with a hydrogen flame detector. Glass columns (6 ft × 3.0 mm i.d. and 12 ft × 3.0 mm i.d.) bent in a U shape were used. The column substrates and solid supports used in the GLC analyses were obtained from Applied Science Laboratories or from Hewlett-Packard Analytical Instruments. Melting points were obtained on a Fisher-Jones apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tn.

General Procedure for Treatment of Diethyl Bis(3,4-dichlorobenzyl)malonate (12), Ethyl β-(1-Adamantyl)-β-oxopropionate (14), and 4-Carbethoxy-3-methyl-2-cyclohexen-1-one (16) with Brucine (6), Tropine (7), Nicotine (8), Reserpine (9), Yohimbine Hydrochloride (10), and Quinidine (11). A mixture of 0.5 mmol of the appropriate ester and 4.0 mmol of the appropriate alkaloid in 169 mmol of *o*-xylene was heated at reflux (144–146 °C) for 24 h. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ethyl ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate and analyzed by GLC. A glass column (6 ft, 5% SE-30 on 80/100 mesh Chromosorb W column, nitrogen flow rate 10 mL/min, column temperature 138 °C) was utilized. The appropriate products were identified by comparison of GLC retention times with those of authentic samples. Structural determinations of isolated samples were performed by MS, IR, NMR, and GLC analyses.

Acknowledgment. Support for this research was provided by the Biological and Physical Sciences Institute and the Office of Graduate Studies at Mississippi State University. We are indebted to Professor Lyell Behr and Ms. Shirley Randle for their assistance during the preparation of this paper.

Registry No. 6, 357-57-3; **7**, 120-29-6; **8**, 54-11-5; **9**, 50-55-5; **10**, 65-19-0; **11**, 56-54-2; **12**, 79665-12-6; **13**, 28751-26-0; **14**, 19386-06-2; **15**, 1660-04-4; **16**, 487-51-4; **17**, 1193-18-6.

Stereospecific 1,4-Additions of Methyl Cyanocuprate to Enol Phosphates of α,β-Epoxycyclohexanones: Application to the Total Synthesis of (±)-α-Multistriatin[1]

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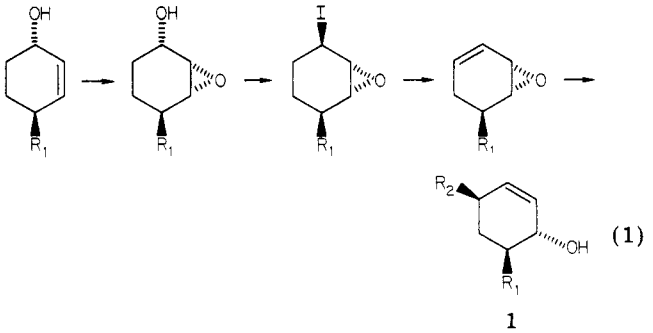
A highly stereospecific synthesis of (±)-α-multistriatin, one of the three components of the aggregation pheromone of the European elm bark beetle, is described. The synthesis involves a new route to substituted cyclohex-2-en-1-ols via trans 1,4-additions to enol phosphates of α,β-epoxycyclohexanones and subsequent reductive cleavage of a β-hydroxy enol phosphate.

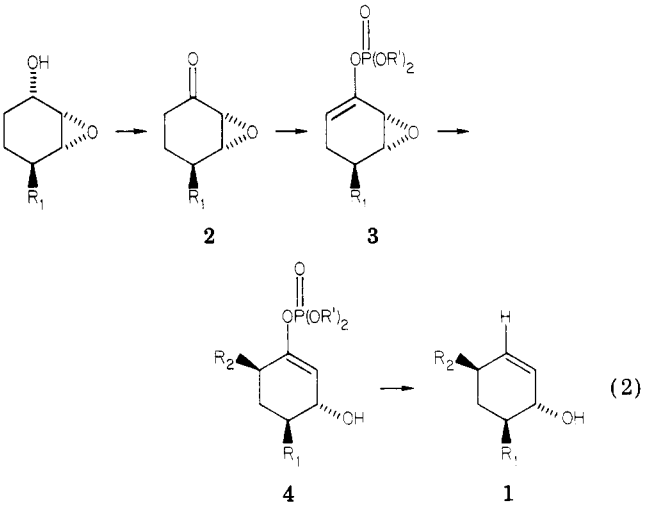
In a preliminary paper,[2] we reported the stereospecific synthesis of cis 4,6-disubstituted cyclohex-2-en-1-ols 1 via sequential trans 1,4-additions of alkyl cyanocuprates to vinyl epoxides. This synthetic sequence required the inversion of a hydroxyl group in order to effect a trans elimination (sequence 1).



