo-7-ethoxy-7-octen-1-al Ethylene Acetal (24c). To a solution of freshly distilled diisopropylamine (1.5 mL, 11 mmol) in 10 mL of cold (–78 °C) dry tetrahydrofuran was added a solution of *n*-butyllithium in hexane (8.1 mL of 1.2 M, 10 mmol). The reaction mixture was stirred at –78 °C for 30 min, warmed to 0 °C for 15 min, and recooled to –78 °C before dropwise addition of a solution of **23a** (1.65 g, 10 mmol) in dry tetrahydrofuran (3 mL). After 1 h at –78 °C, the solution was warmed to 0 °C, and hexamethylphosphoramide (1.72 g, 10 mmol) followed by a solution of 2-ethoxy-3-((methylsulfonyl)-oxy)propene (1.73 g, 10 mmol) in dry tetrahydrofuran (3 mL) was added. The mixture was stirred overnight, poured into water (10 mL), and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated to leave a yellow oil, which was purufied

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by MPLC on silica gel (elution with 50% ethyl acetate in petroleum ether). There was obtained 170 mg of recovered **23a** and 90 mg (50% based on recovered starting material) of **24c**: IR (cm^{-1}, neat) 2960, 2875, 1710, 1650, 1470, 1350, 1050, 790; ^1H NMR ($CDCl_3$) δ 4.6 (s, 1 H), 3.9 (s, 4 H), 3.8 (s, 2 H), 3.7 (*q*, *J* = 3 Hz, 2 H), 2.4 (m, 6 H), 1.2 (t, *J* = 3 Hz, 3 H), 1.0 (s, 6 H).

3,3,5-Trimethyl-8-hydroxybicyclo[3.3.0]octan-2-one (30). A solution of 3-bromopropionaldehyde trimethylene acetal (3.1 g, 0.016 mol) in dry tetrahydrofuran (4 mL) was added dropwise to magnesium turnings (580 mg, 0.024 g-atom) in the same solvent (4 mL). The reaction was initiated with iodine, and the rate of addition was used to moderate the reflux rate. The reaction mixture was then heated for 30 min, cooled to −78 °C, diluted with additional dry tetrahydrofuran (4 mL), and treated with a solution of cuprous bromide–dimethyl sulfide complex (1.0 g, 5.0 mmol) in dry dimethyl sulfide (8 mL). This mixture was stirred at −78 °C for 1 h prior to dropwise addition of a solution of **28**[32] (1.0 g, 8.0 mmol) in dry tetrahydrofuran (4 mL) over a 2-h period. After it had been stirred at −78 °C overnight and at 0 °C for 4 h, the reaction mixture was quenched with saturated ammonium chloride solution and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated to leave a yellow oil, which was immediately taken up in a mixture of acetone (45 mL), water (9 mL), and hydrochloric acid (3 mL). This mixture was stirred for 72 h, concentrated in vacuo, neutralized with saturated sodium bicarbonate solution, and extracted with ether. The combined ethereal layers were washed with brine, dried, and concentrated to give a yellow oil, which was purified by HPLC on silica gel (elution with 25% ethyl acetate in petroleum ether). There was obtained 860 mg (48%) of **30** as a mixture of epimers. The two isomers were separated by MPLC.

For **30** α-OH: IR (cm^{-1}, neat) 3400, 2930, 2860, 1720, 1450, 720; ^1H NMR ($CDCl_3$) δ 4.4 (m, 1 H), 3.1 (m, 1 H), 2.6 (br s, 1 H), 1.9–1.5 (m, 6 H), 1.5 (s, 3 H), 1.1 (s, 3 H), 1.0 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 223.75, 77.68, 68.21, 51.16, 47.64, 43.15, 41.02, 34.89, 30.53, 27.19, 25.12; *m/e* calcd (M^+) 182.1307, obsd 182.1312.

For **30** β-OH: IR (cm^{-1}, neat) 3460, 2940, 2860, 1715, 1450, 1380, 720; ^1H NMR ($CDCl_3$) δ 4.4 (m, 1 H), 3.4 (br s, 1 H), 2.5 (d, *J* = 2.5 Hz, 1 H), 2.0–1.4 (m, 6 H), 1.3 (s, 3 H), 1.15 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 226.78, 75.07, 62.87, 52.25, 48.43, 43.51, 40.05, 35.14, 30.22, 27.25, 25.91, 24.64; *m/e* calcd (M^+) 182.1307, obsd 182.1315.

