(13) Swelling measurements made for **1–5** under triphase conditions and ambient temperature indicate the following degrees of swelling (volume of swelled resin/volume of dry resin): **1** (1.5); **2** (1.4); **3** (2.1); **4** (3.1), and **5** (3.2).
(14) Analogous polar-selectivity features have been observed for certain polymer catalysts in solid/liquid biphase reactions.[7]
(15) W. P. Weber and G. W. Gokel, "Phase-Transfer Catalysis in Organic Synthesis", Springer-Verlag, New York, 1977; E. V. Dehmlow, *Angew. Chem., Int. Ed. Engl.*, **16**, 493 (1977); A. Brändström, *Adv. Phys. Org. Chem.*, **15**, 267 (1977).
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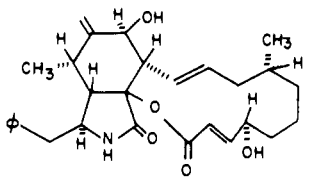
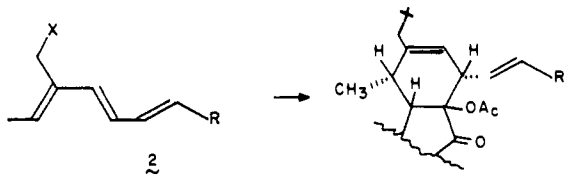
Total Synthesis of Cytochalasin B

Sir:

We report the total synthesis of cytochalasin B (**1**, phomin[1]) a member of a class of natural cytostatic substances endowed with remarkable biological properties. The synthesis was designed on the assumption that a triene such as **2** should undergo regioselective [2 + 4] addition as indicated (for steric, as well as electronic reasons). We further expected that an acyloxy-



1

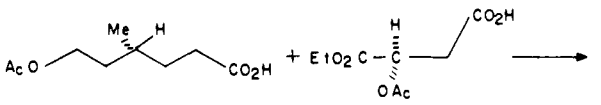


2

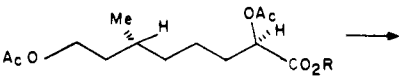
enone system would preferentially lead to the desired vicinal arrangement of the vinyl and acyloxy groups.[2] These expectations were rewarded.

We begin by describing the preparation of the required diene. We found it convenient to generate the chiral secondary methyl and hydroxyl groups of the side chain (the eventual substituents on the lactone ring of **1**) from (+)-citronellol and malic acid, respectively.

The acetate of pure citronellol,[3] $[\alpha]^{20}_D$ +5.12° (*c* 5.86), was converted (O_3, CH_2Cl_2, Zn dust/acetic acid; Jones oxidation of the crude aldehyde) to the acetate of 4(*R*)-methyl-6-hydroxyhexanoic acid (**3**): 81%, bp 112 °C (0.07 mm); $[\alpha]^{20}_D$ +3.1° (*c* 5.7).[4] Kolbe coupling of **3** (1 g) with the acetate of the 1-ethyl ester of (+)-malic acid (**4**)[5] (4.6 g; 80 mL of 0.2% ethanolic sodium ethoxide, ~1.5 A, 45–50 °C, 75 min; solvent removal and reacetylation of the crude mixture) gave, after elution of the coupling product from **3** (24%, *m/e* 287 (M + 1)), the desired cross-coupling product, the diacetate of ethyl 2-(*R*),8-dihydroxy-6(R)-methyloctanoate (**5**), in 42% yield ($[\alpha]^{20}_D$ +14.5° (*c* 13.8); ^{13}C NMR showed the required 15 peaks). Reduction of **5** with $LiAlH_4$ in ether gave 6(*R*)-methyl-2(*R*)-1,2,8-octanetriol (**6**). Its triacetate **7** (silica gel, 4:1 hexane–ethyl acetate, bp (Kugelrohr) 150 °C (0.1 mm)) had $[\alpha]^{20}_D$ +2.5° (*c* 5.0), reported[6] $[\alpha]_D$ +2.3 ± 1°. The secondary hydroxyl and methyl groups are now established with their proper chirality in the triol **6**, which was prepared