(1)

1

As an alternative route to compounds such as 1, we sought to circumvent the dehydration of the hydroxy epoxide intermediate and utilize the keto epoxide system 2. We previously had shown that the double bond of an enol silyl ether is compatible with the trans 1,4-addition of cyanocuprates.[2] Since it is well-known that enol phosphates and phosphoramidates can be reductively cleaved to alkenes,[3] we investigated the use of such ketone derivatives in an effort to produce 1 from 2 (sequence 2). In



2 3

4 1

(2)

this report we present the successful utilization of enol phosphates of α,β-epoxycyclohexanones in the conversion of ketones such as 2 into cis 4,6-disubstituted cyclohex-2-en-1-ols 1. We also describe herein a highly stereospecific

(1) A preliminary report on this synthetic strategy to α-multistriatin was made at the 3rd IUPAC Meeting on Organic Synthesis, Madison, WI, June 15–20, 1980.

(2) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467.

(3) Fetizon, M.; Jurion, M.; Anh, N. T. *Chem. Commun.* **1969**, 112; Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098.

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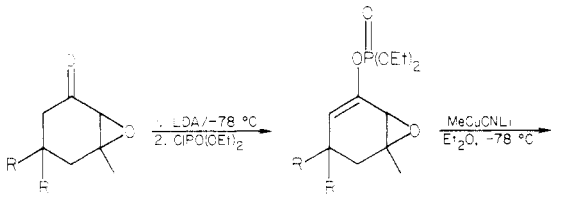
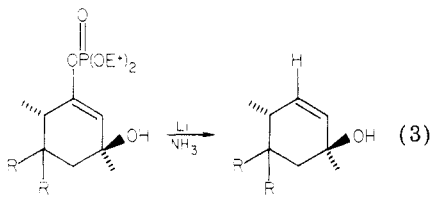
total synthesis of (±)-α-multistriatin from the *cis*-4,6-dimethyl derivative of **1** ($R_1 = R_2 = Me$).

In order to study the individual reaction conditions for conversion of **2** into **1**, we examined the transformations of 2,3-epoxy-3-methylcyclohexanone (**5**) and 2,3-epoxy-3,5,5-trimethylcyclohexanone (**6**). The corresponding diethyl enol phosphates of **5** and **6** were prepared with 1.2 equiv of LDA in THF (−78 °C) and subsequent treatment of the enolates with 1.2 equiv of diethyl chlorophosphonate (eq 3).



5, R = H
6, R = Me

7, R = H (80%)
8, R = Me (75%)



(3)

9, R = H (95%)
10, R = Me (93%)

11, R = H
12, R = Me

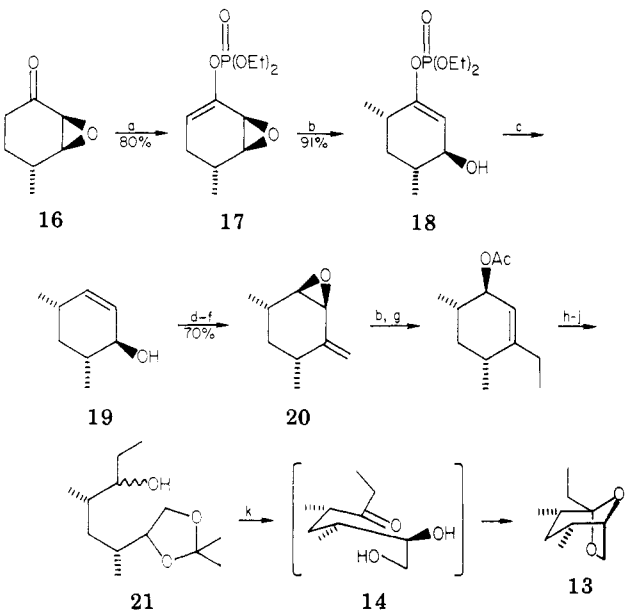
While enol phosphates have been reported to react with organocopper reagents in overall substitution processes,[4,5] our work reports the first 1,4-addition of cuprates to 3-epoxy-substituted enol phosphates.[1] The reactions of methyl cyanocuprate with enol phosphates **7** and **8** occur readily at −78 °C in ether (>90% yield). The new enol phosphates **9** and **10** are formed regiospecifically and represent a unique class of allylic alcohols that are not accessible from β-hydroxycyclohexanones. The presence of the *gem*-dimethyl groups in **10** did not adversely affect the cuprate reaction.

The conversion of enol phosphates and phosphoramidates to alkenes by reducing metals has been amply demonstrated in organic synthesis,[3] but we believe our system is the first example of a reduction on an enol phosphate of an aldol to produce an allylic alcohol stereospecifically. The conversions of **9** and **10** to **11** and **12** were carried out with excess lithium metal in liquid ammonia for 30 min. The reaction mixtures were quenched with methanol, and after a standard extractive workup, the products were isolated by vacuum distillation.

