Total Synthesis of (−)-Maysine

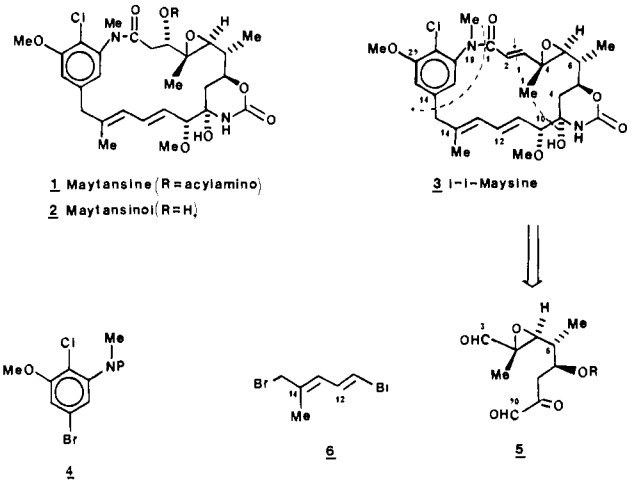
A. I. Meyers,* Kevin A. Babiak, Arthur L. Campbell,[1a] Daniel L. Comins, Michael P. Fleming,[1a] Rainer Henning,[1b] Manfred Heuschmann,[1b] James P. Hudspeth,[1a] John M. Kane, Paul J. Reider,[1a] Dennis M. Roland,[1a] Kimihiro Shimizu, Kyoshi Tomioka, and Robert D. Walkup

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received February 14, 1983*

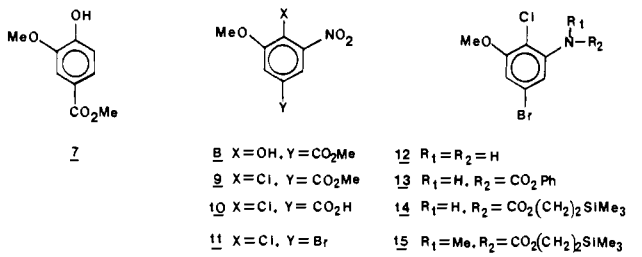
Abstract: A convergent synthesis of the natural macrocycle (−)-maysine (**3**) has been accomplished involving only a single separation of epimers at C-10. The scheme involved the preparation of three major fragments: (a) the western zone, **4**; (b) the southern zone, **6**; and (c) the northeastern zone in enantiomerically pure from (+)-**37**. Each of these components was coupled through the appropriate functionality leading to the target compound.

The synthetic challenge set forth by the 1972 report[2] on the isolation of the antitumor macrocycle maytansine, and related derivatives (**1–3**),[3] has led to considerable activity by various laboratories in their efforts to achieve a total synthesis. This has since culminated in three successful synthetic routes to the maytansinoids.[4] We have previously described, in preliminary form, the total synthesis of racemic *N*-methylmaysenine,[4a] maysine,[4b] and maytansinol.[4c] We now describe for the first time, with full details, the enantioselective synthesis of (−)-maysine (**3**).[5]

The key dissections for reaching (−)-maysine are depicted by the dotted lines in **3**, requiring the aromatic (western zone) **4**, the epoxy aldehyde (northern and eastern zones) **5**, and the dibromo diene (southern zone) **6**. Convergence of these major fragments into a single molecule would then require a two-carbon unit (C-1, C-2) to be inserted as the penultimate step to ring closure. It was anticipated that **5** could be prepared in enantiomerically pure form affixing four chiral centers containing the absolute configuration shown. Coupling of **5** to **6** would, expectedly, lead to another chiral center at C-10 and separations of diastereoisomers may be involved. In spite of this potential shortcoming, coupling to **4** and insertion of a two-carbon unit to complete the macrocycle would be devoid of any other stereochemical consequences. *Thus, at worst, the entire synthetic route may be accomplished with only a single separation of stereoisomers.* Utilizing this strategy, we are able to relate the successful implementation of the synthesis of natural (−)-maysine and a number of useful new synthetic transformations which accompanied the scheme.



Western Zone (4). The suitably protected trisubstituted aniline derivative **4** was prepared in eight steps as the trimethylsilylethyl carbamate **15** starting from methyl vanillate (**7**). Thus, nitration



using nitric acid–glacial acetic acid gave the nitro compound **8** in 78% yield. Transformation to the chloro compound **9** was accomplished in 90% yield using oxalyl chloride in dimethylformamide. In an earlier approach[6] to **9**, the phenolic hydroxyl was replaced by chlorine using thionyl chloride, but the yield was somewhat lower (60%). After hydrolysis with aqueous alkali to the acid **10**, the carboxyl group was smoothly replaced by bromine using a photoassisted Cristol–Firth–Hunsdieker reaction affording **11** in 90% yield. This modification for bromodecarboxylation has been shown to be rather general for a variety of aromatic acids.[7] Reduction of the nitro group was performed using iron powder

(1) (a) National Service Research Award Postdoctoral Fellow. (b) Postdoctoral Fellow of Deutscher Akademischen Austauschdienst (NATO).

(2) Kupchan, S. M.; Komoda, Y.; Court, W. A.; Thomas, G. J.; Smith, R. M.; Karim, A.; Gilmore, C. J.; Haltiwanger, R. C.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 1354.

(3) Additional derivatives of maytansine have also been reported from various plants and microorganisms: (a) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y.; Dailey, R. G.; Zimmerly, V. A.; Summers, W. C. *J. Org. Chem.* **1977**, *42*, 2349. (b) Wani, M. C.; Taylor, H. L.; Wall, M. E. *J. Chem. Soc., Chem. Commun.* **1973**, 390. (c) Asai, M.; Mizuta, E.; Izawa, M.; Haibara, K.; Kishi, T. *Tetrahedron* **1979**, *35*, 1079. (d) Tanida, S.; Hasegawa, T.; Hatano, K.; Higashide, E.; Yoneda, M. *J. Antibiot.* **1980**, *33*, 192. (e) Powell, R. G.; Weisleder, D.; Smith, C. R. *J. Org. Chem.* **1981**, *46*, 4398. (f) Powell, R. G.; Weisleder, D.; Smith, C. R.; Kozlowski, J.; Rohwedder, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 4929.

(4) (a) *N*-Mthylmaysenine: Corey, E. J.; Weigel, L. O.; Floyd, D.; Bock, M. G. *J. Am. Chem. Soc.* **1978**, *100*, 2916. Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *Ibid.* **1979**, *101*, 4732. (b) Maysine: Meyers, A. I.; Comins, D. L.; Roland, D. M.; Henning, R.; Shimizu, K. *Ibid.* **1979**, *101*, 7104. (c) Maytansine, maytansinol: Meyers, A. I.; Reider, P. J.; Campbell, A. L. *Ibid.* **1980**, *102*, 6597. Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *Ibid.* **1980**, *102*, 6615. Isobe, M.; Kitamura, M.; Goto, T. *Ibid.* **1982**, *104*, 4997. (d) Other reported efforts involving routes to the maytansinoids: Gotschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Helv. Chim. Acta* **1977**, *60*, 1416; *Org. Prep. Proc.* **1981**, *13*, 23. Samson, M.; Declerq, P.; DeWilde, H.; Vandewalle, M. *Tetrahedron Lett.* **1977**, 3195. Bonjouklian, R.; Ganem, B. *Ibid.* **1977**, 2835. Elliot, W. J.; Fried, J. *J. Org. Chem.* **1976**, *41*, 2469. Gormley, G.; Chan, Y. Y.; Fried, J. *Ibid.* **1980**, *45*, 1447; Ho, P.-T. *Can. J. Chem.* **1980**, *58*, 858; Ho, P.-T. *Can. J. Chem.* **1980**, *58*, 861. Edwards, O. E.; Ho, P.-T. *Can. J. Chem.* **1977**, *55*, 371. Barton, D. H. R.; Gero, S. D.; Maycock, C. D. *J. Chem. Soc., Chem. Commun.* **1980**, 1089.

(5) A preliminary report on the enantioselective synthesis of the C_3–C_{10} fragment in **1–3** has appeared: Meyers, A. I.; Hudspeth, J. P. *Tetrahedron Lett.* **1981**, *22*, 3925.

(6) Kane, J. M.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 771. For two other approaches to the western zone, see: Corey, E. J.; Wetter, H. F.; Kozikowski, A. P.; Rama Rao, A. V. *Ibid.* **1977**, 777. Ganem, B.; Foy, J. E. *Ibid.* **1977**, 775.

(7) Meyers, A. I.; Fleming, M. P. *J. Org. Chem.* **1979**, *44*, 3405.

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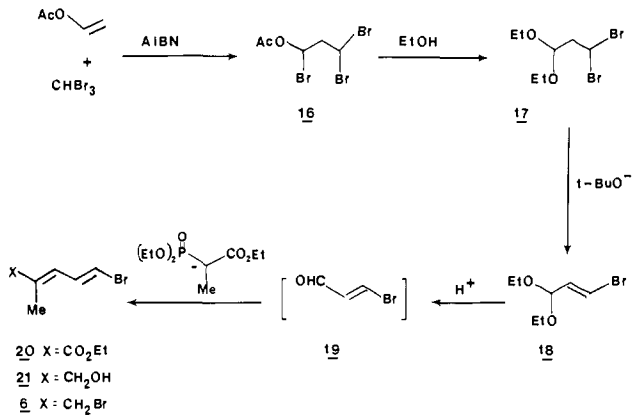
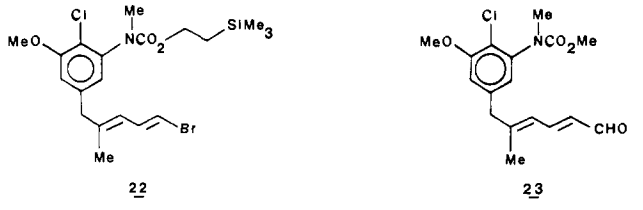
in aqueous ethanolic acid and furnished the trisubstituted aniline **12** in 83% yield. With the four desired substituents in place, it was necessary to protect the amino group with appropriate functionality to withstand the large number of steps to follow, yet be readily removable under mild conditions at the proper stage of the synthesis. Such a protecting group was found in the trimethylsilylethyl urethane **15** which is removable with fluoride ion, producing only gaseous products (CO_2, ethylene, and Me_3SiF).[8] This grouping was introduced by conversion of the aniline **12** into the phenylurethane **13** using phenyl chloroformate in 92% yield. Exchange of urethanes proceeded quantitatively using trimethylsilylethanol and *tert*-butoxide and gave **14**. The final step to the desired aromatic precursor **15** was accomplished by introduction of the *N*-methyl group with methyl iodide and potassium *tert*-butoxide. This sequence leading to **15** gave on several occasions quantities of materials exceeding 50 g.

Southern Zone (6). The dibromo diene **6**, as required by the retrosynthetic scheme, was envisioned as a product of β-bromoacrolein (**19**). However, the only report of this compound was difficult to reproduce,[9] and considerable modification was necessary. The scheme, leading to **6**, began by radical-initiated addition of bromoform to vinyl acetate affording the tribromo acetate **16** in 56–58% yield. Solvolysis in ethanol produced the dibromo acetal **17** as a sensitive oil which was quickly dehydrobrominated to the acetal of β-bromoacrolein (**18**) in 87–97% yield. Since β-bromoacrolein (**19**) is very sensitive, it was not prepared



in the pure state but rather generated in an ether solution by cleavage of the acetal in aqueous oxalic acid–silica gel and added directly to the potassium salt of triethyl 2-phosphonopropionate in THF furnishing the *E,E*-diene ester **20** in 62% yield. The latter was reduced to the bromo allylic alcohol **21** with diisobutylaluminum hydride in 98% yield and transformed into the target southern zone, **6**, by treatment with *N*-bromosuccinimide–dimethyl sulfide[10] in 81% yield.

