Trichothecene Analogues. Total Synthesis of 12,13-Epoxy-14-methoxytrichothecene via Organoiron Complexes[1]

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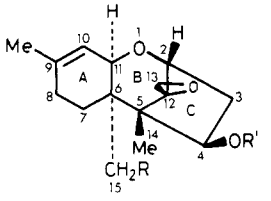
Abstract: The use of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (**4**) as a ring A precursor for 12,13-epoxytrichothecene synthesis is described. Reaction of **4** with methyl 2-oxo-1-potassiocyclopentanecarboxylate gave the diasteromeric complexes **5** and **6**, in quantitative yield. *Both* these isomers were converted to olefin **15**, followed by stereospecific epoxidation to give **16** which was converted to the cyclohexenone **18**. Regio- and stereocontrolled hydrolytic epoxide opening with concomitant Michael cyclization gave the bisnortrichothecane **19** which was converted in five steps to the title trichothecene analogue **25**.

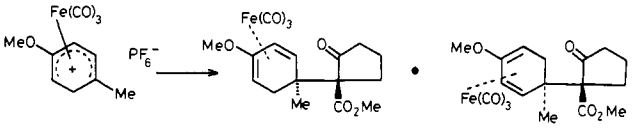
The trichothecenes are a group of tricyclic sesquiterpenes produced by strains of *Fusarium*, *Trichoderma*, *Trichothecium*, and *Myrothecium*, among others, and showing potent antifugal and cytostatic activity.[2] The latter property has led to investigation into their potential antileukemic as well as activity against other tumour types. Typical naturally occurring members of this class of compounds are trichodermol **1**, its derived acetate trichodermin **2**, and verrucarol **3**, which is the 15-hydroxy derivative of trichodermol. Verrucarol and related trichothecenes form the backbone of a number of macrocyclic diesters (roridin and baccharin series) and triesters (verrucarin series) which have evoked much interest as potent antileukemic compounds.[2,3] Unfortunately, these materials are also extremely toxic, so that the development of flexible methods of total synthesis of trichothecenes which produce analogues with modified activity is of considerable interest. Since the 12,13-epoxide is essential for biological activity, any synthetic analogues must incorporate this functionality.[2]



1. R = H, R' = H
2. R = H, R' = Ac
3. R = OH, R' = H

The first total synthesis of trichodermin was reported by Raphael's group in 1971,[4] and there have been numerous other approaches to simple trichothecene derivatives.[5] The Raphael synthesis suffers from the disadvantage of a very low-yielding aldol cyclization to form the five-membered C ring, and this particular step failed completely in their attempted synthesis of verrucarol.[6]

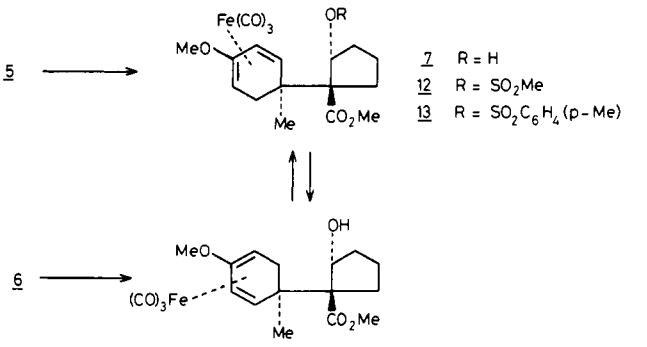
It is therefore of considerable interest to develop synthetic approaches which introduce the C ring intact at an early stage, and the most significant contribution in this respect is the recent synthesis of trichodermol reported by Still.[7] Our own work in this area utilizes our observation that tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate **4** reacts regio- and stereospecifically at the methylated dienyl terminus with a variety of stabilized enolate anions.[8] Reaction with the potassium enolate of methyl 2-oxocyclopentanecarboxylate gives a quantitative yield of the two diastereoisomers **5** and **6**, thus leading to the controlled formation of two contiguous quaternary centers.[9] We now describe the stereocontrolled conversion of *both* of these diasteriosomers to 12,13-epoxytrichothecenes of potential pharmacological interest. Our route also illustrates the usefulness of the $Fe(CO)_3$ group as a diene and dienol ether protection during a number of useful chemical transformations.



4 5 6

Results and Discussion

In these studies our first task was to introduce the C-2 oxygen functionality (trichothecene numbering) in a stereocontrolled fashion onto the most hindered side of the five-membered ring. It appeared likely that this result might be achieved by hydrolysis of an appropriate 2,12-epoxide. To this end the keto ester **5** was



7 R = H
12 R = SO_2Me
13 R = $SO_2C_6H_4$(p-Me)

8

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(6) E. W. Colvin, S. Malchenko, R. A. Raphael, and J. S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 658 (1978).
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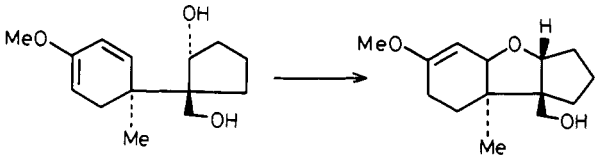
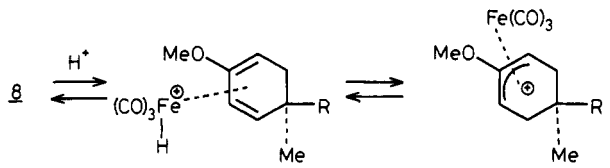
subjected to sodium borohydride reduction, which proceeded stereospecifically to give the hydroxy ester **7** in excellent yield. Similar reduction of the keto ester **6** gave hydroxy ester **8**. Note that the tricarbonyliron group serves as a useful dienol ether protection in **7**, since we have earlier found that similar hydroxy compounds lacking this protection, e.g., **9**, undergo extremely facile and irreversible cyclization to give **10**.



