Synthesis of a 30-Membered Macrocycle Incorporating Two Ruthenium Sandwich Complexes

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Dedicated to Professor Heinrich Nöth on the occasion of his 85th birthday

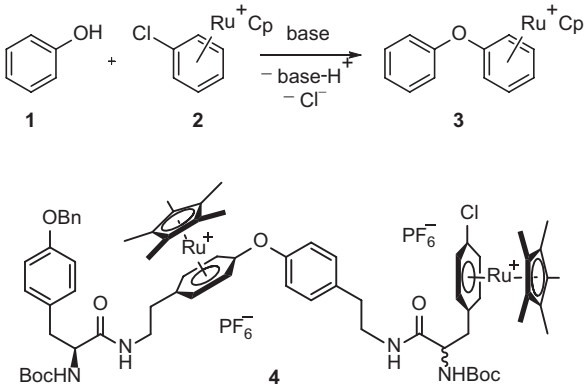
The first macrocycle incorporating two ruthenium sandwich complexes has been synthesised. Key step is a cyclodimerisation by double etherification of a *p*-chlorophenylalanine-derived $[RuCp^*]^+$ complex. Silica-based cation exchange chromatography allowed the separation of dicationic diastereomers. Assignment of the relative configurations was possible by X-ray structure determination. Partial demetalation in acetonitrile proceeded in high yield by irradiation in the presence of biphenyl.

Key words: Cation Exchange Chromatography, Diaryl Ethers, Macrocycles, Ruthenium, Sandwich Complexes

Introduction

Diaryl ethers constitute important structural motifs of peptidic natural products, because they enhance the stability against digestion by proteases [1]. Most prominently, vancomycin A is used clinically as an antibiotic [2]. The possibility of synthesising $[RuCp^*]^+$-complexed diaryl ethers (**3**) by nucleophilic attack of phenolates (**1**) at $[RuCp^*]^+$ sandwich complexes of chlorobenzene derivatives (**2**, Scheme 1) [3 – 6] allows to combine the stable diaryl ether structural motif with metal complexation within a peptidic frame. From a broader perspective, there is clear potential of metal-peptide conjugates for anticancer therapy [7, 8]. In the case of ruthenium, radioactive isotopes might be delivered precisely to biological target structures with the help of the peptide backbone [9 – 12], *e. g.* for bioimaging [13].

Diaryl ether peptides synthesised employing ruthenium sandwich complexes include K-13 and OF-4949-III [14 – 16]. There has also been intense work on the total synthesis of Ru-complexed vancomycin-type diaryl ethers, in particular towards ristotecin A by the Pearson group [17, 18]. We have developed a universal protocol for the modular synthesis of linear, $[RuCp]^+$-[19, 20] or $[RuCp^*]^+$-labeled [21] diaryl ether peptides such as **4** equipped with two $[RuCp^*]^+$ caps. We also developed an efficient protocol for the purification of the charged complexes by semipreparative HPLC. In this paper, we address the questions (a) whether $[RuCp^*]^+$-labeled cyclooligomers can be



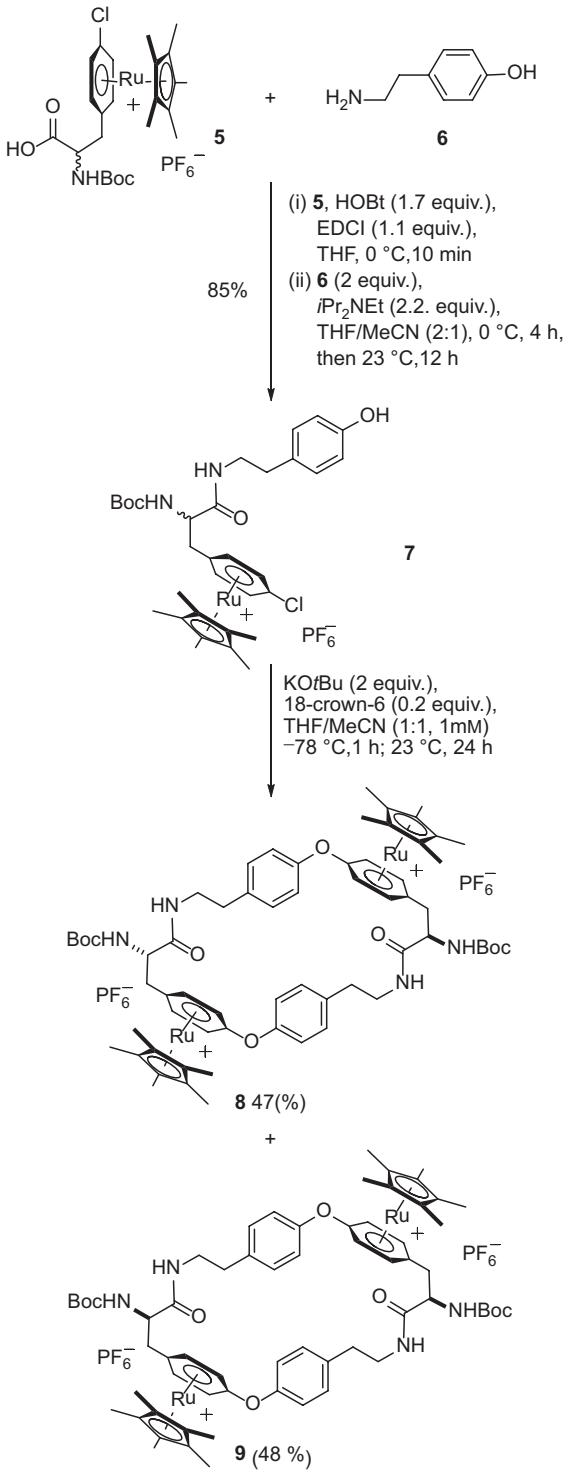
Scheme 1. Synthesis of Ru-complexed diaryl ether **3** by S_NAr reaction of phenolate and $[CpRu]^+$-complexed chloroarene **2**; diaryl ether amide **4** equipped with two $[RuCp^*]^+$ caps.

