Enraf-Nonius CAD4 diffractometer with graphite-monochromatized Mo Kα radiation ($\mu$ = 0.71069 Å). Calculations were performed with the CAD4 structure determination package programs (Enraf-Nonius, Delft, Holland, 1985) and also with UNICS III programs[11] for full-matrix least-squares refinement.

(11) Sakurai, T.; Kobayashi, K. *Rikagaku Kenkyusho Hokoku* **1979**, *55*, 69–77.

Final residuals of $R$ = 0.066 and $Rw$ = 0.068 were obtained, where $w = 1/(0.00651|F_o|^2 - 0.333\ |F_o| + 5.3893)$.

**Supplementary Material Available:** Complete tables of bond lengths, angles, and thermal parameters for **3a** with a table of its crystallographic parameters, $^1$H and $^{13}$C NMR spectra for **1a,b**, **3a,b**, **4a**, **6a**, and **7b**, and $^1$H NMR spectrum for **5a** (34 pages). Ordering information is given on any current masthead page.

# Trichothecene Synthesis Using Organoiron Complexes: Diastereoselective Total Syntheses of (±)-Trichodiene, (±)-12,13-Epoxytrichothec-9-ene, and (±)-Trichodermol

Anthony J. Pearson* and Michael K. O'Brien

*Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106*

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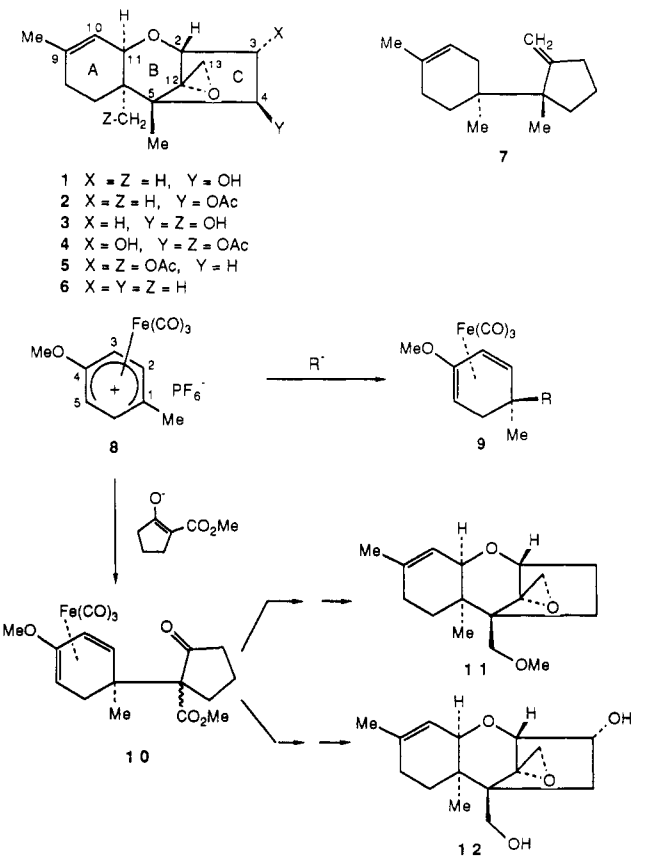
Reactions of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (**8**) with a number of tin enolates are reported. The reaction of **8** with 2-methyl-1-[(tributylstannyl)oxy]cyclopentene and with 3-(dimethylphenylsilyl)-2-methyl-1-[(tributylstannyl)oxy]cyclopentene proceeds regiospecifically by addition to C1 of the dienyl ligand and diastereoselectively to give complexes **23A** and **28A**, respectively, as the major products. Complex **23A** was converted in four steps to (±)-trichodiene and in nine steps to (±)-12,13-epoxytrichothec-9-ene. Complex **28A** was converted in 12 steps to (±)-trichodermol.

## Introduction

Previous work in our laboratory has been aimed at the synthesis of various structural analogues of trichothecenes.[1] These compounds are naturally occurring sesquiterpenes that show diverse biological activity[2] and that are of sufficient structural complexity to pose an interesting challenge for total synthesis.[3] Examples are trichodermol (**1**) and its acetate trichodermin (**2**), verrucarol (**3**), anguidine (**4**), and calonectrin (**5**), as well as the biogenetic precursor trichodiene (**7**). Total syntheses of these have already been reported by other groups.[3] Our own work in this area has focused on the use of the cyclohexadienyliron complex **8** as an A-ring precursor for these compounds, based on the observation that stabilized enolate nucleophiles add to **8** exclusively at the methyl-substituted dienyl terminus to give diene complexes of general structure **9**.

A particular example of this reaction is the conversion of **8** to **10**, which is obtained as an equimolar mixture of two diastereomers in greater than 98% yield, one of which has been converted[1] to the trichothecene analogues **11** and **12**. The latter compound has similarities to calonectrin, and the presence of the 3-hydroxy group makes it of potential interest from the point of view of biological activity. However, while complex **8** lends itself very well to the synthesis of analogues via this route, we considered it imperative to demonstrate that this novel chemistry can




be used to construct natural products of predefined structure with high efficiency.

Raphael's group[4] reported the first total synthesis of trichodermin, and while the strategy was elegant in its

(1) Pearson, A. J.; Ong, C. W. *J. Am. Chem. Soc.* **1981**, *103*, 6686. Pearson, A. J.; Chen, Y. S. *J. Org. Chem.* **1986**, *51*, 1939.

(2) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. Bamburg, J. R.; Strong, F. M. In *Microbial Toxins*; Kadis, S., Ciegler, A., Ajl, S. J., Eds.; Academic Press: New York, 1971; Vol. 7, pp 207–292. 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; p 43. Mirocha, C. J.; Pathre, S. V.; Christensen, C. M. *Economic Microbiology*; Rose, A. H., Ed.; Academic Press: London, 1979; Vol. 3 Chapter 11. *Trichohothecenes and Other Mycotoxins*; Proceedings of The International Mycotoxin Symposium, Sydney, Australia, 1984; Lacey, J., Ed.; Wiley: Chichester, 1985.

(3) For a recent review of trichothecene synthesis, see: McDougal, P. G.; Schmuff, R. N. *Prog. Chem. Org. Nat. Prod.* **1985**, *47*, 153.

(4) Colvin, E. W.; Malchenko, S.; Raphael, R. A.; Roberts, J. S. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 1989.

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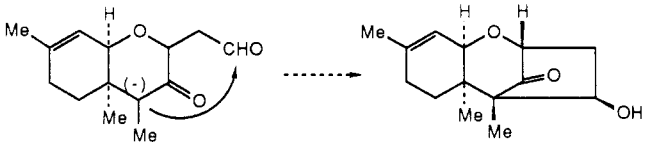
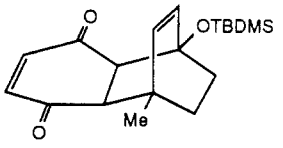
conception, it proved troublesome in its execution. One key step, the aldol cyclization of intermediate **13** to give



**13** **14**

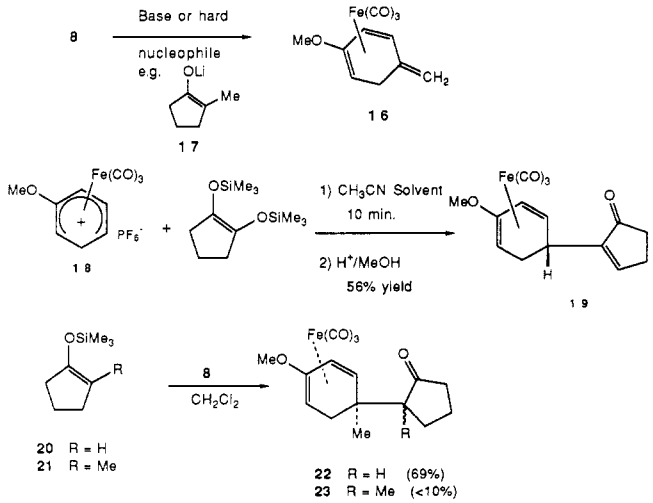
**14**, proved to be prohibitively difficult and, while an ingenious way around the problem was developed, **14** could be obtained in only 7% yield. Thus, while the synthesis was quite short (20 steps from 4-methylanisole, 19 steps to trichodermol), it was impractical.

The synthesis of trichodermol developed by Still and Tsai[5] overcame the problem of C-ring construction, by using a Herz–Favorskii ring contraction of the intermediate **15**. This allowed a successful total synthesis of trichodermol in 24 steps from 4-methylanisole.



**15**

Our ultimate aim was to produce trichodermol in less than 19 steps from 4-methylanisole, using a route that has straightforward high-yielding steps. To circumvent the requirement for ester to methyl reduction, required if complexes of type **10** are employed, it would be necessary to use an enolate derivative of 2-methylcyclopentanone. Complex **8** reacts with a rather narrow range of carbon nucleophiles[6] to give products of carbon–carbon bond formation, and there is a pronounced tendency for "hard", more basic nucleophiles to deprotonate the methyl group of **8** to give complex **16**. In our hands, this was indeed



the result of treating **8** with the thermodynamic lithium enolate **17**. Birch and co-workers have reported[7] that terminally unsubstituted cyclohexadienyliron tricarbonyl

**Table I. Reaction of Complex 8 with Tin Enolates**

| enolate | product(s) (yield, %) | diastereomer ratio (A:B[a]) |
|---|---|---|
| **24** | **22A + B** (83) | 5:7[b] |
| **25** | **22A + B** (82) | 1.7:1[b] |
| **26** | **23A + B** (87) | 5:1 |
| **27** | **28A + B** (86) | 5:1 |
| **29** | **31** (70) | 1:1 |
| **30** | **32** (47) | 1:1 |
| **33** | **35** (64) | 2:1 |
| **34** | **36** (6.5) | 3:1 |

[a] Measured by $^1$H NMR spectroscopy of the mixture. [b] Results taken from ref 8.

complexes such as **18** react with silyl enol ethers to give alkylation products, such as **19**. We found[8] that reaction of **8** with the simple enolsilane **20** gave **22** in 69% yield. However, the reaction is very slow ($CH_2Cl_2$, room temperature, 41 h, then reflux, for 19 h) and required a large excess of **20** (4–5 equiv). Furthermore, reaction of **8** with the methyl-substituted enolsilane **21** gave less than 10% yield of the desired product **23** even after prolonged reaction time (>48 h in refluxing $CH_2Cl_2$).

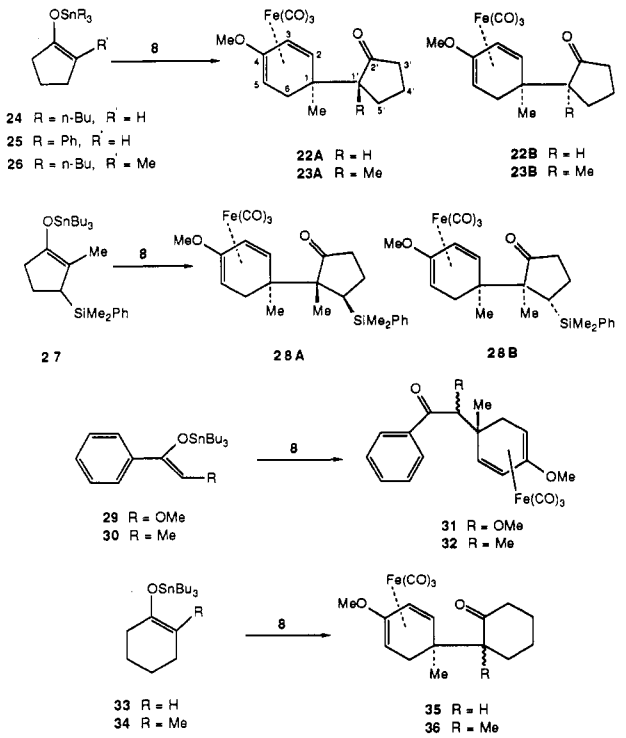
Thus, while this demonstrates that carbon–carbon bond formation is indeed possible using **8** in conjunction with enolsilanes, the sluggishness of the reaction coupled with the low yield of **23** prompted us to examine enolates that are more reactive than **21** but less basic than **17**. Trost and co-workers have found[9] that $\pi$-allylpalladium complexes, which also do not react satisfactorily with lithium enolates and enolsilanes, react cleanly with tin enolates. This encouraged us to examine the reaction of complex **8** with tin enolates and the subsequent application of this new technology in the total synthesis of the three title trichothecene natural products.[10]

## Results and Discussion

**Reactions of Complex 8 with Tin Enolates.** In the early phases of this work, we examined the reactions of tin enolates generated by treatment of the ketone with lithium diisopropylamide, followed by addition of a trialkyltin chloride to the so-formed lithium enolate. While this procedure allowed conversion of **8** to alkylated products at low temperature, the yields were disappointing (10–32%). Therefore, we elected to convert enolsilanes, which could be isolated and purified, to the corresponding tin enolates via sequential treatment with methyllithium and trialkyltin chloride. Reaction of complex **8** with the tin enolate formed in this way usually proceeded to completion in ca. 30 min, at ca. −50 °C. Table I summarizes the results of this study, which is by no means extensive, while details of reaction conditions are given in the Experimental Section.