3 **4**



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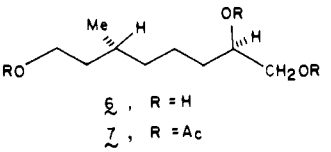
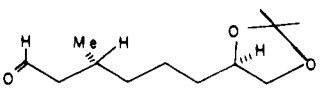


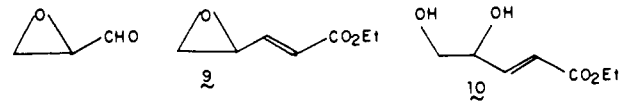
6, R = H
7, R = Ac



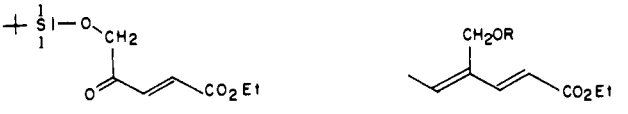
8

for further elaboration to the required triene system by acetonide formation (acetone, *p*-TsOH, room temperature, 3 h), followed by Collins oxidation (1 h, room temperature) to the aldehyde **8**.

Condensation of glycidaldehyde with carbethoxymethylene triphenylphosphorane (30% excess in benzene, 1.5-h reflux) gave the unsaturated ester **9** in 87% yield (bp 96–98 °C (15 mm)). Conversion to the glycol **10** (formic acid, 30 min; concentration under vacuum; aqueous saturated bicarbonate overnight, hexane washing and ethyl acetate extraction; 76% yield) was followed by protection of the primary alcohol as the *tert*-butyl dimethylsilyl ether and, after separation from some disilylated compound, by oxidation (CrO_3·2pyr) to the unsaturated keto ester **11** (78% from **10**; homogeneous by TLC; *H*C=CH, two 1 H d at δ 6.80 and 7.43 (J = 16 Hz)). Condensation of **11** with ethylidenetriphenylphosphorane (THF, −78 °C, 45 min) gave (74% yield) a 5.7:1 ratio of the desired *trans,trans*-dienic ester **12** and its more easily eluted (3% ethyl acetate in hexane) trans,cis isomer. Reduction with sodium bis(methoxyethoxy)aluminum hydride (toluene; ice-methanol cooling, 45 min) gave the corresponding alcohol **13** (89% yield) which was transformed into the phosphonate **14**, required for

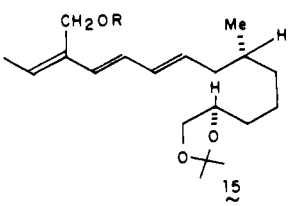


9 **10**



11 **12**

13 R = $-\overset{1}{\underset{1}{Si}}$ **14**



15

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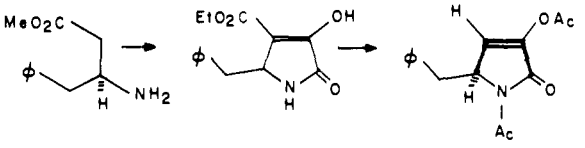
coupling with **8,** by sequential treatment at ~−30 °C of its solution in 3:1 ether-HMPA with butyllithium, followed by toluenesulfonyl chloride (1.1 equiv), and, after 30 min, by sodium diethylphosphite in toluene (1.3 equiv, overnight at room temperature). The dienyl phosphonate **14** (73% yield) was condensed as its sodium salt (sodium hydride in benzene, 0.25 equiv of methanol, 2 h, 55 °C) with the aldehyde **8** (55 °C, overnight), and the desired triene **15** was obtained in 50% yield (neutral alumina, 10% ether-hexane; *m/e* (CI) 423 (M + 1)).