assembled by macrocycloetherification, and (b) which ring size would be preferred. Our experiment was encouraged by results on the related macrocyclic structure of the bastadins from the marine sponge *Ianthella basta*, which are constructed from two tryamine- and two tyrosine-derived units connected by two diaryl ether and two amide bonds [22].

Results and Discussion

Building block **7** (Scheme 2) was available in one step by condensation of tyramine (**6**) with $[RuCp^*]^+$-complexed, racemic Boc-protected *p*-chlorophenylalanine (**5**) which itself was synthesised in two steps from $RuCl_3 \cdot xH_2O$ and the corresponding Boc-protected amino acid ester, followed by saponification with LiOH [21, 23, 24].

In the presence of KO*t*Bu/18-crown-6 under dilution conditions (1 mM, THF/MeCN), amide **7** was consumed almost completely after about 90 min. After 24 h at 23 °C, only two diastereomeric products (**8**, **9**) had been formed almost exclusively which were isolated in yields of 47% and 48%, respectively. To our delight, separation of **8** and **9** was possible on a preparative scale employing a Chromabond SA cation exchange stationary phase and a solution of NaOAc in MeOH as mobile phase. Fig. 1 shows the cation exchange HPLC elution profile (Nucleosil® 100-5 SA, increasing NaOAc concentration in MeOH) with full separation of the two macrocyclic diastereomers. Dimerisation was indicated in the mass spectra under different ionisation conditions with prominent peaks corresponding to the dication (**8**, ESI-MS, found 619.2141) and the monocation with one PF_6^- counterion remaining associated (**9**, MALDI-MS, found 1383.3849). It was not possible to isolate the open-chain intermediate after formation of one diaryl ether bond. NMR signals were assigned on the basis of 2D NMR experiments. Characteristically, the diastereotopic aminomethylene protons of **8** and **9** become clearly separated in the ^1H NMR spectrum ($\delta_H = 3.23,\ 3.45$ ppm), when compared to the starting material **7**. The proton signals of the non-complexed phenyl rings experience a downfield shift by about 0.2 ppm, whereas the aromatic protons of the $[RuCp^*]^+$-complexed moieties are shifted upfield by about 0.2 ppm. In $[D_6]$acetone the signal of the chlorinated carbon atom of the starting material ($\delta_C = 105.7$)



Scheme 2. Synthesis and macrodimerisation of the $[RuCp^*]^+$-labeled amide **7**.

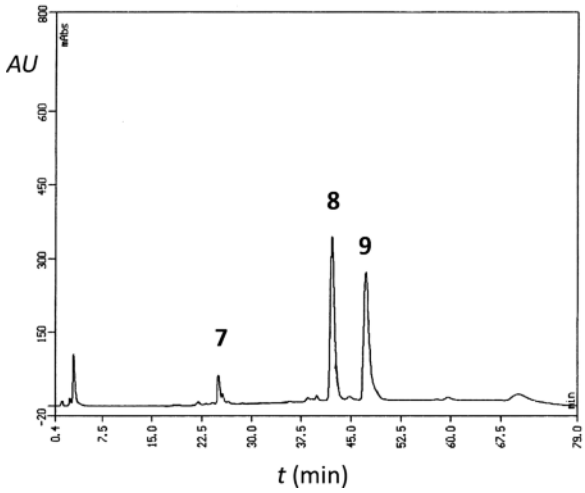


Fig. 1. HPLC elution profile of the crude reaction mixture after macrodimerisation of **7** [stationary phase: Macherey-Nagel EC 250/4 Nucleosil® 100-5 SA (length 25 cm, diameter 1 cm, particle size 5 μm); mobile phase: MeOH (10 min), then gradient MeOH to MeOH/NaOAc·3H_2O (0.74 M) within 40 min, then MeOH/ NaOAc · 3H_2O (0.74 M) for 10 min; flow rate 1 mL min^{-1}; detection wavelength 250 nm].

had disappeared in favour of signals at $\delta_C = 132.2$ (**8**) and $\delta_C = 132.1$ (**9**).

