Organoiron Complexes in Organic Synthesis. Part 4.[1] Direct Ring Connection between Highly Substituted Centres. A Potential Approach to Trichothecane Synthesis

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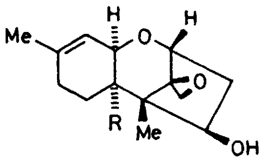
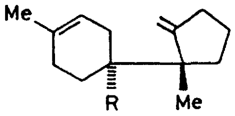
Direct connection of six- and five-membered rings at their most highly substituted positions has been achieved by reaction of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (4) with the potassium enolate of methyl 2-oxocyclopentanecarboxylate. The potential of this reaction in constructing the carbocyclic framework present in trichothecanes is demonstrated. The complex (5) crystallised in the monoclinic space group $P2_1/c$ with a = 11.830(2), b = 6.823(4), c = 22.734(4) Å, β = 102.19(3)°, and Z = 4. The structure was solved by a combination of Patterson and Fourier techniques and refined to R 0.065 for 2 145 unique observed intensities.

THE trichothecanes are a family of polyoxygenated sesquiterpenes showing a number of interesting pharmacological properties,[2] the most common examples being trichodermin (1) and verrucarol (2). The carbon skeleton is shown by (3), which corresponds to the known biosynthetic precursor trichodiene (3; R = Me). These compounds have attracted recent synthetic attention,[3] and most approaches so far reported utilise key intermediates similar to that employed in Raphael's total synthesis of trichodermin [3a] in which the five-membered carbocyclic ring is formed by cyclisation at an advanced stage. This approach failed when applied to verrucarol synthesis,[3b] and an alternative strategy by Musuoka and Kamikawa [3d] by photochemical connection of the ring system has not yet been applied to trichodermin or verrucarol synthesis.



(1) R = Me
(2) R = CH₂OH



(3)

A retrosynthetic analysis of the problem can be envisaged which involves the bond dislocations indicated in Figure 1 (schematic only). An approach using this scheme would require a reversal of polarity at the γ-position of the appropriate cyclohexenone, and this exactly corresponds to the known behaviour of tricarbonyliron derivatives of the 2-methoxycyclohexadienylium cation.[4]

Our current studies in the synthesis of functionalised 4,4-disubstituted cyclohexenones from complexes such as (4) [1,4d-f] suggested an alternative strategy for the construction of the basic unit composed of six- and five-membered rings linked at highly substituted positions. In this approach we envisioned reaction of (4) with the enolate derived from an appropriate oxocyclopentanecarboxylic ester derivative, and the current study on a simple model system using readily available materials was undertaken to derive part of the chemistry required for further transformations. In the first instance we have set out only to determine whether the ester group present in the cyclopentane synthon could be efficiently reduced to methyl, present in the target molecules. This work also reveals some important properties of the intermediates encountered which are useful for future synthetic planning.

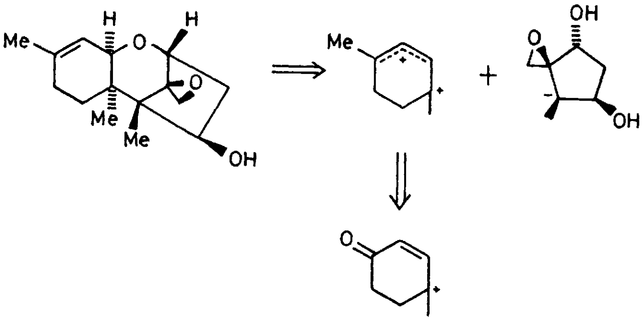
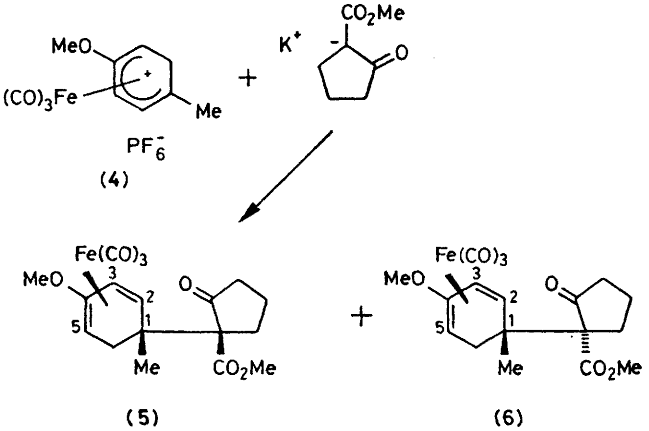