9 **10**

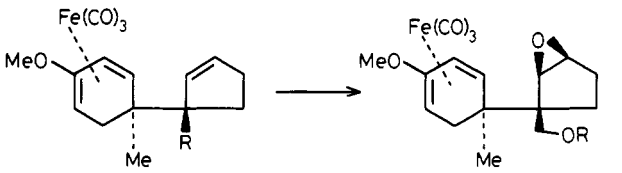
At this point we examined the possibility of converting hydroxy ester **8** to the desired isomer **7**, which possesses the correct stereochemical relationship between the two quaternary centers for trichothecene synthesis. Accordingly, a solution of **8** in dichloromethane was stirred overnight with a catalytic amount of *p*-toluenesulfonic acid, giving rise to a mixture of **7** and **8**, preponderant in **7**, which were readily separated by either fractional crystallization or chromatography (recovery almost quantitative). Thus, it is possible to obtain **7** in yields of at least 80% from the dienylium complex **4**. Very little change in the equilibrium mixture of **7** and **8** was obtained by using different temperatures. This interconversion highlights a useful property of the diene–$Fe(CO)_3$ ring system, since the rearrangement involves initial protonation on the metal, followed by proton transfer to the diene ligand to give the symmetrical allyl complex **11**, which can give either **7** or **8** by reversal of the sequence.[10]



11

Our strategy then required the dehydration of the hydroxy ester **7** to give the alkene derivative **14**. Initially, we examined conversion to mesylate **12**, followed by demesylation on activated alumina.[11] On small scale we were able to obtain **14** from **12** in excellent yields. Similarly, conversion of **7** through the tosylate **13** (obtained in lower yield than the mesylate) followed by base treatment gave moderate yields of **14**. Attempts to repeat these elimination reactions on larger scale gave poor yields.

We next examined the direct dehydration of **7** by using thionyl chloride in pyridine and again obtained the required **14** in good yield on small scale but in lower yield (ca. 40%) on preparative scale due to increased formation of chloride. We eventually discovered that this problem could be overcome by reversing the normal sequence of events; i.e., a solution of the hydroxy ester in pyridine was added slowly to a stirred, cooled solution of thionyl chloride, when the alkene **14** was obtained in satisfactory yields (80%) on a preparative scale, without chloride formation. Reduction of the ester group of **14** was accomplished in excellent yield by treatment with diisobutylaluminum hydride to give the hydroxyalkene **15** which was epoxidized stereospecifically by using the Sharpless procedure[12] to give epoxide **16**, again in excellent yield. We were surprised to find that no decomposition of the iron complex occurred under these oxidizing conditions, since it has been reported that pentacarbonyliron is decomposed upon treatment with *tert*-butyl peroxide.[13]



14 R = CO_2Me
15 R = CH_2OH

16 R = H
17 R = Me
26 R = CH_2OMe
28 R = CHO

For these studies we decided to protect the primary alcohol of **16** as methyl ether **17** (100% yield) and utilize this compound for elaboration to unnatural 12,13-epoxytrichothecenes. Future work will examine alternative groups. The methyl ether **17** was treated with trimethylamine *N*-oxide,[14] followed by mild hydrolysis to give enone **18** (overall yield 60–70%). The hydrolytic cleavage of the epoxide group in **18** was sluggish, requiring 3 days at 45–50 °C and proceeded with concomitant Michael cyclization of the newly formed C-2 hydroxy group to give the tricyclic intermediate **19**, similar to the observations of Still.[7] The NMR and IR spectra of this compound were consistent with the proposed structure, and examination of Dreiding models indicates that the β-hydroxyl produced at C-12 (trichothecene numbering) cannot cyclize onto the enone, so that there is only one possible course for this reaction to take. The subsequent steps were similar to Still's approach.[7] Thus, treatment with methyllithium afforded the tertiary alcohol **20**, which was oxidized to the 12-keto derivative **21**. Both these compounds gave 400-MHz NMR spectra in agreement with the proposed structures (see Experimental Section). Treatment of **21** with phosphorus oxychloride in pyridine afforded two olefinic compounds **22** and **23** in a ratio of 5:1 (95% yield). These were inseparable by chromatography, and we were unable to achieve crystallization, but the NMR spectrum indicated the major compound to be the desired double bond isomer **22**, since this shows a doublet (J = 5.5 Hz) at δ 5.37 characteristic of 10-H of trichothecene derivatives.[4] Infrared spectral data, showing the C=C stretch at the usual frequency of 1675 cm^{-1} confirms this.[4] We have tentatively assigned the structure shown for **23** but were unable to distinguish between this and the alternative endocyclic double-bond isomer on the basis of our data. Methylenation of the 12-keto group of **22** was accomplished in 55% yield under normal Wittig conditions, to give the 14-methoxytrichothecene derivative **24**, which now required epoxidation of the 12,13 double bond for completion of our first objective. This was readily achieved by using *m*-chloroperbenzoic acid (disodium hydrogen phosphate buffer) for a controlled reaction time. The reaction was followed by thin-layer chromatography until the diepoxide began to appear (6 h) and was then worked up and chromatographed to give pure 12,13-epoxy-14-methoxytrichothecene **25**, characterized spectroscopically.