Assignment of the relative configurations of the macrocycles **8** and **9** is not possible by NMR spectroscopy, because the two stereogenic centers are too distant from each other. Fortunately, we obtained crystals which had to be treated very carefully due to loss of acetone molecules already when removed from the mother liquor and exposed to the open atmosphere. Finally, six acetone molecules remained incorporated in the elementary unit. X-Ray structure determination on single crystals of compound **8** (see Table 1 and Experimental Section [25]) eluting earlier revealed inversion symmetry (Fig. 2) which allowed not only to assign the diastereomers to the HPLC peaks, but also to gain information on the preferred conformation of **8**. The $[RuCp^*]^+$ caps are situated in the outer sphere of the ring.

Photochemical demetalation of $[RuCp]^+$- or $[RuCp^*]^+$-complexed diaryl ethers in MeCN is of relevance for natural product synthesis and has been employed on several occasions with varying yields (30 % – 85 %), often *in situ* without work-up of the Ru complex [14, 17]. Having clean material in hands, we investigated the behaviour of macrocycle **8**. Addition

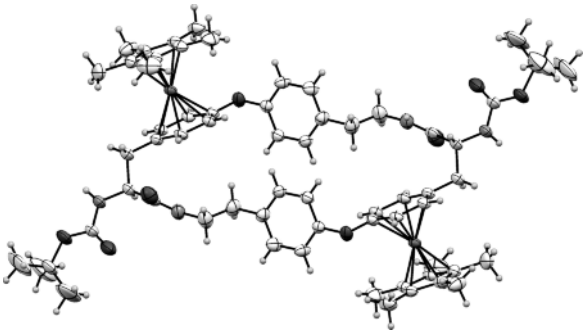
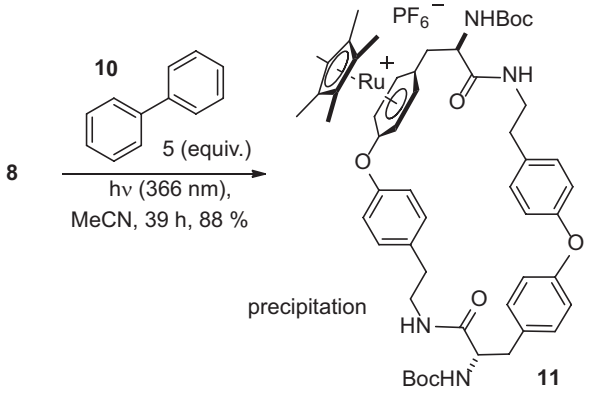


Fig. 2. Molecular structure of **8** in the crystal (displacement ellipsoids 30 %; H atoms as spheres with arbitrary radii). For clarity, PF_6^- counterions and incorporated acetone molecules have been omitted.

Table 1. Crystal data and numbers pertinent to data collection and structure refinement of compound **8**.

	8
Formula	$C_{64}H_{82}N_4O_8Ru_2^{2+} \cdot 2F_6P^- \cdot 6C_3H_6O$
M_r	1875.88
Crystal size, mm^3	$0.23 \times 0.43 \times 0.53$
Crystal system	triclinic
Space group	$P\bar{1}$
a, Å	10.937(2)
b, Å	10.988(3)
c, Å	20.184(6)
α, deg	84.53(2)
β, deg	75.12(2)
γ, deg	82.12(2)
V, Å^3	2317.6(10)
Z	1
$\rho_{calcd.}$, Mg m^{-3}	1.344
μ, mm^{-1}	0.443
Transmission (min / max)	0.9331 / 0.9998
$F(000)$, e	976
Range in *hkl*	±12, ±12, −23
Refl. collected / unique / R_{int}	7505 / 7266 / 0.0133
Data / restraints / parameters	7266 / 104 / 610
$R1$ / $wR2$ [$I > 2\sigma(I)$]	0.0396 / 0.1029
$R1$ / $wR2$ (all data)	0.0462 / 0.1086
Goodness-of-fit (F^2)	1.071
Largest diff. peak / hole, e Å^{-3}	0.500 / −0.464

of the UV absorber biphenyl (**10**), which had been used by Mann and co-workers for the mild photodemetalation of $[CpOs(\eta^6\text{-arene})]^+$ complexes [26], turned out to be of key importance. In a model reaction, we irradiated $[Cp^*Ru(ethylbenzene)]PF_6$ at 366 nm. In the absence of biphenyl, the reaction stopped at about 50 % conversion with the solution having become dark brown. However, in the presence of biphenyl (5 equiv.)