Total Synthesis of α-Multistriatin

In 1975, Silverstein[6a] characterized α-multistriatin **13** as one of the three components in the aggregation pheromone from the European elm bark beetle *Scolytus multistriatus* Marsham. Since that time, no less than six total syntheses of this pheromone have been reported.[6b-h] Only the last two syntheses[6g,h] have yielded pure 1α-multistriatin, free

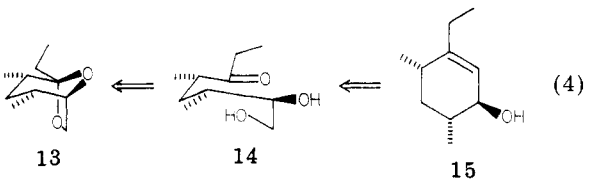
Scheme I[a]



16 17 18 19 20 21 14 13

[a] (a) LDA/THF, −78 °C, $ClPO(OEt)_2$; (b) MeCuCNLi/Et_2O, −78 °C; (c) Li/NH_3, MeOH; (d) MCPBA/CH_2Cl_2, room temperature; (e) $CrO_3/Py_2/CH_2Cl_2$; (f) $Ph_3P{=}CH_2$/THF, 0 °C; (g) AcCl/Pyr/CH_2Cl_2, room temperature; (h) ozone/Et_2O, −78 °C; (i) $LiAlH_4/Et_2O$, 0 °C; (j) acetone, TosOH, room temperature; (k) Jones reagent, 0 °C.

of the 1 γ isomer. As an application of our new synthetic methodology involving vinyl epoxides and as a check on the stereochemical integrity of the individual steps outlined in eq 2, the total synthesis of α-multistriatin was undertaken. The pentultimate precursor to **13** was the acyclic keto diol **14** (eq 4), a compound that had been previously



(4)

13 14 15

used in several of the previously reported syntheses.[6c,d] Our synthetic route to **14** and hence multistriatin centered around the regioselective and stereospecific production of the trisubstituted cyclohex-2-en-1-ol **15**. The overall synthetic scheme to α-multistriatin is outlined in Scheme I.

Our starting point was the *trans*-4-methyl-2,3-epoxycyclohexanone (**16**), which was available[2] in three steps from 1,3-cyclohexadiene monoepoxide (85–90% yield). Formation of the enol phosphate **17** of ketone **16** was affected in 80% yield, while the trans 1,4-addition of methyl cyanocuprate produced the transposed enol phosphate **18** in 91% yield. On application of the lithium reductive cleavage to **18**, *cis*-4,6-dimethylcyclohex-2-en-1-ol (**19**) was isolated in 76% yield. This route to **19** is more efficient than the one previously described by us[2] using a dehydration process.

While there are several possible routes for the conversion of **19** into the requisite cyclohexanol derivative **15**, we sought to maximize the use of stereocontrolled epoxidations and 1,4-additions of organocuprates to vinyl epoxides. To this end, we transformed **19** into the *exo*-methylene epoxide **20**. After the stereospecific epoxidation[2] of **19** with *m*-chloroperoxybenzoic acid and oxidation of the epoxy alcohol, a Wittig reaction was carried out on the epoxy ketone to produce the desired vinyl epoxide **20** (overall yield, three steps, 70%). The use

(4) Blaszczak, L.; Winkler, J.; O'Kuhn, S. *Tetrahedron Lett.* **1976**, 4405.
(5) Sum, F. W.; Weiler, L. *J. Am. Chem. Soc.* **1979**, *101*, 4401.
(6) (a) Gore, W. E.; Pearce, G. T.; Silverstein, R. M. *J. Org. Chem.* **1975**, *40*, 1705. (b) Pearce, G. T.; Gore, W. E.; Silverstein, R. M. *Ibid.* **1976**, *41*, 2797. (c) Elliot, W. J.; Fried, J. *Ibid.* **1976**, *41*, 2475. (d) Mori, K. *Tetrahedron* **1976**, *32*, 1979. (e) Cernigliaro, G. J.; Kocienski, P. J. *J. Org. Chem.* **1977**, *42*, 3622. (f) Sum, P.-E.; Weiler, L. *Can. J. Chem.* **1978**, *56*, 2700. (g) Bartlett, P. A.; Myerson, J. *J. Org. Chem.* **1979**, *44*, 1625. (h) Fitzsimmons, B. J.; Plaumann, D. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1979**, 3925.

of *exo*-methylene epoxides in the synthesis of 3-substituted cyclohex-2-en-1-ols has not received attention in organic synthesis.[7] Methyl cyanocuprate added cleanly (90% yield) to **20** in ether at −78 °C to produce the desired allylic alcohol **15**. After acetylation of **15**, a three-step sequence to the acyclic triol derivative **21** was carried out that involved (1) ozonolysis at low temperature, (2) complete reduction with $LiAlH_4$ to a triol, and (3) selective protection of the 1,2-diol. The stage was set for the selective oxidation of the secondary alcohol to the ethyl ketone with Jones reagent at 0 °C. The intermediate keto ketal was not isolated since it underwent hydrolysis in situ to the keto diol **14**, which in turn cyclized to racemic α-multistriatin.

