Synthesis of Ruthenium-Labelled Tripeptoids with Alternating Amide and Diaryl Ether Bonds

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Free-amino forms of 4-*O*-methyldopamine and 4-*O*-methyltyramine react as nucleophiles in a chemoselective manner with $[RuCp]^+$-complexed *p*-substituted chloroarenes. As a consequence, it is not necessary to use protecting groups for the synthesis of peptoids with alternating amide and diaryl ether bonds. $[RuCp]^+$-labelled diaryl ether tripeptoids containing DOPA- and tyrosine-derived subunits have been assembled as model compounds. The purification of the charged complexes was conveniently achieved employing aminopropyl-functionalised silica as a stationary phase. The free-amino form of tripeptoid **2** resembles the ABB′ partial structure of the macrocyclic bastadins, biologically active natural products from the marine sponge *Ianthella*.

Introduction

Radioactive labelling of peptides holds the promise of selectively binding and destroying tumour cells by combining the biological activity of biooligomers with the physical properties of metals. Ruthenium appears to be an especially suitable metal, because its radioactive isotopes cover a range of half-lives from three days to one year[1] and may be incorporated into peptoids[2] as chemically stable[3] sandwich complexes. Stability against chemoenzymatic degradation may be achieved by the incorporation of diaryl ether structural elements into larger ruthenium-labelled peptoids.[4] Biologically active natural products containing diaryl ethers include the macrocyclic bastadin 5 (**1**, Figure 1) from the marine sponge *Ianthella* sp.,[5] which inhibits Ca^{2+} uptake into the sarcoplasmatic reticulum.[6] Another very important example is the clinically applied glycopeptide antibiotic vancomycin,[7] which has *O*-linked tyrosine and phenylglycine side chains. In an early study, radioactive β-ruthenocenylalanine was used to image the pancreatic gland with low target specificity.[8] Before libraries of ruthenium-labelled peptoids can be analysed, their synthesis and chemical properties must first be explored.

Segal discovered that ruthenium sandwich complexes of diaryl ethers are readily formed by nucleophilic attack of phenolates at $[RuCp]^+$-complexed chlorobenzenes.[9] Pearson, Rich, and Matassa have all used this methodology for the synthesis of ruthenium-free peptidic diaryl ethers.[10]

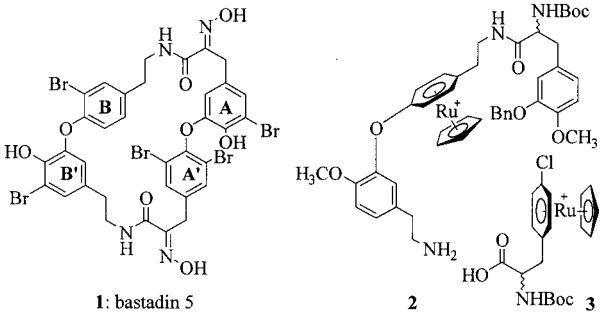

Figure 1. The macrocyclic bis-diaryl ether bastadin 5 (**1**) from the marine sponge *Ianthella basta* consists of two tyrosine (A, A′) and two tyramine units (B, B′); hexafluorophosphate is the counterion of the sandwich complexes **2** and **3**

In this paper, we report the convenient synthesis of the tripeptoid **2**, which resembles the ABB′ partial structure of bastadin 5 (**1**). We were encouraged to pursue this study by our earlier finding that the use of aminopropyl-functionalised silica as a stationary phase allows the reliable purification of $[RuCp(\eta^6\text{-arene})]^+$ complexes by preparative HPLC.[11] Compound **2** is among the largest ruthenium-labelled peptoids characterised thus far and its free amino group may be used for amide coupling with the known $[RuCp]^+$-sandwich complex **3**[12] of chlorophenylalanine.

Results and Discussion

An important question is that concerning the chemoselectivity of the attack at $[RuCp]^+$-complexed chlorobenzenes by ambident nucleophiles. If presented exclusively, both phenolates and amines[13] will react. Preferentially, when synthesising larger peptoids, unnecessary deprotec-

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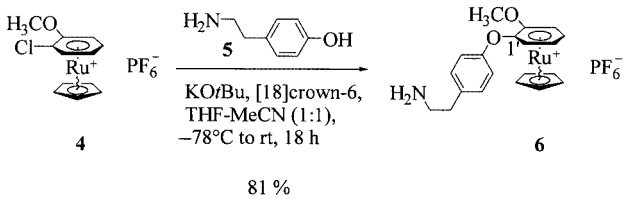
tion steps should be avoided. In a model experiment, racemic [RuCp]$^+$-complexed *o*-chloroanisole (**4**) was treated with unprotected tyramine (**5**) in the presence of equimolar amounts of KO*t*Bu/[18]crown-6 (Scheme 1).