In general, a high-yielding C–C bond forming reaction occurs. The exception is **34**, the tin enolate of 2-methylcyclohexanone, which also gives some addition to C5 of complex **8**. The low overall yield presumably reflects a greater steric demand by the nucleophile, although we have not studied this in detail. Interestingly, enolates **26** and **27** add to **8** with significant diastereoselectivity. While it is tempting to propose a transition-state model to explain

(5) Still, W. C.; Tsai, M. T. *J. Am. Chem. Soc.* **1980**, *102*, 3654.
(6) Reviews: Pearson, A. J. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: New York, 1982; Chapter 58. Pearson, A. J. In *Chemistry of the Carbon-Metal Bond*; Hartley, F. R., Patai, S., Eds.; Wiley: Chichester, 1987; Vol. 4, Chapter 10.
(7) Birch, A. J.; Narula, A. S.; Dahler, P.; Stephenson, G. R.; Kelly, L. F. *Tetrahedron Lett.* **1980**, *21*, 979. Birch, A. J.; Dahler, P.; Narula, A. S.; Stephenson, G. R. *Tetrahedron Lett.* **1980**, *21*, 3817.
(8) Chen, Y. S. Ph.D. Dissertation, Case Western Reserve University, May 1986, and unpublished work of M. K. OBrien.
(9) Trost, B. M.; Verhoeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 881. Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591, 2595.
(10) Preliminary communications: Pearson, A. J.; O'Brien, M. K. *J. Chem. Soc., Chem. Commun.* **1987**, 1445. O'Brien, M. K.; Pearson, A. J.; Pinkerton, A. A.; Schmidt, W.; Willman, K. *J. Am. Chem. Soc.* **1989**, *111*, 1499.

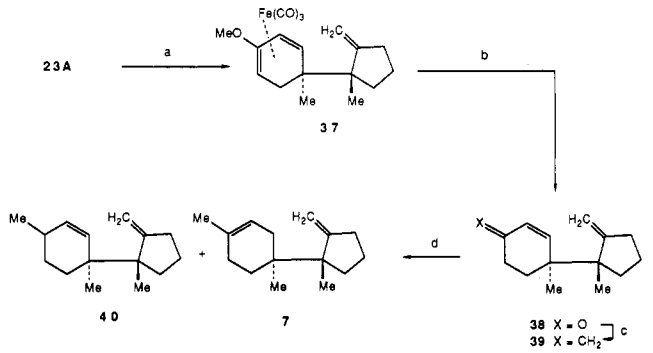



this phenomenon, the limited number of results at hand, coupled with the fact that no diastereoselection in observed in the reactions of **24**, **29**, and **30**, make us reluctant to do so at this time. The relative stereochemistry of the products **23** and **28** was initially assigned by comparison of $^1$H NMR data with those for a series of related ketones previously characterized by us[11] and was subsequently confirmed by X-ray crystal structure determination.[10] At this stage, we regard it as extremely fortunate that the major products **23A** and **28A** have stereochemistry appropriate for elaboration to the trichothecene natural products **6**, **7**, and **1**.

**Conversion of Complex 23A to (±)-Trichodiene and (±)-12,13-Epoxytrichothec-9-ene.** Separation of the diastereomers **23A** and **23B** by flash chromatography, followed by Wittig olefination of **23A**, afforded complex **37** in 61% yield. Decomplexation of **37**, using $CuCl_2$ in ethanol,[12] produced enone **38** quantitatively, which was then subjected to a second olefination to give **39**. Reduction of **39** with sodium in liquid ammonia gave a 9:1 mixture of (±)-trichodiene **7** and the 1,2-reduction product **40**, which were easily separated by flash chromatography on silica gel impregnated with silver nitrate, yielding trichodiene in 73% yield (Scheme I).[13]

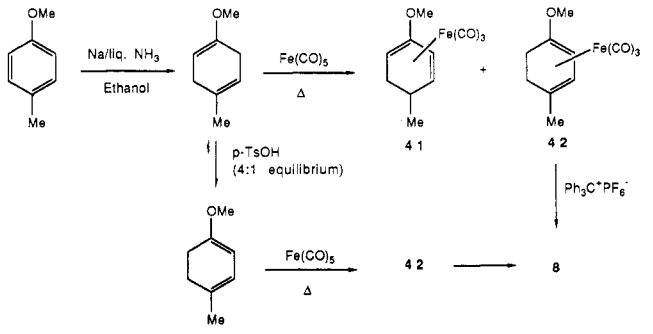
Some comments on this synthesis are in order. First, it requires only five steps from complex **8**, which is readily prepared in batches of 200 g or more from 4-methylanisole. This preparation requires three or four steps, depending on whether or not the intermediate dihydroanisole is subjected to preconjugation (Scheme II). While the shorter route does allow us to boast an eight-step diastereoselective synthesis of **7**, it suffers from the disadvantage of mixture formation during the complexation step (**41** + **42**). Since only one of the complexes, **42**, undergoes hydride abstraction to give **8**, the longer route, which gives

**Scheme I**[a]



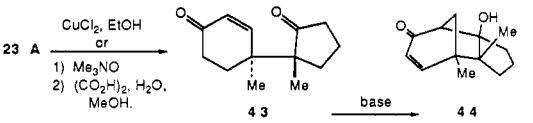

[a] Reagents (yield): (a) $Ph_3PCH_3Br$, $KOBu^t$, $Bu^tOH$, $Et_2O$, reflux, 72 h (61%). (b) Saturated $CuCl_2$ in EtOH, room temperature, overnight (>98%). (c) 6 equiv of $Ph_3PCH_3Br$, 6 equiv of $KOBu^t$, $Bu^tOH$, $Et_2O$, reflux, 4 h (>98%). (d) Na, $NH_3$, THF, −78 °C, 1 h (83% as a 9:1 mixture of **7** and **40**).

**Scheme II**




60–65% overall yield of **8** from 4-methylanisole, is a more practical approach.

Second, the diene–$Fe(CO)_3$ unit in **23A** provides an attractive masked cyclohexenone, which allows a number of potential problems to be circumvented. For example, the Wittig reaction on complex **23A** removes the cyclopentanone functionality, which can be troublesome. Decomplexation of **23A** gives the desired enone product **43**,



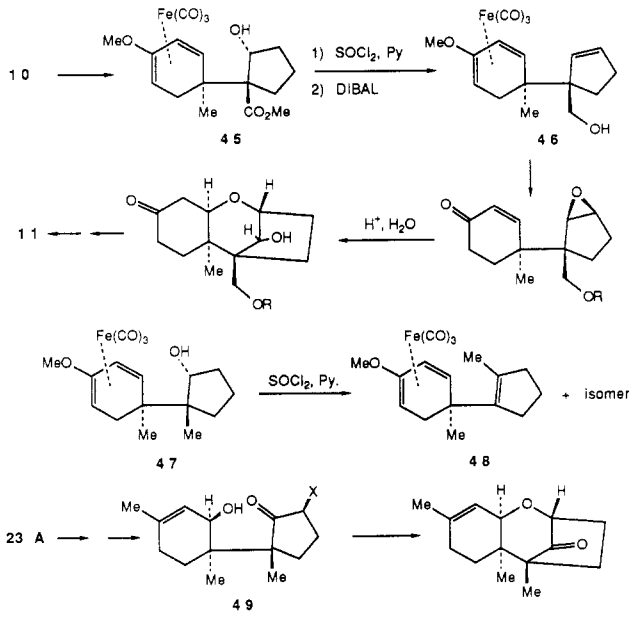

but this is always contaminated with 10–20% of **44**, the product of an internal aldol reaction that occurs under the decomplexation conditions. Furthermore, attempted double Wittig olefination on **43** gives *only* **44** and none of the desired triene **39**. Thus, in this particular instance the diene–$Fe(CO)_3$ system serves a very useful purpose.

To convert complex **23A** to (±)-12,13-epoxytrichothec-9-ene (**6**), further oxygenation of the cyclopentanone ring is required. Our earlier syntheses of compounds **11** (and with modification, **12**) utilized a stereocontrolled epoxidation of complex **46**, produced via dehydration of **45**, and subsequent elaboration as outlined in Scheme III. However, attempted dehydration of the analogous complex **47** resulted in rearrangement, via 1,2-methyl shift, to give **48**. Consequently, an alternative strategy was devised.

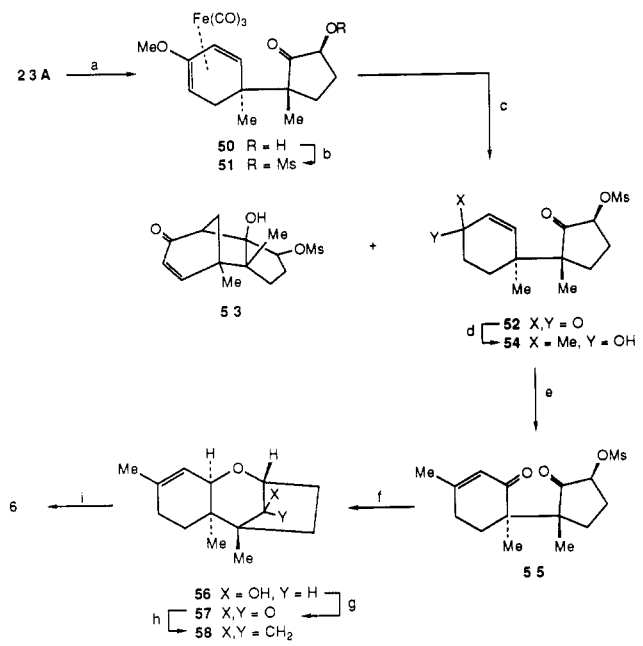
We considered that stereocontrolled introduction of a leaving group $\alpha$ to the cyclopentanone carbonyl would allow cyclization of an intermediate such as **49** to give the trichothecene ring system. This would also provide model studies for the projected synthesis of trichodermol. Accordingly, **23A** was converted stereospecifically to the

(11) Pearson, A. J.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 395. Pearson, A. J.; Mincione, E.; Chandler, M.; Raithby, P. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2774.
(12) Thompson, D. J. *J. Organomet. Chem.* **1976**, *108*, 381.
(13) Gardner, P. D.; Grabbe, R. R.; Meyers, D. Y.; Stroebel, G. G. *J. Phys. Chem.* **1978**, *82*, 1121. Bauld, N. L. *J. Am. Chem. Soc.* **1962**, *84*, 4345, 4347.

**Scheme III**



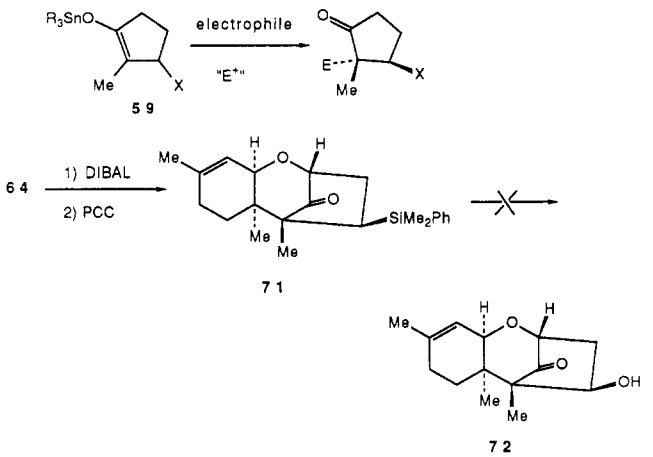
**Scheme IV**[a]



[a] Reagents (yield): (a) 1, LDA, THF, −78 °C, 15 min; 2, MoOPH, −60 °C, 1 h. (b) MsCl, $C_5H_5N$, room temperature, overnight (80% overall for two steps). (c) Saturated $CuCl_2$ in EtOH, room temperature, 6 h (80%). (d) 6 equiv of MeMgBr, THF, −78 °C, 3 h, (87%). (e) Pyridinium chlorochromate, $CH_2Cl_2$, room temperature, 2 h (87%). (f) 3.0 equiv of $(^iBu)_2AlH$, $CH_2Cl_2$, 0 °C to room temperature, 30 min (90%). (g) Pyridinium chlorochromate, NaOAc, $CH_2Cl_2$, room temperature, 2–3 h (90%). (h) 6 equiv of $Ph_3PCH_3Br$, 6 equiv of $KOBu^t$, $Bu^tOH$, $Et_2O$, reflux 4 h (77%). (i) MCPBA, $Na_2HPO_4$, $CH_2Cl_2$, room temperature (52% based on recovered pure starting material).