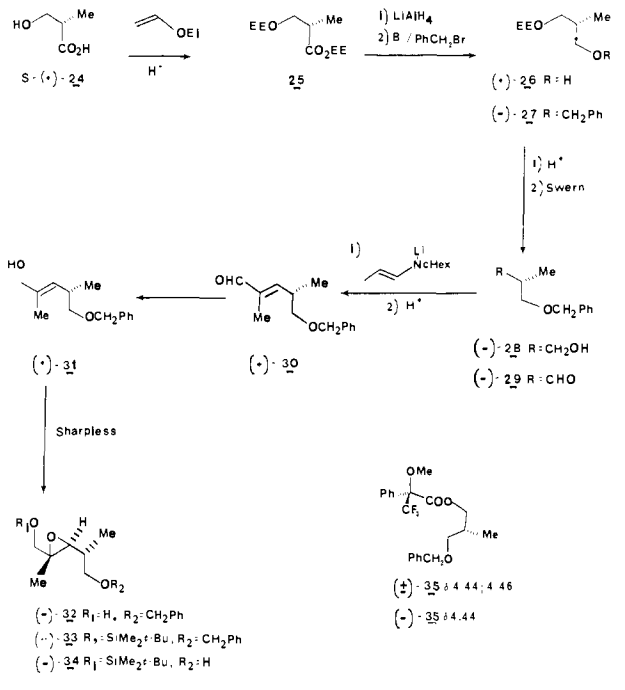
Coupling of Western (15) and Southern Zones (6). With the aromatic bromide **15** and the dibromo diene **6** successfully reached, it remained to couple these to reach the major maytansinoid fragment **22**. In earlier studies, the related intermediate **23** was



prepared,[11] but proved incompatible with the present scheme. This is primarily due to our failure to carry out 1,2-addition to the unsaturated aldehyde. Thus, we reversed the functionality of **22** and **23** and this rendered the former as the nucleophile (vide infra).[12] Addition of *n*-butyllithium at −110 °C to the bromo aromatic **15** followed by treatment with pentynylcopper–hexamethylphosphortriamide gave the mixed cuprate of **15**.[13] Addition of the dibromo diene **6** gave the coupled product **22** in 62% isolated pure form. This now completed the synthesis of the western and southern zones which were to be annexed to the northern and eastern zones as described below.

Northern and Eastern Zones (5). Four of the six chiral centers in (−)-maysine reside in this region of the molecule, suggesting the use of a simple, enantiomerically pure, starting material. By stepwise elaborative techniques, it should be possible to introduce sequentially each additional nonracemic, asymmetric center under the directive influence of the previous one. An appropriate starting material for this sequence was (*S*)-(+)-3-hydroxy-2-methylpropionic acid, available in quantity.[14] Examination of the absolute configuration at C-6 for all the maytansinoids (e.g., **1–3**) shows that they possess the *R* configuration. However the *S*-hydroxy acid **24** may be employed and through the following sequence of reactions leads to the required *R* configuration.

Esterification of the carboxyl and protection of the hydroxyl group in **24** were performed simultaneously in 95% yield leading to **25** (EE = α-ethoxyethyl) which, without purification, was directly reduced with lithium aluminum hydride to the alcohol (+)-**26** in 85% yield. Benzylation using potassium *tert*-butoxide–benzyl bromide in THF gave (−)-**27** which was hydrolyzed, without purification, in acid to the ether–alcohol (−)-**28** (87% from **26**). Oxidation to the aldehyde (−)-**29** was performed using the



Swern technique,[15] and because of the change in priority, this aldehyde now possesses the requisite *R* configuration at C-6.

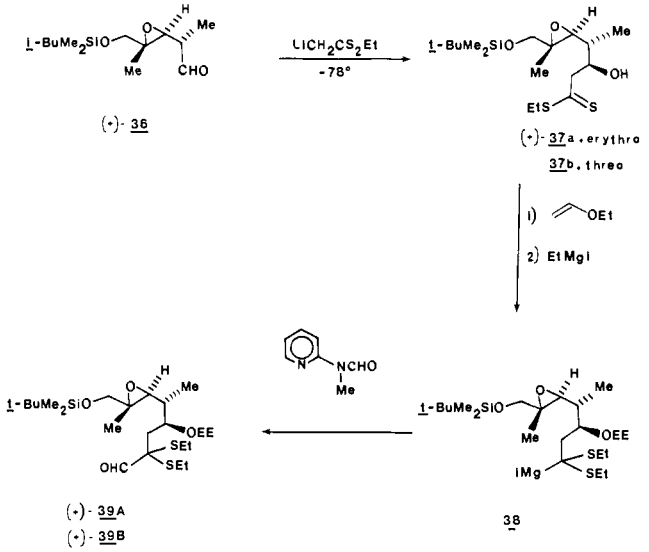
Concerns over racemization during the oxidation of alcohol **28** to aldehyde **29** were addressed by reducing the latter ($NaBH_4$) back to the alcohol and preparing the Mosher ester[16] **35**. When comparing the racemic alcohol (±)-**28** as its diastereomeric Mosher esters, which exhibited two benzylic singlets at δ 4.44 and

(8) Carpino, L. A.; Tsao, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 358.
(9) Protopova, T. V.; Skoldinov, A. P. *Zh. Obshch. Khim.* **1959**, *29*, 963; *Chem. Abstr.* **1960**, *54*, 1288d.
(10) Corey, E. J.; Kim, C. U.; Takeda, M. *Tetrahedron Lett.* **1972**, 4339.
(11) Meyers, A. I.; Tomioka, K.; Roland, D. M.; Comins, D. L. *Tetrahedron Lett.* **1978**, 1375.
(12) The diene aldehyde **23**, however, was successfully employed by the Corey group.[4a,c]
(13) Corey, E. J.; Beam, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.
(14) Goodhue, C. T.; Schaeffer, J. R. *Biotechnol. Bioeng.* **1971**, *13*, 203. Cohen, N.; Eichel, W. F.; Lopresti, R. J.; Neukom, C.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3505. We are indebted to Dr. Cohen of Hoffmann-La Roche for providing the fermentation broth containing the acid. The recovered acid contains 15–20% oligomer which was not removed prior to use.
(15) Mancuso, A. J.; Huangard, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

4.46 (at 360 MHz) with that alcohol obtained by aldehyde reduction, only the singlet at δ 4.44 was visible, thus attesting to the >99% enantiomeric purity of aldehyde **29**. On the other hand, oxidation of (−)-**28** with pyridinium chlorochromate gave the aldehyde containing ~10% of the other enantiomer, as determined by the above technique.

Further elaboration using lithiopropylimine of cyclohexylamine gave, after dehydration, the unsaturated aldehyde (+)-**30** in 62% yield. Reduction with sodium borohydride gave the allylic alcohol (+)-**31** in quantitative yield, and the scene was now set for the elegant Sharpless epoxidation,[17] a process which occurred with >99% selectivity and in 93% yield to the epoxide (−)-**32**. Although the diastereomeric excess of the latter could not be assessed using NMR or HPLC methods, the scheme was continued with the hope that one of the subsequent steps will provide a product which will respond to diastereomer analysis. Silylation of alcohol (−)-**32** was performed using *tert*-butyldimethylsilyl chloride, with imidazole as the base to protect the primary alcohol, and provided (−)-**33** in 90% yield. Evaluation of the diastereomeric excess using various chiral shift reagents again failed to reveal the diastereomer composition so the sequence to the northern zone was continued. Removal of the benzyl group to (−)-**34** was accomplished using sodium–liquid ammonia, affording the alcohol in 93% yield. HPLC analysis showed this compound to contain less than 1% of any other diastereomers. Since the ratios of diastereomers also reflect any enantiomer contamination due to the scheme originating with enantiomerically pure aldehyde **29**, the conclusion was reached that the Sharpless epoxidation proceeded with >99% enantioselectivity.

The functionality required for the eastern zone was incorporated by oxidation of alcohol (−)-**34** to the aldehyde (+)-**36** employing the Collins procedure (84%), and racemization was precluded by reduction back to the alcohol (−)-**34** followed by HPLC analysis. Addition of the lithio thioenolate to the aldehyde (+)-**36** at −120 °C, in THF–hexane, gave a 10:1 ratio of diastereomeric products (**37a,b**). When the addition was carried out at −78 °C, the ratio



of **37a**/**37b** was only 3:1. These ratios and the stereochemical assignment of the products were readily discernible from the coupling constants and found to follow Cram's rule. Purification of **37** from the minor (>10%) isomer was accomplished using preparative liquid chromatography and afforded pure material in 62% yield.[18] With four enantiomerically pure chiral centers in place corresponding to those in maytansine (**1**) or maysine (**3**), it was appropriate at this stage to transform the dithioester into a protected carbonyl and place an aldehyde function in the α position so that coupling to the southern portion could follow. Toward this end, the hydroxyl group was masked by ethyl vinyl ether to a 1:1 mixture of diastereomers. This may appear to be a poor choice for an alcohol protecting group, and one which would not involve diastereomers would have been more desirable. However, no other protecting group investigated could be introduced or removed, when necessary, in satisfactory yields. Nevertheless, the diastereomers would converge to a single product on removal of the EE group at a later stage in the synthesis. Thiophilic addition of ethylmagnesium iodide to the dithioester proceeded smoothly, producing the α-dithioethyl carbanion **38** which was formylated with 2-(*N*-formyl-*N*-methyl)aminopyridine to the aldehyde **39** (83% yield from (+)-**37a**). Both the thiophilic addition[19] and the formylation have been studied for their generality in synthesis and found to have considerable potential.[20]

The route to **39** which represents the synthetic equivalent of **5**, prepared in 14 steps, was now ready for attachment to the aromatic diene **22**. We preferred to utilize the pure epimer of the ethoxyethyl (EE) derivative **39A** or **39B**; these were readily separated (**39A**, $[\alpha]_D$ +112.7°; **39B**, $[\alpha]_D$ +61.8°) and each was employed for the coupling to **22**. As stated above, these products should converge to identical material after removal of the EE group. No effort was made to determine the stereochemistry of **39A** or **39B** at the EE site.

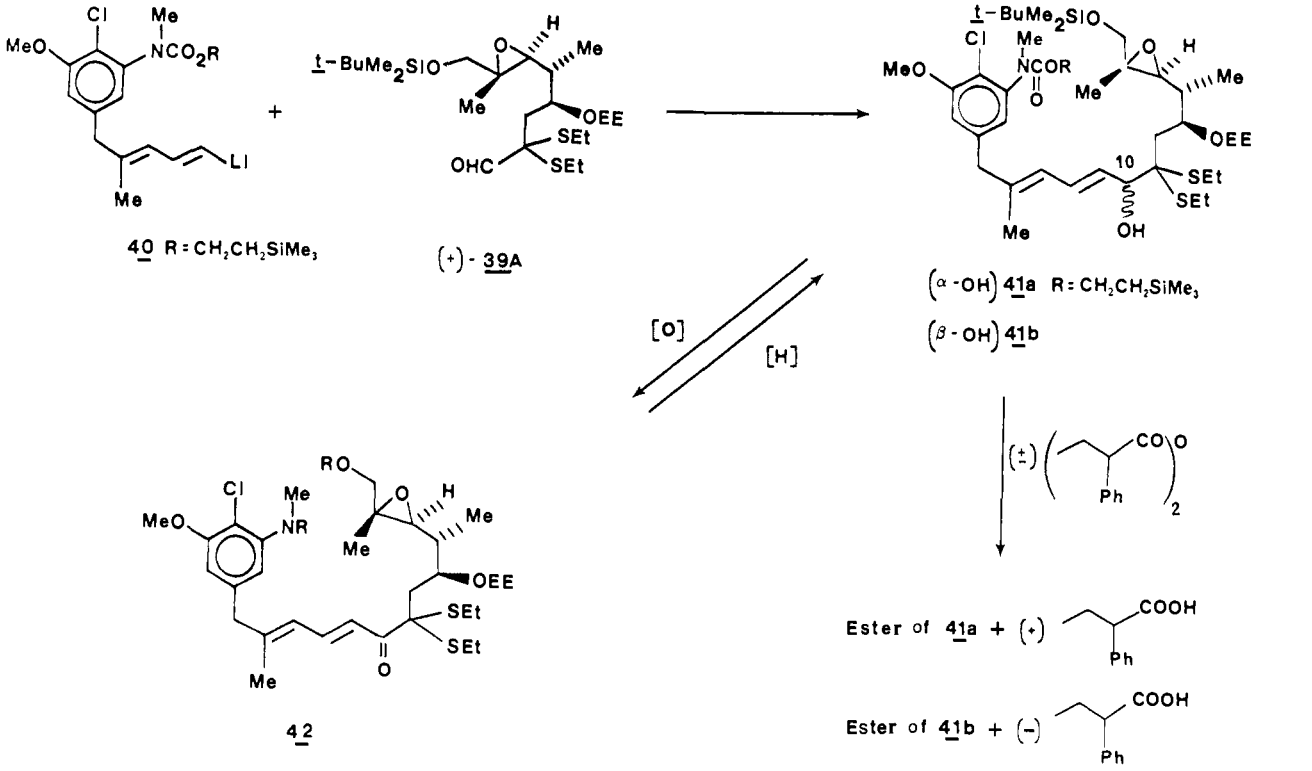
Northeast (39) and Southwest (22) Coupling to (−)-Maysine. The critical coupling of the two major fragments **22** and (+)-**39A** was performed by transformation of the former to the lithio derivative **40** using 2.2 equiv of *tert*-butyllithium[21] at −120 °C and addition of the aldehyde at −120 °C. After workup, the alcohol **41** was obtained, after chromatography, in 73% yield as a 1:1 mixture of α- and β-hydroxy derivatives as determined by HPLC (Scheme I). Thus, no selectivity was observed in this process. The two epimers at C-10 were readily separated by radial chromatography (Chromatotron). Since the α-hydroxy compound **41a** was required for the synthetic scheme, it was necessary to determine which of the two C-10 epimers contained the proper stereochemistry at C-10. Both epimers were therefore subjected to the Horeau method of determining absolute configuration.[22] Since pure EE enantiomers were used (**39A** or **39B**), only two diastereomers resulting from the coupling were present. Using pure C-10 epimers and treatment of each with (±)-2-phenylbutanoic anhydride resulted in a kinetic resolution which allowed recovery of partially resolved 2-phenylbutanoic acid. Examination of the rotation of the recovered butanoic acid showed that the (+) acid was obtained with **41a**, and the (−) acid recovered from reaction with **41b** (Table I). By invoking the stereochemical transition-state model for the Horeau technique, it was concluded that **41a** possesses the α-OH at C-10. This procedure was repeated using the EE epimer **39B** and gave the same results. This is as expected since the Horeau model should not be affected by substituents at a considerable distance from the chiral center to be acylated.