Scheme 3. Monodemetalation of the $[RuCp^*]^+$-complexed macrocycle **8** in the presence of biphenyl.

complete decomplexation had occurred after 11 h, and the solution had turned from colourless to slightly grey. On irradiation of **8** in MeCN at 366 nm in the presence of biphenyl the mono $[RuCp^*]^+$ complex **11** (ESI-MS, found 1001.3946) precipitated from the solution and could be isolated in high 88 % yield after 39 h (Scheme 3). Characteristically, the ratio of aromatic protons of complexed to non-complexed phenyl groups in the ^{1}H NMR spectrum shifted from 1 : 1 in the starting material **8** to 1 : 3 in compound **11**.

In summary, compounds **8** and **9** are the first macrocyclic peptide-like structures with two $[RuCp^*]^+$ caps. Our synthesis features the first macrodimerisation by double diaryl ether formation which will also become useful for the synthesis of bis-diaryl ether natural products. The yields are satisfactory. We did not isolate any trimers or higher oligomers of **7**. A similar preference of macrodimerisation had been observed by Boger and Yohannes who assembled a metal-free bis diaryl ether macrocycle of the same size by amide coupling which differed from **8** and **9** by the presence of a *m*,*p*′- instead of a *p*,*p*′-disubstitution pattern of the diaryl ether moieties [27]. For photochemical demetalation, addition of biphenyl as UV absorber can be recommended. Only very few peptides complexed with more than one $[RuCp]^+$ or $[RuCp^*]^+$ unit have been described. Prior to our compounds **4** [21], **8** and **9**, Sheldrick and co-workers had reported the synthesis of doubly $[RuCp^*]^+$-labeled dipeptides and diketopiperazines [28]. In 2010, Kudinov and co-workers complexed both the tyrosine and the phenylalanine side chains of the decapeptide angiotensin I by a $[RuCp]^+$ unit [29].

Experimental Section

General: Reagents were purchased from Aldrich, Acros, Merck, and Lancaster at high commercial quality and were used without further purification. Reactions were controlled by analytical HPLC and thin-layer chromatography (0.25 mm E. Merck alumina plates NH_2 $F_{254}S$). TLCs were analysed under UV light (λ = 254 nm), followed by heating after treatment with 1,10-phenanthroline (2 M dipping solution in EtOH). Macherey-Nagel Chromabond® SA (particle size 45 μm) was used for semipreparative column chromatography. The HPLC experiments were performed at 25 °C using a Kontron Instruments 322 pump system. The column was a Macherey-Nagel EC 250/4 Nucleosil® 100-5 SA (length 25 cm, diameter 0.4 cm, particle size 5 μm). MeOH was HPLC-grade, NaOAc was superpure. NMR spectra were recorded on a Mercury 200 Varian, a Varian VRX 400S and a Bruker AMX 600 spectrometer. The NMR shifts were calibrated using the solvent peak as internal reference and assigned on the basis of HSQC and HMBC experiments. All infrared spectra were recorded on a IFS 45 Bruker spectrometer. High-resolution fast atom bombardment (FAB), electrospray ionisation (ESI) and matrix-assisted laser desorption ionisation (MALDI) mass spectra were recorded on a Finnigan MAT 95Q and a Bruker Autoflex II mass spectrometer. Melting points were determined with a Electrothermal IA 9000 Series melting point microscope and are uncorrected.

Amide 7

At 0 °C, HOBt (74 mg, 0.54 mmol) and EDCI (68 mg, 0.36 mmol) were added to a solution of amino acid **5** (220 mg, 0.324 mmol, [21]) in THF (15 mL). After 10 min a solution of tyramine (89 mg, 0.65 mmol) and *i*Pr_2NEt (0.13 mL) in THF/MeCN (1 : 1, 15 mL) was added. The mixture was stirred at 0 °C for 4 h and at 23 °C for 12 h. The solvent was removed, followed by addition of $NaPF_6$ (1.1 equiv.) in water (10 mL) and repeated extraction with DCM. The organic phases were combined, and the solvent was removed providing the crude product. Purification by cation exchange column chromatography [Chromabond SA, NaOAc·3H_2O in MeOH (c = 0.74)] and subsequent treatment of the pure fraction with $NaPF_6$ (1.1 equiv.) in water (10 mL), followed by extraction with DCM and concentration to dryness resulted in a pale-yellow powder (220 mg, 85 %); m. p. 118 °C (decomp.). – ^{1}H NMR (200 MHz, [D_6]acetone): δ (ppm) = 1.33 (s, 9H, $(CH_3)_3CO$), 2.01 (s, 15H, η^5-CCH_3), 2.64 (dd, ^2J = 13.2 Hz, ^3J = 5.1 Hz, 1H, η^6-$C_{ar}CHHCH(CO)NH$), 2.67 (t, ^3J = 7.3 Hz, 2H, $C_{ar}CH_2CH_2NH$), 2.90 (dd, ^2J = 13.2 Hz, ^3J = 5.1 Hz, 1H, η^6-$C_{ar}CHHCH(CO)NH$), 3.37 (dt, ^3J = 4.8 Hz, ^3J = 7.3 Hz, 2H, $C_{ar}CH_2CH_2NH$),