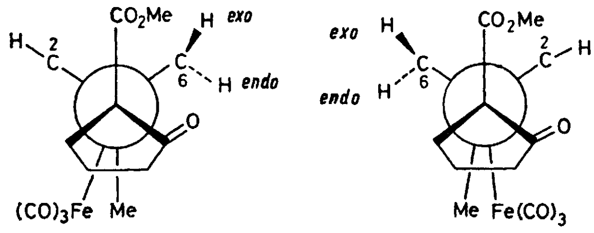
FIGURE 1

RESULTS AND DISCUSSION

Reaction of the hexafluorophosphate salt (4) with the potassium enolate of methyl 2-oxocyclopentanecarboxylate at 0° gave an equimolar mixture of two diastereoisomers (5) and (6) in quantitative yield. Recrystallisation from ether–pentane gave (5) as pale yellow plates, *ca.* 90% pure. Further recrystallisation afforded pure diastereoisomer, this compound being the



more stable of the two. Evaporation of the liquors and recrystallisation gave almost pure (6). The ^{1}H n.m.r. spectra of these two compounds (Experimental), apart from establishing their gross structures by comparison with analogous complexes previously prepared,[1,4d-f] also revealed their stereochemistry. The lower-field doublet of doublets (showing geminal coupling of 16 Hz) corresponding to 6-H was assigned to M-*exo*-6-H, since this proton is expected to project into the deshielding region of one or both carbonyl functions of the β-keto-ester, whilst the M-*endo*-6-H proton projects away from this grouping and is at higher field. This *exo*-6-H signal occurs at lower field for isomer (5) [the resonance for (6) being obscured by the methylene envelope], whilst the high-field *endo*-6-H resonance is approximately the same for both compounds. On the other hand, the doublet corresponding to 2-H is at considerably higher field for (5) than for (6). Inspection of Newman projections for these two molecules, assuming the preferred conformations shown in Figure 2, leads to complete rationalisation of this data. Thus, in (6) 2-H is located in the deshielding region of the ester and ketone groups, whilst in (5) this proton is only influenced by the ester carbonyl. The reverse is true for M-*exo*-5-H, which projects into the deshielding region of both groups in (5) and only the ester group in (6). Since M-*endo*-6-H is remote from this moiety it remains similar for both molecules. [Inspection of the *X*-ray crystal structure of (5) (Figure 3) gives complete support to these arguments.] On this basis, we tentatively assigned the stereochemistry of (5) and (6), and provided the observations of n.m.r. spectra are general, this analysis will be invaluable for future work.



(5) (6)

FIGURE 2

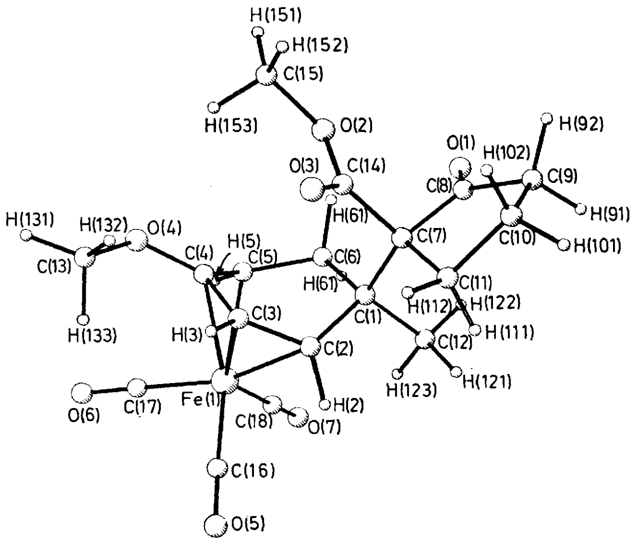


FIGURE 3 PLUTO diagram of compound (5) showing the atom numbering

Description of the Structure.—Molecules of (5) exist in the solid state as neutral, discrete monomers held together only by van der Waals forces. Figure 3 shows the molecular structure and includes the atom numbering scheme adopted, consistent with that used for presentation of the n.m.r. data. Tables 1 and 2 list the inter-bond lengths and angles, respectively.

The iron is co-ordinated to three linear terminal carbonyl groups such that the Fe(CO)$_3$ group has approximate C_{3v} symmetry. The metal is η^4-bound to four of the carbon atoms of the cyclohexadiene ring. This unit is planar and makes an angle of 41.8° with the other fragment of the ring. The axial site on C(7) is occupied by methoxycarbonyl and the C(12)–C(1)–C(7)–C(14) torsion angle is 177.0° (*cf*. Figure 2).

