Total Synthesis of Spatane Diterpenes: The Tricyclic Nucleus

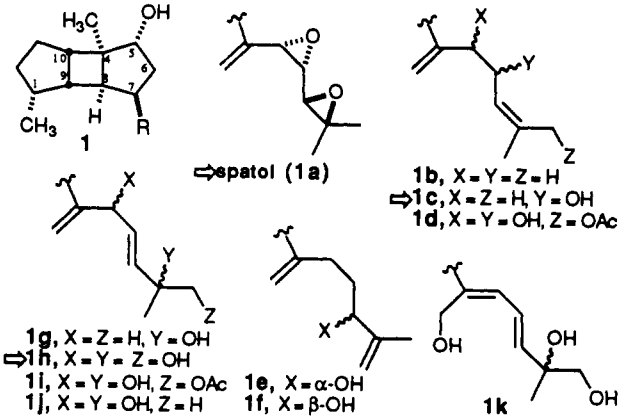
Robert G. Salomon,* Navzer D. Sachinvala, Subhas Roy, Basudeb Basu, Swadesh R. Raychaudhuri, Donald B. Miller, and Ram B. Sharma

Contribution from the Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106-2699. *Received September 6, 1990*

Abstract: A convergent, stereocontrolled construction of the *cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]decane nucleus of spatane diterpenes was achieved by $2\pi + 2\pi$ photocycloaddition of 2-cyclopenten-1-one, as an A-ring precursor, with a carbonyl-masked derivative of 6-methylbicyclo[2.2.1]hept-5-en-2-one as a temporarily bridged C-ring precursor. By design, the temporary bridge assures the correct stereochemical relationship between the B-ring stereocenters and the C-ring hydroxyl substituent that is present in latent form in the oxoethano bridge. Serendipitously, the bridge also fosters a favorable orientation of the photocycloaddition that contrasts with the nonselective $2\pi + 2\pi$ photocycloadditions of unbridged 1-methylcyclopentenes with 2-cyclopenten-1-one. Wittig methylenation of the A-ring carbonyl in photoproduct **24** followed by hydrolysis to **25** and catalytic hydrogenation introduces a methyl group at position 1 with a 10:1 preference for the requisite stereochemistry in **26**. Even higher stereoselectivity was achieved by SO_2-promoted isomerization of the exocyclic C=C bond in **25** to an endocyclic disposition in **29** prior to catalytic hydrogenation. Johnson's sulfoximine method is especially effective for resolution of ketone **29**. The oxoethano bridge in ketone **26n** is oxidized rapidly but nonregioselectively by an H_2SO_4-catalyzed reaction with peracetic acid, producing a 57:43 mixture of **14** and **34**. Regioselective generation of the desired lactone **14** could be accomplished by a much slower oxidation with peracetic acid and no added H_2SO_4. The necessary configuration at position 7 in **49** was generated stereoselectively by a novel homoallylic hydroxyl-directed, pseudointramolecular delivery of hydride to the methylenemalonic ester in the precursor **48**. Conversion of the malonic ester moiety in **49** into an allylic alcohol was accomplished in 92% overall yield by monosaponification, decarboxylative condensation with formaldehyde and reduction of the resulting acrylic ester with *i*-Bu_2AlH. Selective oxidation of the allylic hydroxyl followed by acetylation delivered acetate (+)-**11a**, which is identical with an oxidative degradation product from spatane diterpenes.

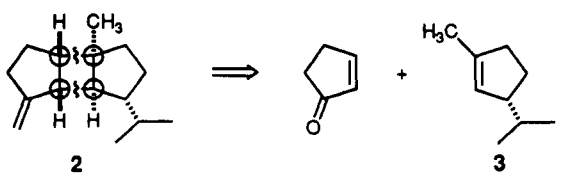
Introduction

The 1,4-dimethyl-5-hydroxy-*cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]decane nucleus (**1**) is common to a wide variety of marine natural products, the spatane diterpenes (**1a–k**).[1] Of these, the allylic

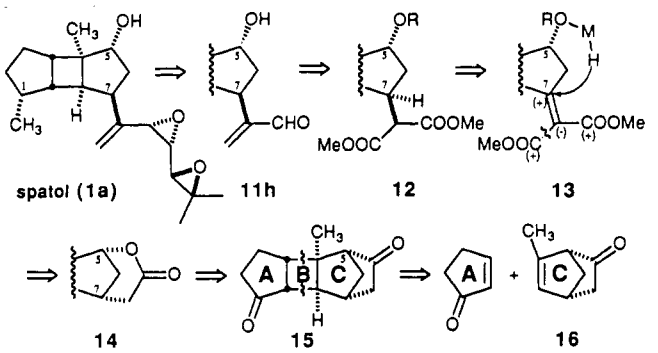


alcohols **1c** and **1h** are weakly antimitotic, while the allylic diepoxide **1a** (spatol) strongly inhibits mitosis of the fertilized sea urchin egg and is cytotoxic toward human skin and brain cancer cells in vitro. These biological activities and the difficulty of isolating sufficient quantities of the natural products for medicinal applications motivated the development of total syntheses of spatane diterpenes, especially spatol.

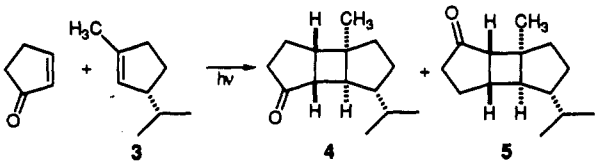
The *cis,anti,cis*-tricyclo[5.3.0.0^{2,6}]decane ring system also occurs in the bourbonane sesquiterpenes as in β-bourbonene (**2**). To-



Scheme I



pological analysis suggests a convergent strategy based on disconnection of two bonds between "common atoms"[2] (circled) for synthesis of this ring system. In fact, efficient assembly of (±)-**2** has been accomplished by $2\pi + 2\pi$ photocycloaddition of 2-cyclopenten-1-one with 3-isopropyl-1-methylcyclopentene (**3**).[3]



Although this reaction is orientationally nonselective, producing a 1:1 mixture of structural isomers **4** and **5**, it is favorably stereoselective owing to a steric approach controlled preference for cycloaddition to the face of the cyclopentene ring opposite the isopropyl substituent. However, similar steric approach control is unfavorable for construction of the tricyclic nucleus of spatane diterpenes via $2\pi + 2\pi$ photocycloaddition methodology. Thus, in spatol (**1a**) the orientation of the allylic diepoxide side chain is cis to the cyclobutane in contrast with the trans isopropyl group in **2**. The allylic diepoxide side chain or its precursor in a me-

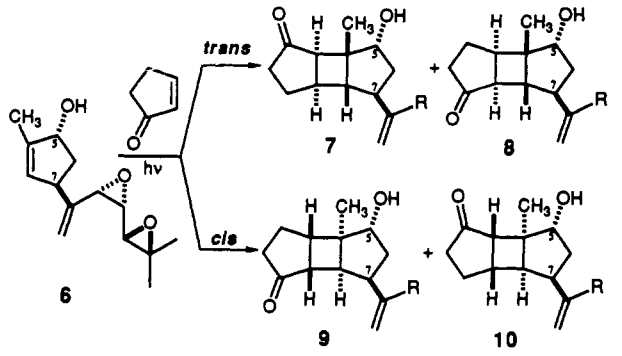
(1) (a) Fernandes, S. L.; Kamat, S. Y.; Paknikar, S. K. *Tetrahedron Lett.* **1980**, *21*, 2249. (b) Gerwick, W. H.; Fenical, W.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (c) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233. (d) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 3325. (e) Ravi, B. N.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 129.

(2) These are defined by Corey as "ring-member atoms which are bonded to *three* or *four* other ring members (but not two)": Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry *J. Am. Chem. Soc.* **1964**, *86*, 478.

(3) White, J. D.; Gupta, D. N. *J. Am. Chem. Soc.* **1968**, *90*, 6171.

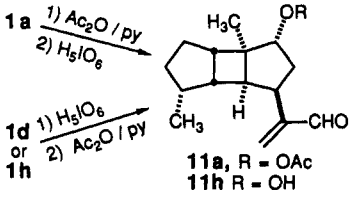
0002-7863/91/1513-3085$02.50/0

thylcyclopentene intermediate, e.g., **6**, can be expected to foster the wrong stereoselectivity in a photocycloaddition with 2-cyclopenten-1-one favoring **7** or **8** rather than the desired adduct **9** or its structural isomer **10**. Our strategy for the total synthesis



of spatane diterpenes surmounts this shortcoming of methylcyclopentene photocycloadditions by exploiting a temporary bridge to shield one face of the cyclopentene ring, precluding cycloaddition to that face (Scheme I).[4] Construction of the side chain by addition of a C-5 nucleophile to an aldehyde electrophile in a precursor **11h** allows dislocation to a precursor **12** with a locally symmetrical malonic ester side chain. The stereochemistry at the 7 position might be controllable by a temporary bridge during pseudointramolecular hydride delivery to an alkylidenemalonic ester as in **13**. Polar analysis of **13** suggests disconnection of the malonic ester unit to an ethanoyl side chain that might be exploited to provide a temporary bridge with the hydroxyl group at position 5 as in lactone **14**. The ketone **15** incorporates the 7-ethanoyl and 5-hydroxyl groups in latent form. Finally, double disconnection of two bonds between two pairs of common atoms in **15** suggests a precursor **16** in which a temporary bridge shields the α-face of the incipient C-ring, enforcing stereoselective cycloaddition of the A-ring precursor, 2-cyclopenten-1-one, trans to the incipient 5-hydroxyl group.

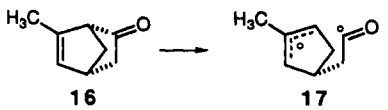
Both the 15-carbon homochiral aldehyde **11h** and its acetate derivative **11a** are known oxidative degradation products from spatane diterpenes **1a**, **1d**, and **1h**. Therefore, the synthetic



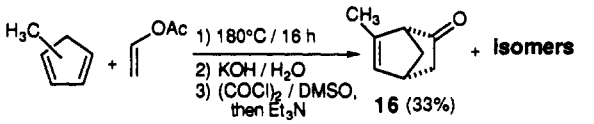
intermediates can be correlated with naturally derived **11a** to facilitate enantiocontrolled total syntheses of spatane diterpenes of correct absolute configuration. Total syntheses of these tricyclic aldehydes are detailed in the present paper. Further elaboration of these intermediates into spatane diterpenes is reported in the accompanying paper.

Results and Discussion

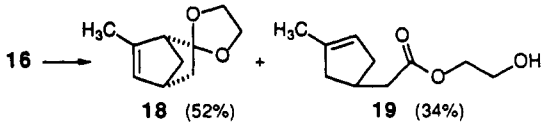
Photocycloaddition. Several considerations recommend masking of the carbonyl group in **16** prior to photocycloaddition with cyclopentenone. This strained bicyclic homoallylic ketone is



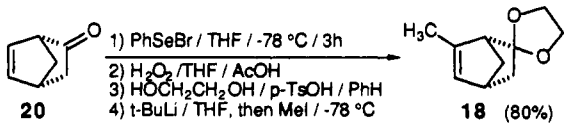
expected to readily undergo photoinduced cleavage to diradical **17**.[5] Furthermore, masking of the carbonyl group in **16** facilitates differentiation from the cyclopentenone-derived carbonyl in the photocycloadduct. Ethylene ketalization of **16** proved unexpectedly difficult. Thus, ketone **16** is readily available in multimolar



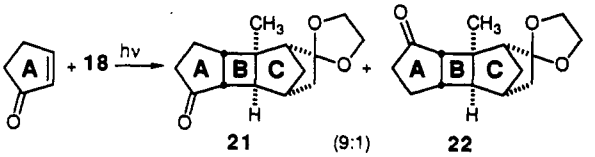
quantities by Diels–Alder reaction of methyl-1,3-cyclopentadiene with vinyl acetate,[6] saponification, and oxidation, since the isomeric coproducts are separable by spinning-band distillation.[7] An improvement in the reported synthesis[6c] was achieved by employing a Swern oxidation[8] (90–97% yield) of the intermediate alcohols instead of oxidation with CrO_3 and H_2SO_4, which only gave a 40% yield. However, only a moderate yield of ketal **18** was available by acid-catalyzed ketalization of **16** under conditions that give an excellent yield of ketal from the 6-unsubstituted analogue, bicyclo[2.2.1]hept-5-en-2-one, owing to a competing fragmentation to **19**.[9] A structurally specific alternative synthesis of ketal **18**



was developed from bicyclo[2.2.1]hept-5-en-2-one (**20**), which is readily available by a Diels–Alder reaction of 1,3-cyclopentadiene with α-chloroacrylonitrile followed by hydrolysis in basic aqueous DMSO.[10] Regioselective replacement of hydrogen with a methyl group and ketalization were accomplished in 80% overall yield by bromoselenation–deselenation, ketalization of an intermediate vinyl bromide, lithium–bromine exchange, and methylation of an intermediate vinyllithium with methyl iodide.[9]



Photocycloaddition of cyclopentenone to **18** was entirely stereoselective, producing only **21** and **22** with cyclobutyl B-rings trans to the temporary bridge across the α-face of the C-ring. An



additional benefit of the temporary bridge was an advantageous structural selectivity favoring the needed isomer **21** over the useless byproduct **22** by 9:1 in contrast with the 1:1 ratio of **4** and **5** produced in the corresponding photocycloaddition of the unbridged 1-methylcyclopentene **3**.

Since an undesirable side reaction interfered with masking of ketone **16** by acid-catalyzed ketalization, a nonacidic alternative was sought. Reaction of **16** with trimethylsilyl cyanide ((TMS)CN) in the presence of a trace of 18-crown-6-KCN quantitatively generated cyanohydrin **23**. Serendipitously, UV irradiation of **23** with cyclopent-2-en-1-one was accompanied by crystallization of the major cycloadduct **24x** from the photoreaction mixture together with the dimer of cyclopentenone from

(4) The foundation of our strategy is exo selectivity in photocycloadditions to bicyclo[2.2.1]heptenes: Hara, M.; Odaira, Y.; Tsutsumi, S. *Tetrahedron* **1966**, *33*, 95.

