η^5-Pentamethylcyclopentadienylruthenium(II) Complexes containing η^6-Co-ordinated Dipeptides with Aromatic Side Chains†

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The η^6-co-ordinated amino acid complexes $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-}HaaOH)][CF_3SO_3]$ [HaaOH = L-HPheOH (phenylalanine) or L-HTrpOH (tryptophan)] were prepared by reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with the relevant amino acid in tetrahydrofuran. Dipeptide complexes of the type $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2(\mu\text{-}\eta^6\text{:}\eta^6\text{-pep})][CF_3SO_3]_2$ [pep = HPhe-PheOH, cyclo(-Phe-Phe-), HTrp-TrpOH, or cyclo(-Trp-Trp-)] may be obtained under analogous conditions. Ultraviolet irradiation of $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-Phe-Phe-})\}][CF_3SO_3]_2$ leads to photochemical release of cyclo(-Phe-Phe-) in quantitative yield. The feasibility of peptide synthesis from individual amino acid complexes was demonstrated by the preparation of $[Ru(\eta^5\text{-}C_5Me_5)\{\eta^6\text{-}cyclo(\text{-Phe-Phe-})\}]Cl$ from $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-}L\text{-HPhe-OMe})]Cl$ by the carbodiimide method. A crystal structure analysis was carried out for $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-Phe-Phe-})\}][CF_3SO_3]_2$.

Interest in organometallic complexes of bioligands has increased rapidly in recent years, with the result that the term bioorganometallic chemistry has been coined to describe research in this area.[1,2] Typical examples are $(\eta^6\text{-}C_6H_6)Ru^{II}$ or $(\eta^5\text{-}C_5Me_5)M^{III}$ (M = Rh or Co) complexes of α-amino acids in which the biological ligands are bi- or tri-dentate.[3] Such organometallic complexes exhibit chiral centres both at the α-carbon atom in the ligand and at the metal and possess considerable potential for enantioselective synthesis of peptides.[4] However, the number of characterised complexes containing direct metal–carbon bonds to ligands of biological interest is still somewhat limited, although the potential of this field has been emphasized in a recent review by Jaouen *et al.*[1] For instance Jaouen and co-workers[5] have successfully developed the carbonylmetalloimmunoassay procedure based on the incorporation of organometallic fragments such as $Cr(CO)_3$ into steroid hormones. The same research team have also investigated the application of $(\eta^5\text{-}C_5Me_5)Ru^{II}$-labelled molecules in the analysis and molecular recognition of active sites in hormone receptors.[6] We have recently employed the same fragment for the first direct preparation of η^6-co-ordinated complexes of the α-amino acids phenylalanine (L-HPheOH), tyrosine (L-HTyrOH) and tryptophan (L-HTrpOH). Reaction of $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ with the respective amino acid (L-HaaOH) in MeOH–Na(OMe) gave $[Ru(\eta^5\text{-}C_5Me_5)(L\text{-HaaOH})]Cl$.[7] The relationship of these sandwich complexes to the established radiopharmaceuticals ruthenocene and ruthenocenylalanine is apparent.[8]

These findings prompted us to investigate whether analogous $(\eta^5\text{-}C_5Me_5)Ru^{II}$ complexes of dipeptides can be prepared either by direct reaction of the peptide with $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ or through a peptide synthesis employing a cation of the type $[Ru(\eta^5\text{-}C_5Me_5)(L\text{-HaaOH})]^+$ as starting material. If successful, the second strategy should enable the synthesis of tailor-made $(\eta^5\text{-}C_5Me_5)Ru^{II}$-labelled peptides from chosen individual building blocks.

Experimental

Solvents were dried and distilled before use. Proton NMR spectra were recorded on a Bruker AM-400 spectrometer, IR spectra as KBr discs on a Perkin-Elmer 1760 spectrometer and FAB mass spectra on a VG Autospec instrument employing 3-nitrobenzyl alcohol as the matrix. Assignments of the resonances of the N (α_1,β_1)- and O (α_2,β_2)-terminal peptide protons were based on H–H correlation spectroscopy (COSY). Elemental analyses were performed on a Carlo Erba 1106 analyser. All reactions were carried out under argon by use of standard Schlenk techniques. The starting compound $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ was prepared from $RuCl_3\cdot xH_2O$ (Heraeus) by the published procedure.[9] The amino acids L-HPheOH and L-HTrpOH were obtained from Janssen, the dipeptides phenylalanylphenylalanine (HPhe-PheOH), cyclophenylalanylphenylalanine [cyclo(-Phe-Phe-)], tryptophyltryptophan (HTrp-TrpOH) and cyclo-tryptophyltryptophan [cyclo(-Trp-Trp-)] from Bachem. These compounds were used as received.

Syntheses.—$[Ru(\eta^5\text{-}C_5Me_5)(L\text{-HPheOH})][CF_3SO_3]$ **1**. The compound L-HPheOH (0.033 g, 0.2 mmol) was added to a solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in tetrahydrofuran (thf) (6 cm^3) and the solution stirred for 12 h at reflux. The yellow precipitate was centrifuged and the product **1** dissolved in a small volume of methanol. After filtration the solvent was removed in vacuum to afford complex **1** in 37% yield (0.041 g) (Found: C, 43.8; H, 4.8; N, 2.4. Calc. for $C_{20}H_{26}F_3NO_5RuS$: C, 43.6; H, 4.8; N, 2.5%). FAB mass spectrum: *m/z* 402 (100, $[M - CF_3SO_3]^+$), 356 (29, $[M - CF_3SO_3 - CO_2H]^+$) and 328 {24%, $[M - CF_3SO_3 - CH(NH_2)CO_2H]^+$}. ^1H NMR (CD_3OD): δ 2.00 (s, 15 H, C_5Me_5), 2.82, 2.83 (2 d, 2 H, β-CH_2), 3.80 (t, 1 H, α-CH) and 5.85 (m, 5 H, η^6-Ph). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3074m (NH) and 1636s (CO).