With the knowledge that **41a** possessed the proper C-10 configuration, it was hoped that the unwanted (**41b**) C-10 epimer could be converted to the desired one (**41a**), resulting in no losses due to stereochemical differences. Oxidation of **41b** using manganese dioxide proceeded quantitatively to the ketone **42**. However, a variety of reducing agents, including those with considerable steric bulk, failed to provide a significant ratio of **41a**:**41b**. The lack of conformational restraints in the open-chain ketone presumably was responsible for lack of stereoselective reduction.

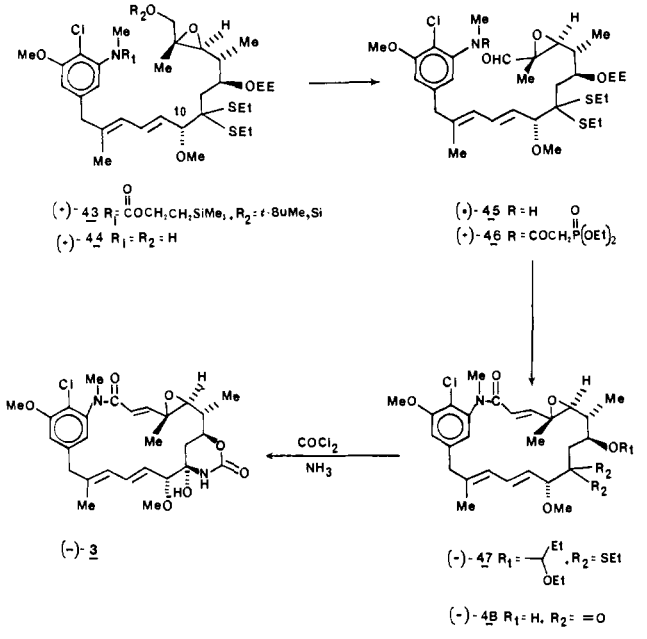
The C-10 hydroxy group in **41a** was transformed to its methyl ether by treatment with sodium hydride and methyl iodide at −20 °C furnishing **43** in 85–90% yield. It was found that the C-10

(17) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(18) The stereoselectivity of lithio dithioester condensation with various aldehydes has been observed to be quite high when compared with lithio esters. The results of this study will be reported in due course (R. Walkup, research in progress).
(19) Meyers, A. I.; Tait, T. A.; Comins, D. L. *Tetrahedron Lett.* **1978**, 4657. Additional studies involving thiophilic additions by organometallics have been reported: Thullier, A.; Saquet, M. *Ibid.* **1980**, 2165. Gosselin, P.; Masson, S.; Thullier, A. *J. Org. Chem.* **1979**, *44*, 2807.
(20) Meyers, A. I.; Comins, D. L. *Tetrahedron Lett.* **1978**, 5179. Meyers, A. I.; Comins, D. L. *Synthesis* **1978**, 403.
(21) Neuman, H.; Seebach, D. *Tetrahedron Lett.* **1976**, 4839.
(22) Horeau, A. In "Stereochemistry"; G. Thieme: Stuttgart, 1977; Vol. 3, p 51.

Scheme I



hydroxy compounds **41a** and **41b** were somewhat sensitive to decomposition, and thus the C-10 mixture of hydroxy epimers was converted, as a mixture, to the methyl ethers immediately after coupling. This caused no problem in reaching the pure C-10 epimer since the epimeric methoxy compounds were also readily separated via radial chromatography. The silyl protecting groups on the aniline and epoxy moieties were cleanly removed using tetrabutylammonium fluoride (anhydrous) in THF at room temperature, producing the amino alcohol **44** in 90% yield. It was also observed that the latter was easily separated into its C-10 epimeric methoxyl compounds by radial chromatography. Thus, subsequent experiments to reach **44** were performed by merely methylating the C-10 hydroxy epimers **41**, followed by desilylation to the amino alcohol **44** (as a mixture at C-10) and separation to reach pure (+)-C-10-α-methoxy **44**. Oxidation of the latter



to the aldehyde **45** using a modified Mukaiyama oxidation[23] gave the aldehyde (+)-**45** in 70% yield. It should be noted here that the β-C-10 hydroxy **41b** was also carried through under identical conditions to the intermediates **43**, **44**, and **45**. Furthermore, the epimeric ethoxyethyl ether (+)-**39b** was also carried through the sequence to **45**, and, since half of this contained the α-C-10 hydroxyl, it was combined after determining that they were identical at the appropriate stage (**48**). The aldehyde (+)-**45** was then acylated at the amino group with 1-(diethylphosphono)acetyl chloride, providing the phosphono acetanilide (+)-**46** in 83% yield.

Cyclization to the macrocycle was carried out via an intramolecular Horner–Emmons–Wadsworth technique[24] using potassium *tert*-butoxide and gave (−)-**47** as the single product in 62% yield (82% based on recovered starting material). It was now appropriate to release the β-hydroxy ketone in (−)-**47**, and this was done by initially removing the ethyl dithioacetal using $CaCO_3$–$HgCl_2$ and treatment of the crude product with 1 N hydrochloric acid in THF at 0 °C. The two-step sequence provided the β-hydroxy ketone, (−)-**48** with an unexpectedly large $[\alpha]_D$ of −577°. The final step to (−)-maysine was to convert the hydroxy ketone to the cyclic urethane; this was performed using phosgene and ammonia at −78 °C. The TLC behavior of the crude product was coincidental with (−)-maysine, and after chromatography there was obtained a crystalline product, mp 169–172 °C, $[\alpha]_D$ −255°, which compared well with natural material (lit. mp 170–172 °C, $[\alpha]_D$ −210°). Comparison spectra at 360 MHz showed both materials to be identical. This identity in physical properties confirmed that the Horeau method for absolute configuration at C-10 was indeed valid in this study since it indicated correctly which of the two C-10 hydroxy epimers in **41** possessed the correct configuration.

Experimental Section[25]

Methyl 3-Nitro-4-hydroxy-5-methoxybenzoate (8). A solution of concentrated HNO_3 (21.0 mL, 0.325 mol) in glacial acetic acid (120 mL)

(23) Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773.

(24) Cycloolefinations in macrocyclic synthesis for various ring sizes have been successfully carried out by others as well: Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4011.

(25) Microanalyses were performed by Midwest Microlabs, Indianapolis, Indiana, and MicAnal, Tucson, Ariz.

was slowly poured into a stirred solution of methyl vanillate (Aldrich, 59.2 g, 0.325 mol) in acetic acid (300 mL) at 0 °C. After several minutes, the reaction became dark and a heavy precipitate began to form. Stirring was continued at room temperature for 2 h. The solid residue was collected by filtration and washed with distilled water until the filtrate was colorless. The yellow powder was dried over P_2O_5 overnight in vacuo to give 57.7 g of aromatic nitro compound (78%). Recrystallization from EtOAc (several crops) gave 55.05 g (74%) of bright yellow needles, mp 154.0–154.5 °C: IR (KBr) 3280, 1735, 1560, 1340 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (d, J = 2 Hz), 7.75 (d, J = 2 Hz), 4.00 (s), 3.93 (s). Hydrolysis (KOH–EtOH–H_2O) gave the known nitrovanillic acid, mp 215–216 °C (lit.[26] mp 214–215 °C).

Methyl 3-Nitro-4-chloro-5-methoxybenzoate (9). A solution of methyl nitrovanillate (**8**) (34.38 g, 0.14 mol) and DMF (300 mL distilled from CaH_2) was cooled to −20 °C, and oxalyl chloride (59.29 g, 0.42 mol) was added dropwise with vigorous stirring. A heavy precipitate formed during addition. The ice bath was removed and the temperature slowly raised to 80 °C. The temperature was maintained at 80° for 3 h at which point the reaction mixture had become clear and dark. After the reaction mixture was cooled, it was poured onto 500 mL of ice with vigorous swirling. When the ice had melted, the dark suspension was filtered, washed with water until the filtrate was colorless, and then taken up in 300 mL of CH_2Cl_2. The organic layer was washed with 2 × 100 mL of $NaHCO_3$ and 1 × 100 mL of NaCl and dried over $MgSO_4$. Removal of the solvent at reduced pressure gave a yellow solid which was recrystallized from EtOAc, providing 32.40 g (88%) of a fluffy yellow solid, mp 102.5–103.0 °C: IR (KBr) 1740, 1540, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.92 (d, J = 1.6 Hz), 7.67 (d, J = 1.6 Hz), 4.05 (s), 4.00 (s). This material was used directly for the next step.

3-Nitro-4-chloro-5-methoxybenzoic Acid (10). Heating **9** at 80 °C in 10% KOH–ethanol for 2 h gave a solution which was acidified with 10% HCl. The resulting precipitate was collected on a fritted funnel under vacuum and washed twice with water. The gray solid was dried under vacuum with P_2O_5 for 24 h to give 34.5 g (100%). This material may be used as is, or recrystallized from ethyl acetate, to give 30 g of a pale yellow solid, mp 212.0–213.5 °C: IR (KBr) 3000, 1715, 1555, 1370 cm^{-1}; ^1H NMR (d_6-acetone) δ 8.03 (d, J = 1.7 Hz), 7.88 (d, J = 1.6 Hz), 4.13 (s); ^{13}C NMR (d_6-acetone), 206.25 (s), 164.91 (s), 157.03 (s), 150.02 (s), 131.51 (s), 117.61 (d), 116.04 (d), 57.71 (q).

Anal. Calcd for $C_8H_6NO_5Cl$: C, 41.49; H, 2.61. Found: C, 40.45; H, 2.61.

2-Chloro-3-nitro-5-bromoanisole (11). A mixture of **10** (10.30 g, 0.045 mol) and red mercuric oxide (14.65 g, 0.067 mol) in 400 mL of carbon tetrachloride was heated at reflux for 15 min and under irradiation from a 100-W, 120-V high-intensity lamp. To this mixture was added in three equal batches, over a 2-h period, a solution of bromine (3.6 mL, 0.067 mol) in 25 mL of CCl_4. Refluxing and irradiation were continued for a total of 5 h. At this point the deep red color of bromine had disappeared and the reaction mixture was peach colored. After cooling to room temperature, the reaction mixture was filtered and the contents of the flask washed with 200 mL of CH_2Cl_2 which was passed through the filter. The combined organic filtrates were washed with 2 × 100 mL of saturated $NaHCO_3$ and 100 mL of NaCl and dried over $MgSO_4$. Evaporation of solvent at reduced pressure gave the aromatic bromide, 10.7 g (89%), as a yellow powder. Recrystallization from 1:1 CH_2Cl_2/hexane provided 7.15 g (60%), mp 106.5–108.5 °C: IR (KBr) 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51 (d, J = 2 Hz), 7.23 (d, J = 2 Hz), 3.97 (s); ^{13}C NMR ($CDCl_3$) 156.52 (s), 149.8 (s), 120.32 (s), 119.16 (d), 118.10 (d), 115.19 (s), 57.21 (q).

Anal. Cacld for $C_7H_5NO_3ClBr$: C, 31.55; H, 1.89. Found: C, 31.82; H, 1.90.