(5) (a) Schenck, G. O.; Steinmetz, R. *Chem. Ber.* **1963**, *96*, 520. (b) Schuster, D. I.; Aselrod, M.; Auerbach, J. *Tetrahedron Lett.* **1963**, 1911.

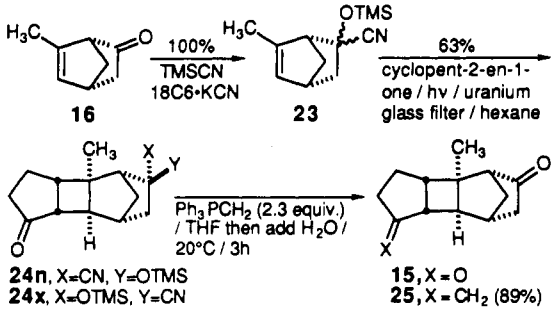
(6) (a) Krieger, H.; Mason, S.-E. *Suomen Kemistil.* **1970**, *B43*, 318. (b) Mason, S.-E.; Krieger, H. *Ibid.* **1969**, *B42*, 1. (c) Brown, H. C.; Peters, E. N.; Ravindranathan, M. *J. Am. Chem. Soc.* **1975**, *97*, 7449.

(7) Goering, H. L.; Chang, C.-S. *J. Org. Chem.* **1975**, *40*, 2565.

(8) Swern, D.; Mancusco, A. J.; Huang, S. L. *J. Org. Chem.* **1978**, *43*, 2480.

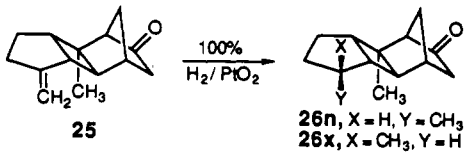
(9) Lal, K.; Salomon, R. G. *J. Org. Chem.* **1989**, *54*, 2628.

(10) Krieger, H. *Suomen Kemistil.* **1963**, *B36*, 68.



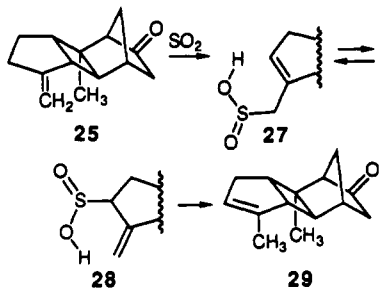
which **24x** was readily separated by trituration with boiling hot hexane, leaving behind pure dimer. Pure **24x** (mp 109–111 °C) was then obtained in 51% yield, based on **23**, by elution of the partially purified product through a column of silica gel with ethyl acetate–hexane. Column chromatography of the hexane-soluble photoproduct afforded a fraction from which nearly pure minor cycloadduct **24n** crystallized together with a little **24x**. This mixture is suitable for Wittig olefination to produce methylidene ketone **25**, vide infra. The combined isolated yield of **24x** plus **24n** exceeds 60%. A sample of pure **24n** (mp 116–118 °C) was obtained by HPLC. The epimeric relationship between **24x** and **24n** was demonstrated by production of the same diketone **15** upon hydrolysis of the cyanohydrin silyl ether masking group. The epimeric relationship between **24x** and **24n** was also proven by production of the same methylidene ketone **25** upon reaction with methylenetriphenylphosphorane followed by hydrolysis of the cyanohydrin silyl ether. The conversion of **24** into **25** was performed as a one-pot procedure affording pure **25** (mp 52–3 °C) in 89% overall yield. The utility of the cyanohydrin silyl ether masking group in the previous transformations is noteworthy. This group introduces stereochemical complexity since the masked ketone **23** and photocycloadducts **24** are epimeric mixtures. However, this is a small price to pay for the otherwise ideal characteristics of the masking group. Thus, it can be introduced under mild neutral reaction conditions; it is sufficiently robust to survive UV irradiation, chromatography on silica gel, and Wittig olefination, but it is readily converted to a carbonyl group by the aqueous base generated upon addition of water to the Wittig reaction mixture.

C-1 Stereocenter. Catalytic hydrogenation of **25** was expected to deliver hydrogen preferentially to the less congested exo face of the C=C bond to give the *endo*-1-methyl epimer **26n**. A



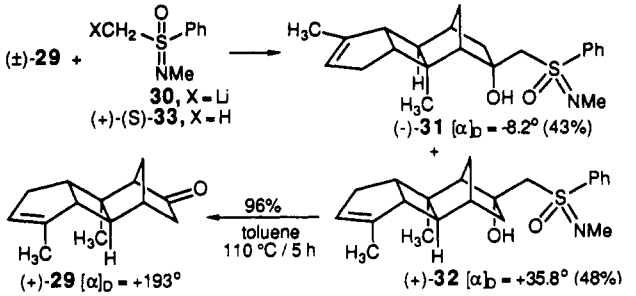
variety of catalysts and solvent systems was explored to optimize the ratio of the desired endo epimer **26n** to the exo epimer **26x**. The results of this study are summarized in Table I. With PtO_2 as catalyst precursor, the requisite endo epimer **26n** was favored over **26x** by ~9:1. A doublet for the secondary methyl and a singlet for the quaternary methyl in **26x** are evident (indicated by arrows) in the crude product mixture (Figure 1, upper trace). Although separation of epimers could not be achieved by normal or reversed-phase HPLC, pure **26n** (mp 53–5 °C; Figure 1, lower trace) is readily isolated from the epimer mixture by fractional crystallization from pentane at −78 °C.

The tedious fractional crystallization only allowed isolation of the requisite endo epimer **26n** in fair yield. To circumvent this separation problem, **25** was isomerized to the endocyclic alkene **29** since steric congestion of the α-face should more effectively control hydrogen delivery to the endocyclic alkene **29** in which the B-ring methyl group and C=C bond are in closer proximity than in the exocyclic alkene **25**. Clean conversion of **25** to **29** occurs in liquid SO_2 presumably by an ene reaction producing **27**, [1.3] sigmatropic rearrangement to **28**, and retro ene elimination.[11] Evaporation of the SO_2 delivers pure crystalline **29** in



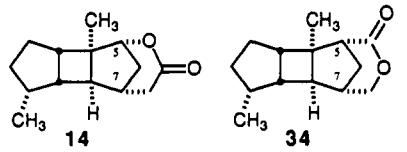
excellent yield. Catalytic hydrogenation of **29** delivers crystalline **26n** nearly quantitatively.

Resolution[12] of ketone **29** was readily achieved by flash chromatography and crystallization of the 1,2-adduct with chiral lithiosulfoximine **30**.[13] Retro ene elimination of the less soluble



dextrorotatory diastereomer (+)-**32** delivers ketone (+)-**29** (mp 67–8 °C), which was correlated with natural spatol by conversion (vide infra) to acetate (+)-**11a**. The sulfoximine (+)-(*S*)-**33** was recovered in 95.9% yield.

Oxidative Cleavage of the Temporary Bridge. The intermediate **26n** contains an extra ring that served as an orientational and stereochemical control element during construction of the tricyclic nucleus of spatane diterpenes. Oxidative cleavage of this ring was intended to introduce the C-5 hydroxyl substituent stereospecifically with the correct configuration. Baeyer–Villiger oxidation of ketone **26n** with *m*-chloroperbenzoic acid proceeded slowly at 85 °C in boiling dichloroethane and afforded only a 46% yield of the desired lactone **14**. In contrast, **26n** reacted rapidly



with peracetic acid at 5 °C in the presence of H_2SO_4. However, this acid-catalyzed oxidation[14] was unselective, producing both the desired lactone **14** and an isomeric lactone **34** in 35% and 26% yields, respectively. Lactone **14** was best prepared by treatment of ketone **26n** with 30–40% peracetic acid in acetic acid[14b] at room temperature. Although completion of the reaction under these conditions required 3–7 days, lactone **14** was obtained in 82–87% yields. Ketone (+)-**26n**, obtained by catalytic hydrogenation of alkene (+)-**29**, provided (+)-**14** by Baeyer–Villiger oxidation with peracetic acid.

Inversion of Configuration at C-7. Since the ethanoyl substituent at position 7 in **14** is part of a temporary bridge, its configuration is necessarily cis to the oxygen substituent at position 5. In the spatane diterpenes, the side chain at C-7 is trans to the hydroxyl

(11) Masilamani, D.; Manahan, E. H.; Vitrone, J.; Rogic, M. M. *J. Org. Chem.* **1983**, *48*, 4918.
(12) Johnson, C. R.; Kirchoff, R. A. *J. Am. Chem. Soc.* **1979**, *101*, 3602.
(13) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418.
(14) (a) Meinwald, J.; Frauenglass, E. *J. Am. Chem. Soc.* **1960**, *82*, 5235. (b) The oxidations without *added* H_2SO_4 catalyst contain a little H_2SO_4 since the peracetic acid used in these reactions was prepared from 90% hydrogen peroxide and acetic acid in the presence of 1% H_2SO_4: Greenspan, F. P. *J. Am. Chem. Soc.* **1946**, *68*, 907.

Table I. Catalytic Hydrogenation of **25**

solvent	catalyst	26n:26x
ethanol	PtO_2	86:14
acetonitrile	PtO_2	90:10
acetic acid	PtO_2	83:17
ethyl acetate	PtO_2	88:12
ethyl acetate	Pt/C	85:15
benzene	$(Ph_3P)_3RhCl$	67:33

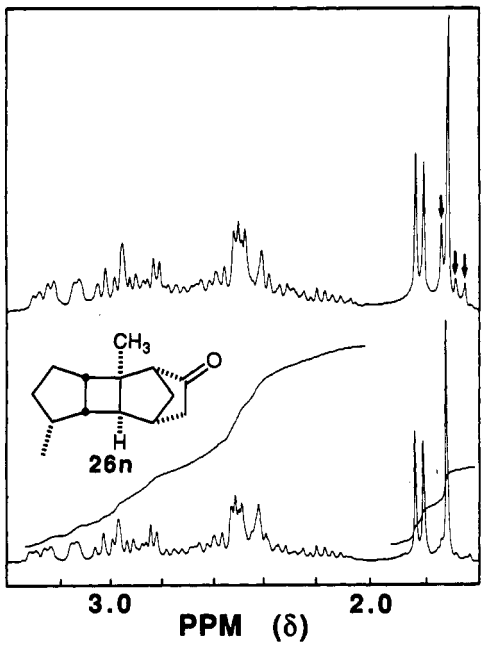
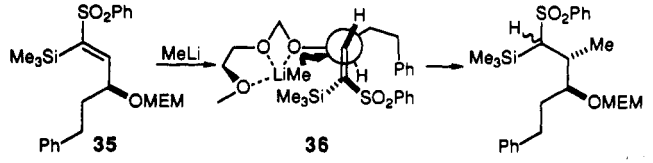


Figure 1. 200-MHz NMR spectra (upfield region) of the hydrogenation product from **25** (upper trace) and pure **26n** (lower trace).

at C-5. Conversion of (+)-**14** into spatane diterpenes required inversion of configuration at C-7. Our strategy for securing the correct configuration at C-7 assumed that some derivative of the C-5 hydroxyl substituent could direct syn Michael addition of hydride to C-7 in an alkylidene malonic ester as in **13** (Scheme I).

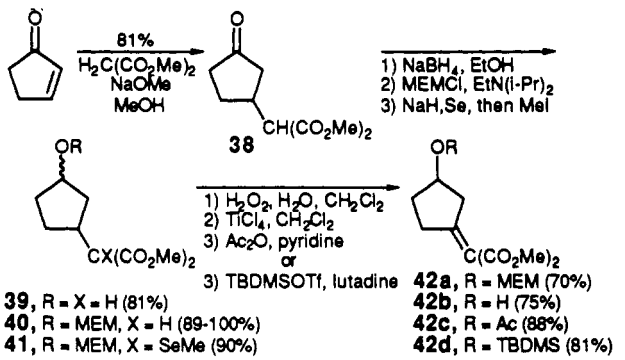
Considering the obvious synthetic utility of stereodirected Michael additions, there are remarkably few examples of such processes. Allylic (methoxyethoxy)methyl (MEM) ether and other alkoxy substituents are known to direct Michael addition of carbanion nucleophiles. A stereodirecting influence of chelation was invoked to explain the stereoselectivity observed in Michael addition of methyllithium to an α-silyl α,β-unsaturated sulfone **35**.[15] Thus, an allylic (γ) MEM group strongly coordinates with



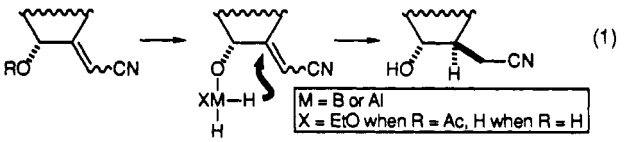
the lithium counter cation as in **36** directing pseudointramolecular addition of the methyl nucleophile with >99% diastereoselectivity. A similar stereodirecting influence was observed with γ-hydroxy-α-silyl-α,β-unsaturated sulfones.[16] Here, strong coordination of the lithium cation with the allylic alkoxide oxygen anchored the MeLi favoring pseudointramolecular Michael addition to one side of the C=C bond, leading to remarkably high acyclic stereoselection. Highly stereoselective 1,4-addition of organolithium and of organocuprate nucleophiles to α,β-unsaturated carbonyl compounds under the stereodirecting influence of an allylic (γ) ether substituent is now well-known.[17] Allylic

(15) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465.
(16) *Idem* **1980**, *21*, 4727.