$[\{Ru(\eta^5\text{-}C_5Me_5)\}_2(HPhe\text{-}PheOH)][CF_3SO_3]_2$ **2**. A solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in thf (6 cm^3) was stirred for 2 d at room temperature together with HPhe-PheOH (0.033 g, 0.1 mmol). The orange-yellow precipitate was centrifuged and the product **2** dissolved in a few cm^3 of methanol. Remaining solid was filtered off and the solvent removed in vacuum to afford complex **2** in 37% yield (0.041 g) (Found: C, 43.5; H, 4.9; N, 2.4. Calc. for $C_{40}H_{50}F_6N_2O_9Ru_2S_2\cdot CH_3OH$: C, 44.2; H, 4.9; N, 2.5%). FAB

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1995, Issue 1, pp. xxv–xxx.

mass spectrum: *m/z* 1085 (76, M^+), 935 (36, $[M - CF_3SO_3]^+$), 785 (24, $[M - 2CF_3SO_3]^+$) and 549 {100%, $[M - 2CF_3SO_3 - Ru(C_5Me_5)]^+$}. ^1H NMR (CD_3OD): δ 1.98 (2 s, 30 H, C_5Me_5), 2.70, 2.87 (2 dd, 2 H, β_2-CH_2), 2.87 (d, 2 H, β_1-CH_2), 4.18 (m, 1 H, α_1-CH), 4.54 (m, 1 H, α_2-CH) and 5.85 (m, 10 H, η^6-Ph). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3380 (sh) (NH) and 1691s (CO).

$[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}][CF_3SO_3]_2$ **3**. The compound cyclo(-Phe-Phe-) (0.029 g, 0.1 mmol) was added to a solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in thf (6 cm^3) and the solution stirred for 2 d at room temperature. The pale yellow precipitate was centrifuged and the product **3** dissolved in a small volume of methanol. After filtration the solvent was removed in vacuum to afford complex **3** in 40% yield (0.038 g) (Found: C, 44.1; H, 4.5; N, 2.7. Calc. for $C_{40}H_{48}F_6N_2O_8Ru_2S_2\cdot 1.5CH_3OH$: C, 44.8; H, 4.9; N, 2.5%). FAB mass spectrum: *m/z* 766 (9, $[M - 2CF_3SO_3]^+$), 531 {100, $[M - 2CF_3SO_3 - Ru(C_5Me_5)]^+$}, 439 {20, $[M - 2CF_3SO_3 - Ru(C_5Me_5)(CH_2Ph)]^+$} and 328 {66%, $[Ru(C_5Me_5)(CH_2Ph)]^+$}. ^1H NMR (CD_3OD): δ 1.95 (s, 30 H, C_5Me_5), 2.46, 2.82 (2 dd, 4 H, β-CH_2), 4.43 (t, 2 H, α-CH), 5.54, 5.77 and 5.83 (m, 10 H, η^6-Ph). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3270s (NH) and 1682vs (CO). Irradiation of a MeCN solution of **3** with a mercury lamp (254–380 nm) for 3 h led to precipitation of cyclo(-Phe-Phe-) in quantitative yield.

$[Ru(\eta^5\text{-}C_5Me_5)(\text{L-}HTrpOH)][CF_3SO_3]$ **4**. A solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in thf (6 cm^3) was stirred for 5 h at reflux together with L-HTrpOH (0.041 g, 0.2 mmol). The solution was filtered and the product precipitated by addition of hexane. After centrifuging, the yellow product **4** was dissolved in a small volume of methanol, the solution filtered and the solvent removed in vacuum to afford complex **4** in 36% yield (0.042 g) (Found: C, 44.6; H, 4.7; N, 4.5. Calc. for $C_{22}H_{27}F_3N_2O_5RuS$: C, 44.8; H, 4.6; N, 4.8%). FAB mass spectrum: *m/z* 441 (100, $[M - CF_3SO_3]^+$) and 366 {50%, $[M - CF_3SO_3 - CH(NH_2)(CO_2H)]^+$}. ^1H NMR (CD_3OD): δ 1.72 (2 s, 15 H, C_5Me_5), 3.20 (m, 2 H, β-CH_2), 3.95 (t, 1 H, α-CH), 5.60 (m, 2 H, indole H^4, H^5), 6.37, 6.39, 6.48, 6.56 (4 d, 2 H, indole H^3, H^6), 7.73 and 7.76 (2 s, 1 H, indole H^9). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3083m (NH) and 1636s (CO).

$[\{Ru(\eta^5\text{-}C_5Me_5)\}_2(HTrp\text{-}TrpOH)][CF_3SO_3]_2$ **5**. The compound HTrp-TrpOH (0.043 g, 0.1 mmol) was added to a solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in thf (6 cm^3) and the solution stirred for 3 d at reflux. After filtering the product was precipitated from the filtrate by addition of hexane. The solid was centrifuged and the orange-yellow product **5** dissolved in a few cm^3 of methanol. After filtration of remaining solid the solvent was removed in vacuum to afford complex **5** in 46% yield (0.055 g) (Found: C, 45.0; H, 4.6; N, 4.6. Calc. for $C_{44}H_{52}F_6N_4O_9Ru_2S_2\cdot CH_3OH$: C, 45.3; H, 4.7; N, 4.7%). FAB mass spectrum: *m/z* 1145 (6, M^+), 994 (23, $[M - CF_3SO_3]^+$), 845 (13, $[M - 2CF_3SO_3]^+$), 609 {17, $[M - 2CF_3SO_3 - Ru(C_5Me_5)]^+$} and 366 {100%, $[M - 2CF_3SO_3 - Ru(C_5Me_5)(C_9H_8N)]^+$}. ^1H NMR (CD_3OD): δ 1.63, 1.64, 1.65, 1.66 (4 s, 30 H, C_5Me_5), 2.24, 2.48 (2 dd, 2 H, β_2-CH_2), 2.74 (2 dd, 2 H, β_1-CH_2), 4.17 (m, 1 H, α_2-CH), 4.32 (m, 1 H, α_1-CH), 5.46 (m, 4 H, indole H^4, H^5), 6.30 (m, 4 H, indole H^3, H^6), 7.34 and 7.44 (2 s, 1 H, indole H^9). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3397m (NH) and 1679s (CO).

