Synthesis of Racemic Fomannosin and Illudol Using a Biosynthetically Patterned Common Intermediate

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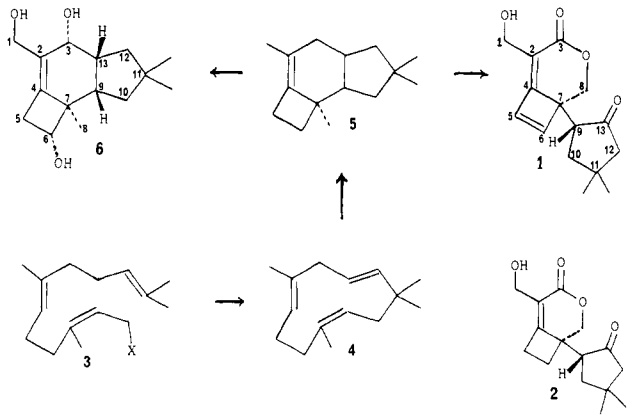
Abstract: The synthesis of fomannosin, a toxic fungal metabolite with a unique methylenecyclobutene structure, is approached in two different ways, making use of rigid tricyclic intermediates to control the configuration at two crucial chiral centers. The first approach was carried through the formation of the cyclobutane ring, using cycloaddition of ethoxyacetylene to a ketene. The stereoselectivity was disappointing, and that strategy was abandoned in favor of an approach which derived from the biosynthesis pathway for fomannosin. In this route, the Diels–Alder reaction of a cyclobutenecarboxylate with the appropriate diene generates the tricyclic protoilludane skeleton stereospecifically. The Diels–Alder adduct is converted through a series of eight steps to racemic illudol, a natural protoilludane sesquiterpene, and through 11 steps to result in the first total synthesis of fomannosin.

Fomannosin (**1**) is a biologically active sesquiterpene metabolite of the wood-rotting fungus *Fomes annosus* which affects pine stands in the Southeastern United States.[1] It was isolated by chloroform extraction of a still culture of *Fomes annosus* and purified by silica gel chromatography. The pure material is an "unstable semisolid"[1a] and was shown to be toxic toward 2-year-old *Pinus tadea* seedlings, *Chlorella pyrenoidosa*, and some bacteria.[1b]

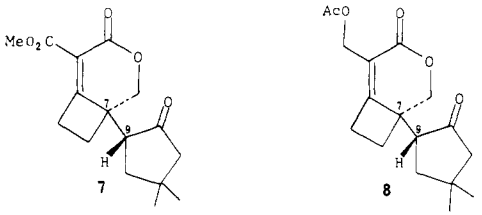
The structure was first established[1a] by an X-ray diffraction study on the *p*-bromobenzylurethane of the 5,6-dihydro derivative, **2**, and the absolute configuration was later defined to be as shown in **1** by a second X-ray diffraction study on the ester of dihydrofomannosin with (−)-camphanic acid.[2] Fomannosin is not a product from simple cationic cyclizations of farnesyl derivatives, and a more complex biosynthesis scheme has been proposed[3] and supported experimentally.[4] Since these results provided a strong hint for the synthesis strategy, a brief summary is included here. Through double ^{13}C-labeling experiments, a pathway was established from farnesyl pyrophosphate (**3**, X = OP_2O_7) through humulene (**4**) and the protoilludane skeleton (**5**) to fomannosin (**1**).[4] While the detailed pathway of conversion of **5** to **1** has not been defined, the connectivity implied in Scheme I points to a synthesis strategy for fomannosin and leads naturally to a consideration of the synthesis of illudol (**6**) from a common intermediate related to **5** in the biosynthesis scheme.

The structure of illudol, a metabolite of *Clitocybe illudens*,[5] was proposed in 1967 on the basis of spectral and chemical evidence,[6] but the absolute configuration has not been determined. A synthesis was reported in 1971 which used a nonstereospecific photochemical [2 + 2] cycloaddition of 1,1-diethoxyethylene with a 2-cyclopentenone derivative to form the crucial cyclobutane unit.[7]

Scheme I, Biosynthesis Connection



No synthesis of fomannosin (**1**) has appeared, but Matsumoto and co-workers[8] have used a scheme parallel with their illudol pathway[7] to prepare the first example of the fomannosin skeleton, **7**, and by a different route Kosugi and Uda have prepared (±)-5,6-dihydrofomannosin acetate (**8**).[9] In both syntheses, the



relative stereochemical relationships at C-7/C-9 were introduced with low stereospecificity during formation of the cyclobutane ring by photochemical [2 + 2] cycloaddition of ethylene. In this paper, we describe efforts directed toward the stereospecific syntheses of (±)-fomannosin and of (±)-illudol, based on the biosynthesis scheme.[10,11]

(1) (a) J. A. Kepler, M. E. Wall, J. E. Mason, C. Basset, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **89**, 1260 (1967); (b) C. Bassett, R. T. Sherwood, J. A. Kepler, and P. B. Hamilton, *Phytopathology*, **57**, 1046 (1967). Isolation form *Fomitopsis insularis* has also been reported: S. Nozoe, H. Matsumoto, and S. Urano, *Tetrahedron Lett.*, 3125 (1971).

(2) D. E. Cane, R. B. Nachbar, J. Clardy, and J. Finer, *Tetrahedron Lett.*, 4277 (1977).

(3) Possible biosynthesis schemes including the relationship between illudol and fomannosin were first brought to our attention by Professor D. Arigoni, ETH, Zurich. Suggestions were published earlier: (a) W. Parker, J. S. Roberts, and R. Ramage, *Q. Rev., Chem. Soc.*, **21**, 331 (1967); (b) "Handbook of Naturally Occurring Compounds", Vol. II, T. K. Devon and A. I. Scott, Eds., Academic Press, New York, 1972, p 56.

(4) (a) D. E. Cane and R. B. Nachbar, *Tetrahedron Lett.*, 2097 (1976); (b) D. E. Cane and R. S. Nachbar, *J. Am. Chem. Soc.*, **100**, 3208 (1978).

(5) M. Anchel, A. Hervey, and W. J. Robbins, *Proc. Natl. Acad. Sci. U.S.A.*, **36**, 300 (1950).

(6) T. C. McMorris, M. S. R. Nair, and M. Anchel, *J. Am. Chem. Soc.*, **89**, 4562 (1967).

(7) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa, and A. Ichibara, *Tetrahedron Lett.*, 3521 (1971). This class of compounds has been reviewed: H. Shirahama and T. Matsumoto, *Kagaku no Ryoiki*, **34**, 22 (1980).

(8) K. Miyano, F. Ohfune, S. Azuma, and T. Matsumoto, *Tetrahedron Lett.*, 1545 (1974).

(9) (a) H. Kosugi and H. Uda, *Chem. Lett.*, 1491 (1977); (b) H. Kosugi and H. Uda, *Bull. Chem. Soc. Jpn.*, **53**, 160 (1980).

(10) Preliminary accounts of the illudol synthesis have appeared: (a) M. F. Semmelhack, S. Tomoda, and K. M. Hurst, "Abstracts of Papers", 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 1980; ORGN 24; (b) M. F. Semmelhack, S. Tomoda, K. M. Hurst, *J. Am. Chem. Soc.*, **102**, 7567 (1980).

(11) For preliminary account of the fomannosin synthesis: American Chemical Society: Washington, D.C., 1980; M. F. Semmelhack and S. Tomoda, *J. Am. Chem. Soc.*, **103**, 2427 (1981).

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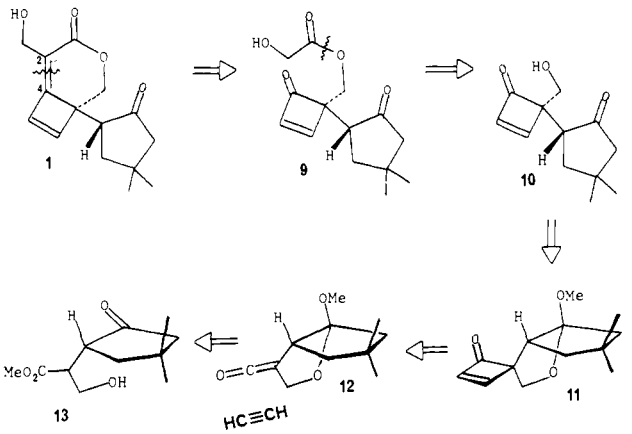
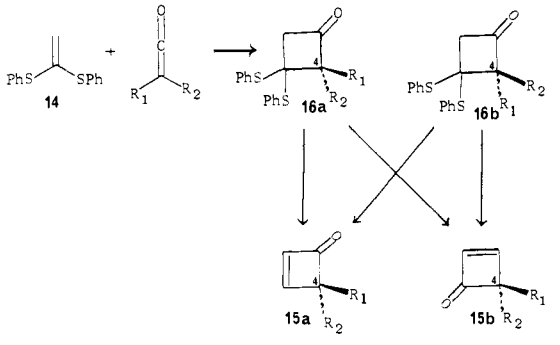
Scheme II. A Strategy for the Synthesis of Fomannosin



Results and Discussion

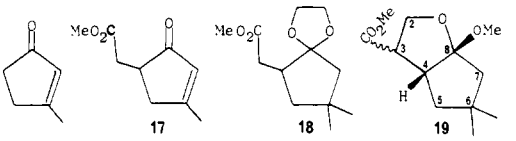
Two features of the structure of fomannosin are primarily important in devising a synthesis strategy. First, there are two adjacent chiral centers (C-7, C-9) and no reason to believe that the natural arrangement (**1**) is more stable than the diastereoisomer; kinetically controlled stereospecific formation of these centers is required. Obviously, the chiral center at C-9 is rather easily epimerizable in acid or base.[12] Second, fomannosin is a delicate molecule, largely due to the strained and electron-deficient methylenecyclobutene portion. Introduction of one or both of the double bonds at a late stage would be a virtue in the synthesis plan. In both of our general strategies the stereochemical relationships are controlled by building rigid tricyclic frameworks, in which it is hoped to prepare one diastereoisomer selectively. In both cases, the four-membered ring is obtained by simple thermal [2 + 2] cycloaddition reactions driven by highly polarized reactants.

The Ketene Cycloaddition Approach to Fomannosin.[13] One retrosynthetic analysis for fomannosin is outlined in Scheme II. Cleavage of the C-2/C-4 bond and the lactone leaves a 4,4-disubstituted cyclobutenone (**10**) which still bears the crucial stereochemical elements. An internal ketal provides a folded bicyclic system (**11**, **12**) where the ketene C=C unit appears from models to have sterically well-differentiated faces. The starting cyclopentanone derivative **13** was unknown but quite simple. An important consideration is the choice of an acetylene equivalent to bring into reaction with **12** and the degree of stereospecificity possible in formation of **11**. Inspection of models leads to the conclusion that the direction of approach of the acetylene is likely to be opposite that required in **11**. It is convenient then to choose a versatile acetylene equivalent with functionality which can be converted into either a C=C or C=O. For example, the ketene thioacetal **14** is known to undergo [2 + 2] cycloaddition with



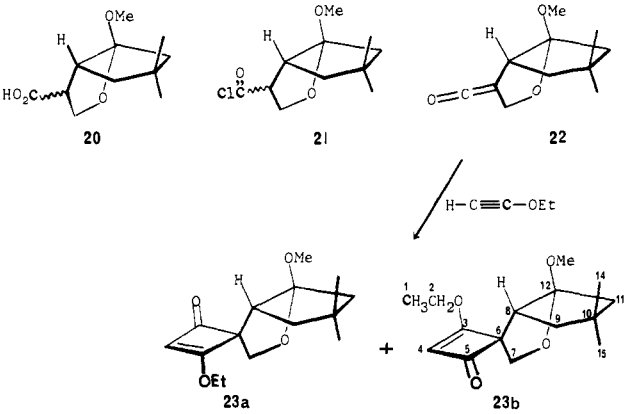
ketenes[14] and offers the possibility of conversion to cyclobutenone **15a** or **15b**. The interconversion of **15a** and **15b** amounts to inversion of configuration at C-4. Proper choice of manipulations of the cycloadducts **16a** and **16b** would allow formation of either isomer of **15**.

The preparation of cyclopentanone **13** was achieved in five steps from 3-methyl-2-cyclopentenone. The kinetic enolate was added to excess methyl bromoacetate to give **17** in variable yield



(20–40%). Reaction with lithium dimethylcuprate followed by ketalization produced ketal ester **18** (88% yield). The ester enolate from **18** reacted with excess monomeric formaldehyde to add the hydroxymethyl group (in **13**). Reaction of **13** with boron trifluoride in methyl alcohol led to the internal ketal, **19** (76% from **18**). A mixture of diastereoisomers from **19** was indicated by a doubling of all but three of the signals in the proton noise-decoupled ^{13}C NMR spectrum. While the enolate anion of **19** could be generated and quenched with deuterium oxide to give high incorporation of deuterium at C-3, a mixture of diastereoisomers remained. Saponification of **19** with potassium hydroxide afforded carboxylic acid **20** in 95% yield as a colorless oil.

Formation of the carboxylic acid chloride (**21**) was successful when scrupulously anhydrous conditions were used in reaction of the sodium salt of **20** with oxalyl chloride. The ketene (**22**) was



generated in situ by reaction with triethylamine in benzene solution and was not stable enough to characterize. With a series of electron-rich alkenes that are known to react with ketenes to give cyclobutanones (1,1-dimethoxyethylene,[15] phenyl vinyl thioether,[16] and *tert*-butyldimethyl(vinyloxy)silane[16b]) added after or during generation of the ketene, no trace of the desired cyclobutanone product was given. In general, discrete 1:1 adducts could not be isolated.

Much more successful was the addition of a solution of **21** in carbon tetrachloride to a mixture of triethylamine and excess ethoxyacetylene at 0 °C. After 40 h, a mixture of 1:1 cycloadducts was obtained (43% yield from **20**) and separated into diastereoisomers **23a** (23% yield) and **23b** (19% yield). The presence of the cyclobutenone moiety was confirmed by the appearance of IR signals at 1752 and 1567 cm^{-1}. The spectral characterizations were in close agreement with those reported for a similar series of 3-ethoxy-2-cyclobutenones.[15]

Evidence for the relative configurations of **23a** and **23b** was also available from spectroscopic analysis and chemical studies. The configuration of spirocyclobutanones has been correlated with ^{13}C and ^{1}H NMR chemical shifts.[17] The relevant data are given

(12) A determination of the ease of epimerization of fomannosin has not been reported. However, during slow chromatography of an extract containing fomannosin, an isomer was detected but not fully characterized. Personal communication of Professor D. E. Cane, Brown University.

(13) Taken in part from the Ph.D. thesis of Susan Boettger, Cornell University, 1978.

(14) For example, see: D. Seebach in "Methoden der Organische Chemie (Houben Weyl)", Vol. 4, E. Mueller, Ed., George Thieme Verlag, Stuttgart, 1971, pp 200–201.

(15) R. Scarpati and D. Sica, *Gazz. Chim. Ital.*, **92**, 1073 (1962).

(16) (a) J. C. Martin, *Chem. Abstr.*, **63**, 9834 (1965); (b) R. H. Hasek, P. G. Gott, and J. C. Martin, *J. Org. Chem.*, **29**, 1239 (1964).

Table I. ^{13}C NMR Data for Isomers **23a**, **23b**

carbon[c]	δ(^{13}C)[a] 23a	23b	carbon	δ(^{13}C) 23a	23b
1	13.88, q[b]	13.98	9	40.26, t	40.81
2	69.01, t	69.28	10	40.26, s	40.63
3	184.72, s	184.30	11	46.96, t	47.25
4	106.63, d	107.16	12	120.96, s	120.90
5	187.50, s	188.04	13	50.20, q	50.27
6	70.37, s	71.94	14	29.74, q	26.69
7	69.50, t	69.52	15	28.62, q	28.36
8	53.14, d	52.13			

[a] In ppm downfield from tetramethylsilane. [b] Multiplicity in SFORD spectrum: s = singlet; d = doublet; t = triplet; q = quartet. [c] The numbering scheme used in this table is from the drawing of structure **23b**.