$\alpha$-hydroxy ketone **50** by using the MoOPH method of Vedejs[14] (Scheme IV). We were unable to drive this reaction to completion, but **50** was obtained in 85% yield, based on consumed starting material at ca. 78% conversion. Since **50** was quite prone to enolization and, therefore, rearrangement of the hydroxy ketone moiety, it was converted directly to the stable mesylate **51**, obtained in 85% yield. Decomplexation afforded the enone **52** in 70% yield, together with 12–15% of aldol cyclization product **53**. It may be noted at this point that attempts to effect Wittig olefination on various protected derivatives of **50** were unsuccessful, due to the greater steric hindrance at the carbonyl group, so that the unwanted aldol side reaction during decomplexation could not be eliminated in this case. Conversion of **52**, via **54**, to the enone **55** proceeded uneventfully in 76% overall yield, and the stage was set for the key cyclization reaction. Reduction of **55** with diisobutylaluminum hydride (3 equiv) proceeded stereospecifically and with concomitant intramolecular displacement of the mesylate to give the cyclized compound **56** in 92% yield, oxidation of which afforded **57**. Although the DIBAL reduction of **55** could be partially controlled to give **57**, there was always obtained a significant amount of overreduction product **56** (using 1.2–1.4 equiv of DIBAL, low temperature), and the two-step procedure described here was found to be more efficient in practice. Wittig olefination of **57**, using the Raphael procedure,[4] gave **58** in 80% yield, epoxidation of which gave the epoxy trichothecene **6**, although the last step is somewhat unselective and low-yielding, as noted by earlier workers.[15]

**Total Synthesis of (±)-Trichodermol.** With the basic strategy for construction of the trichothecene ring system worked out, we turned our attention to applying this to a synthesis of trichodermol. Addition of a tin enolate nucleophile of type **59** (where X is a substituent that can later be converted to OH) to the iron complex **8** would undoubtedly place the OH equivalent (X) in the correct relative stereochemistry, since **8** would add trans to X. The only question concerned the nature of the hydroxyl equivalent. The acetyl group has been used for such purposes,[16] since this is convertible, via Baeyer–Villiger oxidation, to an acetoxy group. However, we considered this to be cumbersome, in view of the need to generate an enolate selectively and differentiate various ketone functionalities later in the synthesis. Consequently, we focused our attention on the dimethylphenylsilyl group, developed by Fleming and others,[17] since this is easily introduced and



(14) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. Vedejs, E.; Larson, S. *Org. Synth.* **1986**, *64*, 127.

(15) Hua, D. H.; Venkataraman, S.; Chan-Yu-King, R.; Paukstelis, J. V. *J. Am. Chem. Soc.* **1988**, *110*, 4741.

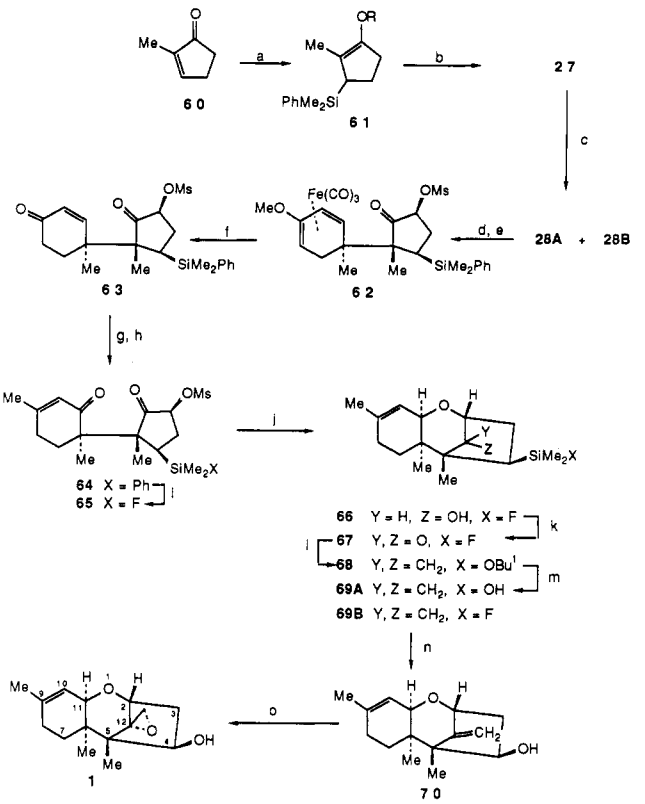
(16) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1972**, *33*, 333. Kojima, K.; Sakai, K. *Ibid.* **1975**, *33*, 2837.

(17) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, *28*, 4229. Fleming, I.; Patel, S. K.; Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2520. Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29. Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. *Organometallics* **1983**, *2*, 1694. Tamao, K.; Ishida, N. *J. Organomet. Chem.* **1984**, *269*, C37. Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 4412. Tamao, K. In *Organosilicon and Bioorganosilicon Chemistry*; Sakurai, H., Ed.; Ellis Horwood: Chichester, 1985; p 231.

there exist several procedures for its conversion to hydroxyl.

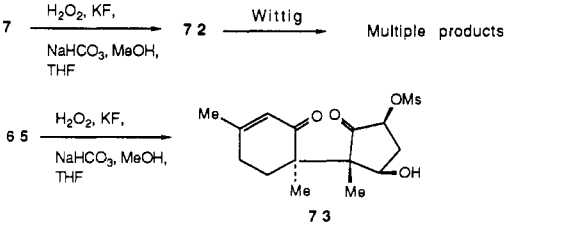
The requisite tin enolate **27** was generated as follows. Treatment of 2-methylcyclopentenone **60** with lithium dimethylphenylsilyl cuprate, followed by in situ reaction of the intermediate enolate with chlorotrimethylsilane, afforded the silyl enol ether **61** (R = $SiMe_3$) in 85% yield, and this was readily isolated and purified (Scheme V). Treatment of **61** with methyllithium, followed by addition of tri-*n*-butyltin chloride, gave the tin enolate **27**, which was allowed to react with complex **8** under carefully controlled conditions to give an approximately 5:1 mixture of racemic **28A** and **28B**, which were separated and individually characterized. No other diastereomers were observed, so that the addition of electrophile to **27** occurs stereospecifically trans to the $PhMe_2Si$ group, as expected, and there is diastereoselectivity about the newly formed C–C bond. By use of a sequence identical with that described earlier, complex **28A** was converted to the enone **64**. The hydroxylation of **28A** again proceeded stereospecifically, despite the presence of the bulky $PhMe_2Si$ group, and compound **62** was readily secured. Decomplexation of **62** was accompanied by intramolecular aldol reaction, as with the earlier examples, but this was a minor side reaction accounting for only 10% of product with the desired intermediate **63** being produced in 87% isolated yield. This compound was readily converted to **64** by using a procedure identical with that described above for conversion **52** → **55**. With enone **64** in hand, there were a number of alternative sequences that could be followed for completion of the synthesis, depending on the point at which the dimethylphenylsilyl group is converted to hydroxyl. The sequence shown in Scheme V proved to be the most effective (see also later discussion of alternatives). Treatment of **64** with anhydrous tetrafluoroboric acid gave the fluorodimethylsilyl derivative[17] **65**, which was readily converted to **66** and then to **67** without problem. At this point the Wittig olefination was carried out, again using the Raphael procedure[4] ($[Ph_3PCH_3]^+Br^-$, $KOBu^t$, $Bu^tOH$, $Et_2O$, reflux), giving the methylene product **68** in excellent (95%) yield. However, methylenation was accompanied by loss of the fluoride group (from mass spectrometry and $^{19}F$ NMR spectroscopy) and incorporation of *tert*-butoxide on silicon. This unusual displacement arises from the use of the *tert*-butoxide/*tert*-butyl alcohol system during the olefination. Compound **68** was always accompanied by small amounts of the fluorosilane derivative (X = F). We were unable to find conditions for the Wittig reaction that would avoid this displacement (use of *n*-BuLi as base in THF solvent, while successful in a number of other trichothecene syntheses,[18] failed to give any of the desired product from **67**), and so the remaining steps were followed by using **68**. Attempted conversion of **68** directly to the hydroxy derivative **70** using the conditions normally employed for fluorosilanes (30% $H_2O_2$, KF, $NaHCO_3$, MeOH, THF) failed. In an attempt to reintroduce the fluoride group, **68** was treated with tetra-*n*-butylammonium fluoride in tetrahydrofuran, but this gave predominantly the silanol derivative **69** in 92% yield, again accompanied by minor amounts of fluorosilane derivative (X = F). This presumably arises either from the water that is present in commercial $Bu_4NF$ solutions or by loss of the *tert*-butyl group via $S_N1$ or elimination mechanisms. Since the silanol **69** could be converted successfully and cleanly to the desired 4-hydroxytrichothecadiene **70**, it was not necessary to pursue this further. Finally, epoxidation of **70** using the literature procedure[5] afforded (±)-trichodermol (**1**), which was spectroscopically identical with the material prepared by Still and Tsai.[5,19]

**Scheme V**[a]




[a] Reagents (yield): (a) $2Me_2PhSiLi$, CuCN, THF, −23 °C then 0 °C, 2 h, followed by enolate trapping with $Me_3SiCl$, $Et_3N$, room temperature, 3 h (80%). (b) 1.2 equiv of MeLi, DME, room temperature, 45 min; 1.2 equiv of $Bu_3SnCl$, −78 °C, 1 h. (c) **8**, $CH_3CN$, −72 °C, 3–4 h (70%). (d) 1, LDA, THF, −78 °C, 15 min; 2, MoOPH, −60 °C, 1 h. (e) MsCl, $C_5H_5N$, room temperature, overnight (80% overall for two steps). (f) Saturated $CuCl_2$ in EtOH, room temperature, 2–4 h monitored by infrared spectroscopy (87%). (g) 6 equiv of MeMgBr, THF, −78 °C, 3 h (70%). (h) Pyridinium chlorochromate, $CH_2Cl_2$, room temperature, 2–3 h (83%). (i) 10 equiv of $HBF_4{\cdot}Et_2O$, $CH_2Cl_2$, 45–50 °C, 20 h, (90%). (j) 3.0 equiv of $(i\text{-}Bu)_2AlH$, $CH_2Cl_2$, 0 °C to room temperature, 30 min (95%). (k) Pyridinium chlorochromate, NaOAc, $CH_2Cl_2$, room temperature, 2–3 h (95%). (l) 6 equiv of $Ph_3PCH_3Br$, 6 equiv of $KOBu^t$, $Bu^tOH$, $Et_2O$, reflux, 18 h (90%). (m) Excess $Bu^nNF$, THF, room temperature, 2 h (90%). (n) 30% aqueous $H_2O_2$ (24 equiv), KF (6 equiv), $NaHCO_3$ (6 equiv), THF/MeOH (1:1), 60 °C, 24 h (80%). (o) MCPBA, $Na_2HPO_4$, $CH_2Cl_2$, room temperature, (65% based on recovered pure starting material at 66% conversion).

As mentioned earlier, there are in principle several points at which the dimethylphenylsilyl group could be converted to hydroxyl, and these alternatives have been briefly investigated. Conversion of intermediate **64** to the tricyclic ketone **71** was accomplished smoothly, but all




(18) Brooks, D. W.; Grothaus, P. G.; Mazdiyasni, H. *J. Am. Chem. Soc.* **1983**, *105*, 4472. Trost, B. M.; McDougal, P. G. *J. Am. Chem. Soc.* **1982**, *104*, 6110.

(19) We are grateful to Professor W. C. Still for a copy of the $^1H$ NMR spectrum of synthetic (±)-trichodermol.

attempts to convert the $PhMe_2Si$ group to OH using known methods[17] completely failed, even when prior bromination of the double bond was examined. Judging the major problem to be the sensitivity of the trichothecene ring system toward electrophilic reagents,[20] such as those used in the first stages of desilylation, we examined the conversion of **67** to **72**. This proceeded satisfactorily on a small scale (<20 mg), but competing Baeyer–Villiger reaction on the cyclopentanone group was noted on scale-up. Furthermore, attempted Wittig olefination of **72** resulted in multiple products, none of which corresponded to **70**, and which appeared to result from retroaldolization of the β-hydroxycyclopentanone (C ring) coupled with olefination of the product. Therefore, if this route were followed, protection of the hydroxyl of **72** would be essential, and so it was not pursued further.

Conversion of **65** to the hydroxy derivative **73** could be accomplished quite cleanly (80% yield), but again this would require protection/deprotection of the hydroxy group, making it somewhat less attractive than the sequence described in Scheme V. Finally, it may be noted that enone **63** underwent the acid-catalyzed aldol cyclization described earlier on attempted conversion of the silyl group to OH. Thus, the most appropriate point to begin this manipulation is at the intermediate **64**. The sequence shown in Scheme V and the alternatives presented have demonstrated the considerable flexibility associated with the use of $PhMe_2Si$ as an OH surrogate that can withstand a range of synthetic reactions without being adversely affected and that can be selectively manipulated without detriment to a number of other functional groups.