4.33 (br. m, 1H, $CH_2CH(CO)NH$), 6.04 (d, $^3J = 6.2$ Hz, 1H, η^6-$C_{ar}HCCH_2$), 6.06 (d, $^3J = 6.6$ Hz, 1H, η^6-$C_{ar}HCCH_2$), 6.30 (d, $^3J = 8.4$ Hz, 1H, $CH_2CH(CO)NH$), 6.36 (d, $^3J = 6.6$ Hz, 1H, η^6-$C_{ar}HCCl$), 6.37 (d, $^3J = 6.2$ Hz, 1H, η^6-$C_{ar}HCCl$), 6.76 (d, $^3J = 8.7$ Hz, 2H, $C_{ar}HC_{ar}HC_{ar}OH$), 7.03 (d, $^3J = 8.7$ Hz, 2H, $C_{ar}HC_{ar}HC_{ar}OH$), 7.38 (t, $^3J = 4.8$ Hz, 1H, $C_{ar}CH_2CH_2NH$), 8.25 (br. s, 1H, OH). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ (ppm) = 11.05 (η^5-CCH_3), 29.48 ($(CH_3)_3CO$), 36.44 ($C_{ar}CH_2CH_2NH$), 37.32 (η^6-$C_{ar}CH_2CH(CO)NH$), 42.77 ($C_{ar}CH_2CH_2NH$), 57.05 ($CH_2CH(CO)NH$), 80.89 ($(CH_3)_3CO$), 90.56 (η^6-$C_{ar}HCCH_2$), 90.58 (η^6-$C_{ar}HCCl$), 90.67 (η^6-$C_{ar}HCCH_2$), 99.38 (η^5 – CCH_3), 102.27 (η^6-$C_{ar}CH_2$), 105.64 (η^6-$C_{ar}Cl$), 117.11 ($HOC_{ar}C_{ar}HC_{ar}H$), 131.54 ($HOC_{ar}C_{ar}HC_{ar}H$), 131.85 ($C_{ar}CH_2CH_2NH$), 156.99 ($NH(CO)OC(CH_3)_3$), 157.75 ($HOC_{ar}C_{ar}HC_{ar}H$), 171.48 ($CH_2CH(CO)NH$). – IR (KBr): $\tilde{\nu} = 3418\ cm^{-1}$ (s), 3085 (vw), 2977 (w), 2924 (m), 1710 (s), 1676 (s), 1516 (s), 1477 (m), 1453 (m), 1388 (m), 1367 (m), 1251 (m), 1168 (m), 843 (vs), 558 (s). – MS ((+)-FAB, NBA): m/z (%) = 654/655/657 (60/100/76) $[M]^+$. – HRMS ((+)-FAB): m/z = 655.1838 (calcd. 655.1877 for $C_{32}H_{42}^{35}ClN_2O_4^{102}Ru$).

*Diastereomeric macrocycles **8** and **9***

To a solution (1 mM) of amide **7** (67 mg, 0.084 mmol) in THF/CH_3CN (1/1) at −78 °C was added KO*t*Bu (18.76 mg, 0.167 mmol) and 18-crown-6 (4.42 mg, 0.017 mmol). After 1 h at −78 °C, the reaction mixture was stirred for 24 h at 23 °C. The solvent was removed, a solution of $NaPF_6$ (1.1 equiv.) in water (10 mL) was added, and the aqueous phase was extracted three times with DCM. The combined organic phases were dried, resulting in the crude product. Purification by cation exchange column chromatography [Chromabond SA, NaOAc·3H$_2$O in MeOH ($c = 0.74$)] and subsequent treatment of the pure fractions with $NaPF_6$ (1.1 equiv.) in water (10 mL), followed by extraction with DCM and concentration to dryness resulted in the isolation of **8** (30.0 mg, 47 %) and **9** (30.6 mg, 48 %) as pale-yellow powders.

