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STEREOCONTROLLED APPROACH TO TRICHOTHECANE DERIVATIVES VIA TRICARBONYLCYCLOHEXADIENEIRON COMPLEXES: SYNTHESIS OF A KEY INTERMEDIATE.

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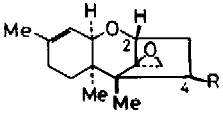
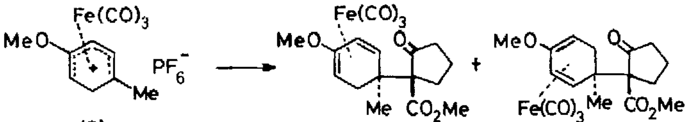
Abstract: The potential of tricarbonyl(4-methoxy-1-methylcyclohexadienylium) iron hexafluorophosphate (2) as a trichothecane precursor is demonstrated by the stereocontrolled elaboration of the advanced intermediate (14).

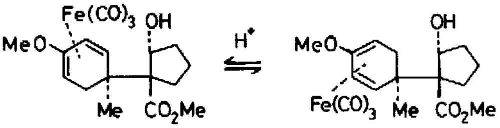
The recent synthesis of trichodermol (1, R=OH) reported by W.C. Still prompts us to disclose results of our own work in this area, which utilises a similar stereo- and regio-specific epoxidation and subsequent glycol formation to obtain the correct stereochemistry at C-2 of the trichothecane ring system, shown by the general formula (1). Whilst our work is initially aimed at the synthesis of trichothecane analogues lacking the usual C-4 oxygen functionality, we envisage that appropriate modification will eventually lead to naturally occurring derivatives such as trichodermol. These and our earlier studies[3] represent the first successful attempts to utilise tricarbonylcyclohexadienyliumiron complexes in synthesis of relatively complex natural products.



(1)

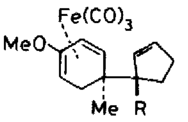


(2) (3) (4)

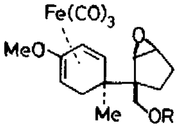


(5) (6)

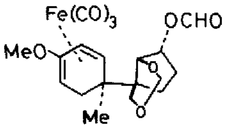
We recently reported[4] the reaction of the hexafluorophosphate (2) with the potassium enolate of methyl 2-oxocyclopentane carboxylate which gave, in 100% yield, an equimolar mixture of diastereoisomers (3) and (4), readily separated by fractional crystallisation. Sodium borohydride reduction of the separate diastereoisomers gave the hydroxy esters (5) and (6), respectively, both obtained as single crystalline epimers in 100% yield[5] (10 equiv. $NaBH_4$, MeOH, 0^oC, 1 h). Treatment of the pure undesired diastereoisomer (6) with 4-toluenesulphonic acid (2% by weight, CH_2Cl_2, 20^oC, overnight) resulted in its conversion to an equimolar mixture of (5) and (6), which were separable by chromatography. In this way pure (5) m.p. 118-119^oC, ν_{max} ($CHCl_3$) 3620, 3450, 2052, 1977, 1719 cm^{-1}, can be obtained in yields in excess of 80% from the hexafluorophosphate (2).[6]


(7) R = CO_2Me

(8) R = CH_2OH


(9) R = H

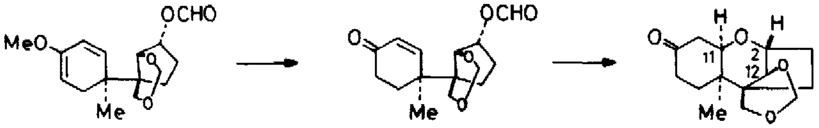
(10) R = CH_2OMe


(11)

Dehydration of (5) (6-8 equiv. $SOCl_2$, pyridine, 0^oC, 20 h, 20^oC, 18 h) proceeded smoothly to give the olefinic ester (7), m.p. 75-76^oC, ν_{max} ($CHCl_3$) 2050, 1970, 1715, 1620 cm^{-1}, in 70-75% yield. Reduction of the ester, whilst not possible with lithium aluminium hydride owing to accompanying decomposition of the complex, was achieved in 95% yield using diisobutylaluminium hydride (2.2 equiv., THF, 0^oC to 20^oC, overnight) giving the hydroxy alkene (8), m.p. 77-78^oC ν_{max}($CHCl_3$) 3580, 2050, 1970, 1610 cm^{-1}.

Whilst di-tert-butyl peroxide has been reported to readily effect decomposition of pentacarbonyliron,[7] we found that the diene-$Fe(CO)_3$ unit is quite stable to hydroperoxides, and stereospecific epoxidation of (8) was readily achieved using the Sharpless procedure[8] (2.5 mole % $VO(acac)_2$, 1.5 equiv. t-BuOOH, benzene, reflux, 1 h, 90% yield) to give the hydroxy epoxide (9), m.p. 105-107, ν_{max} ($CHCl_3$) 3520, 2050, 1980, 845 cm^{-1}. This was readily converted to the methoxymethyl ether (10) (2.0 equiv. $ClCH_2OCH_3$, 2.1 equiv. $Pr_2{}^iNEt$, CH_2Cl_2, reflux, 8 h, 100%). Whilst these cyclopentene oxides are normally only suggishly converted to trans diols[2] we found that treatment of (10) with sodium formate in formic acid (20^oC, 48 h) gave an apparently assisted opening of the epoxide to give the methylene ketal ester (11) in 70% yield, m.p. 109-111^oC, ν_{max} ($CHCl_3$) 2050, 1980, 1725, 1480 cm^{-1}. The formation of this compound established the regiochemistry of the epoxide opening which necessarily gives the correct stereochemistry for the pro-C-2 oxygen functionality. The corresponding methyl ether reacted more slowly under these conditions. Removal of the tricarbonyliron group was readily effected by mild oxidation (25 equiv. anhydrous Me_3NO, benzene, 50^{o}C, 3h, 85% yield) to give the dienol ether (12), which was selectively hydrolysed to the enone (13) (oxalic acid, MeOH, H_2O, 0^{o}C, 30 min, 75%) obtained as a colourless oil, chromatographically pure, ν_{max} ($CHCl_3$) 1725, 1680, 1460 cm^{-1}. Hydrolysis of the formate (2.5 equiv. K_2CO_3, MeOH) occurred with concomitant cyclisation of the resulting alcoholate onto the enone to give the ketone (14), obtained as a white crystalline solid in 40% yield (not optimised) m.p. 154-155^{o}C. ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ($CDCl_3$) 4.29 (1H, m, H-2), 4.10 and 3.65 (each 1H, d, J_{AB} 9 Hz, $OC\underline{H}_2O$), 3.58 (1H, s, br, H-11), 3.41 (1H, d, 2.5 Hz, H-12), 2.54-1.10 (12H, $C\underline{H}_2O$ and 5 x CH_2), 1.17 (3H, s, Me).

The ketone (14) possesses the basic trichothecane ring structure, with the correct relative stereochemistry. We envisage that it can be further elaborated to a number of potentially interesting trichothecane analogues, using similar methodology to that employed by Still[2] and this is currently being pursued. As pointed out by Still, introduction of the five-membered ring intact at an early stage is somewhat advantageous compared with approaches in which this ring is formed at a later stage by a low yielding aldol reaction.[9]



(12) (13) (14)

The approach described here offers the possibility of asymmetric synthesis, since Birch *et al*. have now synthesised the immediate precursor of hexafluorophosphate (2) in optically active form.[10] This work also illustrates the stability of the diene-Fe(CO)$_3$ group to a number of synthetic transformations

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