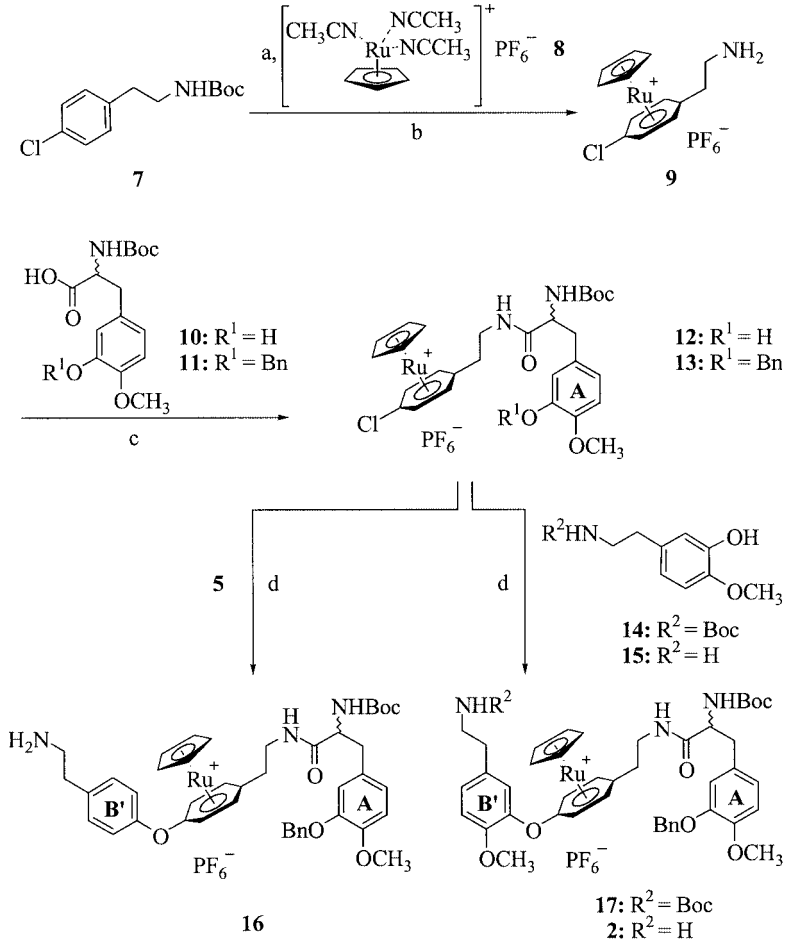


Scheme 1. Chemoselective formation of the diaryl ether **6** by the reaction of the 2-chloroanisole complex **4** with the unprotected, ambident nucleophile tyramine (**5**)

Under mild conditions, the [RuCp]$^+$-labelled diaryl ether **6** was formed without concomitant demethylation. The comparison of the ^{13}C NMR chemical shifts of the aromatic carbon atoms of the free-amino diaryl ether **6** (δ = 125.7 ppm, C-1′) with those of the corresponding *N*-Boc analogue[11] indicates that diaryl ether bond formation was successful. There was no ^{1}H,^{15}N-HMBC correlation observed between any of the aromatic hydrogen atoms and the nitrogen atom.

The unsymmetrical diaryl ether moieties of the bastadins can be assembled by an S_NAr reaction in two ways. We chose [RuCp]$^+$-complexed, methoxy-free *p*-chlorophenylalanine and phenylethylamine as electrophiles, and DOPA derivatives as nucleophiles.[14] As starting points for our synthetic sequences, we compared 3-(*O*-free)- 4-(*O*-Me)-*N*-Boc-DOPA (**10**) with its 3-*O*-benzyl analogue **11** (Scheme 2).[15] The *O*-benzyl group of **11** has the potential to be replaced by polystyrene for solid-phase synthesis. Under standard conditions (EDCI/HOBt/DIEA) the [RuCp]$^+$-complexed amino group of compound **9** (unit B of the bastarane skeleton) was amide-coupled yielding the dipeptoids **12** and **13**, respectively. Compound **9** was obtained from reaction of [RuCp(NCCH$_3$)$_3$]PF$_6$ (**8**)[16] and Boc-protected *p*-chlorophenylethylamine (**7**), followed by the removal of the Boc group.

As in the model reaction (Scheme 1), chemoselectivity for diaryl ether formation with unprotected tyramine (**5**) was observed when the [RuCp]$^+$-labelled, 3-(*O*-Bn)-protected



Scheme 2. Synthesis of the [RuCp]$^+$-labelled tripeptoid diaryl ethers **16**, **17**, and **2** representing the ABB′ partial structure of bastadin 5 (**1**). The counterion is always hexafluorophosphate. a: 1,2-dichloroethane, 4 h, reflux, 65%; b: 4 N HCl/MeOH, 3 h, room temp.; c: EDCI [*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride], HOBt (hydroxybenzotriazol), DIEA (diisopropylethylamine), room temp.; to **12**: THF/MeOH (1:1), 34 h, 49%; to **13**: THF/MeOH (10:1), 44 h, 60%; d: KO*t*Bu, [18]crown-6, THF/MeCN (1:1), −78 °C to 0 °C; to **16**: **5**, 79%; to **17**: **14**, 87%; to **2**: **15**, 64%.

peptoid **13** was used as the acceptor component, yielding the diaryl ether tripeptoid **16** with a free amino group and an alkyl chain *para* to the diaryl ether bridge.

In comparison with **16**, the bastarane partial tripeptoid **2** possesses a diaryl ether linkage *meta* to the alkyl chain of the benzene ring of unit B. We investigated the reactions of both the *O*-protected (**13**) and *O*-free (**12**) amides with *N*-Boc-protected (**14**) and *N*-free (**15**) 4-(*O*-methyl)dopamine. The unprotected (i.e., free OH unit) amide **12** did not yield ABB′ product in any of the runs, despite the use of an excess of the external nucleophile. Apparently, competition by intermolecular condensation is overwhelming.

Nucleophilic substitution proceeded smoothly using the 3-*O*-benzyl amide **13**. Reaction with the Boc-protected dopamine **14** provided the $[RuCp]^+$-complexed diaryl ether/amide **17**. As observed with smaller cationic sandwich complexes, aminopropyl-functionalised silica was a very useful stationary phase for the workup, even for the tripeptoids. The starting material **13** and the less-polar product **17** were separated cleanly from one another by preparative HPLC and also by gravity column chromatography.

Reaction of **13** with the *N*-free dopamine **15** gave the diaryl ether amide **2** as the first $[RuCp]^+$-complexed free amine consisting of three amino acid-derived units. We have evidence by high-resolution mass spectrometry that the reaction of **2** and **3** (Figure 1) yields the corresponding tetrapeptoid, which represents the complete open-chain ABB′A′ system of the bastadins and contains two $[RuCp]^+$-complexed diaryl ether moieties.

The synthetic strategy we have employed for the synthesis of metal-labelled diaryl ether peptoids offers the key advantage of introducing the label in advance of any biological screening and holds the potential to be transferred to the solid phase. Loss of biological activity during the post-assembly labelling of active peptides should be circumvented for conceptual reasons. It is not necessary to use protecting groups for the synthesis of peptoids with alternating amide and diaryl ether bonds. Therefore, the synthesis and purification of the ruthenium-labelled tripeptoids **2**, **16**, and **17** with alternating amide and diaryl ether bonds are important steps towards a protocol suitable for automated synthesis.