## Conclusions

From the above discussion, it is clear that the dienyliron complex **8** is a useful general precursor to a variety of trichothecene natural products, as well as their unnatural analogues. The total syntheses described are (fortuitously) diastereoselective, which means that the syntheses can be made asymmetric. For example, Birch and co-workers have prepared **8** in optically active form using an asymmetric complexation procedure,[21] and multiple recrystallization has provided optically pure material,[22] although this procedure has not yet been fully optimized. Alternatively, the observed diastereoselectivity would allow kinetic resolution to be achieved if the enolate **27** could be produced in optically pure form[23] and allowed to react with racemic **8**. While we have not examined these aspects of dienyliron chemistry, there appears to be considerable potential for asymmetric synthesis.

Trichodiene has been synthesized in a number of laboratories,[24] and three of these syntheses were reported in 1986. Most of these syntheses employed an Ireland modification of the Claisen rearrangement as the key C–C bond-forming step, and this was essentially nondiastereoselective. The overall yields ranged from ca. 8 to 27%. A stereospecific synthesis of trichodiene was reported by Harding and Clement[24d] (9 steps, 5.4–9.5% overall yield). For comparison, our synthesis is diastereoselective and proceeds in greater than 33% overall yield, using five steps from the complex **8** (8–9 steps, 22% overall yield from 4-methylanisole).

Turning our attention to 12,13-epoxytrichothec-9-ene, the most recent synthesis reported at the time of writing is that of Hua et al.,[15] which commences with carvone and proceeds in 18 steps to optically pure **6** (ca. 1.7% overall yield). Two previous diastereoselective syntheses[25] of racemic **6** were reported, involving 15 and 17 steps and giving 0.25 and 0.9% overall yields (not all individual yields were reported in ref 24a). The diastereocontrolled synthesis of racemic **6** reported herein requires 10 steps from complex **8** and gives 7.3% overall yield (13–14 steps and 5% overall yield from 4-methylanisole).

The two previous total syntheses of racemic trichodermol were discussed earlier (Raphael, 19 steps, 0.035% overall yield; Still and Tsai, 25 steps: ca. 0.4% overall yield, both from 4-methylanisole). The synthesis of **1** from complex **8** requires 13 steps and gives 7.7% overall yield (16–17 steps, 5.3% overall yield from 4-methylanisole).

## Experimental Section

**General Techniques.** All $^1H$ NMR, $^{13}C$ NMR, and $^{19}F$ NMR spectra were recorded on a Varian XL-200 or Bruker MSL-400 spectrometer. Except where otherwise noted, deuterated chloroform stored under argon over 4-Å molecular sieves was used as solvent, with $Me_4Si$ as an internal standard for $^1H$ and $^{13}C$ NMR and $CFCl_3$ as internal reference for $^{19}F$ NMR spectra. Melting points are uncorrected. Solvents were used after distillation over a drying agent as follows (solvent/drying agent): tetrahydrofuran (THF)/Na, benzophenone; dichloromethane ($CH_2Cl_2$)/calcium hydride; 1,2-dimethoxyethane (DME)/K, benzophenone; diethyl ether ($Et_2O$)/Na, benzophenone; acetonitrile ($CH_3CN$)/calcium hydride. All reactions were carried out under dry, oxygen-free argon, except for decomplexations using copper(II) chloride. Flash chromatography was carried out using Baker silica gel with an average particle diameter of 40 μm. The purity of all title compounds was judged to be >95% by $^1H$ NMR spectroscopy, unless otherwise noted.

**Tricarbonyl[4-methoxy-1-methyl-1-(1-methyl-2-oxocyclopentyl)-(2–5-η)-cyclohexa-2,4-dienyl]iron (23A).** The following is a typical procedure. The reaction has been carried out with identical results on scales as large as 15 g.

To a stirred solution of 2-methyl-1-[(trimethylsilyl)oxy]cyclopentene (0.86 mL, 4.41 mmol) in 8 mL of DME under argon at room temperature was added 3.15 mL of 1.4 M MeLi (4.41 mmol, in diethyl ether) over a period of several minutes. The solution was stirred for 30 min before cooling to −78 °C and adding 1.2 mL of $Bu_3SnCl$ (4.41 mmol) via syringe. After stirring for 60 min at this temperature, the iron dienylium salt **8** (1.50 g, 3.7 mmol) dissolved in 16 mL of acetonitrile was added dropwise via a pressure-equalizing funnel. After 10 min, the solution was slowly warmed to −10 °C over a period of 1 h. The reaction mixture was then quenched with 50% aqueous tetrahydrofuran and extracted with ether, and the extracts were washed with 5% HCl, $H_2O$ saturated with $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield a mixture of two diastereomers as a viscous gold/brown oil. Flash chromatography on silica gel (5:95 EtOAc/hexane) yielded 1.0 g (75%) of the desired diastereomer (**23A**, slower running band) as yellow crystals along with 150 mg of the undesired diastereomer (**23**, faster running band). Recrystallization of **23A** (ether/hexane) furnished an analytical sample: mp 68–69 °C.

**Diastereomer 23A** (trichothecene precursor): IR ($CHCl_3$) $\nu_{max}$ 2020, 1975, 1730, 1480, 910 $cm^{-1}$; $^1H$ NMR δ 5.01 (1 H, dd, $J_{3,2}$ = 6.6, $J_{3,5}$ = 2.2 Hz, H3), 3.64 (3 H, s, OMe), 3.25 (1 H, q, $J$ =

(20) The trichothecene to apotrichothecene rearrangement is known to occur on treatment of 12,13-epoxytrichothecenes with acid. See the review by Tamm in ref 2. Also, opening and reclosure of the oxygen bridge of the B ring may occur under acidic conditions; see ref 1.

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(25) (a) Musuoka, N.; Kamikawa, T. *Tetrahedron Lett.* **1976**, 1691. (b) Fujimoto, Y.; Yokura, S.; Nakamura, T.; Morikawa, T.; Tatsuno, T. *Tetrahedron Lett.* **1974**, 2523.

2.7 Hz, H5), 2.67 (1 H, d, $J_{2,3}$ = 6.6 Hz, H2), 2.3 (1 H, dd, $J_{gem}$ = 18.1, $J_{3',4'\,cis}$ = 7.9 Hz, H3'), 2.25–2.13 (1 H, m, H3'), 2.13–2.0 (2 H, m, H6 and H5'), 1.96–1.85 (1 H, m, H4'), 1.8–1.65 (1 H, m, H4'), 1.6 (1 H, dd, br, $J_{gem}$ = 12.6, $J_{5',4'\,cis}$ = 7.3 Hz, H5'), 1.44 (1 H, dd, $J_{gem}$ = 14.9, $J_{6,5}$ = 3.2 Hz, H6), 1.08 (3 H, s, Me), 0.96 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{17}H_{20}O_5Fe$ 360.0879, found 359.9846. Anal. Calcd for $C_{17}H_{20}O_5Fe$: C, 56.70; H, 5.60. Found: C, 56.60; H, 5.54.

**Diastereomer 23B**: mp 88–89 °C; IR ($CHCl_3$) $\nu_{max}$ 2020, 1975, 1730, 1480, 910 $cm^{-1}$; $^1H$ NMR $\delta$ 5.10 (1 H, dd, $J_{3,2}$ = 6.6, $J_{3,5}$ = 2.28 Hz, H3), 3.66 (3 H, s, OMe), 3.32 (1 H, q, $J$ = 2.8 Hz, H5), 2.4–1.6 (7 H, m), 2.31 (1 H, d, $J_{2,3}$ = 6.7 Hz, H2), 1.44 (1 H, dd, $J_{gem}$ = 16, $J_{6,5}$ = 3.2 Hz, H6), 0.99 (3 H, s, Me), 0.89 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{17}H_{20}O_5Fe$ 360.0879, found 360.0655. Anal. Calcd for $C_{17}H_{20}O_5Fe$: C, 56.70; H, 5.60. Found: C, 56.82; H, 5.66.

**Tricarbonyl[4-methoxy-1-methyl-1-(1-methyl-2-methylenecyclopentyl)-(2–5-$\eta$)-cyclohexa-2,4-dienyl]iron (37).** To 1.64 g of $Ph_3PCH_3Br$ (4.6 mmol) in 5 mL of dry diethyl ether was added 6.2 mL of 0.742 N $^t$BuOK/$^t$BuOH. The resulting yellow suspension was stirred under argon for 1 h at a gentle reflux before cooling to room temperature and adding the carbonyl compound **23A** (1.5 g, 4.16 mmol) dissolved in 5 mL of diethyl ether. The suspension was stirred at 55 °C (oil bath temperature). At 12-h intervals, the mixture was cooled, the insolubles were allowed to settle, the supernatant liquid was added via canula to a freshly prepared 1.1 equiv of ylide solution (prepared as described above), and the mixture was again heated to 55 °C. After 72 h, the mixture was cooled, poured into water, extracted with ether, dried over $MgSO_4$, concentrated in vacuo, and chromatographed on silica gel (flash chromatography, 10:90 EtOAc/hexane followed by 50:50 EtOAc/hexane as eluant) to yield 865 mg (61%) of pure olefin as a pale yellow oil (90% based on recovered starting material): IR ($CHCl_3$) $\nu_{max}$ 2950, 2860, 2030, 1960, 1660, 1642 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.10 (1 H, dd $J_{3,2}$ = 6.5, $J_{3,5}$ = 1.7 Hz, H3), 4.97 (1 H, s, br, exocyclic vinyl), 4.72 (1 H, s, br, exocyclic vinyl), 3.65 (3 H, s, OMe), 3.22 (1 H, q, $J$ = 2.5 Hz, H5), 2.57 (1 H, d, $J_{2,3}$ = 6.5 Hz, H2), 2.38–2.22 (2 H, m), 1.93 (1 H, d, br, $J$ = 15.1 Hz), 1.82–1.78 (1 H, m), 1.45 (1 H, dd, $J_{gem}$ = 14.9, $J$ = 2.8 Hz, H6), 1.41–1.28 (2 H, m), 1.039 (3 H, s, Me), 0.968 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{18}H_{22}O_4Fe$ 358.1041, found 358.0868.

**1-Methyl-1-(1-methyl-2-methylenecyclopentyl)-2-cyclohexen-4-one (38).** Diene complex **37** (820.3 mg, 2.29 mmol) dissolved in 20 mL of EtOH was added to a saturated $CuCl_2$/EtOH solution (20 mL) and stirred for 8 h. The mixture was then poured into $H_2O$, extracted with ether, washed with liberal amounts of water, dried over $MgSO_4$, and concentrated in vacuo to yield 461 mg of the enone as a pale yellow oil. Flash chromatography on silica gel (10:90 followed by 20:80 EtOAc/hexane) yielded 457 mg (98%) of pure enone **38** as a pale yellow oil: IR ($CHCl_3$) $\nu_{max}$ 2950, 2870, 1665, 1610 $cm^{-1}$; $^1H$ NMR $\delta$ 6.98 (1 H, dd, $J_{2,3}$ = 10.4, $J_{2,6}$ = 2.1 Hz, H2), 5.91 (1 H, dd, $J_{3,2}$ = 10.4, $J_{3,5}$ = 0.59 Hz, H3), 5.04 (1 H, d, $J$ = 0.3 Hz, exo vinyl), 4.86 (1 H, d, $J$ = 2.77 Hz, exo vinyl), 2.53 (1 H, ddd, $J$ = 17.18, $J$ = 14.36, $J$ = 5.6 Hz), 2.41–2.33 (2 H, m), 2.29–2.22 (1 H, m), 2.11 (1 H, dt, $J$ = 13.85, $J$ = 4.93 Hz), 1.8–1.62 (3 H, m), 1.5–1.4 (2 H, m), 1.18 (3 H, s, Me), 1.12 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{14}H_{20}O$ 204.1554, found 204.1517.

**1-Methyl-1-(1-methyl-2-methylenecyclopentyl)-4-methylene-2-cyclohexene (39).** To 2.33 g of $Ph_3PCH_3Br$ (6.23 mmol) in 3 mL of dry diethyl ether was added 8.4 mL of a 0.742 M $^t$BuOK/$^t$BuOH solution, and the resulting yellow suspension was stirred at gentle reflux for 1 h. After cooling to room temperature, the starting enone (318 mg, 1.6 mmol) was added dissolved in 2 mL of ether, and the reaction mixture was stirred at 55 °C for 2 h. Upon cooling, the mixture was poured into water, extracted with ether, dried over $MgSO_4$, and concentrated in vacuo to yield 1.36 g of the crude triene. Flash chromatography on silica gel (2:98 EtOAc:hexane) yielded 310 mg (98%) of the pure triene **39** as a colorless oil: IR ($CHCl_3$) $\nu_{max}$ 3060, 2943, 1638, 1590 $cm^{-1}$; $^1H$ NMR $\delta$ 6.07 (1 H, d, $J_{2,3}$ = 10.1 Hz, H2), 5.85 (1 H, d, $J_{3,2}$ = 10.1 Hz, H3), 4.98 (1 H, d, $J$ = 1.17 Hz, exo vinyl, 5-membered ring), 4.82 (1 H, d, $J$ = 2.5 Hz, exo vinyl, 5-membered ring), 4.76 (1 H, s, exo vinyl, 6-membered ring), 4.73 (1 H, s, exocyclic vinyl, 6 membered ring), 2.44–2.38 (1 H, m), 2.34–2.15 (3 H, m), 1.82–1.76 (1 H, m), 1.72–1.62 (2 H, m), 1.52–1.34 (3 H, m), 1.07 (3 H, s, Me), 1.05 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}$ 202.1716, found 202.1728.

