A Tandem Cycloaddition-Ene Strategy for the Synthesis of (±)-Verrucarol and (±)-4,11-Diepi-12,13-deoxyverrucarol

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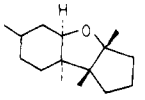
Abstract: A ring expansion of a 6,5 to 6,6 system provides a stereo-controlled entry into the polyhydrochromanones. The steric and electronic requirements of such a process are probed. For the synthesis of verrucarol, such a process involves the synthesis of a norapotrichothecene followed by the rearrangement to the trichothecane skeleton—a process that may be reminiscent of the biogenesis of trichothecanes. The reaction of 1-(trimethylsiloxy)-3-methylbuta-1,3-diene and 2-methyl-2-[1-(methoxycarbonyl)vinyl]-1,3-cyclopentanedione, a new dienophile, provides either the Diels–Alder adduct *or* the product of a further intramolecular Alder ene reaction of this adduct depending upon the reaction conditions. The latter reaction provides a diastereotopic differentiation of the two carbonyl groups. Since the carbonyl group can be subsequently regenerated, the ene–retro ene sequence represents a mild method of carbonyl group protection. The facility of the closure of the tetrahydropyranyl ring permits entry into both the strained 11-epiverrucarol series and the natural verrucarol series from a common intermediate. By adjustment of the temperature of an acid catalyzed hydrolysis of a silyl ether, the product of initial hydrolysis at room temperature cyclizes to the 11-epi series, but the product of hydrolysis at 50 °C cyclizes to the natural series. The 11-epi and natural trichothecene skeletons are available in 10 and 11 steps, respectively, from 2-methylcyclopentane-1,3-dione in 16% overall yield. As a consequence of this synthesis, the two hydroxyl groups are differentiated for further elaboration into the roridins or verrucarins. Verrucarol itself is available in 18 steps in an overall yield of 2%.

The trichothecanes, a group of natural products produced by various cultures of *Fungi imperfecti* and first isolated by Freeman and Morrison,[1] attracted widespread interest because of their potent biological activity ranging from antibacterial to antifungal to cytotoxic.[2] Members of this family are among the most cytostatic agents known.[3] Because of the sensitivity of the sesquiterpene portion to molecular rearrangement, initial structural formulations corresponded to the skeleton represented in **1**,[4] which



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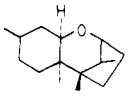

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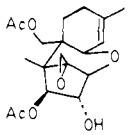
are now called apotrichothecanes.[5] X-ray crystallography settled the structure of trichodermol as possessing the skeleton **2**[6] and all the then known trichothecenes were correlated to trichodermol.[7]

Two types of trichothecenes can be identified: (1) those that consist of the sesquiterpene unit alone such as anguidine **3** and



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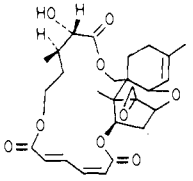

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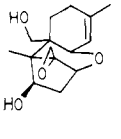

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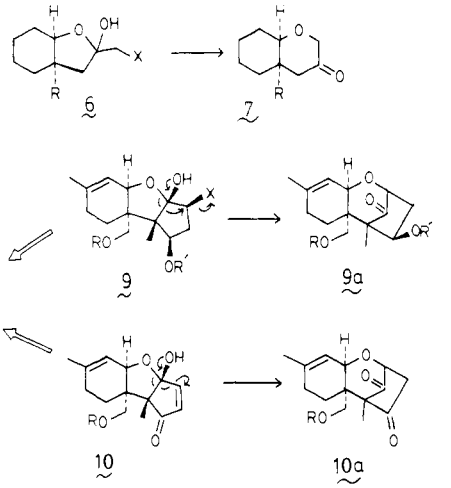
(2) those that consist of a sesquiterpene unit such as verrucarol (**4**) bridged by a macrocyclic ribbon as in verrucarin A (**5**). Recently, seco versions of this latter type have also been isolated.[8] Since so many of this latter family consist of verrucarol or a very close relative so bridged, we embarked upon a synthesis of verrucarol[9] that could be adapted to its close relatives and that could diverge into several bridged derivatives.[10,11]

Synthetic Strategy. Recognizing that a key element of the verrucarol molecule is the construction of a cis fused polyhydrochromanone, we settled on a strategy that capitalizes on the high propensity of a polyhydrobenzofuran such as **6** to be cis fused and then the ring expanded by migration of the oxygen[10c,e,f] to give **7**. In the context of the verrucarol problem, the corresponding



transformation converts **9** to **9a**. In a slight modification of this concept, the migration terminus could be envisioned[10c] to be the

† McElvain Laboratories of Organic Chemistry.
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(1) Freeman, G. G.; Morrison, R. I. *Biochem. J.* **1949**, *44*, 1.
(2) For reviews see: (a) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (b) Bamburg, J. R.; Strong, F. M. In "Microbial Toxins"; Kadis, S., Ed.; Academic Press: New York, 1965. (c) Bamburg, J. R. In "Mycotoxins and other Fungal Related Food Problems"; Rodricks, J. V., Ed.; American Chemical Society: Washington, DC, 1976; Adv. Chem. Ser. No. 149, p 144. (d) Tamm, Ch.; Breitenstein, W. In "The Biosynthesis of Mycotoxins"; Steyn, P. S., Ed.; Academic Press: New York, 1980; pp 69–104. (e) Doyle, T. W.; Bradner, W. T. In "Anticancer Agents Based on Natural Product Models"; Cassady, J. M.; Douros, J. D., Eds.; Academic Press: New York, 1980; Chapter 2. (f) Ong, C. W. *Heterocycles* **1982**, *19*, 1685. (g) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388.
(3) Harri, C.; Loeffler, W.; Sigg, H. P.; Stahelin, Ch.; Tamm, Ch.; Wiesinger, D. *Helv. Chim. Acta* **1962**, *45*, 839.
(4) Freeman, G. G.; Gill, J. E.; Waring, W. W. *J. Chem. Soc.* **1959**, 1105. Gutzwiller, J.; Tamm, Ch. *Helv. Chim. Acta* **1963**, *46*, 1786.
(5) Godtfredsen, W. O.; Grove, J. F.; Tamm, Ch. *Helv. Chim. Acta* **1967**, *50*, 1666.
(6) Abrahamsson, S.; Nilsson, B. *Proc. Chem. Soc., London* **1964**, 188.
(7) Gutzwiller, J.; Mauli, R.; Sigg, H. P.; Tamm, Ch. *Helv. Chim. Acta* **1964**, *47*, 2234. Dawkins, A. W. *J. Chem. Soc.* **1966**, 116. Gotfredsen, W. O.; Vangedal, S. *Acta Chem. Scand.* **1965**, *19*, 1088.
(8) Jarvis, B. B.; Midiwo, J. O.; Stahly, G. P.; Pavanasasivam, G.; Mazzola, E. P. *Tetrahedron Lett.* **1980**, 787. Jarvis, B. B.; Pavanasasivam, G.; Holmlund, C. E.; De Silva, T.; Stahly, G. P.; Mazzola, E. P. *J. Am. Chem. Soc.* **1981**, *103*, 472. Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Midiwo, J. O.; De Silva, T.; Holmlund, C. E.; Mazzola, E. P.; Geoghegan, R. F., Jr. *J. Org. Chem.* **1982**, *47*, 1117.

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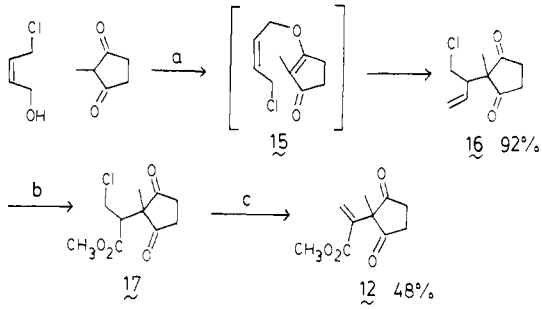
Scheme I. Synthesis of Dienophile

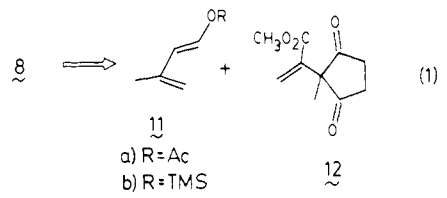


[a] $PhCH_3$, TsOH, and then 1,3,5-$(CH_3)_3C_6H_3$; reflux. [b] $KMnO_4$ and then CH_2N_2. [c] DBU and PhH–ether; room temperature.

β-carbon of an enone as in **10**. Thus, the norapotrichothecenes offer an excellent springboard to construct the tricothecenes. We felt it desirable to conduct a study to define the steric and electronic requirements for such a stereo-controlled approach to polyhydrochromanones.

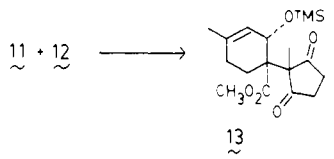
An additional advantage to this strategy becomes apparent when it is recognized that **8** is a logical precursor to either **9** or **1**, which has the effect of reducing the number of chiral centers from the six of verrucarol to two. The two carbonyl groups of **8** are diastereotopic. Their differentiation invokes a thermodynamic preference for formation of a cis, anti, cis tricycle as in **9** and **10** by addition of the hydroxyl group to C(a) compared to formation of a cis, syn, cis tricycle by addition of the hydroxyl group to C(b).

A Diels–Alder strategy provides a rapid entry into **8** as outlined in eq 1. Thus, this strategy reduces to two achiral building blocks



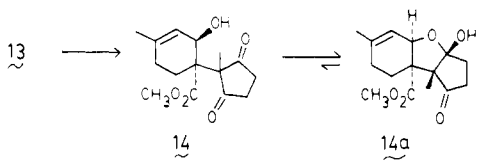
(1)

11 and **12** in which the entire chirality of verrucarol is created



by the Diels–Alder reaction—a type of reaction that responds well to asymmetric induction.[12]

It should be realized that the initial Diels–Alder adduct **13**



would possess the incorrect stereochemistry at the allylic alcohol. However, this small defect should be easily rectified since the adduct **13** should be capable of being isomerized to the β-alcohol **14**, which should be favored due to its ability to exist in the lactol form **14a**. Such a cyclization is unlikely in the alcohol corresponding to **13** since it requires a trans fused 6,5-ring juncture.

Synthesis of Diene and Dienophile. While both dienes **11a** and **11b** are known,[13] we found it most convenient to synthesize **11b** from **11a**. Treatment of **11a** with 2.1 equiv of *n*-butyllithium in hexane followed by quenching of the resultant lithium enolate with TMS-Cl gave a 47% distilled yield of **11b**. Yields up to 76% were obtained by using methyllithium but the reactions were more capricious.

Scheme I summarizes the preparation of the requisite dienophile **12**. Formation of the enol ether **15** required forcing conditions to achieve good conversions. The Claisen rearrangement can be accomplished in the same pot by simply replacing the toluene with mesitylene and refluxing to give **16** in one step from the chlorohydrin and the dione. However, more reproducible yields were obtained by first taking the enol ether up in ether, washing with aqueous bicarbonate, and then refluxing in mesitylene. In this way, **16** was isolated in 92% yield from 2-methylcyclopentane-1,3-dione.

The chemoselective oxidative cleavage of the olefin directly to the carboxylic acid proved successful with potassium permanganate under phase transfer conditions.[15] The acid lacks the characteristic AA'BB' pattern of the dione, suggesting that it exists in the form of a lactol. However, its lability led us to effect immediate esterification with diazomethane to give the ester **17**. Exposure of crude **17** to DBU smoothly effected elimination of the elements of HCl to give the acrylate **12** in 48% yield from **16** as an analytically pure low-melting solid. This two-stage operation provides the potentially versatile and novel acrylate **12** in 44% overall yield from 2-methylcyclopentane-1,3-dione.

Diels–Alder and Alder Ene Reaction. The acetoxy diene **11a** proved sufficiently unreactive that it failed to condense with **12** under any conditions. On the other hand, upon heating of **11b** and **12** at 190 °C in a sealed tube, a 1:1 crystalline adduct resulted; however, NMR spectroscopy clearly showed it was *not* the Diels–Alder adduct. The salient features of the ^1H NMR spectrum included an exo-methylene group (δ 4.78 and 4.97, two d, J = 1.5 Hz) as well as an isolated AX pattern (δ 2.68 and 4.20, two d, J = 5.0 Hz). Although the trimethylsilyl group was intact, the IR spectrum showed a sharp OH stretch at 3580 cm^{-1}. The ^{13}C NMR spectrum showed only one ketone (δ 218.9) and supported the presence of an exo-methylene group (δ 114.5 and 143.2).

(9) For earlier efforts that have resulted in the total synthesis of verrucarol and related trichothecanes, see: (a) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1989. (b) Still, W. C.; Tsai, J.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (c) Kraus, G. A.; Roth, B.; Frazier, K.; Shimagaki, M. *J. Am. Chem. Soc.* **1982**, *104*, 1116. (d) Schlessinger, R. H.; Nugent, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 116. (e) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 658. For a subsequent report of a synthesis of verrucarol, see: Roush, W. R.; D'Ambra, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 1058.

(10) For some reports directed toward the trichothecanes see: (a) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Tetrahedron Lett.* **1974**, 2523. (b) Masuoka, N.; Kamikawa, T. *Tetrahedron Lett.* **1976**, 1691. (c) Trost, B. M.; Rigby, J. H. *J. Org. Chem.* **1978**, *43*, 2938. (d) Snider, B. B.; Admin, S. G. *Synth. Commun.* **1978**, *8*, 117. (e) Anderson, W. K.; Lei, G. E. *J. Org. Chem.* **1980**, *45*, 501. (f) Goldsmith, D. J.; John, T. K.; Kwong, C. D.; Painter, G. R., III *J. Org. Chem.* **1980**, *45*, 3989. (g) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *4*, 4825. (h) Roush, W. R.; D'Ambra, T. E. *J. Org. Chem.* **1981**, *46*, 5045. (i) White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376. (j) Pearson, A. J.; Ong, C. W. *J. Am. Chem. Soc.* **1981**, *46*, 3376. (k) Nakahara, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1980**, *28*, 1981.

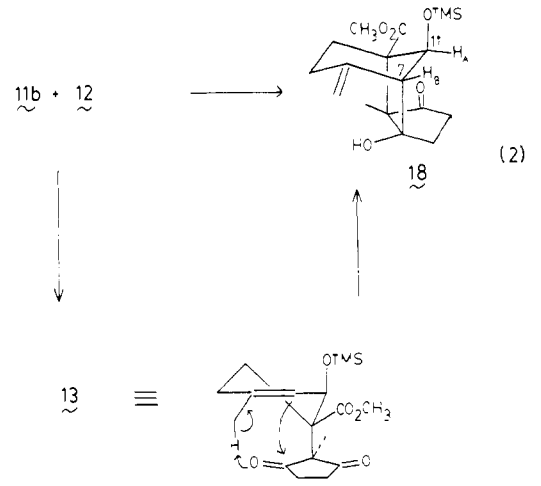
(11) For a preliminary report of a portion of this work see: Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110. Also see: Trost, B. M.; McDougal, P. G.; Rigby, J. "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983.

(12) For use of chiral dienes see: Korolev, A.; Mur, V. *Dokl. Akad. Nauk. SSSR* **1948**, *59*, 251; *Chem. Abstr.* **1949**, *42*, 6675. David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299. David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. David, S.; Eustache, J.; Lubineau, A. *Ibid.* **1979**, 1975. Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595. Most work involves chiral dienophiles. See: Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333. Farmer, R. F.; Hamer, J. *J. Org. Chem.* **1966**, *31*, 6359. Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. Jurczak, J.; Tracy, M. *J. Org. Chem.* **1979**, *44*, 3347. Boeckmann, R. K., Jr.; Naegeby, P. C.; Arthur, S. D. *J. Org. Chem.* **1980**, *45*, 754. Helmchen, G.; Schmierer, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 205. Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F. *Tetrahedron Lett.* **1981**, *22*, 2545.

(13) See ref 10d and Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakly, T. J. R.; Ullah, Z. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1096.

(14) Rosner, A.; Tolkiehn, K.; Krohn, K. *J. Chem. Res. Miniprint* **1978**, 3831.

(15) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. *J. Org. Chem.* **1977**, *42*, 3749. Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1978**, *43*, 1532.