We have performed some preliminary experiments on using alternative protecting groups for the primary alcohol group of the epoxide complex **16**. The methoxymethyl ether **26** was readily prepared in quantitative yield under the usual conditions.[15] In our earlier studies we attempted to effect epoxide opening of this compound by using sodium formate in neat formic acid. We were surprised to find that no deprotection of the ether occurred to regenerate alcohol **16**. A single compound was produced in 70% yield which had lost the methoxy group at δ 3.32 in the NMR spectrum corresponding to the methoxymethyl ether, but retained the characteristic methylene singlet at δ 4.12, and showed the presence of a formate ester (IR, NMR). We initially assigned

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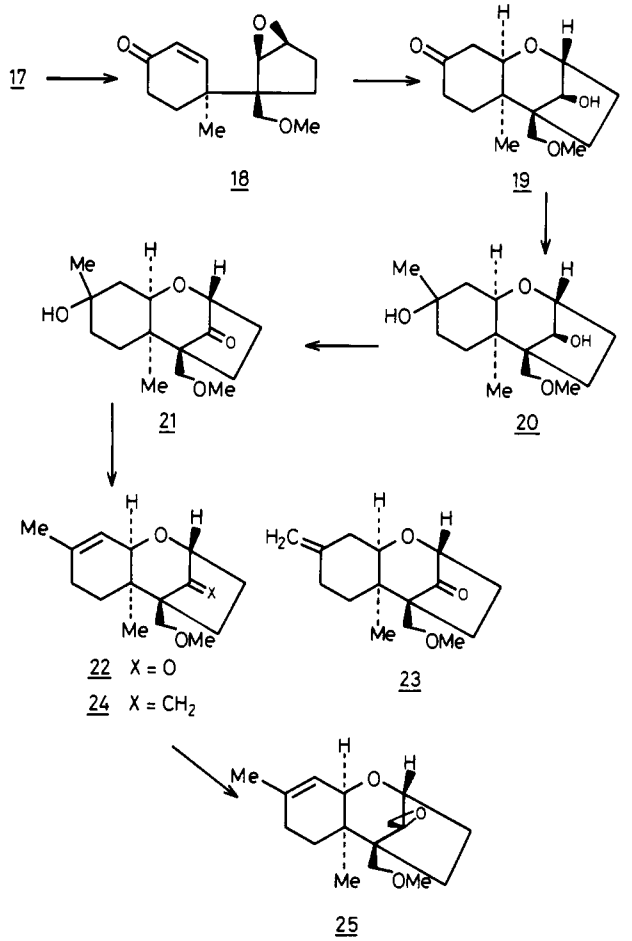
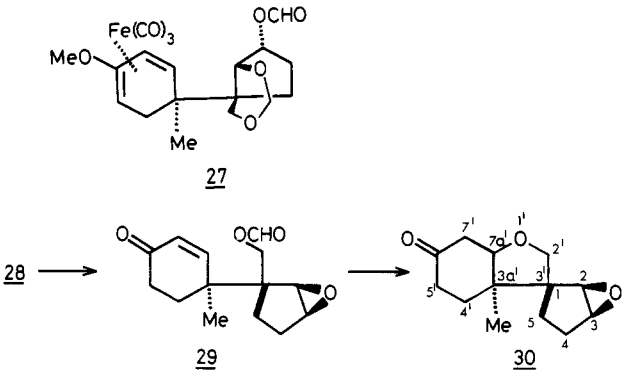


the incorrect structure **27** to this compound.[16] Reexamination of our data revealed that this product in fact has the structure **28**. Hydrolysis of the formate gave the starting material **16**.

It appears most likely that **28** arises by slow deprotection of the methoxymethyl ether **26** to give the alcohol **16**, which is then converted to formate by slightly more rapid esterification under these reaction conditions.

Removal of iron from **28** followed by mild acidic hydrolysis gave the cyclohexenone **29**, and subsequent hydrolysis of the ester occurred with concomitant Michael cyclization of the primary alcohol to give **30**. The facility with which this cyclization occurs indicates the need for protection of the primary alcohol moiety during the construction of the bisnortrichothecane intermediates such as **19** and also the usefulness of performing the operations involved in the presence of the tricarbonyliron group.



Conclusions

We have achieved a stereocontrolled total synthesis of a 12,13-epoxytrichothecene analogue having oxygenation at C-14. The biological properties of this compound are under investigation and will be reported elsewhere. This, together with our other work,[17] including our recent approach to steroid total synthesis,[18] constitutes the first applications of tricarbonyl(dienylium)iron complexes to target-orientated organic synthesis. We note here that the starting material for our work, **4**, has been prepared in optically active form by Birch and co-workers,[19] so that our work may be regarded as potential asymmetric synthesis.

Experimental Section

IR spectra were determined with a Perkin-Elmer 577, mass spectra with A.E.I. MS12 (organometallics) or MS30 (organic compounds), and ^{1}H NMR spectra with Varian EM 390, CFT 20, or Bruker WH 400 (400-MHz) machines. Melting points are uncorrected. All chromatographic operations with iron complexes were conducted under an atmosphere of nitrogen. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone under nitrogen, pyridine was distilled from barium oxide, and dichloromethane was distilled from calcium hydride.

Tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron Hexafluorophosphate (4). Improved Synthesis. Since previous preparations of this compound have been relatively low yielding due to formation of mixtures during the treatment of 1-methoxy-4-methylcyclohexa-2,5-diene with pentacarbonyliron,[20] we investigated a route which gives a single complex. Birch reduction of *p*-methylanisole gave the unconjugated diene which was treated with a catalytic amount of *p*-toluenesulfonic acid (100 mg/100 g diene) at 80 °C under nitrogen for 2 h, followed by distillation to give the equilibrium mixture of 1,4-diene and 1-methoxy-4-methylcyclohexa-1,3-diene (1:3, 93% recovery). This mixture (93.0 g) was stirred with pentacarbonyliron (250 mL) in di-*n*-butyl ether (700 mL) under reflux and nitrogen atmosphere for 48 h (efficient stirring is essential for good yields). The reaction mixture was cooled and filtered through celite, and solvent and excess pentacarbonyliron were removed on the rotary evaporator, to give crude tricarbonyl(1-methoxy-4-methylcyclohexa-1,3-diene)iron (140 g, 58%), which was sufficiently pure for the next step. Treatment with triphenylmethylium tetrafluoroborate (190 g) in dichloromethane (1.5 l) at room temperature for 1 h, followed by evaporation of most of the solvent and precipitation with wet ether give tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron tetrafluoroborate which was converted to the hexafluorophosphate **4** as previously described[8] (yield 184 g, (82%)).