5,7,7-Trimethylbicyclo[3.3.0]oct-1-en-8-one (9). Methanesulfonyl chloride (1.33 mL, 17 mmol) was added dropwise to a stirred solution of **30** (1.50 g, 8.2 mmol) and triethylamine (2.15 g, 21.3 mmol) in dichloromethane at 0 °C. After 30 min at 0 °C, water was added to dissolve the white precipitate that had formed, and the organic phase was washed successively with 10% hydrochloric acid, saturated sodium bicarbonate solution, water, and brine. After drying and concentration, the oily epimeric mesylate mixture was dissolved in dichloromethane (40 mL) containing diazabicycloundecene (2.5 g, 16.4 mmol), and this solution was stirred overnight at room temperature. The organic phase was washed repeatedly with water then brine and ultimately dried. Evaporation of solvent and purification by MPLC on silica gel (elution with 25% ethyl acetate in petroleum ether) gave **9** as a colorless oil: IR (cm^{-1}, neat) 2950, 2840, 1700, 1660; ^1H NMR ($CDCl_3$) δ 6.4 (t, *J* = 1.5 Hz, 1 H), 2.9 (m, 2 H), 2.2–1.8 (m, 4 H), 1.2 (s, 6 H), 1.0 (s, 3 H); *m/e* calcd (M^+) 164.1201, obsd 164.1206.

Prototypical Reaction of 9 with an Organometallic Reagent. The Grignard reagent derived from 3-bromopropionaldehyde trimethylene acetal (238 mg, 1.2 mmol) and magnesium turnings (44 mg, 1.8 mmol) was prepared as described above. A solution of **9** (100 mg, 0.6 mmol) in dry tetrahydrofuran (2 mL) was added dropwise, and the reaction mixture was stirred overnight at room temperature prior to being quenched with saturated ammonium chloride solution and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. MPLC of the residue on silica gel (elution with 25% ethyl acetate in petroleum ether) afforded 70 mg (41%) of **31**: IR (cm^{-1}, neat) 3440, 2920, 2860, 1730, 1450, 1370, 1130; ^1H NMR ($CDCl_3$) δ 4.4–3.4 (series of m, 6 H), 2.6 (s, 1 H), 2.1–1.5 (series of m, 12 H), 1.2 (s, 3 H), 1.1 (s, 3 H), 1.0 (s, 3 H); *m/e* calcd (M^+) 280.2038, obsd 280.2036.

4,4-Dimethyl-8-hydroxybicyclo[3.3.0]octan-2-one (32). A solution of the Grignard reagent of 3-bromopropionaldehyde trimethylene acetal (35 g, 0.182 mol) [from 6.55 g (0.273 mmol) of magnesium turnings in 40 mL of dry tetrahydrofuran] was prepared in the predescribed manner, cooled to −78 °C, diluted with an additional 40 mL of solvent, and treated in one portion with a solution of cuprous bromide–dimethyl sulfide complex (11.7 g, 0.057 mol) in dry dimethyl sulfide (80 mL). The yellow mixture was stirred at −78 °C for 1 h before a solution of 4,4-dimethylcyclopentenone (10.0 g, 0.091 mol) in dry tetrahydrofuran (40 mL) was added dropwise over 2 h. Stirring was maintained overnight at −78 °C and 4 h at 0 °C prior to workup as before. The resulting oil was taken up in acetone (300 mL), water (45 mL), and hydrochloric acid (10 mL), stirred vigorously for 72 h, and processed in the manner described earlier. HPLC purification (silica gel; elution with 25% ethyl acetate in petroleum ether) gave **32** as a mixture of epimers (12.13 g, 79%). These epimers (ratio 1:2.5) were separated by HPLC on silica gel (same solvent system).

For **32** β-OH: IR (cm^{-1}, neat) 3410, 2950, 2860, 1730, 1370, 720; ^1H NMR ($CDCl_3$) δ 4.23 (m, 1 H), 3.42 (m, 1 H), 2.65 (m, 1 H), 2.3-1.3 (series of m, 7 H), 1.10 (s, 3 H), 1.06 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 221.02, 77.07, 66.64, 62.93, 52.01, 50.49, 36.47, 35.99, 30.77, 26.40, 24.76; *m/e* calcd ($M^+ - H_2O$) 150.1045, obsd 150.1040.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.60.

