A Mild Procedure for the Selective Formation of Aryl Ethers and Triaryl Diethers using Arene–M–Cp Cations (M = Fe, Ru; Cp = η^5-cyclopentadienyl)

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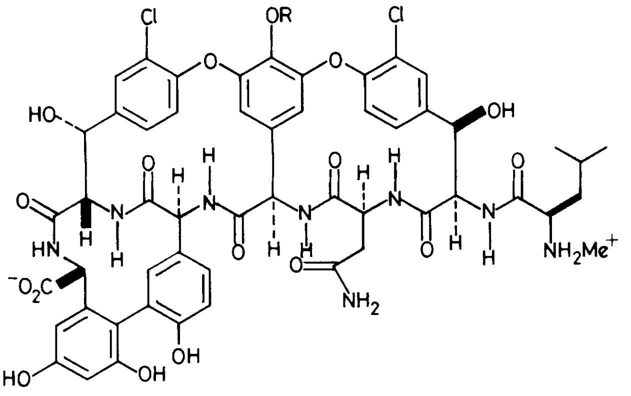
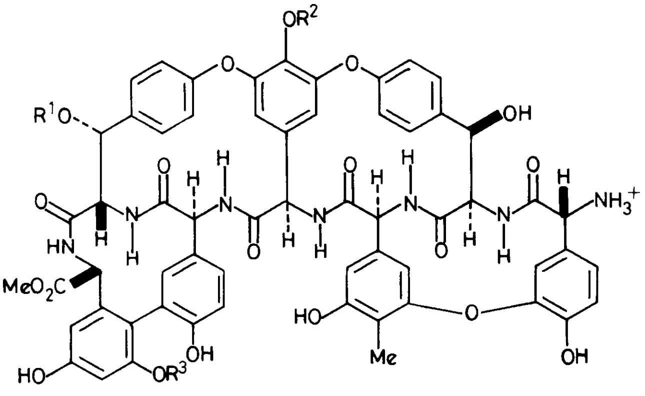
Reaction of (η^6-1,3-dichlorobenzene)(η^5-cyclopentadienyl)iron hexafluorophosphate with aryl oxides from protected tyrosines proceeds under mild conditions to generate aryl ethers, and the halogens may be displaced sequentially, allowing the preparation of unsymmetrical or symmetrical triaryl diethers; (η^6-*N*-acetyl-4-chlorophenylalanine methyl ester)(η^5-cyclopentadienyl)ruthenium hexafluorophosphate was prepared and was shown to react with protected tyrosine aryl oxide to generate dityrosine derivatives, and a mild photochemical method for demetallation of the arene–M–Cp (Cp = η^5-cyclopentadienyl) complexes is described.

The construction of diaryl ethers from phenolic compounds possessing sensitive amino acid functionality in their side chains is an important step in the synthesis of cyclic peptide antibiotics exemplified by OF 4949 I–IV,[1] bouvardin,[2] K-3,[3] and the complex glycopeptides vancomycin (**1**) and ristocetin (**2**).[4] A summary of methods for oxidative coupling of tyrosine derivatives has been presented by Evans and Ellman[5] who have noted the generally poor yields for such reactions, and have developed elegant solutions and methodology for the construction of isodityrosines. In connection with a programme aimed at developing new methods for constructing such diaryl ethers, we recently reported the use of chloroarene–Mn(CO)$_3$ cations for the construction of aryl ethers having phenylglycine units.[6] This methodology is not without drawbacks. In particular, we have been unable to prepare manganese complexes of 4-chlorophenylalanine derivatives or of dichlorobenzenes. This Communication reports preliminary results which offer solutions to these problems, and which promise to give methodology appropriate for construction of molecules in the vancomycin group.