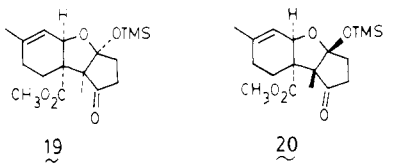
The spectral interpretations suggested **18** as a likely assignment. Mechanistically, such a suggestion is quite reasonable since **18** results from a further ene reaction[16] of the initial Diels–Alder adduct.

To garner additional evidence, a retro ene reaction was attempted. Flash vacuum pyrolysis (16-cm tube, 480 °C, 1.0 mm) of **18** generated an isomer that had all the features of the expected Diels–Alder adduct **13**. The NMR spectrum showed absorptions for the allylic methyl group (δ 2.45–2.78) and an allylic ether (δ 4.56 and 5.39, two s). Performing the initial condensation of **11b** and **12** at 130 °C gives the same product—confirming the assignment as **13**. Heating **13** in refluxing mesitylene converts **13** to **18**—a fact that verifies the origin and assignment of **18**.

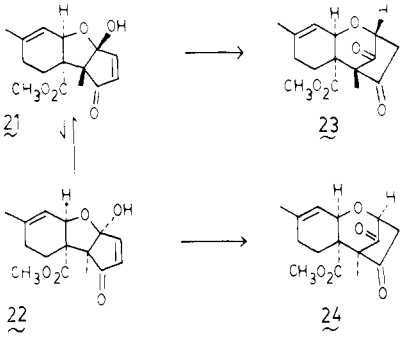
This tandem Diels–Alder and ene sequence establishes five contiguous asymmetric centers with complete control. As the drawing in eq 2 depicts, only one of the diastereotopic carbonyl groups can orient itself to participate in the ene reaction—a fact that provides a chemodifferentiation of these two carbonyl groups. The 5-Hz coupling for H_A–H_B in **18** establishes the axial nature of the trimethylsiloxy group since the opposite stereoisomer is expected to exhibit a 0–2-Hz coupling for these same protons.[17]

With the identity of the adducts **13** and **18** established, protocols for their direct synthesis on a preparative scale were developed. Heating the dienophile **12** with the neat siloxydiene **11b** containing a few drops of BSA[18] at 127–129 °C gives the Diels–Alder adduct in 87% yield based on recovered dienophile (62% conversion). Heating a mesitylene solution of 1.65 equiv of **11b** and 1.0 equiv of **12** at 155 °C for 5 h followed by addition of another aliquot (0.25 equiv) of diene and mesitylene with continued heating for 4 h yields the ene product **18** in 43%, the Diels–Alder product **11** in 22%, and a trace of starting dienophile. Heating the pure Diels–Alder adduct in refluxing mesitylene establishes an equilibrium within 8 h from which the ene adduct **18** is isolated in 90.5% based on recovered starting material (26%). Prolonged heating (20 h) causes substantial decomposition. Thus, by recycling the Diels–Alder adduct, we isolated the ene product in 63% yield based on the starting dienophile **12**.

On large-scale preparations of the ene adduct, a small amount of an additional product was isolated. Spectroscopic data suggest this product is an inseparable mixture of two stereoisomeric apotrichothecenes **19** and **20**. Their structures will be discussed more fully subsequently.



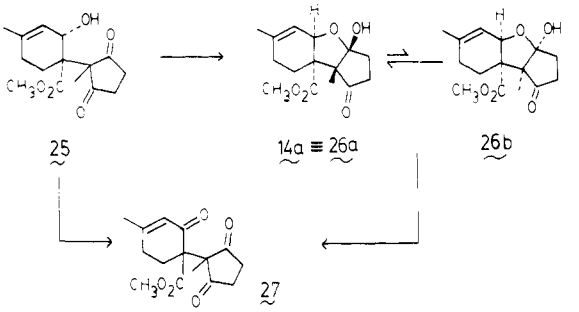
(1) Approach A. An Enone as a Migrating Terminus. The enone intermediate **21** proved attractive since it should resolve



the problem of stereochemistry. Two factors favor **21** going to **23** over **22** to **24**. First, the favored cis, anti, cis ring fusions of **21** should be more stable than the cis, syn, cis ring fusions of **22**, thereby tilting any equilibrium between **21** and **22** toward **21**.

Second, **23** possesses the cyclohexene ring on the exo face of a bicyclo[3.2.1]octane system, whereas **24** possesses this ring on an endo face. The minimization of nonbonded interactions should make **23** more stable than **24** and, presumably, the transition state leading to **23** should be lower in energy than that leading to **24**. Desilylation of **18**, either with fluoride or with aqueous acid at room temperature, gives the alcohol **25**. A very large (12-Hz) coupling exists between the hydroxyl proton and the allylic methine proton. Inspection of molecular models shows that if the bulky methylcyclopentanedione is equatorial, an intramolecular hydrogen bond between the hydroxyl proton and the ester oxygen forces a trans periplanar orientation between the hydroxyl proton and the allylic methine proton—an orientation that gives rise to this large coupling.

The desilylated alcohol **25**, which exists in the open form de-



picted, must be epimerized, as expected, at the alcohol center. Attempts to convert this alcohol into a leaving group to effect S_N2-type displacements failed due to the low nucleophilicity of this hydroxyl group and the high solvolytic reactivity of any resultant derivative. The high solvolytic reactivity resolves the problem since dissolving **25** in methylene chloride containing trifluoroacetic acid at 0 °C gives an 85:15 equilibrium mixture of **26a** and **26b**. To confirm that only epimerization occurs, PCC oxidation[19] converts **25** to the crystalline ketone **27**, which is identical with the single ketone that results upon subjecting **26a** + **26b** to PCC in the presence of molecular sieves.[20]

Direct subjection of the initial Diels–Alder adduct to methanol containing sulfuric acid also achieves epimerization of the alcohol,

(16) For a review see: Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed. Engl.* **1978**, *7*, 476. Also see: Nivda, M.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3148. Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. Williams, J. R.; Cleary, T. P. *J. Chem. Soc., Chem. Commun.* **1982**, 626.

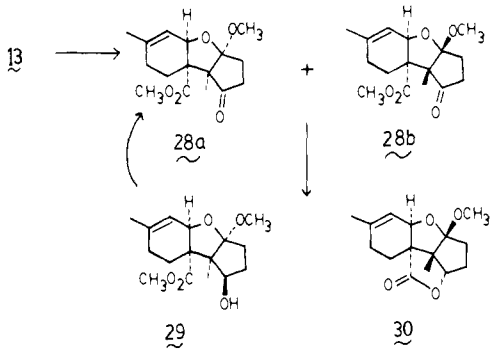
(17) Cf. Yates, P.; Stevens, K. E. *Tetrahedron* **1981**, *37*, 4401. Buchi, G.; Chu, P.-S. *Tetrahedron* **1981**, *37*, 4509. Brussel, W. V.; Van Hooland, J.; De Clercq, P.; Vandewalle, M. *Bull. Soc. Chim. Belg.* **1975**, *85*, 813. Wolff, S.; Schrieber, W. L.; Smith, A. B., III; Agosta, W. C. *J. Am. Chem. Soc.* **1972**, *94*, 7797.

(18) BSA = *O,N*-bis(trimethylsilyl)acetamide; DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; DMAP = 4-(dimethylamino)pyridine.

(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 1647.

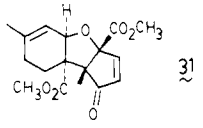
(20) Herscovici, J.; Antonakis, K. *J. Chem. Soc., Chem. Commun.* **1980**, 561.

but under these conditions the internal ketal **28a** and **28b** is isolated in an 85:15 ratio.



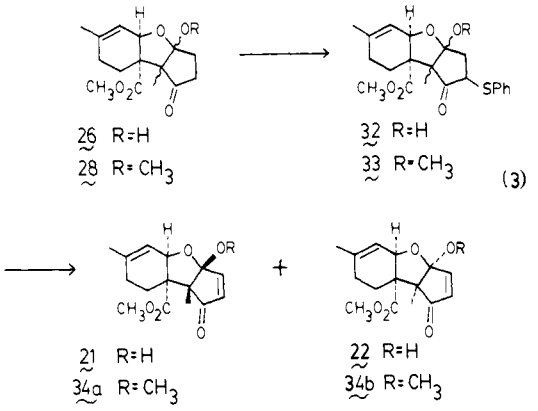
The question of ring fusion stereochemistry in **26** and **28** required resolution. In the case of **28**, reduction of the ketone of the cis, anti, cis isomer from the convex face should produce an alcohol that should readily lactonize to **30**. Experimentally, hydride reduction of the 85:15 mixture gave an 80% yield of a hydroxy ester as the only isolated product (the product from the minor isomer was not isolated) that refused to lactonize under any conditions. Reoxidation of this alcohol returned the major component of the mixture as a pure component. Thus, the cis, syn, cis stereochemistry corresponds to the major isomer rather than the anticipated more stable cis, anti, cis isomer **28b**. This unusual observation presumably results from a kinetic phenomenon where the formation and trapping of the carbonium ion intermediate from the cis, syn series occurs faster than the corresponding intermediate in the cis, anti series. The inability to cleave or equilibrate these ketals reinforces this interpretation.

Since **26** and **28** correspond to norapotrichothecenes, correlation of their NMR spectral properties with **31**, a known transformation



product of verrucarol,[7] offers a simpler approach to stereochemical assignments. Further, such enones represent the type of intermediates required for our proposed synthesis.

Sulfenylation–dehydrosulfenylation[21] provided an excellent strategy for double-bond introduction as shown in eq 3. In the



(3)

case of **28**, inverse quench of the lithium enolate into a HMPA solution of diphenyl disulfide gave **33** in 64% yield. MCPBA oxidation followed by thermolysis of the crude sulfoxide in toluene

Table I. ^{1}H NMR Data on [6.4.0.0^{3,7}] Ring Isomers[22]

COMPOUND	C-9	C-10	C-11	C-12	C-14	C-15	C-16	CO_2CH_3
28a	141.0	117.5	74.4	113.2	14.4	171.7	23.2	51.6
20	137.5	119.5	76.8	112.5	11.5	172.0	23.1	51.6
19	140.7	117.5	74.8	112.2	14.9	171.7	23.1	51.5
26a	137.9	120.5	76.7	111.8	11.9	172.0	23.3	51.6
26b	140.1	118.9	75.2	111.1	15.2	172.0	23.3	51.6

Table II. ^{13}C NMR Data on [6.4.0.0^{3,7}] Ring Isomers[22]

	ISOMER RATIO	COMP'D RING GEOMETRY	H-2	H-3	H-11	CH_3-14
	85	26a C,A,C			4.57 d, J=3.8	1.21
	15	26b C,S,C			5.04 bd, J=3.5	1.06
	15	28b C,A,C			4.61 bs	1.16
	85	28a C,S,C			4.86 d, J=3.3	0.97
	80	20 C,A,C			4.54 d, J=4.0	1.10
	20	19 C,S,C			4.90 d, J=4.0	0.95
	10	34a C,A,C	7.54 d, J=6.0	6.25 d, J=6.0	4.21 d, J=5.0	1.15
	90	34b C,S,C	7.65 d, J=6.0	6.12 d, J=6.0	5.03 d, J=5.0	1.14
	92	21 C,A,C	7.18 d, J=6.0	6.20 d, J=6.0	4.17 d, J=5.0	1.16
	8	22 C,S,C	7.32 d, J=6.0	6.05 d, J=6.0	5.12 d, J=4.5	1.16
		31 C,A,C	7.32 d, J=6.0	6.24 d, J=6.0	4.21 d, J=5.0	1.07
ref 7		C,A,C - cis,anti,cis C,S,C - cis, syn, cis				

in the presence of dihydropyran gave a 94% yield of the enone **34**. Chemoselective sulfenylation of the polyanion from **26** (3 equiv of LDA) in similar fashion gave an excellent yield of the crude sulfide **32**. The ease of establishing at least an equilibrium, albeit unfavorable, between the lactol and hydroxy ketone form of **32** labilizes the sulfide. Thus, the crude sulfide was directly treated with DBU and mercuric chloride to give a 67% overall yield of **21** and **22** in a 92:8 ratio.

Tables I and II summarize the pertinent ^{1}H and ^{13}C NMR spectral characteristics, respectively. Inspection of the ^{1}H NMR data reveals that the shift for the proton at C(11) is most diagnostic, it appears at ~4.2 ± 0.1 in the cis, anti, cis but about 5.1 ± 0.2 in the cis, syn, cis isomer (enone series only). In the saturated ketone series, a similar trend is observed, but the ~ 0.8-ppm shift difference shrinks to a 0.4-ppm difference in the same direction. In the ^{13}C NMR spectra, the shifts of several carbons [C(9), C(10), C(11), C(16)] show systematic variation, but the most diagnostic shift seems to be that for the angular methyl group where it appears at 3.5 ppm higher field in the cis, anti, cis compared to cis, syn, cis isomer, presumably resulting from steric compression.[23] These trends correlate with chemical evidence garnered in the case of **28**, which verifies their validity.

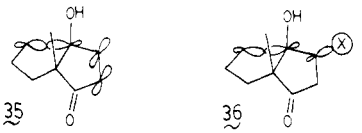
(21) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

(22) To maintain a consistent numbering system throughout the manuscript, atoms are always numbered in the text as if they were incorporated into the tricothecane or apotrichothecane skeleton.

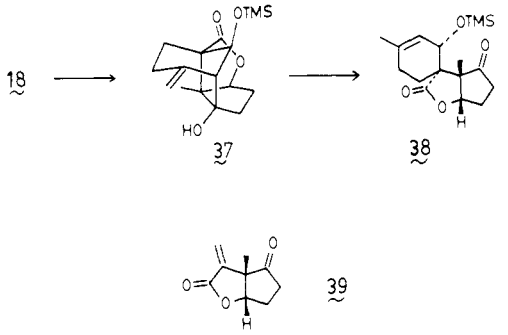
(23) Grant, D. M.; Cheney, B. V. *J. Am. Chem. Soc.* **1967**, *89*, 5319.

On this basis, the stereochemical assignments of the remaining norapotrichothecenes can be made as indicated. In the case of **26**, these assignments also correlate to the expected dominance of the cis, anti, cis isomer at equilibrium.

All attempts to coax either **21** or **34** to isomerize to **23** (or even **24**) failed. While the source of such a failure can stem from either thermodynamics or kinetics, we initially focused on the latter. Inspection of molecular models suggests that the overlap required for migration in **35** may be sufficiently poor to make the isomerization of the enones difficult. In the open form of **35**, a conjugate addition of the oxygen to the enone corresponds to a 5-endo-trig process.[24] Stereoelectronic effects also disfavor such a pathway. Both of these problems are resolved by using a migration terminus that possesses a normal leaving group as in **36**. Such a process would also resolve any thermodynamic problem since the rearrangement would be irreversible.



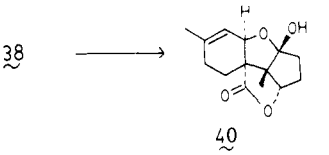
(2) Approach B. Alkyl Bromide as Migration Terminus, 11-Epi Series. In order to realize the transformation of **9** to **9a**, a differentiation of the diastereotopic carbonyl groups of **13** is required. In fact, the tandem cycloaddition–ene reaction not only puts together the carbon skeleton but also effects just such a differentiation. Reduction of the ketone of **18** with sodium borohydride



is complicated by partial overreduction[25] of the ester. Thus, a Collins oxidation is incorporated in the workup sequence to provide the pure lactone **37** directly in 92% yield.

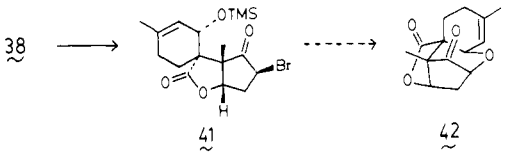
With the chemodifferentiation in place, passing **37** through a hot horizontally mounted empty tube (16 cm, 470 °C) at 1.2–1.5 torr (FVT = flash vacuum thermolysis) unmasks the desired cyclopentanone **38**. Under these conditions, an easily separable 4:1 mixture of the retro ene product and **37** are obtained. After the recovered **37** was recycled, the retro ene product **38** is isolated in 89% yield. At higher temperatures, **38** partially succumbs to a retro Diels–Alder reaction to generate **39**. The advantage of this thermolysis technique over more conventional methods, besides the obvious avoidance of reagents or solvents and minimization of workup procedures, is illustrated by solution thermolysis in dodecane at 210 °C where only a 40% yield of **38** can be obtained. The carbonyl region of the IR spectrum (1783 and 1744 cm^{-1}) as well as appropriate absorptions in the NMR spectrum for a vinyl methyl group (δ 1.71, s) and a trisubstituted olefin (δ 5.31, br s) confirm that the desired isomerization occurred.