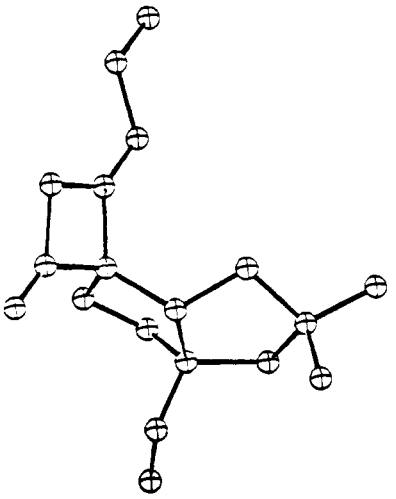
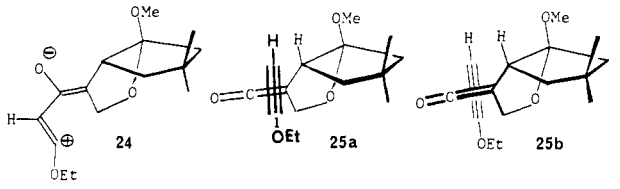


Figure 1. ORTEP drawing from the X-ray diffraction study of **23a**.

in Table I, showing the deshielding of the C-9 methylene group in **23a** due to the proximity of the carbonyl unit, and the ^{13}C signal for C-8 and C-3 appears relatively downfield in **23a** compared to **23b**, consistent with simple analogues.[17] The sterically encumbered position of the carbonyl group in **23b** is indicated by a higher R_f for **23b** on silica gel TLC analysis and a much slower rate of reaction with sodium borohydride in methyl alcohol. Isomer **23a** solidified (mp 43.5–45.5 °C) and was subjected to X-ray diffraction analysis to verify the structural assignment (Figure 1).[18]

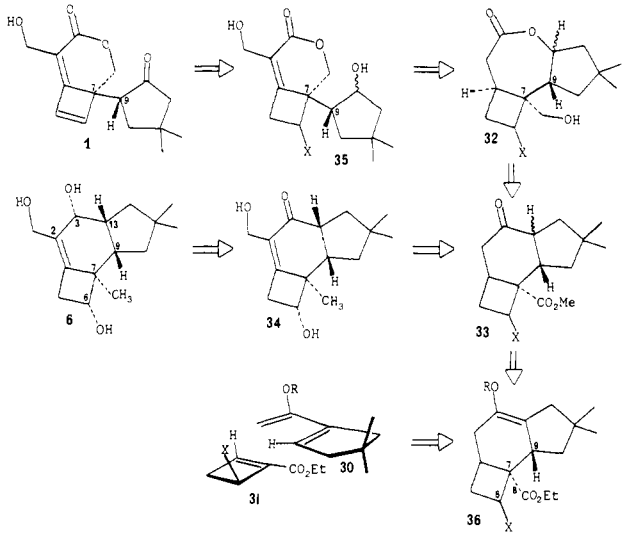
The lack of stereoselectivity in the ketene cycloaddition was disappointing and not easily rationalized, since the faces of the ketene C=C unit appear from models to have very different steric environments. Stepwise addition via a dipolar intermediate (i.e., **24**) in particular seems to require preferential formation of **23a**



from steric considerations. However, ketene addition via a $_{\pi}2_s + {}_{\pi}2_a$ concerted pathway requires the orthogonal approach[19] of the reacting species (in **25**), and only small differences appear in the steric interactions comparing the two modes of addition

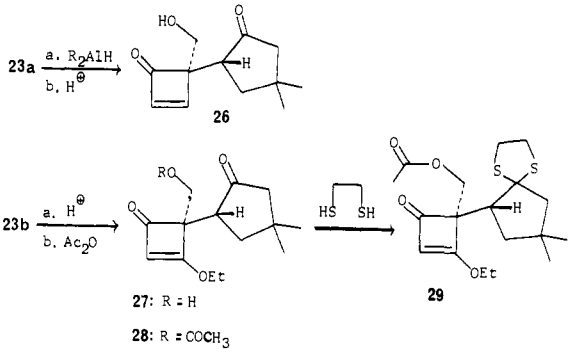
(17) B. M. Trost and P. H. Scudder, *J. Am. Chem. Soc.*, **99**, 7601 (1977).
(18) We thank the Cornell X-Ray Structures Facility and Professor Jon Clardy for carrying out the structure determination of **23a**.
(19) (a) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971); (b) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, 1971, pp 163–168.

Scheme III, Strategy for Synthesis of Fomannosin and Illudol via a Common Intermediate



(**25a**, **25b**). For practical purposes, reaction of **23b** with aqueous sodium hydroxide followed by methylation produced a 3:2 mixture of **23a**:**23b** (O-methyl analogues) in 95% yield. In this way, pure **23b** was obtained in 30% yield overall from the cycloaddition reaction.

In a series of preliminary reactions, further conversions of **23** were studied. Reaction with diisobutylaluminum hydride followed by delicate acid hydrolysis (oxalic acid in a water–ether two-phase system) produced **26** in 64% yield. This product proved to be



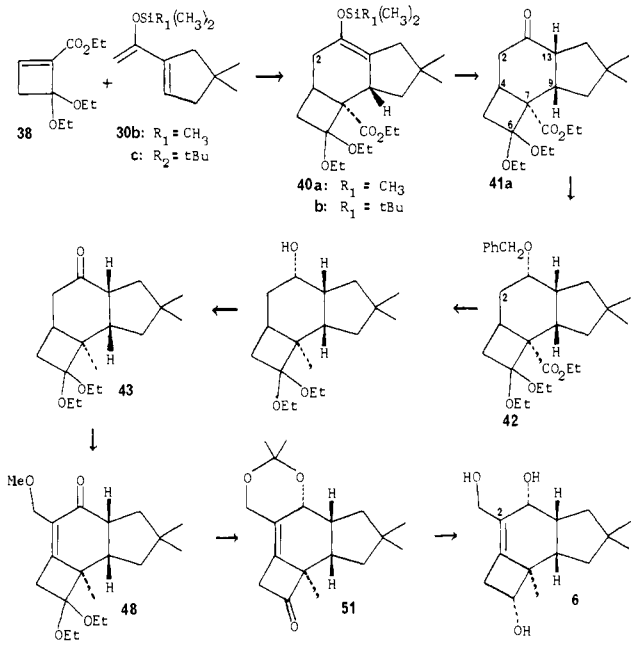
difficult to work with in attempts to add the final three-carbon unit. However, initial hydrolysis of the internal ketal produced **27** which could be acetylated to afford **28**. The cyclopentanone carbonyl group was protected as the thioketal (**29**), but efforts to carry on with intermediates **26**–**29** have not yet been successful.

The Synthesis of Fomannosin and Illudol from a Common Intermediate. The strategy inspired by the biosynthetic relationships is outlined in Scheme III. The skeleton is to be assembled through cycloaddition of a cyclobutenecarboxylate with the diene, **30**.

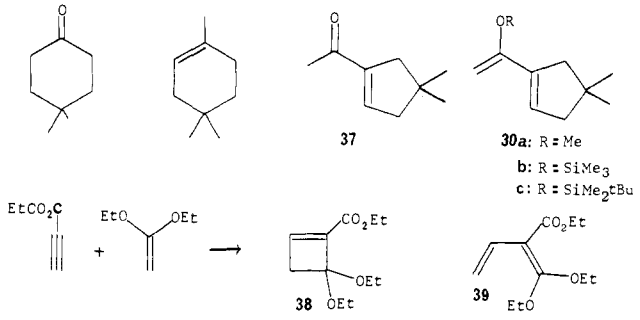
The ester unit in **31** is important in accelerating the cycloaddition and also in providing the oxygen functionality at C-8 in **32** for the lactone of fomannosin; however, it must be fully reduced for illudol. One carbon must be added to **33**, adjacent to a ketone (in **34**) and adjacent to a lactone (in **35**). The critical stereochemical relationships for fomannosin are fixed during cycloaddition. Endo addition (as shown in Scheme III) should be favored and would give the proper 7*R*,9*S*/7*S*,9*R* configuration. Illudol has three additional chiral centers (C-3, C-6, and C-13); the earlier synthesis showed that hydride reduction of carbonyl groups at C-3 and C-6 gives predominantly the correct configuration.[7] The remaining center at a C-13 arises from hydrolysis of the enol ether in **36**; the cis ring fusion may not be strongly favored thermodynamically.

Several versions of diene **30** were prepared (R = CH_3, Si$(CH_3)_2(t\text{-Bu})$, Si$(CH_3)_3$) from ketone **37**, which, in turn, was

Scheme IV, The Synthesis of Illudol



obtained on large scale from isobutyraldehyde and methyl vinyl ketone through 4,4-dimethylcyclohexanone according to Scheme IV. The overall yield is 30–35%.[20] Reaction of **37** with lithium

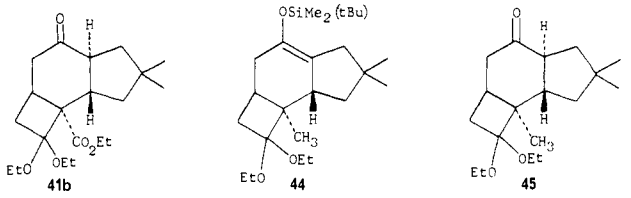


diisopropylamide followed by quenching with methyl *p*-toluenesulfonate produced **30a** in 40% yield. Similarly, by use of the chlorotrialkylsilanes, **30b** (99%) and **30c** (96%) were obtained. A series of test reactions with **30a** proved disappointing; no cycloadduct with simple acrylate derivatives was detected, neither under thermal reaction conditions nor with catalysts. At elevated temperatures (>120 °C) the acrylates polymerized and the diene could be recovered. Nevertheless, it was hoped that the cyclobutenecarboxylate (**31**) would be more reactive than simple acrylates[21] and that the siloxy diene derivatives (**30b,c**) would be more reactive than **30a** for steric and/or electronic reasons.[22]

The highly functionalized cyclobutene **31** is of a type which has recently been prepared by Lewis acid catalyzed [2 + 2] cycloaddition of propiolic esters with electron-rich alkenes.[23] After initial studies using various Lewis acids, we found that a simple thermal reaction of ethyl propiolate with 1,1-diethoxyethylene produces an appropriate cyclobutene (**38**) in 65% yield. As expected, ring opening of **38** occurs rapidly at 90 °C ($t_{1/2}$ = 30 min) to give diene **39** in high yield. This reactivity bodes ill for the desired Diels–Alder reaction with **30**, but under carefully controlled conditions (minimum reaction temperature, extended time), 1:1 adducts were obtained in 70–75% yield and >95% selectivity after purification by column chromatography. Structures **40a** and **40b** were assigned to the adducts on the basis of spectral data. However, the stereochemical assignment was secure only after the conversion to illudol, which requires the configuration shown in **40** (Scheme IV).

Hydrolysis of **40a** and **40b** with either fluoride anion or gentle base produced a mixture of the desired cis ring fusion (**41a**) and the corresponding trans isomer (**41b**) in similar amounts. The pure cis isomer **41a** was converted to a mixture of **41a** and **41b** (≃60:40, favoring **41a**) upon treatment with dilute sodium methoxide in methyl alcohol. However, desilylation of **40a** could be achieved under mild conditions by using 3-Å sieves as catalyst in methyl alcohol to give exclusively the cis product, **41a**. In order to prepare for conversion of the ester unit to a methyl group, we reduced the ketone to an alcohol which was protected as a benzyl ether (**42**). Then following Ireland's procedure,[24] we reduced the ester to an alcohol which was converted to a phosphorodiamidate, and the carbon–oxygen bond was cleaved by lithium metal under special low-temperature conditions; the benzyl protecting group was also cleaved. Then oxidation with Collin's reagent gave the ketone **43** in 56% yield overall from **40a**.

An alternative preparation of **43** without the use of the benzyl protecting group was developed through application of Ireland's reduction method directly on the *tert*-butyldimethylsilyl ether **40b**. The reduced compound **44** was obtained in 74% yield, and de-



silylation with fluoride anion gave a mixture of **43** and the corresponding trans isomer **45** which was separated by chromatography. Equilibration of the trans isomer in dilute sodium methoxide/methyl alcohol gave a mixture of **43**/**45** (60/40) from which **43** was isolated. The combined yield of **43** after two equilibrations was 89%, corresponding to a yield of 65% overall from **40b**.

Functionalization of C-2 in **43** was accomplished by carboxylation of the kinetic enolate anion with carbon dioxide (followed by methylation with diazomethane). Treatment of **46** with lithium diisopropylamide produced an anion which reacted with phenylselenyl chloride to afford a single isomer (37% yield overall from **43**). Since oxidation of **47** to the selenoxide led to efficient (98% yield) elimination at 20 °C to give **48** (Scheme IV), the stereochemistry of **47** is assigned consistent with the required syn-elimination pathway.[25] Reversing the order of the operations (selenylation followed by carboxylation) produced an intermediate

(20) We thank Professor James Burlitch for supervising the large scale preparation of intermediates in Scheme IV by students in the advanced laboratory course.

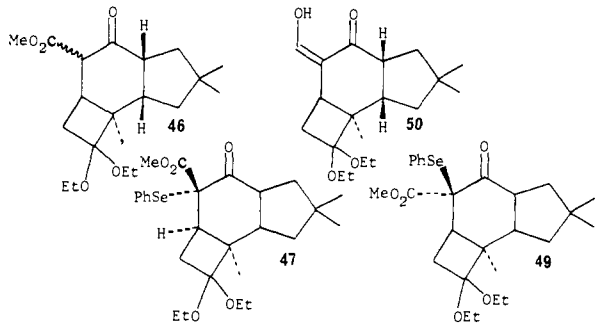
(21) Diels–Alder reactions of cyclobutenes have not been studied extensively; little relevant experimental data are available on systems closely related to **31**. For a discussion of cyclobutene itself in Diels–Alder reactions, see: V. V. Plemenkov and V. P. Kostin, *J. Org. Chem. USSR*, **15**, 1086 (1979). For Diels–Alder reactions of 4,4-dimethylcyclobutenone, see: T. R. Kelly and R. W. McNutt, *Tetrahedron Lett.*, 285 (1975).

(22) While the reasons for more successful reactions of **30b** and **30c** compared to **30a** are not completely clear, two factors seem most likely. The concentration of the cisoid conformer i might be higher for **30b** and **30c** due to smaller gauche reactions with the CH_2 group at C-5 because of the long O–Si bond relative to the O–CH_3 bond in **30a**. The trialkylsilane units might be expected to be somewhat more electron releasing than –CH_3 and thereby increase the electronic driving force. We are aware of no quantitative data which define the influence of siloxy relative to methoxy in the 2-position of a Diels–Alder diene, but one report with 2-(trimethylsilyl)oxy-1,3-butadiene suggests "approximately the same reactivity" at 2-ethoxy-1,3-butadiene: M. E. Jung and C. A. McCombs, *Tetrahedron Lett.*, 2935 (1976).

(23) For examples, see: (a) B. B. Snider, D. J. Rodini, R. S. E. Conn, and S. Sealfon, *J. Am. Chem. Soc.*, **101**, 5283 (1979). (b) R. D. Clark and K. G. Untch, *J. Org. Chem.*, **44**, 248 (1979). Simple thermal [2 + 2] cycloaddition of enamines with propiolate esters also produces cyclobutene-2-carboxylates. (c) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28**, 3134 (1963). (d) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **29**, 818 (1964).

(24) R. E. Ireland, D. C. Muchmore, and U. Hengartner, *J. Am. Chem. Soc.*, **94**, 5098 (1972).

(25) H. J. Reich, F. Chow, and S. K. Shah, *J. Am. Chem. Soc.*, **101**, 6638 (1979), and references therein.

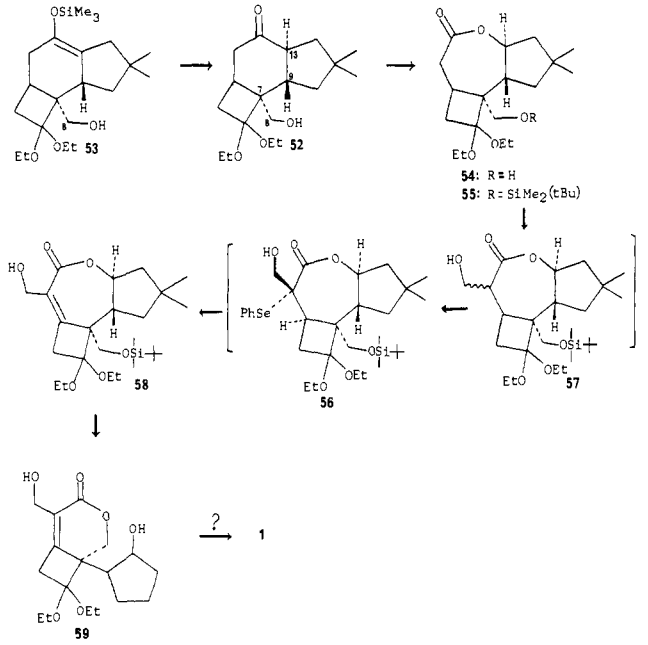


(**49**) from which selenoxide elimination gave only the α-formyl ketone, **50**.

The keto ester **48** was employed in the previous synthesis of illudol,[7] and we made no effort to improve on the published procedure. Reduction of **48** with excess Red-al[26] produced a diol which reacted with acetone (catalytic *p*-toluenesulfonic acid) to give keto acetonide **51**. Hydride reduction and acid-promoted hydrolysis of the acetonide gave a single product, identified as racemic illudol (**6**) by comparison with material from nature.[27]

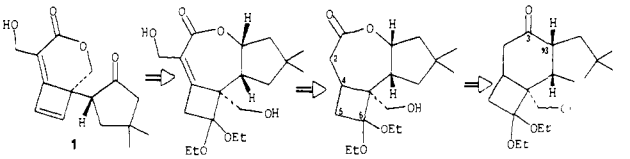
Synthesis of Fomannosin (1). The strategy for conversion of **40** to fomannosin is outlined in Scheme V. There are four crucial steps: (a) oxidative cleavage at C-3/C-13, (b) introduction of the hydroxymethyl unit, (c) trans lactonization to give the fomannosin skeleton, and (d) introduction of the strained cyclobutene double bond.

The initial sequence tested began with reduction of ester **40a** followed by hydrolysis of the enolsilyl ether unit with 3-Å molecular sieves in methyl alcohol as before (with **40a**). In this case, the trans isomer **52** was obtained exclusively (95% yield), presumably the kinetic product after internal proton delivery from the hydroxymethyl group at C-8 in **53**. Baeyer–Villiger oxidation

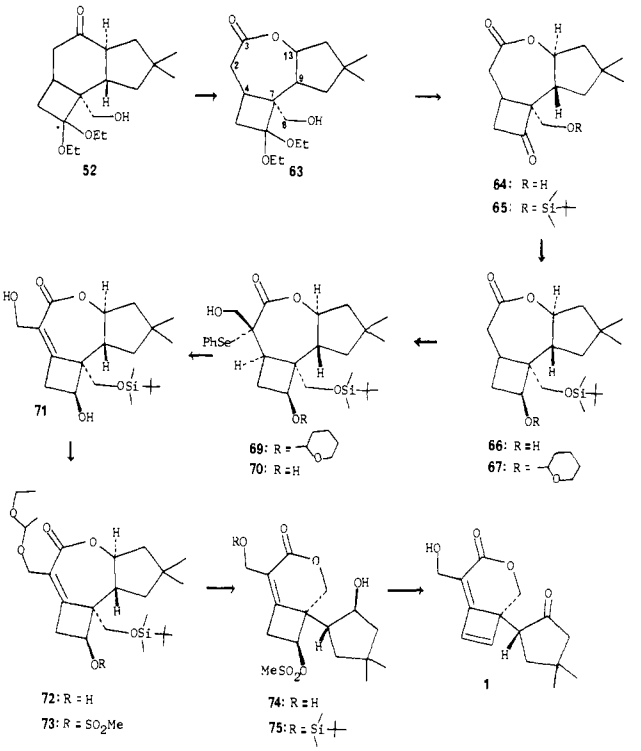


of **52** using buffered *m*-chloroperbenzoic acid produced a single isomer, **54**, and the primary hydroxyl group was protected by reaction with chlorodimethyl-*tert*-butylsilane (**55**; 90% yield from **52**). Formaldehyde was the source of the hydroxymethyl side chain at C-2, using a sequence parallel with that for illudol, Scheme IV. The lithium enolate of **55** was added to excess formaldehyde, and the product was converted to the dianion with

Scheme V, Specific Strategy for Fomannosin from 40

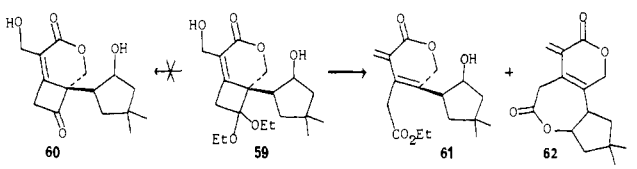


Scheme VI. Synthesis of Fomannosin



lithium diisopropylamide and allowed to react with phenylselenyl chloride. Under optimum conditions, a single product was obtained (**56**), but the yield was only 48%, and 40–45% of the intermediate (**57**) was recovered. Attempts to force complete conversion (by using excess reagents, longer time, higher temperature) did not improve the absolute yield. The stereochemistry of **56** is again based primarily on easy selenoxide elimination (86% yield, 20 °C, 0.3 h) to give **58**. The pattern of reactivity of enolate anions derived from **55** and from **43** indicates preferential electrophile addition syn to the proton at C-4, presumably due to steric effects.