TABLE 1

Bond lengths (Å)

C(16)–Fe(1)	1.777(7)	C(17)–Fe(1)	1.766(8)
C(18)–Fe(1)	1.769(7)	C(5)–Fe(1)	2.105(6)
C(4)–Fe(1)	2.093(5)	C(3)–Fe(1)	2.024(6)
C(2)–Fe(1)	2.073(6)	O(5)–C(16)	1.132(8)
O(6)–C(17)	1.144(9)	O(7)–C(18)	1.151(8)
C(4)–C(5)	1.412(8)	C(6)–C(5)	1.505(9)
C(3)–C(4)	1.390(8)	O(4)–C(4)	1.351(7)
C(2)–C(3)	1.409(8)	C(1)–C(2)	1.529(7)
C(6)–C(1)	1.529(8)	C(12)–C(1)	1.518(8)
C(7)–C(1)	1.580(8)	C(13)–O(4)	1.444(8)
C(11)–C(7)	1.540(8)	C(8)–C(7)	1.538(8)
C(14)–C(7)	1.509(8)	C(10)–C(11)	1.536(10)
C(9)–C(10)	1.518(11)	C(8)–C(9)	1.512(10)
O(1)–C(8)	1.170(7)	O(2)–C(14)	1.329(7)
O(3)–C(14)	1.193(7)	C(15)–O(2)	1.432(7)

Chemical Transformations of (6).—Since the stereochemistry of (6) is that required in the ultimate target molecules (assuming the ketone group would ultimately become an epoxide) we investigated the reduction of the methoxycarbonyl group to methyl, bearing in mind that (a) our ultimate plan is to use a substituted 2-oxocyclopentanecarboxylic ester more closely resembling the five-membered carbocyclic ring of (1) and (2), and (b) any intermediate stages reached during this transformation might serve as useful sources of analogues. We therefore adopted the approach used by Zalkow and Girotra [5] for reduction of similar hindered methyl esters.

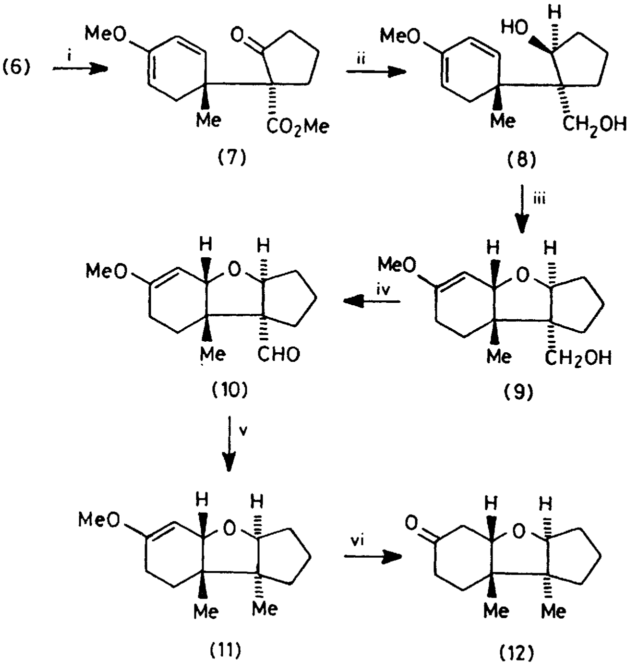
Exposure of (6) to anhydrous trimethylamine *N*-oxide in benzene for 1—2 h at 50° resulted in good yields of (7) containing only a trace of aromatic material.[6] The amount of aromatic material formed in this procedure was found to depend on the quality of amine oxide used, best results being obtained using freshly sublimed material. This compound was subjected to lithium aluminium hydride reduction, and the crude product showed the presence of the expected diol (8) in the n.m.r. spectrum, δ 6.16 (d) and 5.68 (dd), assignable to