Experimental Section

General: All reactions were carried out under an argon atmosphere with distilled, non-anhydrous solvents. Yields refer to purified compounds. Reagents were purchased from Aldrich, Acros, Alfa, and Fluka at high commercial quality and were used without further purification. Reactions were controlled by thin-layer chromatography [0.25-mm E. Merck alumina plates NH_2 $F_{254}S$ (for reactions involving ruthenium sandwich complexes) and 0.25-mm E. Merck alumina plates Si $F_{254}S$]. TLC plates were analysed under UV light (λ = 254 nm), followed by heating after treatment with a 1,10-phenanthroline solution in EtOH, for ruthenium sandwich complexes, and with ninhydrin, for amines and amino acids. E. Merck Al_2O_3 90 standardised (activity grade II-III, particle size 63−200 μm), E. Merck aminopropyl silica LiChroprep NH_2 (particle size 40−63 μm) and E. Merck silica gel (particle size 230−400 mesh) were used for preparative column chromatography. The HPLC experiments were performed at 25 °C using a Merck−Hitachi L6200A Intelligent Pump System. The column was a preparative E. Merck Hibar Pre-Packed Column RT 250−25, customised packing LiChroprep NH_2 (length 25 cm, diameter 2.5 cm, particle size 25−40 μm). MeCN, water and *i*PrOH were HPLC-grade. The detector was a KONTRON ultraviolet spectrophotometer Uvitron 730S LC and the integrator was a Merck−Hitachi D-2500 Chromato-Integrator. The peaks were detected at λ = 254 nm. NMR spectra were recorded on Bruker WM 250, AM 360, AM 500, and Varian INOVA-400 spectrometers. The NMR shifts were calibrated using TMS as the internal reference and are assigned on the basis of HSQC and HMBC experiments. The multiplicities are: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet and br. = broad. All infrared spectra were recorded on a Perkin−Elmer 1600 series FT-IR spectrometer. The UV/Vis-spectra were recorded using a Hewlett−Packard UV-Spectrophotometer HP 8452 Diode-Array System. Fast atom bombardment (FAB) mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Only the three predominant isotopes are listed. EIMS were recorded on a Varian MAT-311 mass spectrometer. Melting points were determined with a Reichert melting point microscope and are uncorrected. Elemental analyses were performed with the automatic microanalyser Foss-Heraeus Vario EL. Systematic names have been generated according to ref.[17]

***rac*-[1-[4-(2-Aminoethyl)phenoxy]-2-methoxy-η⁶-benzene](η⁵-cyclopentadienyl)ruthenium Hexafluorophosphate (6):** Tyramine (**5**, 15.2 mg, 0.111 mmol) was added to a solution of KO*t*Bu (1 equiv.) and [18]crown-6 (0.1 equiv.) in THF/MeCN (1:1, 15 mL). After 30 min the mixture was cooled to 0 °C and transferred to a precooled (−78 °C) solution of *rac*-(1-chloro-2-methoxy-η⁶-benzene)(η⁵-cyclopentadienyl)ruthenium hexafluorophosphate (**4**)[11] (50 mg, 0.111 mmol) in THF/MeCN (1:1, 20 mL). Over 2 h, the mixture was brought to room temp. and stirred for 16 h, before it was filtered and concentrated. Et_2O was added and the collected precipitate was purified by column chromatography on aminopropyl-functionalised silica with MeCN as eluent to remove [18]crown-6 and then with *i*PrOH/H_2O (6:1), followed by recrystallisation from *i*PrOH. Colourless needles (50 mg, 81%), m.p. 148−150 °C (dec.); TLC (NH_2-Si plates): R_f = 0.33 [*i*PrOH/H_2O (6:1)]. ^1H NMR (500 MHz, CD_3OD): δ = 7.36 (d, *J* = 8.4 Hz, 2 H, CH_{ar}), 7.11 (t, *J* = 8.5 Hz, CH_{ar}), 6.51 (d, *J* = 6.1 Hz, η-CH_{ar}), 6.06 (d, *J* = 6.0 Hz, 1 H, η-CH_{ar}), 5.92 (t, *J* = 5.7 Hz, 1 H, η-CH_{ar}), 5.83 (t, *J* = 5.6 Hz, 1 H, η-CH_{ar}), 5.42 (s, 5 H, Cp), 3.94 (s, 3 H, OCH_3), 2.93 (t, *J* = 6.9 Hz, 2 H, CH_2CH_2NH), 2.81 (t, *J* = 7.1 Hz, 2 H, CH_2CH_2NH) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 153.97 [C_{ar}O(η-Ph)], 138.92 (CH_2C_{ar}), 131.93 (C_{ar}H), 128.47 (η-C_{ar}-OCH_3), 125.67 (η-C_{ar}OPh), 121.14 (C_{ar}H), 82.29 (η-C_{ar}H), 81.82 (η-C_{ar}H), 81.35 (Cp), 77.30 (η-C_{ar}H), 73.28 (η-C_{ar}H), 58.49 (OCH_3), 43.86 (CH_2CH_2NH), 38.74 (CH_2CH_2NH) ppm. IR (KBr): $\tilde{\nu}$ = 3420, 3094, 2926, 2855, 2363, 1554, 1528, 1499, 1476, 1473, 1437, 1414, 1276, 1260, 1220, 1178, 1103, 1007, 844, 668, 558 cm^{-1}. UV/Vis (CH_3OH): λ_{max} (ε) = 266 (17300), 224 (43000) 204 nm (90200 $mol^{-1}dm^3cm^{-1}$). MS (FAB+, NBA): *m*/*z* (%) = 410/411/412 (92/100/76) $[M]^+$. HRMS (FAB): calcd. for $C_{20}H_{22}NO_2{}^{102}Ru$ $[M]^+$: 410.0695, found 410.0722.

[1-(2-Aminoethyl)-4-chloro-η⁶-benzene](η⁵-cyclopentadienyl)-ruthenium Hexafluorophosphate Hydrochloride (9): At 70 °C, $[RuCp(MeCN)_3]PF_6$ (**8**, 2.090 g, 5.23 mmol), concentrated from an MeCN solution[16] immediately prior to use, was added to a solution of *N*-Boc-chlorophenylethylamine (**7**, 1.337 g, 5.23 mmol) in