Reaction of **58** with tetra-*n*-butylammonium fluoride[28] removed the silyl protecting group and induced a rapid trans lactonization to the six-membered lactone (**59**; 47% yield) appropriate for fomannosin (**1**). However, at this stage, serious problems were encountered in the hydrolysis of the ketal unit to the cyclobutanone (in **60**). All attempts at acid-catalyzed hydrolysis on **59** and **58**,



and related derivatives, failed to give a cyclobutanone; preliminary characterization of two byproducts (**61, 62**) suggests ring cleavage as the primary process. Other conditions were tested unsuccessfully, including trimethylsilyl iodide.[29]

An alternative ordering of the steps avoided the ring cleavage (Scheme VI). Baeyer–Villiger oxidation directly on **52** gave **63**

(26) Red-al is the trade name (Aldrich Chemical Co.) for a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene; it is also known as Vitride (Eastman Organic Chemicals).

(27) We are grateful to Dr. M. Anchel of the New York Botanical Garden for providing a sample of (−)-illudol.

(28) E. J. Corey and B. B. Snider, *J. Am. Chem. Soc.*, **94**, 2549 (1972).

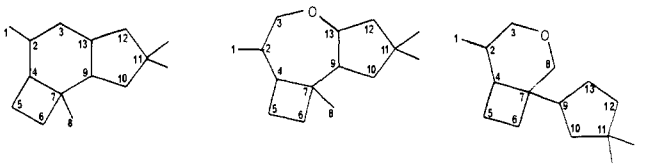
(29) M. E. Jung and M. A. Lyster, *J. Am. Chem. Soc.*, **99**, 968 (1977).

(96% yield), and ketal hydrolysis at −20 °C produced the cyclobutanone **64** (91%). At higher temperature, lactone cleavage products were observed. After protection of the primary hydroxyl group (**65**), the ketone was reduced with sodium borohydride, and the resulting secondary hydroxyl (in **66**) was converted to a tetrahydropyranyl ether (**67**). The configuration of the hydroxyl group at C-6 was tentatively assigned as shown on the basis of a least-hindered approach and potential internal delivery after initial coordination of the reagent with the oxygen at C-8. A single isomer is obtained after column chromatography, in 85% yield from **64**. Introduction of the hydroxylmethyl group and C-2/C-4 double bond followed the procedure used earlier, except that intermediate **69** (obtained in 48% yield) was treated with pyridinium tosylate in methyl alcohol to free the secondary hydroxyl (**70**). Then selenoxide elimination gave the unsaturated lactone **71** in 71% yield. Selective acetylation of **71** at the primary hydroxyl could not be achieved, but reaction with ethyl vinyl ether and 1 molar equiv of pyridinium tosylate at −22 °C afforded **72** in 87% yield. Reaction of **72** with methanesulfonyl chloride served to protect the secondary hydroxyl (in **73**) and to provide the activation needed later for introduction of the cyclobutene double bond. Desilylation of **73** with hydrofluoric acid allowed trans lactonization to occur, producing diol **74**, in 72% yield overall from **72**. The primary hydroxyl was silylated carefully at −22 °C (**75**) and the secondary hydroxyl was oxidized to give **76** in 88% yield from **75**. Treatment of **76** with 1 molar equiv of fluoride anion in tetrahydrofuran at 25 °C gave racemic fomannosin (**1**). After rapid chromatography on silica gel, the pure sample was obtained as a colorless unstable semisolid in 81% yield. Comparison with a sample of natural (−)-fomannosin[30] shows identical TLC properties in two solvent systems and identical ^{1}H NMR and IR spectral data. The ^{13}C NMR spectral data matched well with reported values. The compound shows a remarkable sensitivity toward acid and base. Attempted epimerization to obtain the isomer with opposite configuration at C-9 could not be achieved due to rapid polymerization. Similarly, a solution of **1** in deuteriochloroform deteriorates over a few hours at 25 °C to produce an insoluble film on the NMR sample tube.

Experimental Section

General. Standard NMR techniques were employed, at 60 and 90 MHz for proton spectra and 22.5 MHz for ^{13}C NMR. Chromatographic solvents were purified by simple distillation. Ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under argon immediately before use. *N,N*-Dimethylformamide (DMF), pyridine, triethylamine, and diisopropylamine were distilled from calcium hydride under argon and stored over 4-Å molecular sieves at ambient temperature in a desiccator. Reactions involving organolithium reagents were carried out under dry argon in oven-dried glassware. Analytic thin-layer chromatography (TLC) was generally performed on precoated aluminum sheets (SiO_2 60F-259, 0.2 mm thick) with visualization obtained by UV fluorescence, iodine coloration, or 8 N sulfuric acid spray. Woelm silica gel (32–64 μm) and Merck silica gel for medium pressure liquid chromatography were used for all gravity flow and medium pressure chromatography (MPLC). Melting points are uncorrected unless otherwise noted. The term "flash distillation" refers to a vacuum distillation at 25 °C with a receiver at −78 °C. The term "short-path distillation" refers to the process in which the entire distillation apparatus (a tube closed at one end, held horizontally), with the exception of the receiver, was slowly heated in an air bath from 25 to 150 °C under vacuum; the distillate was collected at −78 °C, and boiling points for fractions refer to the bath temperature range. All boiling points are uncorrected. The term "under argon" means that the system was evacuated with an oil pump and refilled with argon three times, and a positive pressure (ca. 3 torr) of argon was maintained during the experiment. Microanalyses were performed by Scandanavian Microanalytical Labs, Herlev, Denmark.

Only the parent ion in the mass spectra is generally reported, to establish molecular weight. In cases where the spectra have been analyzed, the data are expressed with the nominal fragment weight followed in parentheses by the percent intensity taking the base peak as 100% and a suggestion for the atoms or group lost. Chemical ionization (CI) spectra show a parent ion at *m/e* for the molecule plus a proton (parent + one unit). For assignment of ^{1}H and ^{13}C NMR signals in structures **40–75**, the following numbering schemes were used on the basis of the system for fomannosin.[4]



Preparation of 5-[(Methoxycarbonyl)methyl]-3-methyl-2-cyclopenten-1-one (17). To a solution of diisopropylamine (1.68 mL, 1.21 g, 12 mmol) in THF at −50 °C was added rapidly *n*-butyllithium (4.82 mL of 2.28 M solution in hexane, 11 mmol). The mixture was warmed to 0 °C for 20 min and cooled to −78 °C, and a solution of 3-methylcyclopent-2-en-1-one (960 mg, 10 mmol) in THF (4 mL) was added dropwise via syringe over 30 min. After being stirred for 2 h at −78 °C, the reaction mixture was added over 3 min by means of a syringe to a solution of excess methyl bromoacetate (3.0 mL) at −25 to −30 °C. After being stirred for 5 min at −25 °C, the reaction mixture was cooled to −78 °C and 3 mL of dry methyl alcohol was added, followed immediately by ca. 3 g of dry ice. The mixture was stirred for 30 min at −78 °C, allowed to warm to −20 °C, and then diluted with 100 mL of dry ether, filtered through silica gel (10 g), and washed with ether. The combined ether solutions were concentrated by rotary evaporation to leave a brown residue which was purified by short-path distillation to give a colorless liquid: 550 mg, 31% yield; ^{1}H NMR (CCl_4) δ 5.81 (br s, 1 H, CH=C), 3.82 (s, 3 H, CO_2CH_3), 3.1–2.0 (m, 5 H), 2.12 (br s, 3 H); IR (CCl_4) 2950 (m), 1709 (s, C=O) cm^{-1}; mass spectral mol wt, 168; calcd for $C_9H_{12}O_3$, 168.

Preparation of 4,4-Dimethyl-2-[(methoxycarbonyl)methyl]cyclopentanone. To a suspension of cuprous iodide[31] (33.9 g, 178 mmol) at −50 °C in ether (700 mL) under argon was added dropwise over a few minutes a solution of methyllithium (275 mL of 1.3 M solution in ether, 357 mmol) via syringe. After addition, the mixture was warmed to −30 °C and then cooled to −60 °C and a solution of enone **17** (15.0 g, 89.3 mmol) in 30 mL of ether was added dropwise over 30 min. After being stirred for 1 h at −60 to 0 °C and for 30 min at 0 °C, the reaction mixture was poured into saturated aqueous ammonium chloride solution containing ammonium hydroxide. The blue aqueous phase was extracted three times with ether, and the combined ether solution was washed sequentially with saturated aqueous ammonium chloride solution and brine. After having been dried over anhydrous magnesium sulfate, the solution was concentrated by rotary evaporation to leave a residual oil, greater than 95% pure by ^{1}H NMR analysis, 14.8 g, 90% yield. Distillation in a short-path apparatus [90 °C (0.01 torr)] afforded a pale yellow liquid, 82% yield; analytical GLC showed one component (180 °C, 6 ft, 3% OV-17) of retention time 6.2 min; ^{1}H ($CDCl_3$) δ 1.10 (s, 3 H), 1.20 (s, 3 H), 1.33–2.30 (m, 2 H), 2.15 (s, 2 H), 2.41–2.97 (m, 3 H, $CHCH_2CO_2$), 3.67 (s, 3 H, OCH_3): IR (CCl_4) 2950 (m), 1739 (s, C=O), 1174 (m) cm^{-1}; mass spectral mol wt, 184.1093; calcd: 184.1098.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.47; H, 8.63.

Preparation of 1-Methoxy-4-(methoxycarbonyl)-7,7-dimethyl-2-oxabicyclo[3,3,0]octane (19), (a) 6-[(Methoxycarbonyl)methyl]-8,8-dimethyl-1,4-dioxaspiro[4,4]nonane (18). The formation of the ethylene ketal (in **18**) was carried out according to the method of Marquet et al.[32] From 10.0 g (54.3 mmol) of 4,4-dimethyl-2-[(methoxycarbonyl)-methyl]cyclopentanone was obtained 11.6 g (94% yield) of **18** after short-path distillation [56 °C (0.01 torr)]: ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 4 H), 3.63 (s, 3 H), 2.10–2.95 (m, 3 H), 1.65 (s, 2 H), 2.0–1.22 (m, 2 H), 1.08 (s, 3 H), 1.05 (s, 3 H); IR ($CHCl_3$) 2950 (m), 1727 (s, D=O), 1163 (m) cm^{-1}; mass spectral mol wt, (CI, methane) 229; calcd for $C_{12}H_{20}O_4$, 228.

(b) Hydroxymethylation and Internal Ketalization To Prepare 19. To a solution of lithium diisopropylamide (prepared as before, 26.3 mmol in 300 mL of ether) at −78 °C under argon was added dropwise over 1 h a solution of ester **18** (5.0 g, 21.9 mmol) in 40 mL of dry ether. After 1 h at −78 °C, the pale yellow solution was warmed to −20 °C and gaseous formaldehyde (generated by pyrolysis of paraformaldehyde at 150 °C, 8.0 g) was introduced in a stream of argon. After addition was complete (ca. 3 h), the reaction mixture was partitioned between ether and aqueous ammonium chloride solution. The water layer was washed

(30) We are grateful to Professor David Cane and Mr. Robert Nachbar for samples of natural (−)-fomannosin from fermentation.

(31) The cuprous iodide was obtained as anhydrous material from Alfa Inorganics and used without further treatment.

(32) A. Marquet, M. Dvolaitzky, H. B. Kagan, L. Mamlok, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).

with four portions of ether, and the combined ether extracts were washed sequentially with cold 3% aqueous hydrochloric acid, water, and saturated sodium bicarbonate. From the ether solution was isolated a yellow oil which was dissolved in methyl alcohol (200 mL) containing 2.0 mL of boron trifluoride etherate. After 3 h at 25 °C, the mixture was poured into 30 mL of saturated aqueous sodium bicarbonate solution and concentrated by rotary evaporation. The residual yellow oil was distilled [short path, 60 °C (0.01 torr)] to give acetal **19** (as a mixture of diastereoisomers, 3.8 g, 76% yield from **17**): ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.06 (s, 3 H), 1.15–1.25 (m, 4 H), 2.73–3.05 (m, 1 H), 3.20 and 3.21 (2 s, 3 H, $-OCh_3$, diastereoisomers), 3.35 (q, 1 H, J = 8 Hz), 3.67 (s, 3 H), 3.91–4.35 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 51.6 (C-1), 172.7, 172.2 (C-2), 41.1, 38.3 (C-3), 69.7, 67.7 (C-4), 52.6, 51.3 (C-5), 46.1, 45.3 (C-6); IR ($CHCl_3$) 2941 (m), 1730 (s, C=O), 1176 (m), 1099 (m), 1031 (m) cm^{-1}; mass spectral mol wt (CI), m/e 229; calcd for $C_{12}H_{20}O_4$, 228.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.94; H, 8.72.

Preparation of 4-Carboxy-1-methoxy-7,7-dimethyl-2-oxabicyclo-[3,3,0]octane (20). A mixture of **19** (711 mg, 31.2 mmol) and potassium hydroxide (85%, 231 mg, 3.5 mmol) in 1:1 methanol:water (10 mL) was stirred for 43 h at 25 °C. After the mixture was concentrated by rotary evaporation, the residue was partitioned between water and ether, and the organic layer was discarded. Ether was added to the aqueous phase, and the mixture was stirred in an ice bath while concentrated hydrochloric acid was added (ca. 2 mL). The aqueous layer was extracted twice with ether, and the combined organic layers were washed with water and saturated sodium chloride solution, dried, and concentrated by rotary evaporation to leave a colorless oil (640 mg, 95%). The crude diastereomeric acids **20** showed the following: ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 6 H), 1.20–2.20 (m, 4 H), 2.80–3.15 (m, 1 H, $CHCHCO_2H$), 3.25 (s, 3 H, OCH_3), 3.40 (q, 1 H, J = 8.5 Hz, $CHCO_2H$), 3.93–4.35 (m, 2 H, CH_2O), 10.95 (br s, 1 H, CO_2H); IR ($CHCl_3$) 3267 (m, O–H), 3030 (m), 1706 (s, C=O), 106 (m), 1036 (m) cm^{-1}. It was carried on without further characterization.

Preparation of 4-(Chlorocarbonyl)-1-methoxy-7,7-dimethyl-2-oxabicyclo[3,3,0]octane (21). The sodium salt of acid **20** was prepared by dissolution of the acid **20** (187 mg, 0.87 mmol) and sodium bicarbonate (80 mg, 0.95 mmol) in 1 mL of water. The water was removed by azeotropic distillation with benzene in vacuo (20 torr, followed by 0.01 torr) to leave a white powder. Disodium hydrogen phosphate [dried at 50 °C (0.01 torr); 280 mg, 2 mmol] was added to the flask containing the acid salt and the mixture was suspended in dichloromethane (7 mL) and cooled to −15 °C under argon. Oxalyl chloride (redistilled under argon; 0.09 mL, 1.0 mmol) was added over 2 min with immediate evolution of gas, and the cloudy suspension was warmed to 25 °C over 40 min. The mixture was filtered through Celite under argon directly into a 50-mL flask and concentrated at 0.01 torr to leave a pale yellow oil. After redissolution in a spectral grade solvent, a sample was removed under argon and analyzed. Spectral data for the acid chloride **21**: ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 6 H), 1.34–2.18 (m, 4 H), 2.85–3.10 (m, 1 H, $CHCHCOCl$), 3.10–3.53 (m, 1 H, $CHCOCl$), 3.28 (s, 3 H, OCH_3), 3.95–4.38 (m, 2 H, CH_2O); IR ($CHCl_3$) 2959 (m), 1802 (s, C=O), 1748 (w), 1709 (w), 1111 (m), 1042 (s, C–O) cm^{-1}.

Failure to completely dry the sample of the acid salt or prolonged exposure of the acid chloride to airborne moisture led to partial hydrolysis of the internal ketal functionality.