*Compound **8***: m. p. 209 °C (decomp.). – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ (ppm) = 1.41 (s, 18H, $(CH_3)_3CO$), 2.04 (s, 30H, η^5-CCH_3), 2.66 (br. m, 4H, $C_{ar}CH_2CH_2NH$), 2.67 (dd, $^2J = 12.8$ Hz, $^3J = 4.8$ Hz, 2H, η^6-$C_{ar}CHHCH(CO)NH$), 2.79 (dd, $^2J = 12.8$ Hz, $^3J = 4.8$ Hz, 2H, η^6-$C_{ar}CHHCH(CO)NH$), 3.23 (br. m, 2H, $C_{ar}CH_2CHHNH$), 3.45 (br. m, 2H, $C_{ar}CH_2CHHNH$), 4.25 (m, 2H, $CH_2CH(CO)NH$), 5.84 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCCH_2$), 6.01 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCO$), 6.07 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCCH_2$), 6.12 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCO$), 6.26 (d, $^3J = 6.2$ Hz, 2H, $CH_2CH(CO)NH$), 7.06 (d, $^3J = 8.7$ Hz, 4H, $C_{ar}HC_{ar}HC_{ar}O$), 7.21 (d, $^3J = 8.7$ Hz, 4H, $C_{ar}HC_{ar}HC_{ar}O$), 7.32 (bs, 2H, $C_{ar}CH_2CH_2NH$). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ (ppm) = 11.38 (η^5-CCH_3), 29.56 ($(CH_3)_3CO$), 36.75 ($C_{ar}CH_2CH_2NH$), 36.99 (η^6-$C_{ar}CH_2CH(CO)NH$), 37.03 (η^6-$C_{ar}CH_2CH(CO)NH$), 41.94 ($C_{ar}CH_2CH_2NH$), 42.06 ($C_{ar}CH_2CH_2NH$), 57.65 ($CH_2CH(CO)NH$), 80.84 ($(CH_3)_3CO$), 82.01 (η^6-$C_{ar}HCO$), 82.33 (η^6-$C_{ar}HCO$), 89.52 (η^6-$C_{ar}HCCH_2$), 89.54 (η^6-$C_{ar}HCCH_2$), 98.42 (η^5 – CCH_3), 99.44 (η^6-$C_{ar}CH_2$), 121.50 ($OC_{ar}C_{ar}HC_{ar}H$), 132.20 (η^6-$C_{ar}O$), 132.69 ($OC_{ar}C_{ar}HC_{ar}H$), 138.39 ($C_{ar}CH_2CH_2NH$), 156.40 ($OC_{ar}C_{ar}HC_{ar}H$), 156.81 ($NH(CO)OC(CH_3)_3$), 171.41 ($CH_2CH(CO)NH$), 171.50 ($CH_2CH(CO)NH$). – IR (KBr): $\tilde{\nu} = 3434\ cm^{-1}$ (vs), 2926 (vw), 1636 (m), 1472 (m), 1236 (m), 846 (s), 558 (m). – MS ((+)-FAB, NBA): m/z = 1381/1382/1383 [M$^+$, dication + PF_6^-]. – HRMS ((+)-ESI): m/z = 619.2141 (calcd. 619.2104 for $C_{32}H_{41}N_2O_4^{102}Ru$ (dication)).

*Compound **9***: m. p. 212 °C (decomp.). – ^{1}H NMR (400 MHz, [D$_6$]acetone): δ (ppm) = 1.41 (s, 18H, $(CH_3)_3CO$), 2.04 (s, 30H, η^5-CCH_3), 2.67 (br. m, 4H, $C_{ar}CH_2CH_2NH$), 2.68 (br. m, 2H, η^6-$C_{ar}CHHCH(CO)NH$), 2.96 (br. m, 2H, η^6-$C_{ar}CHHCH(CO)NH$), 3.26 (br. m, 1H, $C_{ar}CH_2CHHNH$), 3.30 (br. m, 1H, $C_{ar}CH_2CHHNH$), 3.34 (br. m, 1H, $C_{ar}CH_2CHHNH$), 3.38 (br. m, 1H, $C_{ar}CH_2CHHNH$), 4.17 (m, 2H, $CH_2CH(CO)NH$), 5.81 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCCH_2$), 5.88 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCO$), 6.10 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCCH_2$), 6.18 (d, $^3J = 6.2$ Hz, 2H, η^6-$C_{ar}HCO$), 6.28 (d, $^3J = 6.6$ Hz, 2H, $CH_2CH(CO)NH$), 7.06 (d, $^3J = 8.4$ Hz, 4H, $C_{ar}HC_{ar}HC_{ar}O$), 7.23 (bs, 2H, $C_{ar}CH_2CH_2NH$), 7.26 (d, $^3J = 8.4$ Hz, 4H, $C_{ar}HC_{ar}HC_{ar}O$). – ^{13}C NMR (100 MHz, [D$_6$]acetone): δ (ppm) = 11.41 (η^5-CCH_3), 29.56 ($(CH_3)_3CO$), 36.75 ($C_{ar}CH_2CH_2NH$), 37.20 (η^6-$C_{ar}CH_2CH(CO)NH$), 42.21 ($C_{ar}CH_2CH_2NH$), 42.34 ($C_{ar}CH_2CH_2NH$), 57.88 ($CH_2CH(CO)NH$), 80.89 ($(CH_3)_3CO$), 81.89 (η^6-$C_{ar}HCO$), 82.73 (η^6-$C_{ar}HCO$), 89.50 (η^6-$C_{ar}HCCH_2$), 98.44 (η^5-CCH_3), 99.83 (η^6-$C_{ar}CH_2$), 121.44 ($OC_{ar}C_{ar}HC_{ar}H$), 132.44 (η^6-$C_{ar}O$), 132.83 ($OC_{ar}C_{ar}HC_{ar}H$), 138.53 ($C_{ar}CH_2CH_2NH$), 156.51 ($OC_{ar}C_{ar}HC_{ar}H$), 157.00 ($NH(CO)OC(CH_3)_3$), 171.51 ($CH_2CH(CO)NH$), 171.61 ($CH_2CH(CO)NH$). – IR (KBr): $\tilde{\nu} = 3424\ cm^{-1}$ (s), 2976 (w), 2927 (w), 1713 (m), 1677 (m), 1533 (w), 1505 (m), 1473 (s), 1236 (s), 1166 (m), 845 (vs), 558 (s). – MS ((+)-FAB, NBA): m/z = 1381/1382/1383 [M$^+$, dication + PF_6^-]. – HRMS (MALDI, sinapic acid): m/z = 1383.3849 (calcd. 1383.3882 for $C_{64}H_{82}F_6N_4O_8P^{102}Ru_2$).