2- and 3-H, respectively, together with a second minor component, δ 4.75 (d). Standing in chloroform, or chromatography on Florisil with chloroform, resulted in exclusive formation of this second compound as a crystalline solid in high overall yield, to which was assigned the cyclised structure (9) on the basis of the following considerations. [An analogous cyclised compound was also formed on reduction of the monoacetal derived from the dienol ether of (6), showing this cyclisation to be exceedingly facile.] The single vinyl ether proton occurred as a doublet at δ 4.79, with the methoxy-singlet at δ 3.60 surrounded by an envelope of four protons α to oxygen. Irradiation at δ 4.79 caused modification in the region centred at δ 4.25, and irradiation at this point caused the vinyl ether signal to collapse to a singlet. The i.r. spectrum showed reduced OH stretching intensity compared with (8), and the only C=C stretching frequency was that due to the vinyl ether group at 1 665 cm^{-1}. Oxidation of (9) by the Sarett procedure [5] gave the aldehyde (10). The stereochemistry of (9) and (10) were assumed on the basis that reduction of the ketone would occur at the least hindered face, *cis* to the ester, whilst ring closure would preferentially lead to a *cis*-ring junction.[7] In this particular study the cyclisation was used as a means of protecting the secondary OH whilst manipulating the primary OH group.

TABLE 2

Bond angles (°)

C(17)–Fe(1)–C(16)	92.1(3)	C(18)–Fe(1)–C(16)	99.4(3)
C(18)–Fe(1)–C(17)	98.1(3)	C(5)–Fe(1)–C(16)	165.6(3)
C(5)–Fe(1)–C(17)	97.5(3)	C(5)–Fe(1)–C(18)	89.9(3)
C(4)–Fe(1)–C(16)	130.0(3)	C(4)–Fe(1)–C(17)	92.2(3)
C(4)–Fe(1)–C(18)	129.1(3)	C(4)–Fe(1)–C(5)	39.3(2)
C(3)–Fe(1)–C(16)	96.5(3)	C(3)–Fe(1)–C(17)	117.3(3)
C(3)–Fe(1)–C(18)	140.4(3)	C(3)–Fe(1)–C(5)	69.6(2)
C(3)–Fe(1)–C(4)	39.4(2)	C(2)–Fe(1)–C(16)	91.5(3)
C(2)–Fe(1)–C(17)	157.5(3)	C(2)–Fe(1)–C(18)	103.2(3)
C(2)–Fe(1)–C(5)	75.6(2)	C(2)–Fe(1)–C(4)	68.8(2)
C(2)–Fe(1)–C(3)	40.2(2)	O(5)–C(16)–Fe(1)	178.0(7)
O(6)–C(17)–Fe(1)	179.0(7)	O(7)–C(18)–Fe(1)	175.9(7)
H(5)–C(5)–Fe(1)	90.9(2)	C(4)–C(5)–Fe(1)	69.9(3)
C(4)–C(5)–H(5)	120.2(3)	C(6)–C(5)–Fe(1)	109.1(4)
C(6)–C(5)–H(5)	120.2(3)	C(6)–C(5)–C(4)	119.7(5)
C(5)–C(4)–Fe(1)	70.8(3)	C(3)–C(4)–Fe(1)	67.6(3)
C(3)–C(4)–C(5)	114.5(5)	O(4)–C(4)–Fe(1)	126.3(4)
O(4)–C(4)–C(5)	117.9(5)	O(4)–C(4)–C(3)	127.3(5)
C(4)–C(3)–Fe(1)	73.0(3)	H(3)–C(3)–Fe(1)	124.0(2)
H(3)–C(3)–C(4)	122.8(3)	C(2)–C(3)–Fe(1)	71.8(3)
C(2)–C(3)–C(4)	114.4(5)	C(2)–C(3)–H(3)	122.8(3)
C(3)–C(2)–Fe(1)	68.0(3)	H(2)–C(2)–Fe(1)	89.0(1)
H(2)–C(2)–C(3)	120.0(3)	C(1)–C(2)–Fe(1)	113.1(4)
C(1)–C(2)–C(3)	119.9(5)	C(1)–C(2)–H(2)	120.1(3)
C(6)–C(1)–C(2)	107.9(5)	C(12)–C(1)–C(2)	110.2(5)
C(12)–C(1)–C(6)	109.0(5)	C(7)–C(1)–C(2)	108.0(4)
C(7)–C(1)–C(6)	113.0(4)	C(7)–C(1)–C(12)	108.8(5)
C(1)–C(6)–C(5)	111.6(5)	H(61)–C(6)–C(5)	108.9(3)
H(61)–C(6)–C(1)	109.0(3)	H(62)–C(6)–C(5)	108.9(3)
H(62)–C(6)–C(1)	108.9(3)	C(13)–O(4)–C(4)	117.2(5)
H(131)–C(13)–O(4)	117.5(4)	H(132)–C(13)–O(4)	111.2(4)
H(133)–C(13)–O(4)	99.1(4)	H(121)–C(12)–C(1)	111.6(3)
H(122)–C(12)–C(1)	110.6(3)	H(123)–C(12)–C(1)	106.1(3)
C(11)–C(7)–C(1)	113.4(4)	C(8)–C(7)–C(1)	113.1(4)
C(8)–C(7)–C(11)	102.6(5)	C(14)–C(7)–C(1)	111.9(4)
C(14)–C(7)–C(11)	107.0(4)	C(14)–C(7)–C(8)	108.2(4)
H(111)–C(11)–C(7)	110.6(3)	H(112)–C(11)–C(7)	110.6(3)
C(10)–C(11)–C(7)	104.9(5)	C(10)–C(11)–H(111)	110.6(4)
C(10)–C(11)–H(112)	110.6(4)	H(101)–C(10)–C(11)	110.9(4)
H(102)–C(10)–C(11)	110.9(4)	C(9)–C(10)–C(11)	103.9(5)
C(9)–C(10)–H(101)	110.9(4)	C(9)–C(10)–H(102)	110.8(5)
H(91)–C(9)–C(10)	110.3(5)	H(92)–C(9)–C(10)	110.3(4)
C(8)–C(9)–C(10)	106.1(6)	C(8)–C(9)–H(91)	110.2(4)
C(8)–C(9)–H(92)	110.3(4)	C(9)–C(8)–C(7)	109.0(5)
O(1)–C(8)–C(7)	126.6(6)	O(1)–C(8)–C(9)	124.3(6)
O(2)–C(14)–C(7)	112.6(5)	O(3)–C(14)–C(7)	125.9(5)
O(3)–C(14)–O(2)	121.5(5)	C(15)–O(2)–C(14)	116.6(5)
H(151)–C(15)–O(2)	113.5(3)	H(152)–C(15)–O(2)	109.7(3)
H(153)–C(15)–O(2)	105.1(3)		