Preparation of Cyclobutenones 23. To a cold (−20 °C) mixture of triethylamine (0.60 mL, 6.9 mmol, passed through active alumina under argon) and 1.50 mL (1.20 g, 20.7 mmol) of ethoxyacetylene (redistilled under argon) in 25 mL of dry carbon tetrachloride was added dropwise the solution of the yellow oil (**21**) in 13 mL of dry carbon tetrachloride. The resulting mixture was allowed to stand for 40 h at 0 °C without stirring, and then cold (0 °C) 30 mL of 10% of aqueous ammonium chloride solution was added. After being stirred for 30 min at 0 °C, the reaction mixture was partitioned between water and ether. The ether phase was washed with water, saturated sodium bicarbonate, and saturated sodium chloride solution; then it was dried and concentrated by rotary evaporation to leave 700 mg of yellow oil. Column chromatography (silica gel; hexane:dichloromethane:ether = 5:2:2) gave 260 mg of cyclobutenone **23a**, 150 mg of cyclobutenone **23b** as colorless crystals (mp 43.5–45.5 °C), and 120 mg of a mixture of cyclobutenones **23a** and **23b** (43%, total yield). Column chromatography of the mixture of cyclobutenones gave 20 mg of **23a** and 80 mg of **23b**. The total yield of **23a** was 22.6% and the total yield of **23b** was 18.5%. Spectral data for cyclobutenone **23a**: ^{1}H NMR ($CDCl_3$) δ 4.85 (s, 1 H, CH=COC_2H_5), 4.25 (q, 2 H, J = 7 Hz, OCH_2CH_3), 3.98, 4.19 (AB q, 2 H, J = 10 Hz, CH_2O), 3.25 (s, 3 H, OCH_3) 2.83 (dd, 1 H, J = 12, 9 Hz, $CHCH_2$), 1.74 (br s, 2 H, CH_2), 1.45 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.15–2.10 (m, 2 H, $CHCH_2$), 1.08 (s, 3 H, CH_3) and 1.02 (s, 3 H, CH_3); ^{1}H NMR (benzene-d_6) 0.85 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.35–2.03 (m, 3 H), 2.40 (t, 1 H, J = 11 Hz), 3.09 (d of d, 1 H, J = 11, 8 Hz), 3.23 (s, 3 H), 3.42 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.13, 4.41 (AB q, 2 H, J = 9 Hz), 4.58 (s, 1 H, vinyl H); ^{13}C NMR, see Table I; IR ($CHCl_3$) 2923 (m), 1751 (s, C=O), 1570 (s, C=C), 1332 (m), 1100 (m), 1005 (m) cm^{-1}; UV max (EtOH) 236.4 nm (ϵ 4000); mass spectrum, m/z (rel intensity) (EI) 266 (6.9), 238 (4.7, −CO), 237 (1.0, $-C_2H_5$), 235 (7.2, $-OCH_3$), 193 (22.5 $-OC_2H_5$ from m/e 228), 192 (36.8 −EtOH from m/e 238), 163 (16.7), 152 (64.4, $C_9H_{12}O_2$), 151 (42.0, $C_9H_{11}O_2^+$), 137 (13.5); high-resolution mass spectral mol wt, 266.1515; calcd for $C_{15}H_{22}O_4$, 266.1517.

Spectral data for cyclobutenone **23b**: ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H), 1.06 (s, 3 H), 1.25–1.90 (m, 4 H), 1.48 (t, 3 H, J = 7 Hz, OCH_2CH_2), 2.91 (t, 1 H, J = 9 Hz, $CHCH_2$), 3.27 (s, 3 H, OCH_3), 4.04, 4.17 (AB q, 2 H, J = 10 Hz, CH_2O), 4.23 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.91 (s, 1 H, vinyl H); ^{1}H NMR (benzene-d_6) 0.87 (t, 3 H, J = 7 Hz), 1.06 (s, 6 H), 1.35–1.80 (m, 2 H), 1.87 (s, 2 H), 3.23 (t, 1 H, J = 9 Hz), 3.37 (s, 3 H), 3.40 (q, 2 H, J = 7 Hz), 4.10, 4.43 (AB q, 2 H, J = 11 Hz), 4.61 (s, 1 H, vinyl H); ^{13}C NMR, see Table I; IR ($CHCl_3$) 2924 (m), 1754 (s, C=O), 1565 (s, C=C), 1331 (m), 1328 (m), 1026 (m), 1005 (w) cm^{-1}; UV (95% EtOH) λ_{max} 235.6 nm (ϵ 5900); mass spectrum, m/e (rel intensity) (EI), 266 (6.3), 237 (1.4), 235 (4.6), 193 (12.9), 192 (21.6), 163 (9.7), 152 (36.3), 151 (24.9), 137 (5.8); high-resolution mass spectral mol wt, 266.1511; calcd for $C_{15}H_{22}O_4$, 266.1517.

Base Hydrolysis of 23b Followed by Methylation To Give the O-Methyl Analogues of 23a/23b. A mixture of 20 mg (0.075 mmol) of keto acetate **23b** and 10% methanolic sodium hydroxide (1 mL) was stirred for 5 h at 27 °C, diluted with 10 mL of cold water, acidified with cold concentrated hydrochloric acid (ca. 1 mL), and then extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed sequentially with water and saturated sodium chloride solution, dried, and concentrated to leave an oily residue. Analytical TLC showed one component, R_f 0.10 using hexane–ether–dichloromethane. To the solution of this residue in 4 mL of ether at 0 °C was added excess diazomethane solution (in ether). After the solution was stirred for 10 min at 0 °C, the solvent was removed by rotary evaporation to leave a pale yellow oil, 19 mg (~100%), a mixture of methyl enol ethers corresponding to **23a** and **23b** in a ratio of 2:3, respectively (this ratio was determined from integration of the signals at δ 4.99 and 4.93 in the ^{1}H NMR spectra of the crude product): ^{1}H NMR ($CDCl_3$) δ 4.99 (s, CH=$COCH_3$ in **23b′**), 4.93 (s, CH=$COCH_3$ in **23a′**), 4.3–3.9 (m, OCH_2), 4.06 (s, OCH_3), 3.31 (s, OCH_3), 2.85 (m, $CHCH_2$) 2.0–1.5 (m, CH_2, $CHCH_2$) 1.12 (s, CH_3), and 1.07 (s, CH_3); these patterns were similar to those of compounds **23a** and **23b**; IR ($CHCl_3$) 1750 (C=O), 1570 (C=$COCH_3$) cm^{-1}; analytical TLC (silica gel; hexane–ether–dichloromethane), R_f 0.36 for **23a′** and 0.30 for **23b′**.

Reaction of 23a with Diisobutylaluminum Hydride Followed by Acid Hydrolysis To Give Cyclobutenone 26. To a cold (−78 °C) solution of 10 mg (0.038 mmol) of keto acetal **23a** in 1 mL of dry ether was added 0.1 mL of diisobutylaluminum hydride (1 M solution in hexane). The reaction mixture was stirred for 10 min at −78 °C and allowed to warm to 0 °C for 10 min. To the reaction mixture was added 1 mL of 5% aqueous oxalic acid solution. After being stirred for 3 h at 0 °C and for 8 h at 27 °C, the reaction mixture was diluted with ether. The ether layer was washed sequentially with water and saturated sodium chloride solution, and then dried and concentrated to leave a colorless oil. Column chromatography (0.40 g of silica gel; ether:dichloromethane = 1:1) gave 5 mg (60%) of cyclobutenone **26**: ^{1}H NMR ($CDCl_3$) δ 6.32 (d, 1 H, J = 3 Hz, $COCH$=CH), 5.93 (d, 1 H, J = 3 Hz, $COCH$=CH), 4.0–3.0 (m, 3 H, CH_2OH, $CHCH_3$), 2.3–1.7 (m, 5 H), 1.24 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3); IR ($CHCl_3$) 3580 (m, OH), 3370 (s, OH), 1770 (s, C=O), 1710 (s, C=O), 1600 (w) cm^{-1}. Analytical TLC showed a single component component (R_f 0.13, silica gel with hexane:dichloromethane:ether = 1:1:1).

Acidic Hydrolysis of Ketal 23b To Give 27. A solution of ketal **23b** (27 mg, 0.10 mmol) in 2 mL of a mixture of acetic acid–water (3:1) was stirred for 18 h at 43–50 °C. The reaction mixture was treated with 20 mL of cold saturated sodium bicarbonate solution and extracted with ether. The ether layer was washed with saturated sodium chloride solution, dried, and concentrated by rotary evaporation to give a colorless solid residue (24.5 mg, 97%), which was keto alcohol **27** (>95% pure): ^{1}H NMR ($CDCl_3$) δ 5.05 ($COCH$=COC_2H_5, s, 1 H), 4.28 (q, 2 H, J = 7 Hz, OCH_2CH_3), 4.00 (br d, 2 H; J = 3 Hz, CH_2OH), 2.74 (dd, 1 H, J = 8, 10 Hz), 2.0–1.65 (m, 3 H, $-CHCH_2-$ and −OH), 2.11 (s, 2 H, $-COCH_2-$), 1.47 (t, 3 H, $-CH_2CH_3$), 1.21 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3); IR ($CHCl_3$) 3400 (w, OH), 1750–1730 (s, C=O), 1675 (CH=COC_2H_5), 1465 (m) and 1330 (m) cm^{-1}.

Preparation of Acetate 27. To a solution of 25 mg (0.10 mmol) of keto alcohol **27** in dry pyridine (0.4 mL) was added 0.4 mL of acetic anhy-

dride. After being stirred for 15 h at 27 °C, the reaction mixture was treated with 20 mL of cold (0 °C) 5% sodium bicarbonate solution for 15 min with shaking and then extracted with ether. The ether layer was washed sequentially with 5% sodium bicarbonate solution and saturated sodium chloride solution and then dried and concentrated by rotary evaporation followed by high vacuum to leave a colorless crystalling residue (29 mg, 99%) which was keto acetate **28**: ^{1}H NMR ($CDCl_3$) δ 5.03 (s, 1 H, $COCH{=}COC_2H_5$), 4.53 (d, 1 H, J = 12 Hz, $-CH_2OCOCH_3$), 4.30 (d, 1 H, J = 12 Hz, $-CH_2OCOCH_3$), 4.25 (q, 2 H, J = 7 Hz, $-OCH_2CH_3$), 2.62 (br t, 1 H, J = 10 Hz, $-CH_2CHCO-$), 2.08 (s, 2 H, $-CH_2CO$), 1.90 (br d, 2 H, J = 10 Hz), 1.42 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 1.17 (s, 3 H, $-CH_3$), 0.99 (s, 3 H, $-CH_3$); IR ($CHCl_3$) 1750–1730 (br s, C=O), 1580 (s, $C{=}COC_2H_5$), 1230 (s), 1210 (s) cm^{-1}.

Preparation of Thioketal 29. To a solution of 6.0 mg (0.020 mmol) of keto acetate **27** in 0.1 mL of dichloromethane and 0.1 mL of freshly distilled ethanedithiol was added 2 drops of boron trifluoride etherate. After being stirred for 2 h at 25 °C, the reaction mixture was poured into 5 mL of cold saturated sodium bicarbonate solution and extracted with ether. The ether layer was washed sequentially with water, aqueous copper sulfate solution, water, and saturated sodium chloride solution; it was then dried and concentrated by rotary evaporation to give pale yellow oil (9 mg, >90% pure). Column chromatography on 0.5 g of silica gel provided pure thioacetal acetate **29** (eluted with hexane:ether:dichloromethane = 2:1:1): ^{1}H NMR ($CDCl_3$) δ 5.07 (s, 1 H, $COCH{=}COC_2H_5$), 4.64 and 4.47 (each, d, 1 H, J = 12 Hz, CH_2OCOCH_3), 4.25 (q, 2 H, OCH_2CH_3), 3.28 (br s, 4 H, SCH_2CH_2S), 2.92 (dd, 1 H, J = 8, 11 Hz, $-CHCH_2-$), 2.30 and 2.22 (each, d, 1 H, J = 15 Hz, $-SCH_2-$), 2.04 (s, 3 H, $OCOCH_3$), 1.8–1.5 (m, 2 H), 1.49 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.14 (s, 3 H, CH_3) and 1.05 (s, 3 H, CH_3); IR ($CHCl_3$) 1750 (s, C=O), 1735 (s, C=O), 1570 (s, $C{=}COC_2H_5$), and 1230 (s) cm^{-1}.

Preparation of 1-(4,4-Dimethyl-1-cyclopenten-1-yl)ethanone (37). To a dry 250-mL three-neck round-bottom flask equipped with a gas dispersion tube, ozone outlet, and thermometer was added 7.10 g (57 mmol) of 1,4,4-trimethylcyclohexene, 60 mL of methanol, and 60 mL of dichloromethane. The temperature was lowered to −78 °C with a dry ice–isopropyl alcohol bath, and ozone was passed through the solution until it became pale blue and a KI/H_3BO_3 trap became dark (ca. 1 h). The solution was purged with O_2 for 5 min, and 6.3 mL (5.3 g, 86 mmol) of dimethyl sulfide was added via syringe to the cold (−78 °C) solution. After being allowed to warm to 25 C and stirred for 4 h, the solution was diluted with 150 mL of benzene and transferred to a 500-mL flask, and 250 mL of solvent was removed. Another 300 mL of benzene was added along with 10 mL of H_2O and 100 mg of *p*-toluenesulfonic acid. The solution was heated at reflux, and the water was removed by azeotropic distillation. The heating was continued for 5 h. The resulting dark solution was poured into 200 mL of hexane and extracted sequentially with 30 mL of saturated sodium bicarbonate solution, 30 mL of water, and 30 mL of saturated sodium chloride solution. The organic solution was dried (Na_2SO_4) and concentrated to leave 7.04 g of a dark oil. Distillation produced 5.8 g (73%) of a colorless oil, bp 98–106 °C (29 torr) (lit.[33] not reported). Gas chromatographic analysis (10 ft, 5% TCEP on Chromosorb P-AW, 130 °C) revealed the presence of two products in the ratio of 91:9. The major component (8 min) was collected and identified as **37**: IR (neat) 1669 (C=O), 1618 (C=C), and 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.64 (br s, 1 H, HC=O), 2.38 (s, 4 H, CH_2), 2.30 (s, 3 H, CH_3), 1.10 (s, 6 H, $C(CH_3)_2$); UV max (isooctane) 231 nm (log ϵ 4.05); mass spectrum (70 eV), m/e (rel intensity) 139 (parent + 1, 38), 138 (parent, 63), 123 (90), 95 (56), 67 (24), 55 (17), and 43 (100).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.95; H, 10.19.

For large scale work, careful fractional distillation produced samples that were greater than 98% pure **37**, but with some sacrifice in yield. The minor product was tentatively identified as 2,5,5-trimethyl-1-cyclopentenecarbaldehyde: IR (neat) 1669 (C=O) and 1629 (C=C) cm^{-1}; ^{1}H NMR (CCl_4) δ 8.9–8.7 (s, 1 H, CHO), 2.30 (t, 2 H, J = 7 Hz, CH_2), 2.05 (s, 3 H, CH_3), 1.60 (t, 2 H, J = 7 Hz CH_2), 1.15 (s, 6 H, CH_3).

Preparation of Enol Ethers 30. To a 25-mL three-neck round-bottom flask under argon equipped with an argon inlet, thermometer, and serum cap containing diisopropylamine (289 mg, 0.374 mL, 2.88 mmol) in THF (3.0 mL) at −78 °C was added dropwise over a few minutes a solution of *n*-butyllithium (2.38 M in hexane, 1.1 mL, 2.6 mmol), and the mixture was stirred at 0 °C for 15 min. After removal of all volatiles at 25 °C (0.01 torr), 3.0 mL of THF was introduced to give a pale yellow solution to which was added slowly over 30 min a solution of 1-acetyl-4,4-dimethylcyclopentene (**37**, 328 mg, 2.38 mmol) in 0.3 mL of THF. The mixture was allowed to stir at −78 °C for 2 h and then quenched as follows.

(a) With Methyl *p*-Toluenesulfonate. A solution of 1.1 molar equiv of methyl *p*-toluenesulfonate[34] in THF was added dropwise over a few minutes, and the solution was stirred at −78 °C for 30 min and 25 °C for 4 h. A precipitate began to form as the reaction temperature approached 0 °C. The reaction mixture was mixed with hexane and washed sequentially with water and brine, dried over sodium sulfate, and concentrated to leave a yellow oil. Distillation [on large scale, bp 100–106 °C (35 torr)] afforded a center cut, 40% yield: ^{1}H NMR (CCl_4) δ 5.73 (br s, 1 H), 3.88 (br s, 1 H), 3.48 (s, 3 H), 2.15 (br s, 4 H), 1.05 (s, 6 H); IR (neat) 2970 (s), 1701 (w), 1667 (w), 1653 (sh), 996 (m), 906 (w) cm^{-1}; mass spectral mol wt, 152; calcd for $C_{10}H_{16}O$, 152.

(b) With Chlorotrimethylsilane. In a similar way, rapid addition of chlorotrimethylsilane (redistilled, 1.0 molar equiv) followed by stirring for 6 h at −78 °C and warming to 25 °C over 15 min gave a suspension which was concentrated by rotary evaporation. The residue was subjected to flash distillation (0.01 torr) to afford a colorless oil, **30b**, in 99% yield: ^{1}H NMR (CCl_4) δ 5.70 (br s, 1 H), 4.11 (br s, 2 H $=CH_2$), 2.19 (br s, 4 H), 1.08 (s, 6 H), 0.19 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 154.1 (s, =C—O), 140.0 (s, C-1), 127.4 (d, C-2), 92.9 (t, CH_2=), 48.2 (t, C-3 or C-5), 47.4 (t, C-3 or C-5), 39.1 (s, C-4), 30.1 (q, CH_3 at C-4), 0.22 (q, $SiCH_3$); mass spectral mol wt, 210.

Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54; Si, 13.35. Found: C, 68.32; H, 10.43; Si, 13.18.

(c) With *tert*-Butyldimethylchlorosilane. In a similar way, reaction with 1.0 molar equiv of *tert*-butyldimethylchlorosilane using a solvent mixture of THF–hexamethylphosphoramide (6:1 by volume) produced, after isolation by aqueous extraction and short-path distillation, a colorless oil, **30c**, in 96% yield: ^{1}H NMR ($CDCl_3$) δ 5.81 (br s, 1 H, CH=), 4.20 (br s, 2 H, CH_2), 2.23 (br s, 4 H), 1.09 (br, s, 6 H), 0.96 (s, 9 H, $-C(CH_3)_3$), 0.16 (s, 6 H, $-SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 154.4 (s, C–O), 140.0 (s, C-1), 127.3 (d, =CH), 92.6 (t, $=CH_2$), 48.2 (t, C-5), 47.5 (t, C-3), 39.9 (s, C-4), 18.5 (s, Si-*t*-Bu), 30.1 (q, CH_3 at C-4), 26.1 (q, Si-*t*-Bu), −4.4 (q, $-SiCH_3$).