The overall conversion of the allylic acetate to purified 1α-multistriatin was affected in 70% yield. The synthetic multistriatin was compared by VPC to an authentic mixture (1α, 1β, 1γ, 1δ) of multistriatins. VPC analysis of our synthetic material indicated pure 1α-multistriatin, and no isomeric multistriatins could be detected. The 360-MHz ^1H and ^{13}C NMR spectra of the synthetic multistriatin were in complete agreement with those published by Silverstein.[6a]

Experimental Section

General Methods. Infrared spectra were obtained on a Perkin-Elmer 457 grating spectrophotometer. ^1H NMR spectra were obtained on a Varian T60A and a Bruker 360-MHz NMR spectrometer with Me_4Si as the standard. ^{13}C NMR spectra were obtained on a JEOL FX90Q spectrometer with deuteriochloroform as the standard ($CDCl_3$, 77.00 ppm). Mass spectra were obtained on a Finnigan automated GC/MS-EICI system mass spectrometer at 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratory. GC analyses were carried out on Shimadzu GCmini-1: 3% SE-30, 2.6 mm × 1.8 m glass column, N_2 flow rate 40 mL/min, H_2 flow rate 40 mL/min. Column chromatography was carried out on EM reagents silica gel 60 (230–400 mesh, ASTM). Diethyl ether and THF were freshly distilled from LAH under nitrogen. Technical-grade cuprous cyanide was purchased from J. T. Baker. Commercial methyllithium (low halide in ether) was obtained from Alfa and titrated prior to use. Nitrogen gas was purified by passage through a column of Ascrite and magnesium perchlorate.

Preparation of Enol Phosphates. General Procedure. The epoxy ketones **5** and **6** were prepared from the corresponding enones by a literature procedure.[8] To a solution of 2.8 mL (2.02 g, 20 mmol) of diisopropylamine in 100 mL of dry THF was added 6.5 mL (2.3 M, 15 mmol) of a *n*-butyllithium solution at 0 °C. After the solution was stirred for 30 min at room temperature, it was cooled to −78 °C, and 10 mmol of the appropriate epoxy ketone was added. Enolate formation was allowed for 30 min, and then 1.7 mL (2.07 g, 12 mmol) of diethyl chlorophosphonate was added. The reaction mixture was slowly warmed to room temperature at which time stirring was continued for 30 min.

The reaction mixture was quenched with a saturated NH_4Cl solution, and the THF was removed on a Rotovap. Ether was added to the aqueous mixture, and the aqueous layer was extracted twice with ether. The combined ether extracts were dried over anhydrous $MgSO_4$. Evaporation of the ether and vacuum distillation of the residue yielded the enol phosphates.

Diethyl 2,3-Epoxy-3-methylcyclohex-6-enyl Phosphate (7). From 1.26 g of **5** in the above general procedure was isolated 2.35 g (82%) of pale yellow oil **7** by vacuum distillation: bp 128–130 °C (1.5 mmHg); IR (neat) 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3 H), 3.06 (d, 1 H, J = 2 Hz), 5.18–5.28 (m, 1 H). Anal. Calcd for $C_{11}H_{19}O_5P$: C, 50.38; H, 7.25. Found: C, 50.32; H, 7.38.

Diethyl 2,3-Epoxy-3,5,5-trimethylcyclohex-6-enyl Phosphate (8). From 1.5 g of epoxy ketone **6** was isolated 2.2 g (75%) of a pale yellow oil, **8**, by vacuum distillation: bp 126–129 °C (1.2 mmHg); IR (neat) 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (s, 3 H), 1.03 (s, 3 H), 1.40 (s, 3 H), 3.07 (d, 1 H, J = 2 Hz, 5.08–5.2 (m, 1 H). Anal. Calcd for $C_{13}H_{23}O_5P$: C, 53.79; H, 7.93. Found: C, 53.75; H, 8.03.

Preparation of Substituted β-Hydroxy Enol Phosphates. General Procedure. To a suspension of 2.95 g (33 mmol) of cuprous cyanide (J. T. Baker) in 200 mL of anhydrous ether was added 18.8 mL of a methyllithium (1.6 M, 30 mmol) solution at −78 °C. After the mixture was stirred for 1 h at −78 °C, 10 mmol of the epoxy enol phosphate was added dropwise. After the reaction mixture was stirred for 1 h at −78 °C and warmed to room temperature, it was quenched with a saturated NH_4Cl solution. The ether layer was separated, washed with water, and dried over anhydrous $MgSO_4$. Evaporation of the ether yields the β-hydroxy enol phosphates. Elemental analyses of this class of compounds proved to be problematic because of slow decomposition.

Diethyl *cis*-3,6-Dimethyl-3-hydroxycyclohexenyl Phosphate (9). From 2.6 g (10 mmol) of diethyl 2,3-epoxy-3-methylcyclohex-6-enyl phosphate (**7**) was isolated 2.64 g (95%) of **9** after evaporation of the ether solvent: IR (neat) 3405, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 7 Hz), 1.24 (s, 3 H), 5.20–5.40 (m, 1 H).