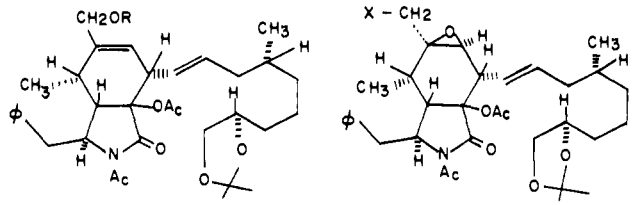
The dienophile for the [2 + 4] cycloaddition to **15** was made from methyl L-3-aminophenylbutyrate[7] (**16**) derived by Arndt-Eistert homologation from *N*-carbobenzoxy-L-alanine (via silver oxide-methanol rearrangement of the diazo ketone, followed by 10% Pd/C hydrogenolysis). The amino ester **16** was converted into the hydroxypyrrolone ester **17**[8] which upon



16 **17** **18**

O,N-diacetylation (acetic anhydride-pyridine, 4,*N*,*N*-dimethylaminopyridine as catalyst, 30 min at room temperature), followed by hydrolysis-decarboxylation (Me_2SO-sodium chloride-water (50:2.8:1), 135–140 °C, 1.5 h, N_2), reacetylation of the liberated hydroxyl, and chromatography on silica (4:1 hexane-ethyl acetate and then 3:2 chloroform-ethyl acetate) afforded pure **18**: $[\alpha]^{25}_D$ +111.1° (*c* 5.04); NMR δ 2.25 (3 H, s, 2.56 (3 H, s), 2.85 (1 H, dd, J = 13.5, 9 Hz), 3.57 (1 H, dd, J = 13.5, 3.5 Hz), 4.90 (1 H, m), 6.89 (1 H, d, J = 2.5 Hz), 7.23 (5 H, m). The substance was optically pure, as determined by NMR and LC studies of the ester with (+)-methoxytrifluoromethylphenylacetate, under conditions which easily resolved diastereoisomeric mixtures from incompletely resolved **18.**

Cycloaddition of the triene **15** (1.05 g) to the pyrrolone **18** (1.59 g) in 9 mL of xylene (170 °C, 4 days) was regioselective[9,10] and gave, in order of elution, recovered triene **15,** the adduct **19** (~40% conversion), a ~1:1 mixture of **19** and its undesired regioisomer, and recovered **18** of essentially unchanged $[\alpha]_D$. The ratio of **19** to the wrong regioisomer was



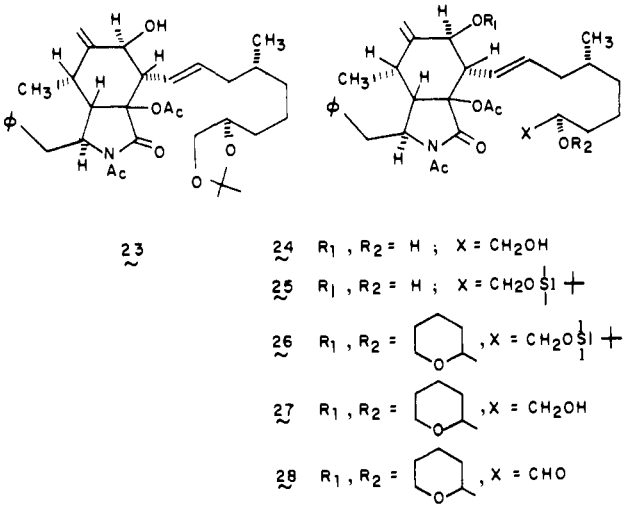
19, R = +Si **21**, X = OH

20, R = H **22**, X = Br

≥4. The adduct **19,** $[\alpha]^{25}_D$ +58° (*c* 5.6), characteristically had the resonance of the (shielded) cyclohexenyl methyl group at δ 0.40 (3 H, d, J = 7 Hz). Also, the *N*-acetyl group of **19** and of the undesired regioisomer were at δ 2.41 and 2.51, respectively.

