Total Synthesis of Spatol and Other Spatane Diterpenes

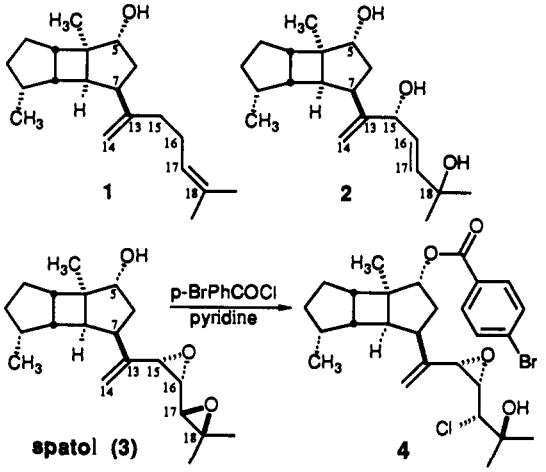
Robert G. Salomon,* Basudeb Basu, Subhas Roy, and Navzer D. Sachinvala

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

Abstract: Total syntheses of three spatane diterpenes stoechospermol (**1**), 5(*R*),15(*R*),18-trihydroxyspata-13,16(*E*)-diene (**2**), and (+)-spatol (**3**) were accomplished from a common intermediate, diol **7**. The total synthesis established as *R* the absolute configuration at the 15-position in **2**. Novel stereospecific transformations of 2,3-epoxy-1,4-diols into vicinal diepoxides were demonstrated and exploited for assembling the sensitive allylic diepoxide in the side chain of spatol. This new synthetic method allows the conversion of both 1,2-*threo*-2,3-*trans*- and 1,2-*erythro*-2,3-*trans*-2,3-epoxy-1,4-diols into vicinal 1,2-*cis*-2,3-*erythro*-1,3-diepoxides. Unexpected stability toward hydroxide anion was found for the allylic diepoxide functional array. This observation provides presumptive evidence that acid catalysis is operative in the epoxide cleaving substitution reaction of spatol by the weakly nucleophilic chloride anion that gives chlorohydrin **4**. A proclivity for erythro-selective epoxidation of allylic silyl ethers was found. The utility of *C*-silyl substituents for reversing this stereoselectivity, i.e., favoring threo-selective epoxidation of allylic silyl ethers, was established.

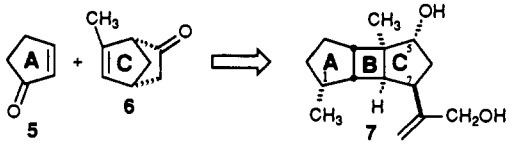
Introduction

The isolation[1] of stoechospermol (**1**) was soon followed by the discovery of a family of marine diterpenes that possesses a structurally novel carbon skeleton.[2] Besides simple dienes as in



1, the side chains of most spatane diterpenes incorporate one or more hydroxyl groups as in **2**. A unique allylic vicinal diepoxide occurs in the side chain of spatol (**3**). The high electrophilicity of this functional array is evidenced by the cleavage of an epoxide ring by chloride. Thus, esterification of **3** by treatment with *p*-bromobenzoyl chloride and pyridine is accompanied by an intriguing attack by the weakly nucleophilic chloride anion at the 17-position of the allylic diepoxide producing **4**. The reactive diepoxide in spatol is reminiscent of the electrophilic vicinal diepoxide in the cytotoxin crotepoxide[3] and the vicinal triepoxide in the antileukemic diterpenes triptolide and tripdiolide.[4] However, while the epoxy groups in these natural products are confined to rigid cyclohexane rings, those in spatol are located in a flexible acyclic side chain. The reactivity of the allylic diepoxide side chain is almost certainly at the heart of spatol's biological activities. Spatol inhibits mitosis of the fertilized sea urchin egg and cell division in human T242 melanoma and 224C astrocytoma neoplastic cell lines.[2] However, investigations of its chemotherapeutic utility are hampered by the difficulty of obtaining sufficient quantities of spatol from natural sources. This need and spatol's structural and functional complexity make the development of a practical total synthesis a worthy challenge.

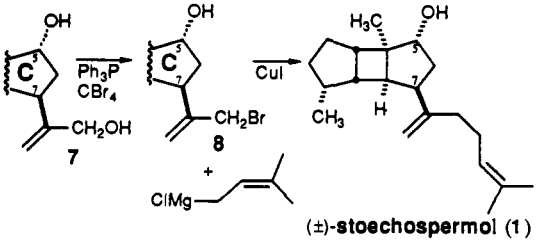
We now report the total syntheses of three spatane diterpenes stoechospermol (**1**), 5(*R*),15(*R*),18-trihydroxyspata-13,16(*E*)-diene (**2**), and (+)-spatol (**3**) from a common intermediate, diol **7**. This diol is available in 16% overall yield in 21 steps from cyclopent-2-en-1-one (**5**) and 6-methylbicyclo[2.2.1]hept-5-en-2-one (**6**). Our stereocontrolled synthesis[5] features $2\pi + 2\pi$



photocycloaddition of **5**, as an A-ring precursor, with a carbonyl-masked derivative of **6**[6] as a temporarily bridged C-ring precursor that incorporates the hydroxyl substituent at position 5 in latent form. Efficient, virtually quantitative resolution of an early intermediate provides homochiral **7** in 8% yield from racemic **6**.

Results and Discussion

Stoechospermol. Completion of the spatane skeleton requires the addition of five carbons to the side chain of diol **7**. The *first* total synthesis[7] of a spatane diterpene was accomplished by selective bromodehydroxylation of the primary allylic hydroxyl group in (±)-**7** followed by a copper(I) iodide catalyzed coupling of the resulting allylic bromide **8** with an excess of prenylmagnesium chloride.[8] The ^{1}H NMR spectrum of the product, (±)-stoechospermol (**1**), is identical with that of (+)-**1** isolated from *Stoechospermum marginatum*.[1,2]

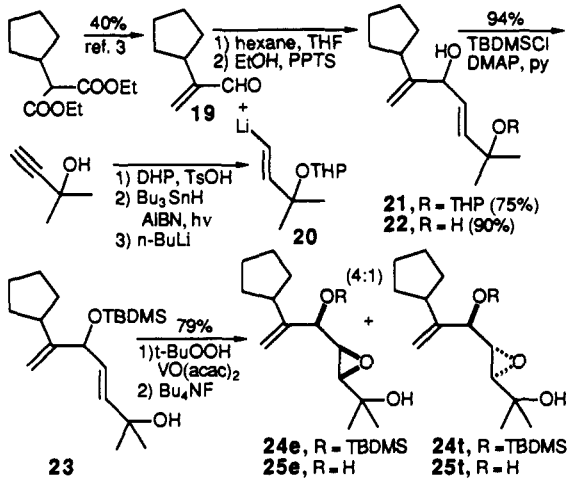


5(*R*),15(*R*),18-Trihydroxyspata-13,16(*E*)-diene. For the *first* total synthesis of trihydroxylated spatane diterpene **2**, the vinyl

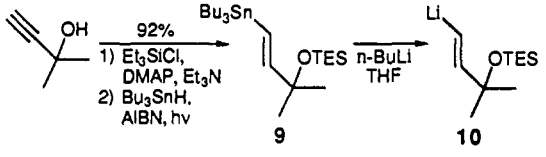
(1) Fernandes, S. L.; Kamat, S. Y.; Paknikar, S. K. *Tetrahedron Lett.* **1980**, *21*, 2249.
(2) (a) Gerwick, W. H.; Fenical, W.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 7991. (b) Gerwick, W. H.; Fenical, W.; Sultanbawa, M. U. S. *J. Org. Chem.* **1981**, *46*, 2233. (c) Gerwick, W. H.; Fenical, W. *J. Org. Chem.* **1983**, *48*, 3325. (d) Ravi, B. N.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 129.
(3) (a) Kupchan, S. M.; Hemmingway, R. J.; Coggon, P.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 2982. (b) Kupchan, S. M.; Hemmingway, R. J.; Smith, R. M. *J. Org. Chem.* **1969**, *34*, 3898.
(4) Becker, A. A.; Janusz, J. M.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 5679.
(5) Salomon, R. G.; Sachinvala, N. D.; Roy, S.; Basu, B.; Raychaudhuri, S. R.; Miller, D. B.; Sharma, R. B. *J. Am. Chem. Soc.* **1991**, *113*, preceding article in this issue.
(6) Lal, K.; Salomon, R. G. *J. Org. Chem.* **1989**, *54*, 2628.
(7) For a preliminary report of this work see: Salomon, R. G.; Sachinvala, N. D.; Raychaudhuri, S. R.; Miller, D. B. *J. Am. Chem. Soc.* **1984**, *106*, 2211.
(8) Kwart, H.; Miller, R. K. *J. Am. Chem. Soc.* **1954**, *76*, 5403.

0002-7863/91/1513-3096$02.50/0 © 1991 American Chemical Society

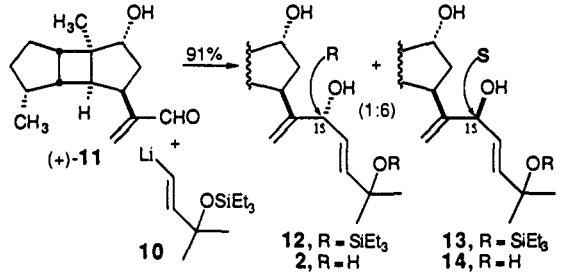
Scheme I



trans nucleophile **10** was generated stereoselectively from 2-methyl-3-butyn-2-ol through a vinyl tin intermediate **9**. The

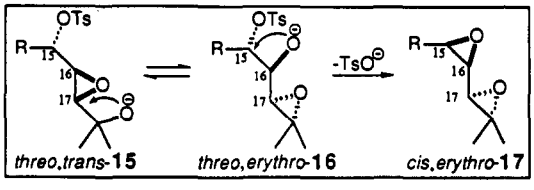


α,β-unsaturated aldehyde (+)-**11**, available from diol (+)-**7** in 96% yield by MnO_2 oxidation, underwent exclusive 1,2-addition of **10** to give two epimeric alcohols **12** and **13** in 91% yield.



Desilylation of the minor adduct **12** delivered the natural product **2** with $[\alpha]^{22}_D$ −32.2° (reported[2] $[\alpha]^{22}_D$ −33.4°). Desilylation of the major adduct **13** afforded **14**, which exhibits $[\alpha]^{22}_D$ −1.01° and is an epimer of the natural product at position 15. The configuration of **2** at position 15 had not been established previously. Our assignment of the *R* configuration to this center in the natural product is based on a conversion of the epimer **14** into spatol (vide infra).

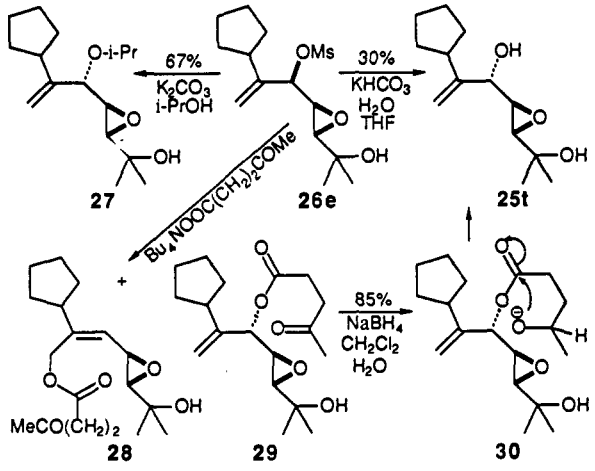
Vicinal Diepoxides from 2,3-Epoxy-1,4-diols. The unique allylic vicinal diepoxide in spatol (**3**) constitutes by far the most challenging aspect of any synthetic approach to this target.[9] Our strategy for assembling the spatol side chain was based on the premise that an appropriately activated derivative, e.g., *threo,trans*-**15** of a 15,16-threo-16,17-trans (spatane numbering) 2,3-



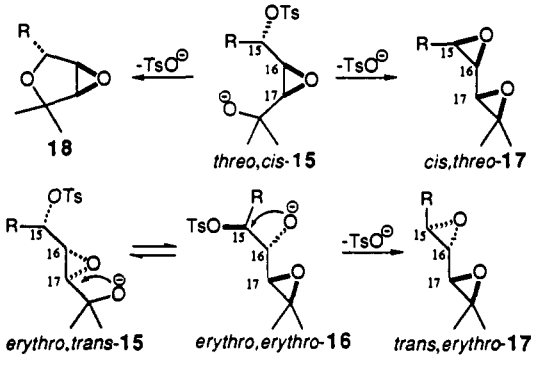
epoxy-1,4-diol (functional array numbering), could stereospecifically interconvert with the corresponding derivative of a 3,4-epoxy-1,2-diol, e.g., *threo,erythro*-**16** by a reversible intra-

(9) For an alternative strategy for construction of the spatol allylic diepoxide side chain, see: Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1985**, *26*, 6109.

Scheme II



molecular S_N2 displacement, a Payne rearrangement.[10] Subsequent irreversible intramolecular S_N2 displacement of a leaving group from the 15-position would deliver the 15,16-cis-16,17-erythro diepoxide array, as in *cis,erythro*-**17**, required for the spatol side chain. A similar synthesis of *cis,threo*-**17** from *threo,cis*-**15** might be derailed by a competing cyclization to an epoxy furan **18**. However, furan formation from *threo,trans*-**15** would not



interfere with the generation of *cis,erythro*-**17** owing to the ring strain that would be created upon formation of a trans fused epoxy furan. A similar double S_N2 displacement process should deliver *trans,erythro*-**17** from *erythro,trans*-**15** via *erythro,erythro*-**16**. To test this hypothesis, model threo and erythro *trans*-2,3-epoxy-1,4-diols were assembled as outlined in Scheme I. To assure epoxidation of the appropriate C=C bond, the tertiary hydroxyl in **21** was depyranylated and the secondary hydroxyl in **22** was selectively silylated to provide **23**. Vanadium-catalyzed epoxidation produced a 4:1 mixture of erythro and threo epoxides **24e** and **24t**, respectively. Desilylation delivered the corresponding epoxy diols.