Anal. Calcd for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18; Si, 11.12. Found: C, 71.11; H, 11.12; Si, 11.35.

Preparation of 3,3-Diethoxy-2-(ethoxycarbonyl)cyclobutene (38). A mixture of ethyl propiolate (5.68 g, 58 mmol) and ketene diethyl acetal[35] (6.72 g, 58 mmol) in dichloromethane (50 mL) was heated at 50 °C under argon for 29 h. Removal of the solvent by rotary evaporation followed by short-path distillation at 40 °C (0.003 torr) provided a colorless oil (8.0 g, 65% yield): ^{1}H NMR ($CDCl_3$) δ 6.90 (t, 1 H, J = 1.3 Hz, =CH), 4.11 (q, 2 H, J = 7.1 Hz, $-OCH_2-$), 3.62 (q, 4 H, J = 7.2 Hz, $-OCH_2-$), 2.55 (d, 2 H, J = 1.3 Hz, $-CH_2-$, 1.19 (t, 3 H, J = 7.1 Hz, $-CH_3$), 1.11 (t, 6 H, J = 7.2 Hz, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 160.9 (s, C=O), 148.6 (d, C-1), 141.9 (s, C-2), 103.4 (s, C-3), 60.2 (t, ester $-CH_2-$), 59.9 (t, ketal $-CH_2-$), 41.9 (t, C-4), 15.5 (q, ketal $-CH_3$), 14.2 (q, ester $-CH_3$); IR (CCl_4) 1715 (s, C=O), 1610 (m, C=C) cm^{-1}; mass spectral mol wt, m/e 214.

Thermal Decomposition of 38. A solution of cyclobutene **38** (32 mg, 0.15 mmol) in dry carbon tetrachloride (0.4 mL) was heated at 90 °C in an NMR sample tube and the reaction was monitored by ^{1}H NMR. After 2 h the starting material **38** was cleanly converted to a new product tentatively identified as diene **39** (from spectroscopic data): ^{1}H NMR (CCl_4) δ 6.28 (dd, 1 H, J = 11, 3 Hz), 5.10 (dd, 1 H, J = 17, 3 Hz), 4.77 (dd, 1 H, J = 11, 17 Hz), 4.01 (m, 6 H), 1.26 (br t, 9 H, J = 7 Hz). Attempts to purify the product by silica gel chromatography provided a diester, tentatively identified as diethyl ethylidenemalonate: ^{1}H NMR (CCl_4) δ 6.89 (q, 1 H, J = 7 Hz), 4.13 (m, 4 H), 1.90 (d, 3 H, J = 7 Hz), 1.26 (m, 6 H); IR (CCl_4) 2980 (m), 1720 (s, C=O), 1255 (s), 1218 (s), 1051 (s), 1648 (w, C=C) cm^{-1}.

(4α,7α,9β)-6,6-Diethoxy-7-(ethoxycarbonyl)-11,11-dimethyl-3-(trimethylsiloxy)tricyclo[10.2.0.0^{9,13}]undec-3-ene (40a). A mixture of 2-(ethoxycarbonyl)-3,3-diethoxycyclobutene (**38**, 2.14 g, 10 mmol) and 4,4-dimethyl-1-[(trimethylsiloxy)ethenyl]cyclopentent (**30b**, 2.52 g, 12 mmol) was heated for 10 days at 48 °C under argon. Column chromatography eluting with hexane:ether:dichloromethane (20:1:1) provided the desired Diels–Alder adduct **40a** (3.05 g, 72% yield): ^{1}H NMR ($CDCl_3$) δ 4.08 (q, 2 H, J = 7 Hz, ester $-CH_2-$), 3.72 (m, 4 H, ketal $-CH_2-$), 2.92–1.15 (26 H, m), 2.92–1.15 (26 H, m), 1.02 (s, 6 H, 6,6-dimethyl), 0.21 (9 H, s, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 171.9 (s, C=O), 140.5 (s, C-3), 118.2 (s, C-13), 103.9 (s, C-6), 60.2 (s, C-7), 59.9 (t, ester $-CH_2-$ at C-7), 58.6 (t, ketal $-CH_2-$ at C-6), 57.8 (t, ketal $-CH_2-$ at C-6), 46.8 (t, C-10), 45.4 (t, C-12), 38.4 (d, C-9), 37.13 (s, C-11), 34.9 (t, C-5), 31.2 (t, C-2), 30.4 (d, C-4), 30.1 (q, CH_3 at C-11), 28.7 (q, CH_3

(33) K. von Auwers and E. Lange, *Ann. Chem.*, **409**, 149 (1915).

(34) Methyl *p*-toluenesulfonate was obtained from Aldrich Chemical Co. and used without further purification.

(35) S. M. McElvain and D. Kundiger, *Org. Synth.*, **23**, 45 (1943).

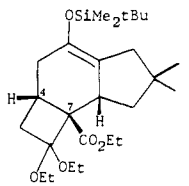
at C-11), 15.6 (q, ketal $-CH_3$), 15.5 (q, ketal $-CH_3$ at C-6), 14.6 (q, ester $-CH_3$), 1.0 (q, $SiCH_3$); IR (CCl_4) 1722 (vs, C=O) cm^{-1}; mass spectral mol wt, 424.

Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49; Si, 6.61. Found: C, 64.88; H, 9.59; Si, 6.64.

(4α,7α,9β)-3-(*tert*-Butyldimethylsiloxy)-6,6-dimethyl-11,11-dimethyl-7-(ethoxycarbonyl)tricyclo[10,2.0,0^{9,13}]undec-3-ene (40b). A mixture of 3,3-diethoxy-2-(ethoxycarbonyl)cyclobutene **38** (286 mg, 1.34 mmol) and diene **30c** (252 mg, 1.00 mmol) was heated at 48–50 °C for 10 days in the presence of three particles of 3-Å Linde molecular sieves. After isolation as for **40a**, the major product (**40b**) was obtained by silica gel column chromatography (hexane:dichloromethane:ether = 20:1:1) as a colorless oil, 335 mg, 72% yield: IR ($CDCl_3$) 1713 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.11 (q, 2 H, J = 7 Hz, ester CH_2), 3.44 (m, 4 H, ethoxy CH_2), 3.2–0.98 (18 H, m), 0.96 (s, 3 H, CH_3 at C-11), 0.92 (s, 3 H, CH_3 at C-11), 0.83 (s, 9 H, Si-*t*-Bu), 0.06 (d, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 171.79 (s, C=O), 140.27 (s, C-3), 117.40 (s, C-13), 103.64 (s, C-6), 59.66 (t, ester CH_2), 58.36 (s, C-7), 58.36 (t, ethoxy CH_2), 57.49 (t, ethoxy CH_2), 46.65 (t, C-10), 42.21 (t, C-12), 38.10 (d, C-9), 36.80 (s, C-11), 34.52 (t, C-5), 30.78 (t, C-2), 30.02 (d, C-4), 29.92 (q, CH_3 at C-11), 28.51 (q, CH_3 at C-11), 25.85 (q, Si-*t*-Bu), 18.11 (s, Si-*t*-Bu), 15.34 (q, ethoxy CH_3), 15.18 (q, ethoxy CH_3), 14.42 (q, ester CH_3), −3.78 (q, $SiCH_3$), −3.94 (q, $SiCH_3$).

Anal. Calcd for $C_{26}H_{46}O_5Si$: C, 66.91; H, 9.93; Si, 6.02. Found: C, 67.04; H, 9.59; Si, 5.98.

A minor product was eluted immediately after **40b** as a colorless oil, 24 mg, 5% yield, and assigned the structure of the Diels–Alder adduct 77 (epimeric at C-7 and C-9 relative to **40b**): IR ($CDCl_3$) 1720 (vs,



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C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (q, 2 H, J = 7 Hz, ester CH_2), 3.49 (4 H, m, ethoxy CH_2), 3.24–0.97 (24 H, m), 0.84 (d, 9 H, Si-*t*-Bu), −0.01 (m, 6 H, $SiCH_3$).

Anal. Calcd for $C_{26}H_{46}O_5Si$: C, 66.91; H, 9.93; Si, 6.02. Found: C, 66.49; H, 10.14; Si, 6.11.

(4α,7α,9β,13β)-6,6-Diethoxy-11,11-dimethyl-7-(ethoxycarbonyl)tricyclo[10,2.0,0^{9,13}]undecan-3-one (41a). To a solution of the Diels–Alder adduct **40a** (2.6 g, 61 mmol) in anhydrous methanol (100 mL) was added Linde 3-Å molecular sieves (25.3 g), and the mixture was stirred for 5.4 h at 25 °C. Ether (800 mL) was then added and the mixture was filtered. The filtrate was washed three times with brine, dried over magnesium sulfate, and concentrated to give the cis keto ester **41a** (homogeneous by the analysis), 2.1 g, 96% yield: ^1H NMR ($CDCl_3$) δ 4.25 (q, 2 H, ester $-CH_2-$), 3.50 (m, 4 H, $-OCH_2-$ at C-6), 3.28–0.90 (26 H, m); ^{13}C NMR ($CDCl_3$) δ 213.45 (s, C-3), 172.00 (s, ester C=O), 101.42 (s, C-6), 60.41 (t, ester $-CH_2-$), 58.08 (s, C-7), 57.81 (t, ethoxy $-CH_2-$), 57.32 (t, ethoxy $-CH_2-$), 50.44 (d, C-13), 45.13 (t, C-10), 44.64 (t, C-12), 40.69 (d, C-9), 39.77 (t, C-2), 37.22 (s, C-11), 34.94 (t, C-5), 30.77 (q, CH_3 at C-11), 29.91 (q, CH_3 at C-11), 27.09 (d, C-4), 14.90 (q, ethoxy CH_3), 14.25 (q, ester CH_3); IR ($CDCl_3$) 1728 (vs, ester C=O), 1710 (vs, ketone C=O) cm^{-1}; mass spectral mol wt, 352. The analytical sample was obtained by chromatography on silica gel.

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.38; H, 9.23.

(3α,4α,7α,9β,13β)-6,6-Diethoxy-11-dimethyl-7-(ethoxycarbonyl)tricyclo[10.2.0.0^{9,13}]undecan-3-ol Benzyl Ether (42). To a solution of cis keto ester **41a** (481 mg, 1.36 mmol) in THF (6.0 mL) was added dropwise over a few minutes a solution of lithium triethylborohydride (1 M in THF, 2.0 mL, 2.0 mmol) at 0 °C under argon. The mixture was stirred at 25 °C for 3 min. Two drops of water was then added, and the mixture was extracted three times with hexane. The combined hexane layers were washed with water, dried over magnesium sulfate, and concentrated to give a colorless oil, homogeneous by analytical TLC, 482 mg, 99% yield: ^1H NMR ($CDCl_3$) δ 4.04 (m, 4 H, ester CH_2 and H-3), 3.50 (m, 4 H, ethoxy CH_2), 2.77–1.01 (31 H, m), 0.96 (s, 3 H, CH_3 at C-11), 0.90 (s, 3 H, CH_3 at C-11); ^{13}C NMR ($CDCl_3$) 174.71 (s, C=O), 102.61 (s, C-6), 66.69 (d, C-3), 60.46 (t, ester CH_2), 46.86 (t, C-10), 41.77 (t, C-12), 41.12 (d, C-13), 36.73 (d and s, C-11 and C-9), 35.97 (t, C-5), 33.10 (t, C-2), 29.26 (q, CH_3 at C-11), 27.47 (q, CH_3 at C-11), 25.57 (d, C-4), 15.23 (q, ethoxy CH_3), 15.06 (q, ethoxy CH_3), 14.20 (q, ester CH_3); IR (CCl_4) 3470 (w, OH), 1723 (vs, C=O) cm^{-1}. The analytical sample was obtained by chromatography on silica gel. The crude product was converted directly to the benzyl ether **42**.

Anal. Calcd for $C_{20}H_{34}O_5$: C, 67.77; H, 9.67. Found: C, 67.72; H, 9.87.

A three-neck flask equipped with a reflux condenser, argon inlet, magnetic stirrer, and serum cap was charged with a mixture of the cis hydroxy ester (above, 482 mg, 1.36 mmol) and benzyl bromide (720 mg, 4.21 mmol) in THF (10 mL). To this solution was added all at once a suspension of sodium hydride (50% oil dispersion, 400 mg, 8.33 mmol, washed twice with THF) in THF (2 mL), and the mixture was heated at reflux for 5 h. After the mixture was cooled, ether (200 mL, saturated with water) was slowly added at 0 °C. The ether layer was washed three times with brine, dried with magnesium sulfate, and concentrated to give a colorless oil, homogeneous by analytical TLC **42** (555 mg, 92% yield): IR ($CHCl_3$) 3090 (w), 3060 (w), 1715 (vs, C=O) 1600 (w, phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (m, 5 H, phenyl), 4.44 (d, 2 H, benzyl CH_2), 4.03 (m, 5 H, ethoxy CH_2 and H-3), 3.6–0.97 (22 H, m), 0.95 (s, 3 H, CH_3 at C-11), 0.90 (s, 3 H, CH_3 at C-11); ^{13}C NMR ($CDCl_3$) δ 173.09 (s, C=O), 139.50 (s, phenyl), 128.34 (s, phenyl), 127.47 (d, phenyl), 127.36 (d, phenyl), 102.12 (s, C-6), 73.08 (d, C-3), 69.94 (t, benzyl CH_2), 60.41 (t, ester CH_2), 59.92 (t, ethoxy CH_2), 57.48 (t, ethoxy CH_2), 46.86 (t, C-10), 41.66 (t, C-12), 39.12 (d, C-13), 38.30 (d, C-9), 37.00 (s, C-11), 34.99 (t, C-5), 20.26 (q, CH_3 at C-11), 28.77 (t, C-2), 27.52 (q, CH_3 at C-11), 25.52 (d, C-4), 15.28 (q, ethoxy CH_3), 15.17 (q, ethoxy CH_3), 14.30 (q, ester CH_3). The analytical sample was obtained by chromatography and showed the same spectral properties.

Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.92; H, 9.19.

Conversion of the Ester Group in 42 to a Methyl Group, Cleavage of the Benzyl Ether, and Oxidation To Give (3α,4α,7α,9β,13β)-6,6-Diethoxy-7,11,11-trimethyltricyclo[10,2.0,0^{9,13}]undecan-3-one (43). To a solution of the benzyloxy ester **42** (555 mg, 1.25 mmol) in dry ether (10 mL) att 0 °C under argon was added in one portion solid lithium aluminum hydride (198 mg, 5.08 mmol). The mixture was stirred for 2 h at 0 °C. Standard isolation procedure provided a colorless oil which was purified by column chromatography (hexane:ether:methylene chloride = 2.5:1:1) to afford the pure C-7 hydroxymethyl derivative (484 mg, 96%): mp 81–83 °C; IR ($cDCl_3$) 3500 (w, OH), 3060 (w, phenyl), 3020 (w, phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (m, 5 H, phenyl), 4.44 (s, 1 H, $ArCH_2$), 4.50 (s, 1 H, $ArCH_2-$), 4.00 (m, 1 H, H-3), 3.50 (m, 6 H, $-OCH_2$), 3.2–1.06 (17 H, m), 1.01 (s, 3 H, CH_3 at C-11), 0.90 (s, 3 H, CH_3 at C-11); ^{13}C NMR ($CDCl_3$) 139.34 (s, phenyl), 130.51 (d, phenyl), 127.31 (d, phenyl), 127.15 (d, phenyl), 104.07 (s, C-6), 73.73 (d, C-3), 69.94 (t, benzyl CH_2), 66.69 (t, C-8), 57.86 (t, ethoxy CH_2), 57.10 (t, ethoxy CH_2), 52.17 (s, C-7), 45.18 (t, C-10), 41.39 (t, C-12), 38.85 (d, C-13), 37.22 (d, C-9), 37.00 (s, C-11), 34.78 (t, C-5), 29.37 (q, t, C-2 and CH_3 at C-11), 26.87 (q, CH_3 at C-11), 25.74 (d, C-4), 15.28 (q, ethoxy CH_3), 15.17 (q, ethoxy CH_3); mass spectral mol wt, 402.

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.75; H, 9.45.

A 25-mL oven-dried two-neck round-bottom flask equipped with argon inlet, serum cap, and magnetic stirrer was charged with a solution of the C-7 hydroxymethyl derivative (above, 487 mg, 1.22 mmol) in THF (20 mL) and cooled to 0 °C. A solution of *n*-butyllithium (2.1 M in hexane, 0.62 mL, 1.30 mmol) was added dropwise over a few minutes, and the mixture was stirred for 10 min at 0 °C. The solvent was removed by evacuation to 0.01 torr. The residue was dissolved in THF (20 mL) and tetramethylethylenediamine (distilled from calcium hydride, 5.0 mL). Then *N,N,N',N'*-tetramethyldiamidophosphorochloridate (2.0 mL, 2.3 mmol) was added all at once by syringe and the mixture was stirred at 25 °C for 3 h. It was then poured into a mixture of hexane (200 mL) and water (50 mL), and the organic layer was separated. The aqueous phase was extracted with three 60-mL portions of hexane. The combined organic layers were washed three times with water, dried over magnesium sulfate, and concentrated to provide the crude C-7 phosphorodiamidate ester (765 mg), which was purified by silica gel chromatography (ether:dichloromethane = 1:1) to give 719 mg (82% yield): IR ($CDCl_3$) 1210 (s), 998 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (br s, 5 H, phenyl), 4.47 (br s, 2 H, benzylic CH_2), 3.96 (br d, 2 H, C-8), 3.42 (m, 5 H, ethoxy CH_2 and H-3), 3.60 (m, 12 H, N-CH_3), 2.4–1.14 (17 H, m), 1.06 (s, 3 H, CH_3 at C-6), 0.95 (s, 3 H, CH_3 at C-6); ^{13}C NMR (C_6D_6) δ 139.25 (s, phenyl), 128.19 (d, phenyl), 126.73 (d, phenyl), 126.52 (d, phenyl), 102.30 (s, C-6), 73.75 (d, C-3), 69.47 (t, benzylic CH_2), 66.65 and 66.49 (both t, C-8, J_{C-P} = 3.7 Hz), 56.96 (t, ethoxy CH_2), 55.66 (t, ethoxy CH_2), 50.84 and 50.51 (both s, C-7, J_{C-P} = 7.3 Hz), 44.66 (t, C-10), 41.36 (t, C-12), 39.30 (d, C-13), 37.37 (d, C-9), 36.05 (s, C-11), 35.88 and 35.72 (8, N-CH_3, J_{CP} = 3.7 Hz), 33.93 (t, C-5), 29.17 (t, C-2), 29.00 (q, CH_3 at C-11), 27.00 (q, CH_3 at C-11), 24.78 (d, C-9), 14.54 (q, ethoxy CH_3).