Introduction of the characteristic methylenecyclohexanol system (cf. **23**) was initiated by removal of the silyl protecting group from **19** (3:1:1 acetic acid-water-THF, room temperature overnight, followed by acetone-*p*-TsOH, 1.5 h at room temperature) to **20** (67% yield, $[\alpha]^{25}_D$ +63.4° (*c* 3.6)). Epoxidation (*tert*-butyl hydroperoxide, $Mo(CO)_6$,[11] 1.5-h reflux in benzene; the *N*-acetyl methyl in **21** is about δ 0.1 higher than in **20**) gave (95% yield) **21**, $[\alpha]^{25}_D$ +32.1° (*c* 4.25), which was finally converted to **23,** $[\alpha]^{25}_D$ +59.7° (*c* 0.33), by way of **22** (carbon tetrabromide, triphenylphosphine; 4 h at room temperature), followed by β-elimination (zinc dust/sodium iodide, acetone, 4-h reflux).

Completion of the synthesis now required transformation of the terminal isopropylidene group to the 4-hydroxy trans-α,β-unsaturated ester system of **29.** This was accomplished in a straightforward fashion by liberation of the 1,2 glycol to give **24** (aqueous acetic acid-THF, 4 h at room temperature) and protection of the primary alcohol as the *tert*-butyl dimethylsilyl ether **25** (74% from **23**), $[\alpha]^{25}_D$ +46.3° (*c* 0.90), and of the two



23

24 R_1, R_2 = H ; X = CH_2OH

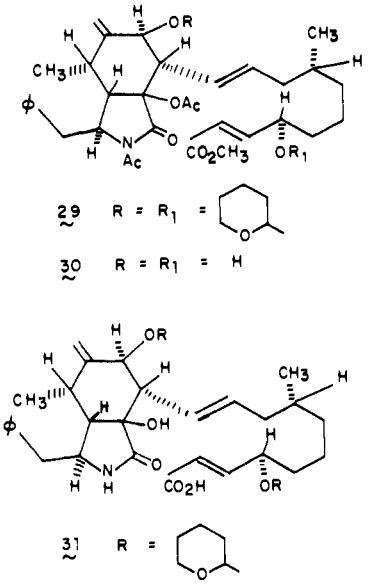
25 R_1, R_2 = H ; X = CH_2OSi +

26 R_1, R_2 = , X = CH_2OSi +

27 R_1, R_2 = , X = CH_2OH

28 R_1, R_2 = , X = CHO

secondary hydroxyls as tetrahydropyranyl ethers to give **26** in 63% yield. Liberation of the primary alcohol **27** (tetrabutylammonium fluoride; some easily separated N-deacetylated compound was also formed), oxidation (Collins) to the aldehyde **28,** and condensation with methyltriphenylphosphoranylidene acetate (1.5-h reflux in benzene) afforded **29** (68% from **27,** $[\alpha]^{25}_D$ +51.9° (*c* 0.56)). This substance gave an IR



29 R = R_1 =

30 R = R_1 = H

31 R =

spectrum superimposable on that of the material derived from natural cytochalasin B,[12] and its identity was rigorously established by conversion to the dihydroxy compound **30** (50% acetic acid-THF, overnight at room temperature) which, after chromatography on silica gel (1:1 hexane-ethyl acetate), gave ^1H NMR, ^{13}C NMR, and IR spectra superimposable on those of the substance derived from natural cytochalasin B. The cyclization of the hydroxy unsaturated acid **31** (derived from **29** and 1 N ethanolic sodium hydroxide, 60 °C, 1 h, followed

by chromatography on silica with 9:1 $CHCl_3$-CH_3OH) to cytochalasin B has been described previously.[13]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their support of this work.