In an early attempt at generating a vicinal diepoxide, the monomesylate derivative **26e** of the erythro diol **25e** was boiled under reflux in 2-propanol in the presence of solid K_2CO_3. Payne rearrangement followed by heterocyclization did not occur. Rather, intermolecular S_N2 displacement produced the isopropyl ether **27** of threo epoxy diol **25t** (Scheme II). To explore the utility of such intermolecular S_N2 displacement for interconversion of threo and erythro epoxy diols **25t** and **25e**, the monomesylate **26e** was heated with aqueous bicarbonate. A low yield of the threo epoxy diol **25t** was obtained. A better route to **25t** was devised, exploiting intermolecular S_N2 displacement of the mesylate in **26e** by levulinate (Scheme II). Whereas reaction in 2-methyl-2-propanol solvent favored net S_N2' substitution delivering **28** virtually quantitatively, in most solvents S_N2 substitution produced the threo levulinate ester **29** (Table I). Reaction in DME provided **29** exclusively in 91% yield. Removal of the levulinate ester to provide threo epoxy diol **25t** in 85% yield was readily accomplished

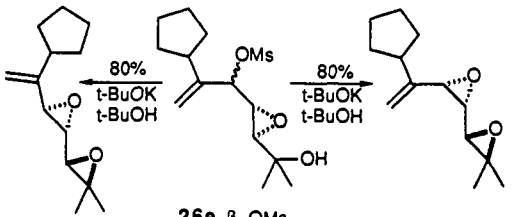
(10) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

Table I. Solvent Effects on Reaction of **26e** with Tetramethylammonium Levulinate

Solvent	temp (°C)	time (h)	**29:28**	yield (%)
$CHCl_3$	61	30	68:32	98
t-BuOH	80	4	0:100	96
CH_3CN	80	4	65:35	94
DMF	80	3.5	100:0	77
DME	80	4.5	100:0	91

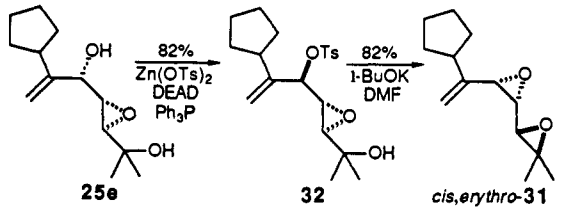
under mild conditions upon treatment of **29** with sodium borohydride.[11]

Since the tertiary hydroxyl group in **26e** is apparently not sufficiently nucleophilic to displace the epoxy leaving group, conditions were sought that would generate an alkoxide from the tertiary hydroxyl. Treatment of the erythro monomesylate **26e** with *t*-BuOK in *t*-BuOH promoted a clean, stereospecific rearrangement and heterocyclization to deliver the diepoxide *trans,erythro*-**31**. Similar treatment of the threo monomesylate



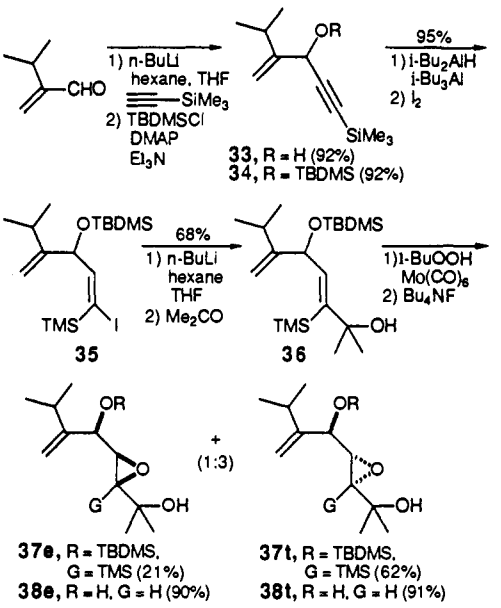
26t provided *cis,erythro*-**31**, which contains an allylic diepoxide resembling the side chain of spatol. Considering the substitution reaction of monomesylate **26e** with aqueous bicarbonate to give **25t** (Scheme II), we expected a similar substitution with tetrabutylammonium hydroxide. Instead, a high yield of diepoxide *trans,erythro*-**31** was obtained. The unexpected stability of this allylic diepoxide product toward hydroxide is especially interesting in view of the epoxide cleaving substitution reaction of spatol with the weakly nucleophilic chloride anion to give chlorohydrin **4** (vide supra). Apparently, the latter reaction is an acid-catalyzed epoxide opening that is induced by pyridinium hydrochloride, a byproduct of the acylation with *p*-bromobenzoyl chloride in the presence of pyridine. It remains an interesting question why chloride attacks the 17-position in spatol to generate **4** rather than inducing cleavage of the presumably weaker allylic C–O bond at position 15. That the reactivity of the side chain functionality is important for spatol's biological activity is supported by the fact that both of the isomeric allylic diepoxides **31** are biologically active.[12]

Recall that epoxidation of **23** favored the erythro over the threo epoxy TBDMS ether by 4:1 (Scheme I). Furthermore, the threo mesyloxy epoxide **26t** is the precursor of the cis,erythro diepoxide required for spatol. Therefore, we sought a route from the *erythro* epoxy alcohol **25e** to an activated derivative of the *threo* epoxy alcohol, i.e., activation with concomitant inversion of configuration.

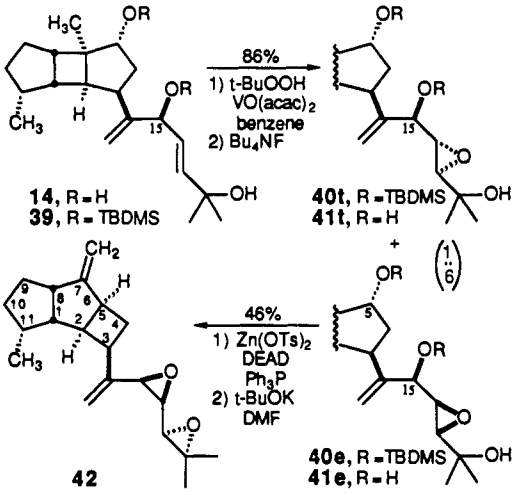


This can be accomplished by the Still modification of the Mitsunobu reaction.[13] Treatment of **25e** with $Zn(OTs)_2$, diethyl azodicarboxylate, and triphenylphosphine gave tosylate **32**, which upon treatment with *t*-BuOK in *t*-BuOH, afforded allylic diepoxide *cis,erythro*-**31** in only 66% yield together with an unidentified byproduct (17%). Solvent strongly influences the ratio of these products (see Experimental Section) with the desired diepoxide being the only product using DMF as reaction solvent.

Scheme III



Scheme IV



Threo Epoxy Alcohols. Since the epoxidation of **23** favored generation of the erythro over the threo epoxy TBDMS ether by 4:1 (Scheme I) and since the threo mesyloxy epoxide **26t** is the precursor of the cis,erythro diepoxide required for spatol, we sought an epoxidation route favoring threo epoxy TBDMS ethers. The possible utility of a C-silyl substituent as a stereocontrol element was explored (Scheme III). Indeed, molybdenum-catalyzed epoxidation of **36** favors the threo epoxide **37t** in contrast with the epoxidation of **23**, which favored the erythro epoxide **24e**. This inversion of stereoselectivity by a C-silyl substituent is analogous to that observed previously for similar epoxidations of secondary allylic *alcohols*[14] as opposed to the TBDMS *ethers* involved here.

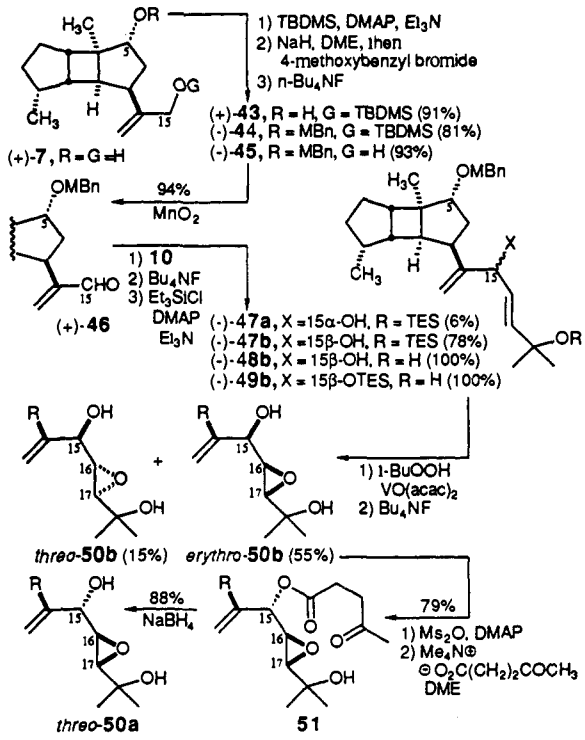
(11) Hassner, A.; Strand, G.; Rubinstein, M.; Patchornik, A. *J. Am. Chem. Soc.* **1975**, *97*, 1614.

(12) The ability of these allylic diepoxides to inhibit microtubule assembly and the mitosis of sea urchin eggs was examined. *cis,erythro*-**31** showed 36% inhibition at 16 μg/mL in the sea urchin egg assay and 74% inhibition of microtubule assembly at 70 μg/mL, and *trans,erythro*-**31** showed 28% inhibition at 16 μg/mL in the sea urchin egg assay and 64% inhibition of microtubule assembly at 70 μg/mL. For details of these techniques, see: Murthi, K. K.; Salomon, R. G.; Sternlicht, H. *Prostaglandins* **1990**, *39*, 611.

(13) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461.

(14) For erythro stereoselectivity in metal-catalyzed epoxidations of allylic *alcohols*, see: (a) Mihelich, E. D. *Tetrahedron Lett.* **1979**, 4729. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733. (c) Takai, K.; Oshim, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 1657. (d) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. For threo stereoselectivity in metal catalyzed epoxidations of C-silyl allylic *alcohols*, see: (e) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387.

Scheme V

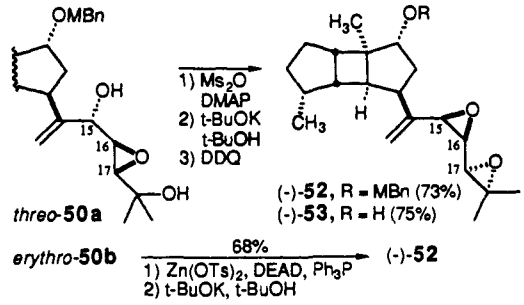


The utility of C-silyl groups as stereocontrol elements in metal-catalyzed epoxidations depends on their stereospecific removal. Treatment of the silyl epoxides **37** with tetrabutylammonium fluoride delivered the corresponding epoxides **38** with retention of configuration as expected.[15]

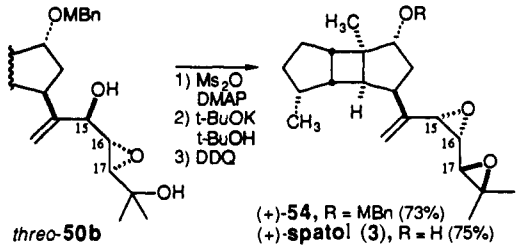
(+)-Spatol. An early attempt at generating the allylic diepoxide side chain in the spatane ring system is outlined in Scheme IV. A selectively disilylated derivative **39** was readily available from triol **14**. Vanadium-catalyzed epoxidation of **39** produced a 1:6 mixture of disilylated epoxides **40t** and **40e** in good yield. The corresponding triols **41** were obtained upon treatment with Bu_4NF. However, generation of an inverted tosylate from the major epimer **41e** followed by treatment with base produced an allylic diepoxide **42** with a rearranged tricyclic nucleus. The *cis,anti,cis*-tricyclo[5.3.0.$0^{2,5}$]decane nucleus of **42** is formed by a Wagner–Meerwein rearrangement of the *cis,anti,cis*-tricyclo[5.3.0.$0^{2,6}$]-decane nucleus of **41e**, apparently owing to unintended activation of the 5-hydroxyl that accompanied the desired activation of the hydroxyl at position 15.

These results suggested that derivatives of epoxy triols **41e** and **41t** with the hydroxyl at position 5 masked would be desirable for generation of the spatol side chain without accompanying rearrangement of the tricyclic nucleus. The lability of the allylic diepoxide array in spatol (**3**) under acidic conditions limited the choice of derivatives to those with masking groups that would be removable under neutral or basic reaction conditions. The further requirement for stability toward a vinyllithium reactant and the presence of unsaturation in the synthetic target agreed with the choice of *p*-methoxybenzyl (MBn) ether derivatives. The MBn masking group is removable under mild conditions by oxidative cleavage with DDQ.[16] The MBn derivatives *erythro*-**50b** and *threo*-**50b** of **41e** and **41t** were prepared from diol (+)-**7** as outlined in Scheme V. Another isomer, *threo*-**50a** was prepared from *erythro*-**50b** by inversion of configuration at position 15 through levulinate ester **51**.

An allylic cis diepoxide (−)-**52** was generated upon treatment of *threo*-**50a** with methanesulfonic anhydride and *p*-(dimethylamino)pyridine followed by reaction of the intermediate secondary monomethanesulfonate with *t*-BuOK. The same diepoxide was

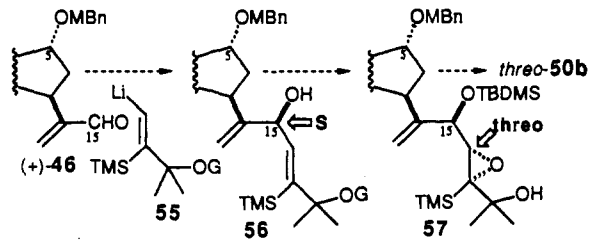


also generated more directly from *erythro*-**50b** in better overall yield upon treatment with $Zn(OTs)_2$, diethyl azodicarboxylate, and triphenylphosphine followed by reaction of the intermediate secondary tosylate with *t*-BuOK. Removal of the MBn masking group by treatment with DDQ converted (−)-**52** into an allylic cis diepoxide (−)-**53**. That (−)-**53** was not spatol (**3**) was evident from its optical activity, $[\alpha]_D = -10.0°$ in contrast with $[\alpha]_D = +45.6°$ reported for the natural product. Small chemical shift differences, e.g., vinyl ^1H NMR resonances at δ 5.14 and 5.09, confirmed that (−)-**53** is epimeric at positions 15, 16, and 17 with (+)-spatol (**3**), which exhibits vinyl resonances at δ 5.13 and 5.02.



Similar stereospecific transformations of *threo*-**50b** produced an allylic cis diepoxide that was identical with the natural product. Each resonance in the ^1H NMR spectrum of synthetic (+)-spatol (**3**) coincided within 0.01 ppm with a spectrum of an authentic sample of natural spatol.[17]

Prospects for a Practical Total Synthesis of (+)-Spatol. Two approaches for achieving a practical synthesis of spatol are suggested by our studies. One route exploits the stereoselectivity discovered for nucleophilic additions to the aldehyde (+)-**46**. The



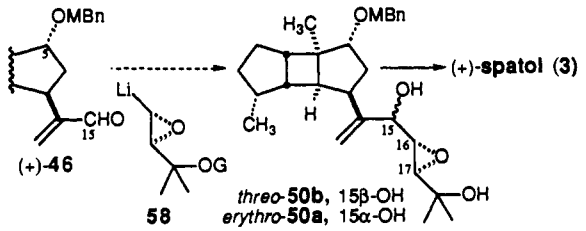
13:1 diastereoselectivity favoring generation of the *S* configuration at position 15 during the (+)-**46** to **47** conversion (Scheme V) did not result in an efficient, practical synthesis of spatol since epoxidation of the major epimer, (−)-**49b**, is erythro-selective. Only the minor epoxidation product from (−)-**49b**, *threo*-**50b**, is a precursor for spatol. We did demonstrate the feasibility of using a C-silyl substituent to promote threo-selective epoxidation of an allylic TBDMS ether (Scheme III). However, the route established for assembling the C-silylated allylic alcohol **36** (Scheme III) is too long to provide a workable solution to this problem. If a vinyllithium **55** were available, a more convergent route to the requisite C-silyl derivative **56** would be possible. Diastereoselective generation of the *S* configuration at the 15-position in **56** is anticipated for the addition of **55** to aldehyde (+)-**46**. Threo-selective epoxidation, as for **36** (Scheme III), would then

(15) Chan, T. J.; Lau, P. W. K.; Li, M. P. *Tetrahedron Lett.* **1976**, 2667.
(16) Oikawa, W.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.