Diethyl *cis*-3,6-Dimethyl-5,5-dimethyl-3-hydroxycyclohexenyl Phosphate (10). From 2.9 g (10 mmol) of the epoxy enol phosphate **8** was isolated 2.7 g (93%) of the title compound **10** by distillation: bp 135–138 °C (1 mmHg); IR (neat) 3430, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (d, 3 H, J = 7 Hz), 2.3–2.4 (m, 1 H + OH), 5.23–5.40 (m, 1 H).

Preparation of Substituted Cyclohexenols. General Procedure. To a solution of 0.7 g (100 mmol) of lithium metal in 150 mL of liquid ammonia was added 10 mmol of the appropriate β-hydroxy enol phosphate. After the reaction mixture was stirred for 30 min, 2 mL of methanol was added, and the solution was neutralized with a saturated NH_4Cl solution. The liquid ammonia was evaporated at room temperature, and the residue was extracted with ether. After the ether extracts were dried over anhydrous $MgSO_4$ and the ether evaporated, the products were isolated by vacuum distillation.

***cis*-1,4-Dimethylcyclohex-2-en-1-ol (11).** From 2.8 g (10 mmol) of enol phosphate **9** was isolated 0.85 g (67%) of **11** by vacuum distillation: bp 87–88 °C (15 mmHg); IR (neat) 3370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (d, 3 H, J = 7 Hz), 1.23 (s, 3 H), 5.3–5.6 (br s, 2 H). Anal. Calcd for $C_8H_{14}O$: C, 76.09; H, 11.11. Found: C, 75.86; H, 11.11.

***cis*-1,4-Dimethyl-5,5-dimethylcyclohex-2-en-1-ol (12).** From 2.5 g (8 mmol) of enol phosphate **10** was isolated 0.96 g (76%) of cyclohexenol **12** by vacuum distillation: bp 94–96 °C (15 mmHg); IR (neat) 3385 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8–1.08 (m, 9 H), 1.22 (s, 3 H), 5.2–5.6 (m, 2 H). Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 77.79; H, 11.54.

Diethyl 2β,3β-Epoxy-4α-methyl-6-cyclohexenyl Phosphate (17). To a solution 2.8 mL (2.02 g, 20 mmol) of diisopropylamine in 100 mL of anhydrous THF was added 6.52 mL (2.3 M, 15 mmol) of *n*-BuLi solution at 0 °C. The reaction mixture was stirred for 30 min at room temperature and cooled to −78 °C. To this solution was added 1.26 g (10 mmol) of *trans*-2,3-epoxy-4-methylcyclohexanone[2] (**16**), and the reaction mixture was stirred for 30 min at −78 °C. Then, 1.73 mL (2.07 g, d = 1.194, 12 mmol) of diethyl chlorophosphonate was added to the reaction mixture which was slowly warmed to room temperature and stirred for 30 min.

The reaction solution was quenched with saturated NH_4Cl solution, and THF was removed under reduced pressure. The residue was extracted with ether (three times), and the ether layer was dried over anhydrous $MgSO_4$. After removal of ether, the residue was distilled under reduced pressure to give 1.88 g (80%) of diethyl 2β,3β-epoxy-4α-methyl-6-cyclohexyl phosphate (**17**): bp 130–135 °C (0.5 mmHg); ^1H NMR (60 MHz, CCl_4) δ 0.96 (d, 3 H, J = 6.5 Hz), 3.02–3.17 (br, 2 H), 5.02–5.22 (br, 1 H); IR (neat) 1670 cm^{-1}; mass spectrum, m/e 263 (M + 1), 220, 155, 127, 99, 49 (base). Anal. Calcd for $C_{11}H_{19}O_5P$: C, 50.38; H, 7.25. Found: C, 50.45; H, 7.18.

Diethyl 2α,4α-Dimethyl-5β-hydroxy-6-cyclohexenyl Phosphate (18). To a solution of 2.95 g (33 mmol) of CuCN in 200 mL of anhydrous ether was added dropwise 18.8 mL (30 mmol) of a 1.60 M CH_3Li solution in ether at −78 °C. The mixture

(7) For a recent report on this strategy from our laboratory see: Marino, J. P.; Abe, H. *Synthesis* **1980**, *11*, 872.

(8) Yang, N. C.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

was stirred for 1 h at −78 °C, and 2.62 g (10 mmol) of diethyl 2β,3β-epoxy-4α-methyl-6-cyclohexenyl phosphate (17) was added dropwise into the solution. The reaction mixture was stirred for 1 h at −78 °C and then warmed to room temperature. After the mixture was quenched with a saturated NH_4Cl solution, the organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated to give 2.52 g (91%) of diethyl 2α,4α-dimethyl-5β-hydroxy-6-cyclohexenyl phosphate. The product slowly decomposed on standing, and elemental analyses could not be obtained: ^1H NMR (60 MHz, CCl_4) δ 0.96–1.60 (m, 12 H), 3.12–3.48 (br, 1 H), 5.40–5.80 (br, 1 H); IR (neat) 3420 cm^{-1}.