References and Notes

(1) For recent reviews of (a) the chemistry and (b) the biological activity of these substances, see (a) M. Binder and Ch. Tamm, *Angew. Chem., Int. Ed. Engl.*, **12**, 370 (1973); (b) S. B. Carter, *Endeavour*, **113**, 77 (1972).
(2) The transition state involving the desired diene should be favored because in that case only a spherically symmetric methyl group, rather than a much more sterically demanding branched chain, extends from the diene plane. See also footnote 2 in G. Stork, S. Wagle, and P. C. Mukharji, *J. Am. Chem. Soc.*, **75**, 3197 (1953).
(3) J. Plesek, *Collect. Czech, Commun.*, **22**, 644 (1957).
(4) All compounds gave spectral data, in particular NMR spectra, in agreement with the postulated structures. Special features are mentioned in the text. Purifications were on silica gel unless otherwise noted, and elution was with hexane–ethyl acetate, usually 4:1. All rotations are for chloroform solution.
(5) Cf. D. H. S. Horn and Y. Y. Pretorius, *J. Chem. Soc.*, 1460 (1954).
(6) W. Rothweiler and C. Tamm, *Helv. Chim. Acta*, **53**, 696 (1970).
(7) Cf. N. C. Charturvedi, W. K. Park, R. R. Smeby, and F. M. Bumpus, *J. Med. Chem.*, **13**, 177 (1970).
(8) Cf. P. L. Southwick and R. T. Crouch, *J. Am. Chem. Soc.*, **75**, 3413 (1953).
(9) We had previously established that acetoxymaleic anhydride gives the correct orientation with model trienes corresponding to **15**.
(10) The importance of *N*-acyl groups on pyrrolone dienophiles has been established by the outstanding work of E. Vedejs and R. C. Gadwood, *J. Org. Chem.*, **43**, 376 (1978), which had been communicated to us prior to its publication.
(11) K. B. Sharpless and N. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973).
(12) The seco acid **31** from cytochalasin B (cf. ref 13) was transformed into **29** by treatment of the methyl ester (diazomethane) with acetic anhydride–pyridine (3.5 h at room temperature). Conversion of **29** from cytochalasin B to the dihydroxy compound **30** was done as we describe for the synthetic material.
(13) S. Masamune, Y. Hayase, W. Schilling, W. K. Chan, and G. S. Bates, *J. Am. Chem. Soc.*, **99**, 6756 (1977).

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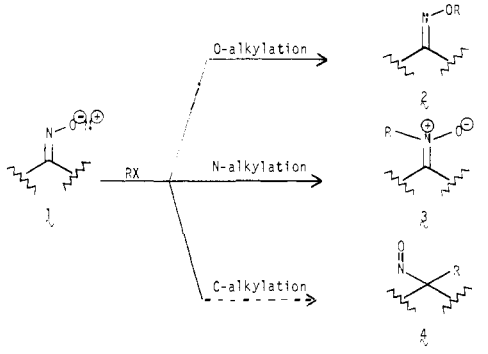
Intramolecular Carbon Alkylation of Oxime Anions. Stereospecific Generation and Rearrangement of Nitrosocyclopropanes and Nitrosocyclobutanes[1]

Sir:

Alkylation of oxime anions is well known to occur both at oxygen (to yield oxime ethers, **1** → **2**)[2] and at nitrogen (to yield nitrones, **1** → **3**).[2] The process of carbon alkylation (to yield tertiary nitroso compounds, **1** → **4**) is extremely rare.[3,4]



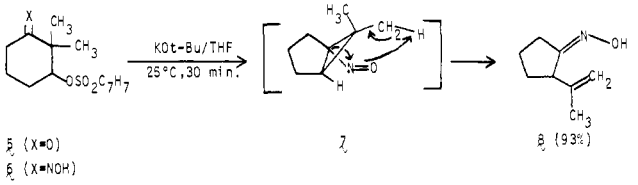
The intramolecular version of oxime alkylation should be very susceptible to kinetic control. In those cases where oxygen or nitrogen alkylation would lead to torsional strain in the imine moiety (Bredt's rule violations) it should be possible to realize carbon alkylation.[4]