Tricarbonyl[methyl 1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2α-hydroxycyclopentanecarboxylate]iron Diastereoisomers 7 and 8. The pure keto ester complex **5** (10.0 g), from our previous studies,[9] was dissolved in methanol (400 mL) and stirred at 0 °C under nitrogen while sodium borohydride (3.5 g) was added. After 1.5 h, the reaction mixture was poured into water (2 L) and the product extracted with ether in the usual way to afford the pure hydroxy ester **7** as a pale yellow crystalline solid (10.0 g): mp 118–119 °C (from hexane); ν_{max} ($CHCl_3$) 3620, 3600–3300, 2052, 1977, 1719, 1489 cm^{-1}; δ ($CDCl_3$) 5.01 (1 H, dd, J = 6.5, 2.5 Hz, 3-H), 4.54 (1 H, br, C*H*OH), 3.71 (3 H, s, CO_2Me), 3.66 (3 H, s, OMe), 3.30 (1 H, m, 5-H), 2.54 (1 H, dd, J = 16, 3.5 Hz, 6-H), 2.09 (1 H, d, J = 6.5 Hz, 2-H), 2.30 (1 H, m), 1.6 (6 H, m) (3 × CH_2 and OH exchange D_2O), 1.45 (1 H, dd, J = 16, 2.5 Hz, 6-H), 1.33 (3 H, s, Me); *m/e* (%) 406 (15), 378 (27), 350 (5), 322 (45), 304 (100). (Anal. Calcd for $C_{18}H_{22}FeO_7$: C, 53.22; H, 5.46. Found: C, 52.97; H, 5.40.) Identical treatment of keto ester **6** gave the hydroxy ester **8**: mp 103–104 °C (from ether–pentane); ν_{max} ($CHCl_3$) 3610, 3500 (br), 2050, 1970, 1714, 1485 cm^{-1}; δ ($CDCl_3$) 5.10 (1 H, dd, J = 6, 2 Hz, 3-H), 4.55 (1 H, br, C*H*OH), 3.68 (3 H, s), 3.66 (3 H, s), 3.28 (1 H, m, 5-H), 2.59 (1 H, d, J = 6 Hz, 2-H), 2.59 (1 H, dd, J = 15, 3 Hz, endo-6-H), 2.38–2.10 and 2.00–1.46 (6 H, m, 3 × CH_2), 1.44 (1 H, dd, J = 15, 3 Hz, exo-6-H), 1.52 (1 H, s, OH, exchange D_2O), 1.18 (3 H, s, Me). (Anal. Calcd for $C_{18}H_{22}FeO_7$: C, 53.22; H, 5.46; M_r 322.0867. Found: C, 53.02; H, 5.38; M_r 322.0841.)

Conversion of Hydroxy Ester 8 to Mixture of 7 and 8. A solution of the hydroxy ester **8** (7.2 g) and *p*-toluenesulfonic acid (0.10 g) in dichloromethane (350 mL) was allowed to stand at room temperature

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under nitrogen for 48 h. The solution was washed with aqueous sodium hydrogen carbonate and water and dried ($MgSO_4$) and solvent removed to give a mixture of **7** and **8** (7.0 g, 97% recovery). Recrsytallization from hexane afforded 95% pure **7** (4.5 g). The liquors could be evaporated to give **8** which can be reconverted to the mixture.

Tricarbonyl[methyl 1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2α-(methanesulfonyloxy)cyclopentanecarboxylate]iron (12). The hydroxy ester **7** (3.5 g) was dissolved in pyridine (56 mL) and stirred at 0 °C under nitrogen while methanesulfonyl chloride (5.3 mL) was added dropwise, maintaining the temperature of the reaction mixture below 4 °C. This temperature was maintained for 24 h, and the reaction mixture was poured into stirred ice-cold water. Ether extraction, followed by washing with 10% aqueous hydrochloric acid, water, aqueous sodium hydrogen carbonate, and water and drying ($MgSO_4$) afforded, after removal of solvent, the crude *mesylate* (4.14 g), obtained from pentane as white crystals (3.47 g (84%)): mp 128–129 °C; ν_{max} ($CHCl_3$) 2040, 1960, 1715, 1490, 1340, 1170 cm^{-1}; δ ($CDCl_3$) 5.52 (1 H, br, C*H*OMs), 5.00 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.70 (3 H, s), 3.62 (3 H, s), 3.27 (1 H, m, 5-H), 3.00 (3 H, s, OSO_2Me), 2.00 (1 H, d, *J* = 5 Hz, 2-H), 2.60–1.40 (8 H, m), 1.27 (3 H, s, Me); M^+ 484. (Anal. Calcd for $C_{19}H_{24}FeO_4S$: C, 47.52; H, 5.00. Found: C, 47.12; H, 5.00.)