Introduction of the leaving group α to the carbonyl group and epimerization of the allylic alcohol or vice versa prime the molecule for the critical rearrangement. Desilylation of **38** [$(C_4H_9)_4NF$, THF] gave a crystalline alcohol (mp 160–162 °C) that epimerized to give **40** with trifluoroacetic acid in methylene chloride. As expected, **40** exists solely as the lactol (one carbonyl band at 1762 cm^{-1} and no ketone carbonyl group in the ^{13}C NMR spectrum



but an absorption at δ 116.9 for the hemiketal carbon). Unfortunately all attempts to generate a dianion from **40** failed.

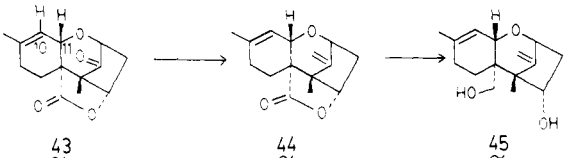
The alternative sequence proved highly successful. Treatment of **38** with lithium 2,2,6,6-tetramethylpiperidide in THF at −20



°C followed by Me_3Si-Cl generated the enol silyl ether in situ. After the resultant solution was cooled to −78 °C, addition of pyridine followed by the bromine–dioxane complex[26] gave a single bromide with the proton vicinal to the bromine appearing as a doublet of doublets (J = 13.1 and 8.2 Hz). The exo stereochemistry of **41** derives from the anticipated approach of the bromine to the less hindered convex face of the enol silyl ether of **38**. By analogy to the earlier epimerization, stirring **41** at −20 to 0 °C gave a mixture that still partially contained a trimethylsilyl group. Believing a trimethylsilyl derivative of a norapotrichothecene intermediate might be responsible, we subjected this crude mixture directly to tetra-*n*-butylammonium fluoride. The product of this reaction had many characteristics of the desired trichothecene skeleton **42**. The beautifully crystalline compound (mp >156 °C dec) had two carbonyl stretches at 1786 and 1770 cm^{-1}. It showed the exact pattern for H_2–H_4[22] expected [H-2, δ 4.32, dd, J = 3.0, 1.3 Hz; H-3 exo, 1.99, ddd, J = 16, 7.3, 3 Hz; H-3 endo, 2.34, d, J = 16 Hz; H-4, δ 4.58, dd, J = 7.2, 1.3 Hz]. The only unexpected property was the lack of observable coupling (<1.5 Hz) between H-10[22] (δ 5.28, br s) and H-11[22] (δ 4.21, br s) in which the corresponding coupling in the natural trichothecenes is 4–5 Hz.

Assessing the lack of observable coupling to the presence of the lactone ring, we continued the synthetic sequence by Wittig olefination of the ketone of **42** (72%) and reduction of the lactone to a diol. The stability of the intermediate lactol made its further reduction to the desired diol very sluggish, requiring 35 h at 24 °C with 6.3 equiv of DIBAL-H (78% yield). All other reducing agents stopped at the lactol stage. Most unsettling was the failure to observe any detectable coupling between H-10 and H-11.[22]

At this point, the likelihood that an 11-epitrichothecene **43**



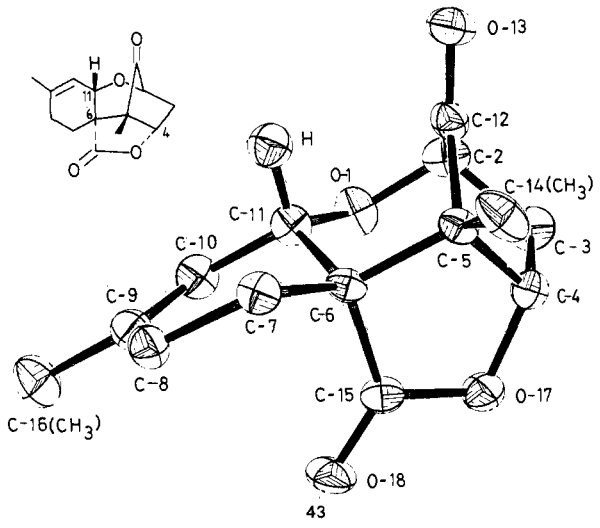
actually formed seemed probable despite the unlikely prospect that formation of such a compound forces the tetrahydropyranyl ring into a strained boat conformation. The almost 90° dihedral angle between H-10 and H-11[22] would agree with a very small coupling between these protons.

Further support for the notion that cyclization proceeded without concomitant epimerization derived from direct treatment of the crude bromide **41** with tetra-*n*-butylammonium fluoride from which the identical ketone was isolated in 62% overall yield from **38**. Under such conditions, epimerization of the allylic alcohol seems unlikely. As this constitutes the first known example of an 11-epitrichothecene, the structure was established unam-

(24) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *39*, 2939, and earlier references cited therein.

(25) Schenker, E. *Angew. Chem.* **1961**, *73*, 81.

(26) We find that the ability to have a clean source of bromine as with the crystalline dioxane–bromine complex gives more satisfactory results. For use of bromine see: Reuss, R. H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1758.

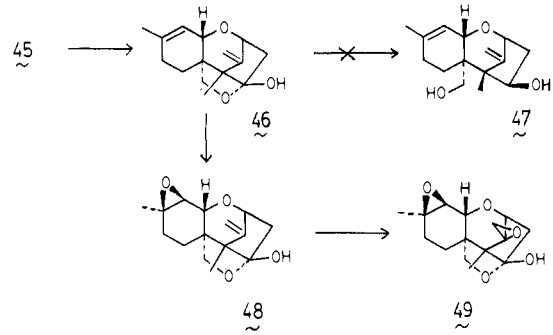


43

Figure 1. ORTEP drawing of **43**.

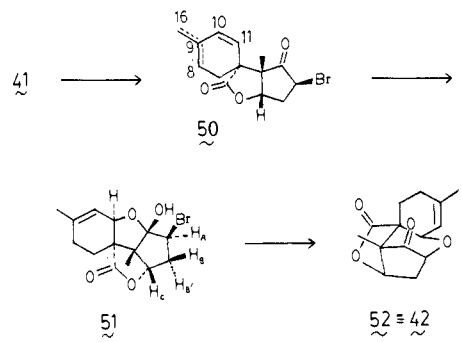
biguously by single-crystal X-ray analysis that not only verifies **43** but clearly shows the boat conformation of the tetrahydropyranyl ring in which C(11) and C(12)[22] occupy the bow positions. Table III (see paragraph at end of paper regarding supplementary material) and Figure 1 give the pertinent structural parameters and depict the molecule, respectively. For clarity, only the H at C(11) is included in the ORTEP drawing (Figure 1).

In order to explore some of the chemistry of this new ring system directed toward 11-epiverrucarol derivatives, the diol **45** was



oxidized with PCC to give cleanly the lactol **46**. Reduction of **46** with DIBAL-H returned the original diol rather than complex with the primary alcohol of the hydroxy ketone form of **46** to deliver the hydride internally and give **47**. Epoxidation of **46** with 1.2 equiv of MCPBA at −24 °C gives only the trisubstituted epoxide **48**. In accord with **48**, the signals for both the olefinic proton H-10 and the vinyl methyl group disappeared while singlets at δ 2.92 (1 H) and δ 1.30 (3 H) grew in. Epoxidation of **46** with excess MCPBA gives a mixture of **48** and **49**.

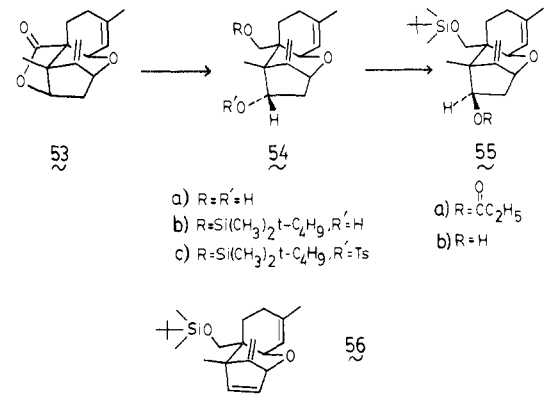
(3) Approach B. Verrucarol. Convinced that thermodynamically we could coax the desired epimerization of the allylic alcohol due to the formation of the very stable lactol ring system, we returned to the acid-catalyzed epimerization. Treating the crude bromo ketone **41** with trifluoroacetic acid in ethylene dichloride



now at room temperature gave a 60:40 mixture of elimination products **50** in which the exocyclic olefin isomer predominated. The isomer with the exocyclic 9,16 double bond displayed two broad singlets at δ 4.99 and 5.02 for the protons at C(16)[22] and two doublets (J = 10 Hz) at δ 5.60 and 6.48 for the protons of the 10,11 double bond, whereas the endocyclic diene displayed absorptions for the vinyl protons at δ 5.60 (br s), 5.41 (d, J = 10 Hz), and δ 6.11 (d, J = 10 Hz) in addition to the signal for the vinyl methyl group at δ 1.82. Warming this mixture to 32–55 °C in the presence of a little water and following the reaction by NMR spectroscopy revealed that the exocyclic isomer reacted more rapidly but both were converted to a new product that was assigned as the isomeric lactol **51**. The 270-MHz NMR spectrum showed a deceptively simple coupling pattern since H_B and $H_{B'}$ were accidentally isochronous [H_A or H_C, δ 4.61, t, J = 5.2 Hz; H_A or H_C, 4.45, t, J = 6.1 Hz; $H_B + H_{B'}$, δ 2.60, dd, J = 6.1, 5.2 Hz]. Irradiation at δ 2.60 collapsed the two triplets to singlets. Whereas DBU failed to rearrange **51**, exposure of **51** to tetra-*n*-butylammonium fluoride smoothly completed the sequence to give **52**. In practice, the three-step sequence of bromination, inversion with trifluoroacetic acid, and fluoride-promoted cyclization was performed as one operation and provided **52** in 70% yield from ketone **38**.

While we were confident we did obtain **52**, since it is isomeric with **45** and its IR (1780 and 1762 cm^{-1}) and NMR absorptions (see Experimental Section) were in accord with this assignment, it was disconcerting that the crucial $J_{10,11}$ was still not observable. However, in this case, upon reduction of the lactone (vide infra) the 5.5-Hz coupling between these two protons, which is so characteristic of the trichothecenes, does indeed appear. In addition, the pattern for H_4[22] changes to a doublet of doublet, J = 10.8 and 5.9 Hz, which is characteristic of the 4α compounds.[27]

Inversion of the C-4 alcohol became the major final hurdle. Olefination of **52** with the Wittig reagent in THF at 60 °C gives the exocyclic methylene compound **53** in 95% yield. Lactone



reduction proceeds more readily than in the 11-epi series to give the desired diol **54a** in 95% yield. Chemoselective silylation of the primary alcohol with *tert*-butyldimethylchlorosilane with DMAP in methylene chloride provides **54b** in 85% yield. Care with respect to temperature and pH in the workup is required to avoid both the loss and scrambling of the silyl group. The sluggishness of the endo secondary alcohol to react required the use of 8 equiv of *p*-toluenesulfonyl chloride in warm (34 °C) pyridine for 60 h to give the tosylate **54c** in 79% yield based upon recovered starting material (14%).

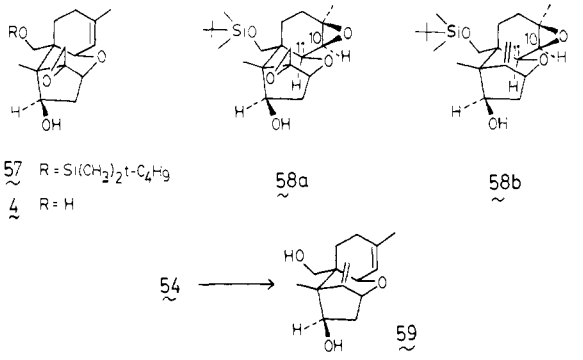
Of the oxygen nucleophiles for inversion, cesium propionate proved vastly superior.[28] We found that use of 1,3-dimethyl-2-imidazolidinone as a solvent rather than DMF or HMPA substantially improved the yield of **55a**. Since desilylation accompanied this reaction, the crude mixture was resilylated during workup. A coequal product with the inverted propionate **55a** is

(27) Hanson, J. R.; Marten, T.; Siverns, M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1033. Riisom, T.; Jakobsen, H. J.; Rastrup-Andersen, N.; Lorik, H. *Acta Chem. Scand., Sect. B* **1978**, *B32*, 499.

(28) Kruizinga, W. H.; Shijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.

the elimination product **56**—itself a quite interesting intermediate for other members of the trichothecene family. Since separation of **55** and **56** proved somewhat tedious, the mixture is chemoselectively hydrolyzed with potassium carbonate in aqueous methanol to give the hydroxy silyl ether **55b**. In this way, **55b** and **56** are isolated in 31% and 39% overall yield from **54c**, respectively.[29]

Schlessinger resorted to protection of the trisubstituted double bond since he was unable to effect the chemoselective epoxidation of the 12,13 double bond of the diol related to **55b**.[9d] The fact that trichodermol does show the desired chemoselectivity led us to suspect that Schlessinger's failure lay in an acceleration of the epoxidation of the trisubstituted double bond by the free primary alcohol.[30] Since the offending alcohol is masked as a silyl ether in **55b**, it was anticipated that the desired chemoselectivity should return. Treatment of **55b** with buffered (disodium hydrogen phosphate) MCPBA in methylene chloride[9a] at −25 °C for 61 h led to a 4:1:1 ratio of **57**:**58a**:**58b** at 60% conversion. Silica gel



apparently destroyed **58a** and **58b** since preparative TLC only allowed isolation of **56a** in 42% yield in addition to a 34% yield of recovered starting material. The NMR spectra of the crude product suggested the β-configuration for the trisubstituted epoxide. In particular, the $J_{10,11}$ appears diagnostic with this coupling being ~5 Hz for the β-epoxide and ~2 Hz for the α-epoxide. These protons (**58a**, δ 2.98 and 3.51 for H-10 and H-11, respectively; **58b**, δ 2.93 for H-10) showed a coupling of 5.1–5.2 Hz in **58a** and **58b**.

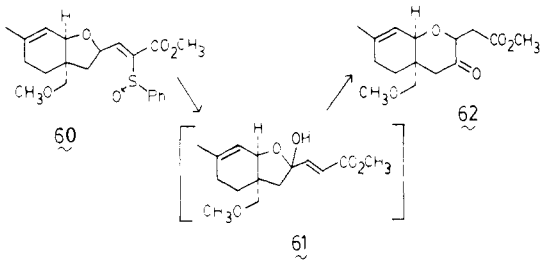
Strongly encouraged by the fact that the chemoselectivity is in the right direction, we explored metal-catalyzed versions to further enhance the selectivity.[31] *tert*-Butyl hydroperoxide with vanadyl acetylacetonoate shows good chemoselectivity, but the reaction is very slow and accompanied by substantial decomposition. On the other hand, molybdenum hexacarbonyl[32] proved excellent. A smooth conversion of **55b** to only the monoepoxide **57** (85% yield) occurred in benzene at 63 °C. The ultimate step of fluoride induced desilylation provided verrucarol (**4**) in 91% yield as a white solid, mp 165.5–167 °C.