(17) All ^1H and ^{13}C NMR spectra of (−)-**53** and (+)-spatol (**3**), including those of an authentic sample of natural spatol, were compared in $CDCl_3$ solutions on the same Brucker 9.4 Tesla MSL-400 FT-NMR spectrometer.

provide **57** from which the intermediate *threo*-**50b** in our spatol synthesis would be available by a stereospecific, one-pot, double desilylation as demonstrated earlier for the **37t** to **38t** conversion.

A second approach for achieving a practical synthesis of spatol that is suggested by our studies depends on the availability of a synthetic equivalent of the hypothetical α-lithioepoxide **58**.[18]



Efficient diastereoselective generation of *threo*-**50b** can be anticipated from the addition of homochiral **58** to aldehyde (+)-**46**. Stereospecific conversion of *threo*-**50b** into spatol was demonstrated earlier. Furthermore, application of the novel transformations of 2,3-epoxy-1,4-diols reported herein to the conversion of the expected minor epimeric adduct, *erythro*-**50a**, into an allylic diepoxide should also produce (+)-spatol (**3**) stereospecifically. This exceptionally convergent strategy for construction of the allylic diepoxide side chain of spatol is especially attractive since it does not depend on stereocontrol at position 15. These plans for optimizing our synthesis are the subject of ongoing research.

Experimental Section[19]

Allylic Bromide 8. A solution of the 5-hydroxy allylic alcohol **7**[5] (9.6 mg, 0.040 mmol) in dry acetonitrile (225 μL) was mixed with triphenylphosphine (12.2 mg, 0.047 mmol, 1.15 equiv). To this mixture was added carbon tetrabromide (44.1 mg, 0.133 mmol, 3.3 equiv), and the mixture was stirred at room temperature for 12 h. Solvents were then evaporated from the reaction mixture under a stream of dry nitrogen. Flash chromatography on a 10 × 150 mm column of silica gel 230–400 mesh with 1% ethyl acetate in methylene chloride afforded the allylic bromide **8** (7.6 mg, 0.025 mmol, 63%): mp 72–73 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (3 H, d, J = 6.1 Hz), 0.99 (3 H, s), 1.19–2.05 (10 H), 2.23 (1 H, dd, J = 5.4, 14.5 Hz), 3.35 (1 H, m), 3.75 (1 H, d, J = 4.7 Hz), 3.84 (2 H, dd, J = 10.2, 15.6 Hz), 4.97 (1 H, s), 5.26 (1 H, s).

(+)-Stoechospermol (1). To copper(I) iodide (1.4 mg, 0.007 mmol) at 0 °C was added prenylmagnesium chloride[8] in tetrahydrofuran (0.7 M, 100 μL, 0.070 mmol). To this reagent at −50 °C[20] was added the allylic bromide **8** (3.0 mg, 0.01 mmol) in tetrahydrofuran (50 μL) and the resulting mixture allowed to warm to room temperature and stirred 14 h. The reaction mixture was quenched with aqueous ammonium chloride (50 mg in 300 μL water) then concentrated aqueous ammonium hydroxide (50 μL) and extracted with ether (5 mL). The aqueous layer was reextracted with ether (5 mL), and the ether extracts were then washed serially with water. The ether layers were combined and concentrated in vacuo to give a product mixture that was flashed chromatographed on a 10 × 150 mm column of 230–400 mesh silica gel with 1% ethyl acetate in methylene chloride. The product, racemic 5-hydroxyspata-13,17(*E*)-diene (**1**) (1.63 mg, 5.6 μmol, 56% yield) exhibited a ^{1}H NMR spectrum identical with that found for the natural product (+)-**1** isolated from *S. marginatum*.[1]

2-Methyl-2-[(triethylsilyl)oxy]-3-butyne. Triethylsilyl chloride (3.0 g, 20 mmol) was added dropwise to a stirring mixture of 2-methyl-3-butyn-2-ol (1.0 g, 12 mmol), triethylamine (2.53 g, 25 mmol), and 4-(dimethylamino)pyridine (145 mg, 1.2 mmol) in methylene chloride (25 mL) at 0 °C under nitrogen. After being stirred an additional 1 h at 0 °C, the mixture was washed with water and dried ($MgSO_4$). The volatiles were removed under water aspirator reduced pressure and the resulting residue was flash chromatographed (hexane) to give the title compound as a colorless oil (2.35 g, 100%): ^{1}H NMR δ 0.46–0.74 (6 H), 0.87–0.98 (6 H), 1.43–1.47 (6 H), 2.36 (H, s). Anal. Calcd for $C_{11}H_{22}OSi$: C, 66.59; H, 11.17. Found: C, 66.43; H, 11.12.

3-Methyl-1-(tri-*n*-butylstannyl)-3-[(triethylsilyl)oxy]but-1(*E*)-ene (9). A mixture of 2-methyl-2-[(triethylsilyl)oxy]-3-butyne (1.0 g, 5.1 mmol), tri-*n*-butyltin hydride (1.6 g, 5.6 mmol), and azo(bisisobutyro)nitrile (20 mg) was irradiated with a sunlamp (110 V, 250 W) for 10 min and then stirred at 90 °C for 2 h. The crude mixture was flash chromatographed (hexane) to yield **9** as a colorless oil (1.76 g, 92%): ^{1}H NMR δ 0.48–0.61 (6 H), 0.82–0.96 (24 H), 1.23–1.60 (12 H), 5.86–6.26 (H). Anal. Calcd for $C_{23}H_{50}OSiSn$: C, 56.44; H, 10.29. Found: C, 56.35; H, 10.32.

(+)-5(*R*),15(*R*)-Dihydroxy-18-[(triethylsilyl)oxy]spata-13,16(*E*)-diene (12) and (+)-S(*R*),15(*S*)-Dihydroxy-18-[(triethylsilyl)oxy]spata-13,16(*E*)-diene (13). *n*-Butyllithium (546 μL, 1.37 mmol, 2.5 M in hexanes) was added dropwise to a stirred solution of the vinylstannane **9** (668 mg, 1.36 mmol) in tetrahydrofuran (3 mL) at −78 °C under nitrogen. After being stirred 2 h at −78 °C and 1 h at −10 °C, a solution of the aldehyde (+)-**11**, (60 mg, 0.256 mmol) in tetrahydrofuran (1 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to room temperature over 3 h and then quenched with methanol (500 μL). After the volatiles were removed by rotary evaporation, the residue was flash chromatographed to afford a minor epimer **12** (14.2 mg, 13%) as a colorless oil (^{1}H NMR δ 0.44–0.60 (6 H), 0.88–0.95 (15 H), 1.28–2.05 (17 H), 2.26 (H, dt, J = 12 and 4 Hz), 2.78–3.0 (H, m), 3.71 (H, d, J = 4 Hz), 4.38 (H, d, J = 8 Hz), 4.90 (H, s), 5.29 (H, s), 5.48 (H, dd, J = 16 and 8 Hz), 5.79 (H, d, J = 16 Hz)) and a major epimer **13** (80 mg, 78%) as a semisolid mass: ^{1}H NMR δ 0.47–0.60 (6 H), 0.82–0.95 (15 H), 1.27–2.04 (17 H), 2.22 (H, dt, J = 12 and 4 Hz), 3.14–3.22 (H, m), 3.70 (H, d, J = 4 Hz), 4.41 (H, bs), 4.88 (H, s), 5.05 (H, s), 5.60 (H, dd, J = 16 and 4 Hz), 5.75 (H, d, J = 16 Hz).

5(*R*),15(*R*),18-Trihydroxyspata-13,16(*E*)-diene (2). A mixture of the triethylsilyl ether **12** (12 mg, 0.028 mmol) in THF (1 mL) and tetrabutylammonium fluoride (140 μL, 0.14 mmol, 1 M in THF) was stirred at room temperature for 40 h. Volatiles were removed by rotary evaporation, and the residue was flash chromatographed on silica gel with 80% ethyl acetate in hexanes as eluant to give the known triol **2**[1] (8.5 mg, 95%): $[\alpha]^{22}_D$ −33.2° (*c* 1.3, $CDCl_3$), reported $[\alpha]_D$ −33.4 (*c* 0.73, $CHCl_3$).

(+)-5(*R*),15(*S*),18-Trihydroxyspata-13,16(*E*)-diene (14). A mixture of the triethylsilyl ether **13** (75 mg, 0.173 mmol) in THF (2 mL) and tetrabutylammonium fluoride (1 mL, 1.0 mmol, 1 M in THF) was stirred overnight at room temperature. The volatiles were removed by rotary evaporation, and the residue was flash chromatographed with 80% ethyl acetate in hexanes as eluant to yield the triol **14** (55.1 mg, 99%) as colorless crystals: mp 124–125 °C; $[\alpha]^{22}_D$ +1.01° (*c* 2.0, $CHCl_3$); ^{1}H NMR δ 0.85 (3 H, d, J = 6.4 Hz), 0.96 (3 H, s), 1.18–2.10 (18 H), 2.23 (H, dt, J = 16 and 4 Hz), 3.16–3.32 (H, m), 3.72 (H, d, J = 4 Hz), 4.44 (H, d, J = 5.5 Hz), 4.90 (H, s), 5.06 (H, s), 5.68 (H, dd, J = 16 and 4 Hz), 5.84 (H, d, J = 16 Hz). Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.95; H, 10.06. Found: C, 74.91; H, 10.12.

Ethyl 2-Cyclopentylacrylate. To a solution of the diethyl cyclopentylmalonate[21] (22.8 g, 0.1 mol) in ethanol (64 mL) at 0 °C was added potassium hydroxide (6.72 g, 0.12 mol) in water (28 mL) very slowly over 1 h. The temperature of the reaction was maintained at 0 °C during the course of the addition and for approximately 2 h after the addition was complete. The reaction mixture was then allowed to attain room temperature and then stirred overnight (10 h). The ethanol was then removed by vacuum transfer to a receiver cooled to −78 °C and the residue partitioned between ether and water. The aqueous layer was washed once more with ether and the ether layers were combined, washed with brine, dried over sodium sulfate, and concentrated in vacuo to recover unreacted starting diethyl cyclopentylmalonate (1.94 g, 8.5 mmol). The aqueous layer was then cooled to −10 °C and acidified to pH 1 at that temperature by slow addition of concentrated hydrochloric acid. Extraction of the aqueous layer with ether (6 × 50 mL) and drying over anhydrous magnesium sulfate followed by rotary evaporation of the solvent yielded the half-acid (17.8 g, 0.089 mol, 89% yield).

A stock solution containing sodium acetate (8.2 g), acetic acid (296.4 mL), 30 aqueous formalin (216 mL), and diethylamine (freshly distilled, 74.1 mL) was prepared at 10 °C. The previous half-acid (63.1 g, 0.32 mol) was added the stock solution (400 mL) at room temperature. The mixture was immersed in an oil bath preheated to 90 °C. After carbon dioxide evolution had ceased, the reaction mixture was cooled and transferred to a separatory funnel with water and ether. The aqueous phase was then extracted with ether (5 × 50 mL) and the organic extracts combined. Removal of acetic acid was accomplished by washing with saturated aqueous sodium bicarbonate solution. The organic phase was then washed with a 10% solution of hydrochloric acid, then with water, and then with brine. The organic phase was dried over anhydrous magnesium sulfate and concentrated in vacuo. Ethyl 2-cyclopentyl-

(18) Silyl-stabilized α-lithio epoxides might serve as synthetic equivalents of **58** since they are readily available by metallation of the corresponding epoxy silanes (Eisch, J. J.; Galle, J. E. *J. Am. Chem. Soc.* **1976**, *98*, 4646. *J. Organomet. Chem.* **1976**, *121*, C10; **1976**, *41*, 2615; **1988**, *341*, 293) and since desilylation can be accomplished with retention of configuration as in the **37t** to **38t** conversion.

(19) For information on "General" experimental details and "Materials" see the Experimental Section of ref 5.

(20) Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, G. *Tetrahedron Lett.* **1977**, 1181.

(21) Joshi, von R. K.; Perlia, X. *Pharm. Acta Helv.* **1979**, *54*, 135.

acrylate thus obtained weighed 28.1 g (0.17 mol, 53% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.3–2.1 (10 H), 2.89 (1 H, quin, J = 8.3 Hz), 4.25 (2 H, q, J = 6.9 Hz), 5.56 (1 H, s), 6.14 (1 H, s). On smaller scale, i.e., 8–10 g, the yields are generally 10% higher. Without further purification, this product was used for preparing 2-cyclopentylallyl alcohol.

2-Cyclopentylallyl Alcohol. To a solution of diisobutylaluminum hydride (12.1 mL, 9.65 g, 68 mmol, 3.0 equiv) in diethyl ether (360 mL) was added ethyl 2-cyclopentylacrylate (3.80 g, 22.6 mmol) dropwise over 10 min at −78 °C. The reaction mixture was then allowed to gradually warm to room temperature over 3 h and stirred for another 2 h. The course of the reaction was monitored by TLC with 10% ethyl acetate in methylene chloride. The R_f valves of the ester and allyl alcohol were 0.69 and 0.33, respectively. The acrylic ester is UV and iodine active but doesn't stain with vanillin; however, the allyl alcohol shows no activity in UV or iodine but stains a blue-green color with the vanillin indicator. Upon loss of UV activity at R_f 0.69, the reaction mixture is cooled to −10 °C and treated very *cautiously* with an excess of freshly distilled methanol (20 mL) added dropwise over approximately 20 min. The mixture containing a suspension of aluminates is then allowed to attain room temperature, the aluminates are dissolved in 10% hydrochloric acid (20 mL) and extracted immediately into ether, and the phases are separated. The aqueous layer is then reextracted with ether (4 × 20 mL). The combined organic extracts were washed once with dilute bicarbonate water and brine. Drying over anhydrous magnesium sulfate and concentration in vacuo afforded 2-cyclopentylallyl alcohol (2.84 g, 88% yield). Without further purification, this product was used for preparing 2-cyclopentylacrylaldehyde. A purified sample was recovered from that oxidation by chromatography on silica gel (vida infra): ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.0–1.9 (8 H), 2.41 (1 H, quin, J = 8.3 Hz), 4.10 (2 H, s), 4.88 (1 H, s), 4.98 (1 H, s). Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.98; H, 11.12.

2-Cyclopentylacrylaldehyde (19). To a solution of the allyl alcohol (5.1 g, 40 mmol) in methylene chloride (160 mL) was added manganese dioxide (24-g portions added every 24 h for 3 days). A total of 72 g (0.83 mol, 20.6 equiv) of manganese dioxide was consumed and the reaction mixture stirred for 4 days. The reaction was monitored by TLC with methylene chloride as the mobile phase. R_f values for the allyl alcohol and the acryl aldehyde were 0.27 and 0.55. The allyl alcohol shows no UV activity but stains a deep blue-green color with vanillin. The acryl aldehyde is UV active, shows an orange color with dinitrophenylhydrazine, but stains only a very faint navy blue to grey with vanillin indicator. After 4 days, the reaction was still incomplete and a strongly vanillin staining (blue) impurity was developing at R_f 0.69. The reaction mixture was filtered through a 3-cm thick layer of Celite that was washed with copious amounts of methylene chloride, and the solvent was then removed at 10 °C by rotatory evaporation. Flash chromatography of the oil (5.3 g) thus obtained on a silica gel column 80 × 180 mm with 10% ether in hexanes (acrylaldehyde R_f 0.19, impurity R_f 0.36, and allyl alcohol stays at the origin), yielded the acrylaldehyde **19** (3.97 g, 32 mmol, 80% yield). The column was then eluted with methylene chloride to recover unreacted allyl alcohol (810 mg, 6.4 mmol, 16% recovery). The acrylaldehyde **19** is very sensitive and should be stored under argon at −78 °C. A 70% solution of **19** in hexanes or pentanes (dry, olefin-free) under argon at −78 °C is stable for months: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.1 (8 H), 2.84 (1 H, quin, J = 8.2), 5.95 (1 H, s), 6.25 (1 H, s), 9.56 (1 H, s).