1,2-dichloroethane (30 mL). After 4 h at reflux, the reaction mixture was concentrated and the residue was dissolved in MeCN. Purification was achieved by sequential chromatography on alumina (MeCN) and on aminopropyl silica (*i*PrOH). Recrystallisation from *i*PrOH gave the Boc-protected sandwich complex as colourless needles that were subsequently treated with hydrochloric acid (diluted to 4 N with MeOH, 300 mL) at room temp. for 3 h. The solvent was removed in vacuo and the residue was recrystallised from *i*PrOH/MeOH (3:1) to afford the deprotected product **9** as colourless needles (1.700 g, 65%). M.p. 175 °C (dec.); TLC (NH_2-Si plates): R_f = 0.29 (*i*PrOH/H_2O, 6:1). ^1H NMR (360 MHz, CD_3OD): δ = 6.75 (d, *J* = 6.0 Hz, 2 H, η-CH_{ar}), 6.49 (d, *J* = 6.1 Hz, 2 H, η-CH_{ar}), 5.59 (s, 5 H, Cp), 3.23 (t, *J* = 7.5 Hz, 2 H, CH_2CH_2NH), 2.93 (t, *J* = 7.3 Hz, 2 H, CH_2CH_2NH) ppm. ^{13}C NMR (90.6 MHz, CD_3OD): δ = 106.43 (η-$C_{ar}Cl$), 102.30 (η-$C_{ar}CH_2$), 88.40 (η-$C_{ar}H$), 88.10 (η-$C_{ar}H$), 84.15 (Cp), 41.03 ($CH_2CH_2NH_2$), 32.11 ($CH_2CH_2NH_2$) ppm. IR (KBr): $\tilde{\nu}$ = 3424, 3082, 1617, 1525, 1457, 1420, 1375, 1286, 1053, 995, 861, 734, 658, 493 cm^{-1}. UV/Vis (CH_3OH): λ_{max} (ε) = 204 nm (33400 $mol^{-1}dm^3cm^{-1}$). MS (FAB+, NBA): *m/z* (%) = 321/322/324 (56/91/69) $[M]^+$. HRMS (FAB): calcd. for $C_{13}H_{15}{}^{35}ClN^{102}Ru$ $[M]^+$ 321.9937, found 321.9941.

***rac*-3-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)propionic Acid (11):** NaOH (880 mg, 22 mmol) was added to a solution of *rac*-2-(*tert*-butoxycarbonylamino)-3-(3-hydroxy-4-methoxyphenyl)propionic acid (**10**)[18] (3.23 g, 10 mmol) in MeOH (30 mL). The mixture was heated under reflux and then benzyl chloride (2.79 g, 2.53 mL, 22 mmol) was added. When the reaction mixture had turned neutral (after 2.5 h), aq. NaOH (25 M, 440 mg, 11 mmol) was added. After 12 h at reflux the solvent was evaporated and the mixture was partitioned between water and $CHCl_3$ (50 mL each). The aqueous layer was acidified with H_2SO_4 (5 N) under vigorous stirring. The precipitate was collected and recrystallised from toluene to obtain a colourless powder (2.60 g, 65%). M.p. 149−150 °C; TLC (Si plates): R_f = 0.18 (EtOAc/TMP, 7:3). ^1H NMR (400 MHz, CD_3OD): δ = 7.45 (d, *J* = 7.2 Hz, 2 H, $OCH_2C_{ar}CH_{ar}$), 7.35 [dd, *J* = 7.2, 7.2 Hz, 2 H, CH_{ar} (Bn)], 7.30 [d, *J* = 7.3 Hz, 1 H, CH_{ar} (Bn)], 6.94 (d, *J* = 1.8 Hz, 1 H, CH_{ar}), 6.85 (d, *J* = 8.1 Hz, 1 H, $H_3COC_{ar}CH_{ar}$), 6.78 (d, *J* = 8.1 Hz, 1 H, CH_{ar}), 5.07 (s, 2 H, OCH_2Ph), 4.20 (dd, *J* = 5.0, 7.0 Hz, 1 H, [CH_2CH(NH)CO]), 3.79 (s, 3 H, OCH_3), 3.07 (dd, *J* = 4.8, 13.6 Hz, 1 H, PhCHHCH), 2.83 (dd, *J* = 7.2, 13.6 Hz, 1 H, PhCHHCH), 1.37 [s, 9 H, OC(CH_3)$_3$] ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 178.49 (*C*=O), 157.37 (*C*=O), 149.75 ($C_{ar}OCH_3$), 149.41 ($C_{ar}OCH_2Ph$), 138.90 ($C_{ar}OCH_2$), 132.60 [$C_{ar}CH_2CH$(NH)CO], 129.45 (*m*-$C_{ar}H$), 128.89 (*o*, *p*-$C_{ar}H$), 123.78 ($C_{ar}H$), 117.20 ($C_{ar}H$), 113.55 ($C_{ar}H$), 79.99 [O*C*(CH_3)$_3$], 72.35 (OCH_2Ph), 58.25 [CH_2CH(NH)CO], 56.72 (OCH_3), 39.34 [CH_2CH(NH)CO], 28.84 [OC(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3534, 3384, 2961, 2928, 2586, 1729, 1684, 1669, 1630, 1606, 1592, 1444, 1365, 1277, 1242, 1167, 1140, 1044, 1024, 849, 808, 730, 700 cm^{-1}. UV/Vis (CH_3OH): λ_{max} (ε) = 280 (4900), 204 (13900), 202 nm (13600 $mol^{-1}dm^3cm^{-1}$). MS (EI, 70 eV): *m/z* (%) = 401 (12) $[M]^+$, 345 (3) $[M - C_4H_8]^+$, 301 (2) $[M - C_5H_9O_2]^+$, 284 (4) $[M - C_5H_9O_2NH]^+$, 227 (68) $[M - CH_2(CO_2H)C_5H_9O_2]^+$, 137 (48), 91 (100). HRMS (EI) calcd. for $C_{22}H_{27}NO_6$ $[M]^+$: 401.1838, found 401.1838. $C_{22}H_{27}NO_6$ (401.45): calcd. C 65.79, H 6.78, N 3.49; found C 65.31, H 7.15, N 3.04.