2-Chloro-3-methoxy-5-bromoaniline (12). A mixture of aromatic nitro compound (18.0 g, 0.068 mol), powdered iron (11.2 g, 0.20 mol), 200 mL of absolute ethanol, and 200 mL of distilled water was stirred mechanically and brought to reflux, during which time a vigorous flow of argon was passed through the mixture to degas it of oxygen. An argon atmosphere was maintained throughout the reaction. After degasing for 30 min, the refluxing mixture was treated with 0.55 mL of concentrated HCl. The darkened mixture was stirred at reflux for 12 h (it may be necessary on occasion to add a fresh batch of iron powder and HCl after the initial 12 h in order to drive the reaction to completion). The reaction mixture was then cooled in an ice bath for 30 min and to it was added 20 g of Celite. Stirring was continued for an additional 10 min and then the contents of the flask was filtered through a Celite bed in a fritted glass funnel at aspirator pressure. The flask was rinsed with 300 mL of ethanol which was used to wash the filter cake. Washing was continued until the filtrate was colorless. The filtrate was then concentrated at reduced pressure to remove ethanol and the dark residue was extracted with 250 mL of ether. The organic layer was washed with 75 mL of brine and dried over $MgSO_4$. Removal of the solvent at reduced pressure gave 13.2 g (83%) of a tan waxy solid which was used further without purification: IR (KBr) 3460 (free NH_2), 3340 cm^{-1} (H-bond NH_2); ^1H NMR ($CDCl_3$) δ 6.70 (d, J = 2 Hz), 6.50 (d, J = 2 Hz), 5.50 (br s), 3.86 (s).

Phenyl Carbamate 13. To a stirred solution at 0 °C of aniline, **12** (11.61 g, 0.050 mol), and pyridine (distilled from BaO, 4.40 mL, 0.055 mol) in 200 mL of CH_2Cl_2 (distilled from P_2O_5) was added phenyl chloroformate (7.02 mL, 0.055 mol) over a 5-min period. Stirring was continued at 0 °C for 10 min and then at room temperature for 1 h. The reaction mixture was washed with 5% citric acid solution (100 mL), saturated $NaHCO_3$ solution (100 mL), and saturated NaCl (100 mL). The organic layer was dried over $MgSO_4$ and the solvent removed at reduced pressure. The brown solid, 16.0 g (92%), obtained could be used directly in the next step or purified by recrystallization from twice its own volume of EtOAc to give 11.77 g (67%) of large amber crystals, mp 126.5–128.0 °C; IR (KBr) 3290, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.04 (d, J = 2 Hz), 7.90 (m), 6.75 (d, J = 2 Hz), 3.80 (s); ^{13}C NMR ($CDCl_3$) 155.12 (s), 150.68 (s), 149.98 (s), 135.85 (s), 129.14 (d), 125.69 (d), 121.20 (d), 120.91 (s), 114.60 (d), 110.05 (d), 109.59 (d), 56.39 (q).

Anal. Calcd for $C_{14}H_{11}NO_3ClBr$: C, 47.15; H, 3.11. Found: C, 47.36; H, 3.09.

β-Trimethylsilylethyl Carbamate 14. To a solution, cooled to 0 °C under argon, of phenyl carbamate **13** (11.77 g, 0.033 mol) and β-trimethylsilylethanol (Fluka, 11.70 g, 0.099 mol) in 250 mL of anhydrous THF was added *t*-BuOK (9.24 g, 0.083 mol) under a blanket of argon. The mixture was stirred overnight at room temperature and then partitioned between ether (300 mL) and saturated NaCl (300 mL). The organic layer was washed with 3 × 100 mL of 5% NaOH and 200 mL of brine and dried over $MgSO_4$. Evaporation of the solvent at reduced pressure gave 13.03 g (100%) of an orange oil. This material could be used directly or be further purified by crystallization from pentane to give a pale amber crystalline solid, mp 52.5–53.0 °C: ^1H NMR ($CDCl_3$) δ 8.00 (d, J = 2 Hz), 7.11 (br s), 6.69 (d, J = 2 Hz), 4.22 (AA′XX′), 3.81 (s), 1.01 (AA′,XX′), 0.02 (s); ^{13}C NMR ($CDCl_3$), 155.12 (s), 152.67 (s), 136.50 (s), 120.85 (s), 114.48 (d), 109.11 (s), 64.04 (t), 56.39 (q), 17.68 (t), −1.47 (q).

Anal. Calcd for $C_{13}H_{19}O_3NClBrSi$: C, 41.01; H, 5.03. Found: C, 41.28; H, 5.22.

***N*-Methylsilyl Carbamate 15.** To a 0 °C solution of silyl carbamate **14** (13.03 g, 0.034 mol) in 250 mL of anhydrous THF was added, under an argon blanket, *t*-BuOK (4.21 g, 0.038 mol). The mixture turned a deep red color as the base went into solution. This solution was stirred at 0 °C for 30 min and to it was then added via syringe (cautiously! exothermic) iodomethane (4.68 mL, 0.075 mol). A yellow precipitate formed after 15 min. The reaction mixture was stirred at room temperature overnight and then partitioned between 150 mL of brine and 200 mL of ether. The aqueous layer was further extracted with 50 mL of ether. The combined organic layers were washed and dried; removal of the solvent at reduced pressure gave 13.19 g (98%) of crude **15**. This product was column chromatographed on 500 g of silica gel using 3% EtOAc/hexane as eluent to give a yellow oil which was homogeneous by TLC (10% EtOAc/hexane). The oil was subsequently crystallized from pentane to give 8.10 g (60%) of a colorless solid, mp 61.0–62.0 °C: IR (KBr) 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.00 (m, ArH, 2), 4.15 (AA′XX′ m, $-OCH_2-$, 2), 3.90 (s, OCH_3, 3), 3.18 (s, NCH_3, 3), 0.90 (AA′XX′ m, $-CH_2Si$, 2), −0.066 (br m, $SiCH_3$, 9); ^{13}C NMR ($CDCl_3$) 156.17 (s), 155.06 (s), 142.39 (s), 124.17 (d), 121.02 (s), 119.79 (s), 114.25 (d), 64.21 (t), 56.56 (q), 36.71 (q), 17.62 (t), −1.528 (q).

Anal. Calcd for $C_{14}H_{21}O_3NClBrSi$: C, 42.60; H, 5.36. Found: C, 42.88; H, 5.37.

1-Acetoxy-1,3,3-tribromopropane (16). Bromoform (Aldrich, 60 mL, distilled from CaH_2) in an oven-dried, nitrogen-purged, 500-mL flask containing a magnetic bar and fitted with a reflux condenser and two addition funnels was heated to 65 °C. Vinyl acetate (distilled from K_2CO_3, 30 mL, 0.325 mol) was placed in one addition funnel, and a solution of 2,2′-azobis(2-methylpropionitrile) (Aldrich, 3.011 g, 0.0183 mol) in bromoform (30 mL) was placed in the other addition funnel. The contents of the two addition funnels were added simultaneously over 2.5 h at a rate such that the temperature was maintained at 65–70 °C. The reaction was not allowed to go above 70 °C. (Caution! The reaction may become very exothermic if addition is too rapid.) The brown solution was heated at 65 °C for an additional 3.5 h (reaction was complete as determined by NMR analysis of an aliquot, no vinyl acetate remaining). Excess bromoform was removed by rotoevaporation in vacuo, and the brown-black liquid was cooled to ambient, diluted with hexanes (300 mL), and stirred with Norite for 15 min (Norit treatment is unnecessary if the product is to be distilled immediately). Filtration through Celite

(26) Pearl, I. A. *J. Am. Chem. Soc.* **1946**, *68*, 1100.

gave a pale-yellow solution which, after concentration in vacuo gave 104.4 g (95%) of a gold-colored liquid which was bulb-to-bulb distilled using a Kugelrohr apparatus under vacuum (0.05 mm initially to remove residual bromoform, then at 0.005 mm, at 25–60 °C) to provide 61.0 g (56%) of a pale yellow oil which could be further purified by dissolving in hexane (25 mL) and storing in the freeze (AIBN impurities crystallized from the mixture and were removed by filtration): ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3), 3.22 (t, J = 7 Hz, 2), 5.67 (t, J = 7 Hz, 1), 6.67 (t, J = 7 Hz, 1). This material was directly carried on to the next step.

1,1-Dibromo-3,3-diethoxypropane (17). A solution of 1-acetoxy-1,3,3-tribromopropane from the previous procedure (48.0 g, 141.7 mmol) in 200 mL of absolute ethanol was heated in an oil bath to 45–50 °C for 3.5 h. The reaction rate was easily controlled at this temperature and the internal temperature was maintained at 48–55 °C. Higher temperatures result in an increase in the yield of a tetraethoxy byproduct. The pale yellow solution was cooled to 0 °C and quenched by the addition of excess solid $NaHCO_3$. The mixture was stirred for 30 min at 0 °C, then filtered and concentrated by rotoevaporation to yield a yellow oil which was taken up in hexane and decolorized with Norite A to provide a pale yellow oil, 40.0 g (97.3%), after filtration and concentration. This compound was distilled in a Kugelrohr apparatus at 60 °C (<0.005 mmHg), yield 70–87%, keeping the distillation temperature below 90 °C: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 6), 2.70 (d of d, J = 5, 7 Hz, 2), 3.63 (m, 4), 4.68 (t, J = 5 Hz, 1), 5.70 (t, J = 7 Hz, 1). This product was carried on to the next step immediately. If the material was distilled, it could be stored in the freezer overnight.

3-Bromoacrolein Diethyl Acetal (18). A solution of potassium *tert*-butoxide (freshly sublimed at 220 °C (0.5 mmHg), 17.0 g, 151.7 mmol) in dry THF (100 mL) was added dropwise to a magnetically stirred solution of 1,1-dibromo-3,3-diethoxypropane (40.0 g, 137.9 mmol) in dry THF (200 mL) and cooled in a Dry Ice/$CaCl_2$(aq) bath at −50 °C at a rate so as to maintain the internal temperature throughout the addition at less than −40 °C. The mixture was allowed to warm very slowly to 0 °C and stirred for 1 h. The progress of the reaction was followed by NMR analysis of aliquots withdrawn periodically. The desired product displayed a signal at δ 4.9 ppm. Some acetylenic material could be detected from the signals at δ 5.3 and 2.6 ppm. When the reaction was judged to be complete, it was poured into saturated NaCl (100 mL). The aqueous phase was separated and washed with ether (3 × 50 mL). The organic phases were combined, washed with water (3 × 50 mL) and brine (100 mL), decolorized (Norit A), dried (K_2CO_3), and concentrated to provide 25.5 g of a yellow oil. Distillation from sodium carbonate through a 30-cm vacuum jacketed column containing glass beads provided 17.7 g (70%), bp 41.5–42.0 °C (1.0 mmHg). This material may be stored in the freeze for 2–3 weeks: ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 6), 3.58 (m, 4), 4.93 (d, J = 5 Hz, 1), 6.22 (d of d, J = 5, 14 Hz, 1).

Ethyl (*E*,*E*)-2-Methyl-5-bromo-2,4-pentadienoate (20). A solution of *trans*-β-bromoacrolein diethyl acetal (**18**, 11.2 g, 53.8 mmol) in 15 mL of anhydrous ether was added to a stirred slurry of 50 g of silica gel and 10 mL of saturated oxalic acid (aq) in 175 mL of anhydrous ether. The reaction was stirred at room temperature for 10 h. Aliquots were removed at regular intervals and examined (in ether) by NMR for the appearance of the aldehyde doublet at δ 9.5 ppm and the disappearance of the acetal methinyl proton at δ 4.9 ppm. The reaction was quenched by the addition of saturated sodium bicarbonate and stirred for 30 min. The mixture was quickly vacuum filtered through Celite followed by filtration through anhydrous potassium carbonate and concentrated in the cold at 50 mmHg to a volume of 30 mL.[27] THF (50 mL) was added and the process repeated; 50 mL was again added and concentrated. This solution of bromoacrolein in THF/ether (30 mL) was used directly in the next step. Triethyl 2-phosphonopropionate (12.8 g, 53.8 mmol, 1.0 equiv) was added dropwise to a solution of freshly sublimed potassium *tert*-butoxide (6.62 g, 59.2 mmol, 1.1 equiv) in 125 mL of anhydrous THF at 0 °C under an argon atmosphere. The reaction mixture (colorless to pale yellow) was stirred at 0 °C for 15 min and then cooled to −78 °C. To this was added dropwise via cannula a precooled −78 °C solution of bromoacrolein in THF/ether (30 mL) from the previous procedure. The yellow solution was stirred at −78 °C for 30 min and then at room temperature for 5 h. The red-brown mixture was poured into 100 mL of water and 100 mL of brine and was extracted with 3 × 100 mL of ether. The combined organic extracts were washed with 5 × 100 mL of water until the aqueous layer was nearly colorless, and then with 50 mL of brine. After drying (K_2CO_3) and removal of the solvent at reduced pressure, the residue was chromatographed on silica with 1:1 CH_2Cl_2–hexanes followed by distillation (62–67 °C at 0.1 mmHg) to provide 7.31 g (pale yellow oil, 62%) of the desired *E*,*E*-diene bromo ester: ^{1}H NMR ($CDCl_3$), δ 1.32 (t, J = 7 Hz, 3), 1.93 (s, 3), 4.22 (q, J = 7 Hz, 2), 6.6–7.3 (m, 3); IR (film) 1725 cm^{-1}. Without further purification, this material was carried on to the next step.