2-Methyl-2-[(tetrahydropyranyl)oxy]-3-butyne. The procedure of Corey, Ulrich, and Fitzpatrick[22] was modified. A mixture of 2-methyl-3-butyn-2-ol (8.4 g, 0.1 mol, 9.67 mL), dihydropyran, freshly distilled over sodium (11 mL, 10.1 g, 0.12 mmol, 1.2 equiv), and methylene chloride (84 mL) was cooled to 0 °C and treated with a catalytic amount of *p*-toluenesulfonic acid (7 mg). The reaction was exothermic, and without the ice–water bath, it was violent. The mixture was stirred and allowed to attain room temperature. The progress of the reaction was monitored by TLC with neat methylene chloride as the eluant; R_f values for the alkynol, dihydropyran, and the tetrahydropyranyl ether were 0.18, 0.38, and 0.53 respectively. The spots were visualized with vanillin indicator. Within 2–2.5 h, all the starting alkynol was consumed. The reaction mixture was then washed with a solution of saturated sodium bicarbonate and then brine and dried over anhydrous potassium carbonate. Methylene chloride and some dihydropyran were removed by rotory evaporation, and the resulting liquid was fractionally distilled to remove excess dihydropyran (85–87 °C (760 mmHg)). The tetrahydropyranyl ether boiled between 120–124 °C (760 mmHg) (15.9 g, 94.5% yield).[22]

3-Methyl-3-[(tetrahydropyranyl)oxy]-1-(tri-*n*-butylstannyl)-1(*E*)-butene. In a 300-mL round-bottom flask, a mixture containing tri-*n*-butyltin hydride (47.5 g, 0.163 mol), 2-[(tetrahydropyranyl)oxy]-2-methyl-3-butyne (24.9 g, 0.148 mol) and AIBN (900 mg) was irradiated with a GE 475-W, 110-V sunlamp and then, after ~10 min, immersed in an oil bath preheated to 80 °C. Although the initial reaction is very (often violently) exothermic, heating is necessary to ensure that all of the alkyne is consumed. The use of a reaction flash 4× the total volume of the liquid facilitates control of the reaction. The progress of the reaction was monitored by TLC with 10% ethyl acetate in hexanes as the mobile phase. R_f values of the hydride, the alkyne, and the vinylstannane were 0.91, 0.48, and 0.65, respectively. The vinyl stannane was less polar than the alkyne and stained a deep purple with vanillin indicator. The reaction went to completion in 3 h. The crude mixture was chromatographed in 20-g batches on a 120 × 180 mm silica gel flash column and eluted with 5% ethyl acetate in hexanes (R_f trans vinyl stannane 0.40). Removal of solvents in vacuo gave vinylstannane (57 g, 85%).[22] Note that the vinyl stannane can trap a considerable amount of solvents; therefore, it was stirred vigorously at room temperature under high vacuum (0.02 mmHg) to remove all traces of solvents.

6-Cyclopentyl-5-hydroxy-2-methyl-2-[(tetrahydropyranyl)oxy]-3-(*E*),6-heptadiene (21). To a solution of 3-methyl-3-[(tetrahydropyranyl)oxy]-1-(tributylstannyl)-1(*E*)-butene (4.59 g, 10 mmol) in THF (15 mL) at −78 °C was added *n*-BuLi in hexane (2.6 N, 10.5 mmol, 4.43 mL). The mixture was stirred 1 h at −78 °C and 1 h at −5 °C. It was again cooled to −78 °C, and a solution of acrylaldehyde **19** (595 mg, 4.80 mmol) in THF (1 mL) was added dropwise. Aftering the solution was stirred 2 h at −78 °C, excess vinyl anion was destroyed by addition of methanol (5 mL) and the mixture was allowed to attain room temperature. Water (50 mL) was added, and the resulting mixture was extracted with ether. The ether layer was washed with H_2O and dried ($MgSO_4$). Removal of the solvent followed by flash chromatography over silica gel with 10% EtOAc in hexane gave the (tetrahydropyranyl)oxy dienol **21** (994 mg, 75%) as a viscous oil: ^{1}H NMR δ 1.17–1.82 (21 H), 2.37 (H, quin, J = 8 Hz), 3.32–3.43 (H, m), 3.87–3.96 (H, m), 4.58 (2 H, bs, J = 4.7 Hz), 4.93 (H, s), 5.08 (H, s), 5.56 (H, ddd, J = 3.6, 16 Hz), 5.79 (H, dd, J = 6 and 16 Hz); mass spectrum m/z (M^+) for $C_{18}H_{30}O_3$ calcd 294.2195, found 294.2203.

6-Cyclopentyl-2,5-dihydroxy-2-methyl-3(*E*),6-heptadiene (22). A solution of the tetrahydropyranyl ether **21** (220 mg, 0.79 mmol) in EtOH (5 mL) was stirred with pyridinium *p*-toluenesulfonate (20 mg, 0.079 mol) at 55 °C in a preheated oil bath for 20 min. The solution was then immediately cooled to 0 °C and ethanol was removed at 0 °C by rotary evaporation. The residue was subjected to flash chromatography over silica gel with 30% EtOAc in hexane to afford the diol **22** (149 mg, 90%) as a semisolid: ^{1}H NMR δ 1.18–1.86 (16 H, including a 6 H singlet at δ 1.32 owing to 2 methyls), 2.37 (H, quin, J = 8 Hz), 4.59 (H, d, J = 6 Hz), 4.93 (H, s), 5.07 (H, s), 5.65 (H, dd, J = 6, 16 Hz), 5.88 (H, dd, J = 0.87, 16 Hz); mass spectrum m/z (M^+) for $C_{13}H_{22}O_2$ calcd 210.1620; found 210.1609.

5-[(*tert*-Butyldimethylsilyl)oxy]-6-cyclopentyl-2-hydroxy-2-methyl-3-(*E*),6-heptadiene (23). To a solution of the diol **22** (100 mg, 0.475 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (50.8 mg, 0.502 mmol, 70 μL) and 4-(dimethylamino)pyridine (10 mg, 0.082 mmol) at room temperature. The mixture was stirred at that temperature for 10 min. Then, *tert*-butyldimethylsilyl chloride (93 mg, 0.62 mmol) was added, and the solution was stirred at room temperature overnight. The solvent was removed, and the residue was flash chromatographed over silica gel with 10% EtOAc in hexane as eluant to give the silyl ether **23** (145 mg, 94%): ^{1}H NMR δ 0.03–0.10 (6 H), 0.86–0.91 (9 H), 1.25–1.82 (15 H, including one singlet at δ 1.32), 2.38 (H, quin, J = 8 Hz), 4.56 (H, d, J = 6 Hz), 4.85 (H, d, J = 0.92 Hz), 5.05 (H, t, J = 1.36 Hz), 5.54 (H, dd, J = 6 and 16 Hz), 5.80 (H, dd, J = 1.1 and 16 Hz); mass spectrum m/z (M^+) for $C_{19}H_{36}O_2Si$ calcd 324.2485, found 324.2488.

5-[(*tert*-Butyldimethylsilyl)oxy]-6-cyclopentyl-3,4-epoxy-2-hydroxy-2-methyl-6-heptenes 24e and 24t. To a solution of the hydroxydiene **23** (130 mg, 0.477 mmol) in benzene (4 mL) was added vanadyl acetylacetonate (12 mg, 0.045 mmol) at room temperature. The mixture was stirred at 40 °C for 4 min while the solution became blueish green. Then, *tert*-butyl hydroperoxide (60.4 mg, 0.67 mmol) was added at room temperature, and the resulting mixture was stirred at 40 °C for 30 min. After the solvent was removed by rotary evaporation, the residue was chromatographed over silica gel with 10% EtOAc in hexane as eluent to afford a mixture of epoxides **24** (117 mg, 86%) in a ratio of 4:1 according to ^{1}H NMR analysis. The ^{1}H NMR spectrum of the mixture showed different signals for the SiOCH proton. The major isomer showed a peak at δ 4.10 (d, J = 4 Hz) and the minor isomer at δ 3.90 (d, J = 8 Hz): Mass spectrum m/z (M^+) for $C_{19}H_{36}O_3Si$ calcd 340.2432, found 340.2398.

6-Cyclopentyl-2,5-dihydroxy-3,4-epoxy-2-methyl-6-heptenes 25e and 25t. A solution of the epoxy silyl ethers **24** (123 mg, 0.367 mmol) in THF (1.2 mL) was stirred with tetrabutylammonium fluoride (2.32 mL,

(22) Corey, E. J.; Ulrich, R.; Fitzpatrick, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 222.

2.32 mmol, 1 M in THF) at room temperature overnight. Solvent was removed, and the residue was purified by flash chromatography over silica gel with 50% EtOAc in hexane to furnish the epoxy diols **25e** and **25t** (80 mg, 98%). The two isomers were separated by HPLC on a μ-Partisil column with 5% 2-propanol–10% EtOAc–85% isooctane as eluting solvent to provide **25e** and **25t** in a 4:1 ratio, respectively (75 mg, 92% total yield). Major product **25e**: ^{1}H NMR δ 1.20 (3 H, s), 1.31 (3 H, s), 1.38–1.98 (10 H), 2.48 (H, quin, J = 8 Hz), 3.09 (H, d, J = 2.4 Hz), 3.21 (H, t, J = 2.7 Hz), 4.35 (H, brs), 5.02 (H, s), 5.12 (H, s); mass spectrum m/z (M^+) for $C_{13}H_{22}O_3$ calcd 226.1569, found 226.1532.

Minor product **25t**: ^{1}H NMR δ 1.21 (3 H, s), 1.30 (3 H, s), 1.40–2.16 (10 H), 2.50 (H, quin, J = 8 Hz), 2.98 (H, d, J = 2.34 Hz), 3.18 (H, dd, J = 2.38 and 4.8 Hz), 3.99 (H, bs), 5.01 (H, s), 5.14 (H, s); mass spectrum m/z (M^+) for $C_{13}H_{22}O_3$ calcd 226.1569, found 226.1546.

Mesylate 26e. To a solution of epoxy diol **25e** (15 mg, 0.066 mmol) in anhydrous methylene chloride (2.0 mL) was added 4-(*N*,*N*-dimethylamino)pyridine (48 mg, 0.392 mmol), and the resulting mixture was stirred 10–15 min at 0 °C under a blanket of nitrogen. Methanesulfonic anhydride (recrystallized from dry ether) (34 mg, 0.194 mmol) was then added, and the reaction mixture was stirred 4 h at 0 °C. The solvent was removed, and the residue was triturated with carbon tetrachloride and passed through a pipette containing a cotton plug. Evaporation of the solvent furnished a residue that was subjected to HPLC with 50% EtOAc in hexane as a solvent. Some diol **25e** was recovered (1.5 mg). The mesylate **26e** was obtained as an oil (12 mg, 66%): ^{1}H NMR ($CDCl_3$) δ 5.27 (1 H, s), 5.22 (1 H, d, J = 1.2 Hz), 5.01 (1 H, d, J = 4.4 Hz), 3.28 (1 H, dd, J = 4.4 and 2.2 Hz), 3.12 (1 H, d, J = 2.2 Hz), 3.02 (3 H, s), 2.53 (1 H, m), 2.08–1.46 (9 H), 1.33 (3 H, s), 1.27 (3 H, s).

Isopropyl Ether 27. Methanesulfonyl chloride (228 mg, 2.00 mmol) was added dropwise to a stirring mixture of erythro epoxy diol **25e** (50 mg, 0.221 mmol) and pyridine (536 μL, 6.63 mmol) in methylene chloride (3 mL) at 0 °C. The mixture was stirred 6 h at 0 °C. Solvent was then removed by rotary evaporation, and the residue was triturated with CCl_4 and the solution filtered. Solvent was removed by rotary evaporation, the residue was dissolved in 2-propanol (1 mL), and the resulting solution was boiled 6 h under reflux over K_2CO_3 (50 mg). After being cooled to room temperature, the solution was filtered and the 2-propanol was removed by rotary evaporation. The residue was purified by HPLC with 20% ethyl acetate in hexanes to give the isopropyl ether **27** as an oil (40 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 5.08 (1 H, s), 5.02 (1 H, s), 3.65 (1 H, hept, J = 6.1 Hz), 3.57 (1 H, d, J = 6.7 Hz), 3.14 (1 H, dd, J = 2.3, 6.8 Hz), 2.84 (1 H, d, J = 2.4 Hz), 2.43 (1 H, quin, J = 7.2 Hz), 1.3–2.1 (9 H), 1.28 (3 H, s), 1.18 (3 H, s), 1.14 (6 H, d, J = 6.2 Hz); mass spectrum m/z (M^+) for $C_{16}H_{28}O_3$ calcd 268.2038, found 268.2040.

Reaction of Mesylate 26e with Tetramethylammonium Levulinate. To a solution of mesylate **26e** (9 mg, 0.03 mmol) and tetramethylammonium levulinate (28 mg, 0.15 mmol) in freshly distilled chloroform (4 mL) was added sodium bicarbonate (2 mg), and the reaction mixture was heated 30 h under gentle reflux under nitrogen. TLC showed the disappearance of starting material. Solvent was removed in vacuo, and the residue was flash chromatographed over silica gel, eluting with 35% EtOAc in hexance to afford a mixture of levulinate esters **28** and **29**. The mixture was separated by HPLC with 35% EtOAc in hexane as solvent. S_N2' product **28** (2.9 mg, 31.5%): ^{1}H NMR ($CDCl_3$) δ 5.20 (1 H, d, J = 9 H), 4.56 (2 H, s), 3.74 (1 H, dd, J = 9 and 2.4 Hz), 3.07 (1 H, m), 2.88 (1 H, d, J = 2.4 Hz), 2.76 (2 H, t, J = 6.2 Hz), 2.60 (2 H, t, J = 6.2 Hz), 2.19 (3 H, s), 1.88–1.46 (9 H), 1.34 (3 H, s), 1.27 (3 H, s); mass spectrum m/z (M^+) for $C_{18}H_{28}O_5$ calcd 324.1937, found 324.1934.

S_N2 product, levulinate ester **29** (6.3 mg, 67%): ^{1}H NMR ($CDCl_3$) δ 5.2–5.0 (3 H), 3.20 (1 H, dd, J = 6.4 and 2.4 Hz), 2.90 (1 H, d, J = 2.4 Hz), 2.78–2.68 (2 H), 2.64–2.50 (2 H), 2.42 (1 H, quin, J = 8 Hz), 2.16 (3 H, s), 1.92 (9 H), 1.29 (3 H, s), 1.20 (3 H, s); mass spectrum m/z (M^+) for $C_{18}H_{28}O_5$ calcd 324.1937, found 324.1925. The ratio of products **28**:**29** and overall yield varied with reaction solvent (See Results and Discussion; Table I).