Scheme II

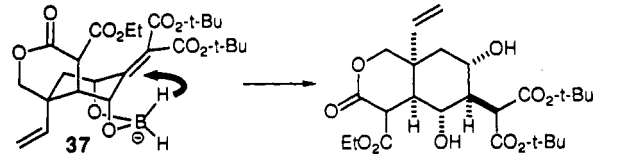


alkoxide-directed pseudointramolecular hydride delivery has been invoked to account for the stereoselective reduction of certain γ-acetoxy-α,β-unsaturated nitriles (eq 1).[18] The closest precedent



(1)

for our intended hydroxyl-directed Michael addition of hydride in **13** (see scheme I) is provided by the intramolecular delivery of hydride to an alkylidenemalonic ester by an *allylic* borate ester in **37**.[19]



To explore the efficacy of various *homoallylic* substituents as stereodirecting groups during hydride reduction, dimethyl (3-hydroxycyclopentylidene)malonate and several hydroxyl-protected derivatives **42a–d** were prepared as outlined in Scheme II. The Michael adduct **38**[20] from cyclopent-2-en-1-one and dimethyl malonate was reduced with borohydride to provide an epimeric (1:1) mixture of alcohols **39**. The hydroxy group in **39** was masked as a MEM ether. Dehydrogenation of malonic ester **40** was performed by a two-step selenation–dehydroselenation process. Methyl selenation[21] of **40** provided **41**, which was oxidatively dehydroselenated to deliver alkylidenemalonic ester **42a**. Possible elimination of the homoallylic oxygen substituent in **42a–d** generating a conjugated diene was a concern during the synthesis of these vinylogous β-hydroxy malonic ester derivatives. However, generation of a conjugated diene did not accompany removal of the MEM protecting group upon treatment with $TiCl_4$,[22] which afforded **42b** from which the acetate **42c** and silyl ether **42d** were readily available.

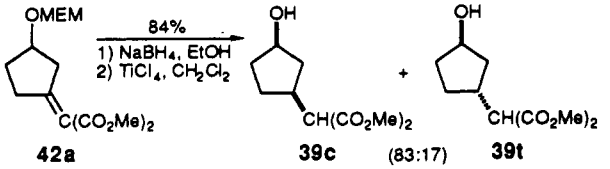
Borohydride reduction of MEM-protected alkylidenemalonic ester **42a** followed by removal of the MEM group with $TiCl_4$

(17) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, 2327; *J. Am. Chem. Soc.* **1981**, *103*, 1224; **1982**, *104*, 2027. (b) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465; **1980**, *21*, 4727. (c) Tatsuta, K.; Amemiya, Y.; Maniwa, S.; Kinoshita, M *Ibid.* **1980**, *21*, 2840. (d) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Ibid.* **1981**, *22*, 3997. (e) Ziegler, F. E.; Gilligan, P. J. *J. Org. Chem.* **1981**, *46*, 3874. (f) Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, *22*, 4017. (g) Roush, W. R.; Lesur, B. M. *Tetrahedron Lett.* **1983**, *24*, 2231. (h) Salomon, R. G.; Miller, D. B.; Raychaudhuri, S. R.; Avasthi, K.; Lal, K.; Levison, B. S. *J. Am. Chem. Soc.* **1984**, *106*, 8296.
(18) Lansbury, P. T.; Vacca, J. P. *Tetrahedron Lett.* **1982**, *23*, 2623.
(19) Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *J. Am. Chem. Soc.* **1978**, *100*, 1940.
(20) Katsube, J.; Shimomura, H.; Matsui, M. *Agr. Biol. Chem.* **1971**, *35*, 1828. *Idem.* **1975**, *39*, 657.
(21) Liotta, D.; Zima, G.; Barum, C.; Sundane, M. *Tetrahedron Lett.* **1980**, 3043.
(22) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Table II. Hydride Reduction of **42b**

entry	reagent	solvent	26n:26x	yield (%)
1	$LiAl(OMe)H_3$	THF	1:1	100
2	$LiAl(O\text{-}s\text{-}Bu)H_3$	THF	1:1	92
3	$LiAl(O\text{-}t\text{-}Bu)_3H$	THF	1:1	90
4	$NaBH_4$	EtOH	3:2	92
5	$NaBH_4$	THF	3:1	86
6	NaH then BH_3	THF	4:1	60

affords the cis epimer **39c** with a 5:1 preference over the corresponding trans epimer **39t**. Thus, *the MEM ether substituent*



42a **39c** (83:17) **39t**

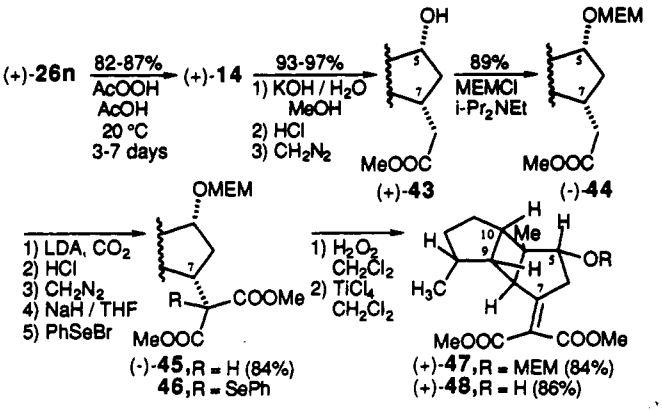
functions as a bulky steric hindrance to syn approach of the hydride. This contrasts with the presumed syn stereodirecting effect of a MEM ether substituent serving as a putative chelating ligand during conjugate addition of MeLi to **35**. Borohydride reduction of the corresponding acetate derivative **42c** is slightly less selective while reduction of the TBDMS derivative **42d** is slightly more selective in *favoring anti delivery of hydride* to the C=C bond of a *homoallylic* alkylidenemalonic ester.

Most significantly for our synthetic approach to the spatane diterpenes, the stereochemical outcome was reversed by first removing the MEM protecting group in **42** followed by treatment of the hydroxyalkylidenemalonic ester **42b** with $NaBH_4$. Reduction of **42b** with various hydride reagents is summarized in Table II. The slight preference for hydride delivery syn to the hydroxyl evident with $NaBH_4$ in ethanol (entry 4) is amplified in aprotic solvent (entry 5). Thus, the remote hydroxyl group fosters syn hydride delivery. Presumably, this involves a preference for pseudointramolecular hydride delivery via an alkoxyborohydride intermediate. Exploiting an alternative method for generating an alkoxyborohydride intermediate, reaction of the sodium alkoxide from alcohol **42b** with BH_3 affords an even greater preference for syn hydride delivery (entry 6); however, the overall yield with this protocol is unsatisfactory. It is noteworthy that aluminum hydrides (entries 1–3) do not react stereoselectively, presumably because replacement of a hydride by the alkoxy substituent derived from **42b** deactivates the hydride donor so that pseudointramolecularity no longer provides sufficient benefit to compete effectively with intermolecular hydride delivery from the starting hydride reagent (Table II, entries 1 and 2). But replacement of a hydride in $NaBH_4$ by an alkoxy substituent activates the hydride donor.[23] Thus, pseudointramolecularity provides little benefit for the $NaBH_4$ reduction of **42b** in ethanol where $Na(EtO)_nBH_{4-n}$ competes intermolecularly. In THF, however, intermolecular hydride delivery by $NaBH_4$ is somewhat less effective than pseudointramolecular reaction via an alkoxyborohydride.

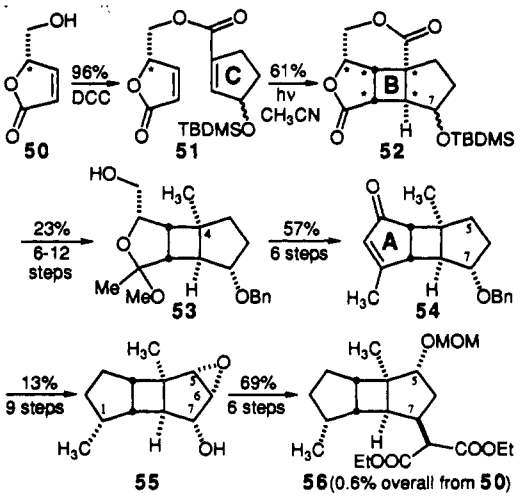
The hydroxyalkylidenemalonic ester intermediate (+)-**48** required for our total synthesis of spatane diterpenes was prepared from tetracyclic ketone (+)-**26n** as outlined in Scheme III. The pure (phenylseleno)malonic ester **46** was isolated by column chromatography in 88% yield. However, owing to the instability of this intermediate, the unpurified phenylselenation product was generally converted directly to **47** by treatment with H_2O_2. In this manner, (+)-**47** was obtained in 84% yield overall from (−)-**45**.

The crucial stereocontrolled Michael reduction was then examined. Reduction of the MEM ether **47** with $NaBH_4$ in ethanol followed by removal of the MEM protecting group afforded a 2:1 mixture, respectively, of the *cis*-hydroxy malonic ester and its C-7 epimer, the desired *trans*-hydroxy malonic ester **49**. As with the

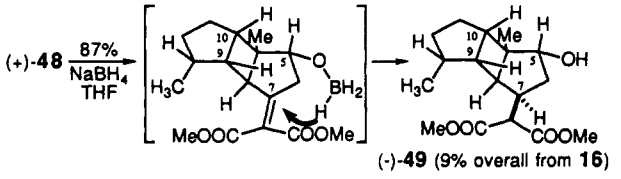
Scheme III



Scheme IV



model **42a**, the MEM ether substituent in **47** sterically hinders the desired syn delivery of hydride. In contrast with **42a**, anti delivery of hydride is also hindered for **47** by the hydrogens at positions 9 and 10, resulting in nonstereoselective reduction. Most gratifyingly, the combination of this steric hindrance to anti hydride delivery with the syn stereodirecting influence of a homoallylic hydroxyl substituent results in highly stereoselective reduction of hydroxyalkylidenemalonic ester **48**. Thus, (+)-**48** afforded (−)-**49** with no trace of its C-7 epimer upon treatment with $NaBH_4$ in THF.

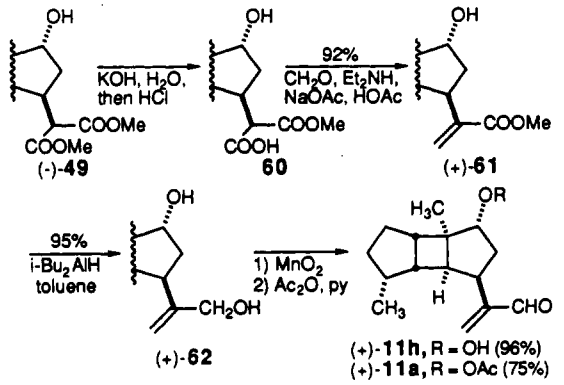


A homochiral intermediate **56** similar to (−)-**49** has been assembled by a different strategy employing photocycloaddition to generate the B-ring and a stereocontrolling temporary bridge (Scheme IV).[24] However, in that synthesis a temporary bridge is needed to assure the correct stereochemical relationship between the B-ring stereocenters and an extra chiral center derived from a precursor **50** that is available in homochiral form from L-glutamic acid. In contrast with our photocycloadduct **24**, the intermediate **52** lacks a methyl group at position 4 or an A-ring. These must be generated in **53** and **54**, respectively, by multistep sequences. The difficulty encountered in introducing the requisite oxygen substituent at position 5 in the A-ring during the **54** to **55** conversion underscores the importance of having this substituent

(23) (a) Brown, H. C.; Mead, E. J.; Shoaf, D. J. *J. Am. Chem. Soc.* **1956**, *78*, 3616. (b) Brown, H. C.; Muzzio, X. *J. Am. Chem. Soc.* **1966**, *88*, 2811. (c) Rickborn, B.; Wuesthoff, M. T. *J. Am. Chem. Soc.* **1970**, *92*, 6894.

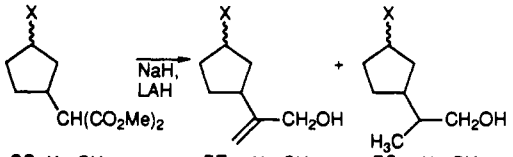
(24) Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 3035.

Scheme V



present, albeit in latent form, in our key intermediate, photocycloadduct **24**.

13,14-C=C Bond. Conversion of the malonic ester group in **49** into a suitable precursor of the C-13–C-20 side chain of spatane diterpenes requires a reduction that produces the Δ^{13}C=C bond. A particularly attractive solution for this synthetic operation involved the one-pot transformation of the malonic ester group into an allyl alcohol by Marshall reduction of the sodium enolate with lithium aluminum hydride (LAH).[25] In a model study, treatment of the sodium enolate from dimethyl (3-hydroxycyclopentyl)malonate (**39**) with LAH generated no 2-(3-



hydroxycyclopentyl)prop-2-en-1-ol (**57a**). Rather, overreduction product **58a** was formed. This contrasted with the reduction of dimethyl cyclopentylmalonate (**59**), which provided an 82:18 mixture of 2-cyclopentylprop-2-en-1-ol (**57b**) and overreduction[25c] product **58b** upon treatment with NaH followed by LAH. Postulating that the hydroxyl group in **39** was fostering overreduction, the MEM-masked derivative **40** was converted to a sodium enolate and then reduced with LAH. As expected, an 83:17 mixture of allylic alcohol **57c** and overreduction product **58c** was generated.

The Marshall reduction is a convenient synthesis of allylic alcohols from malonic esters, but excellent yields are not generally available owing to the coproduction of the corresponding saturated propanols. While this may often be only a minor inconvenience, in the context of multistep syntheses losses owing to overreduction are a serious problem. Therefore, an alternative method for achieving this transformation was sought. Conversion of malonic ester **49** into allylic alcohol **62** and then aldehyde **11h** was achieved in excellent yield as outlined in Scheme V. Selective monosaponification of malonic ester **49** is readily achieved. Mannich condensation with subsequent decarboxylative elimination generated α,β-unsaturated ester **61** from the monoacid **60** in a one-pot process.[26] The conversion of (−)-**49** into (+)-**61** was achieved in 92% overall yield without the need for purification of the intermediate monoacid **60**. Reduction of this acrylic ester (+)-**61** with i-Bu_2AlH[27] gives the target allylic alcohol (+)-**62** without any trace of overreduction. Selective allylic oxidation then provides the target aldehyde (+)-**11h**, which was converted to acetate (+)-**11a** for optical correlation with a degradation product from spatane diterpenes. The totally synthetic acetate showed $[\alpha]^{22}_D$ = +25.1°, which compares well with the naturally derived acetate that showed $[\alpha]^{22}_D$ = +26.5°.[1]

(25) (a) Marshall, J. A.; Andersen, N. H.; Hochstetler, A. R. *J. Org. Chem.* **1967**, *32*, 113. (b) Salomon, R. G.; Coughlin, D. J.; Ghosh, S. G.; Zagorski, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998. (c) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408.

