Cycloaddition Reactions of Allyliron Complexes: Synthesis of Cyclopentanoid Derivatives such as (±)-Sarkomycin

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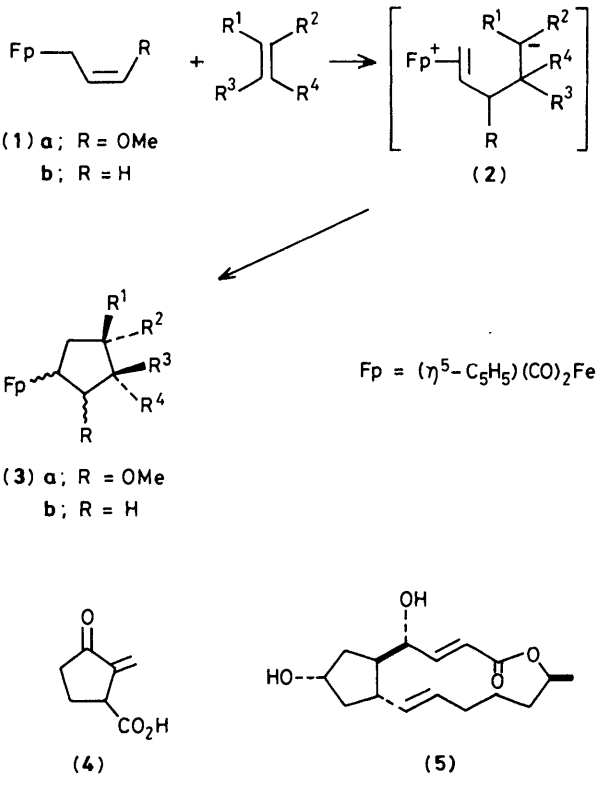
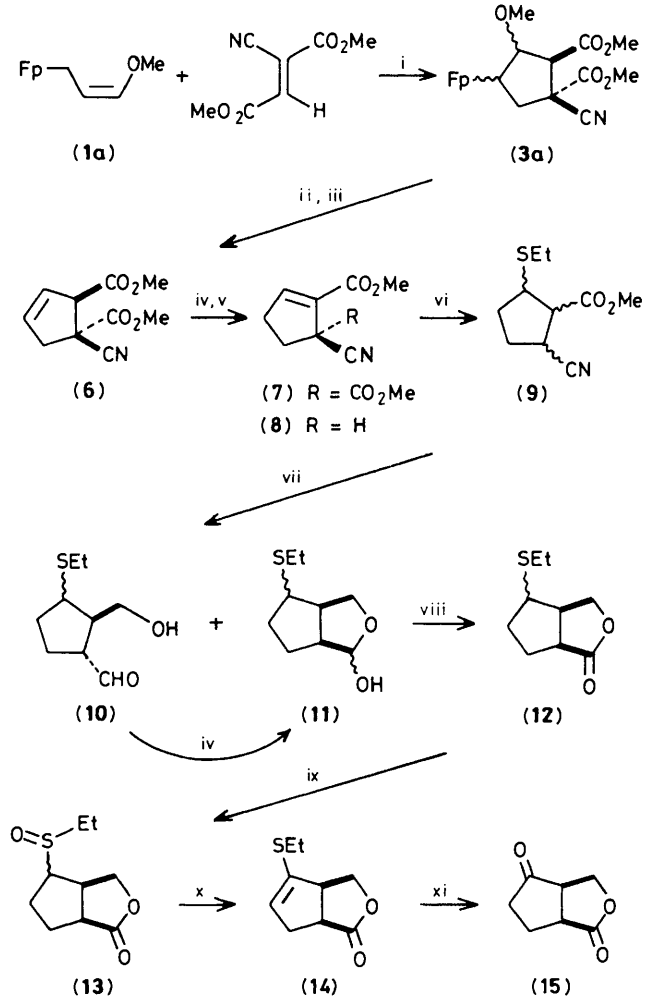
A cycloaddition reaction between dimethyl 2-cyanofumarate and (σ-3-methoxyallyl)(η^5-cyclopentadienyl)dicarbonyliron has yielded a cyclopentanoid derivative which has been used in a synthesis of sarkomycin; a precursor to brefeldin A has also been prepared from the same intermediate.