For **32** α-OH: IR (cm^{-1}, neat) 3440, 2940, 2860, 1730, 1365, 725; ^1H NMR ($CDCl_3$) δ 4.5 (m, 1 H), 3.05–2.7 (m, 2 H), 2.5–1.3 (series of m, 7 H), 1.15 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 220.66, 73.49, 66.94, 58.14, 53.77, 52.49, 36.90, 35.38, 30.83, 26.34, 24.46; *m/e* calcd ($M^+ - H_2O$) 150.1045, obsd 150.1040.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.60.

4,4-Dimethylbicyclo[3.3.0]oct-8-en-2-one (33). Methanesulfonyl chloride (2.34 g, 0.021 mol) was added dropwise to a solution of **32** (1.7 g, 0.010 mol) and triethylamine (2.69 mL, 0.026 mol) in dichloromethane (50 mL) at 0 °C. After 30 min of stirring at 0 °C, the usual workup was carried out to give a yellow oil, which was immediately taken up in dichloromethane (40 mL) containing diazabicycloundecene (3.1 mL, 0.020 mol). This reaction mixture was stirred overnight at room temperature and processed as before to furnish an oil that was purified by HPLC on silica gel (elution with 25% ethyl acetate in petroleum ether). There was isolated 1.15 g (76%) of **33**: IR (cm^{-1}, neat) 2950, 2860, 1695, 1650; ^1H NMR ($CDCl_3$) δ 6.4 (q, *J* = 1 Hz, 1 H), 3.2 (m, 1 H), 2.7 (m, 2 H), 2.3 (d, *J* = 2 Hz, 2 H), 2.2–1.6 (series of m, 2 H), 1.1 (s, 3 H), 0.9 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 201.90, 148.98, 133.63, 59.84, 58.74, 37.87, 28.10, 26.03, 22.51; *m/e* calcd (M^+) 150.1045, obsd 150.1048.

2,4,4-Trimethylbicyclo[3.3.0]oct-1-en-8-one (10). To a solution of **33** (900 mg, 6.0 mmol) in dry ether (30 mL) cooled to −78 °C was added methyllithium in hexane (12 mL of 1.2 M, 12 mmol). The resulting mixture was allowed to come to room temperature, stirred overnight, and poured into water (50 mL). Following neutralization with dilute hydrochloride acid, the product was extracted into ether and the combined organic phases were washed with brine, dried, and concentrated to give a golden oil (1.0 g, 100%), which was dissolved in dichloromethane (10 mL) and added to a rapidly stirred slurry of pyridinium chlorochromate (2.7 g, 10 mmol) and oven-dried Celite (80 °C, 12 h, 6 g). The mixture was stirred overnight at room temperature; ether (50 mL) was added, and solids were removed by filtration through Celite. The residue was washed with ether, and the combined filtrates were washed with 5% sodium hydroxide solution, 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine prior to drying. Concentration in vacuo followed by chromatography on silica gel (elution with 25% ethyl acetate in petroleum ether) gave pure **10** (687 mg, 70%): IR (cm^{-1}, neat) 2940, 2850, 1700, 1650; ^1H NMR ($CDCl_3$) δ 3.1 (m, 1 H), 2.5 (t, *J* = 1.5 Hz, 2 H), 2.1–1.4 (series of m, 7 H), 1.20 (s, 3 H), 0.93 (s, 3 H); *m/e* calcd (M^+) 164.1205, obsd 164.1201.