$[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-}Trp\text{-}Trp\text{-})\}][CF_3SO_3]_2$ **6**. A solution of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ (0.102 g, 0.2 mmol) in thf (6 cm^3) was stirred for 3 h at reflux together with cyclo(-Trp-Trp-) (0.037 g, 0.1 mmol). The dark green solution was filtered and the product precipitated by addition of hexane. The dark green product was subsequently dissolved in a small quantity of methanol, the solution filtered and the solvent removed in vacuum to afford complex **6** in 33% yield (0.038 g) (Found: C, 45.6; H, 4.6; N, 4.3. Calc. for $C_{44}H_{50}F_6N_4O_8Ru_2S_2\cdot CH_3OH$: C, 45.9; H, 4.6; N, 4.8%). FAB mass spectrum: *m/z* 845 (39, $[M - 2CF_3SO_3]^+$), 609 {45, $[M - 2CF_3SO_3 - Ru(C_5Me_5)]^+$} and 366 {100%, $[M - 2CF_3SO_3 - Ru(C_5Me_5)(C_9H_8N)]^+$}. ^1H NMR (CD_3OD): δ 1.65 (m, 30 H, C_5Me_5), 2.74 (m, 4 H, β-CH_2), 4.26 (m, 2 H, α-CH), 5.44 (m, 4 H, indole H^4, H^5), 6.26 (m, 4 H, indole H^3, H^6), 7.35 and 7.46 (2 s, 2 H, indole H^9). IR (KBr disc): $\tilde{\nu}/cm^{-1}$ 3270s (NH) and 1679vs (CO).

$[Ru(\eta^5\text{-}C_5Me_5)(Bu^tOCO\text{-}Phe\text{-}Phe\text{-}OMe)]Cl$ **7**. The compound phenylalanine methyl ester (HPhe-OMe) (0.057 g, 0.32 mmol) was added to a solution of $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ (0.100 g, 0.16 mmol) in methanol (50 cm^3) and the solution stirred for 3 h at 80 °C. After removal of the solvent, the resulting yellow solid was dissolved in methanol (3 cm^3) and the solution filtered. Addition of CH_2Cl_2 (3 cm^3) led to precipitation of $[Ru(\eta^5\text{-}C_5Me_5)(HPhe\text{-}OMe)]Cl$, which was filtered off and dried (yield 0.113 g, 94%). FAB mass spectrum: *m/z* 416 (78%, $[M - Cl]^+$). ^1H NMR (CD_3OD): δ 2.01 (s, 15 H, C_5Me_5) and 6.04 (m, 5 H, η^6-Ph). The peptide complex **7** was prepared by the carbodiimide method.[10] The complex $[Ru(\eta^5\text{-}C_5Me_5)(HPhe\text{-}OMe)]Cl$ (0.076 g, 0.2 mmol) was added to a solution of the N-protected amino acid Bu^tOCO-PheH (0.036 g, 0.2 mmol) in CH_2Cl_2 (5 cm^3). After addition of triethylamine (0.2 mmol) and the coupling reagent *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide the suspension was stirred for 12 h at −50 °C. The mixture was then treated with water (5 cm^3), 1 mol dm^{-3} citric acid (5 cm^3) and Na_2CO_3 (5 cm^3) to afford complex **7** as a light brown solid after solvent removal (yield 0.128 g, 92%) (Found: C, 58.0; H, 6.4; N, 3.8. Calc. for $C_{34}H_{45}ClN_2O_5Ru$: C, 58.5; H, 6.5; N, 4.0%). FAB mass spectrum: *m/z* 663 (100%, $[M - Cl]^+$). ^1H NMR (CD_3OD): δ 1.34 (m, 9 H, Bu^t), 2.02 (s, 15 H, C_5Me_5), 2.98 (m, 4 H, β-CH_2), 3.75 (m, 3 H, CH_3), 4.30 (m, 1 H, α-CH), 4.70 (m, 1 H, α-CH), 5.83 (m, 5 H, η^6-Ph) and 7.25 (m, 5 H, Ph).

$[Ru(\eta^5\text{-}C_5Me_5)\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}]Cl$ **8**. The Bu^tOCO protecting group in complex **7** (0.140 g, 0.2 mmol) was removed in 98% acetic acid (10 cm^3) with the solvent being removed in vacuum after 2 h. The cyclisation to **8** was performed in a mixture of *sec*-butyl alcohol (10 cm^3) and toluene (2 cm^3) according to Nitecki and Westley.[11] After stirring for 2 h at 80 °C the solvent was removed to afford complex **8** in 90% yield (0.102 g) (Found: C, 58.8; H, 5.8; N, 4.5. Calc. for $C_{28}H_{33}ClN_2O_2Ru$: C, 59.4; H, 5.9; N, 4.9%). FAB mass spectrum: *m/z* 529 (100%, $[M - Cl]^+$). ^1H NMR (CD_3OD): δ 1.95 (s, 15 H, C_5Me_5), 2.95 (m, 4 H, β-CH_2), 4.10, 4.31 (2 m, 2 H, α-CH), 5.73 (m, 5 H, η^6-Ph) and 7.29 (m, 5 H, Ph).

X-Ray Crystallography.—Suitable crystals of $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}][CF_3SO_3]_2\cdot 1.5MeOH$ were obtained by layering a solution of complex **3** in CH_2Cl_2–MeOH (80:20) with hexane.

Crystal data. $C_{40}H_{48}F_6N_2O_8Ru_2S_2\cdot 1.5CH_3OH$, M = 1113.1, orthorhombic, space group $P2_12_12_1$, a = 11.896(5), b = 16.996(6), c = 22.694(5) Å, U = 4588(3) $Å^3$ (by least-squares refinement on diffractometer angles for 25 automatically centred reflections, λ = 0.710 73 Å), T = 173 K, Z = 4, D_c = 1.60 g cm^{-3}, $F(000)$ = 2244. Pale yellow plates. Crystal dimensions: 0.53 × 0.36 × 0.31 mm, μ(Mo-Kα) = 8.29 cm^{-1}.