A 100-mL oven-dried two-neck round-bottom flask equipped with argon inlet, serum cap, and a magnetic stirrer was charged with lithium metal (220 mg, 31.9 mmol). The flask was cooled to 0 °C (ice–salt bath)

and dry ethylamine (20 mL) was transferred into the flask. Upon being stirred for 2 min at 0 °C, the mixture turned deep blue. A solution of the phosphorodiamidate (719 mg) in THF (5 mL) containing *tert*-butyl alcohol (80 mg, 1.08 mmol) was slowly added at 0 °C over 20 min. The blue color was maintained during the addition, and the mixture was stirred for an additional 1 h. The reaction was stopped by adding hexane (200 mL) and water (50 mL). The aqueous layer was extracted three times with hexane. The combined hexane layers were washed three times with brine, dried over magnesium sulfate, and concentrated. The crude colorless oil was purified by column chromatography (hexane:ether:dichloromethane = 2:1:1) to provide the alcohol as a colorless oil (373 mg, 94% yield): IR ($CDCl_3$) 3600 (w, OH), 1042 (s, C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (m, 1 H, H-3), 3.39 (m, 1 H, ethoxy CH_2), 2.54 (2 H, m), 2.2–1.1 (16 H, m), 1.08 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 103.74 (s, C-6), 67.98 (d, C-3), 57.69 (t, ethoxy CH_2), 56.34 (t, ethoxy CH_2), 47.07 (s, C-7), 46.42 (t, C-10), 42.09 (t, C-12), 41.33 (d, C-13), 40.57 (d, C-9), 36.78 (s, C-11), 33.96 (t, C-5), 33.58 (t, C-2), 30.93 (d, C-4), 29.90 (q, CH_3 at C-11), 27.73 (q, CH_3 at C-11), 22.53 (q, C-8), 15.38 (q, ethoxy CH_3).

Chromium trioxide (1.09 g, 10.9 mmol) was added at 0 °C to a magnetically stirred solution of pyridine (1.76 mL, 21.8 mmol) in dichloromethane (20 mL). The mixture was stirred at 0 °C for 15 min. A solution of the alcohol (538 mg, 1.81 mmol) in 5 mL of dichloromethane was then added in one portion, and the mixture was vigorously stirred at 25 °C for 2.5 h. The solution was decanted for the tarry residue, which was thoroughly washed with ether. The combined organic solutions were washed sequentially with 5% aqueous sodium hydroxide, water, and brine and were dried over anhydrous magnesium sulfate. Concentration followed by silica gel column chromatography (hexane:ether:dichloromethane = 2:1:1) provided 464 mg (87% yield) of keto acetal **43** (as a colorless solid): mp 41–42 °C (hexane–ether); ^1H NMR ($CDCl_3$) δ 3.41 (m, 4 H, ethoxy CH_2), 3.12–1.40 (m, 11 H), 1.17 (t, 6 H, ethoxy CH_3), 1.20 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 214.20 (s, C-3), 103.04 (s, C-6), 57.64 (t, ethoxy CH_2), 56.66 (t, ethoxy CH_2), 50.66 (d, C-13), 47.30 (s, C-7), 45.73 (t, C-10), 45.35 (t, C-12), 40.04 (t, C-2), 38.74 (s, C-11), 34.57 (t, C-5), 33.97 (d, C-9), 29.58 (q, CH_3 at C-11), 27.20 (q, CH_3 at C-11), 27.20 (q, CH_3 at C-11), 15.17 (q, CH_3 of ethoxy), 14.74 (q, ethoxy CH_3), 21.89 (q, C-8); IR ($CDCl_3$) 3600 (w, OH), 1042 (s, C–O) cm^{-1}.

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.19; H, 10.14.

(4α,7α,9β)-3-(*tert*-Butyldimethylsiloxy)-6,6-diethoxy-7,11,11-trimethyltricyclo[10.2.0.0^{9,13}]undec-3-ene (44). To a solution of the Diels–Alder adduct **40b** (248 mg, 0.531 mmol) in anhydrous ether (2.3 mL) at 0 °C was added in one portion solid lithium aluminum hydride (69 mg, 1.77 mmol), and the mixture was stirred for 0.5 h. Ether (20 mL, saturated with water) was then slowly added at 0 °C to destroy the residual lithium aluminum hydride, followed by 10 g of ice. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine three times, dried over anhydrous magnesium sulfate, and concentrated to provide a colorless oil, which was purified by silica gel chromatography (hexane:dichloromethane:ether = 10:1:1) to afford 220 mg (97% yield) of the C-7 hydroxymethyl derivative: IR ($CDCl_3$) 3510 (w, OH), 1704 (w, C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.49 (m, 6 H, ethoxy CH_2 and CH_2 at C-7), 3.29–1.23 (m, 17 H), 1.16 and 1.02 (each 3 H, s, *gem*-dimethyl), 0.97 (s, 9 H, Si-*t*-Bu), 0.14 (s, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) 141.23 (s, C-3), 119.67 (s, C-13), 15.64 (s, C-6), 65.01 (t, C-8), 58.13 (t, ethoxy CH_2), 57.16 (t, ethoxy CH_2), 55.04 (s, C-7), 43.40 (t, C-10), 42.69 (t, C-12), 38.20 (s, C-11), 35.81 (t, C-5), 32.99 (t, C-2), 29.43 (q, CH_3 at C-10), 28.01 (d, C-4), 27.58 (q, CH_3 at C-11), 25.79 (q, Si-*t*-Bu), 18.04 (s, Si-*t*-Bu), 15.33 (q, ethoxy CH_3), 15.06 (q, ethoxy CH_3), –3.95 (q, $SiCH_3$), –3.84 (q, $SiCH_3$).

A three-neck round-bottom flask, equipped with a magnetic stirrer, an argon inlet, and a reflux condenser, was charged with a solution of the C-9 hydroxymethyl derivative from above (351 mg, 0.287 mmol) in dry 1,2-dimethoxyethane (7.0 mL). Tetramethylethylenediamine (distilled from calcium hydride, 2.1 mL), sodium hydride (231 mg, 50% oil dispersion, 4.8 mmol), and *N,N,N',N'*-tetramethyldiamidophosphorochloridate (distilled, 2.1 mL, 2.42 mmol) were successively added in this order. The mixture was heated at 55 °C for 20 h. It was then poured into a mixture of ether (200 mL) and water (50 mL) and the organic layer was separated. The aqueous layer was extracted with three 20-mL portions of ether. The combined ether layers were washed with three portions of water, dried over magnesium sulfate, and concentrated to provide the crude product (620 mg). Silica gel column chromatography (ether:dichloromethane = 1:1) provided the phosphorodiamidate ester as a colorless oil (397 mg, 86% yield): IR ($CDCl_3$) 1706 (m, C=C), 1250 (m), 1208 (s), 992 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.02 (m, 2 H, CH_2OPO), 3.48 (m, 4 H, ethoxy CH_2), 2.72 (m, 12 H, NCH_3), 2.5–1.04 (m, 22 H), 0.95 (s, 9 H, Si-*t*-Bu), 0.11 (s, 6 H, $SiCH_3$); ^{13}C NMR ($CDCl_3$) δ 140.13 (s, C-3), 119.66 (s, C-13), 103.73 (s, C-6), 66.35 and 66.57 (both t, C-8), J_{C-P} = 4.9 Hz), 58.01 (t, ethoxy CH_2), 57.52 (t, ethoxy CH_2), 53.19 and 53.57 (both s, C-7, J_{C-P} = 8.5 Hz), 44.36 (t, C-10), 42.84 (t, C-12), 38.15 (d, C-9), 37.99 (s, C-10), 36.66 and 36.83 (both q, NCH_3, J_{C-P} = 3.7 Hz), 35.36 (t, C-5), 33.09 (t, C-2), 31.68 (d, C-4), 29.89 (q, CH_3 at C-11), 28.32 (q, CH_3 at C-11), 25.99 (q, Si-*t*-Bu), 18.25 (s, Si-*t*-Bu), 15.37 (q, ethoxy CH_3), 15.27 (q, ethoxy CH_2), –3.49 (q, $SiCH_3$), –3.75 (q, $SiCH_3$).

Anal. Calcd for $C_{28}H_{55}N_2O_5PSi$: C, 60.18; H, 9.92; N, 5.01; P, 5.54; Si, 5.03. Found: C, 59.98; H, 10.04; N, 5.02; P, 5.57; Si, 5.18.

A 100-mL three-neck round-bottom flask equipped with an argon inlet, serum cap, and a magnetic stirrer was charged with lithium metal (450 mg, 65.2 mmol) and cooled to –78 °C. Dry ethylamine (30 mL) was transferred into the flask and the mixture was stirred for 2 h at –78 °C. The phosphorodiamidate ester (1.841 g, 3.30 mmol) was slowly added at –78 °C over 30 min. The deep blue color persisted during the addition. The mixture was further stirred for 2 h at –78 °C and then quenched by addition of aqueous ammonium chloride solution. The resulting mixture was poured into an ether (500 mL)–water (200 mL) mixture. After the solution was vigorously stirred for 10 min at 25 °C, the organic layer was separated and the aqueous phase extracted three times with ether. The combined organic layers were washed with water and brine, dried over magnesium sulfate, and concentrated to give 1.217 g of colorless spectroscopically pure **44** (90% yield). The analytical sample was obtained by silica gel column chromatography (hexane:ether:dichloromethane = 10:1:1): ^1H NMR ($CDCl_3$) δ 3.40 (q, 4 H, ethoxy CH_2), 1.17 (t, 3 H, OCH_2CH_3), 1.14 (t, 3 H, ethoxy CH_3), 1.08 (s, 3 H, C-8), 0.96 (s, 6 H, CH_3 at C-11), 0.92 (s, 9 H, Si-*t*-Bu), 0.08 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 140.64 (s, C-3), 120.27 (s, C-13), 103.91 (s, C-6), 57.26 (t, ethoxy CH_2), 50.71 (s, C-7), 43.94 (t, C-10), 43.12 (t, C-12), 40.31 (d, C-9), 38.41 (s, C-11), 35.65 (t, C-5), 34.67 (d, C-4), 32.94 (t, C-2), 29.64 (q, CH_3 at C-11), 28.17 (q, CH_3 at C-11), 25.95 (q, Si-*t*-Bu), 18.69 (q, C-8), 18.15 (s, Si-*t*-Bu), 15.50 (q, ethoxy CH_3), 15.28 (q, ethoxy CH_3), –3.84 (q, $SiCH_3$), –3.74 (q, $SiCH_3$); IR ($CDCl_3$) 1702 (m, C=C), 1250 (s, C–O), 1050 (s, C–O), 840 (s) cm^{-1}.

Anal. Calcd for $C_{24}H_{44}O_3Si$: C, 70.53; H, 10.85; Si, 6.87. Found: C, 70.24; H, 10.98; Si, 6.62.

The Reaction of 44 with Tetra-*n*-Butylammonium Fluoride. A solution of enol ether **44** (1.644 g, 4.03 mmol) in THF (50 mL) at 0 °C was treated with tetra-*n*-butylammonium fluoride trihydrate (1.42 g, 4.50 mmol) for 20 min. The mixture was diluted with water and extracted with ether. The ethereal extracts were combined, washed twice with water and with brine, dried over magnesium sulfate, and concentrated to afford 1.41 g of a colorless oil, which was purified by silica gel chromatography (hexane:ether:methylene chloride = 5:1:1) to give 675 mg (56% yield) of cis keto acetal (**43**) and 490 mg (40% yield) trans keto acetal (**45**). For the trans keto acetal: IR ($CDCl_3$) 1700 (vs, C=O), 1252 (s, C–O), 1190 (vs, C–O), 1046 (s, C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.40 (m, 4 H, ethoxy CH_2), 3.3–1.3 (m, 17 H), 1.18 (s, 3 H, CH_3), 1.05 (s, 6 H, CH_3).

Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27. Found: C, 73.25; H, 10.28.

Carboxylation of 43 To Give (4α,7α,9β,13β)-6,6-Diethoxy-2-(methoxycarbonyl)-7,11,11-trimethyltricyclo[10.2.0.0^{9,13}]undecan-3-one (46). To a stirred solution of lithium diisopropylamide (2.58 mmol, from *n*-butyllithium and diisopropylamine) in THF (25 mL), cooled at –78 °C under argon, was added dropwise over 40 min a solution of keto acetal **43** (693 mg, 2.37 mmol) in 5 mL of THF. After the solution was stirred for 1 h at –78 °C, dry carbon dioxide (generated from dry ice and passed through a calcium chloride column under argon) was bubbled into the mixture for 50 min at –58 °C (chloroform–dry ice bath). Then aqueous hydrochloric acid (3.65%, 2.6 mL, 2.6 mmol) was slowly injected at –58 °C, and the mixture was quickly warmed to 0 °C with an ice bath. Ethereal diazomethane, generated from nitrosourea (4.0 mL, 1.33 M, 5.32 mmol), was added dropwise to the cooled mixture. After being stirred for 5 min, the mixture was partitioned between ether and water. From the ether solution was isolated 828 mg of a colorless oil, which was identified as **46** on the basis of the following spectral properties: IR ($CDCl_3$) 1735 (m), 1690 (m), 1644 (s), 1605 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H, COOMe), 3.37 (q, 4 H, OCH_2), 1.26 (s, 3 H, CH_3), 1.03 (s, 6 H, 2 × CH_3), 3.2–1.3 (16 H, m). It was used without further purification.

Preparation of (4α,7α,9β,13β)-6,6-diethoxy-11,11-dimethyl-2-(methoxycarbonyl)-7-methyl-2-(phenylselenyl)tricyclo[10.2.0.0^{9,13}]undecan-3-one (47). To a stirred THF (30 mL) solution of lithium diisopropylamine (2.36 mmol), cooled at –78 °C under argon, was added a solution of crude α-keto ester **46** (828 mg, 2.36 mmol) in THF (6.0 mL) over 20 min. After the solution was stirred for an additional 10 min at this temperature, a solution of phenylselenyl chloride (455 mg, 2.37 mmol) in 1 mL of THF was quickly added via syringe, and the mixture was

stirred for a further 10 min. Addition of aqueous ammonium chloride and the usual ether/water extractive isolation procedure followed by silica gel column chromatography (hexane:dichloromethane:ether = 10:3:2) afforded a light yellow oil, **47** (437 mg, 37% yield from keto acetal **43**): IR ($CDCl_3$) 3300 (w, phenyl C–H), 1725 (s, C=O), 1708 (s, C=O), 1245 (s, C–O), 1046 (s, C–O) cm^{-1}; ^1H NMR ($CDCl_3$) 7.35 (m, 5 H, phenyl), 3.57 (s, 3 H, CO_2CH_3), 3.36 (q, 4 H, ethoxy CH_2), 1.20 (s, 6 H, CH_3), 0.96 (s, 3 H, CH_3), 3.2–1.1 (m, 15 H).

Anal. Calcd for $C_{26}H_{36}O_5Se$: C, 61.53; H, 7.15; Se, 15.56. Found: C, 61.31; H, 7.26; Se, 15.33.

Selenoxide Elimination To Give (7α,9β,13β)-6,6-Diethoxy-2-(methoxycarbonyl)-8,11,11-trimethyltricyclo[7,2.0.0^{9,13}]undecan-1-en-3-one (48). To a solution of the selenide **47** (437 mg, 0.82 mmol) in methylene chloride (30 mL) was added dropwise a solution of aqueous hydrogen peroxide (15%, 1.69 mmol). After the mixture had been stirred for 20 min at 25 °C, 10% aqueous sodium hydrogen carbonate (10 mL) was added. The mixture was stirred for an additional 5 min and then extracted three times with ether. The combined ether layers were washed with saturated brine twice, dried over magnesium sulfate, and concentrated in vacuo. The semisolid product was purified by column chromatography on silica gel (hexane:dichloromethane:ether = 2:1:1) to provide 289 mg of pure **48** (96% yield): mp 87–88.5 °C (hexane) (lit.[7] mp 83–84 °C); IR ($CDCl_3$) 1725, 1705, 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H, CO_2CH_3), 3.32 (s, 2 H, H-5), 0.99 (s, 3 H, CH_3), 1.13 (s, 6 H, CH_3), 3.5–1.2 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 197.79 (s, C-3), 176.89 (s, ester C=O), 163.23 (s, C-4), 124.28 (s, C-2), 102.89 (s, C-6), 58.73 (t, ethoxy CH_2), 58.19 (t, ethoxy CH_2), 55.26 (s, C-7), 52.28 (q, ester CH_3), 51.58 (d, C-13), 42.85 (t, C-10), 41.72 (t, C-5 or -12), 41.39 (t, C-5 or -12) 39.66 (s, C-11), 35.87 (d, C-9), 29.26 (q, CH_3 at C-11), 27.74 (q, CH_3 at C-11), 19.40 (q, C-8), 15.12 (q, ethoxy CH_3), 1490 (q, ethoxy CH_3 at C-11).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.79; H, 8.88.