1-Hydroxy-2-methyl-5-bromo-2,4-pentadiene (21). A solution of diisobutylaluminum hydride (1.4 M/hexane, 30 mL, 42.0 mmol) was added dropwise to a stirred solution of the diene ester (2.298 g, 10.49 mmol) in 20 mL of distilled hexanes at 0 °C under nitrogen during 25 min. The colorless solution was stirred at 0 °C for 1 h, and 8 mL of water was cautiously added dropwise at 0 °C over 30 min. (Caution! Too rapid an addition will cause a vigorous foaming.) Sulfuric acid (4 M, 15 mL) was added at 0 °C over 10 min followed by 2–3 g of sodium sulfite, and stirring was continued at 0 °C for 1.75 h. The cold mixture was poured into brine (50 mL) and the aqueous phase was washed with ether (2 × 20 mL). The combined organic extracts were washed with water (2 × 20 mL) and brine (20 mL) and dried (K_2CO_3). Rotoevaporation (25 °C) gave 1.827 g (98%) of a pale yellow oil. This material was purified on silica by preparative thin layer chromatography (PTLC) with 10% EtOAc/hexane immediately prior to use: ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3), 2.0 (br s, OH, 1), 4.02 (br s, 2), 5.95 (d of q, J = 1, 10 Hz, 1), 6.33 (d, J = 13 Hz, 1), 6.93 (d of d, J = 10, 13 Hz, 1); IR (film) 3340, 3080, 2930, 2880, 1590, 1455, 1395, 1295, 1230, 1175, 1140, 1075, 1015, 940 cm^{-1}.

1,5-Dibromo-2-methyl-2,4-pentadiene (6). To a magnetically stirred solution of *N*-bromosuccinimide (1.62 g, 9.00 mmol) in 25 mL of dry dichloromethane, freshly distilled dimethyl sulfide (0.79 mL, 10.8 mmol) was added at 0 °C under argon in 5 min. The suspension was stirred for 15 min, then cooled to −25 °C. The diene alcohol (1.062 g, 6.00 mmol) was added via syringe in 5 min. The mixture was stirred at 0 °C for 3 h, diluted with 75 mL of pentane, and poured into 50 mL of ice water. The organic phase was washed with 20 mL of brine and filtered through 8 g of silica gel. Removal of the solvents yielded 1.164 g (81%) of a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.85 (d, J = 1.2 Hz, 3), 3.96 (s, 2), 6.08 (d of q, J = 11.2, 1.2 Hz, 1), 6.38 (d, J = 13.3 Hz, 1), 6.89 (d of d, J = 11.2, 13.3 Hz, 1); ^{13}C NMR ($CDCl_3$) δ 15.4 (q), 40.3 (t), 110.7 (d), 126.5 (d), 133.0 (d), 134.7 (s). Because of the unstable nature of the material, it was used immediately after isolation. If storage is necessary, it may be kept at −20 °C for 5–7 days.

Coupling of 15 to 6. Preparation of 22. To a magnetically stirred solution of aromatic bromide **15** (1.58 g, 4.00 mmol) in 15 mL of dry THF, cooled to −110 °C under argon, a solution of *n*-BuLi in hexanes (1.60 mL, 4.05 mmol) was added dropwise via syringe during 10 min. The pale yellow solution was allowed to warm to −78 °C, stirred at −78 °C for 1.5 h, and cooled again to −110 °C. Hexamethylphosphortriamide (1.37 g, 8.40 mmol) was added to a suspension of pentynylcopper (0.549 g, 4.20 mmol) in 7 mL of dry THF and stirred under argon until a pale green solution was formed. It was cooled to −110 °C and transferred to the solution of the above via cannula over 5 min. The yellow green solution was allowed to warm to −78 °C, stirred for 2.5 h, and cooled again to −110 °C. A solution of diene dibromide **6** (0.720 g, 3.00 mmol) was cooled to −110 °C and added rapidly to the mixed cuprate through a short Teflon cannula. The clear yellow green solution was stirred at −78 °C for 4.5 h, poured into a mixture of 100 mL of ether and 30 mL of saturated ammonium sulfate, and thoroughly shaken. The organic phase was washed with 1 N HCl (2 × 30 mL), water (30 mL), saturated $NaHCO_3$ (2 × 30 mL), and brine (30 mL) and dried (K_2CO_3). Removal of the solvent gave 2.140 g of a pale yellow oil, which was separated by PTLC (three 40 cm × 20 cm silica gel plates, 20% EtOAc/hexanes, developed twice, R_f 0.35) to yield a colorless oil (0.929 g, 65%) which was dissolved in 1.5 mL of hexanes and allowed to crystallize at −20 °C, 0.888 g (62%), mp 56–58 °C. A second recrystallization raised the melting point to 63–64 °C: ^{1}H NMR ($CDCl_3$) δ −0.09 (s, 9), 0.86 (AA′XX′, 2), 1.68 (s, 3), 3.18 (s, 3), 3.30 (s, 2), 3.87 (s, 3), 4.14 (AA′XX′, 2), 5.84 (d of q, J = 11.1, 1.2 Hz, 1), 6.24 (d, J = 13.3 Hz, 1), 6.69 (s, 2), 6.94 (d of q, J = 13.3, 11.1 Hz, 1); ^{13}C NMR ($CDCl_3$) δ −1.7 (q), 16.5 (q), 17.3 (t), 36.6 (q), 45.5 (t), 56.0 (q), 63.7 (t), 107.6 (d), 111.2 (d), 119.0 (s), 121.2 (d), 123.9 (d), 133.4 (d), 137.8 (s), 138.4 (s), 155.1 (s), 155.4 (s).

Anal. Calcd for $C_{20}H_{29}O_3NClBrSi$: C, 50.58; H, 6.16. Found: C, 50.81; H, 6.12.

1′-Ethoxyethyl (2*S*)-3-(1′-Ethoxyethoxy)-2-methylpropionate (25). A solution of *S*-(+)-**24**[14] (1.20 g, 11.5 mmol) in 10 mL of ether was cooled to 0 °C and treated with 10 mL of ethyl vinyl ether (distilled from K_2CO_3) and 1 mg of *p*-toluenesulfonic acid. After stirring at 0 °C for 20 min the mixture was allowed to warm to 25 °C and stirred for 1 h. The solution was quenched in 10% $NaHCO_3$ (20 mL) and the layers separated. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to give 2.7 g (95%) of crude product: IR (film) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.87 (q, 1), 4.63 (q, 1), 3.2–3.9 (m, 6), 2.73 (sextet, 1), 1.05–1.5 (m, 15). This crude material was used for the next step.

(27) It was found advantageous, on occasion, to add 100 mg of hydroquinone prior to concentration.

(2*R*)-(+)-3-(1′-Ethoxyethoxy)-2-methylpropanol (26). A solution of the above crude ester (2.20 g, 8.87 mmol) in 10 mL of THF was added to a solution of $LiAlH_4$ (0.30 g, 7.9 mmol) in 25 mL of THF cooled to 0 °C. The mixture was stirred at 0 °C for 30 min and then warmed to 25 °C for 2 h. The hydride solution was quenched sequentially with water (0.3 mL), NaOH solution (15%, 0.3 mL), and water (1 mL). The resulting suspension was removed by filtration and the clean filtrate was dried (Na_2SO_4) and concentrated to give 1.16 g (85%) of *R*-(+)-**26** as an oil. Purification was performed using PTLC on silica gel with dichloromethane as eluent: $[\alpha]_D^{25}$ +7.82° (*c* 10.9, $CHCl_3$); IR (film) 3600–3200, 3000–2800, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.60 (q, 1), 3.20–3.80 (m, 6), 2.9 (br s, 1), 1.95 (octet, 1), 1.25 (d, J = 5 Hz, 3), 1.20 (t, J = 8 Hz, 3), 0.90 (d, J = 7 Hz, 3).

(2*R*)-(-)-Benzyl 3-(1′-Ethoxyethoxy)-2-methylpropyl Ether (27). Alcohol **26** (1.50 g, 9.3 mmol) was dissolved in 30 mL of THF and cooled to 0 °C. Potassium *tert*-butoxide (1.30 g, 11.6 mmol) was added and the mixture stirred for 20 min at 0 °C. Benzyl bromide (1.50 mL, 12.6 mmol) was added and the mixture was allowed to warm to 25 °C and stirred overnight. The white suspension was poured into 50 mL of ether and 30 mL of water; the organic layer was separated and washed with brine. Drying (Na_2SO_4) and concentration gave an oily residue which was eluted through a silica gel column with dichloromethane. The clear oil, $[\alpha]_D^{25}$ −1.07° (*c* 11.06, $CHCl_3$), was used for the next step.

(*S*)-(-)-3-Benzyloxy-2-methylpropanol (28). The ether (-)-**27** (2.7 g, 10.7 mmol) was dissolved in 10 mL of THF, cooled to 0 °C and then treated with 1 N HCl (10 mL) and stirred for 3 h at room temperature. The mixture was poured into 20 mL of water and 60 mL of ether and the layers were separated. The aqueous layer was extracted with 30 mL of ether and the combined organic layers were washed with 20 mL of 10% $NaHCO_3$ and then 20 mL of brine. After drying (Na_2SO_4) and concentration, an oil was obtained, 1.45 g (87% from **26**) which was purified by eluting through silica gel first with hexane then with ether: $[\alpha]_D^{25}$ −11.3° (*c* 16.05, $CHCl_3$); IR (film) 3600–3200, 3000–2800, 1460, 1100, 1050, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15 (s, 5) 4.38 (s, 2), 3.3–3.7 (m, 4), 2.7 (br s, 1), 2.0 (octet, 1), 0.9 (d, J = 7 Hz, 3). No further purification was performed, and this material was carried on to the next step.

(*R*)-(-)-3-Benzyloxy-2-methylpropanal (29). Dimethyl sulfoxide (0.34 mL, 4.79 mmol) was added dropwise to oxalyl chloride (0.2 mL, 2.3 mmol) in 10 mL of dry dichloromethane cooled to −60 °C. The mixture was stirred for 15 min and alcohol **28** (0.36 g, 2.0 mmol) in 5 mL dichloromethane was added dropwise. After stirring at −60 °C for 15 min, 1.4 mL of triethylamine was added slowly and the suspension was allowed to warm to −25 °C and stirred at this temperature for 15 min. Ether (30 mL) and water (20 mL) were added and the layers separated. The organic layer was washed with water and then with brine, dried (Na_2SO_4), filtered, and concentrated to give 0.35 g (98%) of (-)-**29** as an oil: $[\alpha]_D^{25}$ −28.17° (*c* 1.4, $CHCl_3$); IR (film) 2740, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.67 (d, J = 2 Hz, 1), 7.27 (s, 5), 4.50 (s, 2), 3.63 (d, J = 5 Hz, 2), 2.6 (m, 1), 1.1 (d, J = 7 Hz, 3). This material was carried forward without further purification.

(*R*)-(+)-5-Benzyloxy-2,4-dimethyl-(*E*)-2-pentenal (30). Butyllithium (2.23 M, 3.82 mL, 8.52 mmol) was added to a solution of diisopropylamine (1.19 mL, 8.53 mmol) in 20 mL of THF cooled to −78 °C. The mixture was stirred for 20 min at −78 °C and *N*-cyclohexylpropylimine (1.18 g, 8.5 mmol) in 10 mL of THF was added dropwise. The solution was stirred for 15 min and the aldehyde **29** (1.33 g, 7.45 mmol) in 10 mL of THF was added dropwise. The mixture was stirred at −78 °C for 1 h and allowed to warm to 25 °C over 2 h. Oxalic acid dihydrate (2.0 g, 15.9 mmol) in 30 mL of methanol was added to the mixture which had been cooled to 0 °C. The resulting suspension was heated to reflux for 1 h; 10 mL of water was added and the reflux continued for 1.5 h. The mixture was cooled to 25 °C and poured into 40 mL of ether and 20 mL of water. The aqueous phase was extracted with 30 mL of ether; the organic layers were combined, washed with saturated $NaHCO_3$ and then brine, dried (Na_2SO_4), and concentrated to give 1.01 g (62%) of (+)-**30** as an oil which was purified by passing down a silica gel column with dichloromethane: $[\alpha]_D^{25}$ 26.04° (*c* 1.80, $CHCl_3$); IR (film) 3000–3200, 2800–3000, 2710, 1690, 1650, 1460, 1370, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.42 (s, 1), 7.30 (s, 5), 6.33 (d of q, J = 1, 9 Hz, 1), 4.50 (s, 2), 3.5 (m, 2), 2.8–3.3 (m, 1), 1.80 (d, J = 2 Hz, 3), 1.17 (d, J = 7 Hz, 3).