(26) Johnson, F.; Parker, W. L. *J. Org. Chem.* **1973**, *38*, 2489.

(27) (a) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822. (b) Evans, D. A.; Wong, R. Y. *J. Org. Chem.* **1977**, *42*, 350. (c) Evans, D. A.; Truesdale, L. K.; Carrol, G. L. *J. Chem. Soc., Chem. Commun.* **1973**, 55. (d) Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, 4929.

Experimental Section

General Methods. All melting points are uncorrected and were recorded on a Thomas Hoover capillary melting point apparatus. All proton NMR spectra were recorded on a Varian A-60-A, EM-360-A, or XL-200 spectrometer. ^{13}C NMR spectra were recorded on a Varian XL-200 spectrometer at 50 MHz in the FT mode. ^{1}H and ^{13}C NMR spectral data are reported on the δ scale relative to tetramethylsilane (δ 0.00). Abbreviations used are as follows: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet. High-resolution mass spectra were recorded on a Kratos/AEI MS-30 dual-beam, double-focusing, magnetic sector mass spectrometer with a DS-50S Nova-3 computer. Samples were run to 70 eV. The heat source was at 200 °C with direct probe insertion. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI 49951. Preparative thin-layer chromatography (TLC) was performed with use of precoated silica gel plates (20 × 20 cm, Merck). Flash column chromatography was performed with silica gel (230–400 mesh, Merck).

Materials. All reactions were performed in an inert moisture-free atmosphere under a positive pressure of nitrogen or argon except when working in aqueous media. Purification and handling of all solvents was conducted under a nitrogen atmosphere. All solvents were reagent grade. Benzene was boiled under reflux over potassium benzophenone ketyl followed by distillation. Methylene chloride was boiled under reflux over phosphorus pentoxide followed by distillation. Pentane was stirred over concentrated sulfuric acid for 2 days, washed with water, saturated sodium bicarbonate, and water, and then dried over anhydrous magnesium sulfate and distilled over phosphorus pentoxide. Tetrahydrofuran was boiled under reflux over potassium benzophenone ketyl followed by distillation. Hexane was distilled over sodium hydride. Ethyl acetate was boiled under reflux over phosphorus pentoxide followed by distillation. Ethyl ether was boiled under reflux over lithium aluminum hydride followed by distillation. Toluene was boiled under reflux over sodium benzophenone ketyl followed by distillation. Hexamethylphosphoric triamide was distilled over sodium, and the constant boiling fraction 70 °C (1 mmHg) was collected and used. Diisopropylamine was freshly distilled over sodium prior to use. Bone-dry carbon dioxide gas (Matheson) was used without further purification.

Methylbicyclo[2.2.1]hept-5-en-2-ones.[6,7] To a solution of oxalyl chloride (98%, 102 mL, 1.1 mol) in methylene chloride (1 L) at −60 °C was added dimethyl sulfoxide (187 g, 170 mL, 2.4 mol) in methylene chloride (50 mL) over 15 min and stirring continued for an additional 3 min. A methylene chloride (250-mL) solution of the isomeric alcohols (124 g, 1 mol) obtained from a Diels–Alder reaction between methylcyclopenta-1,3-diene and vinyl acetate followed by saponification[6] was added over 7 min and the resulting mixture stirred for 20 min, and then the mixture was treated with triethylamine (508 g, 700 mL, 5.03 mol) added over 18 min and stirred for 10 min at −60 °C. The reaction mixture was allowed to warm to room temperature, washed with water (3 × 200 mL), and concentrated in vacuo. The residue was dissolved in ether, washed with 1% hydrochloric acid solution (3 × 300 mL) and then water (2 × 250 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting yellow oil and solid triethylamine hydrochloride were triturated with pentane, and the triethylamine hydrochloride was removed by filtration and washed with pentane, the solvent removed in vacuo from the combined filtrate, and the oil purified by distillation. The fraction collected between 58–67 °C (12 mmHg) contained the isomeric ketones (109 g, 0.894 mol, 89.4% yield). The combined product (787 g) from oxidation of a total of 879 g of alcohols was fractionally distilled through a spinning band,[7] affording 6-methylbicyclo[2.2.1]hept-5-en-2-one (**16**) (217 g, 2.3 mol, 25% yield; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.7–2.5 (7 H), 2.73–2.87 (1 H, s), 2.93–3.19 (1 H, bs), 5.98–6.16 (1 H, s)) and 5-methylbicyclo[2.2.1]hept-5-en-2-one (250 g, 2.7 mol, 29% yield), which was reported previously.[6c]

6-Methyl-2-[(trimethylsilyl)oxy]bicyclo[2.2.1]hept-5-ene-2-carbonitriles (23). A mixture of the ketone **16** (40 g, 0.328 mol), trimethylsilyl cyanide (38.9 g, 48.9 mL, 0.392 mol, 1.2 equiv), and the potassium cyanide 18-crown-6 catalyst[27] (189 mg, 0.6 mmol, 1.7 m equiv) was boiled 30 min under reflux and then cooled. The ^{1}H NMR spectrum of the reaction mixture showed that no starting material remained. The reaction mixture was then distilled under aspirator vacuum to remove excess trimethylsilyl cyanide (10 mL, bp 25–120 °C). The residual oily product was distilled under high vacuum to give the cyanohydrins **23** (71.0 g, 0.321 mol, 98%): bp 65 °C (1 mmHg); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.23 (9 H), 1.1–2.0 (6 H), 2.35 (1 H, dd, J = 4.8 Hz), 2.7–3.1

(2 H), 5.83 (1 H, broad s); mass spectrum m/z (M^+) for $C_{12}H_{19}ON$ calcd 221.1236, found 221.1255.

Photoaddition of 2-Cyclopenten-1-one to the Cyanohydrin Silyl Ethers 23. To a clean, dry Pyrex photoreactor under nitrogen was added the bicyclic trimethylsilyl cyanohydrins **23** (17.2 g, 0.078 mol) and dry olefin-free pentane (500 mL). Cyclopentenone (38 g, 0.46 mol) was added in 2-mL aliquots every 5 h. The mixture was irradiated through a uranium glass filter with a Hanovia 450-W lamp. Total irradiation time was 100 h. Much of the cyclopentenone dimer and the photoadduct **24x** crystallized from the reaction mixture and was periodically removed by filtration or washing the immersion well with acetone. The combined insolubles were triturated with boiling hot hexane (4 × 50 mL) to afford pure insoluble dimer of 2-cyclopentenone (21 g, 0.13 mol) and a mixture of dimer and the photoproduct **24x** (11 g), which were separated by chromatography on silica gel 60–200 mesh (380 g) with ethyl acetate in hexanes, a 20% solution (2 L) and then a 25% solution (2 L), followed by washing the column with neat ethyl acetate (1 L). Pure major photoadduct (7.1 g, 0.23 mol, 50.5%), 8-methyl-4-oxo-10-*endo*-(trimethylsiloxy)-*cis*,*anti*,*cis*-tetracyclo[7.2.1.$0^{2,8}$.$0^{3,7}$]dodecane-10-*exo*-carbonitrile (**24x**) was obtained: mp 109–111 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.25 (9 H, s), 1.29 (1 H, dd, J = 3.5, 13 Hz), 1.37 (3 H, s), 1.75 (2 H), 1.77 (1 H, s), 1.98–2.15 (2 H, d, J = 12 Hz), 2.05–2.85 (2 H), 2.22 (1 H, s), 2.26 (1 H, d, J = 7.5 Hz), 2.28 (1 H, s), 2.45 (1 H, dd, J = 7.5, 13 Hz), 2.55 (1 H, t, J = 9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 0.6, 17.0, 22.6, 33.4, 37.7, 39.0, 41.8, 42.7, 43.4, 47.3, 49.6, 54.2, 75.5, 122.8, 221.7. Anal. Calcd for $C_{17}H_{25}NO_2Si$: C, 67.28; H, 8.30. Found: C, 67.31; H, 8.47.

The pentane-soluble photoproducts were concentrated by rotary evaporation and most of the unreacted starting cyanohydrins removed by distillation under aspirator vacuum up to 120 °C (6.4 g, 0.029 mol). The pot residue was dissolved in ethyl acetate (10 mL), seeded with the photoadduct **24x**, and kept at −5 °C for 3 days. The impure crystalline **24x** that separated was purified together with the same isomer isolated previously. The mother liquor was chromatographed on silica gel to afford a fraction (6.3 g) from which a mixture of photoadducts **24x** and **24n** crystallized (1.2 g, 0.004 mol, 9%) and another fraction containing mainly the starting cyanohydrins **23** (5.1 g, 0.023 mmol).

By use of the same procedure as above, a large-scale preparation of **24x** and **24n** was conducted with bicyclic trimethylsilyl cyanohydrins **23** (90 g, 0.407 mol) and cyclopent-2-en-1-one (180 g, 2.19 mol). The irradiation time was 2 days. Compounds **24x** and **24n** contaminated with some cyclopentenone dimer were purified by chromatography on a Waters Prep LC system 500A with one prep pack-500 silica gel column (Waters Associates), column chamber pressure 32 atm, column pressure limit 17 atm, and pump set at 2 L/min (7 atm), with 50% ethyl acetate in hexanes as eluting solvent. Each injection was approximately 80 mL of the mobile phase, containing 10–15 g of the product mixture. The RI relative response was 1, chart speed 1 cm/min, and each run used 2 L of the solvent mixture. The first peak with a retention time of 3 min contained the desired photoadducts **24x** and **24n**. The second peak with a retention time of 4.8 min had a shoulder. This was then recycled to separate the desired photoadducts **24n** and **24x** and the cyclopentenone dimer. After purification, the desired photoadducts **24x** and **24n** weighed 57 g (0.188 mol, 61% yield). A pure sample of the minor epimer **24n** was isolated by a shave recycle sequence (3.0 g, 0.01 mol, 3%), mp 116–118 °C.

8-Methyl-*cis*,*anti*,*cis*-tetracyclo[7.2.1.$0^{2,8}$.$0^{3,7}$]dodecane-4,10-dione (15). The epimeric relationship between cyanohydrin silyl ethers **24x** and **24n** was proven by production of the same diketone **15** upon hydrolysis. Thus, the cyanohydrin silyl ether (80 mg) was dissolved in methanol (10 mL) to which was added 5% aqueous sodium hydroxide solution (1 mL) and tetrahydrofuran (5 mL). After being stirred 3 h at room temperature, the reaction mixture was concentrated to half the original volume, diluted with water (1 mL), and extracted with pentane (5 × 5 mL). The pentane extracts were combined, washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo to provide the dione **15**: mp 71–74 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.16 (3 H, s), 1.4–2.8 (16 H); mass spectrum m/z (M^+) for $C_{13}H_{16}O_2$ calcd 204.1150, found 204.1158.

Tetracyclic Methylidene Ketone 25. A suspension of methyltriphenylphosphonium bromide (14.4 g, 40 mmol) in THF (80 mL) was cooled to 0 °C and treated with methyllithium (1.3 N, 27.6 mL, 36.0 mmol). The mixture was stirred 2 h at 20 °C and then cooled to 0 °C. Ketone **24x** (4.8 g, 16.1 mmol) in tetrahydrofuran (20 mL) was added. After being stirred 15 h at 20 °C, water (30 mL) was added and the resulting mixture stirred vigorously 3 h, poured into saturated aqueous sodium chloride solution (100 mL), and extracted with pentane (4 × 100 mL). The extracts were serially washed with water (5 × 50 mL) and then with brine solution (50 mL). Solvent was removed from the combined extracts by rotary evaporation after being dried over anhydrous magnesium sulfate. The crude product was chromatographed with silica gel 60–200 mesh (380 g) with 5% ethyl acetate in hexanes as eluting solvent to afford pure methylidene ketone **25** (2.90 g, 14.3 mmol, 89%): mp 52–53 °C; ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.99 (3 H, s), 1.2–2.7 (13 H), 4.82 (2 H, bs); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.20, 27.76, 33.02, 34.19, 38.83, 39.70, 42.42, 42.88, 46.04, 51.56, 59.07, 105.15, 155.99, 215.88; mass spectrum m/z (M^+) for $C_{14}H_{18}O$ calcd 202.1357, found 202.1388.

Catalytic Hydrogenation of the Methylidene Ketone 25. Tris(triphenylphosphine)rhodium chloride (14 mg, 0.015 mmol) was dissolved in benzene. The reaction vessel was evacuated by use of an aspirator vacuum and then filled with hydrogen. The tetracyclic methylidene ketone **25** (202 mg, 1.0 mmol) dissolved in benzene (600 μL) was introduced through a serum cap by use of a hypodermic syringe and the hydrogenation started. After 3 h, hydrogen (22.4 mL) consumption stopped abruptly. Stirring under a hydrogen atmosphere was continued for 1 additional hour. Filtration through a column of Florisil and rotary evaporation of the solvent gave a product (204 mg, 1.0 mmol) that was an epimeric mixture of *endo*- and *exo*-methyl ketones **26n** and **26x**. A 2:1 ratio, respectively, was determined by ^{1}H NMR at 200 MHz by expanding the γ 0.8–1.0 region and integrating over the two methyl hydrogen doublets. The *exo*-methyl in **26n** appears at δ 0.99 (3 H, d, J = 5.7 Hz), while the *endo*-methyl in **26n** appears at δ 0.96 (3 H, d, J = 6.3 Hz). Compound **26n** was isolated subsequently and characterized by ^{1}H, ^{13}C NMR, and elemental analysis vide infra. Catalytic hydrogenations of **25** with other catalysts and solvents were performed and analyzed similarly. The results are presented in Table I.