Tricarbonyl[methyl 1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-2α-(4-toluenesulfonyloxy)cyclopentanecarboxylate]iron (13). To a solution of hydroxy ester **7** (0.15 g) in pyridine (1 mL) at 0 °C was added *p*-toluenesulfonyl chloride (0.15 g). The reaction mixture was set aside at 0 C for 30 h, and worked up as for the mesylate above, to afford the crude *tosylate* which was subjected to preparative layer chromatography to give recovered **7** (65%) and the tosylate **13** (30%). Use of extended reaction times did not lead to improvements in yield on the basis of reacted **7**, since the product was prone to elimination and decomposition. The pure tosylate gave a melting point of 124–126 °C: ν_{max} ($CHCl_3$) 2050, 1975, 1600, 1485, 1370, 1172 cm^{-1}; δ ($CDCl_3$) 7.50 (4 H, m), 5.35 (1 H, m, C*H*OTs), 4.95 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.71 (3 H, s), 3.62 (3 H, s), 3.25 (1 H, m, 5-H), 2.50 (3 H, s), 2.30–1.30 (9 H, m), 1.15 (3 H, s). This compound was unstable and was used directly for the next step.

Tricarbonyl[methyl 1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopent-2-enecarboxylate]iron (14). (a) From Hydroxy Ester 7. Thionyl chloride (1.35 mL, freshly distilled) was stirred briskly in pyridine (37.5 mL) at 0 °C under nitrogen, while a solution of complex **7** (3.0 g) in pyridine (37.5 mL) was added dropwise over a period of 4 h. Stirring was continued at 0 °C for 24 h, after which time a further quantity of thionyl chloride (1.35 mL) in pyridine (10 mL) was added dropwise. After a further 6 h at 0 °C the stirred reaction mixture was allowed to warm slowly to room temperature overnight, after which it was poured onto stirred ice–water, and extracted with ether in the usual way. The extracts were washed with dilute hydrochloric acid, water, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated to give the crude product (2.64 g). Chromatography on silica gel afforded unreacted hydroxy ester (1.4 g) which was recycled and the alkene derivative **14** (1.19 g, 80% based on reacted starting material) as pale yellow crystals: mp 74.5–76 °C; ν_{max} ($CHCl_3$) 2060, 1940, 1715, 1620, 1490 cm^{-1}; δ ($CDCl_3$) 5.72 (2 H, m), 4.95 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.62 (3 H, s), 3.58 (3 H, s), 3.20 (1 H, m, 5-H), 2.38 (1 H, d, *J* = 6.5 Hz, 2-H), 2.35–1.6 (5 H), 1.40 (1 H, dd, *J* = 15, 2.5 Hz, exo-6-H), 1.00 (3 H, s). (Anal. Calcd for $C_{18}H_{20}FeO_6$: C, 55.69; H, 5.20; M_r 388.0610. Found: C, 55.49; H, 5.30; M_r 388.0596.)

(b) From Mesylate 12. Neutral alumina (Woelm, grade I, 12.5 g) was placed in a Pyrex flask and heated at 350 °C under high vacuum for 6 h. After the solid alumina had cooled to room temperature, the mesylate **12** (0.55 g) in dichloromethane (25 mL) was added and the slurry was stirred under nitrogen for 2 h. The mixture was filtered and the alumina was washed several times with ether. The combined extracts were evaporated to give the pure complex **14**, identical with that prepared above (0.42 g (95%)).

(c) From Tosylate 13. The tosylate **13** (50 mg) dissolved in dry dimethyl sulfoxide (Me_2SO, 3 mL) was added to a solution of potassium *tert*-butoxide (28 mg) in Me_2SO (2 mL) under nitrogen. The solution was stirred at room temperature for 3 h, poured into water, and extracted with ether in the usual way. The crude produce was subjected to preparative TLC to give pure complex **14** (21 mg (60%)).

Tricarbonyl[1-(hydroxymethyl)-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopent-2-ene]iron (15). The ester complex **14** (2.4 g) was stirred in THF (20 mL) under nitrogen at −78 °C while diisobutylaluminum hydride (20 mL, 1 M solution in hexane) was added via a rubber septum. The stirred mixture was allowed to attain room temperature overnight and worked up by addition of ethanol (20 mL) followed by water (20 mL). After being stirred for 0.5 h, the mixture was filtered through celite and the filter cake washed with ether. The extracts were washed with water, dried ($MgSO_4$), and evaporated to give the pure *alcohol* **15** as pale yellow crystals: mp 76.5–78 °C (2.12 g (95%)); ν_{max} ($CHCl_3$) 3580, 3450 (br), 2050, 1970, 1610, 1485 cm^{-1}; δ ($CDCl_3$) 6.00 (1 H, m, =CH), 5.35 (1 H, m, =CH), 5.06 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.65 (3 H, s), 3.45 (2 H, ABq, CH_2OH), 3.28 (1 H, m, 5-H), 2.45 (1 H, d, *J* = 6.5 Hz, 2-H), 2.35 (2 H, m), 1.98 (1 H, dd, *J* = 15, 3.5 Hz, endo-6-H), 1.8 (3 H, m), 1.43 (1 H, dd, *J* = 15, 3 Hz, exo-6-H) 1.10 (3 H, s). (Anal. Calcd for $C_{17}H_{20}FeO_5$: C, 56.69; H, 5.60; M_r 360.0660. Found: C, 56.80; H, 5.72; M_r 360.0678.)

Tricarbonyl[1β-(hydroxymethyl)-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopentene 2,3β-oxide]iron (16). The hydroxyalkene complex **15** (1.5 g) was stirred in dry benzene (60 mL) under nitrogen at 50 °C while bis(acetylacetonyl)vanadium oxide [$VO(acac)_2$] (0.08 g) was added in one portion. Anhydrous *tert*-butyl hydroperoxide (0.70 mL) was added, and the mixture was stirred for a further 45 min at 50 °C. Removal of vanadium complex by washing through a short column of basic alumina with ether, followed by removal of solvent, afforded the pure crystalline complex **16**: mp 105–107 °C; ν_{max} ($CHCl_3$) 3520, 2050, 1980, 1485, 845 cm^{-1}; δ ($CDCl_3$) 5.00 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.85 (1 H, br, d, *J* = 10 Hz, epoxide), 3.60 (3 H, s) 3.55 (2 H, br, CH_2OH), 3.30 (1 H, m, 5-H), 3.18 (1 H, d, *J* = 1.5 Hz, epoxide), 2.28 (1 H, d, *J* = 6.5 Hz, 2-H), 2.20 (1 H, dd, *J* = 15, 3 Hz, endo-6-H), 2.1–1.3 (6 H), 1.00 (3 H, s). (Anal. Calcd for $C_{17}H_{20}FeO_6$: C, 54.28; H, 5.36; M_r 376. Found: C, 54.42; H, 5.38; M_r 376.)