7-Hydroxy-2,2,4-trimethyltricyclo[6.3.0.0^{4,8}]undecan-9-one (35). Treatment of **10** (400 mg, 2.4 mmol) with the Grignard reagent derived from 3-bromopropionaldehyde delivered 279 mg (68%; 71% = 48% overall) of **35** as a clear, isomerically pure, colorless oil: IR (cm^{-1}, neat) 3460, 2940, 2840, 1720, 1450, 1180, 1100, 1070; ^1H NMR ($CDCl_3$) δ 4.25 (dd, *J* = 11 and 6 Hz, 1 H), 2.6 (d, *J* = 8 Hz, 1 H), 2.57 (br s, 1 H), 2.43 (dd, *J* = 16 and 11 Hz, 2 H), 1.95–1.16 (series of m, 8 H), 1.11 (s, 3 H), 1.06 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 226.36 81.50, 71.61, 58.20, 54.80, 52.74, 42.06, 39.81, 32.04, 29.92, 26.34, 24.58, 19.97; *m/e* calcd (M^+) 222.1417, obsd 222.1419.

2,2,4-Trimethyltricyclo[6.3.0.0^{4,8}]undec-6-en-9-one (36). To a solution of **35** (490 mg, 2.2 mmol) in dry pyridine (8 mL) was added 4-methylphenyl thiochloroformate (607 mg, 3.26 mmol) in dry tetrahydrofuran (1 mL), and stirring was maintained overnight at room temperature. Following the addition of water, the product was extracted into ether, and the combined organic layers were washed with 10% hydrochloric acid and brine. Drying and solvent removal gave an orange oil, which was purified by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether). The thionocarbonate was obtained as a colorless crystalline solid (687 mg, 84%): ^1H NMR ($CDCl_3$) δ 7.0 (q, *J* = 8 Hz, 4 H), 5.5 (dd, *J* = 8 and 4 Hz, 1 H), 2.9–0.9 (series of m, 9 H) with distinguishable singlets at 2.3 (3 H), 1.6 (2 H), 1.2 (3 H), 1.15 (3 H), 0.9 (3 H).

Distillative pyrolysis of this solid at 200 °C and 25 mm afforded a clear, colorless oil, which was taken up in ether. The ethereal solution was washed with 10% hydrochloric acid and brine, dried, and evaporated.

MPLC purification of the residue (silica gel, elution with 5% ethyl acetate in petroleum ether) gave ketone **36** as clear, colorless oil (377 mg, 100%): IR (cm^{-1}, neat) 3040, 2900, 1720, 1440, 1180; ^1H NMR ($CDCl_3$) δ 5.83 (dt, J = 6 and 2 Hz, 1 H), 5.38 (dt, J = 6 and 2 Hz, 1 H), 2.51 (ddt, J = 17, 10, and 7 Hz, 2 H), 2.43-1.56 (series of m, 7 H), 1.08 (s, 3 H), 1.06 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 222.49, 134.68, 133.21, 78.05, 58.37, 56.83, 53.81, 52.34, 42.28, 39.63, 29.30, 28.96, 26.12, 23.44; m/e calcd (M^+) 204.1514, obsd 204.1518.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.19; H, 9.96.

2,2,4,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undeca-6,9-diene (37). Methyllithium (12 mL of 1.2 M in hexane, 1.47 mmol) was added dropwise to a cold (-78 °C), magnetically stirred solution of **36** (300 mg, 1.47 mmol). The reaction was allowed to proceed for 6 h at -78 °C and then overnight at room temperature. The mixture was poured into water, neutralized with dilute hydrochloric acid, and extracted with ether. The combined organic layers were washed with brine, dried, and concentrated. The clear, colorless oil thus obtained (320 mg, 100%) was dissolved in dry benzene (20 mL) containing p-toluenesulfonic acid (50 mg, 0.26 mmol) and heated at reflux under a Dean-Stark trap. The cooled reaction mixture was washed with saturated sodium bicarbonate solution and brine prior to drying and concentration.

Anal. Calcd for $C_{15}H_{22}$: C, 89.04; H, 10.96. Found: C, 88.93; H, 10.91.

Monoepoxidation of 37. To a cold (0 °C), stirred mixture of **37** (100 mg, 0.50 mmol), sodium carbonate (50 mg, 0.58 mmol), and dichloromethane (7 mL) was added 40% peracetic acid (118 μL, 0.50 mmol). The reaction mixture was stirred at 0 °C for 6 h and at room temperature overnight. Water was added and the organic layer was separated, dried, and concentrated. There was isolated 110 mg (100%) of **38** as a clear, homogeneous oil: IR (cm^{-1}, neat) 3040, 2930, 2860, 1445, 1380, 1365, 1245, 1080, 1005, 830, 735, 710; ^1H NMR ($CDCl_3$) δ 5.72 (m, 2 H), 3.42 (s, 1 H), 1.96 (m, 2 H), 1.88 (m, 3 H), 1.84 (s, 2 H), 1.33 (s, 3 H), 1.21 (s, 3 H), 1.00 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 136.51, 130.61, 73.86, 67.24, 63.25, 60.30, 55.16, 51.50, 49.64, 38.10, 30.99, 30.67, 27.82, 27.66, 15.41; m/e calcd (M^+) 218.1671, obsd 218.1676.