(**1**) Vancomycin (R = sugar unit)



(**2**) Ristocetin A (R^1–R^3 = sugar units)

1,3-Dichlorobenzene(cyclopentadienyl)iron hexafluorophosphate (**3**) was prepared by the literature procedure.[7,8] Treatment of this complex with the phenoxide from *N*-benzyloxycarbonyl tyrosine methyl ester (**4**) [1.0 equiv., tetrahydrofuran(THF), −78 °C, 10 min; room temp., 30 min] followed by aqueous work-up, extraction into dichloromethane and precipitation with ether, afforded the product (**5**) of monosubstitution, m.p. 83—85 °C, in 86% yield (see Scheme 1). The remaining chloride could be displaced by treatment with dimethyl sodiomalonate[8] (THF, room temp., 30 min) to give (**6**) or with a second equivalent of (**4**) to give (**7**), m.p. 92—95 °C, in 87% yield.† It may be noted that these reaction conditions are considerably milder than those required for standard Ullmann coupling, and those previously reported[8] for similar reactions of complex (**3**). Earlier reports indicated that the Fe–Cp group (Cp = η^5-cyclopentadienyl) can be removed from the cationic arene complexes by a pyrolytic sublimation process.[9] Since we considered these conditions to be too harsh for amino acid derivatives, an alternative, milder method, was developed. Irradiation of complexes (**5**), (**6**), or (**7**) in acetonitrile (General Electric 275 W Sun Lamp) under argon, at room temperature for 30—40 min, resulted in complete decomplexation to give the aryl ether derivatives (**8**), $[\alpha]_D$ −14° (*c* 0.59, EtOH); (**9**), $[\alpha]_D$ −8.4° (*c* 1.03, EtOH); and (**10**), $[\alpha]_D$ +41.8° (*c* 0.505, CH_2Cl_2) in high yield. According to ^{1}H n.m.r. spectroscopy in the presence of the chiral lanthanide shift reagent (+)-tris[3-(heptafluorobutyryl)-camphorato]europium(III), no detectable racemization occurs throughout this sequence.

Treatment of (racemic) *N*-acetyl-4-chlorophenylalanine methyl ester with $[CpRu(MeCN)_3]PF_6$[10] in 1,2-dichloroethane at 40—45 °C under an argon atmosphere for 72 h furnished the complex (**11**) in 65% yield.‡ We have not

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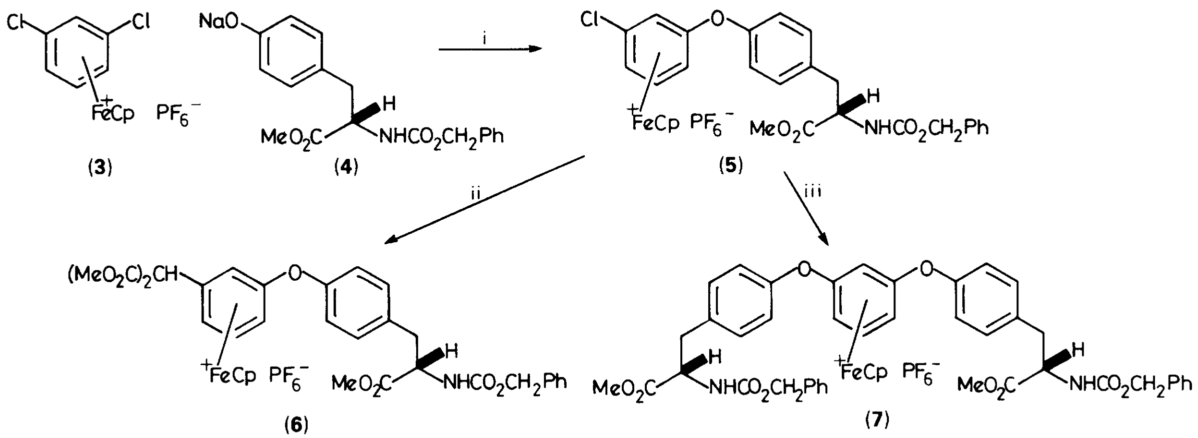
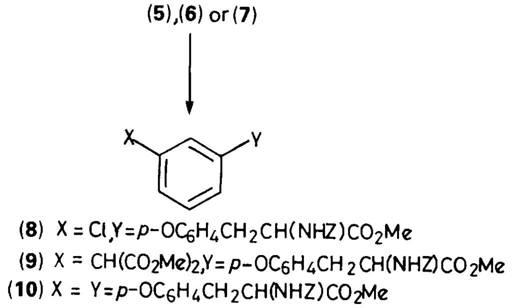
† All new compounds were characterized by 200 MHz ^{1}H n.m.r. spectroscopy, i.r. spectroscopy, and high resolution mass spectrometry. Non-cationic compounds were homogeneous on t.l.c., while arene–M–Cp systems were ascertained to be pure by elemental analysis. Representative n.m.r. data follows, for compound (**8**): ($CDCl_3$) δ 7.34 (5H), 7.24 (1H, t), 7.08 (2H, d, *J* 8.3 Hz), 7.07 (1H, m), 6.95 (1H, m), 6.92 (2H, d, *J* 8.3 Hz), 6.85 (1H, d, *J* 2.4 Hz), 5.25 (1H, d, *J* 7.8 Hz, NH), 5.10 (2H, s), 4.68 (1H, d^t, *J* 7.8, 6.0 Hz), 3.74 (3H, s), 3.14 (1H, dd, *J* 14, 6 Hz), 3.07 (1H, dd, *J* 14, 6 Hz).