Tricarbonyl[1β-(methoxymethyl)-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopentene 2,3β-oxide]iron (17). The epoxy alcohol derivative **16** (4.00 g) in THF (80 mL) was added via a rubber septum to a stirred suspension of sodium hydride (0.606 g, from dispersion in mineral, washed with pentane) in THF (10 mL). Methyl iodide (14 mL) was added and the mixture was stirred at room temperature for 16 h. Excess sodium hydride was destroyed by addition of wet ether (200 mL). The ether extract was washed three times with water, dried ($MgSO_4$), and evaporated to yield the pure complex **17**: mp 81–83 °C; ν_{max} ($CHCl_3$) 2050, 1970, 1485, 1090, 850 cm^{-1}; δ ($CDCl_3$) 4.98 (1 H, dd, *J* = 6.5, 2.5 Hz, 3-H), 3.61 (1 H, m, obscured, epoxide), 3.60 (3 H, s), 3.31 (2 H, br, obscured, CH_2OMe), 3.24 (4 H, s, OMe and 5-H), 3.09 (1 H, d, *J* = 1.0 Hz, epoxide), 2.48 (1 H, dd, *J* = 15, 3 Hz, endo-6-H), 2.33 (1 H, d, *J* = 6.5 Hz, 2-H), 1.6–1.3 (4 H), 1.5 (1 H, dd, *J* = 15, 3.5 Hz, exo-6-H), 1.00 (3 H, s). (Anal. Calcd for $C_{18}H_{22}FeO_6$: C, 55.40, H, 5.68%; M_r 390. Found: C, 55.56; H, 5.57; M_r 390.)

1β-(Methoxymethyl)-1-(1-methyl-4-oxocyclohex-2-enyl)cyclopentene 2,3β-oxide (18). The complex **17** (4.0 g) was stirred in benzene (200 mL) at 50 °C with anhydrous trimethylamine *N*-oxide (34 g) for 2.5 h. The mixture was cooled and filtered through celite, and the cake washed well with ether. The combined extracts were washed with water and brine and dried ($MgSO_4$). Removal of solvent afforded crude dienol ether as a semisolid (2.4 g, 93%). This compound (2.0 g) was dissolved in methanol (100 mL) and the solution stirred at 0 °C while a solution of oxalic acid (4.5 g) in water (25 mL) was added. Stirring was continued at 0 °C for 1 h, and the mixture was poured into sodium hydrogen carbonate solution and extracted with ether in the usual way to give the pure white crystalline enone **18**: mp 71–72 °C (1.3–1.5 g (65–75%)); ν_{max} (CCl_4), 1685, 1470, 1400, 860 cm^{-1}; δ ($CDCl_3$) 7.09 (1 H, dd, *J* = 10.5, 1.5 Hz), 5.82 (1 H, d, *J* = 10.5 Hz), 3.56–3.22 (4 H, m, CH_2–O and epoxide), 3.26 (3 H, s), 2.44–1.31 (8 H), 1.22 (3 H, S). (Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53; M_r 236. Found: C, 71.00; H, 8.29; M_r 236.)

12β-Hydroxy-14-methoxy-9-oxo-13,16-bisnortrichothecane (19). The enone **18** (0.50 g) was dissolved in acetone (100 mL), and 2% aqueous sulfuric acid (100 mL) was added. the reaction mixture was stirred at 50 °C under nitrogen for 72 h. Aqueous workup and chloroform extraction followed by recrystallization (pentane–carbon tetrachloride) afforded the white crystalline trichothecane **19** (0.35 g (65%)): mp 133.5–135 °C; ν_{max} ($CHCl_3$) 3660, 3440, 1715, 1400, 1090 cm^{-1}; δ ($CDCl_3$) 4.37 (1 H, br, s, 2-H), 4.18 (1 H, m, 11-H), 3.85 (1 H, s, 12-H), 3.78 and 3.58 (2 H, ABq, J_{AB} = 10 Hz, CH_2OMe), 3.36 (3 H, s), 3.37 (1 H, obscured, exchange D_2O, OH), 2.55–1.15 (10 H), 1.09 (3 H, s). (Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72; M_r 254. Found: C, 65.87; H, 8.79; M_r 254.)

9,12-Dihydroxy-14-methoxy-13-nortrichothecane (20). To a stirred solution of ketone **19** (0.35 g) in THF (50 mL) under nitrogen at −20 °C was added methyllithium (1.6 M solution in ether, 11 mL). The reaction mixture was allowed to reach 0 °C over 2 h, and excess methyllithium was destroyed with wet ether. Most of the solvent was evaporated and the product was taken up in ethyl acetate, washed with water and brine, dried ($MgSO_4$), and evaporated to give the diol **20** as white crystals: mp 125–127 °C (0.35 g (94%)); ν_{max} ($CHCl_3$) 3640, 3450 cm^{-1}; δ ($CDCl_3$, 400 MHz), 4.50 (1 H, s, 2-H), 4.17 (1 H, d, *J* = 4.5 Hz, 11-H), 3.82 (1 H, d, *J* = 9 Hz) and 3.56 (1 H, d, *J* = 9 Hz) (CH_2OMe), 3.58 (1 H, s, 12-H), 3.35 (3 H, s), 2.27 (1 H, td, *J* = 14, 4.5 Hz), 2.11 (1 H, tt, *J* = 13, 4.5 Hz, 10-H), 1.97 (1 H, td, *J* = 12, 3