Comparison of IR and NMR spectra of both **4** and **57** with those of samples of both the natural product and its monosilyl derivative, prepared from the natural product as described by Fraser-Reid et al.,[33] demonstrated the identity of the compounds in all respects except optical purity. In addition, the NMR spectrum of 12,13-deoxyverrucarol (**59**), obtained from natural sources,[34] was indistinguishable from that of a sample of this material obtained from **54** by treating with cesium propionate in DMF followed by potassium carbonate in methanol.[35]

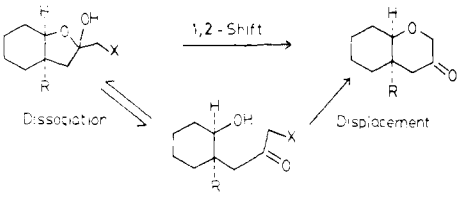
Discussion

The new dienophile **12** should prove a useful building block for natural products. By delicate temperature control either the Diels–Alder adduct or the ene product is directly available. The facility with which it participates in the tandem Diels–Alder and Alder ene reactions allows construction of a flexible polycyclic framework with five contiguous asymmetric centers of a single relative configuration. The concept of using an intramolecular ene reaction to achieve diastereotopic differentiation and as a mild protecting group opens the question of its broader generality. The totally neutral nonoxidative nor reductive conditions of the unmasking stand in contrast to virtually any other carbonyl protecting group. The rarity of a ketone carbonyl group serving as an enophile in a thermal ene reaction suggests that the unfavorable dipole interactions present in cyclopentane-1,3-dione[36] make it particularly prone to participate.

The failure of the 1,2-migration in **21** is surprising, at first glance, in light of the fact that the rearrangement of **61** is so facile



that **61** cannot even be detected in the conversion of **60** to **62**. It should be pointed out that, for the present purposes, no distinction is being made between a 1,2-shift and a dissociation–displacement



mechanism. In terms of thermodynamics, the major difference between **61** → **62** and **21** → **23** lies in the strain of the oxabicyclo[3.2.1]octane system. It would seem that such a factor should not be the major culprit in the failed rearrangement. The most reasonable explanation would appear to be the stereoelectronic restriction imposed by constraining the addition of the oxygen to the enone of **21** to be a 5-endo-trig process, which should be disfavored. By switching to the bromide route, we obviated any such problem. This study combined with our earlier work points to the utility of employing a ring expansion from a [6,5] to a [6,6] ring system as a stereo-controlled synthesis of polyhydrochromanones. The importance of fluoride ion as the base to induce the rearrangement is attested to by the failure of oxygen or amine bases to effect the reaction. Its special effect may derive from the fact that while it is a base that can accept the hydroxl proton, its conjugate acid should be particularly effective in hydrogen bonding with the departing bromide and thereby make it a good leaving group. The growing use of fluoride ion as a base rejuvenates a technique used some time ago in heterocyclic synthesis and carbonyl condensations.[37]

(29) An alternative procedure based upon oxidation to the C(4) ketone followed by dissolving metal reduction with internal protonation of the intermediate ketyl by the primary hydroxyl group to control stereochemistry has not been explored but may offer an advantage. Cf.: Gibbons, E. G. *J. Am. Chem. Soc.* **1982**, *104*, 1767.

(30) Zurcher, W.; Gutzwiller, J.; Tamm, Ch. *Helv. Chim. Acta* **1965**, *48*, 840.

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(35) Racemic **59**: mp >176 °C; NMR δ 1.16 (3 H, s), 1.40–2.05 (7 H, m), 1.68 (3 H, s), 2.59 (1 H, dd, J = 15.1, 7.8 Hz), 3.58 (1 H, d, J = 12.1 Hz), 3.71 (1 H, d, J = 5.5 Hz), 3.76 (1 H, d, J = 12.1 Hz), 4.35 (1 H, d, J = 5.5 Hz), 4.71 (1 H, s), 4.72 (1 H, dd, J = 7.7 (3.0 Hz), 5.14 (1 H, s), 5.40 (1 H, d, J = 5.5 Hz).

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This chemistry also opens an approach to the apotrichothecenes. The excellent success of the sulfenylation–dehydrosulfenylation sequence in this series is particularly striking. These compounds, at first thought to represent the actual structures of the trichothecenes and which are transformation products derived from trichothecenes, may represent biosynthetic intermediates of the trichothecenes. Thus, a synthetic entry to them would aid in investigating their role in the full biochemical story[2d,34,38] of trichothecenes and verrucarins.

Another feature of this approach is the ready accessibility of both the verrucarol and 11-epiverrucarol series in 11 and 10 steps, respectively, from 2-methylcyclopentane-1,3-dione. From a common intermediate **41**, simple manipulation of the acid treatment provides both series. The dramatic structural consequences of the epimerization at C(11) may make this series very interesting from a biological point of view.

This route provides verrucarol with the two hydroxy groups already differentiated. Considering the capricious nature of the chemoselectivity of the two hydroxyl groups toward various electrophiles, removing such doubts for the specific elaboration to verrucarins and roridins enhances the utility of this strategy. For example, **59** with the secondary alcohol specifically propionated is directly available from **54** and in 16 overall steps from 2-methylcyclopentane-1,3-dione. Verrucarol with the primary alcohol specifically silylated, i.e., **57**, is available in 17 steps. This approach provides verrucarol itself in 18 steps from this same starting material.

Experimental Section

2-(4-Chloro-1-buten-3-yl)-2-methyl-1,3-cyclopentanedione (16). To a refluxing suspension of 2-methyl-1,3-cyclopentanedione (56 g, 0.5 mol) in toluene (1 L) were added 1-chloro-*cis*-2-buten-4-ol[39] (106.4 g, 1.0 mol) and *p*-toluenesulfonic acid monohydrate (6.0 g) with azeotropic removal of water. After the mixture was refluxed for 1.5 h, the trap was drained of the aqueous toluene and more chlorobutenol (26.6 g, 0.25 mol), pTSA (1.5 g), and dry toluene (100 mL) were added. This procedure was repeated after 5 and 11 h. After 16 h the mixture was cooled to room temperature and filtered to collect the unreacted dione (22.1 g). The filtrate was diluted with ether (700 mL) and washed with saturated aqueous sodium bicarbonate (2 × 100 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield an orange oil. The oil was taken up in mesitylene (600 mL) and heated at reflux for 9 h. When the solution was cooled, a precipitate formed that was filtered and washed with ether (200 mL) to yield more dione (14.5 g). The filtrate was concentrated in vacuo and the residue eluted through a silica gel column (5 × 60 cm) with hexane (400 mL), 10% ethyl acetate–hexane (200 mL), and 40% ethyl acetate–hexane to yield a yellow oil. The oil was distilled in a kugelrohr apparatus (94–101 °C, 0.5 mm) to yield the olefin **16** (32.2 g, 92.8% based on recovered starting material) as a colorless oil: IR (neat) 2980, 1765, 1729, 1455, 1425 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.11 (3 H, s), 2.81 (4 H, m), 2.93 (1 H, dt, J = 9.9, 7.4 Hz), 3.54 (1 H, dd, J = 11, 7.4 Hz), 3.61 (1 H, dd, J = 11, 7.4 Hz), 5.21 (1 H, dd, J = 17, 1.5 Hz), 5.26 (1 H, dd, J = 10.5, 1.5 Hz), 5.81 (1 H, dt, J = 17, 10 Hz); MS (70 eV) m/e (rel intensity) 202 (2.8), 200 (8.4), 156 (5.6), 151 (100), 123 (7.5), 112 (10.9), 95 (17.1), 81 (10.0), 67 (12.1), 55 (48.8), 53 (15.7), 41 (11.1). Anal. Calcd for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.53; M_r 200.0604. Found: C, 59.86; H, 6.44; M_r 200.0597.

2-Methyl-2-[1-(methoxycarbonyl)ethen-1-yl]-1,3-cyclopentanedione (12). (All temperatures stated are internal.) A solution of potassium permanganate (26.86 g, 0.17 mol) and water (170 mL) was mixed with methylene chloride (30 mL). A solution of the olefin **16** (8.5 g, 0.0425 mol) in methylene chloride (140 mL) and acetic acid (35 mL) containing cetyltrimethylammonium bromide (0.8 g) was added at 5 °C over a 15-min period. The mixture was stirred at 5–10 °C for 1.5 h and then warmed to room temperature over a period of 0.5 h. After the mixture was recooled to 5 °C, sodium bisulfite (20 g) was added in portions so the temperature remained below 15 °C, followed by the addition of 6 M aqueous hydrochloric acid (60 mL). Chloroform (150 mL) was added and the mixture filtered through a pad of Celite in a sintered glass funnel. The precipitate was washed with 10% aqueous hydrochloric acid (40 mL) and chloroform (100 mL). The organic layer was separated and the aqueous layer extracted with more chloroform (2 × 200 mL) and ether–ethyl acetate (1:1 mixture, 100 mL). The combined organic layers were washed with brine (100 mL), which after separating the organic layer was extracted with fresh chloroform (100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Toluene (50 mL) was added and removed in vacuo. This procedure was repeated to remove the last traces of acetic acid. The resulting yellow oil (8.1 g) was dissolved in ether (80 mL) and a solution of diazomethane in ether added until no more bubbling was observed. The mixture was again dried ($MgSO_4$) and concentrated in vacuo to yield the β-chloro ester as an orange oil. The oil was immediately dissolved in ether (50 mL), and DBU[18] (6.08 g, 40 mmol) in benzene (10 mL) was added dropwise at 0 °C. The reaction was stirred at room temperature for 20 min and then poured onto a Florisil column (3 × 35 cm) packed in ether. The gummy residue in the reaction flask was washed well with acetone (2 × 15 mL) which was then diluted with ether (30 mL) and poured onto the column. The column was eluted with ether (400 mL). Upon concentration, an oil was obtained which was further purified by HPLC (one column, 18% ethyl acetate–hexane). This yielded at 3–4 column volumes the acrylate **12** (4.0 g, 48%) as an oil, which solidified upon standing: mp 30–32 °C (not recrystallized); IR (CCl_4) 2290, 1728, 1700, 1635, 1440, 1338 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.19 (3 H, s), 2.81–2.96 (4 H, m), 3.64 (3 H, s), 5.87 (1 H, s), 6.51 (1 H, s); MS (70 eV) m/e (rel intensity) 196 (100.0), 168 (14.0), 137 (10.4), 136 (40.1), 109 (23.6), 108 (21.8), 59 (14.4), 55 (25.8), 53 (26.8), 43 (10.1). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.17; M_r 196.0735. Found: C, 60.9; H, 6.10; M_r 196.0745.

3-Methyl-1-(trimethylsiloxy)butadiene (11b). To *n*-butyllithium (170 mL of a 1.5 M solution, 0.225 mol) in hexane was added the acetoxydiene **11a**[13] (15.3 g, 0.121 mol) in THF (30 mL) dropwise at −78 °C. After the addition (0.5 h), the reaction was warmed to 0 °C when neat trimethylsilyl chloride (28.9 g, 0.266 mol) was added. After being stirred at 0 °C for 0.5 h, the reaction was diluted with pentane (250 mL) and quenched slowly with saturated aqueous sodium bicarbonate (100 mL), all at 0 °C. The mixture was further diluted with pentane (150 mL), washed with 10% aqueous sodium bisulfite (1 × 80 mL), saturated aqueous sodium bicarbonate (1 × 80 mL), and aqueous brine (1 × 80 mL), and dried (sodium sulfate), and the solvent was removed by distillation. The residue was distilled through a Vigreaux column at 43 mm to yield the diene **11b** (11.0 g, 58.3%) in a fraction boiling at 63–95 °C. ^1H NMR spectroscopy showed this to be contaminated with some *n*-butyl compound so the distillate was redistilled (bp 70–75 °C at 43 mm; lit.[14] bp 47–52 °C at 13 mm) to give pure diene (8.9 g, 47.2%), contaminated with a trace of the cis diene: ^1H NMR (100 MHz, $CDCl_3$) δ 0.3 (9 H, s), 1.84 (3 H, s), 4.68 (2 H, m), 5.59 (1 H, d, J = 12 Hz), 6.38 (1 H, d, J = 12 Hz).

(1*S,2*R**,6*R**,7*R**,11*S**)-6-Hydroxy-2-methyl-1-(methoxycarbonyl)-8-methylene-3-oxo-11-(trimethylsiloxy)tricyclo[5.3.1.0^{2,6}]undecane (18).** 3-Methyl-1-(trimethylsiloxy)butadiene **11b** (11.53 g, 0.0739 mol), the dienophile **12** (8.78 g, 0.0448 mol), and BSA[18] (0.19 g) in mesitylene (40 mL) were heated at 155 °C for 5 h, and then additional mesitylene (40 mL) and diene (1.7 g) were added. The resultant mixture was refluxed for 4 h and, after more mesitylene (30 mL) was added, the refluxing was continued for 3 h. Upon cooling of the mixture, crystals formed that were dissolved by the addition of chloroform. The whole mixture was poured on a silica gel column (6 × 80 cm) and developed first with hexane (700 mL) to remove the mesitylene and then with 5% ethyl acetate–hexane to 60% ethyl acetate–hexane. The ethyl acetate–hexane fractions were concentrated and further purified by HPLC (two columns, 15% ethyl acetate–hexane). At 1.2–1.5 column volumes was obtained **19** and **20** (1.2 g, 7.7%). At 1.5–2.5 column volumes was obtained the Diels–Alder adduct **13** (2.5 g, 22.2%) as an oil that solidified upon storage at 0 °C. At 2.5–4 column volumes was obtained the ene product **18** (5.3 g) as a solid. At 4–5.5 column volumes was obtained a mixture of the ene product (1.46 g) and the starting dienophile **12** (0.54 g, 6.1%), which could be separated by distilling the dienophile in a kugelrohr apparatus (110–111 °C, 0.1 mm). The ene was obtained in a total yield of 42.9%. When the Diels–Alder adduct was reequilibrated, as described, the ene product could be obtained in a total yield of 63%: mp (CCl_4) 147–148.5 °C; IR ($CHCl_3$) 3580 (s), 2975, 1740, 1650, 1450,

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1435 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (9 H, s), 1.16 (3 H, s), 1.9–2.4 (7 H, m), 2.63 (1 H, dt, J = 18, 9.9 Hz), 2.68 (1 H, d, J = 5 Hz), 3.66 (3 H, s), 4.20 (1 H, d, J = 5 Hz), 4.78 (1 H, d, J = 1.5 Hz), 4.97 (1 H, d, J = 1.5 Hz); ^{13}C NMR (15.04 Mhz, $CDCl_3$) δ 0.1, 13.71, 23.38, 26.92, 36.63, 38.07, 51.21, 57.09, 59.55, 63.56, 71.67, 81.27, 114.54, 143.17, 172.61, 218.90; MS (70 eV) m/e (rel intensity) 352 (0.7), 337 (17.4), 320 (47.6), 185 (11.0), 181 (10.5), 180 (25.0), 151 (25.9), 119 (13.1), 113 (36.0), 85 (60.1), 83 (100), 75 (22.8), 73 (50.5), 47 (20.6). Anal. Calcd for $C_{18}H_{28}O_5Si$: C, 61.4; H, 7.95; M_r = 352.1706. Found: C, 61.18; H, 7.77; M_r = 352.1704.

19 + 20: IR (CCl_4) 2950, 1745, 1735 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10 (9 H, s), 1.10 (3 H, s), 1.66 (3 H, br s), 1.70–2.49 (8 H, m), 3.70 (3 H, s), 4.54 (1 H, d, J = 4.0 Hz), 5.52 (1 H, br s, $W_{1/2}$ = 9 Hz), minor isomer has peaks at 0.18 (s), 0.95 (s), 1.11–1.22 (m), 4.90 (d, J = 4 Hz); ^{13}C NMR (15.04 MHz, $CDCl_3$) δ 217.0 (assigned to major isomer **20**), 215.1 (assigned to minor isomer **19**), 172.1, 137.6, 119.5, 117.4, 112.6, 77.0 (assigned to major isomer **20**), 75.0 (assigned to minor isomer **19**), 63.3, 54.6, 51.8, 38.9 (assigned to minor isomer **19**), 36.6 (assigned to major isomer **20**), 34.0 (assigned to major isomer **20**), 32.3 (assigned to minor isomer **19**), 28.8 (assigned to minor isomer **19**), 27.2 (assigned to major isomer **20**), 26.0 (assigned to minor isomer **19**), 23.5, 23.3, 15.2 (assigned to minor isomer **19**), 11.9 (assigned to major isomer **20**), 1.8; MS (70 eV) m/e (rel intensity) 352 (2.0), 239 (34.8), 186 (10.4), 185 (100), 175 (14.8), 168 (18.2), 161 (13.1), 75 (13.6), 73 (52.9). Calcd for $C_{18}H_{28}O_5Si$: M_r 352.1706. Found: M_r 352.1707.