***rac*-{1-(2-*N*-[2-(*tert*-Butoxycarbonylamino)-3-(3-hydroxy-4-methoxyphenyl)]propionylamino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (12):** At 0 °C, HOBt (93 mg, 0.69 mmol) and EDCI (120 mg, 0.506 mmol) were added to a solution of Boc-protected 4-OMe-DOPA (**10**) (95 mg, 0.46 mmol) in THF/CH_3OH (1:1, 10 mL). After 15 min a solution of [1-(2-aminoethyl)-4-chloro-η^6-benzene](η^5-cyclopentadienyl)-ruthenium hexafluorophosphate hydrochloride (**9**) (269 mg, 0.46 mmol) in MeOH (1.2 mL) and *i*Pr_2NEt (0.16 mL, 0.92 mmol) was added. The mixture was stirred at 0 °C for 4 h, at room temp. for 30 h, and then concentrated. Water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ and brine. After drying with Na_2SO_4 the solution was concentrated to 2 mL and treated with Et_2O (70 mL). The brown precipitate was collected, dried, and purified by preparative HPLC on aminopropyl silica (*i*PrOH/H_2O, 9:1; 17 mg each injection, flow rate 15 $mL{\cdot}min^{-1}$) to obtain a light-brown powder (171 mg, 49%). TLC (NH_2-Si plates): R_f = 0.53 (*i*PrOH/ H_2O, 6:1), HPLC retention volume: 179 mL (*i*PrOH/H_2O, 9:1). ^1H NMR (360 MHz, CD_3OD): δ = 6.87 (d, *J* = 8.7 Hz, 1 H, CH_{ar}), 6.68 (d, *J* = 2.0 Hz, 1 H, CH_{ar}), 6.68 (dd, *J* = 2.0, 8.8 Hz, 1 H, CH_{ar}),6.59 (dd, *J* = 1.3, 6.1 Hz, 1 H, η-CH_{ar}), 6.55 (d, *J* = 6.1 Hz, 1 H, η-CH_{ar}), 6.23 (dd, *J* = 1.3, 5.0 Hz, 1 H, η-$C_{ar}H$), 5.99 (d, *J* = 6.4 Hz, 1 H, η-CH_{ar}), 5.49 (s, 5 H, Cp), 4.11 (t, *J* = 7.3 Hz, 1 H, CH_2CH(CO)NH), 3.83 (s, 3 H, OCH_3), 3.40 (dt, *J* = 6.8, 14.1 Hz, 1 H, CH_2CHHNH), 3.26 (dd, *J* = 6.7, 13.7 Hz, 1 H, CH_2CHHNH), 2.87 (dd, *J* = 7.0, 13.4 Hz, 1 H, CH*H*CH(CO)NH), 2.73 (dd, *J* = 7.7, 13.4 Hz, 1 H, C*H*HCH(CO)NH), 2.52 (m, 2 H, CH_2CH_2NH), 1.39 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (90.6 MHz, CD_3OD): δ = 174.46 (*C*=O), 155.27 (*C*=O), 147.79 ($C_{ar}OCH_3$), 147.31 ($C_{ar}OH$), 130.95 [$C_{ar}CH_2CH$(CO)NH], 121.70 ($C_{ar}H$), 117.38 ($C_{ar}H$), 112.85 ($C_{ar}H$), 105.96 (η-$C_{ar}Cl$), 104.39 (η-$C_{ar}CH_2$), 88.01 (η-$C_{ar}H$), 87.94 (η-$C_{ar}H$), 87.66 (η-$C_{ar}H$), 87.58 (η-$C_{ar}H$), 83.56 (Cp), 80.40 [*C*(CH_3)$_3$], 57.63 [CH_2CH(CO)NH], 56.28 (O*C*H_3), 40.76 (CH_2CH_2NH), 38.45 [CH_2CH(CO)NH], 34.42 (CH_2CH_2NH), 28.31 [C(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3418, 3087, 2976, 2935, 1700, 1669, 1591, 1512, 1456, 1368, 1275, 1247, 1164, 1132, 1092, 1024, 842, 732, 558 cm^{-1}. UV/Vis (CH_3OH): λ_{max} (ε) = 280 (750), 254 (895), 204 nm (22350 $mol^{-1}dm^3cm^{-1}$). MS (FAB+, NBA): *m/z* (%) = 614/615/617 (69/100/74) $[M]^+$, 558/559/561 (11/13/11) $[M - C_4H_8]^+$. HRMS (FAB) calcd. for $C_{28}H_{34}{}^{35}ClN_2O_5{}^{102}Ru$ $[M]^+$: 615.1205; found 615.1200.

***rac*-{1-(2-*N*-[3-(3-Benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)]propionylamino)ethyl-4-chloro-η^6-benzene}(η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (13):** At 0 °C, HOBt (120 mg, 0.896 mmol) and EDCI (129 mg, 0.657 mmol) were added to a solution of the triply protected DOPA derivative **11** (239 mg, 0.597 mmol) in THF (10 mL). After 15 min a solution of [1-(2-aminoethyl)-4-chloro-η^6-benzene](η^5-cyclopentadienyl)-ruthenium hexafluorophosphate hydrochloride (**9**) (300 mg, 0.597 mmol) in MeOH (1.2 mL) and *i*Pr_2NEt (0.2 mL) was added. The mixture was stirred at 0 °C for 4 h, at room temp. for 40 h, and then concentrated. The product was purified by column chromatography (Si-NH_2), followed by preparative HPLC on aminopropyl silica (*i*PrOH/MeCN, 4:1), 10 mg each injection, flow rate 12 $mL{\cdot}min^{-1}$). Recrystallisation from water-*i*PrOH yielded the colourless, microcrystalline product (310 mg, 60%). M.p. 174 °C (decomp); TLC (NH_2-Si plates): R_f = 0.22 (*i*PrOH); HPLC retention volume: 224 mL (*i*PrOH/MeCN, 4:1). ^1H NMR (360 MHz, [D_6]acetone): δ = 7.50 (d, *J* = 7.2 Hz, 2 H, *o*-CH_{ar} (Bn)), 7.38 (t, *J* = 7.5 Hz, 2 H, *m*-CH_{ar} (Bn)) 7.34 (d, *J* = 7.2 Hz, 1 H, *p*-CH_{ar} (Bn)), 6.99 (d, *J* = 1.9 Hz, 1 H, CH_{ar}), 6.93 (d, *J* = 8.2 Hz, 1 H, CH_{ar}), 6.81 (dd, *J* = 1.9, 8.1 Hz, CH_{ar}), 6.71 (d, *J* = 6.1 Hz, 1 H, η-CH_{ar}), 6.68 (d, *J* = 6.2 Hz, 1 H, η-CH_{ar}), 6.43 (d, *J* = 5.2 Hz, 1 H, η-CH_{ar}), 6.20 (d, *J* = 5.5 Hz, 1 H, η-CH_{ar}), 6.08 (br. d, 1 H, CHN*H*Boc), 5.61 (s, 5 H, Cp), 5.09 (s, 2 H, OCH_2Ph), 4.21 [br. q, *J* = 6.3 Hz, 1 H, CH_2CH(CO)NH], 3.82 (s, 3 H, OCH_3), 3.50 (br.