Hz), 1.68 (3 H, m), 1.58 (1 H, d, J = 16.5 Hz), 1.41 (1 H, td, J = 14, 4.5 Hz), 1.26 (1 H, d, J = 16.5 Hz), 1.13 (3 H, s), 0.86 (3 H, s). Irradiation of the doublet at δ 4.17 caused collapse of the triplet of triplets at δ 2.11 to a triplet of doublets. No further assignments of methylene protons has been attempted. (Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69; M - H_2O, 252.1725. Found: C, 66.52; H, 9.52; M - H_2O, 252.1717.)

9-Hydroxy-14-methoxy-12-oxo-13-nortrichothecane (21). Pyridine (1.71 mL) was stirred in dichloromethane (30 mL) while chromium trioxide (1.056 g, dried in vacuo over phosphorus pentoxide) was added. The mixture was stirred for 0.5 h, and the diol **20** (0.35 g) in dichloromethane (12 mL) was added. Stirring was continued for 0.5 h, the mixture allowed to settle, and the supernatant decanted. The residue was washed three times with dichloromethane and solvent removed from the combined extracts. The product was taken up in ethyl acetate, filtered, washed with cold dilute hydrochloric acid, aqueous sodium hydrogen carbonate, brine, and dried ($MgSO_4$). Evaporation of solvent afforded the pure ketone **21**: mp 89–91 °C (0.275 g (79%)); ν_{max} ($CHCl_3$) 3650, 3500, 1750 cm^{-1}; δ ($CDCl_3$, 400 MHz) 4.02 (1 H, s, 2-H), 3.88 (1 H, d, J = 5.5 Hz, 11-H), 3.59 and 3.39 (1 H, d, each, J = 12 Hz, CH_2OMe), 3.33 (3 H, s), 2.15–1.70 (8 H, complex), 1.62 (1 H, dm, J = 9 Hz), 1.43 (1 H, td, J = 18, 5.5 Hz), 1.37 (1 H, dm, J = 9 Hz), 1.14 (3 H, s), 0.95 (3 H, s). Irradiation of the doublet at δ 3.88 caused simplification of a signal at δ 1.87. (Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; M_r 268.1675. Found: C, 67.34; H, 9.18; M_r 268.1663.)

14-Methoxy-12-oxo-13-nortrichothec-9-ene (22). To a stirred solution of the keto alcohol **21** (0.100 g) in pyridine (11.2 mL) at 0 °C was added dropwisee phosphorus oxychloride (0.7 mL, 20 equiv). The reaction mixture was stirred overnight, allowing it to reach room temperature. Excess phosphorus oxychloride was destroyed by cooling the mixture to −78 °C, adding water to it dropwise, and allowing it to warm slowly to room temperature. Extraction with ethyl acetate, followed by washing with dilute hydrochloric acid, aqueous sodium hydrogen carbonate, and brine and drying ($MgSO_4$), gave the crude product which was purified by preparative layer chromatography to give an oil (0.089 g (95%)) shown to be a 5:1 mixture of **22** and **23** (NMR) inseparable on TLC: ν_{max} ($CHCl_3$) 1750, 1675 cm^{-1}; δ ($CDCl_3$, 80 MHz) for **22** 5.40 (1 H, d, J = 5.5 Hz, 10-H), 3.97 (1 H, d, J = 5.5 Hz, 11-H), 3.80 (1 H, d, J = 4 Hz, 2-H), 3.61 and 3.37 (1 H, d, ea, ABq, J_{AB} = 9.5 Hz, CH_2OMe), 3.31 (3 H, s), 2.2–1.75 (8 H), 1.68 (3 H, br, s, MeC=C), 0.88 (3 H, s). (Anal. Calcd for $C_{15}H_{22}O_3$: M_r 250.1569. Found: M_r 250.1567.)

14-Methoxytrichotheca-9,12-diene (24). Triphenylphosphonium bromide (165.5 mg) was stirred in THF (5 mL) under nitrogen while n-butyllithium (0.29 mL, 15% w/w in hexane) was added. Stirring was continued for 30 min, and the mixture of **22** and **23** from above (89 mg) in THF was added. The mixture was heated at reflux for 8 h. Aqueous workup and ethyl acetate extraction afforded the crude product. Separation of the two isomers (from **22** and **23**) was achieved at this stage by PLC (silica gel, 20% ethyl acetate in light petroleum) to give the trichothecene **24** (40 mg (55%)) as a colorless oil: ν_{max} ($CHCl_3$) 1670, 1600 cm^{-1}; δ ($CDCl_3$) 5.34 (1 H, d, J = 5.5 Hz, 10-H), 5.06 (1 H, d, J = 0.7 Hz, =CH_2), 4.63 (1 H, d, J = 0.7 Hz, =CH_2), 4.29 (1 Hz, br, s, 2-H), 3.72 (1 H, d, J = 5.5 Hz, 11-H), 3.51 (2 H, s, CH_2OMe), 3.33 (3 H, s), 2.04–0.88 (8 H), 1.67 (3 H, s), 0.86 (3 H, s). (Anal. Calcd for $C_{16}H_{24}O_2$: M_r 248.1777. Found: M_r 248.1769.)