**Trichodiene 7.** Liquid ammonia predistilled over sodium was transferred by distillation to a three-neck flask equipped with a silica gel drying tube and dry ice/acetone condenser, containing Na (34 mg, 1.5 mmol), THF (1 mL), and a stir bar. The flask was cooled to −78 °C, and the starting triene (50 mg, 0.247 mmol) dissolved in 1 mL THF was added dropwise. The mixture was stirred at −78 °C for 45 min before being quenched with an excess of ethanol (dropwise addition). After evaporation of the $NH_3$, the mixture was extracted with ether, washed with water, 10% HCl, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield after flash chromatography (2% EtOAc/hexane) 42 mg of a 9:1 mixture of trichodiene and the 1,2 reduction product. A second flash chromatographic separation on silica gel impregnated with $AgNO_3$ (12.5% in $CH_3CN$) yielded 37 mg (73%) of trichodiene **7** (hexane used as eluant) as the fast-running band, isolated as a colorless oil: IR ($CHCl_3$) $\nu_{max}$ 2945, 2860, 1640, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.30 (1 H, m, H3), 4.96 (1 H, dt, $J$ = 2.6, $J$ = 1.3 Hz, exo vinyl), 4.74 (1 H, dt, $J$ = 2.6, $J$ = 1.3 Hz, exo vinyl), 2.32 (1 H, dd, $J$ = 15.7, $J$ = 5.6 Hz), 2.25–2.16 (1 H, m), 2.03–1.6 (4 H, m), 1.6–1.51 (3 H, m), 1.64 (3 H, s, vinyl Me), 1.5–1.3 (3 H, m), 1.04 (3 H, s, Me), 0.86 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{24}$ 204.1878, found 204.1867.

**Tricarbonyl[4-methoxy-1-methyl-1-(3-hydroxy-1-methyl-2-oxocyclopentyl)-(2–5-$\eta$)-cyclohexa-2,4-dienyl]iron (50).** To a stirred solution of LDA (27 mL, 0.77 M in THF, pretitrated) at −78 °C under argon was added (dropwise via a pressure equalizing funnel) the ketone **23A** (5.75 g, 0.016 mol) dissolved in 80 mL of THF. The resulting orange solution was stirred at −78 °C for 30 min before the crystalline MoOPH reagent (11.1 g, 25.6 mmol) was added in one portion. The solution was slowly warmed to −60 °C and allowed to stir for an additional 45 min before the reaction mixture was quenched with saturated sodium sulfite solution (50 mL), warmed to 20 °C, and diluted with sufficient water to allow the formation of two homogeneous layers. The mixture was stirred for an additional 15 min, the layers were separated, and the organic products were extracted with ether. The organic extracts were washed with 10% HCl to remove pyridine, and the mixture was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (30:70 EtOAc/hexane) yielded 4.45 g of the alcohol **50** as a white foam along with 760 mg of recovered starting ketone (74%, 85% based on recovered pure starting material). It was important that the $\alpha$-hydroxy ketone was mesylated directly to avoid keto–enol tautomerism which resulted in formation of the rearranged 2-hydroxy ketone. Yields of **50** were somewhat variable, ranging from 60 to 75%; IR ($CHCl_3$) $\nu_{max}$ 3520, 2960, 2865, 2040, 1960, 1730 $cm^{-1}$; $^1H$ NMR $\delta$ 4.94 (1 H, dd, $J_{3,2}$ = 6.5, $J_{3,5}$ = 2.1 Hz, H3), 4.15–4.05 (1 H, m, C*H*OH), 3.59 (3 H, s, OMe), 3.23 (1 H, q, $J$ = 2.7 Hz, H5), 2.89 (1 H, s, br, OH), 2.53 (1 H, d, $J_{2,3}$ = 6.5 Hz, H2), 2.44–1.86 (4 H, m), 1.68–1.32 (2 H, m), 1.0 (3 H, s, Me), 0.974 (3 H, s, Me). High-resolution mass spectrum calcd for ($C_{17}H_{20}O_6Fe$ − CO) 348.0660, found 348.0664.

**Tricarbonyl[4-methoxy-1-methyl-1-(3-((methylsulfonyl)-oxy)-1-methyl-2-oxocyclopentyl)-(2–5-$\eta$)-cyclohexa-2,4-dienyl]iron (51).** To 1.7 g of the starting alcohol (4.52 mmol) stirred in pyridine (50 mL) at 0 °C under argon was added methanesulfonyl chloride (0.525 mL, 6.78 mmol). After this was stirred for 15 h at 0 °C, water was added, and the organics were extracted with diethyl ether, washed with 10% HCl (5 × 50 mL), water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield yellow/brown crystals. Flash chromatography on silica gel (30% EtOAc/hexane as eluant) yielded 1.75 g (85%) of the crystalline mesylate **51**. A small amount was recrystallized (EtOAc/hexane) to yield pale yellow crystals (mp 160–161 °C): IR ($CHCl_3$) $\nu_{max}$ 2968, 2930, 2040, 1970, 1360, 1175 $cm^{-1}$; $^1H$ NMR $\delta$ 5.2 (1 H, t, br, $J$ = 10 Hz, H3'), 4.97 (1 H, dd, $J_{3,2}$ = 6.3, $J_{3,5}$ = 2.15 Hz, H3), 3.64 (3 H, s, OMe), 3.33 (3 H, s, $OSO_2Me$), 3.25 (1 H, q, $J$ = 2.7 Hz, H5), 2.54 (1 H, d, $J_{2,3}$ = 6.4 Hz, H2), 2.5–2.0 (3 H, m), 2.0–1.58 (2 H, m), 1.43 (1 H, dd, $J_{gem}$ = 15.0, $J_{6,5}$ = 3.2 Hz, H6), 1.05 (3 H, s, Me), 1.02 (3 H, s, Me). Anal. Calcd for $C_{18}H_{22}O_8SFe$: C, 47.59; H, 4.88. Found: C, 47.58; H, 4.86. High-resolution mass spectrum calcd for $C_{18}H_{22}O_8SFe$ 454.0384, found 454.0308.

**1-Methyl-1-(3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)cyclohex-2-en-4-one (52).** To a suspension of the iron tricarbonyl complex **51** (800 mg, 1.76 mmol) dissolved in ethanol (marginally soluble) was added 30 mL of a saturated $CuCl_2$/EtOH solution. The suspension was stirred for 6 h at room temperature. After the disappearance of the starting material (TLC, IR) the reaction mixture was poured into 200 mL of $H_2O$ and extracted with ether (3 × 100 mL). The organic extracts were washed repeatedly with water to remove $CuCl_2$/EtOH, dried over $MgSO_4$, and concentrated in vacuo to yield the crude enone **52** as a white foam. Flash chromatography (30:70 EtOAc/hexane as eluant) yielded 364 mg of the enone as a white foam (70% yield). Recrystallization from ether/hexane produced white crystals with a melting point of 96–97 °C. A small amount of tricyclic alcohol **53** also formed as a result of an intramolecular adol condensation; IR ($CHCl_3$) 2965, 1748, 1670, 1360, 1175 $cm^{-1}$; $^1H$ NMR $\delta$ 7.14 (1 H, dd, $J_{2,3}$ = 10.5 Hz, $J_{2,6}$ = 2.1 Hz (w coupling), H2), 5.93 (1 H, d, $J_{2,3}$ = 10.7 Hz, H3), 4.92 (1 H, dd, $J_{3',4'}$ = 11.6, $J_{3',4'}$ = 8.8 Hz, H3'), 3.2 (3 H, s, $OSO_2Me$), 2.66–2.36 (3 H, m), 2.25–1.84 (3 H, m), 1.82–1.54 (2 H, m), 1.14 (3 H, s, Me), 1.12 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{14}H_{20}O_5S$ 300.1031, found 300.1032.

**1,4-Dimethyl-4-(3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-2-cyclohexen-1-ol (54).** To a solution of the enone **52** (700 mg, 2.33 mmol) in THF (20 mL) at −78 °C under argon was slowly added 3.9 mL of 3.0 M MeMgBr solution in ether (11.65 mmol). After stirring for 3–4 h at this temperature, 50 mL of a 1:1 THF:water solution was added dropwise via a pressure-equalizing funnel. The products were then extracted with ethyl acetate, washed with $H_2O$, dried over $MgSO_4$, and concentrated in vacuo to yield 604 mg of alcohol **54** as a white foam (87%). This was used in the next step without further purification; IR ($CHCl_3$) $\nu_{max}$ 3580, 1743, 1660, 1360, 1170 $cm^{-1}$; $^1H$ NMR $\delta$ 5.55 (2 H, m, H2, H3 vinyl, appears as very narrow ABq), 4.85 (1 H, t, $J$ = 8 Hz, H3'), 3.14 (3 H, s, $OSO_2Me$), 2.56–2.34 (1 H, m), 2.08–1.48 (7 H, m), 1.44–1.28 (1 H, m), 1.18 (3 H, s, Me (vinyl)), 1.03 (3 H, s, Me), 0.95 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O_5S$ 298.1239, found 298.1227.

**3,6-Dimethyl-6-(3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-2-cyclohexen-1-one (55).** This procedure was modeled after that of Dauben and Michno.[26] To a suspension of pyridinium chlorochromate (340 mg, 1.58 mmol) in 6 mL of dichloromethane at room temperature under argon was added the tertiary alcohol **54** (250 mg, 0.79 mmol) dissolved in $CH_2Cl_2$. After this was stirred for 3 h, 30 mL of diethyl ether was added, the organic layer was decanted, and the remaining black tarry residue was washed two more times in the same manner. The combined ether fractions were washed with 10% NaOH, 10% HCl, $H_2O$, saturated $NaHCO_3$, and brine before drying over $MgSO_4$ and concentrating in vacuo. Flash chromatography (30:70 EtOAc/hexane) yielded 215 mg (87%, 75% overall from **52**) of pure enone **55** as a white foam. Recrystallization ($Et_2O$/hexane) produced white needles (mp 107–107.5 °C): IR ($CHCl_3$) $\nu_{max}$ 2960, 1743, 1650, 1350, 1173 $cm^{-1}$; $^1H$ NMR $\delta$ 5.69 (1 H, s, br, H2), 5.48 (1 H, dd, $J$ = 8.79, 11.2 Hz, H3'), 3.16 (3 H, s, $OSO_2Me$), 2.71–2.13 (5 H, m), 2.11–1.8 (2 H, m), 1.91 (3 H, s, Me, vinyl), 1.64 (1 H, dd, $J$ = 11.6, $J$ = 7.3 Hz), 1.15 (3 H, s, Me), 1.07 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O_55$ 314.1188, found 314.1184. Anal. Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.38; H, 7.15.

**13-Nortrichothec-9-en-12-ol (56).** To a solution of the enone **55** (230 mg, 0.732 mmol) in 12 mL of dichloromethane at 0 °C under argon was slowly added 2.5 mL of 1.0 M diisobutylaluminum hydride (DiBAH) in hexane (2.5 mmol). The solution was immediately warmed to room temperature and stirred for 30 min before quenching with water. After stirring an additional 15–30 min, the products were extracted with ether, washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (50:50 EtOAc/hexane) yielded 150 mg (92%) of pure tricyclic alcohol **56** as a white crystalline solid: mp 94–97 °C; IR ($CHCl_3$) $\nu_{max}$ 3570, 1601 $cm^{-1}$; $^1H$ NMR $\delta$ 5.40 (1 H, d, br, $J_{10,11}$ = 4.1 Hz), 4.07 (1 H, dd, $J_{2,3}$ = 4.4 Hz, $J_{2,12}$ = 2.64 Hz, H2), 3.69 (1 H, d, br, $J_{11,10}$ = 4.8 Hz, H11), 3.38 (1 H, dd, br, $J$ = 7.0, $J$ = 1.8 Hz, H12), 2.34 (1 H, ddd, $J$ = 12.9, $J$ = 11.9, $J$ = 7.0 Hz, H4 or H3), 2.09 (1 H, d, $J$ = 7.5 Hz, OH), 2.03 (1 H, ddd, $J$ = 14.0, $J$ = 10.3, $J$ = 3.8 Hz, H8), 1.97–1.83 (3 H, m, H8, H7 and H4 or H3), 1.79–1.65 (1 H, m, H3), 1.71 (3 H, s, Me vinyl), 1.45 (1 H, dd, $J$ = 13.2, $J$ = 5.1 Hz, H7), 1.23 (1 H, ddd, $J$ = 13.5, $J$ = 12.5, $J$ = 6.3 Hz, H4), 1.07 3 H, s, Me), 0.78 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1619.