(*R*)-(+)-5-Benzyloxy-2,4-dimethyl-(*E*)-2-pentenol (31). Sodium borohydride (0.3 g, 7.9 mmol) was dissolved in 20 mL of ethanol and cooled to 0 °C. The aldehyde (+)-**30** (1.01 g, 4.63 mmol) in 10 mL of ethanol was added dropwise. The mixture was allowed to warm to 25 °C and stirred for 3 h. Acetic acid (2.0 mL) in 10 mL of water was added and the mixture was poured into 30 mL of ether and 20 mL of water. The aqueous layer was extracted with 30 mL of ether and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give 0.971 g (95%) of the alcohol **31**: $[\alpha]_D^{25}$ 21.5° (*c* 1.69, $CHCl_3$); IR (film) 3600–3200, 3000–3100, 3000–2800, 1450, 1360, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 3), 5.17 (d of heptet, J = 10, 1 Hz, 1), 4.47 (s, 2), 3.93 (br s, 2), 3.5 (m, 2), 2.8 (heptet, J = 7 Hz, split into dodecent, J = 2 Hz, 1), 2.0 (br s, 1), 1.67 (d, J = 1 Hz, 3), 1.03 (d, J = 7 Hz, 3).

(2*S*,3*S*,4*R*)-(-)-5-Benzyloxy-2,3-epoxy-2,4-dimethylpentanol (32). Titanium tetraisopropoxide (1.32 mL, 4.44 mmol) was added to 25 mL of dichloromethane at −25 °C and then diethyl (+)-tartrate (0.8 mL, 0.47 mmol) was added dropwise. The mixture was stirred for 10 min at −25 °C, and unsaturated alcohol (+)-**31** (0.977 g, 4.44 mmol) in 5 mL of dichloromethane was added dropwise. Dry *tert*-butyl hydroperoxide was prepared by dissolving (1.14 g, 8.85 mmol of 70% solution) it in 40 mL of dichloromethane and stirring over sodium sulfate. Filtration gave a clear dichloromethane solution which was evaporated (in vacuo), and an additional 20 mL of dichloromethane was added. The latter solution was then added to the above alcohol–tartrate–titanium mixture and placed in the freezer (−25 °C) overnight. The reaction flask from the freezer was placed in a −25 °C bath and an aqueous solution of tartaric acid (20 mL, 10%) was added; the mixture was stirred for 30 min at −25 °C, then allowed to warm to 25 °C over an hour. The mixture was poured into 50 mL of dichloromethane and 30 mL water. The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was dissolved in 50 mL of ether and cooled to 0 °C. A solution of sodium hydroxide (30 mL, 1 N) was added. The mixture was stirred for 30 min at 0 °C and poured into 40 mL of ether and 20 mL of water; the ethereal layer was separated, washed with water and then brine, dried (Na_2SO_4), filtered, and concentrated to give 0.973 g (93%) of (-)-**32** as an oil: $[\alpha]_D^{25}$ −14.03° (*c* 2.05, $CHCl_3$); IR (film) 3200–3600, 3000–3080, 2800–3000, 1450, 1100, 1040, 730, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23 (s, 5), 4.45 (s, 2), 3.60 (m, 4), 2.82 (d, J = 9 Hz, 1), 2.1 (br s, 1), 1.9 (m, 1), 1.33 (s, 3), 1.10 (d, J = 7 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 138.13, 128.14, 127.39, 127.15, 73.09, 72.74, 65.50, 63.86, 62.05, 33.27, 15.05, 14.64.

Anal. Calcd for $C_{14}H_{20}O_3$ (236.3137): C, 71.16; H, 8.53. Found: C, 70.85; H, 8.81.

(2*R*,3*S*,4*S*)-(-)-5-*tert*-Butyldimethylsilyloxy-3,4-epoxy-2,4-dimethylpentyl Benzyl Ether (33). Imidazole (0.7 g, 10.3 mmol) was added to a stirred solution of epoxy alcohol **32** (0.973 g, 4.12 mmol) in 10 mL of DMF (distilled from CaH_2). *tert*-Butyldimethylsilyl chloride (0.7 g, 4.64 mmol) was added and the mixture stirred for 24 h at 25 °C. The contents was poured into 50 mL of ether and 50 mL of water and the layers were separated. The ether layer was washed with water (2 × 50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The ether solution was dried Na_2SO_4) and concentrated. The crude material was purified on a Waters Prep 500 using a 1-in. column and eluting with 5% ether–hexane to give 1.30 g (90%) as an oil; $[\alpha]_D^{25}$ −4.46° (*c* 6.28, $CHCl_3$); IR (film) 3000–3200, 2800–3000, 1470, 1255, 1100, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (s, 5), 4.45 (s, 2), 3.55 (d, J = 1 Hz, 2), 3.35 (d, J = 6 Hz, 2), 2.63 (d, J = 10 Hz, 1), 2.1–1.7 (m, 1), 1.21 (s, 3), 1.05 (d, J = 7 Hz, 3) 0.85 (s, 9), 0.05 (s, 6); ^{13}C NMR ($CDCl_3$) δ 138.31, 128.15, 127.33, 127.21, 73.15, 72.91, 67.83, 64.33, 61.99, 35.50, 25.97, 18.44, 14.82, 9.39, −5.27.

Anal. Calcd for $C_{20}H_{34}O_3Si$ (350.5781): C, 68.52; H, 9.78. Found: C, 68.60; H, 9.94.

(2*R*,3*S*,4*S*)-(-)-5-*tert*-Butyldimethylsilyloxy-3,4-epoxy-2,4-dimethylpentanal (34). Benzyl ether **33** (1.035 g, 2.96 mmol) was dissolved in 20 mL of anhydrous ether in a 100-mL three-necked flask containing a magnetic stirrer. Ammonia (50 mL) distilled from sodium was condensed in the flask and cooled to −78 °C. Sodium metal (0.4 g, 17.4 mmol) was added and the mixture stirred for 2 h at −78 °C. Solid ammonium chloride (~2 g) was added until the blue color faded. The ammonia was allowed to evaporate and 30 mL of water and 50 mL of ether was added. The ether layer was separated and washed with 25 mL of water and 20 mL of brine, dried (Na_2SO_4), and concentrated to give 0.716 (93%) of **34** as an oil. HPLC analysis using 10% acetone–hexane at 2 mL/min showed >99% diastereomeric purity: $[\alpha]_D^{25}$ −5.33° (*c* 1.59, $CHCl_3$); IR (film) 3600–3200, 3000–2800, 1470, 1460, 1250, 1100, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53 (m, 4), 2.62 (d, J = 9 Hz, 1), 1.87 (br s, 1) 1.7 (m, 1), 1.33 (s, 3), 1.05 (d, J = 6 Hz, 3), 0.95 (s, 9), 0.05 (s, 6); ^{13}C NMR ($CDCl_3$) δ 67.95, 65.03, 64.21, 61.82, 35.20, 25.80, 18.21, 14.82, 14.30, −5.44.

Anal. Calcd for $C_{13}H_{28}O_3Si$ (260.452): C, 59.95; H, 10.84. Found: C, 60.23; H, 10.80.

(2*R*,3*S*,4*S*)-(+)-5-*tert*-Butyldimethylsilyloxy-3,4-epoxy-2,4-dimethylpentanal (36). The Collins reagent was prepared by adding chromium trioxide (8.33 g, 83.3 mmol) to pyridine (14 mL) in 300 mL of dichloromethane at 0 °C. The mixture was stirred at 0 °C for 30 min and then transferred via cannula to a 1-L Morton flask, fitted with a mechanical stirrer. The flask and its contents were cooled to −25 °C and the alcohol **34** (2.0 g, 7.69 mmol) in 15 mL of dichloromethane was added dropwise to the rapidly stirred Collins reagent. Stirring was

continued for 30 min at −25 °C, 300 mL of hexane was added, and the mixture was filtered through 100 g of Florisil. The filtrate was concentrated to give 1.673 g (85%) of the aldehyde as an oil, 94.2% by GLC: $[\alpha]^{25}_D$ 18.7° (*c* 6.2, $CHCl_3$); IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.64 (d, *J* = 1 Hz, 1), 3.57 (AB q, *J* = 5, 11 Hz, 2), 2.77 (d, *J* = 8 Hz, 1), 2.33 (m, 1), 1.84 (d of d, *J* = 6, 2 Hz, 1), 1.25 (d, *J* = 7 Hz, 3), 1.25 (s, 3), 0.80 (s, 9), 0.02 (s, 6); ^{13}C NMR ($CDCl_3$) δ 200.54, 66.96, 61.30, 59.90, 46.23, 25.62, 18.01, 14.35, 11.72, −5.57. The product was used in the next step without further purification.

(3*S*,4*R*,5*S*,6*S*)-(+)-37a. Lithium diisopropylamide (15.25 mmol) in 30 mL of THF was cooled to −78 °C, and ethyl dithioacetate (1.78 mL, 15.25 mmol) was added dropwise with stirring. The solution was stirred at −78 °C for 30 min and cooled to −120 °C. A solution of the aldehyde **36** (1.973 g, 7.64 mmol in 15 mL of THF was cooled to −120 °C and transferred via cannula to the thioenolate solution. The mixture was stirred for 6 h at −120 °C; acetic acid (1 mL) was added and the mixture poured into 70 mL of ether and 30 mL of saturated $NaHCO_3$ solution. The aqueous phase was extracted with 50 mL of ether and the combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by chromatography on a Waters Prep 500 with 15% acetone–hexane on the 1-in. column at 100 mL/min to give 1.67 g (62%) of a yellow oil and 0.3 g of recovered starting aldehyde **36**: $[\alpha]^{25}_D$ +36.8° (*c* 5.98, $CHCl_3$); IR (film) 3200–3600, 2800–3000, 1465, 1260, 1100, 840, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.0 (quint, *J* = 2 Hz, 1), 3.4 (AB q, *J* = 11, 3 Hz, 2), 3.1 (q, 2), 3.1 (d, 2), 2.66 (d, *J* = 9 Hz, 1), 1.44 (m, 1), 1.24 (t, 3), 1.24 (s, 3), 1.08 (d, 3), 0.90 (s, 9), 0.04 (s, 6); ^{13}C NMR ($CDCl_3$) δ 127.91, 73.03, 68.13, 63.63, 61.82, 55.92, 37.53, 30.46, 25.74, 18.09, 14.70, 12.66, 11.90, −3.86, −5.50. This material was carried on without further purification to the next step.

Ethoxyethyl Ether of 37a as a Mixture of Diastereomers. The dithioester **37a** from above (1.304 g, 3.45 mmol) was dissolved in 10 mL of dry ether and the solution cooled to 0 °C. Ethyl vinyl ether (10 mL, distilled from K_2CO_3) was added along with a single crystal of *p*-toluenesulfonic acid and the mixture stirred for 10 min at 0 °C and 1 h at 25 °C. A solution of $NaHCO_3$ (10%, 1 mL) was added and the resulting solution poured into 50 mL of ether and 20 mL of saturated $NaHCO_3$ solution. The ether layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified on PTLC (silica gel) using 15% acetone–hexane to give 1.252 g (81%) of product as a mixture of diastereomers. No attempt was made at this stage to separate this material.

(4*S*,5*R*,6*S*,7*S*)-(+)-39A and -(+)-39B. The mixture of diastereomeric dithioesters from above (1.710 g, 3.8 mmol) was dissolved in dry THF and cooled to −25 °C. Ethylmagnesium iodide (2 M, ether, 4.17 mL, 8.34 mmol) was added slowly and the resulting white suspension was stirred for 2 h at −25 °C. *N*-Methylaminopyridineformamide (1.78 mL, 15.1 mmol) was added to the suspension at −25 °C and the mixture stirred for 2 h. A solution of $NaHCO_3$ (2 mL, 10%) was added and the total contents poured into 100 mL of ether and 30 mL of $NaHCO_3$ solution. The layers were separated and the organic phase was washed with brine, dried (Na_2SO_4), and evaporated. The residue was purified by PTLC with 10% acetone–hexane (two elutions) to give two bands corresponding to each diastereomer, total yield 1.6026 g (83%). The faster moving band **39A** gave $[\alpha]^{25}_D$ +112.72° (*c* 1.41, $CHCl_3$); IR (film) 2800–3000, 2715, 1715, 1450, 1370, 1250, 1090, 830, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.78 (s, 1), 4.50 (q, 1), 3.8 (2 t, *J* = 3, 9 Hz, 1), 3.48 (s, 2), 3.38 (q, 2), 2.70 (d, *J* = 9 Hz, 1), 1.7–2.6 (m, 7), 0.83 (s, 9), 0.01 (s, 6); ^{13}C NMR ($CDCl_3$) δ 187.82 (d), 102.10 (d), 77.00 (d), 69.88 (s), 68.07 (t), 62.87 (d), 62.29 (s), 61.99 (t), 37.18 (d), 36.01 (t), 25.91 (q), 23.40 (t), 21.06 (t), 19.84 (q), 18.38 (s), 15.52 (q), 15.40 (q), 14.70 (q), 13.83 (q), 13.65 (q), −5.27 (q).