12,13-Epoxy-14-methoxytrichothecene (25). A mixture of the diene **24** (38 mg), *m*-chloroperbenzoic acid (41.7 mg), and disodium hydrogen phosphate (231 mg) in dichloromethane (25 mL) was stirred at room temperature for 6 h. The reaction mixture was diluted with dichloromethane (25 mL) and washed with ice-cold aqueous sodium hydrogen carbonate followed by brine and the organic layer dried ($MgSO_4$). Evaporation to dryness, followed by preparative layer chromatography, afforded the product **25** as white crystals: mp 69–70 °C (14 mg (38%)); ν_{max} (CCl_4) 1680, 1400, 1120, 1060, 990 cm^{-1}; δ ($CDCl_3$, 400 MHz) 5.39 (1 H, d, J = 4.9 Hz, 10-H), 3.68 (1 H, d, J = 4.9 Hz, 11-H), 3.67 (1 H, d, J = 5.4 Hz, 2-H), 3.34 and 3.30 (1H, d, each, J_{AB} = 9.5 Hz, CH_2OMe), 3.20 (3 H, s), 3.15 (2 H, close AB_q, J_{AB} = 4 Hz, epoxide), 2.03–1.5 (8 H), 1.69 (3 *H*, s, =CMe), 0.89 (3 H, s). (Anal. Calcd for $C_{16}H_{24}O_3$: M_r 264.1725. Found: M_r 264.1714.)

Tricarbonyl[1-(2-5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)-1-(((methoxymethylene)oxy)methyl)cyclopentene 2,3-oxide]iron (26). The epoxy alcohol complex **16** (1.32 g) was refluxed under nitrogen in dichloromethane (100 mL) with chloromethyl methyl ether (1.94 mL) and diisopropylethylamine (3.08 mL) for 5 h. The mixture was cooled, washed with water, dried ($MgSO_4$), and evaporated to give the crude methoxymethyl ether, purified chromatographically to give a yellow oil (1.58 g (100%)): ν_{max} ($CHCl_3$) 2050, 1970, 1490, 850 cm^{-1}; δ ($CDCl_3$) 4.95 (1 H, dd, J = 6.5, 2.5 Hz), 4.51 (2 H, s), 3.61 (1 H epoxide), 3.59 (3 H, s), 3.43 (2 H, s, CH_2O–), 3.53 (1 H, m, 5-H), 3.32 (3 H, s), 3.07 (1 H, d, J = 2.5 Hz, epoxide), 2.30 (1 H, d, J = 6.5 Hz), 2.80–1.10 (6 H), 1.05 (3 H, s); M^+ 420.

Tricarbonyl[1-((formyloxy)methyl)-1-(2–5-η-4-methoxy-1-methylcyclohexa-2,4-dienyl)cyclopentene 2,3-oxide]iron (28). To a stirred solution of sodium formate (288 mg, from sodium carbonate) in formic acid (3 mL) under nitrogen was added the methoxymethyl ether derivative **26** (290 mg). The mixture was stirred at room temperature for 48 h and then poured into stirred ice-cold sodium hydrogen carbonate solution, and the mixture extracted with ether in the usual way. Preparative layer chromatography afforded the complex **28**, as a pale yellow crystalline solid (208 mg (75%)): mp 109–111 °C. ν_{max} ($CHCl_3$) 2050, 1980, 1725, 1480, 850 cm^{-1}; δ ($CDCl_3$) 8.00 (1 H, s, OCHO), 4.95 (1 H, dd, J = 6.5, 2.5 Hz), 4.15 (2 H, s, CH_2O), 3.60 (3 H, s), 3.30 (2 H, m, 5-H and epoxide), 3.07 (1 H, d, J = 2.5 Hz, epoxide), 2.25 (1 H, d, J = 6.5 Hz), 1.43 (1 H, dd, J = 15, 3 Hz), 2.6–1.1 (5 H), 1.00 (3 H, s). (Anal. Calcd for $C_{18}H_{20}FeO_7$: C, 53.50; H, 4.99; M_r 404. Found: C, 53.87; H, 5.38; M_r 404.)

1-((Formyloxy)methyl)-1-(1-methyl-4-oxocyclohex-2-enyl)cyclopentene 2,3-Oxide (29). Removal of iron from **28** using trimethylamine *N*-oxide, followed by dienol ether hydroylsis as described above for the preparation of **18** afforded the enone **29** (0.60 g (87%)) as a colorless oil: ν_{max} ($CHCl_3$) 1725, 1680, 850 cm^{-1}; δ ($CDCl_3$) 8.05 (1 H, s), 7.00 (1 H, dd, J = 10.5, 1.5 Hz), 5.90 (1 H, d, J = 10.5 Hz), 4.35 (2 H, ABq, J = 12 Hz), 3.50 (2 H, m, epoxide), 2.80–1.50 (8 H), 1.22 (3 H, s). (Anal. Calcd for $C_{14}H_{18}O_4$: M_r 250. Found: M_r 250.)

3a′-Methyl-6′-oxospiro[cyclopentane-1,3′-hexahydrobenzofuran] 2,3-Oxide (30). The enone derivative (0.60 g) was dissolved in methanol (15 mL) containing potassium carbonate (0.742 g), and the mixture was stirred at room temperature for 2.75 h. Aqueous workup and chloroform extraction, followed by recrystallization from ether–pentane gave **30** as white crystals: mp 155–156 °C (0.215 g (40%)); ν_{max} ($CHCl_3$) 1720, 855 cm^{-1}; δ ($CDCl_3$) 4.29 (1 H, m, 7a′-H), 4.09 and 3.66 (1 H, d, each, ABq, J_{AB} = 9 Hz, 2′-H_2), 3.58 (1 H, 2-H), 3.41 (1 H, d, J = 2.5 Hz 3-H), 2.54–1.23 (10 H), 1.17 (3 H, s). (Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%; M - H, 221.1178. Found: C, 70.00; H, 8.23; M - H 221.1158.)

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