2α,4α-Dimethyl-5-cyclohexen-1β-ol (19). To a solution of 0.69 g (100 mmol) of lithium metal in liquid ammonia was added 2.78 g (10 mmol) of diethyl 2β,3β-epoxy-4α-methyl-6-cyclohexenyl phosphate (18). After the reaction mixture was stirred for 30 min, methanol (2 mL) was added, and the solution was neutralized with a saturated NH_4Cl solution.

The ammonia was evaporated at room temperature, and the residue was extracted with ether. The ether solution was dried over $MgSO_4$, concentrated, and distilled under reduced pressure to give 0.96 g (76%) of 2α,4α-dimethyl-5-cyclohexen-1β-ol: bp 86–88 °C (23 mmHg); ^1H NMR (360 MHz, $CDCl_3$) δ 0.921 (d, 3 H, J = 7.08 Hz), 1.041 (d, 3 H, J = 6.35 Hz), 3.65–3.78 (br, 1 H), 5.50–5.60 (br s, 2 H); IR (neat) 3320 cm^{-1}; mass spectrum, m/e 126 (M^+), 111, 95, 84 (base); GC (column temperature 80 °C): 2.7 min from THF, >99% pure; ^{13}C NMR (22.5 MHz, $CDCl_3$) 134.75, 130.20, 73.59, 39.19, 37.72, 31.12, 21.58, 78.76 ppm. Anal. Calcd for $C_8H_{14}O$: C, 76.19; H, 11.11. Found: C, 75.97; H, 11.10.

2β,3β-Epoxy-4α,6α-dimethylcyclohexan-1β-ol. To a solution of 1.90 g (13 mmol) of MCPBA (85%) in 50 mL of CH_2Cl_2 was added 1.26 g (10 mmol) of 2α,4α-dimethyl-5-cyclohexen-1-ol (19). The reaction mixture was stirred for 20 hours at room temperature. The solution was washed with a saturated Na_2SO_3 solution, a saturated $NaHCO_3$ solution, and a saturated NaCl solution and dried over $MgSO_4$.

The solvent was removed under reduced pressure, and the residue was chromatographed on silica-gel column with ether–petroleum ether (1:1) as an eluant to give 1.07 g (75%) of 2β,3β-epoxy-4α,6α-dimethylcyclohexan-1β-ol: ^1H NMR (60 MHz, $CDCl_3$) δ 2.98–3.18 (m, 1 H), 3.20–3.42 (m, 1 H); IR (neat) 3430 cm^{-1}. Anal. Calcd for $C_8H_{14}O_2$: C, 67.64; H, 9.86. Found: C, 67.93; H, 9.97.

2β,3β-Epoxy-4α,6α-dimethylcyclohexanone. To a solution of 7.91 g (100 mmol) of dry pyridine in 100 mL of CH_2Cl_2 was added 5 g (50 mmol) of chromium trioxide at 0 °C. The mixture was stirred for 30 min at 0 °C. To the oxidizing solution was added 1.42 g (10 mmol) of 2β,3β-epoxy-4α,6α-dimethylcyclohexan-1β-ol, and the mixture was stirred for 1.5 h at room temperature. The organic solution was separated from the gummy residue by decantation, and the residual gum was rinsed well with CH_2Cl_2. The combined CH_2Cl_2 solution was washed with a saturated NaCl solution and dried over $MgSO_4$.

After removal of the solvent, the residue was chromatographed on a silica gel column with ether–petroleum ether (1:1) as an eluant to give 1.02 g (73%) of 2β,3β-epoxy-4α,6α-dimethylcyclohexanone: ^1H NMR (60 MHz, $CDCl_3$) δ 0.96 (d, 3 H, J = 9 Hz), 1.05 (3 H, d, J = 9 Hz), 3.22 (br s, 2 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) 209.73, 64.92, 55.49, 42.55, 36.75, 28.89, 18.76, 13.99 ppm; IR (neat) 1726, 1715 cm^{-1}. Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.51; H, 8.55.

1β,2β-Epoxy-3-methylene-4α,6α-dimethylcyclohexane (20). To a solution of 2.81 mL (20 mmol) of diisopropylamine in 50 mL of anhydrous tetrahydrofuran was added 9.1 mL (20 mmol) of a 2.3 M solution of n-butyllithium in hexane at 0 °C. The mixture was stirred for 15 min at 0 °C under nitrogen. This solution was transferred at 0 °C by a transfer needle to a solution of 7.14 g (20 mmol) of methyltriphenylphosphonium bromide suspended in 20 mL of anhydrous tetrahydrofuran. After the mixture was stirred for 15 min at 0 °C, 1.0 g (7.14 mmol) of 2β,3β-epoxy-4α,6α-dimethylcyclohexanone was added dropwise to the mixture, and the reaction mixture was stirred for 2 h at room temperature under nitrogen.

The solution was quenched with saturated NH_4Cl solution, and tetrahydrofuran was removed under reduced pressure. The residue was extracted with ether, and the ether layer was washed with a saturated NaCl solution and dried over $MgSO_4$.