Deprotection of Levulinate 29. Sodium borohydride (5 mg, 0.132 mmol) was added to a stirring solution of **29** (9 mg, 0.028 mmol) in methylene chloride (1 mL) and water (120 μL) at room temperature, and the mixture was stirred for an additional 30 min. Volatiles were removed in vacuo, and the residue was dissolved in CH_2Cl_2 and dried ($MgSO_4$). Removal of solvent and flash chromatography of the resulting residue (50% ethyl acetate in hexanes) gave **25t** (5.4 mg, 85%).

Allylic Diepoxide *trans*,*erythro*-31 from the Erythro Epoxy Diol 25e. To a solution of the erythro epoxy diol **25e** (20 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added pyridine (600 μL, 587 mmol), and the solution was stirred at that temperature for 15 min. To this solution, methanesulfonyl chloride (94 μL, 1.21 mmol) was added at −78 °C and the resulting mixture stirred 1 h at −78 °C and 1 h at 0 °C. The reaction mixture was concentrated to dryness in vacuo, and the residue was triturated with CCl_4 and filtered through a cotton plug. Solvent was removed by rotary evaporation to give the crude mesylate **26e**, which without further purification was dissolved in *t*-BuOH (500 μL) and was stirred 1 h at room temperature with potassium *tert*-butoxide (13 mg, 0.12 mmol). The mixture was then filtered through a short dry-packed column of silica gel with 10% EtOAc in hexane. After removal of solvents, the crude product was purified further by HPLC with 5% EtOAc in hexane as eluent to afford the diepoxide *trans*,*erythro*-**31** (15.3 mg, 83%): ^{1}H NMR δ 1.33 (3 H, s), 1.38 (3 H, s), 1.43–1.98 (8 H), 2.44 (H, quin, J = 8 Hz), 2.59 (H, d, J = 6.5 Hz), 2.70 (H, dd, J = 2, 6.5 Hz), 3.36 (H, d, J = 2 Hz), 4.90 (H, t, J = 1.4 Hz), 5.0 (H, d, J = 1 Hz); mass spectrum m/z (M^+) for $C_{13}H_{20}O_2$ calcd 208.1463, found 208.1485.

Table II. Products from Reaction of Tosylate **32** with *t*-BuOK under Various Conditions

solvent	temp (°C)	time	*cis*,*erythro*-**31**: byproduct	yield (%)
benzene	10–25	1 h	12:88	85
toluene	−78	4 h	5:95	79
toluene	22	1 h	30:70	80
THF	22	1 h	71:29	82
DME	45	30 min	88:12	83
DME	85	5 min	85:15	73
DMF	35–40	30 min	100:0	82
t-BuOH	22	1 h	80:20	83
t-BuOH	55	30 min	80:20	78

Allylic Diepoxide *cis*,*erythro*-31 from Threo Epoxy Diol 25t. To a solution of the threo epoxy diol **25t** (15 mg, 0.083 mmol) in CH_2Cl_2 (1.5 mL) at −78 °C was added pyridine (450 μL, 440 mmol), and the solution was stirred 15 min at that temperature. To this solution was added methanesulfonyl chloride (71 μL, 0.91 mmol) at −78 °C, and the mixture was stirred 1 h at −78 °C and 1 h at 0 °C. Solvents were removed in vacuo, and the residue was triturated with CCl_4 and the solution filtered through a cotton plug. Solvent was removed by rotary evaporation, and the residue, crude mesylate **26t**, without further purification was dissolved in *t*-BuOH and stirred 1 h at room temperature with potassium *tert*-butoxide (10 mg, 0.09 mmol). The mixture was filtered through a short dry-packed column of silica gel with 10% EtOAc in hexane as eluent. Solvent was removed by rotary evporation and the residue purified by HPLC with 5% EtOAc in hexane as eluent to afford the diepoxide *cis*,*erythro*-**31** (11 mg, 80%): ^{1}H NMR δ 1.31 (3 H, s), 1.43 (3 H, s), 1.4–2.0 (8 H), 2.4–2.6 (2 H, including a doublet at 2.50, J = 8 Hz), 2.90 (H, dd, J = 4.2, 8.1 Hz), 3.55 (H, d, J = 4 Hz); mass spectrum m/z (M^+) for $C_{13}H_{20}O_2$ calcd 208.1463, found 208.1479.

Tosylate 32. To a solution of **25e** (30 mg, 0.13 mmol) in benzene (3 mL) at room temperature were added triphenylphosphine (173 mg, 0.66 mmol) and zinc tosylate[10] (28.5 mg, 0.70 mmol). To the resulting suspension was added dropwise 104 μL of diethyl azodicarboxylate (DEAD, 115 mg, 0.66 mmol). The resulting clear light yellow solution was stirred 2 h at room temperature. Solvent was removed and the residue was chromatographed rapidly over silica gel, eluting with 40% ethyl acetate in hexane to afford the inverted tosylate **32** (41 mg, 82%). The tosylate is unstable neat but can be stored at 20 °C in solution: ^{1}H NMR ($CDCl_3$) δ 7.79 (2 H, d, J = 7.8 Hz), 7.32 (2 H, d, J = 7.8 Hz), 5.12 (1 H, s), 5.05 (1 H, s), 4.74 (1 H, d, J = 6.4 Hz), 3.28 (1 H, dd, J = 6.4, 2.2 Hz), 2.91 (1 H, d, J = 2.2 Hz), 2.44 (3 H, s), 2.37 (1 H, m), 1.91–1.43 (9 H), 1.29 (3 H, s), 1.18 (3 H, s).

***cis*,*erythro*-31 from Tosylate 32.** To a stirred solution of tosylate **32** (15 mg, 0.039 mmol) in dry 2-methyl-2-propanol (500 μl) was added potassium *tert*-butoxide (8 mg, 0.070 mmol) under a blanket of nitrogen. The reaction mixture immediately turned yellow. Stirring was continued 1 h at room temperature. TLC showed the disappearance of starting material. The solvent was removed, and the residue was flash chromatographed over silica gel eluting with 5% ethyl acetate in hexane, affording an excellent separation of *cis*,*erythro*-**31** (4.5 mg, 55%) identical by ^{1}H NMR with a sample prepared from threo epoxy diol **25t** (vide supra) and an unidentified, UV-active byproduct (1.2 mg): ^{1}H NMR ($CDCl_3$) δ 6.67 (d, 1 H, J = 13 Hz), 5.83 (1 H, d, J = 13 Hz), 4.84 (1 H, s), 4.80 (1 H, s), 4.69 (1 H, s), 2.58 (1 H, m), 1.92–1.49 (8 H), 1.41 (3 H, s), 1.32 (3 H, s). The influence of reaction conditions on the yield of the desired product, *cis*,*erythro*-**31**, was examined (Table II).

3-Hydroxy-4-isopropyl-1-(trimethylsilyl)pent-4-en-1-yne (33). To a solution of (trimethylsilyl)acetylene (2 g, 0.02 mol) in THF (10 mL) at −78 °C was added dropwise a solution of *n*-BuLi in hexane (12 mL, 0.024 mol, 2.0 M), and the resulting mixture was allowed to stir 1 h at −78 °C and 30 min at 0 °C. Then, the mixture was again cooled to −78 °C, and a solution of 2-isopropylacrolein (2 g, 0.02 mol) in THF (3 mL) was added dropwise, during which time the solution turned light blue. It was

stirred 1 h at the same temperature. Then, saturated aqueous NH_4Cl was added, the cooling bath was removed, and the resulting mixture was allowed to warm to room temperature and extracted with ether, and the ether extract was washed twice with brine and dried ($MgSO_4$). Rotary evaporation of the solvent and flash chromatography of the residue over silica gel with 10% EtOAc in hexane gave alcohol **33** (3.7 g, 92%): ^1H NMR δ 0.15 (9 H, t, J = 3.5 Hz), 1.07 (3 H, s), 1.11 (3 H, s), 1.86 (1 H, d, J = 6.5 Hz), 2.50 (1 H, quin, J = 8 Hz), 4.84 (1 H, d, J = 6.5 Hz), 4.97 (1 H, s), 5.31 (1 H, s); mass spectrum m/z (M^+) for $C_{11}H_{20}OSi$ calcd 196.1275, found 196.1283.

3-[(*tert*-Butyldimethylsilyl)oxy]-4-isopropyl-1-(trimethylsilyl)pent-4-en-1-yne (34). To a solution of the alcohol **33** (500 mg, 2.55 mmol) in CH_2Cl_2 (4 mL) were added Et_3N (261 mg, 2.58 mmol, 3.60 μL) and DMAP (10 mg, 0.082 mmol) at room temperature, and the solution was stirred for 10 min. Then, *tert*-butyldimethylsilyl chloride (480 mg, 3.18 mmol) was added, and the resulting mixture was stirred at room temperature overnight. The solvent was removed by rotary evaporation, and the residue was chromatographed over silica gel with hexane as eluent to give the silyl ether **34** (730 mg, 92%) as a volatile liquid: ^1H NMR δ 0.12–0.16 (15 H, m), 0.90 (9 H, s), 1.05 (3 H, s), 1.09 (3 H, s), 2.52 (1 H, quin, J = 8 Hz), 4.84 (1 H, d, J = 1.0 Hz), 4.90 (1 H, d, J = 1.0 Hz), 5.26 (1 H, t, J = 1.0 Hz). Anal. Calcd for $C_{17}H_{34}OSi_2$: C, 63.73; H, 11.03. Found: C, 63.88; H, 10.97.

3-[(*tert*-Butyldimethylsilyl)oxy]-1-iodo-4-isopropyl-1-(trimethylsilyl)-penta-1(*E*),4-diene (35). To a solution of the acetylene **34** (165 mg, 0.532 mmol) in Et_2O (660 μL) at room temperature was added a solution of triisobutylaluminum in heptane (792 μL, 0.532 mmol, 0.67 M), and the resulting mixture was stirred for 5 min. A solution of diisobutylaluminum hydride in heptane (251 μL of 2.34 M, 0.532 mmol) was added to the reaction mixture, and stirring was continued for 4 h. Then, a solution of iodine (338 mg, 1.33 mmol) in Et_2O (500 μL) was added dropwise to the mixture at −78 °C. The resulting mixture was stirred 1 h at −78 °C and 2 h at 0 °C. Then, crushed ice and 10% HCl were added. The product was extracted into ether, and the ether layer was washed with 10% aqueous $Na_2S_2O_3$, saturated $NaHCO_3$, and finally with brine and dried ($MgSO_4$). Removal of solvent afforded an oil that was purified by flash chromatography over silica gel with hexane as eluent to give the iodide **35** (222 mg, 95%): ^1H NMR δ 0.05 (6 H, d, J = 1.6 Hz), 0.28 (9 H, s), 0.88 (9 H, s), 1.03 (3 H, d, J = 7 Hz), 1.04 (3 H, d, J = 7 Hz), 2.26 (H, quin, J = 7 Hz), 6.67 (H, dd, J = 1.1 and 9 Hz), 4.90 (H, dd, J = 1.0 Hz), 5.06 (H, t, J = 1.0 Hz), 6.97 (H, d, J = 9 Hz); mass spectrum m/z (M^+) for $C_{17}H_{35}OSi_2I$ calcd 438.1274, found 438.1271.

3-[(*tert*-Butyldimethylsilyl)oxy]-6-hydroxy-2-isopropyl-6-methyl-5-(trimethylsilyl)hepta-1,4(*Z*)-diene (36). To a solution of the iodide **35** (212 mg, 0.484 mmol) in THF (2 mL) at −78 °C was added dropwise a solution of *n*-BuLi in hexane (388 μL of 2 M, 0.771 mmol), and the resulting mixture was stirred 30 min at −78 °C. Then, acetone (190 μL, 2.58 mmol) was added at −78 °C, and the mixture was stirred 1 h at that temperature. Methanol was added, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. Solvent was removed, and the residue was chromatographed over silica gel with 10% EtOAc in hexane as the eluent to afford the alcohol **36** (120 mg, 68%): ^1H NMR δ 0.05 (6 H, d, J = 5 Hz), 0.21–0.24 (9 H), 0.85–0.90 (9 H), 1.03 (6 H, t, J = 7 Hz), 1.36 (6 H, d, J = 3 Hz), 2.39 (H, quin, J = 7 Hz), 4.85–4.97 (3 H), 5.89 (1 H, d, J = 8.6 Hz); mass spectrum m/z (M^+) for $C_{20}H_{42}O_2Si_2$ calcd 370.2723, found 370.2723.

3-[(*tert*-Butyldimethylsilyl)oxy]-4,5-epoxy-6-hydroxy-2-isopropyl-6-methyl-5-(trimethylsilyl)-hept-1-enes 37t and 37e. To a solution of the hydroxy diene **36** (16 mg, 0.043 mmol) in CH_2Cl_2 (500 μL) at room temperature was added $Mo(CO)_6$ (1.2 mg, 0.0043 mmol) followed by *tert*-butyl hydroperoxide (8.0 mg, 0.090 mmol, 9 μL), and the mixture was boiled 3 h under reflux. Solvent was removed, the residue was filtered through silica gel, solvents were removed by rotary evaporation, and the products were isolated by HPLC with 5% EtOAc in hexane as eluent to give the major threo isomer **37t** (10.5 mg, 62%) and the minor erythro isomer **37e** (3.6 mg, 21%) in a 3:1 ratio. ^1H NMR of the major isomer **37t**: δ 0.05–0.26 (15 H), 0.89 (9 H, s), 1.04 (3 H, d, J = 1.6 Hz), 1.07 (3 H, d, J = 1.6 Hz), 1.14 (3 H, s), 1.28 (3 H, s), 2.46 (H, quin, J = 8 Hz), 3.11 (H, d, J = 8 Hz), 4.09 (H, d, J = 8 Hz), 4.96 (1 H, s), 5.08 (1 H, s).

^1H NMR of the minor isomer **37e**: δ 0.01–0.06 (6 H, s), 0.24 (9 H, s), 0.88 (9 H, s), 1.08 (6 H, t, J = 6.5 Hz), 1.16 (3 H, s), 1.29 (4 H, s for CH_3 and bs for OH at base line), 2.46 (1 H, quin, J = 8 Hz), 3.07 (1 H, d, J = 8 Hz), 4.16 (1 H, d, J = 8 Hz), 4.97 (1 H, s), 5.05 (1 H, s).

***threo*-3,6-Dihydroxy-4,5-epoxy-2-isopropyl-6-methylhept-1-ene (38t).** To a solution of the silyl epoxide **37t** (8.5 mg, 0.022 mmol) in THF (400 μL) at room temperature was added a solution of Bu_4NF in THF (110 μL of 1 M, 0.11 mmol), and the resulting mixture was stirred overnight. Solvent was removed by rotary evaporation, and the residue was purified by filtration through silica gel, eluting with 25% EtOAc in hexane to afford the diol **38t** (4.0 mg, 91%): ^1H NMR δ 1.06 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 1.21 (3 H, bs), 1.30 (3 H, s), 1.74 (1 H, bs), 2.06 (1 H, bs), 2.33 (1 H, quin, J = 7 Hz), 2.98 (1 H, d, J = 2 Hz), 3.16 (1 H, dd, J = 2, 5 Hz), 3.98 (1 H, bs), 5.02 (1 H, s), 5.17 (1 H, s); mass spectrum m/z (M^+) for $C_{11}H_{20}O_3$ calcd 200.2802, found 200.1411.