(3*R,4*R**)-1-Methyl-4-(2-methyl-1,3-dioxocyclopentan-2-yl)-4-(methoxycarbonyl)-3-(trimethylsiloxy)-1-cyclohexene (13).** The acrylate **12** (1.0 g, 5.10 mmol) and diene **11b** (1.59 g, 10.2 mmol) containing BSA[18] (3 drops) were heated at 127–129 °C for 20 h. The mixture was eluted through a column (silica gel, 3 × 20 cm) with 2% ethyl acetate–hexane to 50% ethyl acetate–hexane, and all fractions containing the product and starting material were collected. These were then purified by HPLC (one column, 15% ethyl acetate–hexane) to yield the Diels–Alder adduct **13** (975 mg, 87.6% based on recovered starting material) mp 54–58 °C (crystallized upon standing) and starting dienophile **12** (384 mg, 38%): IR (CCl_4) 2975, 1754 (w), 1723 (s), 1455, 1436, 1425 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.10 (9 H, s), 1.21 (3 H, s), 1.53 (3 H, br s), 1.82–1.92 (2 H, m), 2.10 (1 H, dt, J = 14, 7.5 Hz), 2.21 (1 H, dd, J = 14, 6.5, 5 Hz), 2.45–2.78 (4 H, m), 3.55 (3 H, s), 4.56 (1 H, br s), 5.39 (1 H, br q, J = 1.2 Hz); ^{13}C NMR (15.04 MHz, $CDCl_3$) δ 0.83, 17.4, 22.8, 24.2, 27.8, 34.4, 35.5, 51.2, 56.0, 56.9, 69.1, 124.1, 134.9, 172.9, 214.4, 215.0; MS (30 eV) m/e (rel intensity) 352 (0.4), 293 (3.3), 240 (10.6), 235 (16.9), 225 (27.5), 219 (19.5), 168 (32.0), 156 (27.0), 137 (22.6), 136 (28.2), 82 (28.6), 75 (100), 73 (78.0), 55 (29), 43 (32). Anal. Calcd for $C_{18}H_{28}O_5Si$: C, 61.4; H, 7.95; M_r 352.1706. Found: C, 61.77; H, 7.88; M_r 352.1711.

Ene Product 18 from Diels–Alder Adduct 13. The Diels–Alder adduct **13** (2.91 g, 8.27 mmol) was refluxed in mesitylene (45 mL) for 8 h. Upon cooling of the mixture to room temperature, enough chloroform was added to dissolve the precipitate and the mixture was eluted through a silica gel column (3 × 54 cm) with hexane (200 mL) and 50% ethyl acetate–hexane. A fraction was collected that was a mixture of the ene product **18** and Diels–Alder adduct **13** (1.79 g) and a fraction of pure product **18** (1.04 g) was also obtained. The mixed fraction was purified by flash chromatography (silica gel, 4 × 6 cm) with 25% ethyl acetate–hexane (500 mL) and 45% ethyl acetate–hexane to yield starting material **13** (770 mg, 26.4%) and product **18** (900 mg, 89% based on recovered starting material).

(3S*,4S*)-3-Hydroxy-1-methyl-4-(2-methyl-1,3-dioxocyclopentan-2-yl)-4-(methoxycarbonyl)-1-cyclohexene (25): **(1) From Acid Hydrolysis.** To the Diels–Alder adduct **13** (593 mg, 1.68 mmol) in THF (4 mL) containing water (0.5 mL) was added aqueous HCl (1 M, 2 drops). The reaction was stirred for 1 h at room temperature, then poured into ether containing 10% ethyl acetate (150 mL), and washed with saturated aqueous sodium bicarbonate (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield an oil that was purified by chromatography (silica gel plate, 20 × 40 cm) in 50% ethyl acetate–hexane. The alcohol **25** was obtained (397 mg, 84%) as a white solid.

(2) From Fluoride Desilylation. To the Diels–Alder adduct **13** (46 mg, 0.131 mmol) in dry THF (0.7 mL) was added tetrabutylammonium fluoride (68.5 mg, 0.261 mmol). The reaction was stirred for 1 h at room temperature, poured into ether containing 10% ethyl acetate (80 mL), and washed with 10% aqueous potassium carbonate (8 mL). The organic layer was dried ($MgSO_4$) and concentrated to yield a slightly yellow oil. The oil was purified as above, yielding the alcohol **25** (32.5 mg, 89%) as a white solid: mp 85.5–89 °C (not recrystallized); IR (CCl_4) 3500, 2975, 1722 (v s), 1540, 1450 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.23 (3 H, s), 1.61 (3 H, br s), 1.85–2.32 (4 H, m), 2.53–3.10 (4 H, m), 3.69 [1 H, d, J = 12.1 Hz (this signal disappears upon addition of D_2O)], 3.79 (3 H, s), 4.04 [1 H, br d, J = 12.1 Hz (this signal collapses to a broad singlet upon addition of D_2O], 5.33 (1 H, br s); MS (30 eV) m/e (rel intensity) 169 (7.7), 168 (100), 167 (7.1), 153 (8.8), 137 (18.6), 136 (34.5), 113 (24.5), 84 (14.9), 55 (10.1). Calcd for $C_{15}H_{20}O_5$: M_r 280.1311. Found: M_r 280.1307.

(3R*,4S*)-3-Hydroxy-1-methyl-4-(2-methyl-1,3-dioxocyclopentan-2-yl)-4-(methoxycarbonyl)-1-cyclohexene Hemiketal (26a,b). To the Diels–Alder adduct **13** (133 mg, 0.378 mmol) in methylene chloride (4 mL) at 0 °C was added trifluoroacetic acid (0.5 mL). The mixture was stirred for 3 h at 0 °C, poured into ether (150 mL), and washed with 10% aqueous potassium carbonate (2 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a yellow oil that was purified by chromatography (silica gel plate, 20 × 20 cm) in 50% ethyl acetate–hexane to yield the hemiketal **26a,b** as a colorless oil that crystallized upon standing. ^{1}H and ^{13}C NMR spectra showed this compound to be a mixture of configurational isomers (85:15, **26a**:**26b**): mp 123–124.5 °C (not recrystallized); IR (CCl_4) 3620 (s), 3400, 2940, 1754, 1747, 1450 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.06 (peaks due to the minor isomer **26b**) (s), 1.21 (s), 1.72 (s), 1.70–2.13 (m), 2.3–2.5 (m), 3.60 (br s), 3.72 (s), 4.57 (d, J = 3.8 Hz), 5.04 (peaks due to the minor isomer **26b**) (br d, J = 3.5 Hz), 5.52 (peaks due to the minor isomer **26b**) (br s), 5.59 (br s). ^{13}C NMR (25.25 MHz, acetone-d_6, SW set so that ketone carbonyls are not seen) for major isomer **26a** δ 172, 137.9, 120.5, 111.8, 76.7, 62.1, 55.3, 51.6, 37.0, 33.6, 27.7, 24.2, 23.3, 12.0; ^{13}C NMR for minor isomer **26b** δ 172, 140.1, 118.9, 111.1, 75.2, 63.1, 58.0, 51.6, 39.1, 31.6, 29.0, 26.6, 23.3, 15.2; MS (70 eV) m/e (rel intensity) 280 (0.1), 221 (26.5), 168 (100.0), 137 (11.1), 136 (22.6), 119 (10.6), 113 (47.0), 91 (14.0), 55 (16.3), 43 (14.3), 41 (11.7). Calcd for $C_{15}H_{20}O_5$: M_r 280.1310. Found: M_r 280.1309.

1-Methyl-4-(2-methyl-1,3-dioxocyclopentan-2-yl)-4-(methoxycarbonyl)-1-cyclohexen-3-one (27). (1) From 25. To the alcohol **25** (25.5 mg, 0.091 mmol) in methylene chloride (1 mL) was added pyridinium chlorochromate (PCC) (35.3 mg, 0.164 mmol). After the mixture was stirred for 50 min at room temperature more PCC (35.3 mg) was added and stirring continued for 11 h. The reaction was poured into ether (60 mL), washed with 10% aqueous sodium bisulfate (15 mL) and 10% aqueous potassium carbonate, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was purified by chromatography (silica gel plate, 20 × 20 cm) in 50% ethyl acetate–hexane to yield the product **27** (22.2 mg, 87.7%), which crystallized upon standing.

(2) From 26a,b. To the alcohol **26a,b** (58.2 mg, 0.207 mmol) in methylene chloride (1.5 mL) were added molecular sieves (150 mg, 3 Å, powered) and PCC (133 mg, 0.62 mmol). The mixture was stirred for 6 h when more PCC (133 mg) and sieves (150 mg) were added. After being stirred another 14 h, the mixture was poured into methylene chloride (40 mL) and washed with 10% aqueous potassium carbonate (2 × 10 mL) and 10% aqueous sodium bisulfate (1 × 10 mL). All the aqueous washes were reextracted with fresh methylene chloride (15 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was purified by chromatography [silica gel plate, (1–20) × 20] in 50% ethyl acetate–hexane to yield the product **27** (51.9 mg, 90.2%) as an oil that crystallized upon standing: mp 106–109 °C; IR (CCl_4) 2940, 1730 (br), 1671, 1640 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.25 (3 H, s), 1.90 (3 H, s), 2.2–3.1 (8 H, m), 3.70 (3 H, s), 5.85 (1 H, s); MS (70 eV) m/e (rel intensity) 278 (1.5), 220 (9.7), 219 (100), 168 (8.9), 109 (4.9), 82 (62.0). Calcd for $C_{15}H_{18}O_5$: M_r 278.1155. Found: M_r 278.1155.

(1R*,3S*,7R*,8S*)-7,11-Dimethyl-3-methoxy-8-(methoxycarbonyl)-2-oxa-6-oxotricyclo[6.4.0.0^{3,7}]dodec-11-ene (28b) and Isomer (1R*,3R*,7S*,8S*) (28a). A solution of the Diels–Alder adduct **13** (721 mg, 2.05 mmol) in anhydrous methanol (15 mL) containing 10% methanolic sulfuric acid (0.75 mL) was refluxed for 3.5 h. Upon being cooled, the mixture was diluted with ether (200 mL), washed with 10% aqueous potassium carbonate, dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel plate, 20 × 40 cm) in 33% ethyl acetate–hexane to yield **28a,b** (517 mg, 85.7%) as a colorless oil. The minor isomer **28a** is present in approximately 15%: IR (CCl_4) 2980, 2960, 1736, 1450 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) for **28b** δ 0.97 (3 H, s), 1.12–1.25 (1 H, m), 1.72 (3 H, s), 1.75–2.53 (7 H, m), 3.38 (3 H, s), 3.74 (3 H, s), 4.86 (1 H, d, J = 3.3 Hz), 5.59 (1 H, br s); minor isomer **28a** has singlets at δ 1.16, 3.34, and 3.74 as well as broad singlets at δ 4.61 and 5.58; ^{13}C NMR (15.04 MHz, $CDCl_3$) for **28b** only δ 215.0, 171.7, 141.0, 117.5, 113.2, 74.4, 63.1, 57.0, 51.6, 48.7, 38.3, 28.6, 27.6, 26.0, 23.2, 14.4; MS (60 eV) m/e (rel intensity) 295 (0.5), 235 (33.1), 234 (44.2), 175 (100), 168 (60.4), 161 (16.7), 151 (16.7), 127 (85.7), 126 (22.2), 119 (20.9), 113 (38.5), 91 (30.4), 55 (25.1), 41 (26.5). Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53; M_r = 294.1467. Found: C, 64.97; H, 7.59; M_r 294.1467.

(1R*,3S*,6R*,7S*,8S*)-7,11-Dimethyl-6-hydroxy-3-methoxy-8-(methoxycarbonyl)-2-oxatricyclo[6.4.0.0^{3,7}]dodec-11-ene (29). To the ketone **28a,b** (331 mg, 1.12 mmol) in methanol (5 mL) at 0 °C was

added sodium borohydride (43 mg, 1.12 mmol). The mixture was stirred for 1 h at 0 °C, poured into ether (150 mL), washed with 10% aqueous potassium carbonate (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a colorless oil. The oil was purified by chromatography (silica gel plate, 20 × 40 cm) in 50% ethyl acetate–hexane to yield the alcohol (267 mg, 80.5%) as a white solid: mp 119.5–121 °C (CCl_4–hexane); IR (CCl_4) 3600, 3520, 2975, 2840, 1742, 1715, 1380 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.09 (3 H, s), 1.62–2.28 (7 H, m), 1.72 (3 H, s), 2.68 (1 H, br d, J = 13 Hz), 2.80 (1 H, d, J = 2.5 Hz, *OH*), 3.30 (3 H, s), 3.72 (3 H, s), 3.96 (1 H, td, J = 9.2, 2.5 Hz), 4.43 (1 H, d, J = 5.0 Hz), 5.56 (1 H, m, $W_{1/2}$ = 10 Hz), irradiation at δ 5.56 collapses δ 4.43 to a singlet; MS (70 eV) m/e (rel intensity) 264 (13.6), 205 (100), 161 (54.2), 137 (17.0), 127 (17.9), 119 (20.4), 111 (18.9), 93 (22.4), 91 (27.2), 55 (16.8), 43 (19.2), 41 (22). Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16; M_r 296.1625. Found: C, 64.69; H, 8.24; M_r 296.1625.

(1*R,3*S**,7*R**,8*S**)-7,11-Dimethyl-3-methoxy-8-(methoxycarbonyl)-2-oxa-6-tricyclo[6.4.0.0^{3,7}]dodec-4,11-diene (34b) and 1*R**,3*R**,7*S**,8*S** Isomer (34a).** To a solution of lithium diisopropylamide [1.66 mmol in THF–hexane (1.7 mL of a 1:1 mixture)] was added the ketone **28a,b** (212 mg, 0.721 mmol) at −78 °C in THF (2 mL). The reaction was stirred at −78 °C for 1 h and then transferred via cannula into a solution of diphenyl disulfide (188 mg, 0.864 mmol) in HMPA (1 mL) at 0 °C. After being stirred at 0 °C for 15 min the mixture was poured into ether–hexane (1:1, 150 mL), washed with 10% aqueous sodium bisulfate (15 mL) and 10% aqueous potassium carbonate (15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was purified by chromatography (silica gel column, 15 × 3 cm) with hexane to 30% ethyl acetate–hexane to yield the sulfide **33** (185.4 mg, 64%) as a colorless oil.

This oil was dissolved in methylene chloride (2.5 mL) and MCPBA (138 mg, 0.681 mmol based on 85% purity) in methylene chloride (1.5 mL) added at −78 °C. The reaction was stirred at −50 °C for 1.5 h before quenching with methyl sulfide (0.1 mL) and warming to 0 °C. The reaction was poured into ether (150 mL), washed with 10% aqueous potassium carbonate (2 × 20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a pale yellow oil.

Without purification, the oil was refluxed in toluene (3 mL) containing dihydropyran (146 mg, 1.65 mmol) for 0.75 h. The reaction was poured into ether (100 mL), washed with saturated sodium bicarbonate (15 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting oil was purified by chromatography (silica gel plate, 20 × 40 cm) in 40% ethyl acetate–hexane to yield the enone **34a,b** (125.5 mg, 94.6%) as a colorless oil with **34b** predominating.

34a,b: IR (CCl_4) 1940, 1728(b), 1342 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (3 H, s), 1.48 (1 H, m), 1.71 (3 H, br s), 1.68–2.18 (3 H, m), 3.48 (3 H, s), 3.77 (3 H, s), 5.03 (1 H, d, J = 4.5 Hz), 5.60 (1 H, br m, $W_{1/2}$ = 10 Hz), 6.12 (1 H, d, J = 6.0 Hz), 7.65 (1 H, d, J = 6.0 Hz); minor isomer **34** has signals at δ 1.15 (s), 3.54 (s), 3.74 (s), 4.21 (d, J = 5.0 Hz), 5.53 (br s), 6.25 (d, J = 6.0 Hz), and 7.54 (d, J = 6.0 Hz); MS (70 eV) m/e (rel intensity) 168 (18.2), 85 (36.2), 56 (12.9), 44 (100). Calcd for $C_{16}H_{20}O_5$: M_r 292.1311. Found: M_r = 292.1310.