q, J = 5.8 Hz, 1 H, CH_2CHHNH), 3.40 (br. q, J = 5.7 Hz, 1 H, CH_2CHHNH), 3.02 [dd, J = 6.4, 13.7 Hz, 1 H, $CHHCH(CO)NH$], 2.81 [dd, J = 8.0, 13.9 Hz, 1 H, $CHHCH(CO)NH$], 2.68 (q, J = 7.1 Hz, 2 H, CH_2CH_2NH), 1.36 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (90.6 MHz, [D$_6$]acetone): δ = 173.16 (*C*=O), 156.54 (*C*=O), 149.81 ($C_{ar}OCH_3$), 149.33 ($C_{ar}OCH_2Ph$), 138.63 ($C_{ar}CH_2O$), 131.28 [$C_{ar}CH_2CH(CO)NHBoc$], 129.39 (*m*-$C_{ar}H$), 128.79 (*p*-$C_{ar}H$), 128.71 (*o*-$C_{ar}H$), 123.27 ($C_{ar}H$), 116.71 ($C_{ar}H$), 113.44 ($C_{ar}H$), 105.62 (η-$C_{ar}Cl$), 104.56 (η-$C_{ar}CH_2$), 88.02 (η-$C_{ar}H$), 87.96 (η-$C_{ar}H$), 87.80 (η-$C_{ar}H$), 83.65 (Cp), 79.76 [$OC(CH_3)_3$], 71.76 ($PhCH_2O$), 57.23 [$CH_2CH(CO)NHBoc$], 56.52 (OCH_3), 40.60 (CH_2CH_2NH), 38.46 [$CH_2CH(CO)NH$], 34.46 ($CH_2CH_2NH_2$), 28.70 [$OC(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3420, 3290, 3065, 2975, 2929, 1706, 1663, 1512, 1457, 1419, 1364, 1259, 1162, 1139, 1090, 1021, 852, 746, 698, 626 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 282 (3800), 242 nm (8000 mol^{-1}dm^{3}cm^{-1}). MS (FAB+, NBA): *m*/*z* (%) = 704/705/707 (62/100/76) $[M]^+$, 648/649/651 (9/14/11) $[M - C_4H_8]^+$. HRMS (FAB) calcd. for $C_{35}H_{40}{}^{35}ClN_2O_5{}^{102}Ru$ $[M]^+$: 705.1676; found 705.1685. $C_{35}H_{40}ClF_6N_2O_5PRu$ (850.20): calcd. C 49.44, H 4.74, N 3.29; found C 49.22, H 4.88, N 3.18.

***rac*-{1-[4-(2-Aminoethyl)phenoxy]-4-(2-*N*-[3-(3-benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)]propionylamino)-ethyl-η^6-benzene}(η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (16):** Tyramine (**5**, 5.8 mg, 0.0424 mmol) was added to a solution of KO*t*Bu (1.0 equiv.) and [18]crown-6 (0.1 equiv.) in THF/MeCN (1:1, 15 mL). After 30 min the mixture was cooled to 0 °C and transferred to a pre-cooled (−78 °C) solution of the dipeptoid **13** (40 mg, 0.042 mmol) in THF/MeCN (1:1, 20 mL). After 1 h the reaction mixture was slowly brought to 20 °C and, after 16 h, filtered and concentrated. The product was purified by column chromatography on aminopropyl silica (*i*PrOH/MeCN, 6:1, to remove [18]crown-6, then *i*PrOH/H_2O, 6:1), followed by recrystallisation from *i*PrOH to yield a yellowish powder (35 mg, 79%), m.p. 104 °C (decomp); TLC (NH_2-Si plates): R_f = 0.42 (*i*PrOH/H_2O, 6:1). ^1H NMR (360 MHz, CD_3OD): δ = 7.45 [d, J = 7.4 Hz, 2 H, *o*-CH_{ar} (Bn)], 7.36 [d, J = 8.7 Hz, 2 H, CH_{ar} (tyramine)], 7.36 [t, J = 7.0 Hz, 2 H, *m*-CH_{ar} (Bn)], 7.31 [d, J = 7.0 Hz, 1 H, *p*-CH_{ar} (Bn)], 7.10 [d, J = 8.7 Hz, 2 H, CH_{ar} (tyramine)], 7.02 [d, J = 8.6 Hz, 1 H, CH_{ar} (dopa)], 6.93 [d, J = 2.1 Hz, 1 H, CH_{ar} (dopa)], 6.83 [dd, J = 2.1, 8.2 Hz, 1 H, CH_{ar} (dopa)], 6.72 (d, J = 8.6 Hz, 1 H, η-CH_{ar}), 6.07 (dd, J = 1.7, 7.4 Hz, 1 H, η-CH_{ar}), 6.04 (dd, J = 1.7, 6.2 Hz, 1 H, η-CH_{ar}), 5.79 (d, J = 6.2 Hz, 1 H, η-CH_{ar}), 5.38 (s, 5 H, Cp), 5.07 (s, 2 H, OCH_2Ph), 4.15 [t, J = 7.5 Hz, 1 H, $CH_2CH(CO)NH$], 3.91 (s, 3 H, OCH_3), 3.39 [br. dd, J = 6.6, 12.8 Hz, 1 H, $CH_2CHHNH(CO)$], 3.25 [dd, J = 7.0, 13.6 Hz, 1 H, $CH_2CHHNH(CO)$], 2.91 (m, 2 H, CH_2CH_2NH), 2.87 [m, 1 H, $CHHCH(CO)NH$], 2.79 [m, 1 H, $CHHCH(CO)NH$], 2.67 (t, J = 7.4 Hz, 1 H, CH_2CH_2NH), 2.45 (q, J = 6.6 Hz, 2 H, CH_2CH_2NH), 1.38 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (90.6 MHz, CD_3OD): δ = 174.52 (*C*=O), 157.56 (*C*=O), 152.47 [$C_{ar}O$(η-Ph)], 150.14 ($C_{ar}OCH_3$), 149.48 ($C_{ar}OCH_2Ph$), 139.73 ($C_{ar}CH_2CH_2NH_2$), 138.62 ($C_{ar}CH_2O$), 134.54 [$C_{ar}CH_2CH(CO)NH$], 132.21 [$C_{ar}H$ (tyramine)], 131.28 (η-$C_{ar}OPh$), 129.54 (*m*-$C_{ar}H$), 129.04 (*p*-$C_{ar}H$), 128.88 (*o*-$C_{ar}H$), 123.68 ($C_{ar}H$), 122.00 [$C_{ar}H$ (tyramine)], 116.43 ($C_{ar}H$), 113.66 ($C_{ar}H$), 102.16 (η-$C_{ar}CH_2$), 86.29 (η-$C_{ar}H$), 81.97 (Cp), 80.71 [$OC(CH_3)_3$], 76.53 (η-$C_{ar}H$), 76.40 (η-$C_{ar}H$), 71.20 ($PhCH_2O$), 57.85 [$CH_2CH(CO)NHBoc$], 56.66 (OCH_3), 41.86 (CH_2CH_2NH), 43.73 (CH_2CH_2NH), 41.06 [$CH_2CH(CO)NH$], 38.84 ($CH_2CH_2NH_2$), 34.52 ($CH_2CH_2NH_2$), 28.70 [$OC(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3420, 3336, 3087, 2932, 2370, 1684, 1653, 1589, 1559, 1517, 1507, 1476, 1457, 1419, 1368, 1252, 1163, 1137, 1018, 838, 746, 699 cm^{-1}. UV/Vis (CH_3OH): λ_{max} (ε) = 280 (12400), 230 (24700), 206 (82800) 204 nm (83600 mol^{-1}dm^{3}cm^{-1}). MS (FAB+, NBA): *m*/*z* (%) = 805/806/808 (63/100/52) $[M]^+$. HRMS (FAB) calcd. for $C_{43}H_{50}N_3O_6{}^{102}Ru$ $[M]^+$: 806.2755; found 806.2753.