***erythro*-3,6-Dihydroxy-4,5-epoxy-2-isopropyl-6-methylhept-1-ene (38e).** To a solution of the silyl epoxide **37e** (5.8 mg, 0.015 mmol) in THF (200 μL) at room temperature was added a solution of Bu_4NF in THF (75 μL, 0.075 mmol, 1 M), and the resulting mixture was stirred overnight. Solvent was removed by rotary evaporation, and the residue was purified by filtration through silica gel, eluting with 25% EtOAc in hexane to afford the diol **38e** (2.7 mg, 90%): ^1H NMR δ 1.07 (3 H, d, J = 7 Hz), 1.08 (3 H, d, J = 7 Hz), 1.20 (3 H, s), 1.30 (3 H, s), 1.84 (H, bs), 2.07 (1 H, bs), 2.33 (1 H, quin, J = 7 Hz), 3.10 (1 H, d, J = 2.4 Hz), 3.18 (1 H, t, J = 2.4 Hz), 4.35 (1 H, bs), 5.01 (1 H, s), 5.13 (1 H, s); mass spectrum m/z (M^+) for $C_{11}H_{20}O_3$ calcd 200.2802, found 200.1417.

Bis(silyl ether) 39. A solution of the triol **14** (68 mg, 0.21 mmol), 4-(*N*,*N*-dimethylamino)pyridine (2.6 mg, 0.021 mmol), *tert*-butyldimethylsilyl chloride ((TBDMS)Cl, 90 mg, 0.060 mmol) and triethylamine (118 μL, 0.85 mmol) in anhydrous methylene chloride (5 mL) was heated under gentle reflux, and the reaction was monitored by TLC. After 26 h, (TBDMS)Cl (32 mg, 0.21 mmol) and triethylamine (25 μL, 0.21 mmol) were added, and the resulting mixture was boiled under reflux for an additional 22 h where upon TLC analysis showed no remaining starting material. All volatiles were removed by rotory evaporation, and the residue was purified by flash chromatography over silica gel (30 mm × 7 in). Elution with 15% EtOAc in hexane gave the bis(silyl ether) **39** (110 mg, 94.5%): ^1H NMR ($CDCl_3$) δ 5.76–5.56 (2 H, m), 4.93 (1 H, s), 4.80 (1 H, s), 4.37 (1 H, d, J = 5 Hz), 3.61 (1 H, d, J = 3.6 Hz), 3.37 (1 H, m), 2.16–1.38 (11 H), 1.32 (6 H, s), 0.92–0.82 (6 H), 0.87 (s, 9 H), 0.84 (s, 9 H), 0.06 (s, 3 H), 0.01 (s, 3 H), 0.01 (s, 3 H), 0.01 (s, 3 H).

Epoxy Bis(silyl ethers) 40. To a magnetically stirred solution of bis(silyl ether) **39** (90 mg, 0.16 mmol) in dry benzene (10 mL) was added $VO(acac)_2$ (4.3 mg, 0.016 mmol), and the resulting mixture was stirred 5 min at 40–45 °C under nitrogen. Then, *tert*-butyl hydroperoxide (50 μL, 0.50 mmol) was added dropwise to the reaction mixture whereupon it turned straw yellow, which gradually disappeared during the next 15 min. The reaction mixture was stirred at 40–45 °C with progress monitored by TLC. After 4 h, the mixture still contained starting material. Therefore, 25 μL of *tert*-butyl hydroperoxide was added dropwise, and stirring was continued at the same temperature. After 2 h, TLC showed no starting material and the reaction was stopped. Rotary evaporation of solvents followed by flash chromatography of the residue over silica gel, using 10% EtOAc in hexane, afforded a diastereomeric mixture of epoxy bis(silyl ethers) **40** (80 mg, 86.3%). According to the vinyl ^1H NMR resonances, the erythro to threo ratio was 6:1: ^1H NMR ($CDCl_3$) δ 5.19 (1 H, s), 4.93 (3 H, s), 4.03 (1 H, d, J = 3.4 Hz), 3.62 (1 H, d, J = 3.6 Hz), 3.25 (1 H, m), 3.07 (1 H, dd, J = 3.6, 2.4 Hz), 2.94 (1 H, d, J = 2.4 Hz), 2.22–1.36 (10 H), 1.28 (3 H, s), 1.24 (3 H, s), 0.87 (3 H, d, J = 6.2 Hz), 0.87 (3 H, s), 0.85 (9 H, s), 0.84 (9 H, s), 0.06 (3 H, s), 0.05 (3 H, s), 0.02 (3 H, s), 0.01 (3 H, s).

Epoxy Triols 41. The epoxy bis(silyl ethers) **40** (97 mg, 0.17 mmol) were dissolved in tetrahydrofuran (5 mL), and tetra-*n*-butylammonium fluoride (1.0 mL, 1 M solution in THF) was added. The reaction mixture was stirred at room temperature for 5 days since one of the two silyl ethers was difficult to remove. After 5 days, solvent was removed by rotary evaporation and the residue was flash chromatographed over silica gel with 80% EtOAc in hexane as eluting solvent. Two fractions were separated: the first contained a mono(silyl ether) (18.3 mg, 23.6%), and the second contained a 5.8:1 diastereomeric mixture of epoxy triols **41e** and **41t**, respectively. This mixture was separated by HPLC with 14% isopropanol in hexanes as eluting solvent. Erythro major epoxy triol **41e** (31.8 mg, 54.9%): ^1H NMR ($CDCl_3$) δ 5.17 (1 H, s), 4.98 (1 H, s), 4.16 (1 H, d, J = 3 Hz), 3.71 (1 H, d, J = 4 Hz), 3.23 (1 H, m), 3.15 (1 H, dd, J = 5.4 and 2.4 Hz), 3.08 (1 H, d, J = 2.4 Hz), 2.32–1.32 (13 H), 1.29 (3 H, s), 1.24 (3 H, s), 0.96 (3 H, s), 0.83 (3 H, d, J = 6.4 Hz).

Threo minor epoxy triol **41t** (5.5 mg, 9.5%): ^1H NMR ($CDCl_3$) δ 5.22 (s, 1 H), 4.96 (1 H, s), 3.89 (1 H, d, J = 3.8 Hz), 3.72 (1 H, d, J = 4 Hz), 3.37–3.26 (4 H), 3.23 (1 H, dd, J = 4, 2.4 Hz), 2.94 (1 H, d, J = 2.4 Hz), 2.32–1.91 (4 H), 1.82–1.35 (6 H), 1.28 (3 H, s), 1.21 (3 H, s), 1.01 (3 H, s), 0.82 (3 H, d, J = 6.4 Hz).

Mono(silyl ether): ^1H NMR ($CDCl_3$) δ 5.19 (1 H, s), 5.00 (1 H, s), 4.27 (1 H, d, J = 2.8 Hz), 3.66 (1 H, d, J = 3.6 Hz), 3.24 (1 H, m), 3.19 (1 H, dd, J = 5.2 and 2.8 Hz), 3.14 (1 H, d, J = 2.8 Hz), 2.26–1.56 (12 H), 1.33 (3 H, s), 1.27 (3 H, s), 0.91 (3 H, s), 0.87 (3 H, d, J = 6.2 Hz), 0.87 (9 H, s), 0.02 (3 H, s), 0.01 (3 H, s).

Rearranged Allylic Diepoxide 42. The epoxy triol **41e** (20 mg, 0.059 mmol) and triphenylphosphine (124 mg, 0.47 mmol) were dissolved in anhydrous benzene (2 mL), and zinc tosylate (14.5 mg, 0.035 mmol) was added. To the resulting suspension was added diethyl azodicarboxylate (DEAD, 75 μL, 0.48 mmol) dropwise under nitrogen. After being stirred 10 min, the light yellow reaction mixture became turbid and some solid precipitated. TLC analysis of the reaction mixture showed the complete disappearance of starting triol. The solvent was rotary evaporated, and the residue was flash chromatographed over silica gel and eluted very rapidly with 40% ethyl acetate in hexanes to yield a tosylate (15 mg): ^{1}H NMR ($CDCl_3$) δ 7.80 (2 H, d, J = 8.4 Hz), 7.32 (2 H, d, J = 8.4 Hz), 5.49 (1 H, s), 5.12 (1 H, s), 4.72 (1 H, d, J = 6.4 Hz), 4.64 (2 H, s), 3.19 (1 H, dd, J = 6.4, 2 Hz), 3.00 (1 H, d, J = 2 Hz), 2.44 (3 H, s), 2.44 (1 H, m), 2.17 (1 H, d, J = 4.6 Hz), 2.04–1.94 (3 H), 1.72–1.58 (3 H), 1.49–1.24 (5 H), 1.29 (s, 3 H), 1.17 (s, 3 H), 0.97 (3 H, d, J = 6.4 Hz). This tosylate clearly incorporates the rearranged tricyclic skeleton of **42** with the 7-methylidene hydrogens appearing as a singlet at δ 4.64.

This tosylate (15 mg) was dissolved in anhydrous dimethylformamide (500 μL) and treated with solid potassium *tert*-butoxide (10 mg) under a blanket of nitrogen. The reaction mixture immediately turned yellow. It was stirred 1.5 h at 30–35 °C. Solvent was then removed by azeotropic distillation with *n*-heptane on the rotary evaporator. Water (4 drops) was added to the residue. The resulting mixture was triturated with 40% ethyl acetate in hexanes, and the solution was filtered and dried by passing through a small bed of dry-packed $MgSO_4$ and silica gel. After evaporation of the solvent, diepoxide **42** (8 mg, 46% overall from **41e**) was obtained as an oil: ^{1}H NMR ($CDCl_3$) δ 5.24 (1 H, s), 5.12 (1 H, s), 4.67 (2 H, s), 3.50 (1 H, d, J = 4.2 Hz), 2.94 (1 H, dd, J = 7.8, 3.8 Hz), 2.56 (1 H, m), 2.52 (1 H, d, J = 7.8 Hz), 2.21 (1 H, d, J = 4.8 Hz), 2.08–1.98 (2 H), 1.86–1.58 (3 H), 1.46–1.22 (5 H), 1.43 (3 H, s), 1.30 (3 H, s), 0.97 (3 H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 160.2, 142.2, 112.2, 98.7, 58.4, 58.1, 57.9, 56.0, 49.2, 47.5, 44.6, 43.2, 43.1, 38.0, 35.0, 31.8, 24.3, 19.2, 15.6; mass spectrum m/z (M^+) for $C_{20}H_{28}O_2$ calcd 300.2089, found 300.2090.

Mono(Silyl Ether) (+)-43. A solution of diol (+)-7[3] (200 mg, 0.846 mmol), triethylamine (172 mg, 1.70 mmol), 4-(*N*,*N*-dimethylamino)-pyridine (10.4 mg, 0.845 mmol), and *tert*-butyldimethylsilyl chloride (160 mg, 1.06 mmol) in anhydrous methylene chloride (15 mL) was heated 2.5 h under gentle reflux. The reaction mixture was then cooled and the solvent and volatiles were removed by rotary evaporation. The residue was purified by chromatography over silica gel with ethyl acetate–hexanes (1:4) as eluant to furnish the monosilylated product (+)-**43** (270 mg, 91%) as an oil: $[\alpha]^{22}_D$ + 23.7° (c 1.44, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ 5.16 (1 H, t, J = 1.6 Hz), 4.82 (1 H, t, J = 1.6 Hz), 4.00 (1 H, d, J = 12 Hz), 3.93 (1 H, d, J = 12 Hz), 3.71 (1 H, d, J = 4 Hz), 2.94 (1 H, m), 2.27 (1 H, ddd, J = 13.5, 12, 4 Hz), 2.06–1.30 (9 H), 0.96 (3 H, s), 0.88 (9 H, s), 0.85 (3 H, d, J = 6.5 Hz), 0.03 (3 H, s), 0.02 (3 H, s).

***p*-Methoxybenzyl Ether (−)-44.** To a stirred suspension of NaH (36 mg, 0.75 mmol, from NaH in oil prewashed twice with hexanes) in DME (10 mL) was added the alcohol (250 mg, 0.713 mmol) in DME (2 mL), and then the resulting mixture was stirred 30 min at room temperature. 4-Methoxybenzyl bromide (201 mg, 1.0 mmol) was added dropwise at room temperature. After the resulting solution was boiled 18 h under reflux, TLC analysis showed complete reaction. The mixture was cooled to room temperature. Then, H_2O (30 μL) was added very carefully, followed by ethyl acetate (25 mL). Anhydrous $MgSO_4$ was added, the solution was filtered, and the solvent was rotary evaporated. The residue was then chromatographed over silica gel with ethyl acetate–hexanes (1:19) as eluant. The benzyl ether (−)-**44** was obtained as a colorless oil (270 mg, 81%): $[\alpha]^{22}_D$ −37° (c 1.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22 (2 H, d, J = 8 Hz), 6.83 (2 H, d, J = 8 Hz), 5.17 (1 H, s), 4.83 (1 H, s), 4.47 (1 H, d, J = 12 Hz), 4.27 (1 H, d, J = 12 Hz), 3.99 (1 H, d, J = 12 Hz), 3.92 (1 H, d, J = 12 Hz), 3.77 (3 H, s), 3.35 (1 H, d, J = 4 Hz), 2.84 (1 H, m), 2.16–1.14 (10 H), 0.98 (s, 3 H), 0.88 (s, 9 H), 0.84 (3 H, d, J = 6.4 Hz), 0.03 (3 H, s), 0.02 (3 H, s).

Allylic Alcohol (−)-45. To a solution of the silyl ether (−)-**44** (270 mg, 0.57 mmol) in THF (10 mL) was added *n*-Bu_4NF (1.7 mL of 1 M solution in THF), and the resulting mixture was stirred 16 h at room temperature. Then, solvent was rotary evaporated, and the residue was chromatographed over silica gel with ethyl acetate–hexanes (1:3) as eluant to afford the allylic alcohol (−)-**45** (190 mg, 93%) as an oil: $[\alpha]^{22}_D$ −35.5° (c 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22 (2 H, d, J = 8.5 Hz), 6.83 (2 H, d, J = 8.5 Hz), 5.13 (1 H, s), 4.88 (1 H, s), 4.47 (1 H, d, J = 12 Hz), 4.28 (1 H, d, J = 12 Hz), 4.00 (1 H, d, J = 12 Hz), 3.94 (1 H, d, J = 12 Hz), 3.77 (3 H, s), 3.37 (1 H, d, J = 4 Hz), 2.96 (1 H, m), 2.39 (1 H, m), 2.21–1.21 (10 H), 0.99 (3 H, s), 0.84 (3 H, d, J = 6.4 Hz). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.48; H, 9.04. Found: C, 77.47; H, 8.97.

Acrylaldehyde (+)-46. To a solution of the allylic alcohol (−)-**45** (150 mg, 0.42 mmol) in CH_2Cl_2 (25 mL) was added active MnO_2 (225 mg, 2.59 mmol), and the reaction mixture was stirred 24 h at room temperature. It was then filtered through a bed of Celite, which was washed with ethyl acetate (5 × 10 mL). The combined organic solutions were evaporated in vacuo to afford the acrylaldehyde, which was purified by column chromatography over silica gel with an ethyl acetate–hexanes (1:9) eluant. The aldehyde (+)-**46** was obtained (140 mg, 94%) as a colorless oil: $[\alpha]^{22}_D$ +12.6° (c 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 9.40 (1 H, s), 7.15 (2 H, d, J = 7.8 Hz), 6.77 (2 H, d, J = 7.8 Hz), 6.12 (1 H, s), 5.96 (1 H, s), 4.40 (1 H, d, J = 12 Hz), 4.23 (1 H, d, J = 12 Hz), 3.70 (3 H, s), 3.34 (1 H, d, J = 4 Hz), 3.23 (1 H, m), 2.17–1.12 (10 H), 0.94 (3 H, s), 0.57 (3 H, d, J = 6 Hz); mass spectrum m/z (M^+) for $C_{23}H_{30}O_3$ calcd 354.2195, found 354.2191.