(3*R,4*S**)-3-Hydroxy-1-methyl-4-(2-methyl-1,3-dioxocyclopent-4-en-2-yl)-4-(methoxycarbonyl)-1-cyclohexene Hemiketal (21; 22).** To the ketone **26a,b** (144 mg, 0.514 mmol) in THF (1 mL) was added by syringe 4 mL of a LDA solution (1.54 mmol, in 1:1 THF–hexane) at −78 °C. The mixture was stirred at −78 °C for 10 min and warmed to 0 °C over a period of 15 min. At this time the reaction had developed a large precipitate. At 0 °C, diphenyl disulfide in HMPA (1 mL) was added and the reaction was allowed to warm to room temperature where it was stirred for 15 min. The mixture was poured into ether (120 mL), washed with 10% aqueous sodium bisulfate (20 mL) and 10% aqueous potassium carbonate (20 mL), dried ($MgSO_4$), concentrated in vacuo, and pumped on at 0.2 mm for 5 h.

The crude residue was dissolved in THF (2 mL) and mercuric chloride (163 mg, 0.6 mmol) added. At room temperature DBU (0.36 mL, 2.4 mmol) was added dropwise, producing a precipitate. The reaction was stirred for 15 h at room temperature, then poured into ether (120 mL), washed with 10% aqueous copper sulfate (2 × 20 mL), dried ($MgSO_4$), treated with Norite, and concentrated in vacuo. The residue was purified by chromatography (silica gel plate, 20 × 20) to yield the enones **21** and **22** (97 mg, 67%) as a colorless oil. This sample was contaminated with a trace (<10%) of the starting material. A pure sample could be obtained by passing the crude keto sulfide **32** down a column (silica gel, 3 × 17 cm) with hexane to 40% ethyl acetate-hexane as eluant. When this material was treated with mercuric chloride and DBU, as above, a pure sample of enones, mp 116.5–120 °C (crystallized upon standing, not recrystallized), was obtained: IR (CCl_4) 3600 (sh), 3400 (br), 1735, 1722, 1448, 1437 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (3 H, s), 1.68 (3 H, s), 1.68–2.10 (4 H, m), 3.62 [1 H, br s (disappears upon addition of D_2O)], 3.70 (3 H, s), 4.17 (1 H, d, J = 5.0 Hz), 5.49 (1 H, m), 6.20 (1 H, d, J = 6.0 Hz), 7.18 (1 H, d, J = 6.0 Hz); minor isomer has peaks at δ 3.74 (s), 5.12 (d, J = 4.5 Hz), 6.05 (d, J = 6.0 Hz), 7.32 (d, J = 6.02 Hz). MS (70 eV) m/e (rel intensity) 219 (20.8), 169 (11.4), 168 (100), 136 (15.4), 83 (11.1), 43 (10.7), 40 (10.0). Calcd for $C_{15}H_{18}O_5$: M_r = 278.1155. Found: 278.1155.

(1S*,4S*,7R*,8R*,12S*,13S*)-7-Hydroxy-12-methyl-9-methylene-13-(trimethylsiloxy)-3-oxatetracyclo[5.4.1.1^{1,8}.0^{4,12}]tridecan-2-one (37). To the ketone **18** (1.35 g, 3.83 mmol) in anhydrous methanol (15 mL) was added sodium borohydride (0.29 g, 7.67 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature before pouring into ether (2 × 150 mL) and washing with water (60 mL) and 10% aqueous potassium carbonate (50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to yield a colorless oil that foamed under high vacuum. In a separate flask containing methylene chloride (20 mL) and chromium trioxide (1.15 g, 11.49 mmol) was added pyridine (1.81 g, 22.98 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature before adding the oil obtained above in methylene chloride (10 mL). After being stirred for 35 min at room temperature the mixture was poured into a separatory funnel containing methylene chloride (150 mL). The chromium residue in the flask was extracted with 10% aqueous potassium carbonate and methylene chloride, and both extracts were added to the separatory funnel. The organic layer was washed with 10% aqueous potassium carbonate (2 × 50 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting orange residue was passed down a silica gel column (2.5 × 15 cm) with ether to yield a yellow oil (1.41 g, 114%) that crystallized from CCl_4–hexane to give the lactone **37** (1.01 g, 81.9%). The mother liquors were purified by chromatography (silica gel plate, 20 × 20 cm) in 50% ethyl acetate–hexane to yield more lactone (0.145 g, total yield was 92.4%): mp 95.5–97 °C; IR ($CHCl_3$) 3540, 2950, 1780, 1452 cm^{-1}; NMR (270 MHz) δ 0.1 (9 H, s), 1.17 (3 H, s), 1.45–1.82 (2 H, m), 2.05 (1 H, br s), 2.15–2.60 (6 H, m), 2.75 (1 H, d, J = 4.5 Hz), 4.34 (1 H, d, J = 4.5 Hz), 4.47 (1 H, dd, J = 9.5, 8 Hz), 4.86 (1 H, br s), 5.08 (1 H, br s); MS (36 eV) m/e (rel intensity) 332 (2.0), 232 (21.4), 1.56 (39.8), 146 (12.1), 125 (16.3), 105 (10.3), 97 (34.0), 91 (24.1), 75 (42.9), 73 (100), 55 (32.8), 43 (49.6), 41 (39.6). Anal. Calcd for $C_{17}H_{26}O_4Si$: C, 63.31; H, 8.31; M_r 322.1601. Found: C, 63.27; H, 8.06; M_r 322.1591.

(1R*,2'R*,4R*,8R*)-8-Methyl-3-oxabicyclo[3.3.0]octa-2,7-dione-1-spiro-1'-(4'-methyl-2'-(trimethylsiloxy)-3'-cyclohexene) (38). The ene lactone **37** (760 mg, 2.36 mmol) was divided into three 25-mL flasks. Each portion was distilled (1.2–1.5 mm) through a hot tube (16 cm, 470 °C), producing a slightly yellow oil. The oil was purified by chromatography [silica gel plates, (3–20) × 40 cm] in 50% ethyl acetate–hexane, yielding the product **38** (566 mg, 74.5%) as a white solid and at a slightly lower R_f slightly impure starting material (159 mg). The recovered starting material was again subjected to vacuum pyrolysis and purified as above [one 20 × 40 cm plate] to yield 108 mg of additional product for a total yield of 88.7%: mp (CCl_4–hexane) 125–126.5 °C; IR (CCl_4) 2925, 1783, 1744, 906, 868 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 0.09 (9 H, s), 1.06 (3 H, s), 1.71 (3 H, s), 1.71–2.01 (4 H, m), 2.2–2.42 (3 H, m), 2.72 (1 H, ddd, J = 16.8, 14.1, 9.0 Hz), 4.62 (1 H, br s), 4.66 (1 H, d, J ≈ 4.2 Hz), 5.31 (1 H, br s); ^{13}C NMR (15.04 MHz, $CDCl_3$) δ 0.66, 15.6, 23.0, 25.6, 26.7, 27.1, 36.4, 53.7, 54.1, 67.7, 83.9, 122.2, 135.6, 173.9, 216.3; MS (26 eV) m/e (rel intensity) 307 (14.6), 227 (22.8), 226 (100), 211 (74.8), 156 (89.1), 141 (85.7), 136 (57.8), 75 (25.4), 73 (31.6). Anal. Calcd for $C_{17}H_{26}O_4Si$: C, 63.3; H, 8.13; M_r 322.1600. Found: C, 63.44; H, 8.04; M_r 322.1585.

(1R*,2'R*,4R*,8R*)-8-Methyl-3-oxabicyclo[3.2.0]octa-2,7-dione-1-spiro-1'-(2'-hydroxy-4'-methyl-3'-cyclohexene) (38-Alcohol). To the silyl ether **38** (92 mg, 0.286 mmol) in THF (2 mL) was added tetrabutylammonium fluoride (0.57 mL of a 1 M solution in THF, 0.571 mmol). The mixture was stirred at room temperature for 1 h, poured into 20% ethyl acetate–ether (80 mL), washed with 10% aqueous potassium carbonate, dried ($MgSO_4$), and concentrated in vacuo to yield white crystals. The material was purified by chromatography [silica gel plate, one 20 × 20 cm] in 50% ethyl acetate–hexane to yield the alcohol corresponding to **38** as white crystals: mp 160.5–162 °C (CCl_4); IR ($CHCl_3$) 3565 (sh), 2930, 1762, 1743, 1660, 1460, 1445, 1385 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (3 H, s), 1.73 (3 H, br s), 1.77–2.5 (8 H, m), 2.71 (1 H, ddd, J = 17, 14, 8.8 Hz), 4.56 [1 H, br d, J = 7.7 Hz (upon addition of D_2O this signal collapses to a broad singlet)], 4.78 (1 H, d, J = 3.7 Hz), 5.34 (1 H, br s); ^{13}C NMR (15 MHz, $CDCl_3$) δ 217.2, 175.0, 137.0, 122.2, 84.6, 65.2, 54.4, 54.1, 35.9, 27.1, 26.5, 25.3, 22.8, 14.7; MS (70 eV) m/e (rel intensity) 250 (0.3), 232 (2.2), 154 (73.4), 136 (53.2), 97 (67.3), 96 (13.6), 84 (100), 83 (11.1), 82 (24.9), 55 (14.1), 44 (25.4), 43 (23.4), 41 (24.9). Calcd for $C_{14}H_{18}O_4$: M_r 250.1205. Found: M_r 250.1199.

(1R*,2'S*,4R*,8R*)-8-Methyl-3-oxabicyclo[3.3.0]octa-2,7-dione-1-spiro-1'-(hydroxy-4'-methyl-3'-cyclohexene) Hemiketal (40). The alcohol derived from **38** (190 mg, 0.76 mmol) was dissolved in methylene chloride

(5 mL) and at −25 °C trifluoroacetic acid (0.25 mL, 3.24 mmol) was added. The green-yellow mixture was kept at −24 °C for 20 h and then warmed to room temperature for 40 min. Workup consisted of pouring into ether (100 mL), washing with 10% aqueous potassium carbonate (2 × 20 mL), drying ($MgSO_4$), and concentrating in vacuo to yield a yellow oil. The oil was purified by chromatography [silica gel plate, one 20 × 40] in 40% ethyl acetate–hexane to yield, in addition to some diene at higher R_f, **40** (145 mg, 76.3%): mp 92–94.5 °C (CCl_4–hexane); IR ($CHCl_3$) 3520, 2920, 1762, 1675, 1460, 1375 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24 (3 H, s), 1.76 (3 H, s), 1.77–1.95 (3 H, m), 2.10–2.29 (5 H, m), 2.71 [1 H, br s (OH signal)], 4.44 (1 H, ddd, J = 7.0, 4.1, 1.0 Hz), 4.72 (1 H, br s), 5.62 (1 H, br s); ^{13}C NMR (15.04 MHz, $CDCl_3$) δ 181.2, 137.7, 123.0, 116.9, 88.7, 81.2, 59.9, 54.5, 35.0, 29.2, 26.4, 24.1, 23.4, 16.0; MS (70 eV) m/e (rel intensity) 250 (0.9), 235 (3.8), 154 (100), 136 (41.1), 121 (29.8), 119 (11.7), 97 (42.1), 91 (11.7), 55 (10.0), 44 (16.2), 43 (11.2), 41 (14.5). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.2; M_r 250.1205. Found: C, 67.11; H, 7.12; M_r 250.1206.

(1*R,3*S**,8*S**,11*S**,14*S**)-5,14-Dimethyl-2,10-dioxa-9,13-dioxotetracyclo[6.4.2.0^{3,8}.0^{11,14}]tetradecan-4-ene (43).** To the ketone **38** (202 mg, 0.627 mmol) in dry THF (0.5 mL) at −20 °C was added freshly prepared lithium tetramethylpiperidide (1.32 mL of a 0.7 M solution in 1:1 THF–hexane, 0.92 mmol). Immediately an orange color was observed and stirring was continued for 30 min at −20 °C, 30 min at −10 °C, and 10 min at 0 °C over which time a precipitate was formed. At 0 °C chlorotrimethylsilane (0.166 mL, 1.31 mmol) was added all at once and stirring continued at room temperature for 15 min. Upon recooling of the mixture to −78 °C methylene chloride (2 mL), pyridine (0.094 mL, 1.19 mmol) and a bromine–dioxane complex (0.658 mL of a 1 M solution in methylene chloride, 0.658 mmol) were added sequentially. After 8 min at −78 °C the reaction mixture was poured quickly into ether (100 mL) and washed with 10% aqueous sodium thiosulfate and saturated aqueous sodium bicarbonate (1 to 1 mixture, 10 mL), 10% aqueous $NaHSO_4$ (1 × 15 mL), and saturated sodium bicarbonate (1 × 10 mL). After the mixture was dried (Na_2SO_4) and concentrated in vacuo an orange oil was obtained, which was shown by ^1H NMR spectroscopy to be approximately 90% the brominated ketone **41**. The oil was immediately taken up in dry THF (5 mL), tetrabutylammonium fluoride (1.57 mL of a 1 M solution in THF, 1.57 mmol) added, and the mixture stirred for 1.5 h. Workup consisted of pouring into ether (120 mL), washing with saturated aqueous sodium bicarbonate (2 × 20 mL), drying (Na_2SO_4), treating with activated charcoal, and concentrating in vacuo. The resulting oil was recrystallized from ether to yield the product **43** (62 mg) as fine needles. The mother liquors were purified by chromatography (silica gel column, 2.5 × 15 cm) with hexane to 40% ethyl acetate–hexane to yield more product (34.6 mg, total yield was 62.1%) as a white powder: mp >156 °C dec (CCl_4–hexane); IR ($CHCl_3$) 2980, 2920, 1775–1760 (br), 1460, 1442 cm^{-1}; IR (CCl_4) 1786, 1770 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24 (3 H, s), 1.63 (1 H, ddd, J = 14, 10.5, 8 Hz), 1.73 (3 H, br s), 1.89–2.06 (2 H, m), 1.99 (1 H, ddd, J = 15.8, 7.3, 3.0 Hz), 2.34 (1 H, d, J = 15.8 Hz), 2.70 (1 H, dt, J = 17.2, 8.5 Hz), 4.20–4.24 (2 H, m), 4.58 (1 H, dd, J = 7.2, 1.3 Hz), 5.28 (1 H, pentet, J = 1.5 Hz), 4.58 (1 H, d, J = 1.3 Hz); ^{13}C NMR (15.04 MHz, $CDCl_3$) δ 210.0, 174.5, 138.1, 117.6, 81.0, 79.0, 77.5, 57.0, 53.6, 35.6, 27.3, 24.2, 22.1, 11.0. MS (70 eV) m/e (rel intensity) 248 (17.6), 155 (10.3), 154 (100), 137 (27.0), 136 (46.3), 96 (35.5), 95 (25.9), 82 (38.1), 55 (39.1), 41 (20.8). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.70; H, 6.50; M_r 248.1034. Found: C, 67.67; H, 6.45; M_r 248.1019.

Enol Silyl Ether: IR (CCl_4) 2960, 1780, 1632 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (3 H, s), 0.19 (3 H, s), 1.6–2.3 (4 H, m), 2.38 (1 H, ddd, J = 15.9, 5.6, 1.9 Hz), 2.69 (1 H, ddd, J = 15.9, 8.9, 2.8 Hz), 4.22 (1 H, br d, J = 4.2 Hz), 4.4 (1 H, br d, J = 8.9, 5.6 Hz), 4.43 (1 H, br s), 5.31 (1 H, br s).

41: ^1H NMR (270 MHz, $CDCl_3$) δ 0.11 (9 H, s), 1.18 (3 H, s), 1.72 (3 H, br s), 1.71–1.96 (3 H, m), 2.21 (1 H, ddd, J = 14.2, 13.1, 4.1 Hz), 2.33 (1 H, br m), 2.96 (1 H, dd, J = 14.2, 8.1 Hz), 4.58 (1 H, br s), 4.60 (1 H, d, J = 4.2 Hz), 4.79 (1 H, dd, J = 13.1, 8.2 Hz), 5.33 (1 H, br s).