Tetracyclic *endo*-Methyl Ketone 26n. A mixture of the methylidene ketone **25** (3.03 g, 15 mmol) in ethyl acetate (50 mL) and Pt(0) from PtO_2 (50 mg prereduced) was stirred under an atmosphere of hydrogen. After 350 mL of hydrogen was consumed (theoretical 336 mL), absorption stopped abruptly. After filtration through Celite and removal of solvent by rotary evaporation, the crude product was dissolved in pentane (100 mL) and the solution cooled in an ultralow temperature freezer to −80 °C in an Erlenmeyer flask (215 mL) with a male 24/40 joint topped with a 150-mL medium-porosity sintered-glass funnel with a 24/40 female joint. The resulting crystals were collected by filtering the cold suspension under N_2 pressure to afford the pure *endo*-methyl epimer **26n** (1.38 g, 6.75 mmol, 45%), mp 58.0–58.5 °C. The mother liquor was concentrated to 20 mL and again cooled to −80 °C in a 25-mL cylindrical vessel with a 24/40 male joint topped with a medium-porosity sintered-glass funnel with a 24/40 female joint. Crystals obtained from the second (150 mg), third (290 mg), and fourth (280 mg) crop were pure endo epimer **26n**. The fifth crop was crystalline (620 mg) but was a 77:23 mixture of the *endo*-**26n** and *exo*-**26x** epimers. The total of pure endo epimer **26n** isolated was 2.1 g, (10.3 mmol, 68.5%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (3 H, s), 0.96 (3 H, d, J = 6.3 Hz), 1.2–2.2 (12 H), 2.26 (1 H, d, J = 3 Hz), 2.40 (1 H, dd, J = 3.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.62, 16.05, 28.16, 32.81, 34.91, 36.45, 38.83, 39.91, 42.12, 42.69, 43.01, 44.91, 58.82, 215.65. Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.37; H, 9.84.

Endocyclic Alkene 29. Methylidene ketone **25** (3.95 g) was placed in a pressure bottle with a magnetic stirring bar. Then, SO_2 (12 mL) was condensed at −78 °C. The bottle was closed, and the contents were allowed to warm to room temperature and then stirred 2 h. After being cooled to −78 °C, the bottle was opened and the SO_2 was evaporated under a stream of dry nitrogen. The white crystalline residue was dissolved in ether (150 mL), transferred to a separatory funnel, washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), dried over anhydrous magnesium sulfate, and filtered, and solvent was removed in vacuo to give **29** (3.81 g, 96.3%): mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 5.31 (1 H, s), 2.56 (1 H, bs), 2.50–2.35 (5 H), 2.14 (H, s), 2.03 (1 H, dd, J = 18.2, 5.1 Hz), 1.85–1.50 (3 H), 1.67 (3 H, s), 0.96 (3 H, s).

Homochiral Sulfoximine Adducts with Racemic Ketone 29. To a solution of (+)-*N*-methylphenylsulfoximine (+)-(*S*)-**33** (3.55 g, 21.0 mmol) in anhydrous THF (30 mL) was added *n*-butyllithium (14 mL, 1.5 M in hexane) dropwise with magnetic stirring at 0 °C. After the addition was complete, the ice bath was removed and the reaction mixture was stirred for 20 min at room temperature. The clear yellow solution was then cooled to −78 °C, and ketone (±)-**29** (4.04 g, 20.0 mmol) in THF was added dropwise. The reaction mixture was then stirred 1 h at −78 °C, then allowed to warm to −15 °C, and transferred to a separatory funnel containing saturated ammonium chloride solution (50 mL). The product was extracted with ether (3 × 100 mL). The combined ether extracts were washed with water (50 mL) and dried over $MgSO_4$. Rotary evaporation of the solvent gave a pale yellow oil (7.46 g). TLC of the product in ethyl acetate–methylene chloride (1:19) showed two spots with R_f 0.26 and 0.18. The mixture was flash chromatographed over silica gel with ethyl acetate–methylene chloride (1:24) as eluting solvent. Chromatographic separation afforded a less polar diastereomer (+)-**32** (R_f 0.26; 3.57 g, 48%) that was recrystallized from ether–hexane (1:1):

mp 132–33 °C; $[\alpha]^{22}_D$ + 35.8° (*c* 2.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.90–7.82 (2 H), 7.68–7.53 (3 H), 5.29 (1 H, s), 3.46 (1 H, d, *J* = 13.8 Hz), 3.24 (1 H, d, *J* = 13.8 Hz), 2.67–2.18 (6 H), 2.59 (3 H, s), 2.04 (1 H, d, *J* = 4.8 Hz), 1.71–1.57 (6 H), 1.45 (3 H, s), 1.44–1.30 (2 H). Anal. Calcd for $C_{22}H_{29}NO_2S$: C, 71.12; H, 7.87. Found: C, 71.07; H, 8.01.

A more polar diastereomer (–)-**31** (R_f 0.18; 3.2 g, 43%) was obtained as a viscous oil: $[\alpha]^{22}_D$ –8.2° (*c* 1.85, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.90–7.82 (2 H), 7.43–7.35 (3 H), 5.29 (1 H, s), 3.35 (1 H, s, *J* = 13.8 Hz), 3.25 (1 H, d, *J* = 13.8 Hz), 2.7–2.3 (6 H), 2.58 (3 H, s), 1.95 (1 H, d, *J* = 4.6 Hz), 1.64 (3, s), 1.6–1.1 (5 H), 1.48 (3 H, s).

Ketone (+)-29. The less polar diastereomer (+)-**32** (10.3 g, 27.7 mmol) was dissolved in toluene (400 mL) and boiled 5 h under reflux after which no starting material could be detected by TLC (1:4 ethyl acetate–hexanes). The solvent was removed in vacuo, and the residue was flash chromatographed over silica gel with ethyl acetate–hexanes (1:9) as eluting solvent. The ketone (+)-**29** (5.5 g, 96.3%) was obtained as a white crystalline solid: mp 67–68 °C; $[\alpha]^{22}_D$ + 193.2 ($CHCl_3$). The column was then washed with ethyl acetate to recover the homochiral sulfoximine (+)-(*S*)-**33** (4.5 g, 95.9%).

Tetracyclic *endo*-Methyl Ketone (+)-26n. PtO_2 (200 mg) was added to a solution of ketone (+)-**29** (2.3 g, 11.4 mmol) in ethyl acetate (40 mL), and the mixture was stirred under an atmosphere of hydrogen. The uptake of hydrogen was completed in 1 h. The catalyst was then removed by filtration, and the filtrate was concentrated in vacuo to furnish (+)-**26n** (2.2 g, 94.7%): mp 31–32 °C; $[\alpha]^{22}_D$ + 244.8° ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.46–1.23 (14 H), 0.95 (3 H, d, *J* = 6.4 Hz), 0.84 (3 H, s).

Oxidation of the Tetracyclic *endo*-Methyl Ketone 26n. To a solution of the *endo*-methyl ketone **26n** (40 mg, 0.195 mmol) in acetic acid (180 μL, 4.5 μL/mg ketone) and sulfuric acid (70 μL, 1.75 μL/mg ketone) was added at 0–5 °C a 40% solution of peracetic acid (80 μL)[14] via an automatic pipette. The reaction was monitored by TLC with 30% ethyl acetate in hexanes as the developing solvent. After 2 h at 5 °C, the reaction mixture was treated with sodium metabisulfite followed by dilution with ether (1.5 mL). The ether solution was transferred into a separatory funnel containing sodium carbonate (350 mg) in water (4 mL). The mixture was shaken vigorously until gas evolution ceased. The aqueous layer was extracted with ether (4 × 10 mL), the combined organic extracts were washed once with saturated sodium bicarbonate (2 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to give the crude product (35 mg). This was dissolved in 20% ethyl acetate in hexanes (150 μL) and purified by HPLC on a Whatmann analytical silica gel column, 4.5-mm i.d., 25-cm length, with 20% ethyl acetate in hexanes as eluting solvent. Each injection was 20 μL in volume. Three peaks appeared; the first peak had 2.7 mg of the starting ketone **26n**, the second peak had 12.6 mg of the desired lactone **14** (mp 96.5–98 °C), and the third peak contained 9.5 mg of the lactone **34**. The retention times of the three peaks were 3.5, 8, and 9.5 min, respectively.

Lactone **14**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (3 H, d, *J* = 6 Hz), 1.07 (3 H, s), 1.1–2.2 (10 H), 2.3–2.6 (2 H), 2.80 (1 H, dd, *J* = 4.13 Hz), 4.21 (1 H, d, *J* = 3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.56 (2 carbons), 27.78, 32.58, 34.59, 36.12, 37.80, 39.62, 41.22, 43.76, 46.53, 47.36, 86.06, 170.71. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.14; H, 9.14.

Lactone **34**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (3 H, d, *J* = 6.9 Hz), 1.58 (3 H, s), 1.3–3.0 (14 H); mass spectrum *m/z* (M^+) for $C_{14}H_{20}O_2$ calcd 220.1463, found 220.1556; (M + 1) for $C_{14}H_{21}O_2$ calcd 221.1541, found 221.1561.

Tetracyclic *endo*-Methyl δ-Lactone 14. A solution of ketone **26n** (148.7 mg, 0.728 mmol) in acetic acid (400 μL) was treated with a solution of peracetic acid[14] (40% in acetic acid, 325 μL) at 10 °C and then allowed to stir at room temperature in a flask protected from light for 3 days. The volatiles were then removed in vacuo, and the crude material was chromatographed on two 0.5-mm silica gel plates with 35% ethyl acetate in hexanes as developing solvent to afford lactone **14** (R_f = 0.24; 139 mg, 0.63 mmol, 87%), mp 96.5–98 °C. None of the isomeric lactone **34** was isolated.

Lactone (+)-14. A solution of the ketone (+)-**26n** (2.66 g) in peracetic acid[14] (16 mL, 34%) was stirred 48 h at room temperature. The volatiles were then removed in vacuo, and the residue was flash chromatographed over silica gel with 3% ethyl acetate in methylene chloride as eluting solvent. Desired lactone (+)-**14** (2.37 g, 82.6%) was obtained: $[\alpha]^{22}_D$ + 42.5° (*c* 2.2, $CHCl_3$); mp 97–98 °C; ^{1}H NMR ($CDCl_3$) δ 4.17 (1 H, bs), 2.74 (1 H, dd, *J* = 19, 5.4 Hz), 2.48–2.34 (2 H), 2.07–1.26 (10 H), 1.03 (3 H, s), 0.93 (3 H, d, *J* = 6 Hz).

Hydroxy Ester (+)-43. The lactone (+)-**26n** (4.6 g, 20.9 mmol) was dissolved in methanol (170 mL) and treated with 40% KOH in water (75 mL). The mixture was boiled 6 h under reflux, cooled to room temperature, and diluted with water (100 mL), and half of the methanol was removed by distillation. The reaction mixture was then washed with $CHCl_3$ (2 × 50 mL). The chloroform washings were back-extracted with water (20 mL). The combined aqueous solutions were cooled to 0 °C and then acidified with concentrated hydrochloric acid. The resulting mixture was extracted with ether (3 × 50 mL) and dried over $MgSO_4$. Rotary evaporation of the solvent gave a residue that was treated with excess diazomethane in ether. Evaporation of the excess diazomethane under a stream of dry nitrogen and concentration in vacuo afforded a crude product that was purified by column chromatography over silica gel with 20% ethyl acetate in hexanes as eluting solvent. Hydroxy ester (+)-**43** (4.9 g, 93%) was obtained: $[\alpha]^{22}_D$ + 4.67° (*c*, 2.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.87 (1 H, dd, *J* = 5.2, 2.8 Hz), 3.61 (3 H, s), 2.45–2.30 (3 H), 2.18–1.18 (11 H), 0.92 (3 H, s), 0.89 (3 H, d, *J* = 6.4 Hz). A sample of the racemic hydroxy ester **43** was prepared similarly: mass spectrum *m/z* (M^+) for $C_{15}H_{24}O_3$ calcd 252.1725, found 252.1771.

MEM Ether (–)-44. The hydroxy ester (+)-**43** (4.9 g, 19.4 mmol), (MEM)Cl (6.05 g, 48.7 mmol), and diisopropylethylamine (8.48 mL, 48.7 mmol) in methylene chloride (50 mL) were mixed at room temperature. After being stirred 3 days, TLC analysis showed completion of the reaction. Solvents were removed in vacuo, and the residue was flash chromatographed with 15% ethyl acetate in hexane as eluting solvent. MEM ether (–)-**44** (5.88 g, 89%) was obtained: $[\alpha]^{22}_D$ –21° (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.71 (1 H, d, *J* = 7 Hz), 4.61 (1 H, d, *J* = 7 Hz), 3.81 (1 H, t, *J* = 4.4 Hz), 3.67–3.61 (5 H), 3.55–3.50 (2 H), 3.37 (3 H, s), 2.39–1.18 (13 H), 0.89 (3 H, d, *J* = 6.2 Hz); 0.88 (s, 3 H). A sample of racemic MEM ether **44** was prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.59, 14.01, 27.48, 34.44, 36.76, 37.04, 39.82, 41.92, 44.22, 46.32, 47.87, 51.29, 59.03, 66.75, 71.81, 76.38, 87.06, 94.67, 173.75; mass spectrum *m/z* (M^+) for $C_{19}H_{32}O_4$ calcd 340.2249, found 340.2253.