Data collection and processing. Siemens P4 diffractometer, ω mode with scan speed 2.1–22.6° min^{-1}, graphite-monochromated Mo-Kα radiation; 3877 unique reflections measured ($4.0 \leqslant 2\theta \leqslant 45°$, $+h,k,l$), absorption correction for the low-temperature data with DIFABS,[12] no significant alterations observed in the control intensities monitored every 100 reflections.

Structure analysis and refinement. Direct methods (Ru atoms) followed by standard heavy-atom procedures. Full-matrix least squares on $|F^2|$ with hydrogen atoms for the phenyl, piperazine and one of the C_5Me_5 rings [C(51)–C(55)] at calculated positions. The second C_5Me_5 ligand [C(51')–C(55')] is disordered with site occupation factors (s.o.f.) of 0.41(2) and 0.59(2). The C_5Me_5 ring systems were refined as rigid groups. Disorder was also observed for the second $CF_3SO_3^-$ anion

Table 1 Fractional atomic coordinates (× 10^4) for complex **3** with estimated standard deviations (e.s.d.s) in parentheses

Atom	x	y	z	Atom	x	y	z
Ru	6 255(1)	5 068(1)	268(1)	C(36')	8 199(11)	8 646(6)	2 290(5)
Ru'	8 880(1)	7 504(1)	2 614(1)	C(1)	5 003(12)	7 978(7)	459(5)
C(31)	6 073(11)	6 362(6)	308(4)	O(1)	4 004(7)	7 804(5)	359(4)
C(32)	5 187(12)	5 998(8)	611(5)	C(2)	5 858(10)	7 786(6)	1(5)
C(33)	5 382(14)	5 448(8)	1 080(5)	N(2)	7 013(9)	8 022(6)	158(4)
C(34)	6 473(12)	5 243(8)	1 230(5)	C(3)	5 853(10)	6 912(6)	−187(4)
C(35)	7 366(12)	5 604(10)	934(5)	C(1')	7 292(10)	8 443(6)	629(5)
C(36)	7 197(10)	6 154(7)	473(5)	O(1')	8 244(7)	8 732(5)	682(4)
C(41)	5 831(5)	3 851(3)	91(3)	C(2')	6 488(10)	8 498(7)	1 127(5)
C(42)	7 001(5)	3 963(3)	−12(2)	N(2')	5 343(8)	8 340(5)	945(4)
C(43)	7 123(5)	4 520(3)	−477(2)	C(3')	6 827(10)	7 918(7)	1 625(5)
C(44)	6 028(5)	4 751(3)	−662(2)	S(100)	607(3)	5 316(2)	897(2)
C(45)	5 229(5)	4 338(3)	−311(2)	O(110)	112(9)	6 027(6)	1 109(5)
C(51)	5 316(7)	3 309(4)	546(4)	O(120)	759(10)	5 303(6)	266(5)
C(52)	7 949(7)	3 561(5)	316(4)	O(130)	137(9)	4 608(6)	1 141(6)
C(53)	8 224(6)	4 813(5)	−730(4)	C(100)	2 029(14)	5 376(11)	1 178(7)
C(54)	5 760(7)	5 335(5)	−1 146(3)	F(110)	2 522(8)	6 028(7)	1 014(5)
C(55)	3 963(7)	4 405(5)	−358(4)	F(120)	2 042(9)	5 336(7)	1 755(4)
C(41')	8 407(10)	7 354(7)	3 554(5)	F(130)	2 640(10)	4 787(7)	998(6)
C(42')	9 549(10)	7 118(7)	3 476(5)	S(200)	3 781(4)	8 517(3)	2 473(2)
C(43')	9 572(10)	6 493(7)	3 056(5)	O(211)	2 884(13)	8 887(13)	2 807(6)
C(44')	8 444(11)	6 342(7)	2 874(6)	O(221)	4 761(12)	8 273(14)	2 809(7)
C(45')	7 723(10)	6 874(8)	3 182(6)	O(231)	4 010(17)	8 868(14)	1 904(6)
C(51')	7 991(15)	8 000(11)	3 961(8)	O(212)	2 855(12)	8 571(19)	2 887(7)
C(52')	10 562(14)	7 471(11)	3 786(8)	O(222)	4 891(10)	8 677(14)	2 703(7)
C(53')	10 613(14)	6 064(11)	2 841(9)	O(232)	3 552(15)	8 772(13)	1 880(5)
C(54')	8 074(17)	5 725(11)	2 431(8)	C(201)	3 589(16)	7 474(13)	2 414(8)
C(55')	6 454(15)	6 921(12)	3 124(9)	F(211)	3 772(17)	7 235(12)	2 970(7)
C(41'')	8 005(9)	7 144(6)	3 419(4)	F(221)	4 301(17)	7 080(16)	2 066(9)
C(42'')	9 195(9)	7 123(6)	3 500(4)	F(231)	2 549(15)	7 239(14)	2 270(8)
C(43'')	9 646(8)	6 545(5)	3 109(4)	C(202)	3 540(18)	7 476(13)	2 322(8)
C(44'')	8 735(8)	6 208(5)	2 787(4)	F(212)	3 420(17)	6 901(12)	2 739(8)
C(45'')	7 720(8)	6 578(5)	2 979(4)	F(222)	4 337(18)	7 177(17)	1 953(10)
C(51'')	7 185(13)	7 673(9)	3 745(6)	F(232)	2 576(17)	7 417(14)	2 000(9)
C(52'')	9 864(13)	7 628(9)	3 927(6)	C(301)	6 150(44)	1 014(29)	923(13)
C(53'')	10 879(11)	6 328(9)	3 047(7)	O(301)	6 071(21)	1 274(12)	292(11)
C(54'')	8 827(12)	5 568(7)	2 322(6)	C(302)	6 182(50)	525(26)	879(20)
C(55'')	6 545(11)	6 400(9)	2 753(7)	O(302)	6 135(34)	1 380(16)	712(18)
C(31')	7 973(11)	8 065(7)	1 855(5)	C(303)	4 553(87)	5 214(43)	2 542(41)
C(32')	8 898(10)	7 624(6)	1 646(4)	O(303)	4 047(51)	4 512(31)	2 240(23)
C(33')	9 978(14)	7 762(8)	1 850(5)	O(304)	4 067(52)	5 211(36)	2 752(24)
C(34')	10 195(13)	8 338(7)	2 294(5)	C(304)	3 554(38)	5 484(24)	3 321(18)
C(35')	9 250(11)	8 767(7)	2 521(5)				