Reactions of (σ-allyl)dicarbonyl(η^5-cyclopentadienyl)iron complexes (**1**) and electron-deficient olefins have been previously reported[1—3] to yield cyclopentanoid derivatives (**3**). The reaction, which constitutes a formal [3 + 2] cycloaddition, has been shown[4] to proceed *via* a two-step process involving initial formation of a dipolar ion (**2**) followed by cyclisation. It is apparent that for the reaction to proceed, stabilisation of the intermediate zwitterion is required by electron-withdrawing groups on the olefin-derived carbon atoms. Despite the high efficiency of some of these cycloadditions and the ease of demetallation of the adducts, no application of such chemistry has been made to the synthesis of natural products. We now report the first such application in the synthesis of the antitumour agent sarkomycin (**4**)[5,6] and an intermediate which could be employed in the syntheses of brefeldin A (**5**).[7]

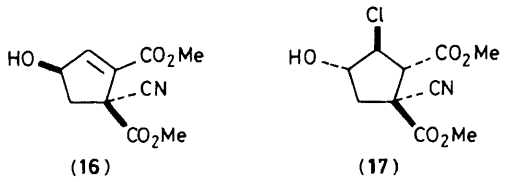
The complex (σ-3-methoxyallyl)(η^5-cyclopentadienyl)dicarbonyliron (**1a**) was chosen as the starting point since previous work has demonstrated that regiospecific demetallation of its derived adducts can be achieved.[2b] Thus treatment of a dichloromethane solution of (**1a**) with dimethyl 2-cyanofumarate (1.1 equiv.) for 3 h at room temperature gave the cyclopentyl adduct (**3a**) as a mixture of diastereoisomers in 86% yield. Exposure of (**3a**) to anhydrous hydrogen chloride in dichloromethane followed by irradiation with visible light yielded the cyclopentene (**6**), b.p. 142—144 °C at 0.5 mmHg,[8] in 65% yield after column chromatography. Isomerisation of (**6**) to (**7**) was achieved quantitatively with sodium methoxide in methanol. Decarboxylation of the tertiary group of (**7**) using lithium iodide in dimethylformamide (DMF) afforded the key intermediate (**8**), b.p. 95 °C at 0.1 mmHg, $\nu_{max.}$ ($CHCl_3$), 2250s, 1725s, and 1635w cm^{-1}; ^1H n.m.r. δ 2.2—2.5 (2H, m, $CNCHCH_2$), 2.6—2.9 (2H, m, allylic), 3.83 (3H, s, CO_2CH_3), 3.78—3.96 (1H, m, $CNCHCH_2$), and 7.03 (1H, m, vinylic), in 67% yield.

The introduction of an oxygen functionality at C-2 of (**8**) could not be achieved directly, but it did prove possible to add





Scheme 1. *Reagents and conditions:* i, CH_2Cl_2, room temp.; ii, HCl, CH_2Cl_2; iii, *hv*, CCl_4; iv, NaOMe, MeOH, room temp.; v, LiI, DMF, reflux; vi, LiSEt, tetrahydrofuran, −70 °C; vii, Bu^i_2AlH (3.3 equiv.), Et_2O, −20 to 0 °C; viii, Ag_2CO_3 on Celite, benzene, reflux; ix, *m*CPBA (1.1 equiv.), CH_2Cl_2, 0 °C; x, $(CF_3CO)_2O$, CH_2Cl_2, room temp.; xi, $HgCl_2$, MeCN–H_2O (3 : 1), reflux.



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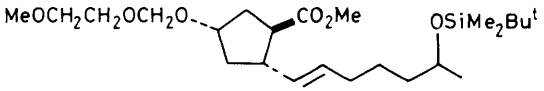

(18)

a thioalkyl group which could be transformed to the required ketone *via* a Pummerer rearrangement. Conjugate addition of the lithium anion of ethanethiol to (**8**) gave a 70% yield of (**9**) as a mixture of diastereoisomers. The necessary modifications to the oxidation levels of the cyclopentane substituents were achieved by the following sequence. Reduction with di-isobutylaluminium hydride followed by work-up (2% H_2SO_4) yielded both the free hydroxy aldehydes (**10**), $\nu_{max.}$ ($CHCl_3$), 3400br. and 1720s cm^{-1}; ^1H n.m.r. δ 9.73 (1H, d), and the lactols (**11**), ^1H n.m.r. δ 5.26 (1H, s). The hydroxy aldehydes (**10**) could be easily converted into (**11**) by base-catalysed epimerisation. Quantitative oxidation of (**11**) to give the lactone (**12**), $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1}, was achieved with silver carbonate on Celite and this was followed by *m*-chloroperbenzoic acid (*m*CPBA) oxidation to give the sulphoxide (**13**) in 98% yield, $\nu_{max.}$ ($CHCl_3$) 1760s and 1025s cm^{-1}. The Pummerer rearrangement could not be effected with acetic anhydride, but treatment with trifluoroacetic anhydride at room temperature gave the thioenol ether (**14**) in 79% yield. This was hydrolysed to give the ketolactone (**15**), m.p. 44—46 °C, yield 90%, the immediate precursor of sarkomycin (**4**).[6]

A further application of these cycloaddition reactions is demonstrated by the synthesis of (**16**), a possible precursor to brefeldin A (**5**). This was achieved by the treatment of (**6**) with t-butyl hypochlorite to produce a mixture of (**16**), b.p. 101—103 °C at 0.1 mmHg, and (**17**), b.p. 109—112 °C at 0.1 mmHg in a ratio of 4 : 1 with a combined yield of 77%. The cyclopentene (**16**) could be converted into (**18**), an intermediate for the synthesis of brefeldin A.[8]

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