*Monodemetalation of **8***

In a water-cooled quartz apparatus a degassed solution of doubly [RuCp*]$^+$-complexed macrocycle **8** (10.0 mg, 0.0065 mmol) and biphenyl (**10**, 5.04 mg, 0.0327 mmol) in MeCN (4 mL) was irradiated with a Desaga UV high-

pressure lamp (366 nm) in an argon atmosphere. A precipitate formed, and after 39 h the solvent was removed, and the crude product mixture was purified by HPLC (Nucleosil® 100-5 SA, NaOAc gradient in MeOH). The resulting acetate was dissolved in DCM and treated with $NaPF_6$ (1.1 equiv.) in water (10 mL), followed by concentration of the organic phase to dryness affording **11** as a yellowish solid (6.6 mg, 88 %); m. p. 147 °C (decomp.). – ^{1}H NMR (600 MHz, CD_3OD): δ (ppm) = 1.33 (s, 9H, $(CH_3)_3CO$), 1.38 (s, 9H, $(CH_3)_3CO$), 2.01 (s, 15H, η^5-CCH_3), 2.55 – 2.71 (m, 6H, CH_2), 2.86 (m, 1H, CH_2), 2.94 (m, 1H, CH_2), 3.17 (m, 1H, CH_2), 3.23 (m, 1H, CH_2), 3.47 (m, 1H, CH_2), 3.53 (m, 1H, CH_2), 3.70 (br. s, 2H, NH), 3.77 (br. s, 1H, NH), 4.20 (m, 2H, CHNH), 5.38 (m, 1H, NH), 5.56 (m, 1H, η^6-$C_{ar}H$), 5.82 (d, ^3J = 6.5 Hz, 1H, η^6-$C_{ar}H$), 5.85 (d, ^3J = 6.1 Hz, 1H, η^6-$C_{ar}H$), 6.01 (d, ^3J = 5.3 Hz, 1H, η^6-$C_{ar}H$), 6.90 (d, ^3J = 7.3 Hz, 2H, $C_{ar}H$), 6.91 (d, ^3J = 8.6 Hz, 2H, $C_{ar}H$), 7.02 (d, ^3J = 8.6 Hz, 2H, $C_{ar}H$), 7.10 (d, ^3J = 8.1 Hz, 2H, $C_{ar}H$), 7.15 (d, ^3J = 7.3 Hz, 2H, $C_{ar}H$), 7.17 (d, ^3J = 8.1 Hz, 2H, $C_{ar}H$). – ^{13}C NMR (150 MHz, CD_3OD): δ (ppm) = 10.67 (η^5-CCH_3), 28.95 ($(CH_3)_3CO$), 28.97 ($(CH_3)_3CO$), 35.63 (CH_2), 35.92 (CH_2), 36.01 (CH_2), 40.86 (CH_2), 41.70 (CH_2), 55.08 (CH), 56.25 (CH), 80.93 ($(CH_3)_3CO$), 87.54 (η^6-$C_{ar}H$), 88.83 (η^6-$C_{ar}H$), 98.26 (5C, η^5-CCH_3), 98.28 (C_q), 120.97 ($C_{ar}H$), 121.11 ($C_{ar}H$), 131.62 ($C_{ar}H$), 131.67 ($C_{ar}H$), 132.29 (C_q), 132.40 ($C_{ar}H$), 137.95 (C_q), 157.33 (C_q), 157.42 (C_q), 169.51 (C_q), 174.29 (C_q). – MS (ESI+): m/z = 1000/1001/1003 $[M]^+$. – IR (KBr): $\tilde{\nu}$ = 3427 cm^{-1} (m), 2924 (vs), 2853 (s), 1700 (m), 1659 (m), 1502 (m), 1469 (m), 1235 (m), 1166 (m), 842 (s). – HRMS ((+)-ESI): m/z = 1001.3946 (calcd. 1001.3996 for $C_{54}H_{67}N_4O_8^{102}Ru$).

Crystal structure determination

Single-crystal intensity data were collected on colourless single crystals of **8** on a Nonius MACH3 four-circle diffractometer. Graphite-monochromatised Mo K_α radiation (λ = 71.073 pm) was used, and the measurement temperature was 295(2) K. An empirical absorption correction based on ψ-scans was applied to the data. The structure was solved by Direct Methods and refined with full-matrix least-squares on F^2 (SHELX-93 [30, 31]). The hydrogen atoms were included in a riding model. All other atoms were refined with anisotropic displacement parameters. Displacement parameter and distance restraints were used in case of the PF_6^- anion which was split. Crystallographic data have been deposited [25].