Reagents: i, Me$_3$NO; ii, LiAlH$_4$; iii, Florisil-CHCl$_3$; iv, CrO$_3$-py; v, N$_2$H$_4$-KOH; vi, H$_3$O$^+$

The aldehyde (10) was successfully reduced by the Huang-Minlon method,[8] albeit in low yield, to produce the sensitive tricyclic derivative (11), the enol ether of which was readily hydrolysed to give the ketone (12).

The sequence demonstrates the potential applicability of complexes of type (4) in synthesis by means of connection between two rings and complements our other work in rational synthesis by means of these cations.

EXPERIMENTAL

I.r. spectra were determined with a Perkin-Elmer 577, mass spectra with A.E.I. MS30, and ^{1}H n.m.r. spectra with Varian EM360 (60 MHz) or HA100 (100 MHz) instruments. M.p.s were measured on a Kofler block and are uncorrected.

Tricarbonyl[methyl 1-(η-2—5,4-*methoxy*-1-*methylcyclohexa*-2,4-*dienyl*)-2-*oxocyclopentanecarboxylate*]*iron, Diastereoisomers* (5) *and* (6).—To a stirred solution of potassium t-butoxide (7.0 g) in dry tetrahydrofuran (300 ml) under nitrogen was added dropwise methyl 2-oxocyclopentanecarboxylate (10.0 g) in tetrahydrofuran (100 ml). The suspension was stirred for 30 min and then cooled to 0 °C. With back flushing of nitrogen the flask was opened whilst tricarbonyl(4-methoxy-1-methylcyclohexa-2,4-dienylium)-iron hexafluorophosphate (4) [4b] (20.0 g) was added in portions. Complete reaction was evidenced by dissolution of (4) (*ca.* 15 min), whereupon most of the tetrahydrofuran was removed on the rotary evaporator at 40—50 °C. Ether extraction in the usual way afforded the crude partly crystalline mixture of diastereoisomers which was recrystallised from 30% ether in pentane (−40°; overnight) to give yellow crystals of (5), *ca.* 90% single diastereoisomer (9.0 g, 45%). Further recrystallisation afforded pure (5), m.p. 125—127°, $\nu_{max.}$(CHCl$_3$) 2 045, 1 975, 1 750, and 1 720 cm^{-1}; δ 5.00 (1 H, dd, $J_{2,3}$ 6, $J_{3,5}$ 2.5 Hz, 3-H), 3.70 (3 H, s, CO$_2$Me), 3.63 (3 H, s, OMe), 3.30 (1 H, m, 5-H), 2.79 (1 H, dd, J_{gem} 16, $J_{5,6}$ 2.5 Hz, *exo*-6-H), 2.41 (1 H, d, $J_{2,3}$ 6 Hz, 2-H), 2.6—1.7 (6 H, m, 3 × CH$_2$), 1.50 (1 H, dd, J_{gem} 16, $J_{5,6}$ 3.5 Hz, *endo*-6-H), and 1.09 (3 H, s, Me); *m/e* 404 (M^+) (Found: C, 53.3; H, 5.1. $C_{18}H_{20}FeO_7$ requires C, 53.5; H, 5.0%).