Malonic Ester (–)-45. To a solution of α,α′-dipyridyl (100 mg) in tetrahydrofuran (150 mL) was added diisopropylamine (4.9 mL, 34.5 mmol). After being cooled to –78 °C, *n*-butyllithium (14.2 mL, 2.5 M in hexane) was added and the resulting dark red solution was stirred 10 min. The MEM ether (–)-**44** (5.88 g, 17.3 mmol) in tetrahydrofuran (20 mL) was then added, and the resulting mixture was stirred 15 min. A stream of bone-dry carbon dioxide gas was bubbled through the reaction mixture for 2 min until the red color of the solution faded. The reaction mixture was allowed to warm slowly to room temperature over 1 h, during which time dissolved carbon dioxide gas escaped. The mixture was then acidified with 20% hydrochloric acid (caution: effervescence) and extracted with chloroform (3 × 100 mL). The combined chloroform extracts were washed with water and then with saturated aqueous $NaHCO_3$ solution. The bicarbonate extracts were cooled to 0 °C, acidified with concentrated hydrochloric acid, and then extracted with ether (4 × 60 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to afford the crude half acid. The racemic crude half acid, prepared similarly, was characterized by ^{1}H NMR ((60 MHz, $CDCl_3$) δ 0.8–1.0 (6 H, bs), 1.1–2.5 (13 H), 3.31 (3 H, s), 3.71 (3 H, s), 3.4–3.9 (4 H), 4.60 (2 H, s), 6.7–7.0 (1 H, bs)).

Treatment of the crude half acid from (–)-**44** with excess diazomethane in ether gave malonic ester (–)-**45** (5.8 g, 84.3%): $[\alpha]^{22}_D$ –31° (*c* 2.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.68 (1 H, d, *J* = 7 Hz), 4.59 (1 H, d, *J* = 7 Hz), 3.79 (1 H, t, *J* = 3 Hz), 3.68–3.49 (11 H), 3.36 (3 H, s), 2.48–1.22 (11 H), 0.89 (3 H, s), 0.87 (3 H, d, *J* = 7.4 Hz).

Data for the racemic malonic ester **45**, prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.48, 14.11, 27.52, 34.43, 34.89, 36.74, 43.93, 45.42, 45.92, 45.96, 46.27, 52.29, 52.33, 55.85, 59.04, 55.74, 71.76, 85.04, 94.19, 169.37, 169.47; mass spectrum *m/z* (M^+) for $C_{21}H_{34}O_7$ calcd 398.2304, found 398.2263.

***cis*-5-Hydroxy Malonic Ester.** During the preparation of **45** mentioned previously, some loss of the MEM protecting group occurred. Chromatography on silica gel yielded *cis*-5-(MEM)O malonic ester **45** (R_f 0.32; 551 mg, 1.38 mmol, 79.9%), the corresponding *cis*-5-hydroxy malonic ester **63**, mp 103–105 °C (R_f 0.12; 77 mg, 0.25 mmol), and unreacted starting material **44** (R_f 0.45, 119 mg, 0.35 mmol). The material balance was thus 94%. *cis*-5-Hydroxy malonic ester **63**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (3 H, d, *J* = 6.3 Hz), 0.90 (3 H, s), 1.1–1.8 (11 H), 1.94 (1 H, m), 2.35 (1 H, m), 3.65 (3 H, s), 3.66 (1 H, d, *J* = 11 Hz), 3.67 (3 H, s); mass spectrum *m/z* (M^+) for $C_{16}H_{26}O_5$ calcd 310.1780, found 310.1817.

3-(Dicarbomethoxymethyl)cyclopentan-1-one (63).[20] Sodium (0.24 g, 10.2 mmol) was dissolved in dry methanol (30 mL), and dimethyl malonate (2.61 g, 2.26 mL, 19.8 mmol) was added at 0 °C. After 15 min, cyclopent-2-en-1-one (1.71 g, 1.74 mL, 21.2 mmol) was added dropwise during 15 min at –10 °C. The resulting clear yellow solution was cooled to –78 °C and then acidified with a stream of anhydrous hydrogen chloride gas until the yellow color was bleached to give a colorless solution. The solvent was removed in vacuo and the residue passed through a plug of silica gel (finer than 200 mesh) with 50% ethyl acetate in

hexanes (70 mL) as the eluting solvent. The crude product was chromatographed on a Prep 500-A (Water Associates) silica gel column. The peak with a retention time of 6 min afforded **63** (3.42 g, 81% yield). In a large-scale synthesis of **63**, the crude reaction mixture was distilled bp 125–126 °C (1 mmHg), to give **63** (11.8 g, 92% yield). Earlier fractions, bp 70–90 °C (1 mmHg), contained 2-cyclopenten-1-one and dimethyl malonate. The R_f values of **63** in various solvent systems are as follows: 30% ethyl acetate in hexanes, 0.13; 20% ethyl acetate in chloroform, 0.58; 10% ethyl acetate in methylene chloride, 0.30; 20% ethyl acetate in methylene chloride, 0.46. Data: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.3–3.2 (7 H), 3.33–3.46 (1 H, d, J = 9 Hz), 3.75 (3 H, s), 3.77 (3 H, s).

3-(Dicarbomethoxymethyl)cyclopentan-1-ol (39). A solution of 3-(dicarbomethoxymethyl)cyclopentan-1-one (**63**) (6.0 g, 0.028 mol) in anhydrous methanol (100 mL) was cooled to 0 °C (ice–salt bath) and treated with sodium borohydride (1.06 g, 0.028 mmol) added portionwise over 10 min. The reaction mixture was warmed to room temperature, stirred 1 h, and monitored by TLC with 50% ethyl acetate in hexane as developing solvent. Then, 1.0 N hydrochloric acid solution (43 mL) was added very slowly until the pH of the solution reached 3. Methanol was removed on the rotary evaporator and the aqueous mixture extracted with methylene chloride (6 × 20 mL). The combined extracts were dried over anhydrous magnesium sulfate, and concentrated in vacuo to give an oil (5.89 g). Flash chromatography on a silica gel column (230–400 mesh, 100 × 150 mm) with 55% ethyl acetate in hexane (4.5 L) as eluting solvent gave the pure alcohol **39** (4.90 g, 22.7 mmol, 81% yield): ^{1}H NMR (60 MHz, CCl_4) δ 0.9–2.8 (7 H), 2.30 (1 H, s), 3.03–3.20 (0.5 H, d, J = 9 Hz), 3.23–3.38 (0.5 H, d, J = 9 Hz), 3.70 (6 H, s), 4.06–4.40 (1 H, bs); mass spectrum m/z (M^+) for $C_{10}H_{16}O_5$ calcd 216.0998, found 216.1097; (M + 1) for $C_{10}H_{17}O_5$ calcd 217.1076, found 217.1713. It should be noted that in $CDCl_3$ the positions of the malonyl proton and the splitting pattern changes: at 60 MHz δ 3.20–3.52 (1 H, two doublets **39t** (3.15–3.35 (0.5 H, d, J = 9 Hz)) and **39c** (3.37–3.42 (0.5 H, d, J = 9 Hz))). Thus, in subsequent experiments the assignment of abundance of the cis epimer **39c** with respect to the trans epimer **39t** at 60 MHz was done by integrating over the two doublets after expanding the region δ 3.05–3.40 and using carbon tetrachloride as the solvent.

3-(Dicarbomethoxymethyl)-1-[(2-methoxyethoxy)methoxy]cyclopentane (40). A solution of the alcohol **39** (216 mg, 1.0 mmol) in methylene chloride (2 mL) was treated with (2-methoxyethoxy)methyl chloride (187 mg, 171 μL, 1.5 mmol) and diisopropylethylamine (194 mg, 261 μL, 1.5 mmol) at 25 °C for 4 h. Solvent was removed on the rotory evaporator and the residue suspended in 20% ethyl acetate in hexane (10 mL) and passed through a 1 × 2 cm column of 230–400-mesh silica gel. The column was rinsed with 20% ethyl acetate in hexane (80 mL). Rotory evaporation of the solvent afforded the MEM ether **40** (304 mg, quantitative yield): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.70–2.30 (7 H), 3.16–3.83 (4 H), 3.35 (3 H, s), 3.72 (6 H, s), 3.92–4.40 (1 H, m), 4.67 (2 H, s); mass spectrum m/z (M + 1) for $C_{14}H_{25}O_7$ calcd 305.1600, found 305.1599.

For large-scale preparation of 3-(dicarbomethoxymethyl)-1-[(2-methoxyethoxy)methoxy]cyclopentane (**40**), the following procedure was used. To a mixture of the alcohol **39** (2.15 g, 10 mmol) and (2-methoxyethoxy)methyl chloride (2.62 g, 2.40 mL, 21 mmol, 2.1 equiv) in methylene chloride (22 mL, 10 mL/g alcohol) was added diisopropylethylamine (2.71 g, 3.66 mL, 21 mmol, 2.1 equiv) at 0 °C. The reaction vessel was allowed to warm to room temperature and monitored for disappearance of starting material **39** by TLC in 30% ethyl acetate in hexanes (R_f values for **39** and **40** are 0.05 and 0.18, respectively). After 3 days, the reaction was essentially complete. The contents of the flask were transferred to a separatory funnel containing some ice, water, and methylene chloride. The aqueous layer was thoroughly extracted with methylene chloride, and the organic extracts were combined, washed once with water and then with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude reaction product was purified by flash column chromatography with a 40 × 178 mm column of silica gel (230–400 mesh, Merck) with 30% ethyl acetate in hexanes as eluting solvent to afford MEM ether **40** (2.72 g, 8.92 mmol, 89.2% yield).

Dimethyl [3-[(2-Methoxyethoxy)methoxy]cyclopentyl](methylseleno)-propanedioate (41). To a suspension of sodium hydride (from 330 mg of 57% in oil, 7.3 mmol that was washed with dry pentane) in tetrahydrofuran (13 mL) was added hexamethylphosphoric triamide HMPA (3.5 mL, 2.0 mmol). The solution was cooled to 0 °C, and malonic ester **40** (1.44 g, 6.65 mmol) in tetrahydrofuran (3.3 mL) was added. The ice bath was then removed, the mixture allowed to warm to room temperature, and stirred 1 h. Selenium metal (565 mg, 7.1 mmol) was then added to the mixture from a bent addition tube, and the dark red to brown solution was then stirred 24 h at 20 °C. Then, the resulting mixture was cooled to 0 °C, treated with methyl iodide (0.50 mL, 8.0 mmol), and stirred for 2 min. The reaction mixture was then quenched with saturated aqueous ammonium chloride (3.3 mL) and diluted with 20% ethyl acetate in hexanes (67 mL). After equilibration of the phases, the organic extract was separated, washed with water (2 × 67 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo to give the crude selenide **41** (1.94 g, 96%). This was chromatographed on the prep 500-A (Waters Associates) on a silica gel column with 30% ethyl acetate in hexanes as eluting solvent with an elution rate of 300 mL/min. A peak with a retention time of 8 min afforded pure methyl selenide **41** (1.82 g, 90% yield): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 0.8–3.1 (7 H), 2.07 and 2.10 (3 H, 2 singlets), 3.35 (3 H, s), 3.4–3.8 (4 H), 3.73 (6 H, s), 4.02–4.42 (1 H, m), 4.70 (2 H, s); mass spectrum m/z (M^+) for $C_{15}H_{26}O_7Se$ calcd 397.1278, found 397.1448.

Dimethyl [3-[(2-Methoxyethoxy)methoxy]cyclopentylidene]malonate (42a). The general procedure of Liotta, Zima, and Sundane[21] was used. A solution of the methyl selenide **41** (6.67 g, 16.8 mmol) in methylene chloride (168 mL) was cooled to 0 °C and treated with aqueous 30% hydrogen peroxide solution (1.21 g, 35.6 mmol, 4.04 mL). The solution was stirred 15 min at 10 °C. Water was then added and the organic layer separated, dried, and concentrated in vacuo to give an oil (5.1 g). Distillation gave [3-[(2-methoxyethoxy)methoxy]cyclopentylidene]-malonic ester **42a** (3.57 g, 11.82 mmol, 70.3% yield): bp 144–146 °C (0.05 mmHg); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.60–2.40 (2 H), 2.65–3.00 (4 H), 3.38 (3 H, s), 4.05–4.50 (1 H, m), 4.68 (2 H, s); mass spectrum m/z (M^+) for $C_{14}H_{22}O_7$ calcd 302.1365, found 302.1382; (M + 1) for $C_{14}H_{23}O_7$ calcd 303.1444, found 303.2828.

Tricyclic *cis*-5-(MEM)O α-(Phenylseleno)malonic Ester 46p. A mixture of the tricyclic *cis*-5-(MEM)O malonic ester **45** (200 mg, 0.501 mmol), sodium hydride (60% in oil, 34.1 mg, 0.852 mmol, 1.7 equiv) and HMPA (27 mg, 26 μL, 0.150 mmol, 0.03 equiv) in tetrahydrofuran (3.5 mL) was boiled 10 h under reflux, cooled to room temperature, and then treated with a solution of phenylselenyl bromide (343.6 mg, 1.35 mmol, 2.7 equiv) in tetrahydrofuran (1.35 mL) in the dark. The reaction mixture was monitored by TLC with 10% ethyl acetate–10% hexane–80% methylene chloride as developing solvent. R_f values of **45** and **46** are 0.29 and 0.39 (UV active), respectively. After 4 h, TLC analysis indicated no starting material remained unreacted. The reaction mixture was cooled to 0 °C, quenched with saturated sodium bicarbonate solution (1.0 mL), diluted with 20% ethyl acetate in hexanes (2 mL), and extracted (5 × 2 mL) with 1:5 ethyl acetate in hexanes. The organic extracts were combined, washed with brine (2 × 2 mL), dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude oil (429 mg) was then chromatographed to separate excess diphenyldiselenide, the starting *cis*-5-(MEM)O malonic ester **45**, and the desired product **46**. Preparative thin-layer chromatography on a silica gel plate (2 mm, Merck) with two developments in 10% ethyl acetate–10% benzene–80% methylene chloride yielded the desired α-(phenylseleno)-malonic ester **46** from a band between R_f 0.43–0.58 (200 mg, 0.361 mmol, 73% yield) and the starting *cis*-5-(MEM)O malonic ester **45** from a band between R_f 0.23–0.32 (12 mg, 0.03 mmol). Alternatively, the crude reaction mixture was flash column chromatographed with the aforementioned solvent system. Phenyl selenide **46**: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.8 (3 H, s), 0.98 (3 H, d, J = 6 Hz), 1.2–.28 (11 H), 3.38 (3 H, s), 3.58 (3 H, s), 3.73 (3 H, s), 3.4–3.8 (4 H), 4.13 (1 H, dd, J = 4.6 Hz), 4.68 (2 H, s), 7.2–7.8 (5 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.04, 14.60, 26.58, 34.58, 35.77, 37.65, 44.18, 45.78, 45.89, 47.41, 49.10, 52.58, 52.52, 59.03, 63.17, 66.78, 71.78, 86.29, 94.75, 127.19, 128.79 (2 C), 129.73, 138.02 (2 C), 168.74 (2 C); mass spectrum m/z (M^+) for $C_{27}H_{38}O_7Se$ calcd 553.2217, found 553.2287 and (M + 1) 554.2207.