Table 2 Selected bond lengths (Å)

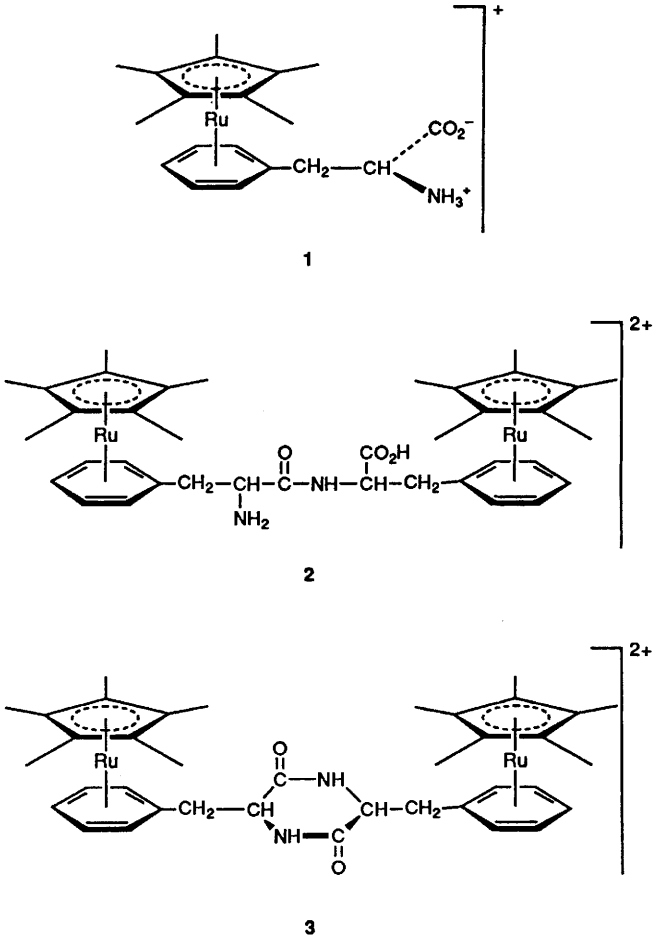
Ru–C(31)	2.211(9)	Ru'–C(31')	2.245(11)
Ru–C(32)	2.172(13)	Ru'–C(32')	2.206(9)
Ru–C(33)	2.210(13)	Ru'–C(33')	2.215(13)
Ru–C(34)	2.218(11)	Ru'–C(34')	2.230(12)
Ru–C(35)	2.204(13)	Ru'–C(35')	2.201(12)
Ru–C(36)	2.209(11)	Ru'–C(36')	2.228(11)
Ru–C(41)	2.167(5)	Ru'–C(41')	2.222(11)
Ru–C(42)	2.172(5)	Ru'–C(42')	2.212(11)
Ru–C(43)	2.189(5)	Ru'–C(43')	2.153(12)
Ru–C(44)	2.195(5)	Ru'–C(44')	2.125(13)
Ru–C(45)	2.181(5)	Ru'–C(45')	2.168(13)
C(31)–C(3)	1.49(1)	C(31')–C(3')	1.48(2)
C(3)–C(2)	1.54(2)	C(3')–C(2')	1.55(2)
C(2)–C(1)	1.49(2)	C(2')–C(1')	1.48(2)
C(1)–O(1)	1.25(2)	C(1')–O(1')	1.24(1)
C(2)–N(2)	1.48(2)	C(2')–N(2')	1.45(2)
C(1)–N(2')	1.33(2)	C(1')–N(2)	1.33(1)

[S(200), C(200), s.o.f. 0.5 for the O and F positions] and for the methanol molecules which display four different sites (s.o.f. 0.56, 0.40, 0.39 and 0.15). Anisotropic thermal parameters were introduced for those non-hydrogen atoms which were not disordered. Weighting scheme: $w = 1/[\sigma^2(F_o^2) + (0.0807P)^2 + 5.57P]$ with $P = [\max(F_o^2, 0) + 2F_c^2]/3$. Final reliability indices: $R = 0.049$ [2974 reflections with $I > 2\sigma(I)$] and 0.068 for all 3877 reflections, $wR_2 = 0.122$ [$I > 2\sigma(I)$] and 0.139 (all data). Maximum, minimum residual electron density: 0.60, −0.55 e Å^{-3}. Structure solution and refinement with SHELXS[13a] and SHELXL.[13b] Fractional atomic coordinates are listed in Table 1, selected bond lengths in Table 2.

Additional material available from the Cambridge Crystallographic Data Centre comprises thermal parameters and remaining bond lengths and angles.

Results and Discussion

Reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with the phenylalanine derivatives L-HPheOH, HPhe-PheOH and cyclo(-Phe-Phe-) in thf leads to the formation of the η^6-co-ordinated complexes **1**–**3** in satisfactory yields. The ^{1}H NMR spectra (400 MHz, CD_3OD) of these sandwich complexes all exhibit a characteristic upfield shift for the phenyl protons from δ 7.2–7.4 in the free amino acid or peptide to δ 5.54–5.85 in the η^6-co-ordinated ligand, as has been observed for other η^6-co-ordinated arenes.[6,7] At the beginning of this work it was not certain from previous studies whether the potential N and O donor atoms in L-HPheOH or the dipeptides HPhe-PheOH and cyclo(-Phe-Phe-) would inhibit η^6 co-ordination of the $(\eta^5\text{-}C_5Me_5)Ru^{II}$ moiety to the phenyl ring. For instance, effectively quantitative formation of the κ^2N,O-co-ordinated chelate



complex $[Ru(\eta^5\text{-}C_5Me_5)Cl(\text{L-HPheO})]^-$ is observed in the reaction of $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ with L-HPheOH in methanol at temperatures below 0 °C. In contrast, the entropically favoured sandwich complex $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-L-HPheOH})]^+$ may be prepared in 88% yield by the same reaction at reflux. However, the reaction mixture still contains about 10% of the κ^2N,O-co-ordinated half-sandwich complex. Use of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ as a starting material leads only to the precipitation of the η^6-co-ordinated complexes **1**–**3** during the course of the reaction. Whereas more forcing conditions are required for **1** (12 h reflux), the reaction with the dipeptides may be performed at room temperature (2 d). This kinetic aspect may reflect the fact that the competitive formation a κ^2N,O-co-ordinated five-membered chelate ring as for L-HPheOH will be energetically much less favourable for HPhe-PheOH and is not possible for cyclo(-Phe-Phe-).