Anal. Calcd for $C_{24}H_{48}O_5S_2Si$ (508.86116): C, 56.65; H, 9.51. Found: C, 57.17; H, 9.61.

The slower moving band **39B** gave $[\alpha]^{25}_D$ +61.82° (*c* 1.43, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.87 (s, 1), 4.63 (q, *J* = 5 Hz, 1), 4.07 (m, 1), 3.45 (s, 2), 3.4 (q, 2), 2.73 (d, *J* = 9 Hz, 1), 1.8–2.6 (m, 7); ^{13}C NMR ($CDCl_3$) δ 187.12 (d), 97.61 (d), 73.21 (d), 69.47 (s), 67.88 (t), 63.05 (d), 67.76 (s), 59.95 (t), 35.95 (t), 34.85 (d), 25.91 (q), 23.05 (t), 21.65 (t), 19.49 (q), 18.32 (s), 15.23 (q), 15.05 (q), 13.65 (q), 13.13 (q), −5.32 (q).

Anal. Found: C, 57.01; H, 9.59.

Coupling of Diene Bromide 22 to Epoxy Aldehyde 39A To Form 41a,b. The following was performed using the fast-moving epoxy aldehyde **39A**. To a stirred solution of 237 mg (0.50 mmol) of diene bromide **22** in 10 mL of anhydrous THF cooled to −120 °C was added 1.64 mL (1.13 mmol) of *tert*-butyllithium in pentane (0.69 M) at a slow dropwise rate. The resulting pale yellow solution was stirred at −120 °C (ethanol–liquid N_2) for 30 min and then allowed to warm slowly to −95 °C over a 30-min period. The solution turned to deep yellow and was again recooled to −120 °C. Addition of epoxy aldehyde **39A** (254 mg, 0.50 mmol) was performed by precooling a solution in 10 mL of THF to −120 °C and transferring this material in a single portion through a Teflon cannula. The reaction mixture became nearly colorless and stirring was continued at −120 °C for 30 min followed by stirring at −78 °C for 1 h. At this temperature 100 μL of acetic acid was introduced in 1 mL of THF and stirring continued for 1–2 min, after which the mixture was poured into 10 mL of saturated $NaHCO_3$ solution. The mixture was extracted (2 × 30 mL) with ether and (2 × 30 mL) ethyl acetate. The combined organic phase was washed with 10 mL of saturated $NaHCO_3$, 10 mL of brine (buffered at pH 9), dried (K_2CO_3), and evaporated to give 500 mg of a yellow oil. Preparative TLC on silica gel using 20% acetone–hexane (two elutions) gave the desired product as the lowest of three bands (R_f 0.3). The yield after PTLC was 330 mg (73%). HPLC analysis (μ-Porasil, 20% ethyl acetate–hexane, 2.0 mL/min) showed the presence of two products, **41a** and **41b**, in nearly 1:1 ratio, with retention times of 3.9 and 3.5 min, respectively. The epimeric alcohols were separated using radial chromatography on silica gel (Chromatotron)[28] with 30% ethyl acetate–hexane. Three recycles were necessary to effect complete separation of pure (HPLC analyses) **41a** (slow eluting) and **41b** (fast eluting). Because of lability of the C-10 hydroxy pair, only the spectra (^1H, ^{13}C) were recorded (Table II).

Table I. Optical Rotations for Recovered 2-Phenylbutanoic Acid after Reaction with 41 (Slow and Fast Eluting Alcohols)

wavelength[a]	slow eluting alcohol	fast eluting alcohol
From 39A (Epimer at C-7 Ethoxyethyl)		
589 (Na)	+0.069	−0.022
578 (Hg)	+0.073	−0.024
546	+0.083	−0.027
436	+0.157	−0.049
365	+0.260	−0.083
From 3B (Epimer at C-7 Ethoxyethyl)		
589 (Na)	+0.008	−0.004
578 (Hg)	+0.009	−0.006
546	+0.010	−0.007
436	+0.015	−0.015
365	+0.025	−0.028

[a] A Perkin-Elmer 241 automatic polarimeter was employed thermostated to 23.7 °C.

Determination of Absolute Configuration at C-10 of 41a and 41b via Horeau Method. Each of the alcohols **41a** (slow eluting, 3.9 min) and **41b** (fast eluting, 3.5 min) was treated separately as follows. A solution of 25 mg of the C-10 hydroxy compound in 300 μL of anhydrous pyridine containing 36 mg of racemic (*RR*, *SS*, meso) 2-phenylbutanoic anhydride was stirred at room temperature for 24 h. Water (50 μL) was added and the solution stirred for another 30 min to destroy excess anhydride. Sodium hydroxide (1 N, 250 μL) was added and stirring continued for 15 min and the mixture extracted (2 × 5 mL) with chloroform. The chloroform solution was extracted with 5 mL of saturated $NaHCO_3$ and the aqueous layers were combined and acidified to pH 2–3 with 1 N HCl. The acidic solution was extracted (2 × 10 mL) with benzene and the benzene solution concentrated at reduced pressure. The residue was dissolved and diluted to 1.00 mL in benzene in a volumetric flask; this solution of 2-phenylbutanoic acid was examined for its optical rotation. Since **41a** and **41b** were similarly treated the rotations observed at various wavelengths are given in Table I. Furthermore, **41c** and **41d** were separated from the reaction of **22** with **39B**. From the data obtained in Table I, the slow-eluting alcohol gave the dextrorotatory acid and corresponds to an α-C-10 hydroxyl, while the faster eluting alcohol corresponds to the β-C-10 hydroxyl. In the case of each epimer for C-7 ethoxyethyl (**39A**, **39B**), the slower eluting alcohol also possessed the desired absolute configuration (α) at C-10.

Methyl Ether 43. To a −20 °C slurry of 50 mg of NaH in 3.0 mL of anhydrous THF was added a solution of 10 mg of **41a** in 1.0 mL of THF. After 15 min, freshly distilled methyl iodide (0.5 mL) was added and the reaction mixture stirred at −20 °C for 10 min and allowed to warm to ambient overnight. The mixture was poured into cold saturated $NaHCO_3$ (10 mL) and extracted with ether (3 × 20 mL). The combined extracts were washed with pH 9 buffered brine (5 mL) and dried over K_2CO_3. Evaporation, in vacuo, gave 10 mg of a pale yellow oil, which on HPLC examination (μ-Porasil, 10% ethyl acetate–hexane, 2.0 mL/min) showed a single peak at t_R 3.5 min. When a mixture of **41a** and **41b** was treated in an identical fashion with NaH–methyl iodide, HPLC analysis showed two roughly equal peaks at t_R 3.5 and 3.1 min, the latter

(28) Harrison Research, 840 Moana Ct., Palo Alto, Calif.

Table II. NMR Spectral Data (^1H, ^{13}C)[a]

position	41a		41b[b]	43		44		45		46[c]		47	
	^1H	^{13}C	^1H	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
C-1													164.75
C-2												5.71	121.37
C-3	3.50, 3.65	68.2	3.54, 3.61	3.35, 3.59	68.2	3.45, 3.58	67.4	8.82	199.9	8.82	199.79	6.42	148.76
3-OSi$\underline{CH}_3$	0.06	−5.2	0.06	0.06	−5.1								
3-OSi$\underline{C}(CH_3)_3$		18.4			18.4								
3-OSi$\underline{C}(\underline{CH}_3)_3$	0.90	26.2	0.90	0.90	26.0								
C-4		62.4			62.4		61.9		63.3		63.34		59.84
4-CH_3	1.37	15.2	1.38	1.38	15.7	1.41	15.6	1.49	15.6	1.49	15.58	1.29	16.16
C-5	2.84	63.3	2.88	2.84	63.3	2.93	64.4	2.86[d]	65.1	2.81	65.27	2.60	68.18
C-6	2.00	38.1	2.00	1.90	38.2	1.90	38.2	1.90[d]	38.0	1.90[d]	38.06	1.85[d]	36.54
6-CH_3	1.07	13.2	1.09	1.08	13.4	1.11	13.0	1.09	12.1	1.10	10.91	1.13	13.83
C-7	4.10	77.0	4.10	4.01	76.2	4.12	77.0[d]	4.07[d]	74.4	4.1[d]	74.67	3.96[d]	80.09
7-O$\underline{CH}(CH_3)OCH_2CH_3$	4.88	100.5	4.84	4.92	100.6	4.92	100.4	4.07[d]	100.0	4.90	100.12	4.84	102.46
7-O$\underline{CH}(\underline{CH}_3)OCH_2CH_3$	1.26	18.4	1.28	1.28	20.9	1.28	20.9	1.23	20.9	1.23	20.89	1.26	21.24
7-OCH(CH$_3$)O$\underline{CH}_2$CH$_3$	3.50	61.6	3.50	3.50	61.6	3.60	61.6	3.45	61.9	3 46	62.00[d]	3.51	62.46
7-OCH(CH$_3$)O$\underline{CH}_2\underline{CH}_3$	1.22	15.6	1.19	1.18	15.7	1.21	15.6	1.21	15.6	1.22	15.58	1.25	15.64
C-8	1.97, 2.15	38.8	2.10	1.95, 2.09	38.3	1.94, 2.12	38.5	2.08, 2.11	38.7	2.00, 2.11[d]	38.47	2.25, 2.54[d]	40.10
C-9		67.6			65.6		65.4		63.2		63.05		67.19
9-S$\underline{CH}_2$CH$_3$	2.70	20.8, 24.0	2.70	2.70	23.6, 24.2	2.70	24.4, 23.6	2.66	23.6, 24.2	2.67	23.58, 24.22	2.76	22.76, 25.10
9-SCH$_2\underline{CH}_3$	1.22, 1.26	13.9	1.19, 1.22	1.18, 1.22	13.8	1.18, 1.21	13.9	1.18, 1.21	13.8	1.20, 1.22	12.78	1.25	14.06, 15.05
C-10	4.23	78.3	4.23	3.87	88.4	3.82	88.4	3.79	88.6	3.82	88.50	3.94[d]	88.97
10-OH	3.03		3.68										
10-OCH_3				3.25	56.8	3.24	56.7	3.24	56.8	3.25	56.97	3.27	56.86
C-11	6.00	139.3	5.97	5.76	131.2	5.63	131.8	5.70	131.6	5.85	128.15	5.74	128.85
C-12	6.59	129.5	6.59	6.49	128.3	6.48	127.4	6.48	127.2	6.41	131.18	6.49	132.64
C-13	6.02	126.5	6.03	6.01	126.2	5.99	125.2	5.98	125.2	5.97	126.16	6.02	125.34
C-14		139.3			139.2		139.1		139.2		137.49		137.90
14-CH_3	1.70	16.5	1.70	1.72	16.6	1.74	16.8	1.75	16.7	1.73	16.51	1.64	17.39
C-15	3.33	46.2	3.33	3.34	46.1	3.31	46.9	3.31	46.8	3.38	46.06	3.3[d]	46.46
C-16		137.7			137.6		139.1		139.2		140.29		141.52
C-17	6.67	121.5	6.68	6.69	121.4	6.16	104.6	6.16	104.4	6.85	121.90	6.79	122.37
C-18		141.4			141.3		145.7		145.7		141.52		140.12
C-20		111.4			111.4		101.5		101.5		119.04		117.93
C-21		155.7			155.6		155.1		155.0		155.94		155.76
Ar-OCH_3	3.88	56.4	3.88	3.89	56.4	3.86	56.2	3.86	56.1	3.92	56.45	3.98	56.57
C-22	6.67	119.3	6.67	6.69	119.2	6.16	104.6	6.16	104.4	6.79	112.38	6.69	112.38
19-CH_3	3.18	37.0	3.18	3.18	36.9	2.89	30.6	2.89	30.7	3.20	36.01	3.22	36.01
19-$\underline{COOCH}_2ClI_2Si(CH_3)_3$		155.7			155.6								
19-$\underline{COOCH}_2CH_2Si(CH_3)_3$	4.14	64.1	4.15	4.15	64.0								
19-COOCH$_2\underline{CH}_2$Si(CH$_3$)$_3$	0.93	17.7	0.93	0.91	17.6								
19-COOCH$_2\underline{CH}_2$Si$(\underline{CH}_3)_3$	−0.09	−1.4	−0.10	−0.10	−1.5								

[a] Data are given in ppm, relative to Me_4Si standard (^1H) or $CDCl_3$ signals (^{13}C). All spectra were measured in $CDCl_3$. [b] ^{13}C spectrum not available. [c] Signals due to 19-(α-diethylphosphonyl)acetyl group: ^1H NMR 2.96 ($CO\underline{CH}_2P(O)(OEt)_2$), 4.19 ($P(O)(O\underline{CH}_2CH_3)_2$), 1.35 ($P(O)(OCH_2\underline{CH}_3)_2$); ^{13}C NMR 164.82 ($\underline{C}OCH_2P(O)(OEt)_2$), 62.82 ($P(O)(O\underline{CH}_2CH_3)_2$), 32.86 ($CO\underline{CH}_2P(O)(OEt)_2$), 13.83 ($P(O)(OCH_2\underline{CH}_3)_2$). [d] Signal partially obscured by other signals; assignment supported by decoupling experiments, known precedents, and peak integration values.

corresponding to the β-C-10-methoxy derivative. These could be separated on silica gel using radial chromatography (30% ethyl acetate–hexane, three recycles). Similarly, **41**, derived from the C-7 epimer **39B**, after methylation of the C-10 hydroxy mixture, showed on HPLC analysis, two equal peaks at t_R 2.8 and 2.3 min for the α-methoxy and β-methoxy, respectively. Only the α-methoxy derivative **43** was carried on to the next step. Proton and carbon spectra for **43** are given in Table II.