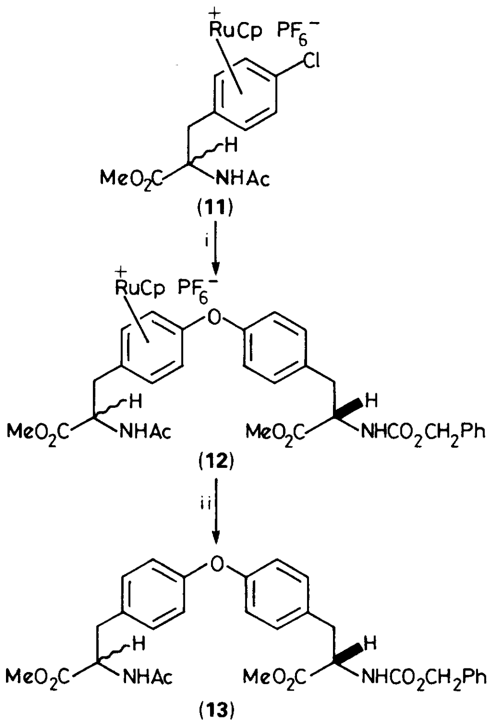
‡ Complexation of *p*-chlorophenylalanine derivatives is considerably slower than that of *N*-acetylphenylalanine methyl ester itself, owing to inductive electron withdrawal from the ring. We have found that *N*-acetylphenylalanine methyl ester is converted to the arene–Ru–Cp complex in *ca.* 70% yield after a reaction time of 18 h in 1,2-dichloroethane at 40—45 °C, in agreement with the results of Moriarty (ref. 10). Furthermore, optically pure *N*-acetylphenylalanine methyl ester is complexed and decomplexed without detectable racemization. Prolonged reaction times do not adversely affect this result. Thus, while commercially available racemic 4-chlorophenylalanine was used in the present study, there is every reason to suppose that optically pure complexes can be prepared without difficulty.



Scheme 1. *Reagents and conditions*: i, THF, −78 °C to room temp.; ii, $NaCH(CO_2Me)_2$; iii, (**4**), THF, −78 °C to room temp.



Scheme 2. *Conditions*: sun lamp, MeCN, room temp., 30—40 min, 50—100%.



Scheme 3. *Reagents and conditions*: i, (**4**), THF, room temp., 3 h; ii, sun lamp, MeCN, room temp., 1.5 h.

attempted to prepare the analogous arene–Fe–Cp complex because of the harsher conditions used in the formation of these complexes. Treatment of (**11**) with the phenoxide (**4**) (THF, room temp., 3 h) gave complex (**12**), which was difficult to purify and was therefore submitted to photochemical demetallation (sunlamp, MeCN, 1.5 h) to afford the dityrosine derivative (**13**) in 66% overall yield from (**11**) (see Scheme 2). This establishes that aromatic amino acids can be directly coupled under mild conditions, providing methodology that is suitable for the preparation of sub-units found in OF 4949, bouvardin, and K-13. Future work will be directed toward the application of this chemistry in total synthesis of these important compounds.

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Note added in proof: Better yields may be obtained from the decomplexation of arene–Fe–Cp complexes by including 3 equiv. triethyl phosphite in the reaction mixture. See also: T. P. Gill and K. R. Mann, *J. Organomet. Chem.*, 1981, **216**, 65.