Allylic Alcohols (−)-47a and (−)-47b. To a solution of the vinyl stannane **9** (550 mg, 1.12 mmol) in THF (4 mL) was added *n*-butyllithium (450 μL, 1.12 mmol, 2.5 M in hexane) at −78 °C under nitrogen over 10 min. After the addition was complete, the mixture was stirred 2 h at −78 °C and 1 h at −10 °C. It was again cooled to −78 °C, and a solution of aldehyde (+)-**46** (82 mg, 0.231 mmol) in THF (2 mL) was added dropwise. The reaction mixture then was allowed to warm to room temperature over 4 h, methanol (1.7 mL) was added, and then the volatiles were removed by rotary evaporation. The residue was flash chromatographed, eluting with ethyl acetate–hexanes (1:9) to afford an epimeric mixture of allylic alcohols (−)-**47b** and (−)-**47a**. This mixture was separated by HPLC with ethyl acetate–hexanes (1:9) as a eluant to yield (−)-**47b** (100 mg, 78%): $[\alpha]^{22}_D$ −19.2° (c 7.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.25 (2 H, d, J = 8 Hz), 6.87 (2 H, d, J = 8 Hz), 5.81 (1 H, d, J = 16 Hz), 5.66 (1 H, dd, J = 16, 5.4 Hz), 5.11 (1 H, s), 4.95 (1 H, s), 4.51 (1 H, d, J = 12 Hz), 4.47 (1 H, d, J = 5.4 Hz), 4.31 (1 H, d, J = 12 Hz), 3.81 (3 H, s), 3.40 (1 H, d, J = 4 Hz), 3.22 (1 H, m), 2.12–1.38 (10 H), 1.32 (6 H, s), 1.03–0.87 (15 H), 0.59 (6 H, q, J = 8 Hz).

Also isolated was (−)-**47a** (7.5 mg, 6%): $[\alpha]^{22}_D$ −28° (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.26 (2 H, d, J = 8.8 Hz), 6.88 (2 H, d, J = 8.8 Hz, 5.85 (1 H, d, J = 16 Hz), 5.56 (1 H, dd, J = 16 and 7 Hz), 5.35 (1 H, s), 4.98 (1 H, s), 4.52 (1 H, d, J = 12 Hz), 4.47 (1 H, d, J = 7 Hz), 4.33 (1 H, d, J = 12 Hz), 3.84 (3 H, s), 3.41 (1 H, d, J = 4 Hz), 2.91 (1 H, m), 2.14–1.40 (10 H), 1.33 (6 H, s), 1.04–0.91 (15 H), 0.58 (6 H, q, J = 8 Hz).

Diol (−)-48b. To a solution of the silyl ether (−)-(**47b**) (90 mg, 0.16 mmol) in THF (2 mL) was added *n*-Bu_4NF (450 μL, 1.0 M solution in THF), and the resulting mixture was stirred 20 h at room temperature. The volatiles were removed in vacuo, and the residue was purified by flash chromatography over silica gel. Elution with 1:1 ethyl acetate–hexane afforded the diol (−)-**48b** (72 mg, 100%): $[\alpha]^{22}_D$ −27.1° (c 1.24, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.23 (2 H, d, J = 8.8 Hz), 6.85 (2 H, d, J = 8.8 Hz), 5.89 (1 H, d, J = 16 Hz), 5.65 (1 H, dd, J = 16, 5.6 Hz), 5.09 (1 H, s), 4.94 (1 H, s), 4.48 (1 H, d, J = 12 Hz), 4.45 (1 H, d, J = 5.6 Hz), 4.29 (1 H, d, J = 12 Hz), 3.79 (3 H, s), 3.38 (1 H, d, J = 4 Hz), 3.19 (1 H, m), 2.10–1.38 (10 H), 1.32 (6 H, s), 1.01 (3 H, s), 0.86 (3 H, d, J = 6.5 Hz).

Triethylsilyl Ether (−)-49b. A solution of diol (−)-**48b** (72 mg, 0.16 mmol), DMAP (3.6 mg, 0.029 mmol), triethylamine (33 mg, 0.34 mmol), and triethylsilyl chloride (42 mg, 0.28 mmol) in methylene chloride (6 mL) was stirred at room temperature. After 4 h, TLC analysis showed complete silylation of the secondary hydroxyl group. Solvents and volatiles were removed by rotary evaporation, and the residue was chromatographed over silica gel, eluting with a mixture of ethyl acetate and hexane (1:4) to afford the silyl ether (−)-**49b** (90 mg, 100%): $[\alpha]^{22}_D$ −18.1° (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.26 (2 H, d, J = 8.8 Hz), 6.88 (2 H, d, J = 8.8 Hz), 5.79 (1 H, d, J = 16 Hz), 5.61 (1 H, dd, J = 16, 6.4 Hz), 5.11 (1 H, s), 4.92 (1 H, s), 4.61 (1 H, d, J = 12 Hz), 4.48 (1 H, d, J = 6.4 Hz), 4.31 (1 H, d, J = 12 Hz), 3.83 (3 H, s), 3.41 (1 H, d, J = 3 Hz), 3.20 (1 H, m), 2.16–1.40 (10 H), 1.36 (6 H, s), 1.03–0.90 (15 H), 0.63 (6 H, q, J = 8 Hz); mass spectrum m/z (M^+) for $C_{34}H_{54}O_4Si$ calcd 554.3793, found 554.3791.

Epoxy Alcohols *erythro*-50b and *threo*-50b. To a solution of the allylic alcohol (−)-**49b** (75 mg, 0.135 mmol) in benzene (7.5 mL) was added $VO(acac)_2$ (3.6 mg, 0.014 mmol), and the mixture was stirred 5 min at 40–45 °C. The temperature was then raised to 60 °C, and *tert*-butyl hydroperoxide (27 μL, 0.28 mmol) was added during which time the mixture turned straw yellow, which disappeared in the next 15 min. After the solution was stirred 2 h at 60 °C, more *tert*-butyl hydroperoxide (13.5 μL, 0.13 mmol) was added and the resulting mixture stirred for another 1 h. It was then cooled to room temperature. Volatiles were removed by rotary evaporation, and the residue was chromatographed over silica gel. Elution with ethyl acetate–hexane (1:9) furnished a diastereomeric mixture of threo and erythro epoxy alcohol silyl ethers (58.5 mg, 76%) in a ratio of 3.7:1 as judged from the ratio of vinyl H

resonances at δ 5.22 and 4.99 (major) versus δ 5.20 and 4.96 (minor).

To a solution of the above diastereomeric mixture of epoxy alcohol silyl ethers (58.5 mg, 0.102 mmol) in THF (6 mL) was added *n*-Bu_4NF (450 μL of 1.0 M in THF), and the resulting mixture was stirred at room temperature. After 16 h, TLC analysis indicated that the reaction was complete. Solvents were removed in vacuo, and the residue was purified by flash chromatography over silica gel. Elution with ethyl acetate–hexane (1:1) afforded a mixture of epoxy diols that was separated by HPLC with 2-propanol–hexane (1:9) as eluting solvent to give *erythro*-**50b** (33.6 mg, 72.1%): $[\alpha]^{22}_D$ −34.2° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.23 (2 H, d, *J* = 8.8 Hz), 6.85 (2 H, d, *J* = 8.8 Hz), 5.21 (1 H, s), 5.04 (1 H, s), 4.48 (1 H, d, *J* = 12 Hz), 4.30 (1 H, d, *J* = 8.6 Hz), 4.29 (1 H, d, *J* = 12 Hz), 3.80 (3 H, s), 3.39 (1 H, d, *J* = 4 Hz), 3.28–3.13 (3 H), 2.12–1.38 (10 H), 1.32 (3 H, s), 1.24 (3 H, s), 1.02 (3 H, s), 0.86 (3 H, d, *J* = 6.5 Hz); mass spectrum *m*/*z* (M^+) for $C_{28}H_{40}O_5$ calcd 456.2877, found 456.2875.

Also isolated are *threo*-**50b** (9.3 mg, 20.0%): ^1H NMR ($CDCl_3$) δ 7.23 (2 H, d, *J* = 8.6 Hz), 6.86 (2 H, d, *J* = 8.6 Hz), 5.27 (1 H, s), 5.02 (1 H, s), 4.50 (1 H, d, *J* = 11.6 Hz), 4.31 (1 H, d, *J* = 11.6 Hz), 3.91 (1 H, br s), 3.80 (3 H, s), 3.40 (1 H, d, *J* = 4 Hz), 3.33–3.18 (2 H), 2.96 (1 H, d, *J* = 2.4 Hz), 2.06–1.27 (10 H), 1.32 (3 H, s), 1.23 (3 H, s), 1.02 (3 H, s), 0.85 (3 H, d, *J* = 6.4 Hz).

Levulinate Ester 51. A solution of the epoxy diol *erythro*-**50b** (5.0 mg, 0.011 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2.8 mg, 0.023 mmol) in CH_2Cl_2 (500 μL) was stirred 10 min at 0 °C. Then, methanesulfonic anhydride (4.0 mg, 0.023 mmol, freshly crystallized from anhydrous ether and dried under vacuum) was added. The resulting mixture was then stirred 5 h at 0–5 °C. Solvents were removed by rotary evaporation, and the residue was triturated with CCl_4 and the solution filtered. After rotary evaporation of the solvent, the resulting crude mesylate was dissolved in 1,2-dimethoxyethane (500 μL), and tetramethylammonium levulinate (10 mg, 0.053 mmol) and sodium bicarbonate (1 mg) were added. The resulting mixture was stirred 7 h at 85–90 °C and then cooled to room temperature. The solvents were rotary evaporated, and the residue was chromatographed over silica gel, eluting with ethyl acetate–hexane (2:3) to furnish levulinate ester **51** (4.8 mg, 79%): $[\alpha]^{22}_D$ −8.8° (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.21 (2 H, d, *J* = 8.6 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 5.26 (1 H, s), 5.05 (1 H, d, *J* = 7 Hz), 5.04 (1 H, s), 4.47 (1 H, d, *J* = 11.4 Hz), 4.29 (1 H, d, *J* = 11.4 Hz), 3.80 (3 H, s), 3.37 (1 H, d, *J* = 3.4 Hz), 3.16 (1 H, dd, *J* = 7, 2.2 Hz), 3.01 (1 H, d, *J* = 2.2 Hz), 2.94 (1 H, m), 2.80–2.61 (4 H), 2.18 (3 H, s), 2.16–1.34 (10 H), 1.28 (3 H, s), 1.16 (3 H, s), 1.02 (3 H, s), 0.85 (3 H, d, *J* = 6.2 Hz).

Epoxy Diol *threo*-50a. To a solution of the levulinate ester **51** (4.0 mg, 0.007 mmol) in dioxane (500 μL) and water (25 μL) was added sodium borohydride (1.0 mg, 0.026 mmol). The resulting mixture was stirred 3 h at room temperature. Solvents were then rotary evaporated, and the residue was chromatographed on a small column of silica gel. Elution with ethyl acetate–hexane (1:1) furnished the diol *threo*-**50a** (2.8 mg, 88%): $[\alpha]^{22}_D$ −8.9° (*c* 0.28, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.21 (2 H, d, *J* = 8.6 Hz), 6.85 (2 H, d, *J* = 8.6 Hz), 5.39 (1 H, s), 5.05 (3 H, s), 4.47 (1 H, d, *J* = 11.4 Hz), 4.29 (1 H, d, *J* = 11.4 Hz), 3.83 (1 H, d, *J* = 5.8 Hz), 3.80 (3 H, s), 3.39 (1 H, d, *J* = 3.4 Hz), 3.09 (1 H, dd, *J* = 5.8, 2.4 Hz), 3.02 (1 H, d, *J* = 2.4 Hz), 2.94 (1 H, m), 2.20–1.34 (10 H), 1.29 (3 H, s), 1.17 (3 H, s), 1.02 (3 H, s), 0.85 (3 H, d, *J* = 6.2 Hz); mass spectrum *m*/*z* (M^+) for $C_{28}H_{40}O_5$ calcd 456.2877, found 456.2876.

Allylic Diepoxide (−)-52 from *erythro*-50b. To a solution of epoxy diol *erythro*-**50b** (10 mg, 0.022 mmol) in 2 mL of benzene were added triphenylphosphine (35 mg, 0.13 mmol) and zinc tosylate (6 mg, 0.0147 mmol). Diethyl azodicarboxylate (21 μL, 0.33 mmol) was then added dropwise to the resulting mixture to give a pale yellow clear solution. After the solution was stirred 2 h at room temperature, TLC analysis of the reaction mixture showed the presence of starting material. Triphenylphosphine and DEAD (2 equiv of each) were added again to complete the reaction. After 1 h more, TLC analysis showed no remaining starting material. The solvent was rotary evaporated, and the residue was immediately filtered rapidly through a short silica gel column with 30% ethyl acetate in hexanes as eluant. Removal of solvents in vacuo afforded a tosylate intermediate.

The tosylate intermediate was immediately dissolved in anhydrous *N*,*N*-dimethylformamide (1 mL), and to the resulting solution was added potassium *tert*-butoxide (10 mg, 0.089 mmol) under nitrogen. The reaction mixture was stirred 1.5 h at 35 °C until TLC analysis showed no unreacted tosylate. The solvent was removed by repeated azeotropic distillation with *n*-heptane by rotary evaporation. The residue was then triturated with 10% ethyl acetate in hexanes and passed through a short silica gel column to yield the benzyl ether (−)-**52** (6.5 mg, 68% from epoxy diol *erythro*-**50b**): $[\alpha]^{22}_D$ −29° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.22 (2 H, d, *J* = 8.6 Hz), 6.84 (2 H, d, *J* = 8.6 Hz), 5.13 (1 H, d, *J* = 1.2 Hz), 5.09 (1 H, s), 4.48 (1 H, d, *J* = 11.6 Hz), 4.29 (1 H, d, *J* = 11.6 Hz), 3.77 (3 H, s), 3.49 (1 H, d, *J* = 4 Hz), 3.38 (1 H, d, *J* = 2.6 Hz), 3.06 (1 H, m), 2.90 (1 H, dd, *J* = 7.4 and 4 Hz), 2.54 (1 H, d, *J* = 7.4 Hz), 2.15–1.64 (10 H), 1.42 (3 H, s), 1.01 (3 H, s), 1.29 (3 H, s), 1.01 (3 H, s), 0.91 (3 H, d, *J* = 6.4 Hz); mass spectrum *m*/*z* (M^+) for $C_{28}H_{38}O_4$ calcd 438.2771, found 438.2757.