After removal of the ether, the residue was chromatographed on a silica gel column with ether–petroleum ether (1:1) as an eluant to give 0.86 g (87%) of 1β,2β-epoxy-3-methylene-4α,6α-dimethylcyclohexane (20): ^1H NMR (60 MHz, $CDCl_3$) δ 1.0 (d, 3 H, J = 7 Hz), 1.05 (d, 3 H, J = 7 Hz), 3.02 (dd, 1 H, J = 5 Hz, 2 Hz), 3.46 (d, 1 H, J = 5 Hz), 4.08 'br s, 1 H), 5.2 (br s, 1 H). Anal. Calcd for $C_9H_{14}O$: C, 78.26; H, 10.14. Found: C, 78.26; H, 10.12.

3-Ethyl-4α,6α-dimethyl-2-cyclohexen-1β-ol (15). To a solution of 0.896 g (10 mmol) of CuCN in 300 mL of anhydrous ether was added dropwise 6.25 mL (10 mmol) of a solution of 1.6 M CH_3Li in ether at −78 °C under nitrogen. The mixture was stirred for 30 min at −78 °C. Then 0.44 g (3.19 mmol) of 1β,2β-epoxy-3-methylene-4α,6α-dimethylcyclohexane (20) was added to this solution. After the reaction mixture was stirred 1 h at −78 °C, it was quenched with a saturated NH_4Cl solution. The whole mixture was filtered through a Celite pad, and the organic layer of the filtrate was washed with saturated NaCl solution and dried over $MgSO_4$.

After removal of the solvent, the residue was chromatographed on a silica gel column with ether–petroleum ether as an eluant to give 0.44 g (90%) of 3-ethyl-4α,6α-dimethyl-2-cyclohexen-1β-ol (15): ^1H NMR (60 MHz, $CDCl_3$) 0.84–1.18 (m, 10 H), 3.75 (br d, 1 H, J = 7 Hz), 5.25–5.45 (br, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$) 146.12, 124.29, 74.56, 39.67, 37.94, 33.01, 26.51, 19.63, 18.55, 12.20; IR (neat) 3360 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O$: C, 77.92; H, 11.69. Found: C, 77.78; H, 11.74.

1β-Acetoxy-3-ethyl-4α,6α-dimethyl-2-cyclohexene. To a solution of 3.96 g (50 mmol) of dry pyridine and 0.44 g (2.86 mmol) of 3-ethyl-4α,6α-dimethyl-2-cyclohexen-1β-ol in 30 mL of CH_2Cl_2 was added dropwise 2.13 mL (30 mmol, d = 1.104, 2.35 g) of acetyl chloride at 0 °C. The mixture was stirred for 2 h at 0 °C and was then poured into a saturated $NaHCO_3$ solution. The organic layer was washed with a saturated NaCl solution and dried over $MgSO_4$.

After removal of the solvent, the residue was chromatographed on a silica gel column with ether–petroleum ether as an eluant to give 0.55 g (98%) of 1β-acetoxy-3-ethyl-4α,6α-dimethyl-2-cyclohexene: ^1H NMR (60 MHz, $CDCl_3$) δ 0.8–1.15 (m, 10 H), 2.04 (s, 3 H), 4.98 (br d, 1 H, J = 9 Hz), 5.15–5.28 (br, 1 H); IR (neat) 1740 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.23; H, 10.13.

(±)-α-Multistriatin (13). Into a solution of 0.25 g (1.28 mmol) of 1β-acetoxy-3-ethyl-4α,6α-dimethyl-2-cyclohexene in anhydrous ether (100 mL) was passed 1.8 mmol of ozone for 2.5 min (0.72 mmol/min) at −78 °C. The reaction was followed by TLC until the starting material disappeared. After removal of excess ozone by flushing with nitrogen, the solution was warmed to 0 °C and transferred to a solution of 0.18 g (5 mmol) of LAH in anhydrous ether (50 mL) at 0 °C. The reaction mixture was stirred for 2 h at room temperature under nitrogen and quenched with 2 mL of a saturated NH_4Cl solution. The reaction mixture was filtered through a Celite pad, and the Celite pad was washed well with ethyl acetate. The organic filtrate was dried over $MgSO_4$.

After removal of solvent, the residue was taken up in 20 mL of acetone, and 100 mg of p-toluene sulfonic acid was added to the solution. The mixture was stirred for 15 h at room temperature. After removal of acetone, the residue was dissolved in 100 mL of ether, and the ether solution was washed with saturated $NaHCO_3$ solution and saturated NaCl solution and dried over $MgSO_4$.

After removal of the ether, the residue was chromatographed on a silica gel column with ether–petroleum ether as an eluant to give the acetonide 21: 0.24 g; R_f 0.35 (ether–petroleum ether, 1:1).

To a solution of the acetonide in 20 mL of acetone was added dropwise Jones reagent until the solution was orange. The solution was then stirred for 1 h at 0 °C.