[[(2-Methoxyethoxy)methoxy]alkylidene]malonic Ester (+)-47. *n*-Butyllithium (6.0 mL, 15.0 mmol, 2.5 M in hexane) was added dropwise to a stirring mixture of α,α'-dipyridyl (60 mg) and diisopropylamine (2.16 mL, 15 mmol) in tetrahydrofuran (25 mL) at −78 °C under an atmosphere of dry argon. The resulting dark red reaction mixture was stirred 30 min at −78 °C. The malonic ester (−)-**45** (3.0 g, 7.53 mmol) in tetrahydrofuran (5 mL) was then added. After being stirred for an additional 30 min, phenylselenyl bromide (3.6 g, 15.0 mmol) in THF (5 mL) was added. The mixture was then allowed to warm to room temperature over a period of 1 h and then poured into ice-cold hydrochloric acid (10%) and extracted with ether (3 × 50 mL), and the combined organic extracts were washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, and concentrated in vacuo. The residue obtained was dissolved in CH_2Cl_2 (30 mL). Hydrogen peroxide (30 mL, 30%) was added at 0 °C. The solution was stirred 1 h at 0 °C and then 30 min at room temperature. Water was added, and the resulting mixture was extracted with ethyl acetate (3 × 40 mL). The organic layer was washed with saturated $NaHCO_3$ and then brine and dried over $MgSO_4$. After the solvent was removed by rotary evaporation, the residue was flash chromatographed over silica gel, eluting with ethyl acetate–hexanes (1:4) to afford the [[(2-methoxyethoxy)methoxy]alkylidene]malonic ester (+)-**47** (2.51 g, 84%): $[\alpha]^{22}_D$ +58.5° (*c* 2.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.70 (1 H, d, J = 7 Hz), 4.62 (1 H, d, J = 7 Hz), 3.87 (1 H, m), 3.83 (3 H,

s), 3.70 (3 H, s), 3.66–3.61 (2 H), 3.54–3.49 (2 H), 3.36 (3 H, s), 3.20–3.16 (2 H), 3.01 (1 H, d, J = 3.4 Hz), 2.36–2.17 (2 H), 1.98–1.26 (5 H), 0.96 (3 H, s), 0.95 (3 H, d, J = 6.2 Hz).

Data for racemic **47**, prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.27, 14.42, 27.77, 34.84, 37.21, 38.52, 43.77, 46.36, 46.56, 47.37, 51.95, 52.03, 59.04, 66.92, 71.72, 84.78, 94.42, 104.19, 119.03, 165.41, 169.35; mass spectrum m/z (M^+) for $C_{21}H_{32}O_7$ calcd 396.2147, found 396.2186.

(Hydroxyalkylidene)malonic Ester (+)-48. The [5-[(2-methoxyethoxy)methoxy]alkylidene]malonic ester (+)-**47** (5.03 g, 12.7 mmol) was dissolved in methylene chloride (150 mL). The solution was cooled to 0–5 °C, and titanium tetrachloride (14.0 mL, 127 mmol) was added dropwise over 5 min. After 35 min at 0 °C, the excess titanium tetrachloride was destroyed by dropwise addition of concentrated ammonium hydroxide solution (28 mL) and water (50 mL), and the mixture was stirred vigorously at −5 °C until a white precipitate formed. Solvent was removed, the product was extracted with ethyl acetate (4 × 50 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by column chromatography over silica gel with ethyl acetate–hexanes (1:4) to give 5-hydroxyalkylidenemalonic ester (+)-**48** (3.5 g, 89.5%): $[\alpha]^{22}_D$ +133.07° (c 2.33, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.89 (1 H, d, J = 4.2 Hz), 3.74 (3 H, s), 3.71 (3 H, s), 3.32–3.16 (2 H), 3.06 (1 H, m), 2.32–2.13 (2 H), 1.97–1.33 (6 H), 0.97 (3 H, s), 0.96 (3 H, d, J = 7 Hz).

Data for racemic **48**, prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.86, 14.40, 27.94, 34.78, 37.14, 41.21, 43.11, 45.93, 46.99, 47.23, 52.08, 52.18, 80.05, 104.18, 119.43, 165.78, 169.38; mass spectrum m/z (M^+) for $C_{17}H_{24}O_5$ calcd 308.1623, found 308.1638.

Dimethyl (3-Hydroxycyclopentylidene)malonate (42b). The [3-[(2-methoxyethoxy)methoxy]cyclopentylidene]malonic ester **42a** (100 mg, 0.33 mmol) was dissolved in methylene chloride (1.7 mL). The solution was cooled to 0–5 °C, and titanium tetrachloride[22] (886.5 mg, 514 μL, 3.3 mmol, 10 equiv) was added dropwise over 5 min. The reaction mixture was monitored by TLC with 50% ethyl acetate in hexanes as developing solvent for disappearance of starting material **42a** (R_f 0.15). After 35 min at 0 °C, the excess titanium tetrachloride was destroyed by dropwise addition of concentrated ammonium hydroxide solution (1 mL) and water (2 mL) and the mixture was stirred vigorously at −5 °C until a white precipitate formed. Water (10 mL) was added to the mixture and the product extracted with ethyl acetate (8 × 10 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. Preparative thin-layer chromatography on an 0.5-mm silica gel plate (Merck) with two developments in 50% ethyl acetate in hexanes gave a strong UV-active band R_f 0.21–0.28. The band afforded the alcohol **42b** (51.7 mg, 0.243 mmol, 75% yield): ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.68–2.10 (2 H), 2.27 (1 H, s), 2.70–3.12 (4 H), 3.80 (6 H, s), 4.33–4.67 (1 H, quint, J = 5.9 Hz).

Dimethyl (3-Acetoxycyclopentylidene)malonate (42c). A mixture of the alcohol **42b** (34 mg, 0.164 mmol), acetic anhydride (1 mL), pyridine (1 mL), and methylene chloride (2 mL) was stirred 24 h at room temperature. The solvents and reagents were then removed in vacuo and the residue chromatographed on an 0.25-mm silica gel plate (Merck) that was developed twice with 35% ethyl acetate in hexanes (R_f **42b** 0.20, R_f **42c** 0.54). A band between R_f 0.36–0.42 provided the acetoxy alkylidenemalonate **42c** (37.1 mg, 0.146 mmol, 88% yield).

Dimethyl [3-[(*tert*-Butyldimethylsilyl)oxy]cyclopentylidene]malonate (42d). The general procedure for *tert*-butyldimethylsilylation of alcohols established by Corey et al.[28] was used exactly as stated: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.04 (6 H, s), 0.85 (9 H, s), 1.72–1.78 (2 H), 2.59–2.82 (4 H), 3.76 (6 H, s), 4.33–4.37 (1 H).

General Procedure for Conjugate Reduction of 3-Substituted Cyclopentylidenemalonic Esters.[29] To a suspension of sodium borohydride (3.0 mg, 0.076 mol, 0.52 equiv) in ethanol (200 μL) at 0 °C was added a solution of 3-substituted cyclopentylidenemalonic ester (0.145 mmol) in ethanol (100 μL). The reaction mixture was monitored by TLC, with 30% or 50% ethyl acetate in hexanes as developing solvent, for loss of UV activity. Normally, the reaction time for the reductions was 1 h. The excess hydride was then destroyed with 3.7% aqueous hydrochloric acid solution (500 μL). The resulting mixture was diluted with water (2 mL) and extracted with ethyl acetate (8 × 2 mL). The ethyl acetate extracts were washed with brine solution (1 × 2 mL), dried over anhydrous sodium or magnesium sulfate, concentrated in vacuo, and purified by preparative thin-layer chromatography with ethyl acetate in hexanes as developing solvent. In the case of dimethyl [3-[(2-methoxyethoxy)-methoxy]cyclopentylidene]malonate (**42a**), analysis of the reduction product isomer ratio was achieved on the derived alcohols **39** after removal of the MEM protecting group as described before in the synthesis of **42b**. Characterization of the product *cis–trans* epimeric mixtures **39** and the corresponding acetates and TBDMS ethers follow.

Dimethyl (3-Hydroxycyclopentyl)malonate (39c and 39t). The compounds were isolated from the reduction of **42a** followed by removal of the MEM group: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–2.36 (7 H), 2.46 (0.8 H, m), 2.72 (0.2 H, m), 3.08 (0.2 H, d, J = 9 H), 3.29 (0.8 H, d, J = 9 Hz), 3.68 (6 H, s), 4.22 (1 H, m); mass spectrum m/z (M^+) for $C_{10}H_{16}O_5$ calcd 216.0997, found 216.1032; (M + 1) for $C_{10}H_{17}O_5$ calcd 217.1076, found 217.1211.

Dimethyl (3-*cis*- and 3-*trans*-acetoxycyclopentyl)malonates: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31–1.97 (5 H), 2.02 (3 H, s), 2.29 (1 H, m), 2.57 (0.8 H, m), 2.77 (0.2 H, m), 3.24 (0.2 H, d, J = 10 Hz), 3.33 (0.8 H, d, J = 10 Hz), 3.73 (3 H, s), 3.74 (3 H, s); mass spectrum m/z (M^+) for $C_{12}H_{18}O_6$ calcd 258.1103, found 258.1144; (M + 1) for $C_{12}H_{19}O_6$ calcd 259.1182, found 259.1200.

Dimethyl [3-*cis*- and 3-*trans*-[(*tert*-butyldimethylsilyl)oxy]cyclopentyl]malonate: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.26 (2 H, s), 0.87 (9 H, s), 1.17–2.13 (6 H), 2.52 (0.86 H, m), 2.77 (0.14 H, m), 3.22 (0.14 H, d, J = 11 Hz), 3.40 (0.86 H, d, J = Hz), 3.72 (6 H, s), 4.22 (1 H, m); mass spectrum m/z (M^+) for $C_{16}H_{30}O_5Si$ calcd 330.1862, found 330.2119.

Hydride Reduction of Alcohol 42b. With use of ^{1}H NMR analysis to quantify the cis and trans product ratios of (3-hydroxycyclopentyl)-malonates **39c** and **39t**, several hydride reducing reagents were examined to find which hydride reagent would most strongly favor the trans product **39t**. The results are summarized in Table II.

Sodium Borohydride Reduction of the Tricyclic [5-[(Methoxyethoxy)methoxy]alkylidene]malonate Ester 47. To a suspension of sodium borohydride (6.92 mg, 0.182 mmol, 4.0 molar excess) in ethanol (100 μL) at 0 °C was added the tricyclic [[(methoxyethoxy)methoxy]alkylidene]malonic ester **47** (18 mg, 0.046 mmol) in ethanol (300 μL). The solution was stirred 2.5 h at 0–5 °C and monitored by TLC with 10% *tert*-butyl methyl ether–30% ethyl acetate–60% hexane as developing solvent. The R_f of **47** was 0.24, and the R_f of **45** and its trans epimer **64** was 0.28. The starting material **47** is UV active and stains blue with vanillin, whereas the products **45** and **64** are non-UV active and stain red with vanillin. The reaction was then allowed to warm to room temperature, stirred for a total of 6 h, and then cooled to 0 °C, and the excess hydride was destroyed by addition of 3.7% hydrochloric acid solution (100 μL) followed by addition of brine solution (100 μL), and ethyl acetate (400 μL). The crude mixture was extracted with ethyl acetate (8 × 400 μL) with use of a 1-mL syringe. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and then concentrated in vacuo. The crude reaction product weighed 18.6 mg and showed 5 spots by TLC, the major spot being a mixture of **45** and its trans epimer **64** at R_f 0.28. Isolation of the mixture of **45** plus **64** by preparative TLC (10 cm × 20 cm × 0.25 mm silica gel plate), with 10% *tert*-butyl methyl ether–30% ethyl acetate–60% hexanes as developing solvent, gave a mixture of **45** and **64** (7.4 mg, 0.018 mmol, 40.4%). This was dissolved in methylene chloride (225 μL), treated at 0 °C with titanium tetrachloride (33.4 mg, 19.3 μL, 0.18 mmol, 10.0 equiv) for 25 min at 0 °C. The excess titanium tetrachloride was destroyed by addition of concentrated ammonium hydroxide (0.5 mL) and water (0.5 mL), washing the combined extracts with brine solution, and concentration in vacuo after drying over anhydrous sodium sulfate yielded a mixture of the cis and trans tricyclic hydroxy malonic esters (cis) **65** and (trans) **49** (5 mg). The relative yields of these products were 71% for (cis) **65** and 29% for (trans) **49** as judged by the relative integrated areas of the multiplets centered at δ 2.35 (owing to 1 hydrogen in **65**) and 3.36 (owing to 1 hydrogen in **49**), respectively.