15,16,17-Trisepispatol (−)-53. The benzyl ether (−)-**52** (11.5 mg, 0.026 mmol) from *erythro*-**50b** was dissolved in 1 mL of methylene chloride. Water (55 μL) was added, and to the resulting stirred suspension at 0 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 12 mg, 0.052 mmol). After 1 h, TLC showed complete disappearance of the starting material. The solution was filtered through a pipette containing a little $MgSO_4$, which was washed repeatedly with methylene chloride. The filtrate was rotary evaporated and the brown residue was immediately subjected to HPLC with 24% ethyl acetate in hexanes as eluant to deliver 15,16,17-trisepispatol (−)-**53** (7 mg, 84.5%) as a white crystalline solid: mp 69–71 °C; $[\alpha]^{22}_D$ −10.0° (*c* 0.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (1 H, d, *J* = 1.3 Hz), 5.09 (1 H, s), 3.74 (1 H, d, *J* = 4.5 Hz), 3.50 (1 H, d, *J* = 4.0 Hz), 3.09 (1 H, ddd, *J* = 13.2, 5.5, 5.5 Hz), 2.90 (1 H, dd, *J* = 7.5, 4.1 Hz), 2.52 (1 H, d, *J* = 7.5), 2.25 (1 H, ddd, *J* = 13.2, 13.2, 4.3 Hz), 2.15 (1 H, t, *J* = 5.0 Hz), 2.08–2.02 (1 H, m), 1.97 (1 H, t, *J* = 7.4 Hz), 1.88–1.80 (2 H), 1.76–1.66 (2 H), 1.46–1.32 (6 H), 1.30 (3 H, s), 0.98 (3 H, s), 0.92 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR (100.607 MHz, $CDCl_3$, for APT spectra a (+) indicates 0 or 2 attached protons and a (−) indicates 1 or 3 attached protons) δ 141.8 (+), 112.9 (+), 80.13 (−), 58.92 (−), 58.75 (+), 57.32 (−), 55.55 (−), 47.18 (+), 44.27 (−), 43.62 (−), 43.44 (−), 38.03 (−), 36.89 (+), 36.63 (−), 35.26 (+), 27.78 (+), 24.23 (−), 19.34 (−), 14.16 (−), 12.96 (−).

Allylic Diepoxide (−)-52 from *threo*-50a. A solution of the diol *threo*-**50a** (2.0 mg, 0.0044 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2.0 mg, 0.016 mmol) in methylene chloride (500 μL) was stirred 10 min at 0 °C, and then methanesulfonic anhydride (3.0 mg, 0.017 mmol, freshly crystallized from anhydrous ether and dried under vacuum) was added. The resulting mixture was stirred 10 h at 0–5 °C. The solvents were removed by rotary evaporation, and the residue was triturated with CCl_4 and the solution filtered. After removal of CCl_4 in vacuo, the residue was dissolved in 2-methyl-2-propanol (500 μL), and a 1% solution of potassium *tert*-butoxide in 2-methyl-2-propanol (26 μL) was added. The resulting mixture was stirred 1 h at room temperature. Solvents were rotary evaporated, and the residue was dissolved in ethyl acetate–hexane (1:1) and passed through a small bed of silica gel. After rotary evaporation of the solvent, the residue was subjected to HPLC with ethyl acetate–hexanes (1:6) as eluant with a Partisil PXS 10/25 column to afford the allylic diepoxide (−)-**52** (1.4 mg, 72.5%): $[\alpha]^{22}_D$ −29° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.22 (2 H, d, *J* = 8.8 Hz), 6.84 (2 H, d, *J* = 8.8 Hz), 5.13 (1 H, s), 5.09 (1 H, s), 4.48 (1 H, d, *J* = 11.6 Hz), 4.29 (1 H, d, *J* = 11.6 Hz), 3.77 (3 H, s), 3.49 (1 H, d, *J* = 4 Hz), 3.38 (1 H, d, *J* = 2.8 Hz), 3.03 (1 H, m), 2.91 (1 H, dd, *J* = 7.6 and 4 Hz), 2.54 (1 H, d, *J* = 7.6 Hz), 2.15–1.46 (10 H), 1.29 (3 H, s), 1.23 (3 H, s), 1.01 (3 H, s), 0.91 (3 H, d, *J* = 6.6 Hz); mass spectrum *m*/*z* (M^+) for $C_{28}H_{38}O_4$ calcd 438.2771, found 438.2757.

15,16,17-Trisepispatol (−)-53. To a solution of *p*-methoxybenzyl ether (−)-**52** (1.1 mg, 0.0025 mmol) from *threo*-**50a** in a mixture of methylene chloride (500 μL) and water (28 μL) was added DDQ (1 mg, 0.0044 mmol, 1.7 equiv) at 0 °C, and the resulting mixture was stirred 1 h at the same temperature. Solvents were then rotary evaporated, and the residue was passed through a small bed of silica gel with ethyl acetate–hexanes (1:2). The eluate was concentrated, and the residue was purified by HPLC on a Partisil PXS 10/25 column with EtOAc–hexanes (1:3) as eluant to provide trisepispatol (−)-**53** (0.6 mg, 75%), which was identical by ^1H NMR spectroscopy with the sample prepared previously from *erythro*-**50b**.

Allylic Diepoxide (+)-54. To a solution of *threo*-**50b** (6.0 mg, 0.013 mmol) in anhydrous methylene chloride (1.5 mL) were added DMAP (3.0 mg) and dry pyridine (20 μL). The resulting mixture was stirred 5 min at 0 °C under N_2. Methanesulfonic anhydride (35 mg, 0.20 mmol, freshly crystallized from anhydrous ether and dried under vacuum) was then added, and stirring was continued. After 3 h, TLC analysis showed no starting material remaining. Solvents were rotary evaporated, the residue was triturated with carbon tetrachloride several times, and the resulting solution was passed through a small cotton plug in a pipette. The solvent was rotary evaporated, and the mesylate thus obtained was immediately used for the next step.

The mesylate was dissolved in anhydrous 2-methyl-2-propanol (1.5 mL) and potassium *tert*-butoxide (15 mg) was added. The reaction mixture was stirred 1 h at room temperature under a nitrogen atmosphere. The solvent was then rotary evaporated, the residue was triturated with 25% ethyl acetate in hexanes, and the resulting solution was passed through a short silica gel column. The residue obtained after

rotary evaporation of solvent was subjected to HPLC with 15% ethyl acetate in hexanes as eluting solvent. Data for spatol benzyl ether (+)-**54** (3.6 mg, 62.2%) thus obtained: $[\alpha]^{22}_D$ + 8° (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.22 (2 H, d, *J* = 8.2 Hz), 6.83 (2 H, d, *J* = 8.2 Hz), 5.09 (1 H, s), 5.02 (1 H, s), 4.48 (1 H, d, *J* = 11.8 Hz), 4.29 (1 H, d, *J* = 11.8 Hz), 3.77 (3 H, s), 3.43 (1 H, d, *J* = 4.4 Hz), 3.38 (1 H, d, *J* = 3 Hz), 2.93 (1 H, m), 2.87 (1 H, dd, *J* = 7.8, 4.4 Hz), 2.52 (1 H, d, *J* = 7.8 Hz), 2.11-1.61 (10 H), 1.41 (3 H, s), 1.30 (3 H, s), 1.01 (3 H, s), 0.89 (3 H, d, *J* = 6.4 Hz).

(+)-**Spatol (3).** To a magnetically stirred solution of spatol benzyl ether (+)-**54** (3.6 mg, 0.0081 mmol) in methylene chloride (1.5 mL) and water (84 μL) was added DDQ (6.0 mg) at 0 °C, and stirring was continued at the same temperature. After 1 h, TLC analysis showed no unreacted starting material. Solvents were rotary evaporated, and the residue was passed through a short column of silica gel with 30% ethyl acetate in hexanes as eluant. The residue obtained after rotary evaporation was purified by HPLC with 24% ethyl acetate in hexanes as eluant to deliver (+)-**3** (2.1 mg, 81%): $[\alpha]^{22}_D$ +44.2° (*c* 0.66, $CHCl_3$) (reported[2] $[\alpha]_D$ +45.6° (*c* 1.56, $CHCl_3$)): ^1H NMR (400 MHz, $CDCl_3$) δ 5.13 (1 H, dd, *J* = 3.0, 1.5 Hz), 5.03 (1 H, s), 3.74 (1 H, d, *J* = 4.4 Hz), 3.44 (1 H, d, *J* = 3.8 Hz), 3.03 (1 H, ddd, *J* = 14.5, 5.5, 5.5 Hz), 2.87 (1 H, dd, *J* = 7.9, 4.3 Hz), 2.49 (1 H, d, *J* = 7.9 Hz), 2.28 (1 H, ddd, *J* = 13.2, 13.2, 4.3 Hz), 2.12-2.05 (2 H), 1.97 (1 H, t, *J* = 6.8 Hz), 1.89-1.80 (2 H), 1.78-1.65 (2 H), 1.47-1.18 (3 H), 1.41 (3 H, s), 1.29 (3 H, s), 0.99 (3 H, s), 0.91 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR (100.607 MHz, $CDCl_3$, for APT spectra a (+) indicates 0 or 2 attached protons and a (-) indicates 1 or 3 attached protons) δ 141.5 (+), 111.0 (+), 79.96 (-), 58.42 (+), 58.12 (+), 57.06 (-), 55.14 (-), 47.21 (+), 43.79 (-), 43.40 (-), 43.25 (-), 37.82 (-), 36.87 (+), 36.56 (-), 35.18 (+), 27.87 (+), 24.23 (-), 19.26 (-), 14.47 (-), 12.97 (-).

Acknowledgment. This research was assisted financially by Grant CA31595 from the National Cancer Institute of the National Institutes of Health. We thank M. Jirousek, B. Banik, K. Murthy, and A. Valeriu for technical assistance and Professor Fenical for copies of NMR spectra and for an authentic sample of natural spatol.

Registry No. (±)-**1**, 89196-20-3; **2**, 132199-63-4; **3**, 76520-52-0; **5**, 930-30-3; (±)-**6**, 89165-79-7; (±)-**7**, 89165-80-0; (+)-**7**, 127182-28-9; (±)-**8**, 89177-59-3; **9**, 132101-35-0; (+)-**11**, 127182-29-0; (+)-**12**, 132101-36-1; (+)-**13**, 132199-64-5; (+)-**14**, 132199-65-6; **19**, 132101-37-2; **19** alcohol, 26639-84-9; (±)-**20**, 132199-66-7; **21**, 132101-38-3; (±)-**22**, 132101-39-4; (±)-**23**, 132101-40-7; (±)-**24e**, 132101-41-8; (±)-**24t**, 132199-69-0; (±)-**25e**, 132101-42-9; (±)-**25t**, 132199-70-3; (±)-**26e**, 132101-43-0; (±)-**26t**, 132199-71-4; (±)-**27**, 132101-44-1; (±)-**28**, 132101-45-2; (±)-**29**, 132101-46-3; (±)-*trans,erythro*-**31**, 132101-47-4; (±)-*cis,erythro*-**31**, 132199-72-5; (±)-**32**, 132101-48-5; (±)-**33**, 132101-49-6; (±)-**34**, 132101-50-9; (±)-**35**, 132101-51-0; (±)-**36**, 132101-52-1; (±)-**37e**, 132101-53-2; (±)-**37t**, 132101-65-6; (±)-**38e**, 132101-54-3; (±)-**38t**, 132199-73-6; **39**, 132101-55-4; **40t**, 132199-75-8; **40e**, 132101-56-5; **41t**, 132199-74-7; **41e**, 132101-57-6; **42**, 132101-58-7; **42** (tosylate precursor), 132101-66-7; (+)-**43**, 132101-59-8; (-)-**44**, 132101-60-1; (-)-**45**, 132101-61-2; (+)-**46**, 127156-24-5; (-)-**47a**, 132199-67-8; (-)-**47b**, 127135-70-0; (-)-**48a**, 127135-76-6; (-)-**49b**, 127135-71-1; *threo*-**50a**, 132199-68-9; *threo*-**50b**, 127182-31-4; *erythro*-**50b**, 127135-72-2; *threo*-**50b** TES ether, 127182-32-5; *erythro*-**50b** TES ether, 127135-73-3; **51**, 132101-62-3; (-)-**52**, 127135-75-5; (-)-**53**, 127304-32-9; (+)-**54**, 127182-33-6; $HC{\equiv}C(CH_3)_2OH$, 115-19-5; $HC{\equiv}C(CH_3)_2OTES$, 17963-41-6; (±)-$HC{\equiv}C(CH_3)_2OTHP$, 132101-64-5; $HC{\equiv}CSiMe_3$, 1066-54-2; $(CH_3)_2CHC(CHO){=}CH_2$, 4417-80-5; diethyl cyclopentylmalonate, 18928-91-1; monoethyl (±)-cyclopentylmalonate, 132101-63-4; ethyl 2-cyclopentylacrylate, 81143-91-1.

Synthesis and Chemistry of Dynemicin A Models

K. C. Nicolaou,* A. L. Smith,† S. V. Wendeborn,‡ and C.-K. Hwang

Contribution from the Department of Chemistry, Research Institute of Scripps Clinic, 10666 North Torrey Pines Road, La Jolla California 92037, and Department of Chemistry, University of California, San Diego, La Jolla, California 92093. *Received September 25, 1990*

Abstract: The synthesis of the model systems **10** and **22** of dynemicin A (**2**) containing the nitrogen, enediyne, and epoxide functionalities has been achieved. These models are shown to undergo acid-induced triggering to give the corresponding Bergman-cyclized products in the presence of suitable H atom donors. Removal of the N protecting group from **22** gave the unstable free amine **30**, which was shown to cause double-stranded-DNA cleavage, presumably in a manner similar to that of dynemicin A (**2**) itself. Some interesting chemistry related to dicobalt complexes of the enediynes is also presented.

Introduction

A number of years ago, a new series of highly active antibiotics, the esperamicins[1] and calicheamicins,[2] was isolated. These antibiotics, containing a unique 1,5-diyn-3-ene bridging ring, displayed extremely potent antitumor activity with IC_{50} values in the nanogram per milliliter range against a number of murine and human cell lines.[3] The autitumor activity of these compounds has been ascribed to DNA damage resulting from H atom abstraction from the sugar phosphate backbone by a benzenoid diradical. This benzenoid diradical is generated by Bergman cyclization[4] of the enediyne bridge upon triggering by conformational changes brought about by bioreductive cleavage of the trisulfide moiety and 1,4-addition of the resulting thiol. The potency of these molecules has spawned considerable interest in the synthetic community, with the synthesis of a number of model

* To whom correspondence should be addressed at the Research Institute of Scripps Clinic.

† Recipient of a NATO (SERC, U.K.) Postdoctoral Fellowship, 1990-1992.

‡ Recipient of a Verband der Chemischen Industrie Doctoral Fellowship, 1989-1990.

(1) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461-3462. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohjuma, H.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462-3464.

(2) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464-3466. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466-3468.

(3) Long, B. H.; Golik, J.; Forenza, S.; Ward, B.; Rehfuss, R.; Dabrowiak, J. C.; Catino, J. J.; Musial, S. T.; Brookshire, K. W.; Doyle, T. W. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 2-6.

(4) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25-31. Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660-661. Lockhart, T. P.; Gomita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091-4096. (b) Darby, N.; Kim, C. V.; Salaun, J. A.; Shelton, K. W.; Takadar, S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516-1517. (c) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217-220.

0002-7863/91/1513-3106$02.50/0 © 1991 American Chemical Society