**13-Nortrichothec-9-en-12-one (57).** To a suspension of pyridinium chlorochromate (220 mg, 1.1 mmol) and sodium acetate (5 mg) in 5 mL of dichloromethane was added the alcohol **56** (150 mg, 0.69 mmol) in one portion dissolved in dichloromethane. After this was stirred for 3 h at room temperature, diethyl ether was added, the organic layer was decanted, and the black, resinous residue was washed two additional times in a similar fashion. The combined ethereal fractions were washed with 10% NaOH, 10% HCl, $H_2O$, saturated $NaHCO_3$, and brine before drying over $MgSO_4$ and concentrating in vacuo. Flash chromatography on silica gel (20:80 EtOAc/hexane) yielded 136.1 mg (91%) of the carbonyl compound **57** as a white crystalline solid, mp 88–89 °C (recrystallization from $Et_2O$/hexane): IR ($CHCl_3$) $\nu_{max}$ 2970, 1750, 1602 $cm^{-1}$; $^1H$ NMR $\delta$ 5.42 (1 H, dq, $J_{10,11}$ = 5.5, $J_{10,Me}$ = 1.3 Hz, H10), 3.99 (1 H, d, br, $J_{11,10}$ = 5.5 Hz, H11), 3.81 (1 H, d, $J_{2,3}$ = 4.7 Hz, H2), 2.42–2.2 (1 H, m), 2.2–1.78 (4 H, m), 1.66–1.4 (3 H, m), 1.68 (3 H, s, Me (vinyl)), 0.97 (3 H, s, Me), 0.83 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1467. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.22; H, 9.16.

**Trichotheca-9,12-diene (58).** To a suspension of $Ph_3PCH_3Br$ (1.22 g, 3.42 mmol) in dry diethyl ether under argon was added 0.882 N $^t$BuOK/$^t$BuOH (3.88 mL, 3.42 mmol) via syringe. After this was stirred at reflux for 1 h, the bright yellow suspension was cooled to room temperature, the carbonyl compound **57** (135 mg, 0.685 mmol) dissolved in ether was added, and the suspension was stirred at gentle reflux for 4 h. Upon cooling to room temperature, the mixture was poured into water, extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (5:95 EtOAc/hexane as eluant) yielded 116 mg (80%) of diene **58** as a colorless oil: IR ($CHCl_3$) $\nu_{max}$ 2960, 1675 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.38 (1 H, dq, $J_{10,11}$ = 5.3, $J_{10,Me}$ = 1.4 Hz, H10), 4.94 (1 H, d, $J_{gem}$ = 1.0 Hz, H13), 4.59 (1 H, d, $J_{gem}$ = 1.0 Hz, H13), 4.3 (1 H, d, $J_{2,3}$ = 4.6 Hz, H2), 3.71 (1 H, d, br, $J_{11,10}$ = 5.8 Hz, H11), 2.2–2.03 (1 H, m), 1.95–1.64 (4 H, m), 1.61 (3 H, s, Me vinyl), 1.33–1.85 (3 H, m), 0.94 (3 H, s, Me), 0.73 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O$ 218.1671, found 218.1685.

**12,13-Epoxytrichothec-9-ene (6).** The epoxidation of **58** was carried out according to the method described by Hua et al.[15] IR ($CHCl_3$) $\nu_{max}$ 2960, 2860, 1670, 1050 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (1 H, d, br, $J_{10,11}$ = 4.9 Hz, H10), 3.72 (1 H, d, obsc, $J$ = 5.16 Hz, H2), 3.70 (1 H, d, obsc, $J$ = 6.8 Hz, H11), 3.16 (1 H, d, $J_{gem}$ = 4.1 Hz, H13), 2.88 (1 H, d, $J_{gem}$ = 4.0 Hz, H13), 2.18 (1 H, ddd, $J$ = 13.7, $J$ = 9.6, $J$ = 4.5 Hz), 2.05–1.8 (4 H, m), 1.71 (3 H, s, Me, vinyl), 1.59–1.52 (2 H, m), 1.39 (1 H, d, br, $J$ = 11.1 Hz), 0.81 (3 H, s, Me), 0.76 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1619.

**3-(Dimethylphenylsilyl)-2-methyl-1-[(trimethylsilyl)oxy]cyclopentene (61).** (Dimethylphenylsilyl)lithium (25 mL, 0.54 N in THF) was added dropwise to a stirred suspension of CuCN (600 mg, 6.7 mmol) in 2 mL of dry THF under argon at 0 °C. After 20 min, the resulting red solution was cooled to −23 °C, and 2-methylcyclopentenone (585 mg, 6.09 mmol) was added in 4.0 mL of dry THF dropwise over 15 min. The solution was stirred for 45 min and then warmed to 0 °C over 2 h. Triethylamine (2.56 mL, 18.27 mmol) and trimethylsilyl chloride (2.31 mL, 18.27 mmol) were added in succession, and the resulting mixture was stirred at room temperature for 3 h. The mixture was poured into 10–15 mL of saturated $NH_4Cl$ (pH = 8) and extracted with ether. The organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Distillation yielded 1.79 g (80% yield) of the silyl enol ether **61** as a pale yellow oil: bp 133–137 °C (0.25 mmHg); IR ($CHCl_3$) $\nu_{max}$ 2960, 1680 $cm^{-1}$; $^1H$ NMR $\delta$ 7.5–7.24 (5 H, m, Ar), 2.34–2.18 (2 H, m), 2.15–1.98 (2 H, m), 1.90–1.72 (1 H, m), 1.4 (3 H, s, Me), 0.28 (3 H, s, Si$Me_2$Ph), 0.23 (3 H, s, Si$Me_2$Ph), 0.09 (9 H, s, $Me_3Si$).

(26) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

**Tricarbonyl[4-methoxy-1-methyl-1-(5-(dimethylphenylsilyl)-1-methyl-2-oxocyclopentyl)-(2-5-η)-cyclohexa-2,4-dienyl]iron (28A).** The following procedure represents the highest yield obtained. In general, yields ranged from 60 to 70% for pure diastereomer **28A**.

To a flame-dried 250-mL three-neck round-bottomed flask fitted with a pressure-equalizing funnel and containing 60 mL of DME under argon was added the silyl enol ether **61** (6.57 g, 0.0216 mol). MeLi (16.07 mL, 1.4 M in $Et_2O$) was added dropwise, and the resulting orange solution was stirred at room temperature for 45 min. After this was cooled to −78 °C, $Bu_3SnCl$ (7.37 g, 0.225 mmol) was added via syringe, and the reaction was stirred at this temperature for 1 h. At this point, the iron salt **8** (8 g, 0.0196 mol) dissolved in 50 mL of $CH_3CN$ was added slowly via the dropping funnel while the internal temperature of the solution was maintained below −72 °C. After stirring at this temperature for 2–3 h, the reaction was quenched via a dropwise addition of 50% $H_2O$ in THF, warmed to room temperature, extracted with ether, washed with 10% HCl, $H_2O$, and saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo to yield 15 g of the crude iron diene complex (mixture of diastereomers) as a viscous yellow oil. The undesired diastereomer could be crystallized from ether, and the desired diastereomer isolated via flash chromatography (30:70 EtOAc/hexane as eluant) to yield 6.85 g (71%) of pure complex **28A** as a yellow crystalline solid. Recrystallization from EtOAc/hexane yielded the desired diastereomer as yellow crystals (mp 133–134 °C); IR ($CHCl_3$) $\nu_{max}$ 2960, 2035, 1960, 1717 $cm^{-1}$; $^1H$ NMR (400 MHz) δ 7.53–7.48 (2 H, m, Ar), 7.41–7.3 (3 H, m, Ar), 4.96 (1 H, dd, $J_{3,2}$ = 6.5, $J_{3,5}$ = 2.2 Hz, H3), 3.58 (3 H, s, OMe), 3.17 (1 H, m, H5), 2.59 (1 H, d, $J_{2,3}$ = 6.5 Hz, H2), 2.36 (1 H, ddd, $J$ = 7.1, $J$ = 4.2, $J$ = 18.1 Hz), 2.28–2.12 (2 H, m), 2.12–2.0 (1 H, m), 1.9 (1 H, t, $J$ = 8.7 Hz), 1.84–1.7 (1 H, ddd, $J$ = 6.9, $J$ = 8.6, $J$ = 15.5 Hz), 1.28 (1 H, dd, $J_{gem}$ = 15.0, $J_{6,5}$ = 3.2 Hz, H6), 0.98 (3 H, s, Me), 0.97 (3 H, s, Me), 0.38 (3 H, s, Ph$Me_2$Si), 0.36 (3 H, s, Ph$Me_2$Si). High-resolution mass spectrum calcd for ($C_{25}H_{30}O_5SiFe$ − 2CO) 438.1313, found 438.1315. Anal. Calcd for $C_{25}H_{30}O_5SiFe$: C, 60.73 H, 6.10. Found: C, 60.42, H, 6.08.

**28B.** This complex was isolated in 18% yield as pale yellow crystals. Recrystallization from $CHCl_3$/EtOAc gave mp 166–167 °C; IR ($CHCl_3$) $\nu_{max}$ 3000, 2960, 2025, 1960, 1715 $cm^{-1}$; $^1H$ NMR δ 7.65–7.61 (2 H, m, Ar), 7.44–7.41 (3 H, m, Ar), 3.44–3.43 (1 H, m, H3), 3.87 (3 H, s, OMe), 3.16 (1 H, q, $J$ = 2.7 Hz, H5), 2.48 (1 H, dd, $J_{gem}$ = 16.2, $J_{6,5}$ = 2.6 Hz, H6, exo), 2.29–2.25 (2 H, m), 2.06–1.98 (2 H, m), 1.95 (1 H, d, $J_{2,3}$ = 6.6 Hz), 1.79–1.73 (1 H, m), 1.14 (1 H, dd, $J_{gem}$ = 16.2, $J_{6,5}$ = 3.2 Hz, H6 endo), 0.94 (3 H, s, Me), 0.86 (3 H, s, Me), 0.45 (3 H, s, SiMe), 0.34 (3 H, s, SiMe). High-resolution mass spectrum calcd for ($C_{25}H_{30}O_5SiFe$ − 2CO) 438.1313, found 438.1356.

**Tricarbonyl[4-methoxy-1-methyl-1-(5-(dimethylphenylsilyl)-3-hydroxy-1-methyl-2-oxocyclopentyl)-(2-5-η)-cyclohexa-2,4-dienyl]iron.** To a stirred solution of LDA (15.2 mL, 0.85 N in THF, pretitrated) at −78 °C under argon was added dropwise via a pressure-equalizing funnel the ketone **28A** (6.09 g, 12.3 mmol) dissolved in 60 mL of THF. The resulting orange solution was stirred at this temperature for 30 min before the crystalline MoOPH reagent (6.52 g) was added in one portion. The solution was slowly warmed to −60 °C and allowed to stir for an additional 45 min before the reaction mixture was quenched with saturated sodium sulfite solution (40 mL), warmed to 20 °C, and diluted with sufficient $H_2O$ to form two homogeneous layers. This mixture was stirred for an additional 15 min, the layers were separated, and the organic products were extracted with ether. The combined extracts were washed repeatedly with 10% HCl to remove pyridine, and the mixture was dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography yielded 4.0 g of pure alcohol (64%) as a white foam (82% based on unconsumed starting material). The alcohol was used in the next step without further purification; IR ($CHCl_3$) $\nu_{max}$ 3515, 2965, 2875, 2040, 1965, 1730 $cm^{-1}$; $^1H$ NMR δ 7.55–7.47 (2 H, m, Ar), 7.4–7.34 (3 H, m, Ar), 4.93 (1 H, dd, $J_{3,2}$ = 6.4, $J_{3,5}$ = 2.3 Hz, H3), 4.37 (1 H, ddd), 3.56 (3 H, s, OMe), 3.13 (1 H, m, H5), 2.85 (1 H, d, $J$ = 2.7 Hz OH, exch $D_2O$), 2.44 (1 H, d, $J_{2,3}$ = 6.4 Hz, H2), 2.4–2.2 (2 H, m, H6 and H4), 1.78 (1 H, dd, $J_{5',4'}$ = 13.7, $J_{5'4'}$ = 5.9 Hz, H5′), 1.44 (1 H, t, $J$ = 12.1 Hz, H4), 1.24 (1 H, dd, $J$ = 13, $J$ = 3.3 Hz, H6), 1.04 (3 H, s, Me), 0.92 (3 H, s, Me), 0.42 (3 H, s, SiMe) 0.40 (3 H, s, SiMe). High-resolution mass spectrum calcd for ($C_{25}H_{30}O_6SiFe$ − 3CO) 426.1313, found 426.1341.