[1] H. Eickhoff, G. Jung, A. Rieker, *Tetrahedron* **2001**, *57*, 353 – 364.

[2] For a review on cyclic peptides containing diaryl ether moieties, see L. Feliu, M. Planas, *Int. J. Pept. Res. Ther.* **2005**, *11*, 53 – 97.

[3] A. N. Nesmeyanov, N. A. Vol'kenau, I. N. Bolesova, L. S. Shul'pina, *Akad. Nauk. SSSR* **1980**, *254*, 1408 – 1409.

[4] N. A. Vol'kenau, I. N. Bolesova, L. S. Shul'pina, A. N. Kitaigorodskii, *J. Organomet. Chem.* **1984**, *267*, 313 – 321.

[5] J. A. Segal, *J. Chem. Soc., Chem. Commun.* **1985**, 1338 – 1339.

[6] A. J. Pearson, J. G. Park, S. H. Yang, Y.-H. Chuang, *J. Chem. Soc., Chem. Commun.* **1989**, 1363 – 1364.

[7] For a recent review, see: C. G. Hartinger, N. Metzler-Nolte, P. J. Dyson, *Organometallics* **2012**, *31*, 5677 – 5685.

[8] F. Noor, R. Kinscherf, G. A. Bonaterra, S. Walczak, S. Wölfl, N. Metzler-Nolte, *ChemBioChem* **2009**, *10*, 493 – 502.

[9] M. Wenzel, *J. Labelled Comp. Radiopharm.* **1990**, 28, 1001 – 1009, and refs. cited therein.

[10] W. H. Soine, C. E. Guyer, F. F. Knapp, Jr., *J. Med. Chem.* **1984**, *27*, 803 – 806.

[11] D. B. Grotjahn, *Coord. Chem. Rev.* **1999**, 190 – 192, 1125 – 1141.

[12] M. J. Clarke, *Coord. Chem. Rev.* **2003**, *236*, 209 – 233.

[13] J. D. Hoeschele, A. Habtemariam, J. Muir, P. J. Sadler, *Dalton Trans.* **2007**, 4974 – 4979.

[14] C. W. West, D. H. Rich, *Org. Lett.* **1999**, *1*, 1819 – 1822, and refs. cited therein.

[15] A. Marchetti, J. M. Ontoria, V. G. Matassa, *Synlett* **1999**, *S1*, 1000 – 1002.

[16] S. Venkatraman, F. G. Njoroge, V. Girijavallabhan, A. T. McPhall, *J. Org. Chem.* **2002**, *67*, 3152 – 3155.

[17] A. J. Pearson, J. G. Park, *J. Org. Chem.* **1992**, *57*, 1744 – 1752.

[18] A. J. Pearson, D. V. Ciurea, A. Venlankar, *Tetrahedron Lett.* **2008**, *49*, 1922 – 1926, and refs. cited therein.

[19] D. Leone-Stumpf, T. Lindel, *Chem. Eur. J.* **2001**, *7*, 3961 – 3965.

[20] D. Leone-Stumpf, T. Lindel, *Eur. J. Org. Chem.* **2003**, 1853 – 1858.

[21] A. Schmid, T. Lindel, *Angew. Chem. Int. Ed.* **2004**, *43*, 1581 – 1583.

[22] A. R. Carroll, S. M. Kaiser, R. A. Davis, R. W. Moni, J. N. A. Hooper, R. J. Quinn, *J. Nat. Prod.* **2010**, *73*, 1173 – 1176, and refs. cited therein.

[23] A. R. Kudinov, M. I. Rybinskaya, Yu. T. Struchkov, A. I. Yanovskii, P. V. Petrovskii, *J. Organomet. Chem.* **1987**, *336*, 187 – 197.
[24] A. Schmid, H. Piotrowski, T. Lindel, *Eur. J. Inorg. Chem.* **2003**, 2255 – 2263.
[25] CCDC 247119 (**8**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
[26] D. A. Freedman, T. P. Gill, A. M. Blough, R. S. Koefod, K. R. Mann, *Inorg. Chem.* **1997**, *36*, 95 – 102.
[27] D. L. Boger, D. Yohannes, *J. Org. Chem.* **1991**, *56*, 1763 – 1767.
[28] A. J. Gleichmann, J. M. Wolff, W. S. Sheldrick, *J. Chem. Soc., Dalton Trans.* **1995**, 1549 – 1554.
[29] D. S. Perekalin, E. E. Karslyan, P. V. Petrovskii, Y. V. Nelyubina, K. A. Lyssenko, A. S. Kononikhin, E. N. Nicolaev, A. R. Kudinov, *Chem. Eur. J.* **2010**, *16*, 8466 – 8470.
[30] G. M. Sheldrick, SHELX-93, Program for Crystal Structure Determination, University of Göttingen, Göttingen (Germany) **1993**.
[31] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112 – 122.