Complex **1** displays a strong ν(CO) absorption band at 1636 cm^{-1}, a value typical for deprotonated carboxylate groups, which suggests that the η^6-co-ordinated amino acid adopts a zwitterionic structure in this complex. The C_5Me_5 proton resonances in **1**–**3** are observed at respectively δ 2.00 (s), 1.98 (2 s) and 1.95 (s). As may be seen in Fig. 1, the ruthenium(II) sandwich systems in the cation $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{\text{cyclo(-Phe-Phe-)}\}]^{2+}$ **3** adopt orientations which are approximately perpendicular to one another. This conformation, which leads to a minimisation of intramolecular interaction between the constituent π systems, may also be gauged from the torsion angles of −59.5 and 58.8° for C(1)–C(2)–C(3)–C(31) and C(1′)–C(2′)–C(3′)–C(31′) respectively. The central six-membered ring system exhibits a significant deviation from planarity with the atoms C(1′) and C(2′) displaced respectively 0.12 and −0.14 Å from the best least-squares plane through the remaining atoms. Relevant torsion angles are 18.6° for C(2)–N(2)–C(1′)–C(2′), −22.4° for N(2)–C(1′)–C(2′)–N(2′) and 18.2° for C(1′)–C(2′)–N(2′)–C(1). A singlet is observed for the C_5Me_5 methyl protons in CD_3OD solution, indicating the equivalence of the $(\eta^5\text{-}C_5Me_5)Ru^{II}$ sandwiches of **3** on the NMR time-scale. This is also the case for the α-protons which exhibit a triplet at δ 4.43 but not for the β-protons for which doublets of doublets are observed at δ 2.46 ($H^{\beta'}$) and 2.82 (H^{β}) [$J(H^{\beta}H^{\beta'})$ = 14.0, $J(H^{\alpha}H^{\beta})$ = 3.7, $J(H^{\alpha}H^{\beta'})$ = 4.9 Hz]. A similar phenomenon was recorded for the O-terminal β_2 protons in $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2(\text{HPhe-PheOH})]^{2+}$ **2**, which display a $J(H^{\beta_2}H^{\beta_2'})$ value of 8.4 Hz [$J(H^{\alpha_2}H^{\beta_2'})$ = 5.1 Hz]. In contrast, the isochronous N-terminal β_1 protons in **2** yield only a single doublet with $J(H^{\alpha_1}H^{\beta_1})$ = 4.6 Hz.

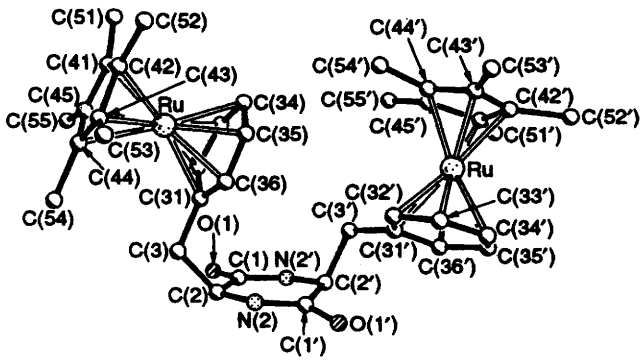
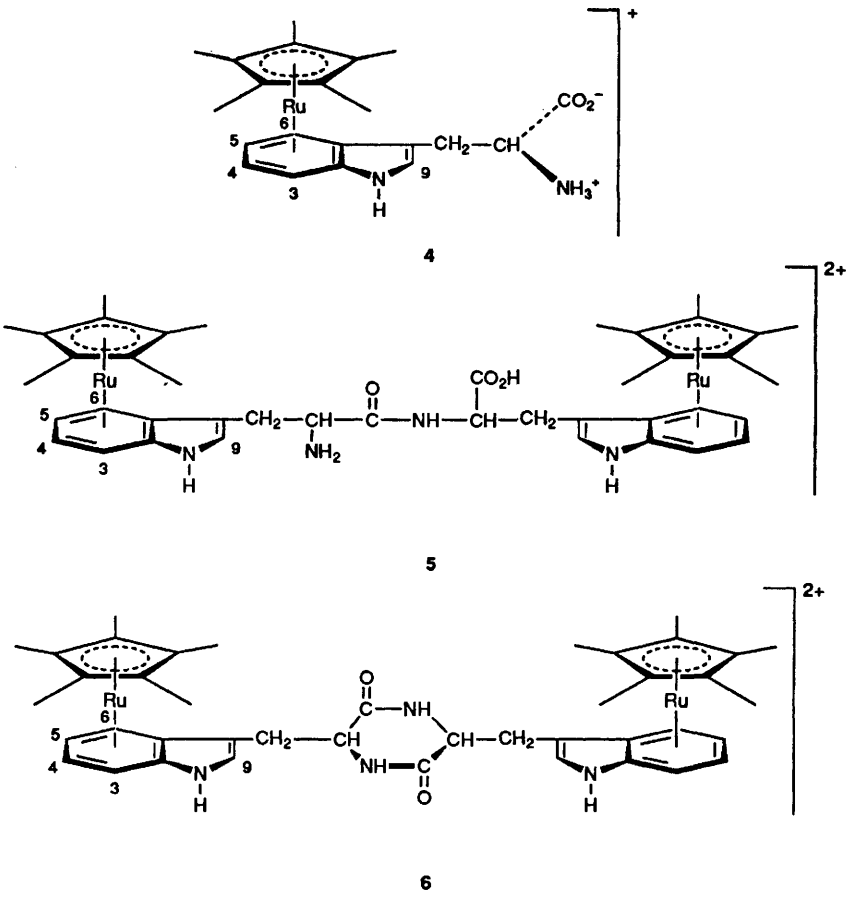