**Tricarbonyl[4-methoxy-1-methyl-1-(5-(dimethylphenylsilyl)-3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-(2-5-η)-cyclohexa-2,4-dienyl]iron (62).** To 1.4 g of the α-hydroxy ketone from the previous step (2.74 mmol) dissolved in 25 mL of pyridine under argon at 0 °C was added methanesulfonyl chloride (318.4 μL, 4.1 mmol). After stirring for 12 h at 0 °C, the reaction mixture was diluted with water, extracted with ether, washed with 10% HCl (5 × 30 mL), water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield the crude mesylate as a yellow crystalline solid. Flash chromatography on silica gel (20:80 EtOAc/hexane) yielded 1.5 g (>95%) of pure mesylate **62** as pale yellow crystals (mp 162–163 °C from ether/hexane); IR ($CHCl_3$) $\nu_{max}$ 2040, 1965, 1745, 1355, 1170 $cm^{-1}$; $^1H$ NMR δ 7.52–7.47 (2 H, m, Ar), 7.40–7.37 (3 H, m, Ar), 5.53 (1 H, dd, $J_{3',4}$ = 11.7, $J_{3'4'}$ = 9.4 Hz, H3′), 5.02 (1 H, dd, $J_{3,3}$ = 6.3, $J_{3,5}$ = 2.2 Hz, H3), 3.64 (3 H, s, OMe), 3.31 (3 H, s, $OSO_2Me$), 3.18–3.16 (1 H, m, H5), 2.46 (1 H, d, $J_{2,3}$ = 6.3 Hz, H2), 2.42–2.2 (2 H, m, H6 endo, H4′), 1.9 (1 H, dd, $J_{5'4'}$ = 13.5, $J_{5'4'}$ = 8.9 Hz, H5′), 1.79 (1 H, m, H4′), 1.27 (1 H, dd, $J_{gem}$ = 15.2, $J_{6,5}$ = 3.3 Hz, H6), 1.12 (3 H, s, Me), 0.94 (3 H, s, Me), 0.46 (3 H, s, SiMe), 0.45 (3 H, 5, SiMe). High-resolution mass spectrum calcd for $C_{26}H_{32}O_8FeSiS$ 588.0936, found 588.0942. Anal. Calcd for $C_{26}H_{32}O_8FeSiS$: C, 53.06; H, 5.48. Found: C, 52.98; H, 5.53.

**4-(5-(Dimethylphenylsilyl)-3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-4-methylcyclohex-2-en-1-one (63).** To a solution of the iron tricarbonyl complex **62** (3.5 g, 5.95 mmol) in 100 mL of ethanol was added 100 mL of saturated $CuCl_2$/EtOH. After stirring for 3 h at room temperature, the solution was diluted with 150 mL of water, extracted with ether, washed with liberal amounts of $H_2O$, dried over $MgSO_4$, and concentrated in vacuo to yield 2.75 g of crude enone as a white foam. Flash chromatography on silica gel (20:80 EtOH/hexane) yielded 2.3 g of pure enone **63** (90%) along with ~200 mg of a side product analogous to **44**, resulting from an intramolecular aldol condensation (mp 50–55 °C); IR ($CHCl_3$) $\nu_{max}$ 2960, 1745, 1670, 1360, 1170 $cm^{-1}$; $^1H$ NMR δ 7.53–7.48 (2 H, m, Ar), 7.41–7.37 (3 H, m, Ar), 6.77 (1 H, dd, $J_{2,3}$ = 10.5, $J_{2,5}$ = 2.3 Hz, H3), 5.83 (1 H, d, $J_{3,2}$ = 10.5 Hz, H2), 5.13 (1 H, dd, $J_{3'4'}$ = 11.9, $J_{3'4'}$ = 8.8 Hz, H3), 3.2 (3 H, s, $OSO_2Me$), 2.6–2.2 (3 H, m), 2.0–1.2 (4 H, m), 1.19 (3 H, s, Me), 1.17 (3 H, s, Me), 0.46 (3 H, s, SiMe), 0.44 (3 H, s, SiMe). High-resolution mass spectrum calcd for $C_{22}H_{30}O_5S$ Si 434.1583, found 434.1596.

**1,4-Dimethyl-1-(5-(dimethylphenylsilyl)-3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-4-hydroxy-2-cyclohexene.** To a solution of the enone **63** (2.5 g, 5.75 mmol) in THF (2.5 mL) at −78 °C under argon was added dropwise 9.6 mL of 3.0 M MeMgBr in ether. After this was stirred for 3–4 h at −78 °C, 50 mL of MeOH:$H_2O$ (1:1) was added dropwise via a pressure-equalizing funnel, and the solution was warmed to 0 °C. The product was extracted with ethyl acetate, washed with water, dried over $MgSO_4$, and concentrated in vacuo to yield 2.45 g of crude tertiary alcohol as a white foam. Flash chromatography on silica gel (30:70 EtOAc/hexane) yielded an analytical sample. The crude alcohol was used without further purification in the next step; IR ($CHCl_3$) $\nu_{max}$ 3585, 2960, 1742, 1360, 1175 $cm^{-1}$; $^1H$ NMR δ 7.53–7.45 (2 H, m, Ar), 7.39–7.33 (3 H, m, Ar), 5.56 (1 H, d, $J_{2,3}$ = 10.4 Hz, H2), 5.45 (1 H, dd, $J_{3,2}$ = 10.4, Hz, $J_{3,5}$ = 1.5 Hz, H3), 5.13 (1 H, dd, $J_{3'4'}$ = 9.5, $J_{3'4'}$ = 11.3 Hz, H3′), 3.18 (3 H, s, $OSO_2Me$), 2.46–2.25 (1 H, m), 1.9–1.5 (6 H, m), 1.25–1.2 (1 H, m), 1.6 (3 H, s, Me), 1.14 (3 H, s, Me), 0.97 (3 H, s, Me), 0.44 (3 H, s, SiMe), 0.43 (3 H, s, SiMe). High-resolution mass spectrum calcd for ($C_{23}H_{33}O_5SSi$ − OH) 432.1962, found 432.1516.

**1,4-Dimethyl-1-(5-(dimethylphenylsilyl)-3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-3-cyclohexen-2-one.** To a suspension of pyridinium chlorochromate (977 mg, 4.5 mmol) in 15 mL of $CH_2Cl_2$ under argon at room temperature was added the (crude) tertiary alcohol from above (1.2 g, 2.7 mmol) dissolved in $CH_2Cl_2$. After stirring for 3 h, the dark brown slurry was diluted with ether, and the liquid organic layer was decanted, leaving a black resinous material that was washed with ether two more times by decantation. The combined organic fractions were washed with 10% NaOH, 10% HCl, water, saturated $NaHCO_3$, and brine, dried over $MgSO_4$, and concentrated in vacuo to yield 1.1 g of crude enone as a white foam. Flash chromatography on silica gel (30:70 EtOAc/hexane) yielded the pure enone **64** in 55%

yield (overall from **63**) as a white foam. All attempts to recrystallize the product resulted in an oil: IR ($CHCl_3$) $\nu_{max}$ 2980, 1740, 1650, 1360, 1175 $cm^{-1}$; $^1H$ NMR $\delta$ 7.51–7.48 (2 H, m, Ar), 7.38–7.3 (3 H, m, Ar), 5.64 (1 H, s, br, H3), 5.59 (1 H, dd, $J_{3'4'}$ = 11.56, $J_{3'4'}$ = 9.33 Hz, H3'), 3.11 (3 H, s, $OSO_2Me$), 2.8–2.2 (5 H, m), 2.05–1.5 (2 H, m), 1.87 (3 H, s, br, vinyl Me), 1.07 (3 H, s, Me), 0.43 (6 H, s, $SiMe_2$). High-resolution mass spectrum calcd for $C_{23}H_{32}O_5SiS$ 448.1740, found 448.1690.

**3,6-Dimethyl-6-(5-(dimethylfluorosilyl)-3-((methylsulfonyl)oxy)-1-methyl-2-oxocyclopentyl)-2-cyclohexen-1-one (65).** To a stirred solution of compound **64** (600 mg, 1.34 mmol) in 20 mL of dichloromethane under argon at room temperature was added 3.26 g (20 mmol) of 30% $HBF_4$-$Et_2O$. The temperature was raised to 50 °C, and the solution was stirred for 20 h. The reaction mixture was cooled to room temperature, water was added, and the products were extracted with ether, washed with saturated $NaHCO_3$, water, and brine, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel (30:70 EtOAc/hexane) yielded 480 mg (90%) of pure **65** as an orange/yellow oil: IR ($CHCl_3$) $\nu_{max}$ 2955, 2870, 1740, 1648, 1360, 1170 $cm^{-1}$; $^1H$ NMR $\delta$ 5.65 (1 H, s, br, H2), 5.58 (1 H, dd, $J_{3'4'}$ = 11.3, $J_{3'4'}$ = 9.0 Hz, H3'), 3.12 (3 H, s, $OSO_2CH_3$), 2.8–2.0 (6 H, m), 2.0–1.8 (1 H, m), 1.88 (3 H, s, br, vinyl Me), 1.17 (3 H, s, Me), 1.11 (3 H, s, Me), 0.32 (3 H, s, SiMe), 0.28 (3 H, s, SiMe). High-resolution mass spectrum calcd for $C_{17}H_{27}O_5SiSF$ 390.1332, found 390.1327.

**4-(Dimethylfluorosilyl)-12-hydroxynortrichothec-9-ene (66).** To a stirred solution of compound **65** (430 mg, 1.1 mmol) in 20 mL of dichloromethane at 0 °C under argon was added 3.31 mL of diisobutylaluminum hydride (1.0 M in hexane). The solution was immediately warmed to room temperature and stirred for 30 min before quenching with water. After this was stirred for an additional 15–30 min, the products were extracted with ether, washed with water, dried over $MgSO_4$, and concentrated in vacuo to yield 325 mg of the tricyclic alcohol **66** as a yellow oil (99%). The crude product was sufficiently pure to use directly in the next step; IR ($CHCl_3$) $\nu_{max}$ 3600, 2950, 1675, 1258 $cm^{-1}$; $^1H$ NMR $\delta$ 5.39 (1 H, dq, $J_{10,11}$ = 5.2, $J_{10,Me}$ = 1.5 Hz, H10), 4.05 (1 H, dd, $J$ = 4.4, $J$ = 2.75 Hz, H2), 3.75 (1 H, d, $J_{11,10}$ = 5.0 Hz, H11), 3.44 (1 H, m, H12), 2.45–1.82 (3 H, m), 1.8–1.36 (3 H, m), 1.36–0.75 (2 H, m), 1.69 (3 H, s, vinyl Me), 1.18 (3 H, s, Me), 0.76 (3 H, s, Me), 0.27 (3 H, s, SiMe), 0.23 (3 H, s, SiMe). High-resolution mass spectrum calcd for $C_{16}H_{27}O_2SiF$ 298.1764, found 298.1798.

**4-(Dimethylfluorosilyl)-12-oxonortrichothec-9-ene (67).** To a suspension of pyridinium chlorochromate (346.3 mg, 1.6 mmol) and sodium acetate (20 mg) in 8 mL of dichloromethane was added in one portion the crude alcohol **66** (370 mg, 1.07 mmol) dissolved in $CH_2Cl_2$. After this was stirred for 3 h at room temperature, diethyl ether (50 mL) was added, and the organic layer was decanted, leaving behind a black resinous residue that was washed with ether two more times in a similar manner. The combined organic fractions were washed with 10% NaOH, 10% HCl, $H_2O$, saturated $NaHCO_3$, and brine before drying over $MgSO_4$ and concentrating in vacuo. Flash chromatography on silica gel (20:80 EtOAc/hexane as eluant) yielded 262 mg of the carbonyl compound **67** as a viscous yellow oil (89%): IR ($CHCl_3$) $\nu_{max}$ 2950, 1748 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.42 (1 H, dq, $J_{10,11}$ = 5.8, $J_{10,Me}$ = 1.3 Hz, H10), 4.07 (1 H, d, br, $J_{11,10}$ = 5.5 Hz, H11), 3.8 (1 H, d, $J_{2,3}$ = 5.26 H2), 2.19 (1 H, dd, $J_{gem}$ = 14.6, $J_{3,4}$ = 11.34 Hz, 3 exo H), 2.05–1.78 (2 H, m), 1.77–1.48 (1 H, ddd, obsc, 3 endo H), 1.68 (3 H, s, vinyl Me), 1.5–1.4 (2 H, m), 1.3–1.1 (1 H, m), 1.05 (3 H, s, Me), 0.81 (3 H, s, Me), 0.22 (3 H, s, SiMe), 0.18 (3 H, s, SiMe). High-resolution mass spectrum calcd for $C_{16}H_{25}O_2SiF$ 296.1608, found 296.1612.