After removal of the acetone, 30 mL of distilled water was added to the residue, and the solution was extracted with ether. The ether layer was washed with a saturated NaCl solution and dried over $MgSO_4$. After removal of the ether, the residue was chro-

matographed on a silica gel column with ether–petroleum ether (1:1) as an eluant to give 0.15 g of (±)-α-multistriatin (70% from starting acetate).

This compound was identical with an authentic sample by VPC, and the ^{1}H NMR, IR, and ^{13}C NMR spectra were consistent with literature data.[6a] VPC analysis revealed that the synthetic material was at least 99.5% pure.

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Registry No. **5**, 21889-89-4; **6**, 10276-21-8; **7**, 79722-56-8; **8**, 79722-57-9; **9**, 79722-58-0; **10**, 79722-59-1; **11**, 79722-60-4; **12**, 79722-61-5; **13**, 54815-06-4; **15**, 77067-72-2; **16**, 79767-70-7; **17**, 79722-62-6; **18**, 79722-63-7; **19**, 79722-64-8; **20**, 79768-50-6; **21**, 79722-65-9; diethyl chlorophosphonate, 814-49-3; (±)-2β,3β-epoxy-4α,6α-dimethylcyclohexan-1β-ol, 79722-66-0; (±)-2β,3β-epoxy-4α,6α-dimethylcyclohexanone, 79767-71-8; (±)-1β-acetoxy-3-ethyl-4α,6α-dimethyl-2-cyclohexene, 79722-67-1.

Synthetic Approach to Cytochalasins[1]

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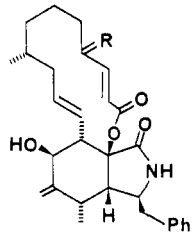
Studies directed toward total synthesis of cytochalasin B (1) and A (2) are described. A simple acyclic unit, **12**, intended for incorporation into the macrolactone ring of the cytochalasins has been prepared in seven steps from citronellol (**5**). The isoindolone nucleus **36** has been prepared by a Diels–Alder strategy via adduct **31**. Conversion of this adduct to methoxy lactam **33** and coupling with tribenzylaluminum afforded lactam **34**. Hydroxylation of the enolate of **34** gave isoindolone **35** containing the five chiral centers necessary for preparation of **1** and **2**. Debenzylation of **35** produced diol **36**, which will be combined with fragment **12** to ultimately complete a cytochalasin total synthesis.

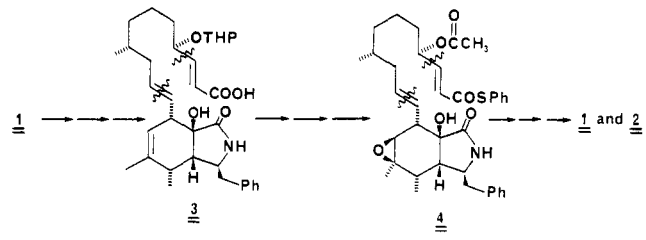
The extensive range of biological activity displayed by the cytochalasins, coupled with their unique structural features,[3] has prompted several research groups to explore synthetic approaches to these fungal metabolites.[1,4-10] Recently, Stork et al. completed the first total synthesis of cytochalasin B (**1**), the most abundant and most thoroughly studied member of this group.[11] During the past few years, we have also been attempting to develop syntheses of cytochalasins B (**1**) and A (**2**),[1,4] and we now report some details of our progress.



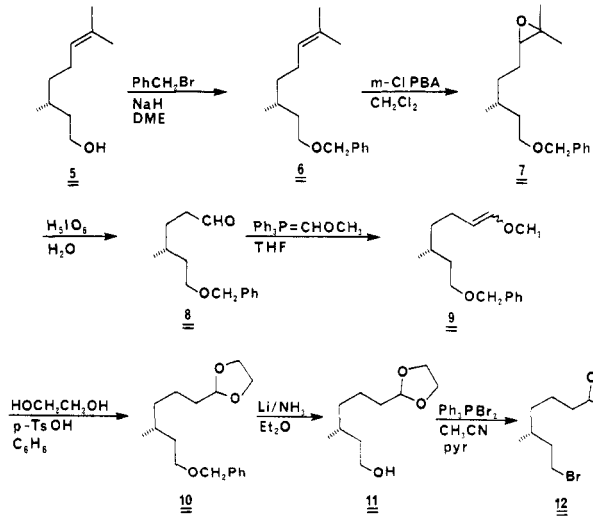
1 R = α-OH, β-H

2 R = O

Scheme I



Scheme II



Our synthetic plan was designed with the knowledge that Masamune et al.[7] had transformed cytochalasin B (**1**) in several steps to the seco acid **3**, which was then successfully converted back to **1** via intermediate epoxy thioester **4** (Scheme I). Turner et al. previously described

(1) (a) Taken from the Ph.D. Thesis of M.Y.K., Fordham University, 1980. (b) A preliminary account of a part of this work has appeared: Kim, M.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, 579.

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