Evaporation of the liquors, followed by recrystallisation from 10% ether in pentane, gave pure (6) (4.5 g). Repeated evaporation of liquors followed by recrystallisation from 5% ether in pentane gave 95% single diastereoisomer (6) (5.5 g) which could be further recrystallised. The total yield of (6) was 9.5 g (48%), m.p. 78—80°, $\nu_{max.}$(CHCl$_3$) 2 045, 1 975, 1 750, and 1 725 cm^{-1}; δ 4.98 (1 H, dd, $J_{2,3}$ 6.5, $J_{3,5}$ 2.5 Hz), 3.70 (3 H, s, CO$_2$Me), 3.64 (3 H, s, OMe), 3.30 (1 H, m, 5-H), 2.91 (1 H, d, $J_{2,3}$ 6.5 Hz, 2-H), 2.50—1.5 (7 H, m, 3 × CH$_2$ and *exo*-6-H), 1.34 (1 H, dd, J_{gem} 15, $J_{5,6}$ 3.5 Hz, *endo*-6-H), and 1.18 (3 H, s, Me); *m/e* 404 (M^+) (Found: C, 53.55; H, 5.1%).

X-*Ray Structural Analysis*.—Transparent crystals of (5) were deposited as platelets from solution in 30% ether in pentane. As the sample showed a tendency to decompose upon prolonged exposure to air several suitable single crystals were mounted in 0.5-mm Lindemann tubes under nitrogen. A crystal with dimensions *ca.* 0.63 × 0.50 × 0.12 mm was mounted on an automated Stoe STADI-2 two-circle diffractometer with its crystallographic *b* axis collinear with the instrument *w* axis. The *a* and *c* unit-cell lengths and the β angle were determined by a least-squares fit to the *w* medians of zero-layer reflections, whilst *b* was determined from diffractometer μ angle measurements. 2 686 Intensities (layers 0—*h*,9,*l*) were recorded using graphite-monochromated Mo-K_α radiation. L_p and numerical absorption corrections were applied; the crystal was bounded by the planes (010), (0$\bar{1}$0), (102), ($\bar{1}$02), ($\bar{1}$0$\bar{2}$), and (10$\bar{2}$), and transmission factors ranged from 0.908 to 0.662. Equivalent reflections were averaged to give 2 145 unique observed [$F > 3\sigma(F)$] intensities.

Crystal data. $C_{18}H_{10}FeO_7$, M = 404.19, monoclinic, a = 11.830(2), b = 6.823(4), c = 22.734(4) Å, β = 102.19(3)°, U = 1 793.6 Å^3, D_m = 1.50, Z = 4, D_c = 1.496 g cm^{-3}. Mo-K_α Radiation, λ = 0.710 69 Å, μ(Mo-K_α) = 8.42 cm^{-1}, F(000) = 839.96, space group $P2_1/c$ from systematic absences.

The iron atom position was derived from a Patterson synthesis and the remaining non-hydrogen atoms were located from a subsequent Fourier difference map. The structure was refined by full-matrix least-squares to R 0.109 with the Fe atom assigned anisotropic thermal parameters and the carbon and oxygen atoms individual isotropic temperature factors. A difference electron-density map calculated using only low-angle data revealed the positions of most of the hydrogen atoms. All the hydrogens were placed in geometrically idealised positions and were constrained to ride 1.08 Å from the relevant carbon atoms. The $\rangle$CH and $\rangle$CH$_2$ groups were assigned a common isotropic thermal parameter as were the methyl hydrogen atoms; the methyl groups were refined as rigid bodies. Refinement continued with all non-hydrogen atoms assigned anisotropic thermal parameters. Other parameters included in the refinement were interlayer scale factors and an empirical extinction parameter x, which refined to 0.0008(5); F_c is multiplied by $(1-0.0001xF_c^2/\sin\theta)$. The constraint $U_{22} = (U_{11} + U_{33})/2$ was applied to reduce correlation involving interlayer scale factors. In the final cycles of refinement a weighting scheme of the form $w = 3.7265/[\sigma^2(F) + 0.004\,285|F|^2]$ was introduced. This minimised the dependence of Δw^2 on $|F_o|$ and $\sin\theta$. The final residuals were R = 0.065 and R' [= $\Sigma w^{\frac{1}{2}}\Delta/\Sigma w^{\frac{1}{2}}|F_o|$] = 0.078. A final difference electron density map showed no remaining regions of significant electron density.