Fig. 1 Molecular structure of the cation $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{\text{cyclo-(-Phe-Phe-)}\}]^{2+}$ of complex **3**

The analogous reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with the tryptophan derivatives L-HTrpOH, HTrp-TrpOH and cyclo(-Trp-Trp-) in thf affords the η^6-co-ordinated sandwich complexes **4**–**6**. As these products are soluble in thf, precipitation must be induced by addition of hexane. η^6-Co-ordination of the indole six-membered ring is confirmed by the characteristic upfield shifts of the NMR proton resonances H^3–H^6 to δ 5.44–5.60 (H^4, H^5) and 6.26–6.56 (H^3, H^6). In contrast, the aromatic proton H^9 of the uncoordinated five-membered ring experiences only a marginal shift (δ 7.34–7.76). Similar chemical shifts have recently been reported by Trudell and co-workers[14] for the indole protons in the analogous η^6-co-ordinated tryptamine (indole-3-ethanamine)derivative $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-trpa})][CF_3SO_3]$. Interestingly, these authors were only able to synthesise this sandwich complex by use of the N-protected η^6-co-ordinated derivatives $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-}Bu^tOCO\text{-trpa})][CF_3SO_3]$ and $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-}PhCH_2OCO\text{-trpa})][CF_3SO_3]$. In contrast to the present study on tryptophan derivatives, direct reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with tryptamine was observed to lead only to the formation of metastable $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_2(\text{trpa})][CF_3SO_3]$, in which the indole derivative displays a κ^1N(amino) co-ordination. Attempts to convert this σ complex into the entropically favoured sandwich complex $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-trpa})][CF_3SO_3]$ were unsuccessful.[14]

Of particular interest is the observation of two singlets at δ 1.72 (approximate ratio 50:50) for the C_5Me_5 methyl protons in $[Ru(\eta^5\text{-}C_5Me_5)(\text{L-HTrpOH})][CF_3SO_3]$ **4**, which are indicative of the presence of diastereomers caused by facial chirality at the ruthenium atom. The use of both sides of the six-membered indole ring for η^6 co-ordination is also evidenced by the observation of four doublets for the protons H^3 and H^6 and two singlets for H^9. Singlets (δ 1.63–1.66) for each of the four possible diastereomers of $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2(\text{HTrp-TrpOH})]^{2+}$ **5** were recorded in the ^1H NMR spectrum of this dipeptide complex. A broad signal at δ 1.65 also indicates the presence of diastereomers in a solution of $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{\text{cyclo(-Trp-Trp-)}\}]^{2+}$ **6**. Surprisingly Trudell and co-workers[14] reported only the presence of singlets for the C_5Me_5 methyl protons in the ^1H NMR spectra of their analogous



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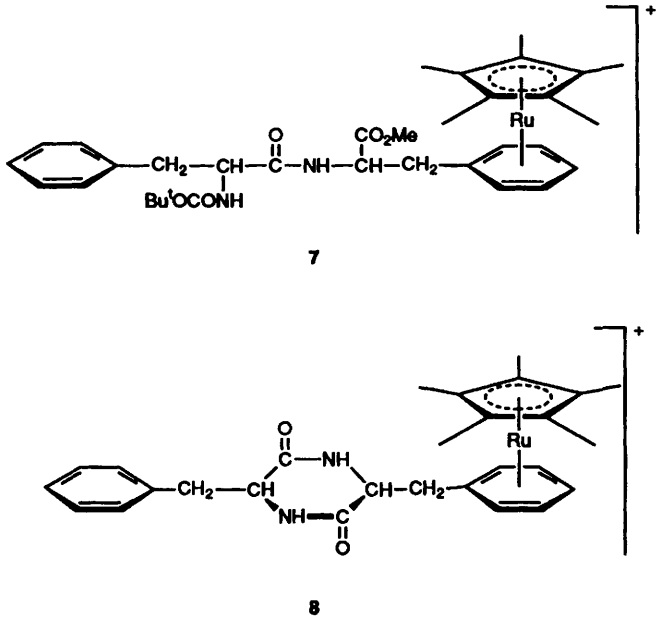
tryptamine derivatives. As for the phenylalanine complex **1**, the IR spectrum of $[Ru(\eta^5C_5Me_5)(L\text{-}HTrpOH)][CF_3SO_3]$ **4** exhibits a strong ν(CO) absorption at 1636 cm^{-1}, indicating that the η^6-co-ordinated amino acid HTrpOH is also present as a zwitterion.

The suitability of η^6-co-ordinated building blocks of the type $[Ru(\eta^5\text{-}C_5Me_5)(HaaOH)]^+$ for the synthesis of $(\eta^5\text{-}C_5Me_5)Ru^{II}$-labelled peptides was investigated using the carbodiimide method[10] for the simple example $[Ru(\eta^5\text{-}C_5Me_5)\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}]^+$ **8**. The required starting material $[Ru(\eta^5\text{-}C_5Me_5)(L\text{-}HPhe\text{-}OMe)]Cl$ was obtained by reaction of $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ with phenylalanine methyl ester (L-HPhe-OMe) in methanol at reflux. This complex was then added to a CH_2Cl_2 solution of the N-protected amino acid Bu^{t}OCO-PheOH in the presence of base (NEt_3) and the coupling reagent *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide to yield the peptide derivative **7**. After removal of the N-protection group in 98% acetic acid, cyclisation to the η^6-co-ordinated ligand cyclo(-Phe-Phe-) was performed in *sec*-butyl alcohol–toluene (4:1) at reflux. The product **8** exhibits respective multiplets at δ 5.73 and 7.29 for the co-ordinated and unco-ordinated phenyl groups. Attempts to prepare the cation $[Ru(\eta^5\text{-}C_5Me_5)\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}]^+$ by direct reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with cyclo(-Phe-Phe-) in a 1:1 molar ratio led to preferred formation of the 2:1 complex **3**.