**4-(Dimethyl-*tert*-butoxysilyl)trichotheca-9,12-diene (68).** A solution of potassium *tert*-butoxide in *tert*-butyl alcohol (1.42 mL, 0.742 M) was added to a stirred suspension of (triphenylmethyl)phosphonium bromide (377.8 mg, 1.057 mmol) in ether (7 mL), and the mixture was stirred under gentle reflux in an atmosphere of argon for 1 h before cooling to room temperature. A solution of the keto silane **67** (52.0 mg, 0.176 mmol) in ether was added, and the solution was heated for 3 h at a gentle reflux. After cooling to room temperature, the mixture was poured into water, extracted with ether, washed with water, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography on silica gel yielded 58 mg (95%) of tricyclic diene **68** as a pale yellow oil. An analytical sample was obtained via flash chromatography (5:95 EtOAc/hexane). It was determined from the spectral analysis that during olefination, the fluorine had been displaced by a $^t$BuO group to yield the silyl ether; IR ($CHCl_3$) $\nu_{max}$ 2955, 1670, 1600 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.35 (1 H, dq, $J_{10,11}$ = 5.6, $J_{10,Me}$ = 1.5 Hz, H10), 4.87 (1 H, s, H13), 4.52 (1 H, s, H13'), 4.22 (1 H, d, $J_{2,3}$ = 4.3, H2), 3.82 (1 H, d, br, $J_{11,10}$ = 5.8 Hz), 2.11–1.66 (4 H, m), 1.64 (3 H, s, vinyl Me), 1.6–1.4 (2 H, m), 1.3–1.1 (1 H, m), 1.2 (9 H, s, O$^t$Bu), 1.13 (3 H, s, Me), 0.76 (3 H, s, Me), 0.07 (3 H, s, Si Me), 0.06 (3 H, s, Si Me); $^{19}F$ NMR, no $^{19}F$ resonance detected; $^{13}C$ NMR $\delta$ 155.16 (C12), 139.3 (C9), 119.83 (C10), 102.47 (C13), 78.96 (C11), 70.43 (C2), 65.871 ($OCMe_3$), 49.69 (C6), 41.41 (C5), 32.052 ($OCMe_3$), 30.02 (C3), 28.75 (C8), 23.46 (C9), 23.31 (C4), 15.98 (C15), 15.28 (C16), 14.77 (C14), 1.318 (SiMe), 0.503 (SiMe). High-resolution mass spectrum calcd for $C_{21}H_{36}O_2Si$ 348.2484, found 348.2490.

**4-(Dimethylhydroxysilyl)trichotheca-9,12-diene and 4-(Dimethylfluorosilyl)trichotheca-9,12-diene (69A and 69B).** To a solution of the silyl *tert*-butyl ether **68** (52 mg, 0.149 mmol) in 3 mL of THF at room temperature was added tetrabutylammonium fluoride (TBAF, 1.49 mL, 1.0 M solution in THF, 1.49 mmol). After stirring for 3 h at this temperature, the mixture was poured into water, extracted with ether, washed with 5% HCl, water, and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to yield a mixture of two compounds, the silyl fluoride **69B** and the silyl alcohol **69A** (40.2 mg, 1:10 mixture, 92% crude yield). This crude mixture was employed in the next step without further purification. An analytical sample was obtained via flash chromatography (20:80 EtOAc/hexane as eluant). **69A** (=OH, major product): IR ($CHCl_3$) $\nu_{max}$ 3665, 2960, 1675, 1605 $cm^{-1}$; $^1H$ NMR $\delta$ 5.35 (1 H, dq, $J_{10,11}$ = 5.4, $J_{10,Me}$ = 1.4 Hz, H10), 4.93 (1 H, d, $J_{gem}$ = 0.7 Hz, H13), 4.58 (1 H, d, $J_{gem}$ = 0.9 Hz, H13'), 4.27 (1 H, d, $J_{2,3}$ = 4.4 Hz, H2), 3.81 (1 H, d, br, $J_{11,10}$ = 5.5 Hz, H11), 2.2–1.8 (2 H, m), 1.8–1.5 (3 H, m), 1.66 (3 H, s, vinyl Me), 1.5–1.15 (1 H, m), 1.14 (3 H, s, Me), 0.78 (3 H, s, Me), 0.11 (3 H, s, SiMe), 0.08 (3 H, s, SiMe); $^{19}F$ NMR, no $^{19}F$ resonances. High-resolution mass spectrum calcd for $C_{17}H_{28}O_2Si$ 292.1941, found 292.1753.

Compound **69B** gave the following spectral data: IR ($CHCl_3$) $\nu_{max}$ 2960, 1670, 1605 $cm^{-1}$; $^{19}F$ NMR $\delta$ −70.86, −74.6; $^1H$ NMR ($CDCl_3$) $\delta$ 5.35 (1 H, dq, $J_{10,11}$ = 5.4, $J_{10,Me}$ = 1.5 Hz, 10 H), 4.90 (1 H, s, H 13), 4.35 (1 H, s, H13'), 4.23 (1 H, d, $J_{2,3}$ = 4.1 Hz, H2), 3.81 (1 H, d, br, $J$ = 5.1 Hz, H11), 2.2–1.85 (2 H, m), 1.85–1.5 (1 H, m), 1.66 (3 H, s, vinyl Me), 1.5–1.2 (2 H, m), 1.09 (3 H, s, Me), 0.76 (3 H, s, Me), 0.03 (3 H, s, SiMe), 0.02 (3 H, s, SiMe). High-resolution mass spectrum calcd for $C_{17}H_{27}OF$ 294.1815, found 294.1801.

**4β-Hydroxytrichotheca-9,12-diene (70).** To a solution of the crude silane **69A** and **69B** (mixture of silyl fluoride and silanol, 35 mg, 0.119 mmol), $NaHCO_3$ (60 mg, 0.714 mmol), and KF (41.5 mg, 0.714 mmol) in 4 mL of 1:1 THF:MeOH was added 30% $H_2O_2$ (320 μL, 2.98 mmol) at room temperature. The mixture was then stirred at 60 °C for 10 h, cooled to room temperature, poured into water, extracted with ether, washed with 10% $NaHSO_3$ and saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to yield 31 mg of the crude alcohol as a viscous oil. Flash chromatography on silica gel (20:80 EtOAc/hexane) yielded 20 mg of pure alcohol **70** (48% overall from **66**) as a white crystalline solid: mp 123–125 °C. (lit.[4] mp 125–126 °C); IR ($CHCl_3$) $\nu_{max}$ 3600, 1672 $cm^{-1}$; $^1H$ NMR $\delta$ 5.35 (1 H, dq, $J_{10,11}$ = 5.6, $J_{10,Me}$ = 1.5 Hz, H10), 5.13 (1 H, d, $J_{gem}$ = 0.5 Hz, H13), 4.71 (1 H, d, $J_{gem}$ = 1.0 Hz, H13'), 4.39 (1 H, d, $J_{2,3}$ = 3.3 Hz, H2), 4.39 (1 H, obsc, m, H4), 3.56 (1 H, d, br, $J_{11,10}$ = 5.37 Hz, H11), 2.59 (1 H, dd, $J_{gem}$ = 15.4, $J$ = 7.4 Hz, H3 exo), 2.0–1.7 (3 H, m, allylic $CH_2$ and H7), 1.68 (3 H, br, s, Me), 1.61 (1 H, ddd, $J_{gem}$ = 15.4, $J_{3,4}$ = 5.4, $J_{3,2}$ = 3.0 Hz, H3 endo), 1.5–1.11 (2 H, m), 1.02 (3 H, s, Me), 0.85 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1622.

**Trichodermol (1).** Epoxidation of compound **70** was carried out according to the procedure of Colvin et al.,[4] giving a yield of 65% based on recovered starting material at 66% conversion; IR ($CHCl_3$) $\nu_{max}$ 3580, 2962, 2925, 1680, 1070 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.39 (1 H, dq, $J_{10,11}$ = 5.6, $J_{10,8}$ = 1.5 Hz, H10), 4.33 (1 H, ddd, $J$ = 10.4, $J$ = 7.7, $J$ = 3.1 Hz, H4 endo), 3.83 (1 H, d, $J_{2,3}$ = 5.4 Hz, H2), 3.51 (1 H, d, br, $J_{11,10}$ = 5.3 Hz, H11), 3.10 (1 H, d, $J$

= 3.9 Hz, H13), 2.81 (1 H, dd, $J$ = 3.9, 0.62 Hz, H 13'), 2.61 (1 H, dd, $J_{gem}$ = 15.6, $J_{3,4}$ = 7.6 Hz, H3 exo), 2.02-1.97 (2 H, m, allylic $CH_2$), 1.93 (1 H, dd, br, H7), 1.9 (1 H, ddd, $J_{gem}$ = 15.7, $J_{3,2}$ = 5.5, $J_{3,4}$ = 3.2 Hz, H3 endo), 1.7 (3 H, q, $J$ = 0.6 Hz), 1.52 (1 H, m, OH, exch $D_2O$), 1.47-1.40 (1 H, m, 7H exo or endo), 0.88 (3 H, s, Me), 0.8 (3 H, s, Me). High-resolution mass spectrum calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1560. Spectral data for (±)-trichodermol have not been previously reported.

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**Supplementary Material Available:** $^1H$ NMR spectra of compounds **1**, **6**, **7**, **23**, **28**, **37-39**, **54-58**, and **61-70** and $^{13}C$ NMR spectra of **68** (31 pages). Ordering information is given on any current masthead page.

# Asymmetric Synthesis of the (4a*S*,8a*R*,8*S*)-Hydrolilolidone System. A Formal Total Synthesis of Unnatural (+)-Aspidospermine

A. I. Meyers* and Daniel Berney

*Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523*

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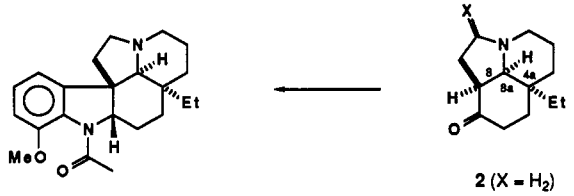
An approach to the aspidosperma alkaloid precursor **15** using chiral, nonracemic bicyclic lactam **3** as starting material is described in 10 steps (8.2% overall).

There have been a number of outstanding efforts over the past 25 years to totally synthesize the *aspidosperma* alkaloids, and the pioneering studies by Stork and Dolfini,[1] along with Ban and co-workers,[2] are particularly noteworthy. These groups were the first to obtain aspidospermine **1** in *racemic* form, whereas Saxton and co-workers[3] completed the racemic total synthesis of a number of C-18-functionalized derivatives. In all of the reported syntheses of the *aspidosperma* alkaloids, the tricyclic hydrolilolidone system (**2** and **15**) has served as a key precursor for the critical Fischer indole synthesis.[4]




**1** **2** (X = $H_2$), **15** (X = O)

Based upon our recent studies with chiral bicyclic lactams of which (+)-**3** is a typical example,[5] we envisioned that under the proper stereochemical control we should be in a position to produce the tricyclic amino ketone **2** or its immediate precursor **15** in nonracemic form. Although this would lead to the unnatural enantiomer of aspidospermine **1**, we felt it would adequately demonstrate our methodology. Our route required that we alkylate (+)-**3** in a sequential manner with ethyl iodide followed by allyl bromide via the enolate.[6] In this manner, we were able to obtain (+)-**4** in 48-50% yield. The ratio of diastereomers was at least 25:1 with the *endo*-allyl isomer as the major component. Transformation to the chiral cyclohexenone **5** was accomplished in 77% yield by Red-Al (Aldrich) treatment followed by mild acidic hydrolysis, as described in earlier reports from this laboratory.[5,7]

The synthetic scheme (see Scheme I) required that the terminal olefin be hydrated to the alcohol, and this was done by treatment of **5** with 9-BBN. The resulting diol **6** was obtained as a 1:1 mixture of diastereomers and was directly oxidized by the Jones reagent to the keto acid **7**, which was isolated in 77% yield for the two steps. A small sample of **7** was transformed into the methyl ester **8** for characterization purposes while the major portion of the material was transformed into the acid chloride **9** using oxalyl chloride. Addition of ammonia gave the amide **10** in 73% yield from the acid.[8]

In order to form the hydroquinolinone system **11**, reported earlier,[2,3] the amide **10** was heated in benzene containing a catalytic amount of *p*-toluenesulfonic acid which produced **11** as a 3:1 mixture of cis-trans isomers. Although these were partially separable, the lackluster ratios demanded another approach before proceeding forward. It was subsequently found that adding ethylene glycol to the mixture of **11** and heating at reflux with the acid catalyst converted the 3:1 mixture to the dioxolane

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(6) The alkylation of (+)-**3** using first allyl bromide and then ethyl iodide also proceeded with equal efficiency (~10:1 crude diastereomeric ratio) to afford the epimer of **4**. Although carrying this through to the enantiomer of **5** would have ultimately given the natural hydrolilolidone system and a formal total synthesis of natural aspidospermine, we elected to proceed with the unnatural series for two reasons: (a) Chromatography would have been necessary to obtain the pure epimer of **4**, rather than simple recrystallization (see the Experimental Section), and we wished to demonstrate that this entire synthetic sequence to **15** could be performed without chromatography. (b) Our belief that a major, but sometimes overlooked, value of asymmetric syntheses is the ability to prepare unnatural materials so their biological properties may be evaluated.
(7) The preparation of **5** has been submitted to *Organic Syntheses* and has been successfully checked. It will appear in a future issue.
(8) Amide **10** was reported by Stork (ref 1) in racemic form.

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