Complex neutral-atom scattering factors were employed throughout.[9] Table 3 lists the final atomic parameters, while details of thermal parameters, molecular planes, and observed and calculated structure factor amplitudes may be found in Supplementary Publication No. SUP 22638 (16 pp.).* All computing was carried out on the University of Cambridge IBM 370/165 computer using SHELX 76,[10] and the plotting program PLUTO written by Dr. W. D. S. Motherwell.

TABLE 3

Atom co-ordinates (× 10^4)

	x/a	*y/b*	*z/c*
Fe(1)	8 517(1)	2 156(1)	648(1)
C(16)	8 594(6)	3 453(10)	−21(3)
O(5)	8 615(6)	4 307(10)	−445(3)
C(17)	9 950(7)	1 298(11)	733(3)
O(6)	10 874(6)	725(10)	781(3)
C(18)	7 795(6)	20(10)	325(3)
O(7)	7 374(5)	−1 435(10)	137(3)
C(5)	8 254(5)	1 290(9)	1 497(3)
C(4)	8 814(5)	3 128(8)	1 540(2)
C(3)	8 257(5)	4 528(8)	1 137(2)
C(2)	7 178(5)	3 925(8)	793(2)
C(1)	6 322(5)	2 846(8)	1 097(3)
C(6)	6 975(5)	1 193(8)	1 478(2)
O(4)	9 853(4)	3 293(7)	1 921(2)
C(13)	10 537(7)	5 003(12)	1 858(4)
C(12)	5 352(6)	1 968(10)	625(3)
C(7)	5 788(5)	4 386(8)	1 481(2)
C(11)	5 182(5)	6 113(9)	1 106(3)
C(10)	4 295(6)	6 865(11)	1 459(4)
C(9)	3 856(7)	5 013(11)	1 706(4)
C(8)	4 819(6)	3 524(9)	1 759(3)
O(1)	4 783(4)	1 941(7)	1 952(2)
C(14)	6 695(5)	5 248(9)	1 982(3)
O(2)	6 969(4)	4 057(6)	2 453(2)
C(15)	7 820(6)	4 753(10)	2 954(3)
O(3)	7 149(4)	6 805(7)	1 974(2)

Removal of Fe(CO)$_3$ *from* (6).—The complex (3.0 g) was stirred in benzene (70 ml) at 50° with anhydrous trimethylamine *N*-oxide (10.0 g) for 2 h. The benzene solution was decanted, the residues washed with a little benzene, the combined extracts washed three times with 10% brine, and dried (MgSO$_4$). Removal of solvent followed by filtration of an ether solution through Florisil gave the crude keto-ester (7) as an oil, the n.m.r. spectrum of which showed it to be *ca.* 95% pure (1.65 g, 84%). An analytical sample was obtained by Kugelrohr distillation, $\nu_{max.}$(CHCl$_3$) 1 750, 1 728, 1 662, and 1 615 cm^{-1}; δ 6.15 (1 H, d, $J_{2,3}$ 10 Hz, 2-H), 5.61 (1 H, dd, $J_{2,3}$ 10, $J_{3,5}$ 2.5 Hz, 3-H), 4.45 (1 H, m, 5-H), 3.70 (3 H, s, CO$_2$Me), 3.50 (3 H, s, OMe), 2.9—1.5 (8 H, 4 × CH$_2$), and 1.15 (3 H, s, Me) (Found: C, 68.05; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%).

Reduction of (7) *and Cyclisation*.—To a stirred suspension of lithium aluminium hydride (0.5 g) in dry ether (20 ml)