(1*R,3*S**,8*S**,14*S**)-5,14-Dimethyl-2,10-dioxa-13-methylene-9-oxatetracyclo[6.4.2.0^{3,8}.0^{11,14}]tetradecan-4-ene (44).** Triphenylphosphonium methylide (3 mL of a 0.33 M solution) was prepared by adding n-butyllithium (0.66 mL of a 1.5 M solution in hexane, 1.0 mmol) to methyltriphenylphosphonium bromide (357 mg, 1.0 mmol) in THF (2 mL) at −78 °C. The solution was warmed to 0 °C to yield an orangish yellow mixture. To the ketone **43** (95 mg, 0.383 mmol) in THF (2 mL) at 52–55 °C was added by syringe the preformed ylide (1.39 mL of a 0.33 M solution, 0.460 mmol). The ylide color disappeared immediately and a white solid appeared. The mixture was kept at 52 °C for 10 min, cooled to room temperature, and poured into ether (100 mL). The organic layer was washed with 10% aqueous potassium carbonate (2 × 15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an oil. The oil was purified by chromatography (silica gel column, 2.5 × 10 cm) with hexane and 40% ethyl acetate–hexane to yield a colorless oil that slowly solidified (84.5 mg, 89.5% mass recovery). The 270-MHz ^1H NMR analysis showed the product to be a 4-to-1 mixture of olefin **44** to starting ketone **43**.

To obtain a purer sample of olefin a 3:1 mixture of olefin **44** to ketone **43** (25 mg, 0.101 mmol) was dissolved in THF (0.5 mL) and potassium triethylborohydride (0.203 mL of a 1 M solution in THF, 0.203 mmol) added at room temperature. The mixture was stored for 2 h and then cooled to 0 °C when methylene chloride (1 mL) was added and the reaction quenched with 10% aqueous sodium bisulfate. The whole mixture was poured into ether (80 mL), washed with 10% aqueous sodium bisulfate (15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield an oil. The oil was purified by chromatography (silica gel column, 2.5 × 10 cm) with hexane to 50% ethyl acetate–hexane to yield a lactol (15.1 mg). The lactol was reoxidized with Collin's reagent (0.245 mmol) in methylene chloride (0.4 mL) at room temperature for 2 h. The mixture was poured into chloroform (60 mL), washed with 10% aqueous sulfuric acid, dried ($MgSO_4$), and concentrated in vacuo to yield a yellow oil. The oil was purified by chromatography (silica gel column, 2.5 × 10 cm) with 30% ethyl acetate–hexane to yield the olefin **44** (8.6 mg) as a white solid, which still shows a small impurity in the NMR that is not ketone **43** or lactone **44**. Spectral analysis performed on this sample suggests it is the lactol corresponding to **44**.

44: IR (CCl_4) 2980, 1773, 1379 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.25 (3 H, s), 1.58–1.75 (1 H, m), 1.70 (3 H, br s), 1.80–2.07 (3 H, m), 1.88 (1 H, ddd, J = 15.0, 7.5, 3.5 Hz), 2.10 (1 H, d, J = 15.0 Hz), 4.17 (1 H, br s), 5.23 (1 H, br s); MS (70 eV) m/e (rel intensity) 246 (0.6), 154 (19.4), 93 (38.4), 92 (29.3), 91 (17.7), 71 (20.8), 69 (37.5), 57 (40.5), 55 (18.8), 43 (64.9), 41 (58.6). Calcd for $C_{15}H_{18}O_3$: M_r 246.1256. Found: M_r 246.1256.

4α,15-Dihydroxy-11-epitrichothecane-9,12-diene (45). To the lactone **44** (56 mg, 0.227 mmol) contaminated with ketone **43** (14 mg) was added diisobutylaluminum hydride (1.61 mL of a 0.88 M solution in hexane, 1.42 mmol). The solution was concentrated to 0.7 mL by blowing dry N_2 gas over the reaction and then was stirred continuously for 35 h at room temperature. The reaction was then diluted with ether (2 mL), quenched at 0 °C with saturated aqueous sodium sulfate, and poured into a 10% ethyl acetate–ether mixture (3 × 50 mL). The organic layer was washed with saturated aqueous sodium sulfate (3 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a colorless oil. The oil was purified by chromatography (silica gel plate, 20 × 20 cm) in 70% ethyl acetate–hexane, yielding the diol **45** (44 mg, 78%) as a coloress oil: IR ($CDCl_3$) 3370, 2980, 1675, 1450, 1380 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$ with D_2O) δ 1.24 (3 H, s), 1.30–1.41 (1 H, m), 1.64 (3 H, s), 1.82–2.10 (4 H, m), 2.45 (1 H, ddd, J = 15.5, 10.0, 5.0 Hz), 3.76 (1 H, d, J = 12.1 Hz), 3.78 (1 H, dd, J = 10.0, 7.5 Hz), 4.00 (1 H, d, J = 12.1 Hz), 4.20 (1 H, br s), 4.47 (1 H, d, J = 5.2 Hz), 4.86 (1 H, s), 5.00 (1 H, s), 5.35 (1 H, br s); ^1H NMR (270 MHz, benzene-d_6) δ 1.19 (3 H, s), 1.22–2.01 (4 H, m), 1.45 (3 H, s), 1.99 (1 H, dd, J = 15.5, 7.5 Hz), 2.18 (1 H, ddd, J = 15.5, 10.0, 7.5 Hz), 3.48 (1 H, dd, J = 10.0, 7.5 Hz), 3.72 (2 H, br s), 3.95 [1 H, d (AB), J = 12.1 Hz], 4.22 [1 H, d (AB), J = 12.1 Hz), 4.30 (1 H, br s), 4.38 (1 H, d, J = 5.0 Hz), 4.60 (1 H, s), 4.70 (1 H, s), 5.62 (1 H, br s); MS (70 eV) m/e (rel intensity) 250 (0.1), 232 (4.3), 175 (28.6), 165 (22.4), 159 (16.3), 147 (19.5), 123 (36.0), 119 (29.3), 110 (38.8), 109 (66.7), 105 (33.5), 95 (100), 94 (78.0), 93 (59.4), 91 (45.0), 79 (35.6), 55 (44.6), 43 (67.1). Calcd for $C_{15}H_{22}O_3$: M_r 250.1569. Found: M_r 250.1569.

15-Hydroxy-4-oxo-11-epitrichothecane-9,12-diene Hemiketal (46). To the diol **45** (19 mg, 0.076 mmol) in methylene chloride (1.1 mL) was added PCC (86 mg, 0.4 mmol). The reaction was stirred for 20 min, poured into methylene chloride (30 mL), washed with 10% aqueous potassium carbonate (10 mL), dried ($MgSO_4$), treated with norite, and concentrated in vacuo to yield a yellow solid. The solid was purified by chromatography (silica gel plate, 15 × 20 cm) in 50% ethyl acetate–hexane to yield the hemiketal **46** (14.7 mg, 78%) as a white solid: mp 148–152 °C (not recrystallized); IR ($CHCl_3$) 3580 (sh), 2955, 1675, 1258 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.01 (3 H, s), 1.50–2.08 (8 H, m with a singlet at δ 1.56), 2.18 (1 H, d, J = 14.7 Hz), 2.47 (1 H, s, upon addition of D_2O this signal disappears), 3.73 [1 H, d (AB), J = 9.2 Hz], 3.85 [1 H, d (AB), J = 9.2 Hz], 3.95 (1 H, br s), 4.50 (1 H, d, J = 4.0 Hz), 4.91 (1 H, s), 5.13 (1 H, s), 5.28 (1 H, br s); MS (70 eV) m/e (rel intensity) 248 (39.9), 233 (42.1), 189 (65.7), 161 (46.1), 159 (51.0), 147 (41.3), 119 (58.7), 110 (53.3), 109 (100), 107 (52.7), 105 (95.5). Calcd for $C_{15}H_{20}O_3$: M_r 249.1413. Found: M_r 248.1413.

(1*R,3*R**,8*S**,11*S**,14*S**)-5,14-Dimethyl-2,10-dioxa-9,13-dioxotetracyclo[6.4.2.0^{3,8}.0^{11,14}]tetradecan-4-ene (42 = 52).** To the ketone **38** (326 mg, 1.01 mmol) in THF (0.6 mL) at −20 °C was added freshly prepared lithium tetramethylpiperidide (2.03 mL of a 0.7 M solution on 1:1 THF–hexane, 0.92 mmol). The reaction was stirred at −20 °C for

30 min, at −10 °C for 30 min, and at 0 °C for 10 min. At 0 °C chlorotrimethylsilane (0.23 mL, 1.42 mmol) was added and stirring was continued at room temperature for 15 min. Upon recooling of the mixture to −78 °C pyridine (0.134 mL, 1.70 mmol) and bromine–dioxane complex (262 mg, 1.06 mmol) as a solution in methylene chloride (1 mL) were added. After 10 min at −78 °C the mixture was poured quickly into ether (100 mL), washed with 10% aqueous sodium thiosulfate and saturated sodium bisulfate (15 mL), dried ($MgSO_4$), treated with norite, and concentrated in vacuo to yield the bromo ketone **41** as a yellow oil. This oil was dissolved in 1,2-dichloroethane (10 mL) and trifluoroacetic acid (1 mL) and water (0.05 mL) were added. The mixture was stirred at 32 °C for 14 h, 45 °C for 1 h, and 55 °C for 15 min. Workup consisted of pouring into ether (150 mL), washing with 10% aqueous potassium carbonate (2 × 25 mL), drying ($MgSO_4$), and concentrating in vacuo. The crude material was then dissolved in THF (5 mL) and tetrabutylammonium fluoride (3.03 mL of a 1 M solution in THF, 3.03 mmol) added. After being stirred for 1.75 h the mixture was poured into ether (150 mL), washed with 10% aqueous potassium carbonate (20 mL), dried ($MgSO_4$), and concentrated to yield a white solid. The solid was immediately chromatographed (silica gel column 2.5 × 20 cm) with hexane to 50% ethyl acetate–hexane, yielding the cyclized ketone **52** (176 mg, 70.3%) as a white solid: mp (ether) 148.5–150.5 °C; IR (CCl_4) 2980, 2948, 2920, 1780, 1762, 1452, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.36 (3 H, s), 1.67 (3 H, s), 1.85–2.18 (5 H, m), 2.31 (1 H, d, J = 15.4 Hz), 4.08 (1 H, br s), 4.42 (1 H, br s), 4.51 (1 H, ddd, J = 7.1, 1.2 Hz), 5.35 (1 H, br s); MS (70 eV) m/e (rel intensity) 248 (5.5), 154 (100.0), 136 (24.7), 121 (27.9), 111 (24.4), 105 (25.0), 96 (25.5), 95 (30.1), 91 (28.6), 83 (25.3), 82 (30.6), 73 (23.2), 69 (23.8), 60 (38.0), 57 (30.9), 55 (78.5), 44 (33.6), 43 (53.5), 41 (34.1). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50; M_r 248.1048. Found: C, 67.35; H, 6.23; M_r 248.1048.

(1*R,3*R**,8*S**,11*S**,14*S**)-5,14-Dimethyl-2,10-dioxa-13-methylene-9-oxotetracyclo[6.4.2.0^{3,8}.0^{11,14}]tetradecan-4-ene (53).** Triphenylphosphonium methylide (8.3 mL of a 0.33 M solution) was prepared by adding *n*-butyllithium (1.78 mL of a 1.4 M solution in hexane, 2.50 mmol) to methyltriphenylphosphonium bromide (893 mg, 2.50 mmol) in THF (5.62 mL) at −78 °C. The solution was warmed to 0 °C and stirred for 20 min. To the ketone **52** (361 mg, 1.45 mmol) in THF (7 mL) at 60 °C was added the preformed ylide (5.73 mL, 1.89 mmol). The ylide color disappeared immediately and the mixture was stirred at 60–62 °C for 6 min. Upon cooling of the mixture to room temperature the reaction was poured into ether (150 mL), washed with 10% aqueous potassium carbonate, dried ($MgSO_4$), and concentrated. The residue was chromatographed (silica gel, 3.5 × 25 cm column) with hexane, 25% ether–hexane, and then ether to yield **53** (339 mg, 95%) as a white solid: mp (ether–hexane) 145.5–144 °C; IR (CCl_4) 2970, 1775, 1686, 1450, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.40 (3 H, s), 1.56 (3 H, br s), 1.82 (1 H, dd, J = 14.8, 8.0, 3.0 Hz), 1.89–2.20 (4 H, m), 2.12 (1 H, d, J = 14.9 Hz), 4.29 (1 H, br s), 4.42 (1 H, d, J = 8.0 Hz), 4.51 (1 H, d, J = 3.0 Hz), 4.86 (1 H, s), 5.01 (1 H, s), 5.27 (1 H, br s); MS (70 eV) m/e (rel intensity) 246 (4.2), 202 (10.0), 154 (77.0), 105 (17.1), 94 (34.9), 93 (99.3), 92 (100), 91 (74.9), 82 (33.9), 79 (34.6), 77 (51.4), 55 (23.5), 53 (27.9), 43 (13.6), 41 (58.0). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; M_r 246.1256. Found: C, 73.07; H, 7.47; M_r 246.1255.

4α,15-Dihydroxytrichothecane-9,12-diene (54a). To the lactone **53** (314 mg, 1.27 mmol) at room temperature was added diisobutylaluminum hydride (5.81 mL of a 1.5 M solution in toluene, 10.21 mmol). The reaction was stirred for 6.5 h at room temperature and cooled to 0 °C, and ether (6 mL) was added. Saturated aqueous sodium sulfate was added dropwise until all bubbling ceased. The mixture was then poured into 10% ethyl acetate–ether (2 × 100 mL), washed with 10% aqueous sodium bisulfate (2 × 30 mL) and 10% aqueous potassium carbonate (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (silica gel, 2.5 × 22 cm) with 30% ethyl acetate–hexane to pure ethyl acetate to yield **54a** (301 mg, 95%) as a colorless oil: IR ($CHCl_3$) 3300 (br), 1680, 1448 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 1.14 (3 H, s), 1.67 (3 H, s), 1.72–2.15 (5 H, m), 2.31 (1 H, ddd, J = 15.6, 10.9, 5.8 Hz), 3.49 [1 H, d (AB), J = 11.2 Hz], 3.54 [1 H, d (AB), J = 11.2 Hz], 3.80 (1 H, dd, J = 10.8, 5.9 Hz), 4.31 (1 H, d, J = 5.7 Hz), 4.59 (1 H, d, J = 5.3 Hz), 4.67 (1 H, s), 5.01 (1 H, s), 5.51 (1 H, br m), 5.61–5.75 (2 H, br s); MS (70 eV) m/e (rel intensity) 219 (14.4), 204 (11.9), 175 (53.6), 161 (16.5), 147 (18.6), 123 (45.4), 121 (17.6), 119 (24.0), 110 (38.7), 109 (59.8), 105 (38.8), 95 (100.0), 94 (69.8), 93 (65.9), 91 (53.3), 85 (29.4), 83 (57.8), 81 (35.3), 79 (40.1), 77 (40.8), 55 (48.8), 53 (31.8), 43 (58.2), 41 (69.9). Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1569.