Amino Alcohol (+)-44. To a 0 °C solution, under argon, of 261 mg (1.0 mmol) of anhydrous tetrabutylammonium fluoride (Fluka, dried by heating the trihydrate at 70–80 °C under 0.002 mmHg overnight) in 5.0 mL of anhydrous THF, was added a solution of 150 mg of **43** in 10 mL of THF. The solution was stirred for 30 min at 0 °C and overnight at ambient, after which it was poured into 10 mL of cold saturated $NaHCO_3$. Extraction (2 × 30 mL) with ether and with ethyl acetate (20 mL) and combining the organic extracts was followed by washing with pH 9 buffered brine. Drying (K_2CO_3) and concentration gave a residue, 90 mg (85%), which showed a single peak (HPLC, μ-Porasil, 25% ethyl acetate–hexane, 3.0 mL/min) with t_R 5.0 min. Similarly, both epimers at C-10, **41a** and **41b**, were desilylated as a mixture, and HPLC showed two equal peaks at 5.0 and 6.0 min, corresponding to the α-methoxy and β-methoxy, respectively. The C-10 methoxy epimers could be separated by radial chromatography on silica gel using 20% ethyl acetate–hexane on a single elution. The β-C-10 methoxyamino alcohol (+)-**44** had $[\alpha]^{25}_D$ +24.1° (*c* 1.89, ethanol) while the α-C-10 methoxyamino alcohol had $[\alpha]^{25}_D$ +17.4° (*c* 2.31, ethanol). Spectral assignments are given for (+)-**44** in Table II.

Amino Aldehyde (+)-45. A modified Mukaiyama[23] procedure was employed. A stock solution of *tert*-butoxymagnesium bromide was prepared by adding 92.5 mg (1.25 mmol) of freshly distilled *tert*-butyl alcohol to a solution of 4.0 mL of 0.25 M isopropylmagnesium bromide in THF at 0 °C. Under argon at 0 °C, 0.81 mL of the butoxymagnesium bromide solution (0.2 mmol, 2.5 equiv) was placed in a reaction vessel; to this was added 52.7 mg (0.081 mmol) of the amino alcohol (+)-**44** in 0.5 mL of THF. The mixture was stirred for 10 min at 0 °C, followed by the addition of 47.7 mg of 1,1′-(azodicarbonyl)dipiperidine (2.5 equiv) in 0.5 mL of THF. The solution was stirred in an insulated cold bath such that the temperature rose gradually to 18 °C over a 12-h period. The mixture was poured into 10 mL of saturated $NaHCO_3$ and extracted (3 × 20 mL) with ether followed by 20 mL of ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified on PTLC (30% acetone–hexane) to give 32 mg (61%), R_f 0.4, and 5 mg of starting alcohol, R_f 0.3. The aldehyde had $[\alpha]^{25}_D$ +55.4° (*c* 1.32, CH_2Cl_2). Spectral data are given in Table II. In several separate experiments the yield of this oxidation ranged from 61 to 77%.

Phosphonoacetamide (+)-46. To a −25 °C solution, under argon, of 28.7 mg (0.044 mmol) of the amino aldehyde (+)-**45** in 5.0 mL of freshly distilled methylene chloride was added 40 μL of pyridine. The 1,1-diethylphosphonoacetyl chloride was prepared by treating diethyl carboxymethyl phosphonate[29] with excess oxalyl chloride in benzene for 5 h at 25 °C, evaporating solvent, and redissolving in dry methylene chloride. The acid chloride (40 mg/mL of CH_2Cl_2) was added to the solution containing pyridine and (+)-**45**, and the resulting solution was allowed to warm to ambient and stirred for 1 h. The mixture was poured into 10 mL of cold saturated $NaHCO_3$ and extracted with ether (3 × 20 mL) followed by extraction with 20 mL of ethyl acetate. The combined organic solutions were dried (Na_2SO_4) and concentrated to give a yellow oil which was purified by PTLC (silica gel, 40% acetone–hexane). The major product, R_f 0.1, provided 30.3 mg (83%): $[\alpha]^{25}_D$ +15.85° (*c* 0.555, ethanol); IR (film) 1725, 1665 cm^{-1}. The proton and carbon NMR spectral data are given in Table II.

Macrocyclization to (−)-47. A stock solution of potassium *tert*-butoxide in THF was prepared by adding 27.0 mg of freshly sublimed material to 3.0 mL of THF at room temperature and kept under argon. From this solution, an aliquot (315 μL) was added to 70 mL of anhydrous THF and the solution cooled to −120 °C. The cold solution was added, via syringe, to a solution of 20 mg of phosphono aldehyde (+)-**46** in 1.0 mL of THF in a dropwise manner. The mixture was stirred at −120 °C for 1 h and then slowly allowed to reach ambient with stirring continuing overnight. After addition of 1.0 mL of saturated $NaHCO_3$, the THF was removed in vacuo, and the residue was treated with 5 mL of water. The aqueous mixture was extracted with ether (4 × 20 mL), then ethyl acetate (2 × 20 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was purified by PTLC using 30% acetone–hexane on silica gel. After two elutions, a single major product was visible (R_f 0.4) which gave 10.1 mg (62%) and 3 mg of recovered starting material (R_f 0.1); $[\alpha]^{25}_D$ −110.4° (*c* 0.24, ethanol); IR (film) 1665 cm^{-1}. The proton and carbon NMR data are given in Table II.

Cyclic Hydroxy Ketone (−)-48. The macrocycle (−)-**47** from above (7.0 mg, 0.01 mmol) was dissolved in 1.0 mL of freshly distilled acetonitrile (from CaH_2) and 0.5 mL of distilled water. To this, at room temperature, was added, in sequence, 4 mg (0.04 mmol) of calcium carbonate and 8 mg (0.03 mmol) of mercuric chloride. A precipitate formed immediately and the mixture was stirred at room temperature for 3 h and then treated with 5 mL of saturated $NaHCO_3$. Extraction followed using ether (3 × 20 mL) and ethyl acetate (2 × 20 mL) and combining the organic solutions. After drying (Na_2SO_4), the solvents were evaporated, leaving a residue which was immediately taken up in 2.0 mL of THF and cooled to 0 °C. Addition of water (50 μL) and 1 N HCl (100 μL) gave a homogeneous solution which was allowed to warm to 25 °C; stirring was continued for 1 h. Saturated $NaHCO_3$ (2 mL) was added cautiously and the mixture extracted with ether (3 × 20 mL), then ethyl acetate (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was purified on PTLC (silica gel, 30% acetone–hexane) and the band at R_f <0.1 was removed. Dissolving the isolated oily material in ether, then evaporating, gave a colorless solid, 4 mg (67%), mp 113–115 °C; $[\alpha]^{25}_D$ −577° (*c* 0.04, ethanol); IR (film) 3400 br, 1730 cm^{-1} br. Copies of the ^1H NMR (100 MHz) and expansions are given as supplementary material.

(−)-Maysine (3). A solution of 4.4 mg (0.01 mmol) of the hydroxy ketone (−)-**48** in 2.0 mL of freshly distilled dichloromethane (distilled from CaH_2) in an argon atmosphere was cooled to −78 °C. To this was added 15 μL of dry pyridine (from CaH_2) followed by 80 μL of a 25% solution of phosgene in toluene (20 equiv). The reaction was stirred at −78 °C for 1 h and 3 mL of dichloromethane saturated with ammonia was added and stirred for an additional 1 h. The mixture was rapidly allowed to reach room temperature and the solvent removed under reduced pressure. TLC showed (ethyl acetate) a single major product which was coincidental with authentic (−)-maysine. The product was purified by PTLC on silica gel (ethyl acetate, distilled) and eluted four times. The isolated band gave 3 mg of product which solidified after dissolving in ether and removal of solvent under reduced pressure at 25 °C, mp 169–172 °C, $[\alpha]^{25}_D$ −255° (*c* 0.14, ethanol). The authentic samples from the Takeda laboratory (Japan) gave mp 170–173 °C, $[\alpha]^{25}_D$ −210° (*c* 0.15, ethanol), whereas the sample from the Kupchan laboratory, courtesy of Dr. A. T. Sneden, gave mp 137–141 °C, $[\alpha]^{25}_D$ −173° (*c* 0.023, ethanol).

Comparison of the ^1H NMR spectrum (360 MHz) taken for both synthetic and natural material showed virtual identity throughout the entire ppm range. HPLC comparison of synthetic and natural material also showed identity using several different solvent systems.

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Registry No. (−)-**3**, 52978-28-6; (*E*,*E*)-**6**, 86046-94-8; **7**, 3943-74-6; **8**, 42590-00-1; **9**, 63603-09-8; **10**, 71001-78-0; **11**, 63603-16-7; **12**, 63603-12-3; **13**, 71694-86-5; **14**, 71650-89-0; **15**, 71650-90-3; **16**, 86046-91-5; **17**, 86046-92-6; (*E*)-**18**, 86046-93-7; (*E*)-**19**, 71653-11-7; (*E*,*E*)-**20**, 71653-12-8; (*E*,*E*)-**21**, 71653-13-9; (*E*,*E*)-**22**, 71653-15-1; (*S*)-(+)-**24**, 26543-05-5; **25**, 86046-95-9; **26**, 86046-96-0; **27**, 86046-97-1; (*S*)-(−)-**28**, 63930-46-1; (*R*)-(−)-**29**, 79026-61-2; (*R*)-(+)-**30**, 80885-47-8; (*R*)-(+)-**31**, 80925-22-0; (−)-**32**, 80925-23-1; (−)-**33**, 86046-98-2; (−)-**34**, 86116-90-7; (+)-**36**, 86116-91-8; (+)-**37a**, 86116-92-9; **37a** (*EE* ether) (isomer 1), 86116-93-0; **37a** (*EE* ether) (isomer 2), 86116-94-1; **39** (isomer 1), 86116-95-2; **39** (isomer 2), 86116-96-3; **41**, 86046-99-3; **43**, 86116-97-4; **44**, 86117-45-5; **45**, 86117-46-6; **46**, 86117-47-7; **47**, 86116-98-5; (−)-**48**, 86116-99-6; $CHBr_3$, 75-25-2; $AcOCH{=}CH_2$, 108-05-4; $(EtO)_2P(O)CH(CH_3)CO_2Et$, 3699-66-9; $CH_2{=}CHOEt$, 109-92-2; CH_3CS_2Et, 870-73-5; $COCl_2$, 75-44-5; NH_3, 7664-41-7; phenyl chloroformate, 1885-14-9; *N*-cyclohexylpropylimine, 1195-49-9; diethylphosphonoacetyl chloride, 34170-81-5; diethyl carboxymethylphosphonate, 3095-95-2.

Supplementary Material Available: Copies of the NMR spectra for (−)-**48** and (−)-**3** (authentic and synthetic) (6 pages). Ordering information is given on any current masthead page.

(29) Coutrot, P.; Snoussi, M.; Savignac, P. *Synthesis* **1978**, 133.