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was added dropwise a solution of crude (7) (1.65 g) in dry ether (20 ml) and the mixture was refluxed overnight. Excess of lithium aluminium hydride was destroyed by addition of ethyl acetate (0.5 ml) followed by water (3—4 ml). The ether was decanted, the residue washed with ether, and the combined organic extracts were washed with water and dried ($MgSO_4$). Removal of solvent gave the crude product as an oil consisting mainly of (8) (see Discussion section) (1.34 g, 90%), $\nu_{max.}$ ($CHCl_3$) 3 200—3 700, 1 660, and 1 612 cm^{-1}; δ 6.17 (1 H, d, $J_{2,3}$ 10 Hz, 2-H), 5.70 (1 H, dd, $J_{2,3}$ 10, $J_{3,5}$ 2.5 Hz, 3-H), 4.6—3.5 (4 H, m, 2 × CHO, CH_2O), 3.55 (3 H, s, OMe), 3.0—1.4 (10 H, 4 × CH_2, 2 × OH), and 1.16 (3 H, s, Me). Chromatography of this compound on Florisil with chloroform gave pure (9) as a crystalline compound [1.20 g, 81% overall from (7)] which could be recrystallised from hexane–ether, m.p. 120—122 °C, $\nu_{max.}$($CHCl_3$) 3 620, 3 550—3 220, and 1 665 cm^{-1}; δ 4.79 (1 H, d, J 6 Hz, vinyl), 4.3—3.4 (4 H, m, CH_2O, 2 × CHO), 3.60 (3 H, s, MeO), 2.7—1.3 [11 H, 5 × CH_2, OH (exchanges with D_2O), and 1.05 (3 H, s, Me) (Found: C, 70.3; H, 9.1%; M^+, 238.1553. $C_{14}H_{22}O_3$ requires C, 70.55; H, 9.3%; M, 238.1569).

Oxidation of (9).—The pure alcohol (9) (0.56 g) in pyridine (10 ml) was added to stirred chromium trioxide (0.7 g) in pyridine (10 ml) and the mixture was stirred overnight at room temperature. Aqueous work-up and ether extraction followed by four washes with water, drying ($MgSO_4$), and removal of ether on the rotary evaporator, followed by removal of residual pyridine under high vacuum, gave the crude aldehyde (10) (0.33 g, 60%) as an oil which was sufficiently pure for the next step. An analytical sample was obtained by Kugelrohr distillation, $\nu_{max.}$($CHCl_3$) 2 712, 1 718, and 1 667 cm^{-1}; δ 9.80 (1 H, s, CHO), 4.9 (1 H, m, partly obscured, CHO), 4.75 (1 H, d, J 6 Hz, vinyl H), 4.15 (1 H, d, J 6 Hz, CHO), 3.56 (3 H, s, MeO), 2.7—1.4 (10 H, 5 × CH_2), and 1.05 (3 H, s, Me) (Found: C, 71.1; H, 8.65. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.54%).

Wolff–Kishner Reduction of (10).—A mixture of the crude aldehyde (10) (0.15 g), diethylene glycol (3 ml), hydrazine hydrate (0.5 ml), and potassium hydroxide (0.35 g) was gently heated to dissolve the latter, and then refluxed for 4 h. Water and hydrazine were distilled off in the usual way,[5] further hydrazine hydrate (0.5 ml) added and the mixture was refluxed for 17.5 h, after which time it was cooled, poured into water, and extracted with ether in the usual way to give crude (11) (50 mg, 35%) as an oil, $\nu_{max.}$($CHCl_3$) 1 668 cm^{-1} (no peak at 1 718 cm^{-1}); δ 4.82 (1 H, d, J 6 Hz, vinyl H), 4.2 (2 H, m, 2 × CHO), 3.67 (3 H, s, OMe), 2.4—1.2 (10 H), 0.90 (3 H, s, Me), and 0.85 (3 H, s, Me); m/e 222 (M^+). The sensitive enol ether group of this compound did not permit isolation of a pure sample by p.l.c. and so it was hydrolysed to the ketone (12) as follows. To a solution of crude (11) (28 mg) in methanol (1.5 ml) was added a solution of oxalic acid (30 mg) in water (0.3 ml), and the mixture was allowed to stand at room temperature for 40 min, after which time it was poured into dilute sodium hydrogencarbonate solution and the product extracted with ether to give crude (12) (20 mg). Preparative layer chromatography (silica gel–ether) afforded (12) as a waxy solid, m.p. 35—38° (15 mg, 58%), $\nu_{max.}$($CHCl_3$) 1 717 cm^{-1}; δ 4.2 (2 H, m, 2 × CHO), 2.65 (2 H, m), 2.45 (2 H, m), 2.2—1.4 (8 H, 4 × CH_2), 1.20 (3 H, s, Me), and 1.10 (3 H, s, Me); m/e 208 (27%), 179 (10), 166 (8), 165 (5), and 151 (100) (Found: M^+, 208.1464. $C_{13}H_{20}O_2$ requires M, 208.1463).

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