15-(*tert*-Butyldimethylsiloxy)-4α-hydroxytrichothecane-9,12-diene (54b). To the diol **54a** (180 mg, 0.72 mmol) in methylene chloride (3 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (162 mg, 1.08 mmol) and DMAP[18] (174 mg, 1.44 mmol). The reaction was stirred for 4.5 h at 0 °C. Workup consisted of pouring into 50% ether–hexane (150 mL), washing with cold 10% aqueous sodium bisulfate (2 × 30 mL) and saturated aqueous sodium bicarbonate (1 × 20 mL), drying ($MgSO_4$), and concentrating in vacuo. The residue, which solidified slowly, was chromatographed [silica gel plates, one 20 × 20, and one 20 × 40 cm] in 40% ethyl acetate–hexane to yield **54b** (215 mg, 85%) as a white solid, mp (hexane) 123–125 °C. In a band at slightly higher R_f some mono secondary silylated material (14.5 mg, 5.5%) could be recovered: IR (CCl_4) 3370 (br), 2960, 2858, 1680, 1472 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 0.02 (3 H, s), 0.04 (3 H, s), 0.88 (9 H, s), 1.15 (3 H, s), 1.65 (3 H, s), 1.82–2.1 (5 H, m), 2.28 (1 H, ddd, J = 15.8, 10.6, 5.8 Hz), 3.54 [1 H, d (AB), J = 11.0 Hz], 3.62 [1 H, d (AB), J = 11.0 Hz), 3.64 [1 H, td, J = 10.3, 6.0 Hz (upon addition of D_2O this collapses to dd, J = 10.4, 5.8 Hz)], 4.24 (1 H, d, J = 5.9 Hz), 4.47 (1 H, d, J = 5.8 Hz), 4.60 (1 H, s), 4.94 (1 H, s), 5.46 (1 H, br d, J = 5.6 Hz), 5.90 [1 H, d, J = 10.2 (upon addition of D_2O this signal disappears)]; MS (70 eV) m/e (rel intensity) 307 (4.6), 289 (7.3), 263 (16.2), 232 (14.3), 197 (17.1), 175 (14.0), 171 (16.6), 147 (17.9), 123 (37.7), 119 (17.8), 110 (30.8), 109 (30.2), 107 (21.0), 105 (59.1), 93 (85.1), 89 (42.8), 75 (95.0), 73 (100.0). Anal. Calcd for $C_{21}H_{36}O_3Si$: C, 69.18; H, 9.95; M_r 364.2434. Found: C, 69.43; H, 10.04; M_r 364.2433.

Mono secondary silyl: Partial ^1H NMR (270 MHz, $CDCl_3$) δ 0.13 (3 H, s), 0.14 (3 H, s), 0.91 (9 H, s), 1.12 (3 H, s), 1.67 (3 H, br s), 2.24 (1 H, ddd, J = 15.7, 10.7, 5.8 Hz), 3.55 (2 H, m), 3.79 (1 H, dd, J = 10.6, 6.0 Hz), 4.30 (1 H, d, J = 5.8 Hz), 4.58 (1 H, d, J = 5.4 Hz), 4.67 (1 H, s), 4.78 [1 H, br d, J = 7.5 Hz (upon addition of D_2O this signal disappears)], 5.00 (1 H, s), 5.52 (1 H, d, J = 5.4 Hz).

15-(*tert*-Butyldimethylsiloxy)-4α-tosyloxytrichothecane-9,12-diene (54c). To the alcohol **54b** (120 mg, 0.33 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (503 mg, 2.63 mmol). The mixture was stirred for 60 h at 34 °C and then cooled to 0 °C and water (0.4 mL) added. After being stirred for 20 min at 0 °C the mixture was poured into 20% ether–hexane (150 mL), washed with 10% aqueous sodium bisulfate (2 × 30 mL) and saturated sodium bicarbonate (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed (silica gel plate, 20 × 40 cm) in 66% toluene–ether to yield the tosylate **54c** (116.5 mg, 79.4% based on recovered starting material) as a white solid, mp (hexane) 120–121 °C. At a lower R_f was recovered the starting alcohol **54b** (17.1 mg, 14%) and some cyclic ether (10.9 mg, 14%).

54c: IR (CCl_4) 2960, 2860, 1690, 1450, 1380, 1192, 1180, 1102, 1060, 943, 861 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.03 (3 H, s), 0.02 (3 H, s), 0.85 (9 H, s), 1.09 (3 H, s), 1.65 (3 H, br s), 1.65–2.01 (4 H, m), 1.97 (1 H, dd, J = 15.8, 5.1 Hz), 2.14 (1 H, ddd, J = 15.8, 10.8, 5.3 Hz), 2.43 (3 H, s), 3.25 (1 H, d, J = 10.7 Hz), 3.89 (1 H, d, J = 5.5 Hz), 4.20 (1 H, d, J = 5.3 Hz), 4.23 (1 H, d, J = 10.7 Hz), 4.39 (1 H, dd, J = 10.8, 5.2 Hz), 4.63 (1 H, s), 4.98 (1 H, s), 5.31 (1 H, s, J = 5.5 Hz), 7.32 (2 H, d, J = 9.0 Hz), 7.78 (2 H, d, J = 9.0 Hz); MS (70 eV) m/e (rel intensity) 229 (14.9), 197 (25.2), 105 (31.2), 93 (100), 92 (15.9), 91 (30.5), 81 (15.4), 75 (20.9), 73 (30.3), 57 (16.1), 56 (13.9), 43 (15.1), 41 (21.3). Anal. Calcd for $C_{28}H_{42}O_5SSi$: C, 64.82; H, 8.16; Si, 5.41. Found: C, 64.68; H, 8.21; Si, 5.72.

Cyclic Ether: IR (CCl_4) 2980, 2930, 2870, 1445, 1431 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (3 H, s), 1.50–2.02 (5 H, m), 1.65 (3 H, br s), 1.89 (1 H, ddd, J = 15.8, 8.8, 4.5 Hz), 3.67 [1 H, d (AB), J = 8.1 Hz], 3.71 [1 H, d (AB), J = 8.1 Hz], 4.16 (1 H, d, J = 8.8 Hz), 4.19 (1 H, br s), 4.34 (1 H, d, J = 4.5 Hz), 4.72 (1 H, s), 4.99 (1 H, s), 5.33 (1 H, br s); MS (70 eV) m/e (rel intensity) 232 (1.2), 202 (4.4), 175 (1.6), 149 (2.8), 93 (8.7), 91 (8.9), 45 (19.2). Calcd for $C_{15}H_{20}O_2$: M_r 232.1463. Found: M_r 232.1463.

15-(*tert*-Butyldimethylsiloxy)-4α-hydroxytrichothecane-9,12-diene (55b) and 15-(*tert*-Butyldimethylsiloxy)trichothecane-3,9,12-triene (56). The tosylate **54c** (29.4 mg, 0.057 mmol) and cesium propionate (233 mg, 1.13 mmol) in 1,3-dimethyl-2-imidazolidinone (0.57 mL) was heated at 149–151 °C for 7 h. Upon being cooled to room temperature, the mixture was poured into ether (60 mL), washed with 10% aqueous potassium carbonate, dried ($MgSO_4$), and concentrated in vacuo. The residue (no effort was made to remove all the imidazolidinone solvent) was put in DMF, *tert*-butyldimethylsilyl chloride (90 mg, 0.60 mmol) and imidazole (82 mg, 1.2 mmol) were added, and the mixture was stirred at 42 °C for 12.5 h. The reaction was poured into hexane (70 mL), washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated to yield an oil. The oil was purified by flash chromatography (silica gel, 1.3 × 16 cm) with hexane to 40% ethyl acetate–hexane to yield first a mixture of silylated ester **55a** and silylated olefin **56** and then a cyclic ether (3.0 mg, 22%).

The mixture of ester **55a** and olefin **56** was dissolved in 15% aqueous methanol (4.2 mL) with potassium carbonate (80 mg) and stirred for 20 h at room temperature. The mixture was then poured into ether (60 mL), washed with 10% potassium carbonate (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 0.8 × 18 cm) with hexane to 40% ethyl acetate–

hexane to yield first the silyl olefin **56** (7.5 mg, 39%) and then the silyl alcohol **55b** (6.4 mg, 31%).

55b: IR (CCl_4) 3620 (sh), 3460 (br), 2940, 2845, 1680, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.03 (6 H, s), 0.91 (9 H, s), 1.12 (3 H, s), 1.55–2.0 (5 H, m), 1.62 (1 H, ddd, J = 15.2, 5.2, 2.8 Hz), 1.68 (3 H, br s), 2.56 (1 H, dd, J = 15.2, 7.1 Hz), 3.50 [1 H, d (AB), J = 10.9 Hz), 3.65 [1 H, d (AB), J = 10.9 Hz], 3.76 (1 H, d, J = 5.5 Hz), 4.41 (1 H, d, J = 5.2 Hz), 4.71 (1 H, s), 4.81 (1 H, dd, J = 7.1, 2.7 Hz), 5.14 (1 H, s), 5.41 (1 H, d, J = 5.5 Hz); MS (70 eV) m/e (rel intensity) 307 (7.6), 197 (13.8), 195 (13.5), 175 (14.8), 128 (29.5), 123 (28.3), 105 (66.8), 89 (48.7), 75 (99.7), 73 (100), 43 (34.1), 41 (35.6). Calcd for $C_{21}H_{36}O_3Si$: M_r 364.2434. Found: M_r 364.2433.

56: IR (CCl_4) 2960, 2923, 2855, 1687, 1470 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.01 (3 H, s), 0.0 (3 H, s), 0.87 (9 H, s), 1.18 (3 H, s), 1.66 (3 H, br s), 1.55–2.02 (4 H, m), 3.31 [1 H, d (AB), J = 10.2], 3.45 [1 H, d (AB), J = 10.2 Hz), 3.86 (1 H, d, J = 4.2 Hz), 4.38 (1 H, s), 4.55 (1 H, d, J = 2.6 Hz), 4.77 (1 H, s), 5.35 (1 H, d, J = 4.0 Hz), 6.00 (1 H, dd, J = 5.9, 2.6 Hz), 6.38 (1 H, d, J = 5.9 Hz); MS (70 eV) m/e (rel intensity) 346 (0.4), 289 (3.6), 254 (12.7), 197 (27.4), 105 (11.4), 93 (13.3), 92 (100), 91 (20.4), 75 (45.2), 73 (37.6). Calcd for $C_{21}H_{34}O_2Si$: M_r 346.2327. Found: M_r 346.2327.

15-(*tert*-Butyldimethylsiloxy)-12,13-epoxytrichothecane-9-ene (57). (1) Method A: MCPBA Oxidation. The olefin **55b** (4.9 mg, 0.0134 mmol), MCPBA (3.2 mg, 0.0161 mmol, based on 85% purity), and disodium hydrogen phosphate (18 mg) in methylene chloride (1.8 mL) was stirred at −25 °C for 61 h. The reaction was poured into ether (40 mL), washed with 10% aqueous sodium thiosulfate and potassium carbonate (1:1 mixture, 10 mL), dried ($MgSO_4$), and concentrated in vacuo. The 270 ^1H NMR analysis revealed approximately 60% conversion of starting olefin to a 4:1:1 mixture of **57**, **58a**, and **58b**, respectively. The product was purified by flash chromatography (silica gel, 0.8 × 15 cm) with hexane to 50% ethyl acetate–hexane. This yielded starting olefin **55b** (1.7 mg, 34%) followed by the desired epoxide (2.15 mg, 64% based on the recovered starting material).

(2) Method B: Molybdenum-Catalyzed Oxidation. To the olefin **55b** (6.2 mg, 0.017 mmol) in benzene (0.25 mL) at 63 °C containing molybdenum hexacarbonyl (1.5 mg, 0.0057 mmol) was added *tert*-butyl hydroperoxide (0.025 mL of a 2.35 M solution in benzene, 0.058 mmol). The reaction was stirred at 63 °C for 1.5 h, poured into ether (50 mL), washed with 10% aqueous sodium thiosulfate and potassium carbonate (1:1 mixture, 10 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a white solid. The material was purified by flash chromatography (silica gel, 0.8 × 18 cm) with hexane to 50% ethyl acetate–hexane to yield **57** (5.47 mg, 84.6%) as a white solid: mp (hexane) 116–118 °C (lit.[33] mp for optically active compound 145–146 °C); IR (CCl_4) 3580, 2942, 2850, 1463, 1248 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.01 (6 H, s), 0.85 (9 H, s), 0.88 (3 H, s), 1.55–2.0 (6 H, m), 1.67 (3 H, br s), 2.51 (1 H, dd, J = 15.4, 7.6 Hz), 2.76 (1 H, d, J = 3.8 Hz), 3.06 (1 H, d, J = 3.8 Hz), 3.42 [1 H, d (AB), J = 10.8 Hz], 3.58 [1 H, d (AB), J = 10.8 Hz), 3.59 (1 H, d, J = 5.5 Hz), 3.77 (1 H, d, J = 5.2 Hz), 4.64 [1 H, m (upon addition of D_2O signal collapses to dd, J = 7.5, 2.9 Hz)], 5.37 (1 H, dm, J = 5.5 Hz); MS (70 eV) m/e (rel intensity) 323 (10.6), 205 (12.7), 159 (11.0), 124 (18.0), 107 (13.5), 105 (46.8), 91 (16.1), 89 (32.7), 81 (16.7), 75 (100), 73 (91.9), 43 (18.3), 41 (25.2). Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53; M_r 380.2382. Found: C, 66.41; H, 9.30; M_r 380.2384.

(±)-Verrucarol 4. To a solution of silylverrucarol **57** (15 mg, 0.0394 mmol) in THF (1 mL) was added tetrabutylammonium fluoride (0.12 mL of a 1 M solution in THF, 0.118 mmol). The reaction was stirred for 2.5 h at room temperature, poured into chloroform (2 × 30 mL), washed with 10% aqueous potassium carbonate (15 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a white solid. The solid was purified by flash chromatography (silica gel, 0.8 × 10 cm) in 50% hexane–ethyl acetate to 1% methanol–ethyl acetate to yield (±)-verrucarol (9.6 mg, 91.6%) as a white solid, mp (ether–chloroform) 165.5–167 °C [lit.[9d] mp (ether) 159–161 °C]. The 270-MHz ^1H NMR spectrum, as reported below, was superimposable on a similar spectrum obtained from (−)-verrucarol: ^1H NMR (270 MHz, $CDCl_3$) δ 0.97 (3 H, s), 1.74 (3 H, br s), 1.74–2.15 (7 H, m), 2.59 (1 H, dd, J = 15.1, 7.6 Hz), 2.81 (1 H, d, J = 3.9 Hz), 3.10 (1 H, d, J = 3.9 Hz), 3.56 (1 H, d, J = 12.1 Hz), 3.64 (1 H, d, J = 5.1 Hz), 3.78 (1 H, d, J = 12.1 Hz), 3.81 (1 H, d, J = 5.1 Hz), 4.64 (1 H, dd, J = 7.6, 3.0 Hz), 5.42 (1 H, d, J = 5.1 Hz).

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Registry No. (±)-**4**, 80514-49-4; (*E*)-**11a**, 52062-24-5; (*E*)-**11b**, 73912-36-4; **12**, 82891-01-8; (±)-**13**, 82902-13-4; (*Z*)-**15**, 87902-36-1; (±)-**16**, 82891-02-9; (±)-**17**, 87902-37-2; (±)-**17** acid, 87902-38-3; (±)-**18**, 82891-03-0; (±)-**19**, 87902-39-4; (±)-**20**, 87936-46-7; (±)-**21**, 87902-40-7; (±)-**22**, 87982-55-6; (±)-**25**, 87902-41-8; (±)-**26a**, 87902-42-9; (±)-**26b**, 87936-47-8; (±)-**27**, 87902-43-0; (±)-**28a**, 87902-44-1; (±)-**28b**, 87982-42-1; (±)-**29**, 87902-45-2; **32**, 87902-46-3; **33**, 87902-47-4; **33** *S*-oxide, 87902-48-5; (±)-**34a**, 87902-49-6; (±)-**34b**, 87936-48-9; (±)-**37**, 82891-04-1; (±)-**38**, 82891-05-2; (±)-**38** alcohol, 87902-50-9; (±)-**38** 7-enol silyl ether, 87902-51-0; (±)-**40**, 87902-52-1; (±)-**41**, 82891-06-3; (±)-**42**, 82916-71-0; (±)-**43**, 82891-07-4; (±)-**44**, 87982-43-2; **44** lactol, 87902-53-2; (±)-**45**, 82916-70-9; (±)-**46**, 87902-54-3; (±)-**53**, 82891-09-6; (±)-**54a**, 82891-10-9; (±)-**54a** 4a,15-cyclic ether, 87921-86-6; (±)-**54b**, 82891-11-0; (±)-**54c**, 82891-12-1; (±)-**55a**, 82891-16-5; (±)-**55b**, 82891-17-6; (±)-**56**, 82891-14-3; (±)-**57**, 82891-18-7; (±)-**58a**, 87902-55-4; (±)-**58b**, 87902-56-5; 2-methyl-1,3-cyclopentanedione, 765-69-5; 1-chloro-*cis*-2-buten-4-ol, 7523-44-6.

Supplementary Material Available: Table III (interatomic distances and angles), general experimental, and X-ray determination (3 pages). Ordering information is given on any current masthead page.