***rac*-{1-[(5-(2-*tert*-Butoxycarbonylaminoethyl)-2-methoxy)phenoxy]-4-(2-*N*-[3-(3-benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)]propionylamino)ethyl-η^6-benzene}(η^5-cyclopentadienyl)-ruthenium Hexafluorophosphate (17):** {2-[(3-Hydroxy-4-methoxy)phenyl]ethyl}carbamic acid *tert*-butyl ester[19] (**14**, 15 mg, 0.053 mmol) was added to a solution of KO*t*Bu (1.0 equiv.) and [18]crown-6 (0.1 equiv.) in THF/MeCN (1:1) (15 mL). After 30 min the mixture was cooled to 0 °C and transferred to a pre-cooled (−78 °C) solution of the dipeptoid **13** (50 mg, 0.053 mmol) in THF/MeCN (1:1, 20 mL). After 1 h the reaction mixture was slowly warmed to 20 °C and, after 16 h, filtered and concentrated. Purification by preparative HPLC on aminopropylsilica (*i*PrOH/MeCN, 4:1, 10 mg each injection, flow rate 15 mL·min^{-1}) followed by recrystallisation from CH_2Cl_2 and Et_2O. Colourless powder (50 mg, 87%), m.p. 101−102 °C (dec.); TLC (NH_2-Si plates): R_f = 0.37 (*i*PrOH); HPLC retention volume: 176 mL (*i*PrOH/MeCN, 4:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 [d, J = 7.3 Hz, 2 H, *o*-CH_{ar} (Bn)], 7.35 [t, J = 7.2 Hz, 2 H, *m*-CH_{ar} (Bn)], 7.27 [8t, J = 6.9 Hz, 1 H, *p*-CH_{ar} (Bn)], 7.11 [dd, J = 1.7, 8.3 Hz, 1 H, CH_{ar} (unit B′)], 6.97 [br. s, 1 H, CH_{ar} (unit A)], 6.96 [d, J = 8.4 Hz, 1 H, CH_{ar} (unit B′)], 6.85 [br. d, J = 8.6 Hz, 1 H, CH_{ar} (unit A)], 6.84 [br. s, 1 H, CH_{ar} (unit B′)], 6.79 [d, J = 8.2 Hz, 1 H, CH_{ar} (unit A)], 6.45 (br. s, 1 H, η-CH_{ar}), 6.36 (br. s, 1 H, η-CH_{ar}), 5.96 (br. t, 5.1 Hz, 2 H, η-CH_{ar}), 5.77 (br. d, J = 7.8 Hz, 1 H, N*H*), 5.33 (s, 5 H, Cp), 5.13 (s, 2 H, OCH_2Ph), 4.79 (br. t, 1 H, N*H*), 4.45 [br. q, J = 4.9 Hz, 1 H, $CH_2CH(CO)NH$], 3.82 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 3.58 (m, 1 H, CH_2CHHNH), 3.46 (m, 1 H, CH_2CHHNH), 3.32 (br. q, J = 6.4 Hz, 2 H, CH_2CH_2NH), 3.08 [dd, J = 4.8, 13.6 Hz, 1 H, $CHHCH(CO)NH$], 2.94 [m, 1 H, $CHHCH(CO)NH$], 2.84 (m, 2 H, CH_2CH_2NH), 2.73 (t, J = 7.1 Hz, 2 H, CH_2CH_2NH), 1.41 [s, 9 H, $C(CH_3)_3$], 1.33 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.78 (*C*=O), 155.94 (*C*=O), 155.45 (*C*=O), 149.63 [$C_{ar}OCH_3$ (unit B′)], 148.39 [$C_{ar}OCH_3$ (unit A)], 148.05 ($C_{ar}OCH_2Ph$), 140.36 [(η-Ph)OC_{ar}], 137.36 ($C_{ar}CH_2O$), 133.08 ($C_{ar}CH_2CH_2NH$), 132.57 (η-$C_{ar}OPh$), 130.02 [$C_{ar}CH_2CH(CO)NHBoc$], 128.43 (*m*-$C_{ar}H$), 128.43 [$C_{ar}H$ (unit B′)], 127.93 (*o*-$C_{ar}H$), 127.72 (*p*-$C_{ar}H$), 122.37 ($C_{ar}H$ (unit B′), 122.37 [$C_{ar}H$ (unit A)], 115.64 [$C_{ar}H$ (unit A)], 113.41 [$C_{ar}H$ (unit B′)], 112.02 [$C_{ar}H$ (unit A)], 102.12 (η-$C_{ar}CH_2$), 85.60 (η-$C_{ar}H$), 85.33 (η-$C_{ar}H$), 80.75 (Cp), 79.35 [$OC(CH_3)_3$], 79.25 [$OC(CH_3)_3$], 74.68 (η-$C_{ar}H$), 71.06 ($PhCH_2O$), 56.43 [$CH_2CH(CO)NHBoc$], 56.11 (OCH_3), 56.07 (OCH_3), 41.80 (CH_2CH_2NH), 39.38 (CH_2CH_2NH), 38.48 [$CH_2CH(CO)NH$], 35.44 ($CH_2CH_2NH_2$), 32.61 ($CH_2CH_2NH_2$), 28.43 [$OC(CH_3)_3$], 28.37 [$OC(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3407, 3066, 2974, 2931, 2371, 1700, 1684, 1663, 1507, 1476, 1442, 1364, 1272, 1232, 1167, 1140, 1121, 1022, 845, 773, 698 cm^{-1}. UV/Vis ($CHCl_3$): λ_{max} (ε) = 280 (7800), 242 nm (11200 mol^{-1}dm^{3}cm^{-1}). MS (FAB+, NBA): *m*/*z* (%) = 935/936/938 (63/100/57) $[M]^+$. HRMS (FAB) calcd. for $C_{49}H_{60}N_3O_9{}^{102}Ru$ $[M]^+$: 936.3387, found 936.3342.