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An analogous $(\eta^5\text{-}C_5Me_5)Ru^{II}$ labelling of biologically relevant peptides could open new analytical perspectives for the investigation of receptor sites. In this respect it is interesting that η^6-co-ordinated arenes in sandwich complexes of the type $[Ru(\eta^5\text{-}C_5Me_5)(\eta^6\text{-arene})]^+$ may be photochemically released.[15] We have studied the feasibility of this procedure for peptide complexes by irradiating a MeCN solution of $[\{Ru(\eta^5\text{-}C_5Me_5)\}_2\{cyclo(\text{-}Phe\text{-}Phe\text{-})\}][CF_3SO_3]_2$ **3** with a mercury lamp (254–380 nm) for 3 h, which leads to release of cyclo(-Phe-Phe-) as a white precipitate in quantitative yield.

Koefod and Mann[16] have demonstrated that kinetically controlled η^6 co-ordination of the $(\eta^5\text{-}C_5Me_5)Ru^{II}$ moiety leads to a preference for partially localised arene π systems (*e.g.* indole) over arene π systems which are highly delocalised (*e.g.* phenyl). This kinetically derived chemospecificity was also confirmed by Trudell and co-workers[14] for *N*-

benzyloxycarbonyl-*N*-methoxytryptamine which affords the η^6-co-ordinated indole derivative $[Ru(\eta^5\text{-}C_5Me_5)(MeO\text{-}PhCH_2OCO\text{-}trpa)][CF_3SO_3]$ in 92% yield. The $(\eta^5\text{-}C_5Me_5)Ru^{II}$ fragment obviously differentiates between two electron-rich arenes, preferring the indole six-membered ring over the highly delocalised phenyl ring of the $PhCH_2OCO$ protection group. This finding prompted us to study the reactions of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ and $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ with mixed dipeptides such as HPhe-TrpOH and HTrp-PheOH. Our preliminary results have demonstrated that only the indole-co-ordinated 1 : 1 complexes $[Ru(\eta^5\text{-}C_5Me_5)(HPhe\text{-}TrpOH)]Cl$ and $[Ru(\eta^5\text{-}C_5Me_5)(HTrp\text{-}PheOH)]Cl$ may be isolated by size-exclusion chromatography (Sephadex LH-20) from the product mixtures which result from the reaction of $[\{Ru(\eta^5\text{-}C_5Me_5)Cl\}_2(\mu\text{-}Cl)_2]$ with the relevant dipeptide in a 1 : 1 molar ratio.

Our present results indicate the potential of $(\eta^5\text{-}C_5Me_5)Ru^{II}$ labelling of peptides with aromatic side chains by demonstrating that the reaction of $[Ru(\eta^5\text{-}C_5Me_5)(MeCN)_3][CF_3SO_3]$ with chosen dipeptides leads to the formation of entropically favoured sandwich complexes rather than the alternative κ^1N- or κ^2N,O-co-ordinated derivatives. Such η^6-co-ordinated bioligands may be photochemically released at a later stage. Preliminary results suggest that a chemospecific co-ordination of indole six-membered rings may be expected.

References

1 G. Jaouen, A. Vessières and I. S. Butler, *Acc. Chem. Res.*, 1993, **26**, 361.

2 D. P. Smith, E. Baralt, B. Morales, M. M. Olmstead, M. F. Maestre and R. H. Fish, *J. Am. Chem. Soc.*, 1992, **114**, 10647.

3 W. S. Sheldrick and S. Heeb, *J. Organomet. Chem.*, 1989, **377**, 357; D. Carmona, A. Mendoza, F. J. Lahoz, L. A. Oro, M. P. Lamata and E. San Jose, *J. Organomet. Chem.*, 1990, **396**, C17; R. Krämer, K. Polborn, H. Wanjek, I. Zahn and W. Beck, *Chem. Ber.*, 1990, **123**, 767; R. Krämer, K. Polborn and W. Beck, *Chem. Ber.*, 1991, **124**, 2429; W. S. Sheldrick, E. Hauck and S. Korn, *J. Organomet. Chem.*, 1994, **467**, 283.

4 W. Beck and R. Krämer, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1467.

5 A. Vessières, M. Salmain, V. Philomin and G. Jaouen, *Immunoanal. Biol. Spec.*, 1992, **31**, 9; M. Salmain, A. Vessières, P. Brossier, I. S. Butler and G. Jaouen, *J. Immunol. Methods*, 1992, **148**, 65.

6 D. Vichard, M. Gruselle, H. El Amouri and G. Jaouen, *J. Chem. Soc., Chem. Commun.*, 1991, 46; D. Vichard, M. Gruselle, H. El Amouri, G. Jaouen and J. Vaissermann, *Organometallics*, 1992, **11**, 976; 2952.

7 W. S. Sheldrick and A. Gleichmann, *J. Organomet. Chem.*, 1994, **470**, 183.

8 M. Wenzel, P. Asindraza and G. Schachschneider, *J. Labelled Compd. Radiopharm.*, 1983, **20**, 1061; W. H. Soine, C. E. Guyer and F. F. Knapp, jun., *J. Med. Chem.*, 1984, **27**, 803.

9 P. J. Fagan, M. D. Ward and J. C. Calabrese, *J. Am. Chem. Soc.*, 1989, **11**, 1698.

10 J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, 1967, **33**, 864; D. F. DeTar, R. Silverstein and F. F. Rogers, jun., *J. Am. Chem. Soc.*, 1966, **88**, 1024.

11 D. E. Nitecki and J. W. Westley, *J. Org. Chem.*, 1967, **33**, 864.

12 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.

13 G. M. Sheldrick, (*a*) SHELXS 86, A Program for Structure Determination, Göttingen, 1986; (*b*) SHELXL 93, A Program for Structure Refinement, Göttingen, 1993.

14 S. A. Lomenzo, S. P. Nolan and M. L. Trudell, *Organometallics*, 1994, **13**, 676.

15 A. M. McNair, J. L. Schrenk and K. R. Mann, *Inorg. Chem.*, 1984, **23**, 2633; J. L. Schrenk, A. M. McNair, F. B. McCormik and K. R. Mann, *Inorg. Chem.*, 1986, **25**, 3501.

16 R. S. Koefod and K. R. Mann, *J. Am. Chem. Soc.*, 1990, **112**, 7287.

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