Reduction of Adduct 40a to Keto Alcohol 52. (a) Reduction of 40a with Lithium Hydride. To a solution of the Diels–Alder adduct **40a** (550 mg, 1.3 mmol) in anhydrous ether (15 mL) was added in one portion solid lithium aluminum hydride (180 mg, 4.6 mmol), and the mixture was stirred for 30 min. Ether (100 mL, saturated with water) was then added dropwise at 0 °C. After most of the residual lithium aluminum hydride had reacted, 100 g of ice water was added and the organic layer was separated. The aqueous phase was extracted three times with ether. The combined ether layers were washed three times with brine, dried over anhydrous potassium carbonate, and concentrated by rotary evaporation at 5 °C to provide a colorless oil (470 mg, 96% yield). The product was homogeneous by the analytical TLC (hexane:dichloromethane:ether = 5:1:1; R_f 0.30) and had the following spectral properties: ^1H NMR (CCl_4) δ 3.36 (m, 6 H), 3.0–0.98 (m, 23 H), 0.12 (s, 9 H); IR (CCl_4) 3540 (w, OH), 1700 (m, C=C), 1250 (s, C–O) cm^{-1}.

(b) Hydrolysis of the Enol Silyl Ether To Give the Trans Ring Fusion (52). To a solution of the 8-hydroxymethyl derivative (**53**) from above (2.735 g, 6.46 mmol) in methanol (anhydrous, 40 mL) was added all at once 3-Å Linde Molecular Sieves (6 g), and the mixture was stirred at 25 °C for 4.5 h. The mixture was partitioned between water and ether, and from the ether solution was obtained a colorless oil, which was purified by column chromatography (silica gel, hexane:dichloromethane:ether = 2:1:1) to provide colorless crystals (1.95 g, 98% yield): mp 74.5–75.5 °C (hexane–ether); ^1H NMR ($CDCl_3$) δ 3.95 (dd, J = 12, 6 Hz, 1 H), 3.73 (dd, J = 7, 12 Hz, 1 H), 3.46 (m, 4 H), 3.07 (dd, J = 7, 6 Hz, 1 H), 2.43 (m, 5 H), 1.63 (m, 5 H), 1.22 (t, J = 7 Hz, 3 H), 1.17 (t, J = 7 Hz, 3 H), 1.06 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR ($CDCl_3$) 212.69 (s, C-3), 104.23 (s, C-6), 63.22 (t, C-8), 58.35 (t, $-OCH_2$), 57.70 (t, $-OCH_2$), 53.69 (s, C-7), 51.20 (d, C-13), 43.67 (t, C-10), 43.29 (d, C-9), 42.58 (t, C-12), 38.03 (t, C-2), 37.06 (s, C-11), 34.84 (t, C-5), 31.64 (q, CH_3 at C-11), 28.99 (d, C-4), 15.28 (q, –OEt), 15.06 (q, –OEt); IR ($CDCl_3$) 3530 (w, OH), 1718 (s, C=O), 1048 (s, C–O) cm^{-1}; mass spectral mol wt, 310.

Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.80; H, 9.81.

Base-Promoted Epimerization of 52 at C-13. Trans keto alcohol **52** (30 mg) was stirred in 6% sodium hydroxide solution (10 mL) at 22 °C for 2 h. After the usual partitioning between water and ether, purification by column chromatography (hexane:ether:dichloromethane = 10:3:3) provided 8 mg of **52** and 13 mg of the corresponding cis ring fusion isomer (epimer at C-13): IR (CCl_4) 3520 (w, OH), 2950 (s, C–H), 1708 (vs, C=O), 1252 (m, C–O), 1149 (m, C–O), 1042 (s, C–O), cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 (dd, J = 7, 11 Hz, 2 H), 3.50 (m, 2 H), 3.20–1.35 (m, 12 H), 1.20 (t, J = 7 Hz, t, J = 7 Hz, 6 H), 1.06 (3 H, s), 0.96 (s, 3 H). The pure cis isomer was treated in the same way (6% methanolic sodium hydroxide solution) and found to give a mixture (60:40) of cis to trans (**52**).

Preparation of Lactone 63. To a solution of keto alcohol **52** (3.00 g, 9.74 mmol) in dichloromethane (200 mL) at 0 °C was added sodium bicarbonate (1.8 g, 21.4 mmol) and *m*-chloroperbenzoic acid (2.44 g, 80–90% technical grade from Aldrich Chemical Co., 11.3–12.7 mmol) and the mixture was stirred at 22 °C for 24 h. The mixture was then diluted with 500 mL of ether and washed with 10% aqueous sodium carbonate solution (500 mL) and with brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography to provide 3.03 g (96% yield) of colorless needles: mp 134.5–135.5 °C (from ether); IR ($CDCl_3$) 3500 (w, OH), 1718 (s, C=O), 1046 (s, C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.79 (ddd, J = 5.4, 7.2, 7.2 Hz, 1 H, H-13), 3.97–1.37 (m, 19 H), 1.19 (t, 2 H, OCH_2CH_3), 1.11 (t, 2 H, OCH_2CH_3), 1.10 (s, 3 H, $-CH_3$), 1.01 (s, 3 H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 173.52 (s, C-3), 104.39 (s, C-6), 81.48 (d, C-13), 63.98 (t, C-8), 59.05 (t, $-OCH_2$), 58.13 (t, $-OCH_2$), 55.37 (s, C-7), 46.05 (d, C-9), 45.73 (t, C-12), 42.37 (t, C-10), 37.38 (s, C-11), 36.14 (t, C-2), 32.94 (t, C-5), 30.10 (q, CH_3 at C-11), 28.82 (q, CH_3 at C-11), 27.79 (d, C-4), 15.39 (q, OEt), 15.06 (q, OEt); mass spectral mol wt, 326.

Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.03; H, 9.29.

Hydrolysis of the Cyclobutanone Ketal To Give Diketone 64. To a vigorously stirred solution of hydroxy lactone **63** (1.55 g, 4.78 mmol) in acetone (300 mL) at −20 °C under argon was added rapidly concentrated hydrochloric acid (1.60 mL). The mixture was stirred at −20 °C for 10 min and then at 0 °C for 30 min. Sodium bicarbonate aqueous solution (10%, 100 mL) was then added slowly, and the mixture was concentrated in vacuo at 22 °C. It was diluted with brine and extracted three times with a 3:1 mixture of ether and dichloromethane. The combined organic layers were washed with brine, dried over anydrous magnesium sulfate, filtered, and concentrated to leave an oil which was chromatographed (ether:dichloromethane = 1:1) to provide 1.09 g of a colorless solid (91% yield); recrystallization from hexane–ether gave mp 110–112 °C: IR ($CDCl_3$) 3580 (w, OH), 1772 (s, ketone C=O), 1725 (s, lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.99 (ddd, J = 4.5, 7.2, 7.2 Hz, 1 H, H-5), 3.81 (m, 2 H, C-8), 3.50–1.18 (m, 11 H), 1.09 (s, 3 H, $-CH_3$), 1.03 (s, 3 H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ 207.38 (s, C-6), 172.92 (s, C-3), 81.90 (d, C-13), 68.75 (s, C-7), 61.06 (t, C-8), 47.57 (t, C-5), 46.92 (d, C-9), 45.51 (t, C-12), 41.17 (t, C-10), 38.02 (s, C-11), 36.25 (t, C-2), 29.85 (q, CH_3 at C-11), 28.39 (q, CH_3 at C-11), 27.41 (d, C-4); mass spectral mol wt, 259.1362; calcd 252.1361.

Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.51; H, 7.99.

Protection of the C-8 Hydroxymethyl Group To Give 65. To a solution of hydroxy keto lactone **64** (1.77 g, 7.08 mmol) in *N,N*-dimethylformamide (16 mL) at 25 °C under argon was added sequentially imidazole (1.9 g, 27.9 mmol) and *tert*-butylchlorodimethylsilane (2.13 g, 14.13 mmol), and the mixture was stirred for 2 h. The reaction mixture was diluted with 10% aqueous sodium bicarbonate and extracted three times with a 3:1 mixture of ether and dichloromethane. The combined organic layers were washed four times with water and then with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by column chromatography (hexane:ether:dichloromethane = 2:1:1) to provide 2.28 g of colorless solid (88% yield); recrystallization from hexane–ether gave mp 138–140 °C: IR ($CDCl_3$) 1775 (s, cyclobutane C=O), 1727 (s, lactone C=O), 840 (vs, O–Si) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.09 (m, 1 H, H-13), 3.73 (ABq, 2 H, H-8), 3.29–1.39 (m, 10 H), 1.08 (s, 3 H, $-CH_3$ at C-7), 1.03 (s, 3 H, $-CH_3$ at C-7), 0.86 (s, 9 H, Si-*t*-Bu), 0.03 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 206.57 (s, C-6), 172.38 (s, C-3), 81.86 (d, C-13), 68.48 (s, C-7), 62.90 (t, C-8a), 47.51 (t, C-5), 47.08 (d, C-9), 45.40 (t, C-12), 41.45 (t, C-10), 38.03 (s, C-11), 36.73 (t, C-2), 30.07 (q, CH_3 at C-11), 29.47 (q, CH_3 at C-11), 28.55 (d, C-4), 25.90 (q, Si-*t*-Bu), 18.15 (s, Si-*t*-Bu), −5.52 (q, $SiMe_2$), −5.63 (q, $SiMe_2$); mass spectral mol wt, 366.2217; calcd 366.2226.

Anal. Calcd for $C_{20}H_{34}O_4Si$: C, 65.53; H, 9.35. Found: C, 65.63; H, 9.42.

Reduction of the Cyclobutanone To Give Cyclobutanol 66. To a solution of keto lactone **65** (2.28 g, 6.23 mmol) in anhydrous methanol (150 mL) cooled at 0 °C under argon was added in one portion solid sodium borohydride (748 mg, 19.8 mmol) and the mixture was stirred for 8 min. The reaction mixture was quenched with 10% aqueous sodium bicarbonate and extracted three times with a 3:2 mixture of ether and dichloromethane. The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was chromatographed (silica gel; hexane:ether:dichloromethane = 2:3:4) to provide 2.15 g of **66** as a colorless solid (94% yield); recrystallization from hexane:ether gave mp 159–160 °C: IR ($CDCl_3$) 3600 (w, OH), 1717 (s, C=O), 1067 (s, C–O), 846 and 838 (s, SiO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.13 (m, 1

H, H-13), 3.82 (d, 1 H, H-8), 3.77 (m, 1 H, H-6), 3.16–3.21 (m, 9 H), 1.13 (s, 3 H, CH_3 at C-11), 1.02 (s, 3 H, CH_3 at C-11), 0.87 (s, 9 H, Si-*t*-Bu), 0.03 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 174.23 (s, C-3), 82.24 (d, C-13), 69.18 (t, C-8), 67.39 (d, C-6), 51.90 (s, C-7), 45.45 (t, C-12), 44.32 (d, C-9), 42.53 (t, C-10), 37.82 (s, C-11), 37.17 (t, C-2), 33.37 (t, C-15), 33.37 (d, C-4), 30.34 (q, CH_3 at C-11), 29.09 (q, CH_3 at C-11), 26.01 (q, Si-*t*-Bu), 18.26 (s, Si-*t*-Bu), −5.52 (q, $SiMe_2$); mass spectral mol wt, 368.2379; calcd 368.2383.

Anal. Calcd for $C_{20}H_{36}O_4Si$: C, 65.17; H, 9.85. Found: C, 65.37; H, 9.92.

Protection of the Cyclobutyl Hydroxy as the Tetrahydropyranyl Ether 67. To a solution of **66** (1.875 g, 5.12 mmol) in dichloromethane (30 mL) at 22 °C under argon was added dihydropyran (1.0 mL, distilled and stored over K_2CO_3, 13.5 mmol) and pyridinium tosylate (270 mg, 1.57 mmol), and the reaction mixture was stirred for 2 h. The reaction was then quenched with 10% aqueous sodium bicarbonate and partitioned between water and ether. From the ether was isolated a colorless oil which was subjected to column chromatography (silica gel; hexane:ether = 2:1) to give pure **67** (2.26 g, 98% yield) as a colorless clear oil: IR ($CDCl_3$) 1718 (s, C=O), 1068 (s, C–O), 838 (s, O–Si) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (m, 1 H, H-13), 4.47 (br s, 1 H), 3.92–1.15 (m, 23 H), 1.15 (br s, 3 H, CH_3 at C-11), 1.03 (br s, 3 H, CH_3 at C-11), 0.88 (s, 9 H, Si-*t*-Bu), 0.05 (s, 6 H, $SiMe_2$).

Anal. Calcd for $C_{25}H_{44}O_5Si$: C, 66.36; H, 9.80. Found: C, 66.10; H, 9.78.

Hydroxymethylation of 67 To Give 68. To a mixture of THF (2 mL) and diisopropylamine (1 mL) at −78 °C under argon was added very slowly *n*-butyllithium (0.30 M, 9.0 mL, 2.70 mmol). After being stirred for 0.5 h at 0 °C, the reaction mixture was exposed to 0.01 torr to remove all volatile materials. The solid lithium diisopropylamide obtained was dissolved in THF (8.0 mL) at −78 °C with stirring. To this was very slowly added a solution of the protected lactone **67** (1.208 g, 2.684 mmol) in THF (5.0 mL) over 1 h at −78 °C. After being stirred for 0.5 h at −78 °C, the mixture was introduced rapidly into a vigorously stirred solution of monomeric formaldehyde (5 g) in ether which had been maintained at −78 °C. After the enolate solution had been added, the reaction mixture was stirred for 0.5 h at −78 °C and then quenched with aqueous ammonium chloride. The aqueous phase was extracted with ether; the ethereal phase was washed with sodium bicarbonate and brine, dried over magnesium sulfate, filtered, and concentrated in vacuo to leave an oil which was purified by silica gel column chromatography (hexane:ether = 1:2) to provide 1.258 g of a colorless oil (98% yield): IR ($CDCl_3$) 3600 (w, OH), 1705 (s, C=O), 1031 (s, C–O), 1057 (s, C–O), 837 (s, O–Si) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.15 (m, 1 H, H-13), 4.51 (br s, 1 H), 4.05–1.20 (m, 27 H), 1.14 (br s, 3 H, CH_3 at C-11), 1.02 (br s, 3 H, CH_3 at C-11), 0.92 (s, 9 H, Si-*t*-Bu), 0.08 (s, 6 H, $SiMe_2$); mass spectral mol wt, 482.

Anal. Calcd for $C_{26}H_{46}O_6Si$: C, 64.69; H, 9.61. Found: C, 64.48; H, 9.80.

Phenylselenation of 68 To Give 69. To a solution of lithium diisopropylamide (4.06 mmol) in tetrahydrofuran (4.0 mL), prepared as described in the previous section, at −78 °C under argon was added very slowly a solution of lactone **68** over 1 h (940 mg, 1.95 mmol) in THF (2.0 mL). The reaction mixture was stirred for an additional 0.5 h at −78 °C and then, with vigorous stirring, was added as rapidly as possible a solution of phenylselenyl chloride (777 mg, 4.06 mmol) in THF (1.0 mL). Within a few minutes after addition, the reaction was quenched with aqueous ammonium chloride and extracted three times with ether. The combined ether layers were washed with sodium bicarbonate solution, with water, and finally with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The yellow residue was purified by silica gel column chromatography (hexane:ether = 1:1) to provide 596 mg of pure **69** (48% yield) and 450 mg of starting material (**68**). For **69**: IR ($CDCl_3$) 3510 (w, OH), 1685 (s, C=O), 1256 (s, C–O), 1035 (s, C–O), 840 (s, O–Si) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H, Ph), 6.22 (m, 1 H, H-13), 4.55 (br s, 1 H); 4.05–1.2 (m, 22 H), 1.16 (br s, 3 H, CH_3 at C-11), 1.08 (br s, 3 H, CH_3 at C-11), 0.96 (s, 9 H, Si-*t*-Bu), and 0.13 (br s, 6 H, $SiMe_2$).

Removal of the Tetrahydropyranyl Ether Group To Give 70. Compound **69** (350 mg, 0.549 mmol) was treated with pyridinium tosylate (200 mg, 0.800 mmol) in methanol (4.0 mL) at 22 °C for 24 h. The reaction mixture was partitioned between water and ether, and from the ether layer was isolated a light yellow oil. The oil was purified by column chromatography (hexane:ether = 1.2) to afford 249 mg (82% yield) of colorless crystals. Recrystallization from hexane–ether gave mp 158–159 °C: IR ($CDCl_3$) 3570 (w, OH), 1680 (s, C=O), 1250 (s, C–O), 1065 (m, C–O), 832 (s, Si–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31 (m, 5 H, Ph), 6.18 (m, 1 H, H-13), 3.96 (m, 1 H, H-6), 3.62 (m, 4 H, C-1), 2.98–1.19 (m, 10 H), 1.11 (s, 3 H, CH_3 at C-11), 1.02 (s, 3 H, CH_3 at C-11), 0.93 (s, 9 H, Si-*t*-Bu), 0.09 (d, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 170.92 (s, C-3), 137.17 (d, SePh), 129.91 (d, SePh), 129.48 (d, SePh), 125.20 (s, SePh), 80.50 (c, C-13), 67.56 (t, C-8), 65.72 (d, C-6), 64.96 (t, C-1), 58.94 (s, C-2), 54.12 (s, C-7), 46.05 (t, C-12), 43.67 (d, C-9), 42.04 (t, C-10), 37.71 (s, C-11), 34.57 (t, C-5), 34.46 (d, C-4), 30.29 (q, CH_3 at C-11), 29.37 (q, CH_3 at C-11), 26.17 (q, Si-*t*-Bu), 18.48 (s, Si-*t*-Bu), −5.20 (q, $SiMe_2$); mass spectral mol wt, 554.1957; calcd 554.1948.

Anal. Calcd for $C_{27}H_{42}O_5SiSe$: C, 58.57; H, 7.65. Found: C, 58.34; H, 7.86.