2,2,4,9-Tetramethyltricyclo[6.3.0.0^{4,8}]undec-6-en-10-one (39). Boron trifluoride etherate (73 mg, 0.52 mmol) was added to a solution of **38** (110 mg, 0.51 mmol) in benzene (5 mL), and the mixture was stirred overnight at room temperature. The resulting black solution was poured into water and extracted with ether. The organic layer was washed with brine, dried, and concentrated. The resulting brown oil was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give **39** as a colorless, homogeneous oil (104 mg, 95%): IR (cm^{-1}, neat) 3020, 2960, 2840, 1730, 1445, 1360, 1125; ^1H NMR ($CDCl_3$) δ 5.55 (dt, J = 7 and 2 Hz, 1 H), 5.50 (dt, J = 7 and 2 Hz, 1 H), 2.42 (ddt, J = 14, 8, and 2 Hz, 2 H), 2.33 (s, 1 H), 2.29 (s, 2 H), 2.16 (q, J = 18 Hz, 1 H), 1.80 (d, J = 2 Hz, 2 H), 1.14 (s, 3 H), 1.02 (s, 3 H), 0.96 (s, 3 H), 0.93 (d, J = 8 Hz, 3 H); ^{13}C NMR (ppm, $CDCl_3$) 221.40, 135.74, 127.12, 70.52, 58.96, 51.55, 49.95, 47.78, 40.18, 37.94, 31.10, 26.51, 25.99, 11.81; m/e calcd (M^+) 218.1670, obsd 218.1676.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.74; H, 9.98.

Silphinene (4). A mixture of **39** (5 mg, 0.02 mmol), hydrazine hydrate (100 μL, 2.0 mmol), anhydrous potassium carbonate (100 mg, 0.72 mmol), and diethylene glycol (1 mL) was heated overnight at 150 °C and at 200 °C for 4 h. The cooled reaction mixture was treated with water and ether, and the separated organic phase was washed with 10% hydrochloric acid and brine prior to drying. Careful concentration in vacuo gave 4 (83% by VPC analysis), which was purified by preparative VPC (5 ft × 0.25 in. 5% SE-30, 130 °C). The 200-MHz ^1H NMR spectrum of this hydrocarbon proved identical in all respects to that of natural silphinene.[2]

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Total Synthesis of (±)-Pentalenene, the Least Oxidized Neutral Triquinane Metabolite of *Streptomyces griseochromogenes*

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Abstract: Pentalenene, the neutral precursor to pentalenic acid and a variety of pentalenolactones, has been synthesized from 4,4-dimethyl-2-cyclopentenone. Following hydrosilation, dichloroketene addition, and hydrolysis, ring expansion to the highly functionalized bicyclo[3.3.0]octanone **22** was achieved with diazomethane. Reduction with zinc and acetic acid led to regiospecific α-chloro enone formation. In six additional steps, an angular propionaldehyde group was introduced and a second double bond was cleanly set in place. At this point, the protocol involved closure of the third five-membered ring, stereocontrolled insertion of the final methyl group, and reductive removal of the carbonyl functionality. The synthetic racemic hydrocarbon exhibited spectral properties identical with those of the natural product.

Sesquiterpenoid metabolities having a tricyclo[6.3.0.0^{4,8}]undecane skeleton that features a bridged spirane arrangement of three cyclopentane rings, together with ring-expanded δ-lactone congeners, have been reported in increasing numbers in recent years.[1] The design of efficient, stereocontrolled pathways to isocomene (**1**),[2-4] silphinene (**2**),[5,6] senoxydene (**3**),[7,8] retigeranic acid (**4**),[9-11] and pentalenolactone E methyl ester (**5**)[12,13] has recently been undertaken in this laboratory. As part of this

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