***rac*-{1-[(5-(2-Aminoethyl)-2-methoxy)phenoxy]-4-(2-*N*-[3-(3-benzyloxy-4-methoxyphenyl)-2-(*tert*-butoxycarbonylamino)]propionylamino)ethyl-η^6-benzene}(η^5-cyclopentadienyl)ruthenium Hexafluorophosphate (2):** 5-(2-Aminoethyl)-2-methoxyphenol (**15**[19], 16 mg, 0.095 mmol) was added to a solution of KO*t*Bu (1.0 equiv.) and [18]crown-6 (0.1 equiv.) in THF/MeCN (1:1) (15 mL). After 30 min the mixture was cooled to 0 °C and transferred to a pre-cooled (−78 °C) solution of the dipeptoid **13** (90 mg, 0.095 mmol) in THF/MeCN (1:1, 20 mL). After 1 h the reaction mixture was

slowly brought to 20 °C and, after 16 h, filtered and concentrated. The product was purified by column chromatography on aminopropyl silica with MeCN (to remove [18]crown-6) and then with *i*PrOH/H_2O (6:1). Pale-yellow powder (60 mg, 64%). TLC (NH_2-Si plates): R_f = 0.43 (*i*PrOH/H_2O, 6:1). ^1H NMR (360 MHz, CD_3OD): δ = 7.46 (d, *J* = 6.6 Hz, 2 H, *o*-CH_{ar}), 7.36 (t, *J* = 7.0 Hz, 2 H, *m*-CH_{ar}), 7.30 (t, *J* = 7.4 Hz, 1 H, *p*-CH_{ar}), 7.22 (dd, *J* = 1.5, 8.7 Hz, 1 H, CH_{ar}), 7.15 (d, *J* = 8.7 Hz, 1 H, CH_{ar}), 7.09 (d, *J* = 1.9 Hz, 1 H, CH_{ar}), 7.01 (d, *J* = 2.1 Hz, 1 H, CH_{ar}), 6.93 (d, *J* = 7.8 Hz 1 H, CH_{ar}), 6.84 (dd, *J* = 1.8, 7.8 Hz, 1 H, CH_{ar}), 6.11 (br. s, 1 H, η-CH_{ar}), 6.05 (br. s, 1 H, η-CH_{ar}), 6.02 (br. d, 6.6 Hz, 1 H, η-CH_{ar}), 5.72 (br. d, 5.7 Hz, 1 H, η-CH_{ar}), 5.36 (s, 5 H, Cp), 5.08 (s, 2 H, OCH_2Ph), 4.15 [m, 1 H, CH_2CH(CO)NH], 3.81 (s, 3 H, OCH_3), 3.80 [s, 3 H, OCH_3), 3.52 (br. m, 1 H, CH_2CHHNH(CO)], 3.41 [br. m, 1 H, CH_2CHHNH(CO)], 3.25 (m, 2 H, CH_2CH_2NH), 3.00−2.75 [m, 6 H, CH_2CH(CO)NH, C$H_2CH_2NH_2$, CH_2CH_2NH(CO)], 1.39 [s, 9 H, C(CH_3)$_3$] ppm. ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 174.51 (*C*=O), 155.45 (*C*=O), 151.30 ($C_{ar}OCH_3$), 150.30 ($C_{ar}OCH_3$), 149.56 ($C_{ar}OCH_2Ph$), 141.91 [(η-Ph)OC_{ar}], 138.68 ($C_{ar}CH_2O$), 134.87 ($C_{ar}CH_2CH_2NH_2$), 134.31 (η-C_{ar}OPh), 131.36 [$C_{ar}CH_2CH$(CO)NHBoc], 129.59 (*m*-C_{ar}H), 129.11 (*o*-C_{ar}H), 128.92 (*p*-C_{ar}H), 123.79 (C_{ar}H, 123.61 (C_{ar}H), 117.41 (C_{ar}H), 116.33 (C_{ar}H), 114.84 (C_{ar}H), 113.76 (C_{ar}H), 102.10 (η-$C_{ar}CH_2$), 86.16 (η-C_{ar}H), 81.65 (Cp), 80.77 [O*C*(CH$_3$)$_3$], 80.02 (η-C_{ar}H), 76.09 (η-C_{ar}H), 75.98 (η-C_{ar}H), 72.52 (Ph*C*H$_2$O), 57.93 [CH_2*C*H(CO)NHBoc], 56.72 (O*C*H$_3$), 56.63 (O*C*H$_3$), 44.06 (CH_2CH_2NH), 41.18 (CH_2CH_2NH), 38.83 [*C*H$_2$CH(CO)NH], 37.71 ($CH_2CH_2NH_2$), 34.63 ($CH_2CH_2NH_2$), 28.75 [OC(*C*H$_3$)$_3$] ppm. MS (FAB+, NBA): *m*/*z* (%) = 835/836/838 (70/100/56) $[M]^+$. HRMS (FAB) calcd. for $C_{44}H_{52}N_3O_7{}^{102}Ru$ $[M]^+$: 836.2851; found 836.2817.

Supporting Information available (^1H and ^{13}C NMR spectra of compounds **6**, **9**, **12**, **16**, **17**).

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