Formation of the Selenoxide and Thermal Elimination To Give 71. To a solution of selenide **70** (249 mg, 0.450 mmol) in dichloromethane (5.0 mL) at 22 °C was added dropwise 30% aqueous hydrogen peroxide (0.10 mL, 0.90 mmol), and the mixture was vigorously stirred for 40 min. The reaction mixture was diluted with ether (100 mL) and washed with 10% aqueous sodium bicarbonate. The organic phase was then washed with water and brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (ether:dichloromethane = 1:1) to afford 153 mg of **71** as a colorless solid (86% yield); recrystallization from hexane–ether gave mp 164–165 °C: IR ($CDCl_3$) 3570 (w, OH), 1663 (s, C=O), 1080 (s, C–O), 835 (vs, Si–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.11 (m, 1 H, H-13), 4.14 (br d, 2 H, H-1), 3.77 (ABq, 2 H, H-8), 3.5–1.2 (m, 10 H), 1.08 (s, 3 H, CH_3 at C-11), 1.02 (s, 3 H, CH_3 at C-11), 0.83 (s, 9 H, Si-*t*-Bu), 0.02 (d, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 167.40 (s, C-3), 161.28 (s, C-4), 128.66 (s, C-2), 81.21 (d, C-13), 67.23 (d, C-6), 64.36 (t, C-8), 61.33 (t, C-1), 59.32 (s, C-7), 46.97 (t, C-10), 43.18 (d, C-9), 40.15 (t, C-12), 39.28 (t, C-5), 35.76 (s, C-11), 31.26 (q, CH_3 at C-11), 31.10 (q, CH_3 at C-11), 25.90 (q, Si-*t*-Bu), 18.26 (s, Si-*t*-Bu), −5.41 (q, $SiMe_2$); mass spectral mol wt, 396.2325; calcd, 396.2332.

Anal. Calcd for $C_{21}H_{36}O_5Si$: C, 63.60, H, 9.15. Found: C, 63.46; H, 9.21.

Protection of the Hydroxy Group at C-1 as the Ethoxyethyl Ether 72. To a mixture of diol **71** (75 mg, 0.19 mmol) and ethyl vinyl ether (1.0 mL) in dichloromethane (3.0 mL) at −22 °C under argon was added in one portion pyridinium tosylate (29 mg, 0.116 mmol). After being stirred for 24 h at −22 °C, the reaction was quenched with 10% aqueous sodium bicarbonate. The mixture was then extracted three times with an ether–dichloromethane mixture (2:1 by volume) and the combined organic phase was washed with water and then with brine. From the organic solution was isolated an oil which was purified by silica gel column chromatography (hexane:ether:dichloromethane = 2:1:1) to afford 77 mg of **72** as a colorless oil (87% yield): IR ($CDCl_3$) 3600 (w, OH), 1680 (s, C=O), 1082 (s, C–O), 839 (s, O–Si) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.03 (m, 1 H, H-13), 4.75 (q, 0.5 H), 4.72 (q, 0.5 H), 4.41–1.40 (br, 18 H), 1.23 (t, 3 H), 1.08 (s, 3 H, CH_3 at C-11), 1.00 (s, 3 H, CH_3 at C-11), 0.83 (s, 9 H, Si-*t*-Bu), 0.01 (s, 6 H, $SiMe_2$).

Anal. Calcd for $C_{25}H_{44}O_6Si$: C, 64.07; H, 9.46. Found: C, 64.15; H, 9.57.

Formation of Methanesulfonate Ester 73. To a solution of protected lactone **72** (77 mg, 0.16 mmol) in dichloromethane (2.0 mL) cooled at −30 °C was added sequentially triethylamine (33 mg, 0.33 mmol) and methanesulfonyl chloride (37 mg, 0.33 mmol), and the mixture was stirred at −30 °C for 2 h. The reaction was quenched by adding 10% aqueous ammonium chloride, and the resulting mixture was extracted three times with an ether–dichloromethane mixture (2:1 by volume). The combined organic phase was washed sequentially with 10% aqueous sodium bicarbonate, water, and brine. The organic extract was dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation to provide a viscous colorless oil. It was purified by silica gel column chromatography (hexane:ether:dichloromethane = 2:1:1) to afford 83.5 mg of **73** as an oil (93% yield): IR ($CDCl_3$) 1680 (s, C=O), 1368 (s, S=O), 1191 (s, S=O), 1042 (s, C–O), 845 (s, Si–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.87 (m, 3 H), 4.52 (m, 2 H), 3.91–2.72 (m, 6 H), 2.26, 2.27 (s, s, 3 H), 2.10–1.19 (m, 11 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 1.01 (s, 9 H, Si-*t*-Bu), 0.09 (s, 6 H, $SiMe_2$). This sample was used without further purification.

Desilylation of the C-8 Hydroxyl and Trans Lactonization To Give 74. The methanesulfonate ester **73** (83.5 mg, 0.178 mmol) was stirred in acetonitrile (3.0 mL) with 48% aqueous hydrofluoric acid (0.15 mL) at 22 °C for 12 h under argon. The colorless reaction mixture was diluted with 10% aqueous sodium bicarbonate and extracted three times with an ether–dichloromethane mixture (2:1). The combined organic phase was washed with water and then brine, dried over anhydrous magnesium sulfate, filtered, and concentrated to provide a colorless oil, which was chromatographed (ether:dichloromethane:acetone = 1:1:1) to afford 46 mg of pure **74** as a foamy solid (72% yield): IR ($CDCl_3$) 3600 (w, OH), 1711 (vs, C=O), 1365 (s, S=O), 1183 (s, S=O) 1025 (s, C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.68 (d, J = 11 Hz, 1 H, H-8), 4.61 (t, J = 7 Hz, 1 H, H-6), 4.25 (m, 4 H, H-8, 1, 13), 3.56 (d, J = 7 Hz, 2 H, H-5), 3.02 (s, 3 H, OSO_2CH_3), 2.56 (m, 1 H, H-9), 1.81 (m, 2 H, H-12), 1.38 (m, 2 H, H-10), 1.06 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3 at C-11); ^{13}C NMR

Table II. Comparison of Data for Samples of Fomannosin (1) from Synthesis and from Nature

synthetic	natural
A. IR Spectra, $CHCl_3$, cm^{-1}	
3580 (w, OH)	3580 (w, OH)
2960 (m, CH)	2958 (m, CH)
1729 (vs, C=O)	1728 (vs. C=O)
1703 (vs, C=O)	1700 (vs. C=O)
1460 (w)	1462 (w)
1402 (w)	1402 (w)
1371 (w)	1370 (w)
1289 (w)	1287 (w)
1261 (w)	1259 (w)
1225 (w)	1224 (w)
1020 (m, C-O)	1020 (m, C-O)
B. ^1H NMR Spectra, $CDCl_3$	
6.87 (d, J = 2.2 Hz, 1 H, H-6)	6.87 (d, J = 2.2 Hz, 1 H, H-6)
6.66 (d, J = 2.4 Hz, 1 H, H-5)	6.65 (d, J = 2.4 Hz, 1 H, H-7)
4.88 (d, J = 10.1 Hz, 1 H, H-8)	4.86 (d, J = 10.1 Hz, 1 H, H-4)
4.35 (s, 2 H, H-1)	4.35 (s, 2 H, H-2a)
4.25 (d, J = 10.1 Hz, 1 H, H-8)	4.24 (d, J = 10.1 Hz, 1 H, H-4)
3.15 (d, d, J = 12.6, 9.5 Hz, 1 H, H-9)	3.15 (d, d, J = 12.5, 9.6 Hz, 1 H, H-8)
2.12 (m)	2.12 (m)
1.99 (m)	1.98 (m)
1.65 (m)	1.65 (m)
1.13 (s, 3 H, CH_3)	1.12 (s, 3 H, CH_3)
1.07 (s, 3 H, CH_3)	1.06 (s, 3 H, CH_3)
C. ^{13}C NMR spectra, $CDCl_3$	
219.03 (C-13)	219.10 (219.3)[a]
166.23 (C-3)	166.15 (166.1)
155.04 (C-4)	155.05 (155.1)
146.78 (C-5)	146.76 (146.5)
139.95 (C-6)	139.93 (140.2)
114.14 (C-2)	114.09 (114.2)
73.95 (C-8)	73.95 (73.7)
58.54 (C-1)	58.56 (58.4)
53.59 (C-12)	53.58 (53.4)
52.81 (C-7)	52.77 (52.7)
46.77 (C-9)	46.70 (46.5)
38.44 (C-10)	38.41 (38.3)
33.89 (C-11)	33.86 (33.7)
29.92 (C-11a)	29.90 (29.7)
28.36 (C-11b)	28.34 (28.1)
D. TLC comparison[c]	
1. ether:CH_2Cl_2 (1:1 by volume) R_f = 0.41.[b]	
2. hexane:ether:CH_2Cl_2 (2:3:3 by volume) developed three times, R_f = 0.41.[b]	

[a] Data from ref 4. [b] Identical R_f for synthetic and natural samples. [c] Analtech Uniplate SiO_2GF, 250 μm, 5 × 20 cm.

($CDCl_3$) δ 164.36 (s, C-3), 150.23 (s, C-2), 124.28 (s, C-4), 74.98 (d, C-13), 73.46 (d, C-6), 73.19 (t, C-8), 57.64 (t, C-1), 54.50 (s, C-7), 49.73 (t, C-12), 47.68 (d, C-9), 41.50 (t, C-10), 39.93 (t, C-5), 38.47 (q, $-SO_2CH_3$), 35.87 (s, C-11), 30.94 (q, CH_3 at C-11); mass spectral mol wt, 360; calcd for $C_{16}H_{24}O_7S$, 360.

Protection of the C-1 Hydroxyl Group as the *tert*-Butyldimethylsilyl Ether 75. To a solution of diol methanesulfonate ester (43 mg, 0.119 mmol) in *N,N*-dimethylformamide (1.0 mL), cooled at −22 °C under argon, was added sequentially imidazole (19.5 mg, 0.286 mmol) and *tert*-butyldimethylsilyl chloride (21.6 mg, 0.1433 mmol) and the mixture was stirred for 10 h at −22 °C. The colorless solution was diluted with 10% aqueous sodium bicarbonate and extracted three times with an ether–dichloromethane (2:1) mixture. The combined organic layers were washed three times with water and once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The colorless residue was purified by column chloromatography (hexane:dichloromethane:ether = 1:2:2) to afford 54 mg of **75** (92% yield): IR ($CDCl_3$) 3600 (w, OH), 1710 (s, C=O), 1362 (m), 1180 (m), 1078 (m), 836 (s, Si–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.70 (d, J = 10 Hz, 1 H, H-8), 4.64 (t, J = 7 Hz, 1 H, H-5), 4.42 (br d, 2 H, H-1), 4.20 (d, J = 10 Hz, 1 H, H-8), 3.63 (m, 2 H, H-5), 4.31 (m, 1 H, H-13), 3.03 (s, 3 H, OSO_2CH_3), 2.63 (m, 1 H, H-9), 1.93–1.18 (m, 5 H, OH, H-12, 10), 1.12 (s, 3 H, CH_3 at C-11), 1.04 (s, 3 H, CH_3 at C-11), 0.88 (s, 9 H, Si-*t*-Bu), 0.06 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 163.23 (s, C-3), 148.66 (s, C-4), 124.36 (s, C-2), 75.09 (d, C-13), 73.79 (d, C-6), 73.26 (t, C-8), 59.92 (t, C-1), 54.66 (s, C-7), 49.73 (t, C-12), 47.84 (d, C-9), 41.72 (t, C-10), 40.47 (t, C-5), 28.47 (q, $-SO_2CH_3$), 35.97 (s, C-11), 30.94 (q, CH_3 at C-11), 30.72 (q, CH_3 at C-11), 26.06 (q, Si-*t*-Bu), 18.42 (s, Si-*t*-Bu), −5.31 (q, $SiMe_2$). This material was used without further characterization.

Oxidation of the C-13 Hydroxyl to Ketone 76. Chromium trioxide (102 mg, 1.02 mmol) was added to a solution of pyridine (160 mg, 2.02 mmol) in dry dichloromethane (4.0 mL), and the mixture was stirred for 1 h at 22 °C under argon. To this mixture was added in one portion a solution of **75** (48 mg, 0.102 mmol) in dichloromethane (1.0 mL), and the reaction mixture was vigorously stirred for 20 min at 22 °C. It was then diluted with 10% aqueous sodium bicarbonate and extracted three times with an ether:dichloromethane (2:1) mixture. The combined extracts were washed sequentially with 10% aqueous sodium bicarbonate, water, and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was chromatographed on silica gel by eluting with hexane:dichloromethane:ether = 1:1:1 to provide 46 mg of **76** as a colorless, viscous oil (92% yield): ^1H NMR ($CDCl_3$) δ 5.11 (d, J = 10.7 Hz, 1 H, H-8), 4.81 (t, J = 6.8 Hz, 1 H, H-6), 4.67 (dd, 1 H, H-1), 4.37 (dd, 1 H, H-1), 4.21 (d, J = 10.5 Hz, 1 H, H-8), 3.64 (m, 2 H, H-5), 3.04 (dd, 1 H, H-9), 2.93 (s, 3 H, SO_2CH_3), 2.13 (br s, 2 H, H-12), 1.96 (dd, 2 H, H-10), 1.25 (s, 3 H, CH_3 at C-11), 1.07 (s, 3 H, CH_3 at C-11), 0.88 (s, 9 H, Si-*t*-Bu), 0.07 (s, 6 H, $SiMe_2$); ^{13}C NMR ($CDCl_3$) δ 217.60 (s, C-13), 163.10 (s, C-3), 148.15 (s, C-4), 124.87 (s, C-2), 73.43 (d and t, C-6, C-8), 60.16 (t, C-1), 54.37 (s, C-7), 53.20 (t, C-12), 45.14 (d, C-9), 42.41 (t, C-10), 40.26 (t, C-5), 37.99 (q, $-SO_2CH_3$), 35.15 (s, C-11), 30.12 (q, CH_3 at C-11), 27.52 (q, CH_3 at C-11), 26.02 (q, Si-*t*-Bu), 18.41 (s, Si-*t*-Bu), −5.32 (q, $SiMe_2$); mass spectral mol wt, 472; calcd for $C_{22}H_{36}O_7SSi$, 472.

Desilylation and Elimination of Methanesulfonic Acid To Give (±)-Fomannosin (1). To a solution of keto lactone **76** (43 mg, 0.088 mmol) in THF (4.0 mL), cooled at −78 °C under argon, was rapidly added a solution of tetra-*n*-butylammonium fluoride trihydrate (28 mg, 0.0887 mmol) in tetrahydrofuran (1.0 mL), and the reaction mixture was stirred at 0 °C for 10 min. The light brown reaction mixture was diluted with 7.5% aqueous ammonium chloride and extracted with an ether–dichloromethane (2:1) mixture. The extract was washed twice with water and then with brine, dried at 0 °C over magnesium sulfate, rapidly filtered, and concentrated by rotary evaporation at 10 °C. The colorless residue was purified by rapid column chromatography (ether:dichloromethane = 1:1) to provide 18.6 mg of (±)-fomannosin (**1**) as a colorless semisolid (81% yield). For spectral and TLC data comparison with a sample isolated from nature, see Table II.

Registry No. (±)-**1**, 79812-97-8; (±)-**17**, 79745-72-5; (±)-**18**, 79745-73-6; (±)-**19** isomer 1, 79745-74-7; (±)-**19** isomer 2, 79812-98-9; (±)-**20** isomer 1, 79745-75-8; (±)-**20** isomer 2, 79812-99-0; **20** sodium salt, 79813-00-6; **21**, 79745-76-9; (±)-**23a**, 79745-77-0; (±)-**23a′**, 79745-78-1; (±)-**23b**, 79813-01-7; (±)-**23b′**, 79813-02-8; (±)-**26**, 79745-79-2; (±)-**27**, 79745-80-5; (±)-**28**, 79745-81-6; (±)-**29**, 79745-82-7; **30a**, 76221-43-7; **30b**, 76221-44-8; **30c**, 76221-45-9; **37**, 73011-50-4; **38**, 76221-41-5; **39**, 79745-83-8; (±)-**40a**, 76221-46-0; (±)-**40b**, 76221-47-1; (±)-**40bc**-7-hydroxymethyl derivative, 79745-84-9; (±)-**40b** phosphorodiimidate ester, 79745-85-0; (±)-**41a**, 76221-38-0; (±)-**41b**, 76249-34-8; (±)-**42**, 76221-48-2; (±)-**42c**-7-hydroxymethyl derivative, 79745-86-1; (±)-**42** phosphorodiimidate ester, 79745-87-2; (±)-**42** alcohol, 76221-49-3; (±)-**43**, 76249-33-7; (±)-**44**, 76221-50-6; (±)-**45**, 76221-40-4; (±)-**46**, 79745-88-3; (±)-**47**, 79745-89-4; (±)-**48**, 34175-77-4; (±)-*trans*-**52**, 78001-80-6; (±)-*cis*-**52**, 79813-03-9; (±)-**53**, 79745-90-7; (±)-**55**, 79745-91-8; **59**, 79745-92-9; (±)-**63**, 78001-81-7; (±)-**64**, 79745-93-0; (±)-**65**, 78001-82-8; (±)-**66**, 79745-94-1; (±)-**67**, 79813-71-1; **68**, 78001-84-0; (±)-**69**, 79813-04-0; (±)-**70**, 79745-95-2; (±)-**71**, 79813-05-1; **72**, 79745-96-3; **73**, 78007-82-6; (±)-**74**, 79813-06-2; (±)-**75**, 79745-97-4; (±)-**77**, 79813-07-3; 3-methylenecyclopent-2-en-1-one, 2758-18-1; methyl bromoacetate, 96-32-2; (±)-4,4-dimethyl-2-[(methoxycarbonyl)methyl]cyclopentanone, 79745-98-5; 1,4,4-trimethylcyclohexene, 3419-71-4; 2,5,5-trimethyl-1-cyclopentenecarboxaldehyde, 69297-16-1; ethyl propiolate, 623-47-2; ketene diethyl acetal, 2678-54-8; diethyl ethylidenemalonate, 1462-12-0; ethoxyacetylene, 927-80-0; (±)-**76**, 79813-08-4.