***trans*-5-Hydroxy Malonic Ester (−)-49.** To a suspension of sodium borohydride (1.9 g, 51.9 mmol) in tetrahydrofuran (30 mL) was added a solution of the hydroxyalkylidenemalonic ester (+)-**48** (1.6 g, 5.19 mmol) in THF (5 mL) at 0 °C. The reaction mixture was monitored for disappearance of the UV-active starting material by TLC with 50% ethyl acetate in hexanes. After the solution was stirred 1 h at 0 °C, the ice bath was removed and the mixture was warmed to room temperature and stirred for 30 min. It was then acidified with aqueous hydrochloric acid (3.7%) and extracted with ethyl acetate (4 × 30 mL). The combined organic extracts were washed once with brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude hydroxy malonic ester (−)-**49**. This was purified by flash chromatography, eluting with ethyl acetate–hexane (1:4) to furnish (−)-**49** (1.40 g, 87%): $[\alpha]^{22}_D$ −16.2° (c 6.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.72 (1 H, d, J = 4.8 Hz), 3.71 (3 H, s), 3.66 (3 H, s), 3.33 (1 H, d, J = 11.6 Hz), 2.99 (1 H, m), 2.08–1.32 (11 H), 0.94 (3 H, s), 0.75 (3 H, d, J = 6.4 Hz).

Data for racemic **49**, prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.85, 13.41, 27.79, 34.58, 36.30, 37.55, 37.66, 40.18, 43.13, 43.38, 46,78, 51.59, 52.28, 52.55, 80.30, 168.69, 169.57; mass spectrum m/z

(28) Corey, E. J.; Hidetsura, C.; Rucker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, 3455.

(29) Marshall, J. A.; Caroll, R. D. *J. Org. Chem.* **1965**, *30*, 2748.

(M^+) for $C_{17}H_{26}O_5$ calcd 310.1780, found, 310.1726.

Marshall Reduction of Cyclopentylmalonic Esters to β-Cyclopentylallyl Alcohols.[25] 2-Cyclopentyl-2-propen-1-ol (57b). Sodium hydride (57% in oil, 2.3 g) was washed with dry olefin-free pentane (2 × 60 mL) and suspended in dry dimethoxyethane (83 mL). Dimethyl cyclopentylmalonate (**59**) (11.9 g, 52 mmol) was added while the mixture was stirred and then the solution boiled 6 h under reflux. After the solution cooled, lithium aluminum hydride (5.2 g) was added cautiously with stirring. After the initial reaction had subsided, the mixture was boiled 3 h under reflux with mechanical stirring. Ethyl formate (19 mL) was added cautiously and the resulting mixture boiled and stirred 1 h under reflux. After the mixture cooled, water (5 mL) was added cautiously followed by 15% aqueous sodium hydroxide solution (5 mL), and the resulting mixture was stirred 1 h. Ether (50 mL) was added to the suspension and the mixture filtered. The filtered cake was thoroughly washed with ether (2 × 50 mL) and the solvent removed in vacuo. Distillation of the residual oil under reduced pressure afforded 3.7 g, bp 85–90 °C (12 mmHg) and 0.5 g, bp 90–100 °C (12 mmHg). These fractions contained impure **57b** (64% yield): ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.7–4.0 (10 H + 2.6 H), 4.09 (2 H, s), 4.90 (2 H, d, J = 6 Hz). The excess integral area in the δ 0.7–4.0 region presumably results from the presence of overreduction[25c] product 2-cyclopentylpropanol (**58b**). Thus, the allylic alcohol **57b** was at best 82% pure.

[3-[(2-Methoxyethoxy)methoxy]cyclopentyl]-2-propen-1-ol (57c). To a suspension of sodium hydride (11.2 mg, 0.28 mmol, 1.7 equiv) in dimethoxyethane (DME, 0.5 mL) was added [3-[(2-methoxyethoxy)-methoxy]cyclopentyl]malonic ester **40** (50 mg, 0.15 mmol) in dimethoxyethane (1.5 mL) and the resulting mixture boiled 2 h under reflux. The mixture was then cooled to room temperature, treated with 1 M lithium aluminum hydride solution in tetrahydrofuran (568 μL, 0.658 mmol, 26.3 mg $LiAlH_4$, 4 molar equiv), boiled 3 h under reflux, and then cooled to 0 °C and diluted with ether (5 mL). The excess hydride was then destroyed by addition of water (30 μL), 10% aqueous sodium hydroxide (30 μL), and water (60 μL). The precipitate was then separated from the ether solution by filtration through a small plug of glass wool in a Pasteur pipette. The precipitate and the reaction vial were washed several times with ethyl acetate. The combined ethyl acetate extracts and washings were concentrated and then purified by preparative thin-layer chromatography on a 0.5-mm silica gel plate that was developed three times with 50% ethyl acetate in hexanes. A band isolated between R_f 0.34 and 0.46 afforded the desired compound **57c** (27.5 mg, 0.120 mmol, 72% yield): ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.91 (0.6 H, d, J = 6 Hz), 1.0–3.0 (10.4 H), 3.36 (3 H, s), 3.3–3.8 (5.5 H), 4.0–4.4 (1 H), 4.12 (2 H, s), 4.72 (2.2 H, s), 4.96 (2 H). The ratio of the integral areas for the doublet at δ 0.91 (owing to a methyl group in the overreduction product **58c**) and the peak at δ 4.96 (owing to the vinyl hydrogens in **57c**) suggest that **57c** was at best 83% pure.

Acrylic Ester (+)-61. To a solution of the hydroxy malonic ester (−)-**49** (400 mg, 1.29 mmol) in methanol (2.0 mL) was added a solution of KOH (108 mg, 1.93 mmol) in water (415 mL), and the reaction mixture was stirred overnight at room temperature. The mixture was then diluted with water (3 mL) and extracted with ether to remove any neutral material. The aqueous layer was then acidified to pH 1 at −5 °C and immediately extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford a monomethyl malonic half ester: ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.85 (3 H, 6 Hz), 0.97 (3 H, s), 2.3 (13 H), 3.35 (d, 1 H, J = 11 Hz), 3.69 (3 H, s), 3.6–3.9 (1 H, m), 6.70 (2 H, s).

A solution was prepared by combining acetic acid (4 mL), sodium acetate (0.11 g), aqueous formalin (2.92 mL), and diethylamine (1.0 mL). The crude half ester was dissolved in 2.5 mL of this solution. The resulting mixture was stirred 5 min at room temperature and then heated at 100 °C for 15 min. The reaction mixture was then cooled to room temperature, diluted with water (15 mL), and extracted with ethyl acetate (5 × 10 mL). The combined extracts were washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to furnish acrylic ester (+)-**61** (307 mg, 90%): $[\alpha]^{22}_D$ + 38.2° (*c* 4.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.20 (1 H, s), 5.47 (1 H, s), 4.82 (1 H, m), 3.76 (1 H, d, J = 4.4 Hz), 3.68 (3 H, s), 3.39 (1 H, m), 2.28–1.20 (10 H), 0.97 (3 H, s), 0.68 (3 H, d, J = 5.8 Hz).

Data for the racemic acrylic ester prepared similarly: ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.02, 13.38, 27.96, 34.55, 36.14, 36.50, 37.76, 41.86, 42.96, 43.21, 46.78, 51.63, 80.19, 123.85, 140.20, 167.65; mass spectrum m/z (M^+) for $C_{16}H_{24}O_3$ calcd 264.1725, found 264.1735.

Allylic Alcohol (+)-62. To a well-stirred solution of the acrylic ester (+)-**61** (225 mg, 0.85 mmol) in toluene (25 mL) at −78 °C was added (DIB)AlH in toluene (3.4 mL, 1.5 M) dropwise, and then the reaction mixture was allowed to come to room temperature and kept overnight at that temperature. The following day, 1.7 mL of MeOH–H_2O (1:1) was added dropwise, and the resulting mixture was stirred 1 h. The slurry was then filtered through a bed of Celite that was washed with ethyl acetate. The combined filtrates were dried ($MgSO_4$) and concentrated to give crystalline allylic alcohol (+)-**62** (190 mg, 94.5%): $[\alpha]^{22}_D$ + 21.7° (*c* 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.08 (1 H, t, J = 1.4 Hz), 4.83 (1 H, t, J = 1.4 Hz), 3.94 (2 H, bs), 3.69 (1 H, d, J = 4 Hz), 2.97 (1 H, m), 2.27 (1 H, ddd, J = 14, 12, 4 Hz), 194–1.18 (9 H), 0.92 (3 H, s), 0.80 (3 H, d, J = 6.4 Hz).

Data for the racemic allylic alcohol **62**, prepared similarly, (100% yield): mp 96.5–98 °C; ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.99, 14.32, 27.88, 35.01, 36.38, 36.48, 37.53, 42.76, 42.80, 43.13, 46.94, 65.97, 80.90, 108.81, 148.12; mass spectrum m/z (M^+) for $C_{15}H_{24}O_2$ calcd 236.1776, found 236.1796.

5-Hydroxy Acrylic Aldehyde (+)-11h. Manganese dioxide (1.35 g, 15.9 mmol) was added to a solution of 5-hydroxy allylic alcohol (+)-**62** (188 mg, 0.795 mmol) in methylene chloride (20 mL). The reaction mixture was stirred 3 days at room temperature. Solids were removed by filtration through a bed of Celite that was then washed with ethyl acetate (5 × 10 mL). The combined washings and filtrate were concentrated in vacuo to afford the 5-hydroxy acrylic aldehyde (+)-**11h** (178 mg, 95.5%): $[\alpha]^{22}_D$ +50.1° (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.48 (1 H, s), 6.20 (1 H, s), 6.05 (1 H, s), 3.77 (1 H, d, J = 4 Hz), 3.40 (1 H, m), 2.33–1.21 (11 H), 0.98 (3 H, s), 0.65 (3 H, d, J = 5.6 Hz). The racemic acrylic aldehyde **11h**, prepared similarly, (100% yield) showed mp 90–91 °C.

5-Acetoxy Acrylic Aldehyde (+)-11a. The hydroxy aldehyde (+)-**11h** (15 mg, 0.064 mmol) was dissolved in methylene chloride (3 mL) and treated with pyridine (1.5 mL) and acetic anhydride (1.5 mL). The mixture was stirred 30 h at room temperature under nitrogen. Then, all volatiles were removed in vacuo. The resulting crude product was chromatographed on a 0.5-mm silica gel plate with 30% ethyl acetate in methylene chloride as developing solvent to give pure acetoxy aldehyde (+)-**11a** (13.3 mg, 75%): $[\alpha]^{22}_D$ +25.1° ($CDCl_3$) (reported[1] $[\alpha]^{22}_D$ +26.5° (*c* 0.54, $CHCl_3$)): ^{1}H NMR ($CDCl_3$) δ 9.49 (1, s H), 6.20 (1 H, s), 6.07 (1 H, s), 4.92 (1 H, d, J = 4.4 Hz), 3.32 (1 H, m), 2.37 (1 H, ddd, J = 13.13, 4.4 Hz), 2.26 (1 H, m), 2.12–1.21 (8 H), 2.01 (3 H, s), 0.89 (3 H, s), 0.65 (3 H, d, J = 6 Hz). A sample of racemic **11a**, prepared similarly in 90% yield, showed mp 68–71 °C: mass spectrum m/z (M^+) for $C_{17}H_{24}O_3$ calcd 276.1722, found 276.1711.

Acknowledgment. This research was assisted financially by Grants CHE8205122 from the National Science Foundation and CA31595 from the National Cancer Institute of the National Institutes of Health. We thank Dr. Bruce Levison for technical assistance.

Registry No. (+)-**11a**, 77136-72-2; (±)-**11a**, 89196-19-0; (+)-**11h**, 127182-29-0; (±)-**11h**, 89165-81-1; (+)-**14**, 132179-07-8; (±)-**14**, 132294-31-6; (±)-**15**, 132179-12-5; (±)-**16**, 89165-79-7; (±)-**16** (5-methyl regioisomer), 132179-14-7; (±)-*exo*-**23**, 89165-82-2; (±)-*endo*-**23**, 89177-42-4; (±)-**24n**, 89196-17-8; (±)-**24x**, 89196-18-9; (±)-**25**, 89165-83-3; (+)-**26n**, 89165-84-4; (±)-**26n**, 127182-27-8; (±)-**26x**, 132294-32-7; (+)-**29**, 127135-67-5; (±)-**29**, 127182-30-3; (−)-**31**, 132294-42-9; (+)-**32**, 127135-68-6; (+)-(*S*)-**33**, 33993-53-2; (±)-**34**, 132179-16-9; (±)-**39c**, 132179-20-5; (±)-**39t**, 132179-08-9; (±)-**39c** (R = Ac), 132179-15-8; (±)-**39t** (R = Ac), 132179-17-0; (±)-**39c** (R = TBDMS), 132179-18-1; (±)-**39t** (R = TBDMS), 132179-19-2; **40**, 132179-21-6; **41**, 132179-22-7; (±)-**42a**, 132179-23-8; (±)-**42b**, 132179-09-0; (±)-**42c**, 132179-10-3; (±)-**42d**, 132179-24-9; (+)-**43**, 132294-33-8; (±)-**43**, 132179-11-4; (−)-**44**, 132294-34-9; (±)-**44**, 89165-86-6; (−)-**45**, 132294-35-0; (±)-**45**, 89177-60-6; **46**, 132294-36-1; (+)-**47**, 132294-37-2; (±)-**47**, 89165-88-8; (+)-**48**, 132294-38-3; (±)-**48**, 89165-89-9; (−)-**49**, 132294-39-4; (±)-**49**, 89165-90-2; **57b**, 26639-84-9; **57c**, 132179-13-6; **59**, 82491-60-9; (+)-**61**, 132294-40-7; (±)-**61**, 89165-91-3; (+)-**62**, 127182-28-9; (±)-**62**, 89165-80-0; (±)-**63**, 132294-41-8; (±)-**64**, 132294-43-0; $Ph_3P^+CH_3Br^-$, 1779-49-3; 2-cyclopentenone, 930-30-3.