Table I

base[a]	temp, °C	time, min[b]
KO-*t*-Bu[c]	25	30
NaO-*t*-Bu[c]	25	35
LiO-*t*-Bu[c]	25	300
NaH[c]	25	45
$(n\text{-}C_4H_9)_4NOH$[d]	25	5
KDPPM[d,e]	0	<1
KDPPM[d,e]	−20	50

[a] 2 equiv. [b] Time for total disappearance of starting material (TLC analysis). [c] Heterogeneous reaction. [d] Homogeneous reaction. [e] 1 *or* 2 equiv.

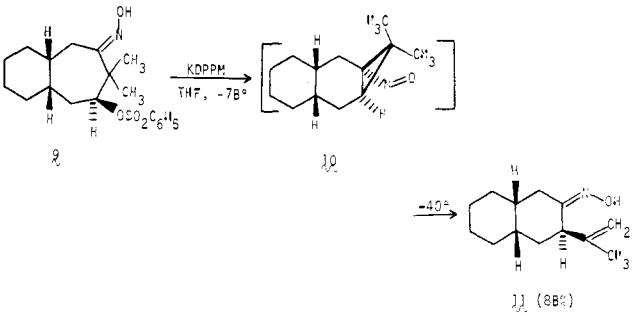
Treatment of keto tosylate **5**[5,6] with 2.2 equiv of hydroxylamine hydrochloride in 25% pyridine–ethanol at room temperature for 12 h produced the anti-oxime tosylate **6**[6-8] (59%, mp 162–163 °C). Reaction of oxime **6** with a suspension of potassium *tert*-butoxide in tetrahydrofuran did not afford isolable cyclopropyl nitroso compound **7**. The sole kinetic reaction product was the ring-contracted syn[8] oxime **8**,[6-8] apparently via a homodienyl [1,5]-hydrogen migration on intermediate **7**.



5 (X=O)
6 (X=NOH)
7
8 (93%)

The reaction (**6** → **8**) shows the counterion effect expected for an anionic displacement, with the more ionic potassium and tetrabutylammonium salts being fastest (Table I). The base of choice for this reaction is the *soluble* reagent, potassium diphenyl-4-pyridylmethide (KDPPM).[10,11] The five-membered-ring analogue of **6** does not undergo the ring contraction reaction.[6-8,12,13]

Thin-layer chromatographic analysis of the reaction of the cycloheptyl oxime **9**[6-8,14] with KDPPM reveals that the starting material is completely consumed within 5 min at −78 °C (syn oxime **11**[6-9] is the only product detected). The color



9
10
11 (88%)

of the −78 °C reaction solution is a light blue, suggestive of the intermediacy of nitroso compound **10**. The blue color fades to produce a colorless solution at ca. −40 °C.[15]

Further evidence of the stereospecificity of the ring-contraction reaction was obtained in the cyclohexyl series. Partial hydrogenation (H_2, PtO_2, C_2H_5OH) of 2-ethyl-2-methyl-1,3-cyclohexanedione[6] yielded a 3:1 mixture of ketols[6] which were subsequently converted[16] to a 3:1 mixture of keto mesylates.[6] Treatment of the keto mesylate mixture with hydroxylamine hydrochloride in 25% pyridine–ethanol afforded a 3:1 mixture of oxime mesylates **12a,b**.[6] Homogeneous major oxime mesylate **12a**[6] (mp 145–146 °C) could be obtained by fractional crystallization of the **12a,b** mixture. The minor oxime mesylate **12b**[6] (mp 110–112 °C) was purified by chromatography (SiO_2) of the crystallization residues.

Reaction of the purified oxime mesylates **12a** and **12b** with

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